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RESEARCH ARTICLE

Antioxidant, Antidiabetic, Antiproliferative Activities, and Verbascoside Content of Four Endemic *Verbascum* Species: *V. leiocarpum*, *V. ozturkii*, *V. alyssifolium*, and *V. tuna-ekimii*

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ABSTRACT

This study, for the first time, investigated the antioxidant, antidiabetic, and antiproliferative properties of methanolic extracts from the aerial and root parts of four endemic *Verbascum* species—*Verbascum leiocarpum* Murb., *Verbascum ozturkii* Karavel., Uzunh. & S.Çelik, *Verbascum alyssifolium* Boiss., and *Verbascum tuna-ekimii* Karavel., A.Duran & Hamzaoğlu—and quantitatively determined their verbascoside content using HPLC-DAD. Antioxidant capacity was evaluated by DPPH and FRAP assays, and total phenolic content (TPC) and total flavonoid content (TFC) were also determined. Antidiabetic activity was assessed through α-glucosidase inhibition, and antiproliferative effects were determined in A549, MDA-MB-453, and HT-29 human cancer cell lines. Among the tested samples, the root of *V. leiocarpum* exhibited the highest TPC (50.89 mg GAE/g extract), FRAP value (124.16 mg TE/g extract), DPPH scavenging ability (IC_{50}: 58.82 µg/mL), and verbascoside content (129.06 mg verbascoside/g extract). This extract also exhibited significant antiproliferative effects against A549 and MDA-MB-453 cells, with inhibition rates of 85% and 69%, respectively. In contrast, both aerial and root extracts of *V. tuna-ekimii* exhibited low biological activity and a lower concentration of verbascoside. Pearson correlation analysis demonstrated strong positive associations between verbascoside content and both antioxidant and antiproliferative parameters. However, no significant correlation was found between verbascoside content and α-glucosidase inhibition, suggesting that other phytochemicals may be responsible for the antidiabetic activity. These findings indicate that *V. leiocarpum*, especially its root extract, may be considered a valuable source of natural antioxidants and antiproliferative agents. The study highlights the pharmacological potential of endemic *Verbascum* species that have not been comprehensively investigated phytochemically or pharmacologically and supports their further evaluation in the context of phytopharmaceutical research.

1 | Introduction

The global increase in chronic diseases—particularly cancer and type 2 diabetes—has significantly intensified the need for innovative, effective, and safe therapeutic agents. Natural products derived from medicinal plants represent a vital source for discovering bioactive compounds due to their structural diversity, multitarget pharmacological activities, and complex biological properties (Chopra and Dhingra 2021; Tüfekçi et al. 2023; Chaachouay and Zidane 2024). Among these, the genus *Verbascum* (mullein), from the family Scrophulariaceae, has attracted considerable attention in recent phytochemical and pharmacological studies due to its diverse bioactive constituents. Comprising more than 360 species worldwide, *Verbascum* is widely distributed across the Mediterranean basin and Western Asia. Türkiye is a center of

Abbreviations: DPPH, 2,2-diphenyl-1-picrylhydrazyl; FRAP, Ferric reducing antioxidant power; TFC, Total flavonoid contents; TPC, Total phenolic contents; VAA V. alyssifolium aerial parts; VAR, V. alyssifolium root; VLA, V. leiocarpum aerial parts; VLR, V. leiocarpum root; VOA, V. ozturkii aerial parts; VOR, V. ozturkii root; VTA, V.tuna-ekimii aerial parts; VTR, V.tuna-ekimii root.

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diversity for *Verbascum*, with around 255 recorded species, nearly 200 of which are endemic (Şimşek et al. 2023). The high level of endemism characterizes the floristic composition of Türkiye as biogeographically distinctive.

Verbascum species have played an important role in traditional medicine. Infusions and decoctions from their leaves and flowers have traditionally been used to treat various ailments—most notably as expectorants and antitussives in respiratory conditions such as coughs, bronchitis, asthma, and tonsillitis, as well as in the management of diabetes, hemorrhoids, rheumatic pain, and hyperpigmentation, and topically for their anti-inflammatory, analgesic, and wound-healing properties to relieve skin irritations, burns, and minor injuries—which may be attributed to their chemically diverse secondary metabolite profile (Şimşek et al. 2023; Gözcü et al. 2024a; Yiğit and Gözcü 2024). These include iridoids, flavonoids, saponins, and phenylethanoid glycosides, particularly verbascoside, which has been investigated for its pharmacological potential and multiple biological effects (Şimşek et al. 2023). Recent phytochemical studies have revealed taxon- and organ-specific differences in the overall secondary metabolite composition of *Verbascum* species (Zengin et al. 2023). In addition, the isolation of novel compounds such as ferruginoside D from *Verbascum leiocarpum* highlights the chemical richness and novelty of endemic taxa (Şimşek et al. 2023). Together, these findings emphasize the considerable phytochemical diversity of Verbascum species and its potential pharmacological relevance. In parallel, several Verbascum species and their constituents, especially verbascoside, have demonstrated antiproliferative and anticancer activities in various cell models (Demirci et al. 2023).

Verbascoside, a well-characterized secondary metabolite of *Verbascum* species, is structurally classified as a caffeoyl phenylethanoid glycoside and has been widely investigated for its various biological activities (Şimşek et al. 2025a). In vitro and in vivo studies have shown that verbascoside exerts antioxidant, neuroprotective, anti-inflammatory, antidiabetic, and antitumor effects, acting through mechanisms such as ROS scavenging and inhibition of AP-1-/NO-mediated pathways (Burgos et al. 2020). Its antioxidant activity is attributed to its polyphenolic structure, which enables free radical scavenging and modulation of redox-related signaling (Vertuani et al. 2011). This contributes to the reduction of oxidative stress at the cellular level and may translate into therapeutic potential in conditions such as neurodegenerative diseases (Burgos et al. 2020). However, the relationship between verbascoside content and biological activity across different plant parts and *Verbascum* species has not been fully elucidated, mainly due to interspecific chemical variability and environmental influences. The specific contribution of verbascoside to the observed pharmacological effects—whether as the primary bioactive constituent or in synergy with co-occurring phytoconstituents—remains incompletely understood.

Oxidative stress is widely implicated in the pathogenesis and progression of chronic diseases, including cancer and diabetes. At the cellular level, this imbalance is associated with molecular damage to DNA, proteins, and lipids, which can disrupt normal functions (Pitocco et al. 2013; Trapali et al. 2025). Oxidative dysregulation also induces pro-inflammatory cytokine activation, contributing to chronic inflammation and metabolic homeostasis disturbance (Rani et al. 2016; Yadav et al. 2016). In light of these mechanisms, quantitative assessment of plant extract antioxidant capacity is critical for evaluating their phytotherapeutic potential. Investigating the effects of natural compounds on oxidative stress-related biomarkers provides a scientific basis for pharmaceutical development and supports their use in functional foods and nutraceuticals (Chen et al. 2016). Therefore, antioxidant evaluations are a fundamental strategy for understanding the regulatory effects of plant-derived compounds on redox systems.

