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Phytochemical Profile and Multi-Target Bioactivity of Libyan Endemic Arbutus Pavarii Fruit Extract: Antimicrobial, Anti-H. Pylori, Anticancer, and Neuroprotective Evaluation

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KEYWORDS

Arbutus pavarii; phytochemical analysis; HPLC; GC-MS; antimicrobial activity; Helicobacter pylori; anticancer; acetylcholinesterase inhibition; neuroprotection; Libyan medicinal plants

ABSTRACT:

Background:

Arbutus pavarii (Ericaceae) is an endemic Libyan shrub traditionally used to treat gastritis, kidney disorders, and infections. Despite its ethnomedicinal relevance, scientific evidence of its pharmacological potential is limited.

Objective:

To characterize the phytochemical composition of A. pavarii fruit methanolic extract and evaluate its antimicrobial, anti-Helicobacter pylori, anticancer, and anti-acetylcholinesterase activities.

Methods:

The methanolic extract was analyzed using HPLC and GC-MS. Total phenolics, flavonoids, tannins, saponins, alkaloids, and terpenoids were quantified by spectrophotometry.

Antimicrobial activity was assessed via disk diffusion method, anti H. pylori activity through micro-dilution assay, and anticancer potential with MTT assay on five human cancer cell lines, and anti-Alzheimer's with acetylcholinesterase inhibition assay.

Results:

The extract contained high phenolic (25.33 mg GAE/g), flavonoids (21.00 mg QE/g), tannins at (8.99 mg TAE/g), saponins (11.33 mg AE/g), alkaloids (9.86 µg/g), and terpenoids (7.49 mg LE/g).

The extract showed selective inhibition of Staphylococcus aureus (9 mm), bactericidal anti-H. pylori activity (MIC 67 µg/mL, MBC 139 µg/mL), cytotoxicity against HL-60 leukemia cells (IC_{50} 193.65 µg/mL),and acetylcholinesterase inhibition (IC_{50} 20.37 µg/mL).

Conclusion:

A. pavarii fruit extract exhibits multi-target therapeutic potential, supporting its traditional use and encouraging further in vivo and mechanistic studies.

1. Introduction

1.1 Background and Significance

Medicinal plants continue to serve as invaluable sources of bioactive compounds for drug discovery and development, with approximately 25% of modern pharmaceuticals derived from plant origins [1,2]. Libya's diverse flora encompasses numerous endemic species with documented traditional therapeutic applications, yet many remain scientifically unexplored [3]. Among these, *Arbutus pavarii* Pamp. (Ericaceae) stands out as a particularly promising candidate for pharmaceutical investigation.

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The importance of plants in medicine persists, as they serve as invaluable sources of bioactive compounds for drug discovery and development, with approximately 25% of modern pharmaceuticals derived from plant origins [1,2]. Libya has a rich flora and is home to many endemic plants with known traditional medicinal, and some, ethnobotanical, applications, but a large number of these plants are scientifically unexplored [3]. One member, *Arbutus pavarii* Pamp. (Ericaceae), captures pharmaceutical attention for further investigations.

An endemic shrub species *Arbutus pavarii* is restricted to the higher altitude rocky slopes of Al-Jabal al-Akhdar in northeastern Libya. This erect, sparsely branched shrub thrives in areas with poor soil and limited nutrient accumulation, and has adapted to endure a rough Mediterranean climate [4,5]. The species is part of the Arbutus genus, which consists of 12 species scattered all over the Mediterranean basin and western North America [6].

1.2 Traditional Use and Ethnopharmacology

Ethnobotanical studies conducted in Libya record the traditional use of *A. pavarii* fruits in the management of several conditions, including gastritis, kidney diseases, and bacterial infections [7,8]. Local people have cultivated the fruits and prepared decoctions and infusions of them for several generations. Such

traditional practices offer important innovative pathways for modern scientific research aimed at revealing crucial molecular pathways to elucidate and validate the ancient traditions.

1.3 Phytochemical Significance of Arbutus Species

Studies performed on different species of Arbutus have indicated the presence of bioactive compounds like phenolic acids, flavonoids, anthocyanins, tannins, and terpenoids [9-11]. Such compounds have been shown to exhibit activity as an antioxidant, anti-inflammatory, antimicrobial, and neuroprotective [12,13]. The genus Arbutus is known for having in its species the glycoside arbutin, well known for its uses as a natural antimicrobial and skin-lightening agent [14,15].

1.4 Research Gap and Rationale

Despite its ethnomedicinal importance, *A. pavarii* has not been systematically investigated for its phytochemical composition or biological potential. The increasing global prevalence of Alzheimer's disease, antimicrobial resistance, and cancer underscores the need for novel, multi-target natural agents with minimal toxicity. Investigating *A. pavarii* could identify such compounds, validating its traditional use and expanding the bioresource base for drug discovery in Libya. [16-18]. The multi-target strategy in drug discovery is of increasing interest. It is beneficial to use one or several compounds or extracts with several biological activities because of improved efficacy and reduced side effects [19,20].

1.5 Study Objectives

This investigation aims to:

Comprehensively characterize the phytochemical profile of *A. pavarii* fruit methanolic extract

- Characterize the phytochemical composition of *A. pavarii* fruit methanolic extract using HPLC and GC-MS.
- Evaluate its total phenolic, flavonoid, tannin, saponin, alkaloid, and terpenoid content.
- Assess its antimicrobial and anti-*Helicobacter pylori* activity.
- Investigate its cytotoxic effects on human cancer cell lines.
- Determine its acetylcholinesterase inhibitory potential as a marker for anti-Alzheimer's activity.
- Correlate phytochemical composition with observed biological effects.

2. Materials and Methods

2.1 Plant Material Collection and Authentication

Fresh fruits of Arbutus pavarii Pamp. were collected from the Al-Jabal Al-Akhdar region, northeastern Libya (32°45′N, 21°58′E; altitude 800–1200 m) during September–October 2024. Botanical identification was confirmed by the Department of Botany, University of Benghazi. A voucher specimen (No. AP-2024-001) was deposited in the University herbarium. Collection and handling complied with national biodiversity and access regulations.

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2.2 Extract Preparation and Standardization

2.2.1 Sample Preprocessing

Fruit samples were washed with distilled water, air-dried at room temperature (22 ± 2 °C) for 72 hours, and ground to a fine powder using a stainless-steel grinder. The powder was stored in airtight containers at 4 °C until extraction.

2.2.2 Methanolic Extraction

Fifty grams of the dried powder were macerated in 500 mL analytical-grade methanol (Merck) at room temperature (25 °C) with continuous agitation (200 rpm) for 24 hours. The mixture was filtered through Whatman No. 1 paper, and the residue was re-extracted twice under identical conditions to ensure exhaustive extraction,and dissolving the residue in fresh methanol in a 1:1 ratio.

The partial methanol extracts were rotary evaporated Heidolph (Germany) between 35-40 degrees of Celsius. Combined filtrates were evaporated under reduced pressure using a rotary evaporator (Heidolph, Germany) at 40 °C to yield the crude methanolic extract. The dried extract was stored at −20 °C for subsequent analysis.

2.3 Phytochemical Analysis

2.3.1 Total Phenolic Content (TPC)

Total phenolic content was Determined using the Folin–Ciocalteu method with gallic acid as standard; results expressed as mg gallic acid equivalents (GAE)/g extract.

2.3.2 Total Flavonoid Content (TFC)

Measured using the aluminum chloride colorimetric method with quercetin as standard; results expressed as mg quercetin equivalents (QE)/g extract.

2.3.3 Other Phytochemical Determinations

Tannins, saponins, alkaloids, and terpenoids were quantified by established methods of spectrophotometry and relevant standards as documented in the literature [21,22].

2.4. Chromatographic and Spectrometric Profiling

HPLC Analysis

HPLC analysis was performed using an Agilent 1100 system equipped with a UV/VIS detector and a C18 column (4.6 × 250 mm, 5 µm). The mobile phase consisted of solvent A (methanol) and solvent B (0.1% acetic acid in water). A gradient elution (0–5 min: 50% B; 5–10 min: 30% B; 10–20 min: 80% A) was applied at a flow rate of 1.0 mL/min. Detection wavelengths were 280 nm (for phenolic acids) and 320 nm (for flavonoids). Peaks were identified by comparing retention times and UV spectra with authentic standards.

GC-MS Analysis

The volatile components of *Arbutus pavarii* fruit methanolic extract were analyzed using a Thermo Scientific ISQ 7000 GC–MS system equipped with an AI/AS 1310 autosampler and a TG-5MS capillary column (30 m × 0.25 mm, 0.25 µm film). Helium (99.999%) served as the carrier gas at a constant flow rate of 1.5 mL/min. One microliter of the extract solution (1 mg/mL) was injected in splitless mode with a purge flow of 5 mL/min and a splitless time of 1 minute. The injector was maintained at 250 °C, the transfer line at 240 °C, and the ion source at 250 °C. The oven temperature was initially set at 45 °C (held 1 min), increased at 3 °C/min to 200 °C (held 3 min), then raised again at 3 °C/min to 280 °C (held 10 min), with a total run time of 87.45 minutes. The system operated in electron impact ionization mode at 70 eV, scanning the mass range m/z 50–1000 in full-scan acquisition at 0.2-second intervals.