Although scientific interest in the pharmacological properties of *Verbascum* species has increased in recent years, studies specifically addressing endemic taxa within the Turkish flora are still limited. Türkiye is recognized as one of the global biodiversity hotspots for the *Verbascum* genus, and its high level of endemism provides a valuable reservoir for natural product-based drug discovery (Dönmez et al. 2018). Despite this potential, species such as *Verbascum leiocarpum* Murb., *Verbascum ozturkii* Karavel., Uzunh. & S.Çelik, *Verbascum alyssifolium* Boiss., and *Verbascum tuna-ekimii* Karavel., A.Duran & Hamzaoğlu, endemic to the Anatolian flora, have not been comprehensively evaluated regarding their antioxidant, antidiabetic, and antiproliferative activities in relation to verbascoside content. These species offer significant potential for contributing to ethnopharmacological knowledge and developing novel bioactive compounds. Therefore, incorporating these underexplored species—part of Türkiye's floristic diversity—into pharmaceutical research presents an opportunity to harness regional botanical resources for modern biomedical applications.

This study aims to contribute to the existing literature by systematically investigating the biological activities and verbascoside content of aerial and root methanolic extracts from four endemic *Verbascum* species. The investigation includes evaluation of antioxidant properties using standard methods such as DPPH, FRAP, total phenolic content (TPC), and total flavonoid content (TFC) assays. In parallel, antidiabetic potential was assessed through the inhibition of α-glucosidase, an enzyme involved in postprandial glycemic regulation. To explore therapeutic potential, antiproliferative activities were evaluated in three human cancer cell lines—A549 (lung), MDA-MB-453 (breast), and HT-29 (colon)—to determine extract-specific antiproliferative profiles. Additionally, verbascoside content was quantified by HPLC-DAD to allow correlation with observed biological activities. Through this integrative methodology, bioactive extracts are highlighted, the pharmacological role of verbascoside is clarified, and a novel perspective is offered on their therapeutic applications.

2 | Material and Methods

2.1 | Plant Material

Plant materials were collected from various locations within the borders of Erzincan province (Türkiye). *Verbascum leiocarpum* Murb. (Herbarium number: Kandemir 10 519), *Verbascum tuna-ekimii* Karavel., A.Duran & Hamzaoğlu (Herbarium number: Kandemir 10 538), *Verbascum alyssifolium* Boiss. (Herbarium number: Kandemir 10 379), and *Verbascum ozturkii* Karavel., Uzunh. & S.Çelik (Herbarium number: Kandemir 10 574) were collected in May and June 2020 from various locations in Erzincan province, including the vicinity of Doğanköy (İliç–Uluyamaç), Bağıştaş region of İliç, and the route between Kemah Yücebelen and Bekiroğlu Plateau. The plants were taxonomically identified by Prof. Dr. Ali Kandemir from the Faculty of Arts and Sciences,

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Department of Biology, Erzincan Binali Yıldırım University. Voucher specimens have been deposited in the EBYU Herbarium.

2.2 | Extraction Procedure

Solid-liquid extraction was individually applied to the aerial and root parts (10 ± 0.1 g each) of plants (Akman et al. 2024a). For each plant part, maceration was conducted with methanol (3 × 100 mL, 3 × 12 hr) at room temperature (25 ± 2°C), and the procedure was repeated in triplicate. After filtration, the combined solvents were concentrated in a rotary evaporator at 40°C under vacuum to dryness. The extracts were stored in dark flasks at + 4°C until utilized. Methanol, a strong polar solvent, is widely used for the extraction of polyphenols and flavonoids due to its ability to dissolve both polar and nonpolar constituents, making it suitable for biological activity evaluation (Zheng et al. 2024). Extraction yields were calculated as the ratio of dried extract mass to the initial dry plant material and expressed as percentage (w/w). Accordingly, the extracts were obtained as amorphous solids, yielding 1.25 g (12.5%, root) and 1.05 g (10.5%, aerial) for *V. leiocarpum*, 1.12 g (11.2%, root) and 0.98 g (9.8%, aerial) for *V. ozturkii*, 1.08 g (10.8%, root) and 0.94 g (9.4%, aerial) for *V. alyssifolium*, and 1.02 g (10.2%, root) and 0.87 g (8.7%, aerial) for *V. tuna-ekimii*.

2.3 | Antidiabetic Activity

The α-glucosidase inhibitory activities of the crude extracts were evaluated according to the method described by Akman et al., (Akman et al. 2023), with minor modifications. Initially, α-glucosidase enzyme (0.1 Unit/mL) was dissolved in 0.1 M phosphate buffer to prepare the enzyme solution. The substrate *p*-nitrophenyl-α-D-glucopyranoside (*p*NPG, 0.375 mM) was also prepared in the same buffer. Each test sample (20 μL), dissolved in buffer or DMSO, was mixed with 10 μL of enzyme solution, followed by 20 μL of substrate to initiate the reaction. Mixtures were incubated at 37°C for 30 min and then terminated by adding 50 μL of 0.2 M sodium carbonate in 0.1 M potassium phosphate buffer. Absorbance was measured at 405 nm using a 96-well microplate reader. All experiments were performed in triplicate ($n = 3$), and results were expressed as mean ± standard deviation (SD). Inhibitory effects were compared with acarbose and expressed as IC_{50} (mg/mL) values.

2.4 | Antiproliferative Activity

The antiproliferative activities of the extracts were evaluated using a modified version of the method described by (Köksal et al. 2025), with minor modifications. The antiproliferative effects of the plant extracts were tested on MDA-MB-453 (breast), HT-29 (colorectal), and A549 (lung) human cancer cell lines. HT-29 cells were cultured in McCoy's 5A medium, A549 in DMEM, and MDA-MB-453 in EMEM, all supplemented with 10% FBS and Pen-Strep. Cells (5×10^3 in 100 μL medium) were plated in 96-well plates and incubated at 37°C with 5% CO_2. After incubation, the medium was removed, cells were washed with PBS, and 100 μL of each extract (250–500 μg/mL in medium) was added. Plates were incubated at 37°C with 5% CO_2 for 24, 48, or 72 h. At each time point, 50 μL of XTT solution (prepared by mixing 100 μL activator with 5 mL XTT reagent) was added, followed by 5 h of incubation. Absorbance was measured at 470/490 nm using a microplate reader. Cell proliferation inhibition percentages were calculated using the following formula:

% Inhibition = 100 − [(Absorbance of treated cells − Absorbance of extract in cell-free medium) / (Absorbance of control cells − Absorbance of control medium)] × 100

2.5 | DPPH Free Radical Scavenging Activity

The DPPH radical scavenging capacity of the extracts was determined following a previously described procedure (Akman et al. 2024b; Gözcü et al. 2024b). Briefly, each extract was prepared at concentrations of 20–400 μg/mL and mixed with 1.0 mL of 0.26 mM $DPPH^{\bullet}$ solution. After vortexing, the mixtures were incubated in the dark at room temperature for 30 min. Absorbance was then measured, converted to % activity, and used to calculate IC_{50} values (μg/mL). Results were compared with standard antioxidants: Trolox, BHT, BHA, and ascorbic acid. All analyses were conducted in triplicate ($n = 3$), and the results are presented as mean ± standard deviation.

2.6 | Ferric Reducing Antioxidant Power (FRAP)

The method described by Albayrak et al. and Şimşek et al. was used to determine the FRAP of the extracts (Albayrak et al. 2024; Şimşek et al. 2025b). Sample and standard solutions (1 mg/mL, 250 μL) were mixed with 1 mL of phosphate buffer (0.2 M, pH 6.6) and 1.25 mL of 1% $K_3Fe(CN)_6$ and then incubated in the dark at 50°C for 20 min. After incubation, 1.25 mL of TCA (10%) and 0.25 mL of $FeCl_3$ (0.1%) were added. The absorbance of the final mixture was measured at 700 nm. All tests were performed in triplicate ($n = 3$). Results were expressed as mg Trolox equivalent (TE)/g extract using a calibration curve (10–100 μg/mL Trolox). Trolox, BHT, BHA, and ascorbic acid were used as standard antioxidants for comparison.

2.7 | Total Phenolic Content

The total phenolic content of the extracts was determined spectrophotometrically using the Folin-Ciocalteu reagent (Varol et al. 2023; Gözcü et al. 2025). Extract and standard solutions (1 mg/mL, 100 μL) were diluted with 4.5 mL distilled water, followed by the addition of 100 μL Folin–Ciocalteu reagent. After incubation at room temperature for 120 min, 300 μL of 2% Na_2CO_3 was added. The mixtures were vortexed, and absorbance was measured at 760 nm. Gallic acid (1–1000 μg/mL) was used to generate the calibration curve, and results were expressed as mg gallic acid equivalent phenolic substance/g extract (mg GAE/g extract). All analyses were conducted in triplicate ($n = 3$), and the results are presented as mean ± standard deviation.

2.8 | Total Flavonoid Content

The total flavonoid content of the extracts was determined following a previously described procedure (Akşit et al. 2022; Adıgüzelli et al. 2024). Extract and standard solutions (1 mg/mL,

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100 μL) were mixed with 4.7 mL methanol, followed by the addition of 100 μL of 1 M NH_4CH_3COO and 100 μL of 10% $AlCl_3$. After vortexing, the mixtures were incubated at room temperature for 45 min. Absorbance was measured at 415 nm. Tests were performed in triplicate ($n = 3$). Results were calculated using a quercetin calibration curve (1–1000 μg/mL) and expressed as mg quercetin equivalent/g extract (mg QE/g extract).

2.9 | HPLC-DAD Quantification of Verbascoside

HPLC-DAD quantification of verbascoside was performed using a Thermo Scientific Ultimate 3000 HPLC system equipped with a Chrometsil C18 column (4.6 × 150 mm, 5 μm), following the method described by Ulutaş et al. with slight modifications (Ulutaş et al. 2025). The mobile phases included deionized water with 2.5% formic acid (A) and methanol (B). The flow rate was set at 1 mL/min. The elution program was applied as follows: 95:5 (A:B) isocratic flow for 2 min, followed by a linear gradient to 5:95 (A:B) over 20 min, then maintained isocratically at 0:100 (A: B) for 3 min, and finally returned to initial conditions of 95:5 (A: B) within 3 min for column equilibration. During separation, the column temperature was maintained at 35°C. Detection was carried out at 330 nm. The standard verbascoside used in this study was purified in our previous publication using preparative HPLC (Şimşek et al. 2025a). A six-point calibration curve was constructed using verbascoside standard solutions at concentrations of 5, 10, 25, 50, 100, and 200 μg/mL ($y = 0.2427 \times -0.1757$ $R^2 = 0.9996$). The linear range, limit of quantification (LOQ), and limit of detection (LOD) were determined by analyzing the dose–response curve and were found to be 5–200, 10.19, and 3.36 μg/mL, respectively. Extracts for analysis were prepared in deionized water at a concentration of 5 mg/mL. Before injection into the system, the solutions were filtered through a 0.22 μm syringe filter and then transferred to vials.

2.10 | Statistical Analyses

Statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). One-way ANOVA was applied to determine differences among data, and Duncan's multiple range test was used for post-hoc comparisons at the $p < 0.05$ significance level. Pearson correlation analysis was conducted to assess the relationships between phytochemical contents and biological activities.

3 | Results and Discussion

3.1 | Antioxidant Activity of Extracts

The antioxidant activities of the plant extracts were evaluated using different assay methods, and the results are presented in Table 1. Significant differences ($p < 0.05$) were observed among species and between plant parts. The DPPH• radical scavenging activity of the extracts was quantitatively evaluated and expressed as IC_{50} values (μg/mL). Among all tested extracts, the root extract of *V. leiocarpum* (VLR) exhibited the highest radical scavenging activity with an IC_{50} value of 58.82 ± 1.45 μg/mL, followed by *V. alyssifolium* root (VAR; 74.41 ± 2.82 μg/mL) and *V. leiocarpum* aerial part (VLA; 79.65 ± 2.02 μg/mL). In contrast, the aerial extract of VTA exhibited the lowest antioxidant activity with an IC_{50} value of 100.60 ± 1.68 μg/mL. When compared to standard synthetic antioxidants such as BHA (8.04 ± 0.69 μg/mL), BHT (10.70 ± 0.73 μg/mL), ascorbic acid (9.91 ± 0.87 μg/mL), and Trolox (8.50 ± 0.77 μg/mL), the extracts demonstrated moderate radical scavenging potential. Among all samples, the VLR exhibited comparatively strong DPPH• scavenging capacity. Statistical analysis showed that the IC_{50} value of VLR was significantly lower ($p < 0.05$) than those of the other extracts, while no significant difference was found between VAR and VLA. On the other hand, VTA exhibited significantly lower scavenging activity compared to all other extracts ($p < 0.05$). These findings suggest that the antioxidant activities of the extracts are species- and organ-dependent, with root extracts generally exhibiting higher radical scavenging potential than aerial parts. The DPPH• scavenging activity observed in the VLR may be primarily attributed to its high total phenolic content, which is consistent with the well-established role of phenolic compounds in antioxidant

TABLE 1 | Total phenolic and flavonoid contents and antioxidant activities of *Verbascum* species.

Plants	Part used	DPPH IC_{50}, μg/mL	TPC, mg GAE/g extract	TFC, mg QE/g extract	FRAP, mg TE/g extract
V. leiocarpum	VLA	79.65 ± 2.02^{c,d}	48.48 ± 1.49^{a}	8.57 ± 0.36^{b}	119.00 ± 0.85^{c}
	VLR	58.82 ± 1.45^{b}	50.89 ± 1.19^{a}	3.00 ± 0.55^{c}	124.16 ± 0.21^{c}
V. ozturkii	*VOA*	82.62 ± 0.58^{c,d}	29.96 ± 1.79^{d}	7.38 ± 1.09^{b}	95.46 ± 1.47^{d,e}
	VOR	93.23 ± 2.89^{d,e}	43.48 ± 2.16^{b}	2.38 ± 0.21^{c}	98.91 ± 1.48^{d,e}
V. alyssifolium	VAA	92.01 ± 1.93^{d,e}	38.67 ± 1.92^{c}	10.12 ± 1.44^{a}	108.59 ± 0.96^{d}
	VAR	74.41 ± 2.82^{c}	36.91 ± 1.40^{c}	5.00 ± 0.18^{b,c}	97.57 ± 0.95^{d,e}
V.tuna-ekimii	VTA	97.07 ± 1.29^{e}	29.59 ± 0.16^{d}	5.83 ± 0.74^{b,c}	87.78 ± 0.82^{e}
	VTR	100.60 ± 1.68^{e}	28.04 ± 0.70^{d}	0.83 ± 0.30^{d}	73.18 ± 1.92^{f}
Trolox		8.50 ± 0.77^{a}	—	—	—
BHA		8.04 ± 0.69^{a}	—	—	338.57 ± 0.31^{a}
BHT		10.70 ± 0.73^{a}	—	—	257.80 ± 1.24^{b}
Ascorbic acid		9.91 ± 0.87^{a}	—	—	383.66 ± 0.98^{a}

$^{a–f}$Different letters in the same column indicate statistical difference ($p < 0.05$).
Abbreviations: VAA, *V. alyssifolium* aerial parts; VAR, *V. alyssifolium* root; VLA, *V. leiocarpum* aerial parts; VLR, *V. leiocarpum* root; VOA, *V. ozturkii* aerial parts; VOR, *V. ozturkii* root; VTA, *V.tuna-ekimii* aerial parts; VTR, *V.tuna-ekimii* root.