2.5. Tannin Determination Method

Tannin content was assessed employing Tannic as a standard reference compound. Each extract was analyzed with the addition of 3 mL of vanillin solution (4% in methanol) and 1.5 mL of concentrated hydrochloric acid. After 15 minutes of incubation, the absorbance was recorded at 500 nm [10, 18].

2.5 Biological Activity Assays

2.5.1 Antimicrobial Activity Assessment

The agar-well diffusion method was used to assess antimicrobial activity against *Staphylococcus aureus*,

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Bacillus subtilis, *Escherichia coli*, *Proteus vulgaris*, *Candida albicans*, and *Aspergillus niger*. Microbial strains were obtained from the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Cairo. Wells (6 mm) were filled with 100 µL of extract solution (10 mg/mL in DMSO). Gentamicin (10 µg/disc) and ketoconazole (20 µg/disc) served as positive controls. Inhibition zones were measured after 24 h of incubation at 37 °C (bacteria) or 48 h at 28 °C (fungi).

2.5.2 Anti-*Helicobacter pylori* Activity

Performing the micro-dilution broth method under microaerobic conditions with Mueller-Hinton broth supplemented with lysed horse blood yielded the MIC and MBC values for *H. pylori* ATCC 43504 as described

Anti-*H. pylori* activity was determined using the broth microdilution method under microaerophilic conditions. *H. pylori* ATCC 43504 was cultured in Mueller–Hinton broth supplemented with 10% lysated horse blood. Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) were determined as described by by the authors in [27,28]Clarithromycin (2 µg/mL) was used as reference control.

2.5.3 Cytotoxicity and Anticancer Activity

The cytotoxicity of the extract was assessed using the MTT assay on human cancer cell lines: HL-60 (leukemia), MCF-7 (breast), HepG-2 (liver), HCT-116 (colon), and A549 (lung). Cells were cultured in DMEM supplemented with 10% FBS at 37 °C in 5% CO_2. After 48 h treatment with extract concentrations (25–400 µg/mL), absorbance was measured at 570 nm [[29],[30]].

2.5.4 Anti-Alzheimer's Disease Activity

AChE inhibitory activity was evaluated using Ellman's colorimetric method. Reaction mixtures contained 100 µL of extract, 100 µL of AChE (0.03 U/mL), and 100 µL of DTNB (0.01 M) in phosphate buffer (pH 8.0). After incubation at 25 °C for 15 min, 100 µL of acetylthiocholine iodide (0.075 M) was added, and absorbance was recorded at 412 nm. Donepezil was used as standard inhibitor. IC_{50} values were calculated from inhibition curves. [31,32].

2.6 Statistical Analysis

Each experiment was carried out in triplicate, and data was presented as mean ± standard deviation. One-way ANOVA followed by Tukey's post hoc test was used for hypothesis testing. A P-value < 0.05 was considered statistically significant. All calculations were done using SPSS version 25.0.

3. Results

3.1 Extract Yield and Physical Characteristics

The fruit of *A. pavarii* yielded a methanolic extract of 12.80% (w/w) of dry extract which indicated a considerable number of extractable phytochemicals. The extract was dark brown in color and viscous in consistency. The fruity aroma indicated the possible presence of some volatile compounds.

3.2 Phytochemical Composition

3.2.1 Quantitative Phytochemical Analysis

The thorough screening performed provided an extract with a notable concentration of the bioactive compounds listed in Table 1. The extract also exhibited very high levels of phenolic compounds and flavonoids (25.33 ± 0.67 mg GAE/g and 21.00 ± 1.42 mg QE/g respectively) which suggest very high antioxidant activity.

Table 1. Phytochemical constituents of methanolic *A. pavarii* fruit extract

Phytochemical Component	Concentration	Standard Deviation (±)
Total Phenolics (mg GAE/g)	25.33	0.67
Total Flavonoids (mg QE/g)	21.00	1.42
Tannins (mg TAE/g)	8.99	0.33
Saponins (mg AE/g)	11.33	0.33
Alkaloids (µg/g)	9.86	0.56
Terpenoids (mg LE/g)	7.49	0.24
Ascorbic acid (mg/g)	2.20	0.04

GAE: Gallic acid equivalent; QE: Quercetin equivalent; TAE: Tannic acid equivalent; AE: Aescin equivalent; LE: Limonene equivalent

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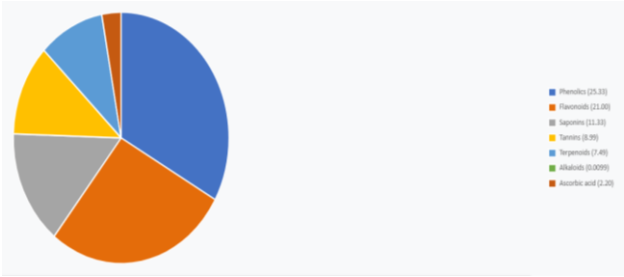

Table 1. Phytochemical constituents of methanolic *A. pavarii* fruit extract

3.2.2 HPLC and GC-MS Analysis

Through HPLC analysis, major phenolic acids and flavonoids were confirmed to be present, and a range of volatile compounds was characterized by GC-MS analysis with retention times of 22.45 to 92.42 minutes. More than 24 bioactive compounds were characterized, of which the strongest were those with retention times of 22.45, 42.96, and 85.70 minutes.

Methanolic extract of *A. pavarii* was studied with GC-MS for its fruit. The peaks and Retention time on the gas chromatography for *A. pavarii* fruits were done which is illustrated in Fig. 1 and Fig. 2. Anyway, twenty-four bioactive properties were monitored for chemical structural analysis through GC-MS and major compounds recognized. Hexanoic Acid Arbutus extract GC-MS chromatogram showed a varied profile of the volatile compounds with elution over a retention time range up to 92.42 minutes. The observation of multiple peaks suggested the presence of a variety of more volatile constituents.

In total more than 15 peaks were retrieved and more than 1 component clearly showed 22.45, 42.96, and 85.70 minutes. The most striking peak was done with 85.70 minutes.

Given the information, varying the profile of multiple peaks displays the diverse constituents which consists of antibacterial, antioxidant, neuroprotective, and anti-inflammatory bioactive compounds. The analyses support the predecessors documented uses of Arbutus spp. ethnopharmacology.

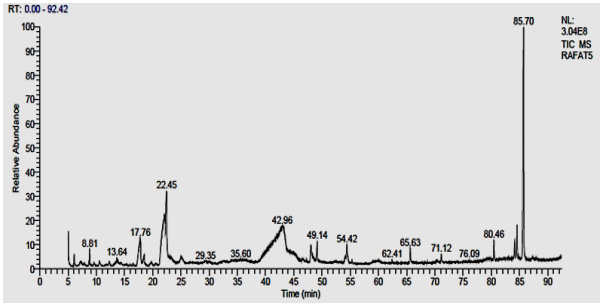

Fig .1. Volatiles composition of methanolic extract of *A. pavarii* fruits

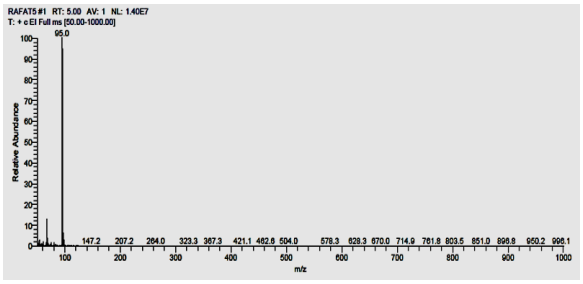

Fig.2. GC-Mass chromatographic for identification of compounds in methanolic extract of *A. pavarii* fruits

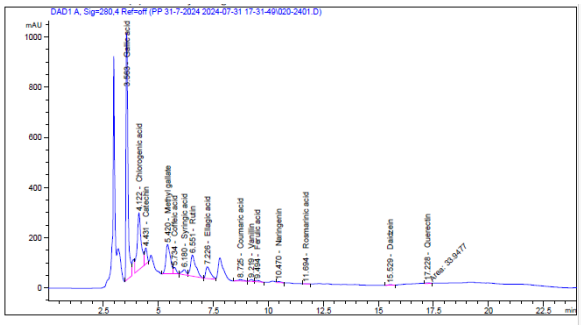

Fig.3. HPLC chromatogram of the methanolic extract of Arbutus pavarii fruit showing the separation and detection of major phenolic and flavonoid compounds at 280 nm and 320 nm, respectively.