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defense (Rajamanickam and Manju 2020; Fan et al. 2024). Although the IC_{50} values of the plant extracts were higher than those of standard antioxidants such as BHA and Trolox, the observed activity indicates a potentially valuable natural antioxidant capacity. This observation is relevant in the context of the increasing interest in plant-derived antioxidants as alternatives to synthetic compounds, which may have certain limitations regarding long-term use (Kulawik et al. 2013).

The reducing power of the extracts was determined by their Trolox equivalent (TE) values, as measured by the FRAP assay. The highest reducing power was observed in VLR (124.16 ± 0.21 mg TE/g extract), followed by VLA (119.00 ± 0.85) and VAA (108.59 ± 0.96). In contrast, the lowest reducing capacity was found in VTR (73.18 ± 1.92). Compared to synthetic antioxidants such as ascorbic acid (383.66 ± 0.98), BHA (338.57 ± 0.31), and BHT (257.80 ± 1.24), the reducing power of the extracts was moderate. According to statistical evaluation, the reducing power of VLR and VLA did not differ significantly ($p > 0.05$), while VTR exhibited significantly lower reducing activity compared to all other samples ($p < 0.05$). These findings are consistent with previous reports demonstrating that plant extracts with high phenolic content exhibit considerable electron-donating capacity, which contributes to their antioxidant potential (Park et al. 2012; Guneidy et al. 2022). The high FRAP values observed in VLR specifically support the idea that nonflavonoid phenolic or other redox-active compounds may be responsible for its strong reducing ability (Ji et al. 2011; Csepregi et al. 2016).

The TPC was found to be the highest in VLR (50.89 ± 1.19 mg GAE/g extract), followed by VLA (48.48 ± 1.49) and VOR (43.48 ± 2.16). The lowest phenolic content was observed in the aerial extract of VTA (28.04 ± 0.70). Statistical comparison indicated that VLR and VLA had significantly higher phenolic contents than the other samples ($p < 0.05$), while the difference between them was not significant. These findings indicate that VLR contains the highest level of phenolic compounds among the tested samples, which may contribute to its strong reducing capacity and $DPPH^{\bullet}$ scavenging activity (Moein et al. 2012; Tusevski et al. 2014). In the TFC analysis, the highest flavonoid concentration was found in the aerial extract of VTA (29.59 ± 0.16 mg QE/g extract), followed by VAA (10.12 ± 1.44) and VOA (7.38 ± 1.09). The lowest flavonoid content was observed in the root extract of VTR (0.83 ± 0.30). Statistical analysis confirmed that VTA had significantly higher flavonoid content compared to all other extracts ($p < 0.05$). The elevated flavonoid content in the aerial parts, particularly in VTA, suggests that flavonoids in *Verbascum* species are more concentrated and more efficiently extracted in the aerial tissues, which is consistent with the general solubility profile of flavonoids in polar solvents (Abidet et al. 2020; Zengin et al. 2023). These observations are also consistent with studies reporting that extraction optimization and ecological factors significantly influence flavonoid yield and antioxidant activity (Zhao et al. 2024).

3.2 | Antidiabetic Activity of Extracts

In this study, the α-glucosidase inhibitory potential of root and aerial extracts from four *Verbascum* species was evaluated and compared with the standard antidiabetic agent acarbose, and the results are presented as IC_{50} values (μg/mL, Table 2). The findings demonstrated significant variability in inhibitory potential both among species and between plant parts. Among the tested samples, most aerial extracts exhibited minimal α-glucosidase inhibitory activity, while several root extracts—especially VLR—demonstrated significant inhibition, suggesting that antidiabetic constituents may be more concentrated in the root tissues of certain *Verbascum* taxa.

TABLE 2 | In vitro α-glucosidase inhibitory activities of extracts from *Verbascum* species.

Sample	Aerial part IC_{50}, mg ml^{-1}	Root IC_{50}, mg ml^{-1}	Acarbose IC_{50}, mg ml^{-1}
V. leiocarpum	7.15 ± 0.16	0.59 ± 0.25[a]	0.71 ± 1.5[a]
V. ozturkii	>100	1.93 ± 1.10[b]	
V. alyssifolium	>100	1.87 ± 0.6[b]	
V. tuna-ekimii	>100	17.9 ± 1.8[c]	

[a–c]Different letters in the same column indicate statistical difference ($p < 0.05$).

Among the investigated species, VLR exhibited the most potent α-glucosidase inhibitory activity (0.59±0.25 mg/mL), with a lower IC_{50} value than the reference compound acarbose (0.71± 1.5 mg/mL), suggesting a higher therapeutic potential. The aerial part of this species exhibited lower activity (7.15±0.16 mg/mL), indicating a possible organ-specific distribution of active constituents. Similarly, the VOR (1.93±1.10 mg/mL) and VAR (1.87± 0.60 mg/mL) demonstrated moderate activity, while their aerial parts showed negligible inhibition ($IC_{50} > 100$ mg/mL). In contrast, *V. tuna-ekimii* exhibited low inhibitory activity in both aerial and root extracts, with the root extract showing the highest IC_{50} value (17.9±1.8 mg/mL) among all tested samples. Statistical analysis revealed that the IC_{50} value of VLR was significantly lower ($p < 0.05$) than those of the other extracts. No significant difference was observed between VOR and VAR, while VTR showed significantly weaker activity ($p < 0.05$).

These findings indicate that the roots of the investigated *Verbascum* species, especially *V. leiocarpum*, may serve as promising sources of natural α-glucosidase inhibitors. The superior activity VLR extract compared to acarbose suggests the presence of bioactive secondary metabolites capable of modulating carbohydrate digestion and glucose absorption. Phytochemical and pharmacological investigations have attributed the antidiabetic potential of *Verbascum* species to their phenylethanoid glycosides, flavonoids, and iridoids, which are known to exert α-glucosidase and α-amylase inhibitory effects (Şimşek et al. 2023). In agreement with our results, (Shahbaz et al. 2022) demonstrated that *V. thapsus* root extracts exhibit significant α-glucosidase inhibitory activity, with methanol extracts showing higher potency (IC_{50} 3.70±0.94 ppm) compared to aqueous extracts (Shahbaz et al. 2022). Similarly, (Alkowni et al. 2023) reported strong α-glucosidase inhibition by *V. fruticulosum* methanolic extract (IC_{50} 75.46±0.66 μg/mL) (Alkowni et al. 2023). Interestingly, the aerial parts of most investigated species exhibited minimal or no α-glucosidase inhibitory activity, highlighting the higher concentration of bioactive constituents in the root extracts. This variation in phytochemical content between plant parts has been documented in previous phytochemical profiling studies, which

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demonstrated that root tissues generally accumulate higher concentrations of glycosidic and iridoid compounds compared to aerial organs (Saleem et al. 2020; Sahoo et al. 2023). Similar trends have been observed in other medicinal plants, showing that root extracts tend to exhibit significantly lower IC_{50} values in enzyme inhibition assays (Zengin et al. 2015; Zengin et al. 2016; Arumugam et al. 2021). Among the tested species, *V. tuna-ekimii* exhibited the lowest α-glucosidase inhibitory activity, notably in the root extract. This suggests a lower concentration or different composition of bioactive constituents in this species compared to *V. leiocarpum*, *V. ozturkii* and *V. alyssifolium*.

Overall, the present study provides the first comparative analysis of antidiabetic potential among different *Verbascum* species and plant parts. The strong α-glucosidase inhibitory activity observed in VLR extract suggests potential for development into plant-based therapeutic agents or functional food ingredients for diabetes management.

3.3 | Antiproliferative Activity of Extracts

The antiproliferative activities of plant extracts were evaluated on three human cancer cell lines: A549 (lung), MDA-MB-453 (breast), and HT-29 (colon). The results, expressed as percentage inhibition of cell proliferation at a defined concentration, are presented in Table 3.

Among the tested samples, VLR exhibited the highest antiproliferative activity against A549 (85%) and MDA-MB-453 (69%) cells, while its effect on HT-29 cells was comparatively lower (18%). The VLA exhibited lower activity, suggesting that antiproliferative constituents are more concentrated in the root tissues. These results are consistent with previous studies reporting organ-specific distribution of bioactive compounds in *Verbascum* species, with roots often containing higher levels of iridoids, phenylethanoid glycosides, and saponins associated with antiproliferative activity (Georgiev et al. 2011; Brownstein et al. 2017). The VAR and VAA showed significant activity against A549 (2% and 9%, respectively) and HT-29 (3% and 6%), while no inhibition was observed in MDA-MB-453 cells. Although the percentages were lower compared to *V. leiocarpum*, the limited effects observed in the colon and lung cell lines suggest the presence of minor antiproliferative constituents. Notably, the VOR demonstrated selective antiproliferative against HT-29 (99% inhibition), with lower activity against A549 (14%) and no observable effect on breast cancer cells. This activity against colorectal cancer cells may indicate a selective mechanism or a metabolite profile more compatible with interacting with this cancer type. In addition, VTR and VTA exhibited relatively low antiproliferative activity in all tested cell lines, with maximum inhibition values of 13% in A549, 9% in MDA-MB-453, and 7% in HT-29 cells. These findings suggest that *V. tuna-ekimii* may not be a promising candidate for further development as an antiproliferative agent.

TABLE 3 | In vitro antiproliferative effects of *Verbascum* species on A549, MDA-MB-453, and HT-29 cell lines.

Plants	Part used	A549	MDA-MB-453	HT-29
V. leiocarpum	VLA	30	18	20
	VLR	85	69	18
V. ozturkii	*VOA*	11	ni	2
	VOR	14	ni	1
V. alyssifolium	VAA	9	ni	6
	VAR	2	ni	3
V.tuna-ekimii	VTA	13	4	7
	VTR	9	ni	7

Note: % inhibition of cell proliferation, ni: no inhibition.
Abbreviations: VAA, *V. alyssifolium* aerial parts; VAR, *V. alyssifolium* root; VLA, *V. leiocarpum* aerial parts; VLR, *V. leiocarpum* root; VOA, *V. ozturkii* aerial parts; VOR, *V. ozturkii* root; VTA, *V.tuna-ekimii* aerial parts; VTR, *V.tuna-ekimii* root.

The differential antiproliferative observed among species and plant parts may reflect variations in secondary metabolite composition. Previous reports have identified several bioactive constituents in *Verbascum* spp., including flavonoids (e.g., luteolin, apigenin), iridoid glycosides (e.g., aucubin), and phenylethanoid glycosides (e.g., verbascoside), many of which have demonstrated antiproliferative and pro-apoptotic activities in various cancer models (Luca et al. 2019; Iliescu et al. 2020). In particular, verbascoside has been shown to exert antiproliferative effects through induction of apoptosis, ROS generation, and inhibition of MAPK and PI3K/Akt pathways (Vasincu et al. 2020; Daneshforouz et al. 2021). The strong activity observed in the VLR extract may be attributed to the presence of such compounds, acting individually or synergistically within a complex phytochemical profile. The pronounced inhibition of HT-29 cells by the VOR extract indicates the need for further phytochemical and mechanistic investigations. In conclusion, VLR and VOR extracts were identified as the most promising candidates based on their antiproliferative effects, exhibiting significant activity against lung and colon cancer cell lines, respectively. These findings support further investigation into the chemical constituents of these species and their mechanisms of action in cancer models. The in vivo studies and bioactivity-guided fractionation are recommended to confirm and further investigate the observed effects.

3.4 | Verbascoside Contents of Extracts

The quantitative determination of verbascoside was conducted through HPLC-DAD, and the corresponding data are detailed in Table 4. The results indicated significant variation in verbascoside levels among the *Verbascum* species and their plant parts examined. According to the results, the VLR exhibited the highest verbascoside concentration (129.06 ± 0.65 mg/g), followed by its aerial part (VLA) (29.62 ± 0.71 mg/g). In contrast, VTA showed the lowest levels, with 5.45 ± 0.31 mg/g in aerial parts and 3.84 ± 0.22 mg/g in roots (VTR). In VAR, verbascoside concentrations were higher in the root tissues (33.52 ± 0.84 mg/g) compared to the aerial parts (VAA; 18.52 ± 0.47 mg/g), while an inverse distribution was noted in VOA, where the aerial parts (22.25 ± 0.53 mg/g) exhibited higher concentrations than the roots (VOR; 13.04 ± 0.39 mg/g). Statistical analysis showed that VLR contained higher verbascoside content compared to all other samples ($p < 0.05$). VLA and VAR exhibited comparably high concentrations, showing no statistically significant differences between them. VOA and VAA showed moderate contents, lower than those of VLR, VLA, and VAR but higher than VOR. VOR showed lower verbascoside content than VOA and VAA, while VTA and VTR showed the lowest concentrations among all extracts. These results indicate that verbascoside accumulation differs between species

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TABLE 4 | Verbascoside content of *V. leiocarpum*, *V. ozturkii*, *V. alyssifolium*, and *V. tuna-ekimii* extracts.

Plant	Part used	mg verbascoside/g extract
Verbascum leiocarpum	VLA	29.06 ± 0.65[b]
	VLR	33.52 ± 0.84[a]
Verbascum ozturkii	VOA	22.25 ± 0.53[c]
	VOR	13.04 ± 0.39[d]
Verbascum alyssifolium	VAA	18.52 ± 0.47[c,d]
	VAR	29.62 ± 0.71[b]
Verbascum tuna-ekimii	VTA	5.45 ± 0.31[e]
	VTR	3.84 ± 0.22[e]

[a–e]Different letters in the same column indicate statistical difference ($p < 0.05$).
Abbreviations: VAA, *V. alyssifolium* aerial parts; VAR, *V. alyssifolium* root; VLA, *V. leiocarpum* aerial parts; VLR, *V. leiocarpum* root; VOA, *V. ozturkii* aerial parts; VOR, *V. ozturkii* root; VTA, *V. tuna-ekimii* aerial parts; VTR, *V.tuna-ekimii* root.

and also between aerial and root organs, rather than following a uniform distribution pattern.

The HPLC-DAD chromatograms of extracts of *Verbascum* species and verbascoside are presented in Figure 1. The chromatographic evaluation shows that verbascoside constitutes a major component in the VLR and VLA extracts, while its content is comparatively lower in VOA and VOR. The lowest verbascoside concentrations were observed in VTA and VTR, suggesting a chemically distinct profile for this species. To fully explain the differences observed in antidiabetic, antioxidant, and antiproliferative activities, further investigation is needed to elucidate the chemical composition of this species and to identify other major or minor bioactive constituents.