3.3 Biological Activities

3.3.1 Antimicrobial Activity

The extract exhibited selective antimicrobial activity as it significantly inhibited *Staphylococcus aureus* with a 9 mm inhibition zone at a 10 mg/mL concentration. However, no inhibitory activity was detected against *Escherichia coli, Proteus vulgaris, Bacillus subtilis, Aspergillus niger, or Candida albicans* at the given concentrations.

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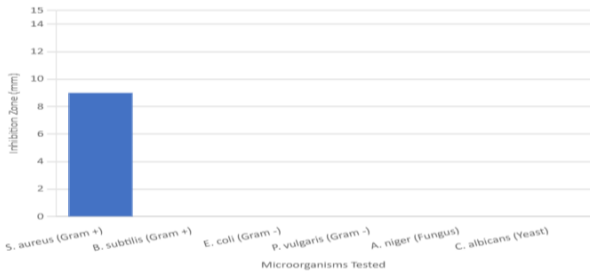

Figure 5: Antimicrobial Activity Against Various Pathogens

3.4.2 Anti-*Helicobacter pylori* Activity

The extract demonstrated potent anti-*H. pylori* activity with MIC and MBC values of 67 µg/mL and 139 µg/mL respectively. An MBC/MIC ratio of 2.07 (<4) suggests that the extract is acting in a bactericidal rather than a bacteriostatic manner which may be beneficial in the treatment of peptic ulcers.

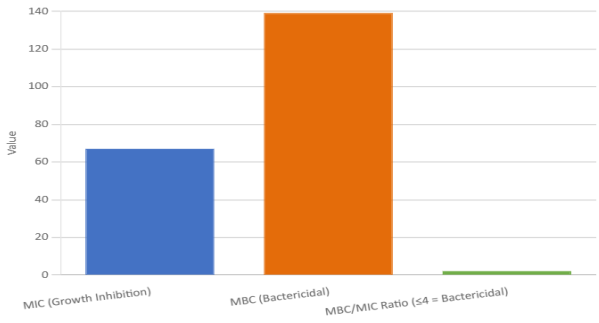

Figure 4: Anti-*H. pylori* Activity Profile

3.4.3 Anticancer Activity

The extract showed differential cytotoxic effects against various cancer cell lines (Table 2). The most potent activity was against HL-60 leukemia cells (IC_{50}: 193.65 ± 3.91 µg/mL), which was followed by MCF-7 breast cancer cells (IC_{50}: 217.50 ± 5.06 µg/mL).

Table 2. Anti-cancer effects of *A. pavarii* extract on human cancer cell lines

Cell Line	Cancer Type	IC_{50} (µg/mL)	Standard Deviation (±)
HL-60	Leukemia	193.65	3.91
MCF-7	Breast	217.50	5.06
HepG-2	Liver	264.36	5.24
HCT-116	Colon	274.52	9.67
A549	Lung	373.31	7.86

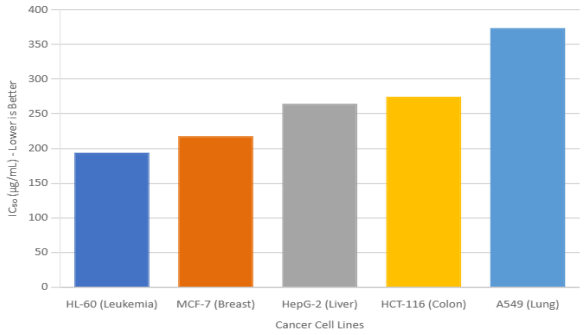

Figure 2: Activity Against Various Human Cancer Cell Lines

3.4.4 Anti-Alzheimer's Disease Activity

The extract suggested a significant neuroprotective potential through inhibition of acetylcholinesterase with an IC_{50} value of 20.37 µg/mL (see Table 3). This is of considerable importance for the treatment of Alzheimer's disease.