The Pearson correlation analysis (Table 5, Figure 2) revealed significant associations between antioxidant activity and phytochemical composition among the evaluated *Verbascum* species. A very strong positive correlation between TPC and FRAP ($r = 0.902$) suggests that phenolic compounds contribute to electron donation in redox-based antioxidant mechanisms. This is in agreement with the well-known mechanism whereby phenolic compounds donate electrons or hydrogen atoms, generating relatively stable radical intermediates that can effectively terminate oxidative chain reactions (Wu et al. 2025). Such mechanisms are also consistent with previous studies reporting that phenolic hydroxyl groups can reduce Fe^{3+} to Fe^{2+}, thereby enhancing the overall reducing capacity of plant extracts (Santana et al. 2015). TPC also showed a strong positive correlation with verbascoside content ($r = 0.703$), supporting its role as a major contributor to total phenolic. However, the correlation is limited, suggesting that other phenolic constituents—such as flavonoids, phenylethanoids (e.g., isoverbascoside, echinacoside), and phenolic acids—also contribute to TPC and antioxidant properties. The moderate correlation between TFC and FRAP ($r = 0.418$) indicates that not all flavonoids exhibit strong reducing activity, possibly due to structural variations in hydroxylation and conjugation. Similarly, the low correlation between TFC and verbascoside ($r = 0.310$) may reflect the distinct structure and biosynthetic origin of verbascoside as a phenylethanoid glycoside. These findings indicate that the antioxidant potential of *Verbascum* species is influenced not only by the total phenolic content but also by the specific composition and relative concentrations of individual phenolic compounds. While TPC shows a strong association with reducing power, the moderate and relatively low correlations observed for flavonoids and verbascoside, respectively, suggest that the antioxidant activity is influenced by the combined effects of different groups of phytochemicals. This complexity is consistent with previous findings indicating that the antioxidant capacity of plant extracts is influenced by the combined effects of multiple phenolic constituents, rather than being attributed to any single compound (Brewer 2011).

Verbascoside content showed a very strong positive correlation with FRAP ($r = 0.826$), indicating its significant role in the reducing capacity of the extracts. This is consistent with previous reports that have demonstrated its ferric-reducing and metal-chelating properties, which are attributed to the presence of catechol moieties (Mira et al. 2002; DeGraft-Johnson et al. 2007). DPPH radical scavenging activity showed strong and significant negative correlations with TPC ($r = -0.669$), FRAP ($r = -0.757$), and verbascoside ($r = -0.926$), reflecting that higher antioxidant capacity is associated with lower IC_{50} values in this assay. The strongest association was with verbascoside, suggesting its contribution to radical scavenging through hydrogen atom transfer (HAT) or single electron transfer (SET) mechanisms. This is consistent with studies reporting its dose-dependent scavenging of DPPH and ABTS radicals (Shirwaikar et al. 2006; Bale et al. 2021). These correlations support the hypothesis that verbascoside exhibits multifunctional antioxidant activity, contributing to both redox-based (FRAP) and radical-scavenging (DPPH) mechanisms (Burgos et al. 2020). Given its high content in VLA and VLR species and associated antioxidant potential, these taxa represent promising candidates for further phytochemical and therapeutic evaluation. The findings highlight the importance of integrating targeted metabolite quantification with comprehensive antioxidant profiling in assessing medicinal plant bioactivity.

According to Figure 3, no statistically significant correlation was observed between the antidiabetic activity and the verbascoside content in the aerial or root extracts of the *Verbascum* species (Table 4 and Table 6). The Pearson correlation coefficients for the aerial ($r = -0.688$) and root ($r = -0.802$) extracts indicated moderate to strong negative associations. However, the statistical insignificance of these correlations suggests that the observed trends cannot be interpreted as conclusive evidence of a direct relationship. Although the negative correlation suggests that higher verbascoside content may be associated with α-glucosidase inhibitory activity, the results indicate that verbascoside cannot be considered the only contributor to the observed antidiabetic potential. This suggests that the antidiabetic potential cannot be attributed to verbascoside alone but is instead the result of multiple secondary metabolites acting individually or in combination. Other phytochemical constituents—such as iridoids, flavonoids, saponins, or other phenylethanoid glycosides—may also contribute to the overall activity. Previous studies have highlighted the contribution of other phenylethanoid glycosides such as isoverbascoside and echinacoside, which also inhibit carbohydrate-hydrolyzing enzymes (Alipieva et al. 2014; Tian et al. 2021). In addition, flavonoids like luteolin and apigenin have demonstrated strong α-glucosidase and α-amylase inhibitory effects (Kim et al. 2000; Tadera et al. 2006), while iridoid glycosides such as aucubin exert protective roles on pancreatic β-cells and modulate glucose metabolism

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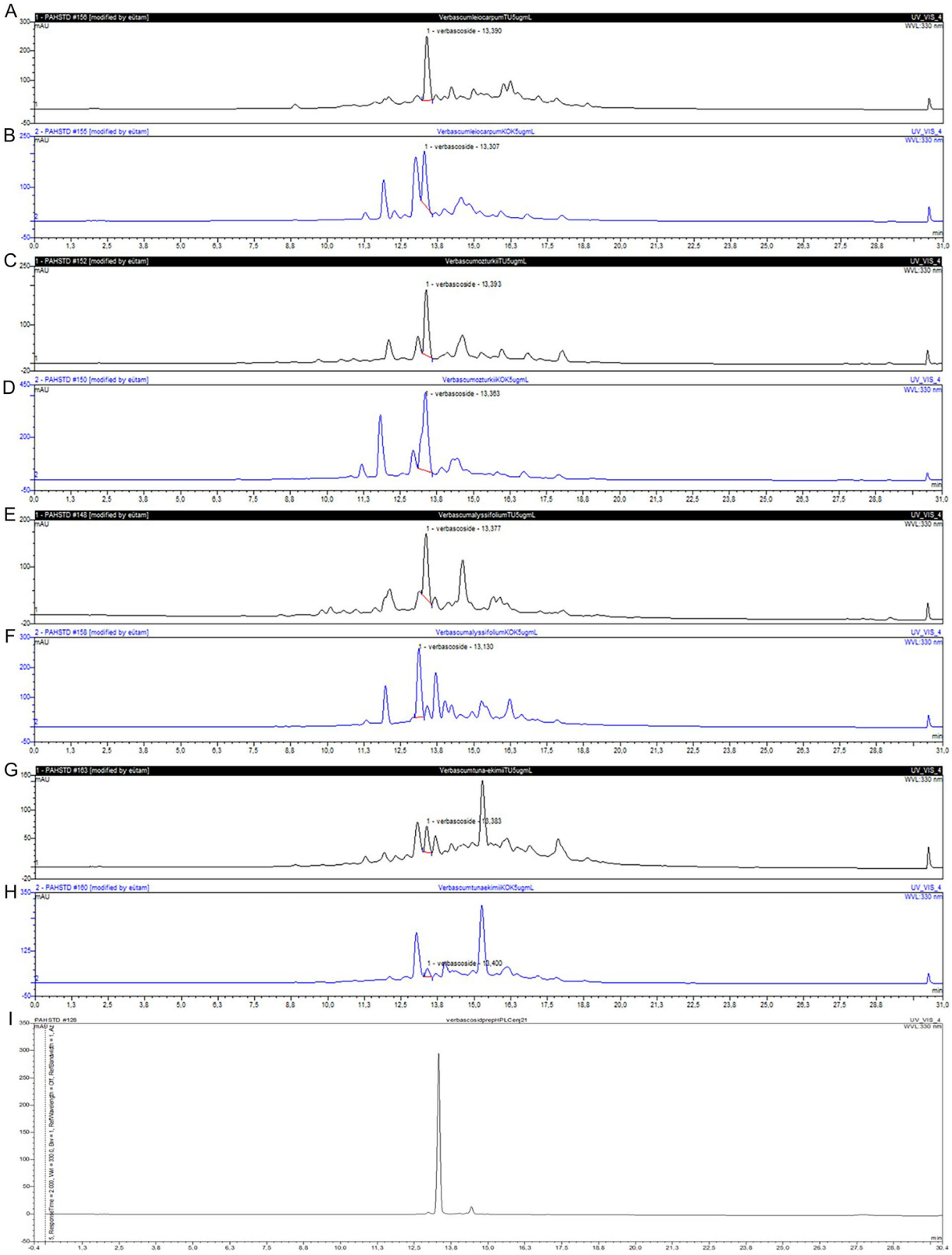