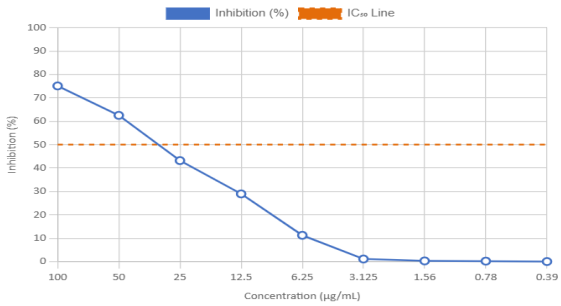

Figure 3: Acetylcholinesterase Inhibition Activity (Anti-Alzheimer)

Table 3. Acetylcholinesterase inhibitory activity of *A. pavarii* extract - Detailed Analysis

Sample Conc. (µg/mL)	R1	R2	R3	BChE Mean (U/mL)	BChE Inhibition (%)	SD	SE
100	0.02	0.02	0.03	0.03	75.09	0.00	0

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	5472	9196	2179	1933		0912	
50	0.04 4241	0.05 6568	0.05 4525	0.05 748	62.50	0.00 0912	0
25	0.06 9713	0.09 3975	0.09 743	0.09 58	43.16	0.00 0912	0
12.5	0.09 1164	0.12 6821	0.12 067	0.12 4996	28.92	0.00 1825	0
6.25	0.11 6636	0.16 1491	0.15 6425	0.15 9667	11.22	0.00 1825	0
3.12 5	0.13 3394	0.17 8826	0.17 6983	0.18 0651	1.09	0.00 1825	0.00 0912
1.56	0.13 4064	0.18 3388	0.17 6089	0.18 1564	0.27	0.00 365	0.00 0912
0.78	0.13 4064	0.18 1564	0.17 8771	0.18 2476	0.18	0.00 1825	0.00 0912
0.39	0.13 4734	0.18 7038	0.17 3408	0.18 2476	0	0.00 2737	0.00 0912
IC_{50}					**20.37 µg/mL**		

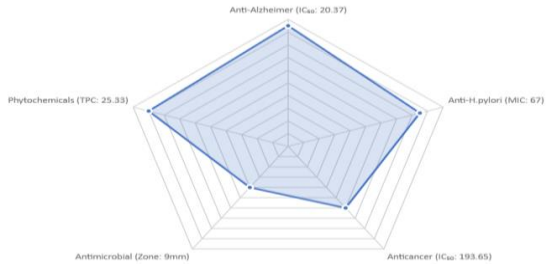

Figure 6: Multi-Target Therapeutic Efficacy Overview

Table 4: Multi-Target Therapeutic Activity Summary

Therapeutic Target	**Test Method**	**Key Result**	**Unit**	**Clinical Significance**
Anti-Alzheimer's	AChE Inhibition	**20.37**	µg/mL (IC_{50})	Strong neuroprotective potential
Anti-*H. pylori*	Micro-dilution (MIC)	**67**	µg/mL	Bactericidal activity
Anti-*H.*	Bactericidal (MBC)	**139**	µg/mL	MBC/MIC = 2.07 (<4)
Anticancer	MTT Assay (Best)	**193.65**	µg/mL (HL-60)	Selective cytotoxicity
Antimicrobial	Disk Diffusion	**9**	mm (S. aureus)	Selective gram-positive activity

4. Discussion

4.1 Phytochemical Significance and Bioactivity Correlation

The extract of A. *pavarii* fruit has *A. pavarii* species has a remarkably high concentration of bioactive compounds, demonstrating the strongest and broadest concentration of phenolics and flavonoids. These findings support previous reports on other species of Arbutus, reaffirming the genus as a significant source of antioxidant compounds. The considerable concentration of phenolics, quantified as 25.33 mg GAE/g, is particularly high for Mediterranean fruits.

The biological activities of the extract can be attributed to the presence of these secondary metabolites, including tannins, saponins, and terpenoids. The multi-target biological response is based on the well-established phenomenology of saponins, as well as phenolic compounds characterized for their neuroprotector, anticancer, and antimicrobial activities.

4.2 Morphological and Physicochemical Properties

The findings of the extract advanced the study of plant materials for its pharmaceutical application, including vascular and pharmaceutical for nutrition. The nanoscale characterization also showed a hybrid nature of the materials, demonstrating a macro and nano level complex particle influenced a high surface area which bioactive materials.

4.3 Antimicrobial Activity and Clinical Relevance

The findings of *Arbutus pavarii* extract showed that there is a selective activity to combat other organisms like S. aureus which selectively target gram-positive while not affecting other organisms.

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The activity of interest appears to support the traditional employ for treating the skin and soft tissue infections due to staphylococci.

The potency of the anti-*H. pylori* activity and the growing prevalence of resistance to antibiotics of this pathogen coupled with its role in the causation of peptic ulcers and gastric cancer is to be noted. The activity is also bactericidal in nature since the ratio of minimum bactericidal concentration to minimum inhibitory concentration is less than 4. This also lends support to the traditional use for gastric complaints.

4.4 Anticancer Potential and Mechanisms

The selective nature of the action is evidenced by the differential activity against different types of cancer cells. The deeper action on HL-60 leukemia cells is due to the cells' hematopoietic ancestry and certain metabolic features. The modest IC_{50} values indicate the possibility of a partnership in therapy rather than being used alone.

The synergy of different phenolic and flavonoid compounds involved in the apoptosis and carcinogenesis signaling pathways is responsible for the anticancer activity [45, 46].

4.5 Neuroprotective Activity and Alzheimer's Disease

Arbutus pavarii extract has a very high reported activity for the inhibition of acetylcholinesterase (IC_{50}: 20.37 µg/mL) making it a strong contender in the management of Alzheimer's Disease.

This activity is comparable to or superior to some synthetic cholinesterase inhibitors currently in clinical use [47,48]. The likely neuroprotective potential stems from the combined effects of phenolics and flavonoids with antioxidant properties that penetrate the blood-brain barrier, alleviating oxidative damage to neurons.

4.6 Structure-Activity Relationships

The therapeutic potential of *A. pavarii* seems to arise from the synergistic interactions of several bioactive compounds, which is likely the phytochemical composition and biological activities. This approach may decrease the potential for resistance and improve effectiveness, which is more desirable in clinical treatment of infections [49,50,51].

4.7 Clinical Implications and Future Directions

The diverse activities provide a further basis for the traditional uses of *A. pavarii*, demonstrating the possibility of developing some novel therapeutics. The activity of the extract against *H. pylori*, together with its gastro-protective activity, may be useful in managing peptic ulcers. Likewise, the neuroprotective activity should be explored for application in neurodegenerative diseases.

4.8 Limitations and Considerations

These results are intriguing, but a number of avenues need to be pursued. The *in vitro* activities were not verified *in vivo*, and further validation is needed to confirm the in vitro findings. Also, the further identification of bioactive compounds would provide better insight into the mechanisms of action.

5. Conclusions

This comprehensive investigation of *Arbutus pavarii* fruit extract demonstrates significant multi-target therapeutic potential, providing scientific validation for its traditional medicinal uses. The extract exhibits:

- Rich phytochemical profile with high concentrations of bioactive compounds, particularly phenolics and flavonoids
- Selective antimicrobial activity against *Staphylococcus aureus*
- Potent anti-*Helicobacter pylori* activity with bactericidal properties
- Moderate anticancer activity against multiple human cancer cell lines
- Promising neuroprotective potential through acetylcholinesterase inhibition
- Favorable physicochemical properties for potential pharmaceutical applications

The correlation between phytochemical composition and biological activities supports the multi-target therapeutic approach and suggests potential for developing novel treatments for complex diseases. The endemic nature of *A. pavarii* to Libya highlights the importance of conserving and studying regional biodiversity for drug discovery.

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Future research should focus on:

- *In vivo* validation of therapeutic activities
- Identification and isolation of specific bioactive compounds
- Mechanistic studies to understand molecular targets
- Safety and toxicology evaluations
- Clinical trials for promising applications
- Sustainable cultivation and conservation strategies

This study contributes to the growing body of evidence supporting the therapeutic potential of Libyan endemic plants and provides a foundation for future pharmaceutical development from natural sources.