FIGURE 1 | HPLC-DAD chromatograms of methanolic extracts from the aerial and root parts of *Verbascum* species (330 nm). (A) *V.leiocarpum* (aerial). (B) *V.leiocarpum* (root). (C) *V. ozturkii* (aerial). (D) *V. ozturkii* (root). (E) *V. alyssifolium* (aerial). (F) *V. alyssifolium* (root). (G) *V. tuna-ekimii* (aerial). (H) *V. tuna-ekimii* (root). (I) Verbascoside standard.

(Kartini et al. 2023). Saponins identified in *Verbascum* species have also been associated with reduced intestinal glucose absorption and improved insulin sensitivity (El Barky et al. 2017; Luo et al. 2020). Consistent with these reports, *V. thapsus* and *V. fruticulosum* root extracts showed significant α-glucosidase inhibition, which was attributed to the combined presence of multiple bioactive constituents rather than verbascoside alone (Shahbaz et al. 2022; Alkowni et al. 2023). Therefore, the notable inhibitory

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TABLE 5 | Pearson correlation coefficients between antioxidant activities and verbascoside content.

	DPPH	TPC	TFC	FRAP	Verbascoside content
DPPH	1	−0.669	−0.04	−0.757	−0.926
TPC	−0.669	1	0.077	0.902	0.703
TFC	−0.04	0.077	1	0.418	0.31
FRAP	−0.757	0.902	0.418	1	0.826
Verbascoside content	−0.926	0.703	0.310	0.826	1

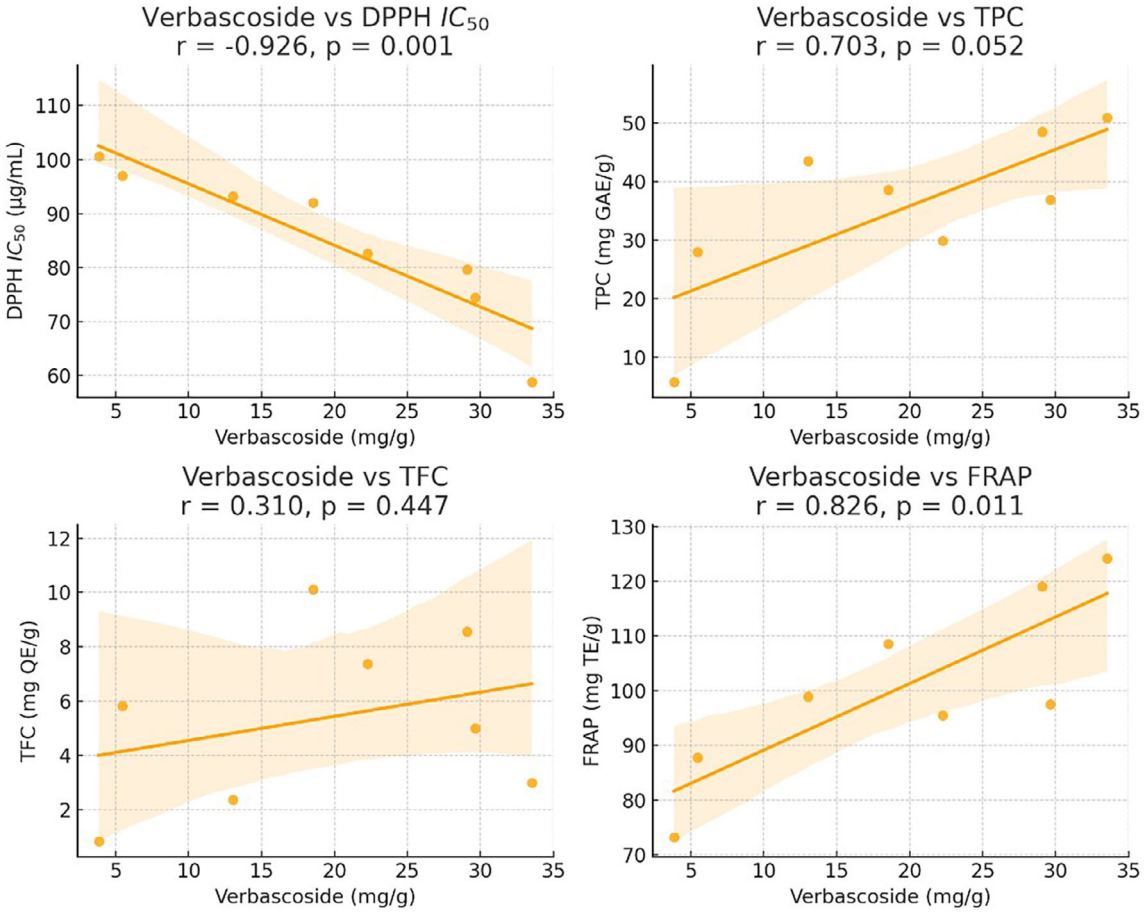


FIGURE 2 | Correlation between verbascoside content and antioxidant activity of *Verbascum* extracts.

effects observed in *V. leiocarpum* root extract in the present study may be attributed to the collective action of phenylethanoid glycosides, flavonoids, iridoids, and saponins, highlighting the complex and synergistic phytochemical basis of the antidiabetic activity in *Verbascum* species. In addition to phytochemical composition, factors such as compound stability, solubility, bioavailability, enzyme specificity, and potential synergistic or antagonistic interactions among constituents may also influence the observed inhibitory activity (Lila and Raskin 2005; Phan et al. 2018).

A moderate positive correlation was observed between the verbascoside content of the extracts (Table 4) and their antiproliferative activity against the tested cancer cell lines (Table 3), as shown in Figure 4 and Table 7. For the A549 cell line, the Pearson correlation coefficient was 0.53, indicating a moderate relationship that was not statistically significant. A similar correlation was observed for the HT-29 cell line ($r = 0.53$). The highest correlation was observed in MDA-MB-453 cells ($r = 0.78$), indicating a stronger association; however, it was not statistically significant, possibly due to the limited number of data points. Although statistical significance was not achieved, the results suggest that verbascoside may contribute to the antiproliferative activity observed in A549 and MDA-MB-453 cells. However, the moderate correlations and the fact that statistical significance was not consistently achieved suggest that additional phytoconstituents or synergistic mechanisms may contribute to the observed antiproliferative effects. Previous reports have demonstrated that verbascoside exhibits antiproliferative activity by inducing apoptosis, inhibiting cell proliferation, and modulating critical regulators of the cell cycle (Vasincu et al. 2020; Daneshforouz et al. 2021). The current findings support the potential role of *Verbascum* extracts containing high levels of verbascoside in cancer research, especially in lung and breast cancer cell lines.

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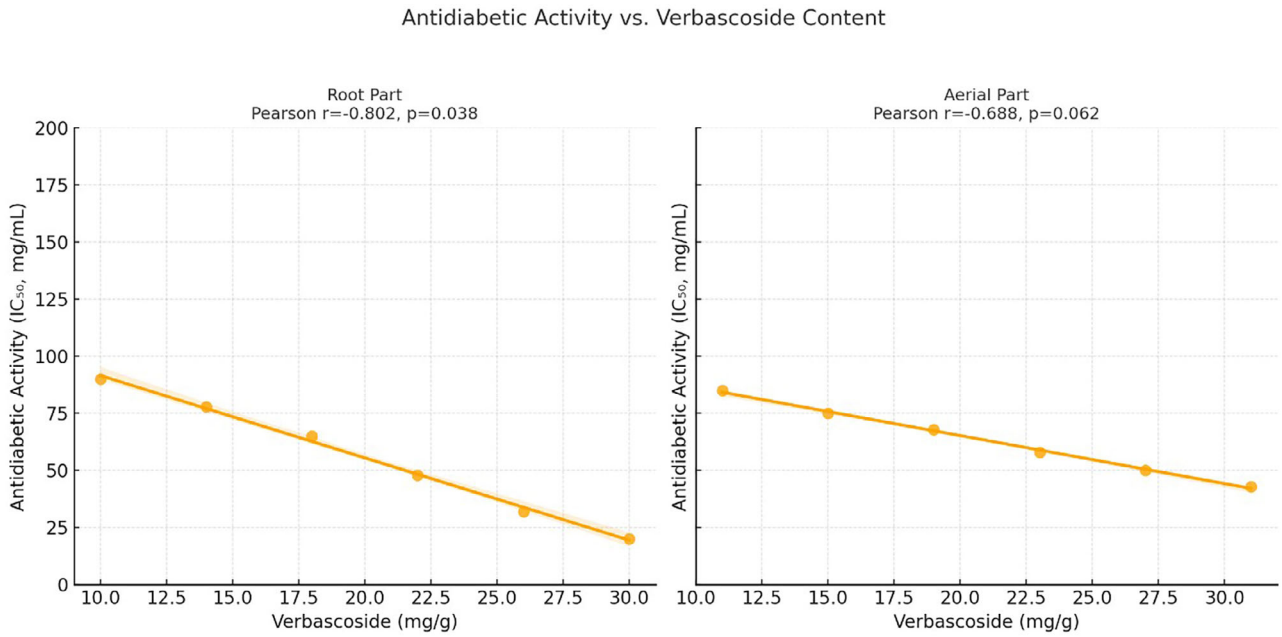


FIGURE 3 | Correlation between verbascoside content and antidiabetic activity of *Verbascum* extracts.

TABLE 6 | Pearson correlation between α-glucosidase inhibitory activity and verbascoside content.

	Verbascoside, Aerial	IC_{50}, Aerial	Verbascoside, Root	IC_{50}, Root
Verbascoside (aerial)	1	−0.688	0.788	−0.926
IC_{50} (aerial)	−0.688	1	−0.645	0.403
Verbascoside (root)	0.788	−0.645	1	−0.802
IC_{50} (root)	−0.926	0.403	−0.802	1

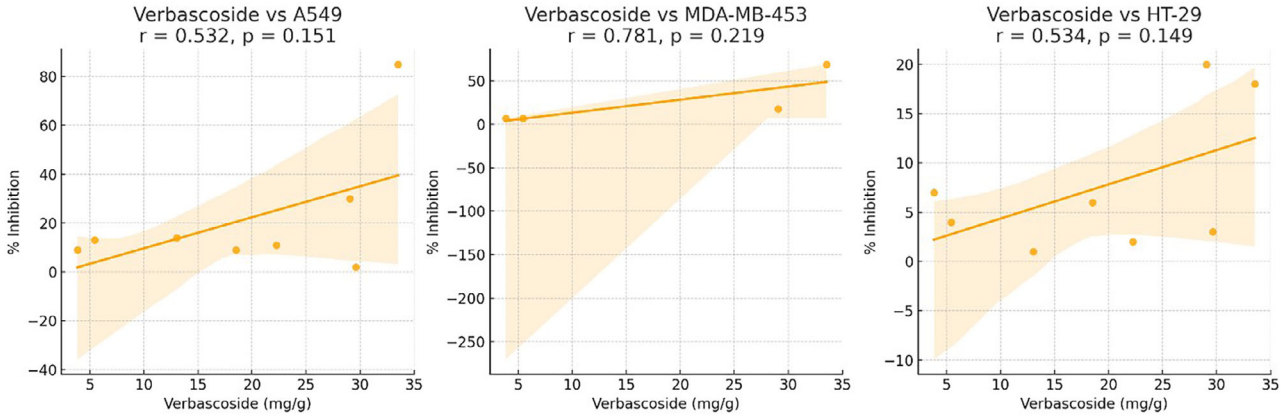


FIGURE 4 | Correlation between verbascoside content and antiproliferative activity against A549, MDA-MB-453, and HT-29 cell lines.

TABLE 7 | Pearson correlation coefficients between antiproliferative activity and verbascoside content.

	A549	MDA-MB-453	HT-29	Verbascoside content
A549	1	0.995	0.745	0.532
MDA-MB-453	0.995	1	0.611	0.781
HT-29	0.745	0.611	1	0.534
Verbascoside content	0.532	0.781	0.534	1

4 | Conclusion

This study comprehensively evaluated the antioxidant, antidiabetic, and antiproliferative activities of methanolic extracts from the aerial and root parts of four endemic *Verbascum* species—*V. leiocarpum*, *V. ozturkii*, *V. alyssifolium*, and *V. tuna-ekimii*—and quantitatively determined their verbascoside content using HPLC-DAD analysis. Among the tested species, the VLR exhibited the strongest bioactivities, including the highest total phenolic content (TPC), the greatest ferric reducing antioxidant power (FRAP), and potent radical scavenging capacity, as well as notable antiproliferative effects on A549 and MDA-MB-453 cancer

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cell lines. In addition, VLR contained the highest verbascoside concentration, supporting a strong correlation between this compound and its antioxidant and antiproliferative activities. In contrast, *V. tuna-ekimii* extracts demonstrated the lowest biological activities and verbascoside content.

Pearson correlation analysis demonstrated a significant positive association between verbascoside content and both antioxidant and antiproliferative activities. However, no significant correlation was observed between verbascoside content and α-glucosidase inhibitory activity, indicating that other phytochemical constituents may contribute to the antidiabetic potential of these extracts. These findings highlight the complexity of phytochemical interactions within *Verbascum* species and the importance of plant part selection in bioactivity screening.

In conclusion, the present study identifies *V. leiocarpum*, specifically its root extract, as a promising candidate for further pharmacological investigation as a potential source of natural antioxidant and antiproliferative agents. The results contribute valuable findings to the insufficiently studied phytopharmacological profile of endemic *Verbascum* species and support the need for isolation of active compounds based on bioactivity screening, as well as in vivo evaluations to elucidate their mechanisms of action and therapeutic relevance.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data will be made available on request.

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