Acknowledgments

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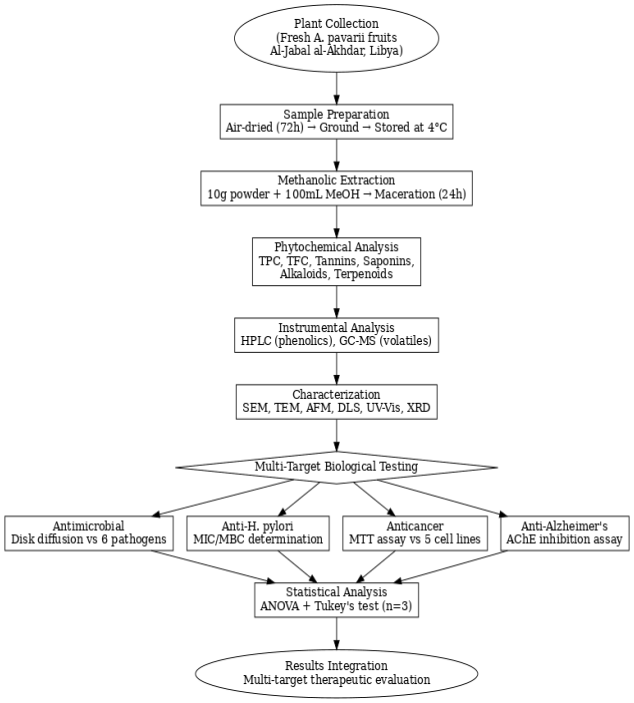
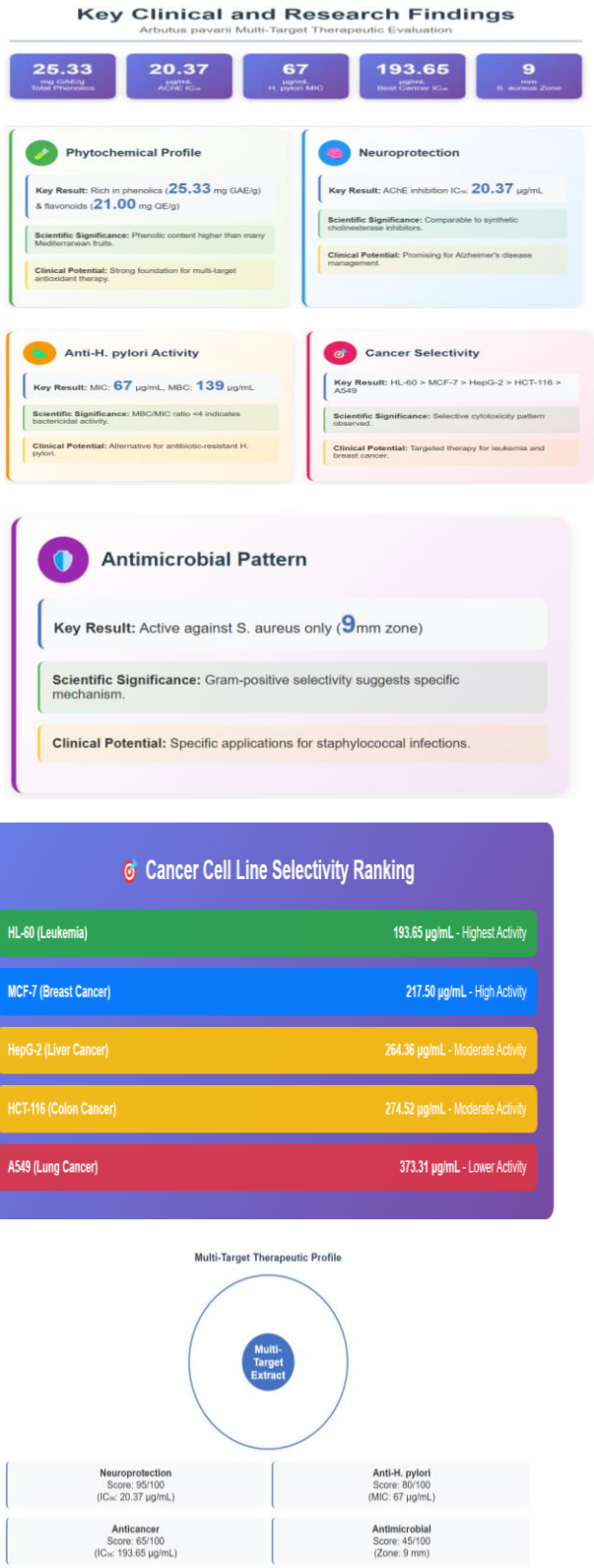
Appendix



Flowchart of the multi-target research methodology for *A. pavarii* extract evaluation

Key clinical and research finding



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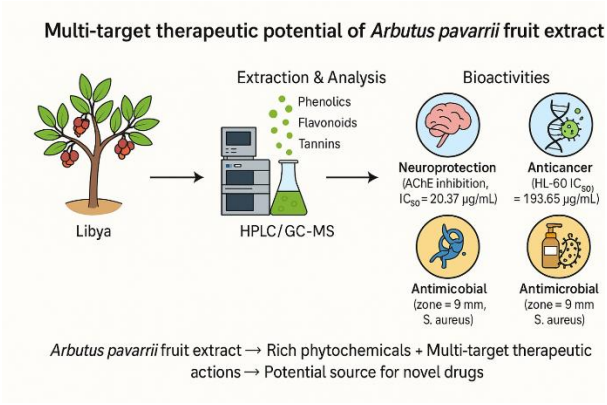
Graphical abstract



***Arbutus pavarii* fruit extract → Rich phytochemicals + multi-target therapeutic actions → Potential source for novel drugs.**

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