https://doi.org/10.31925/farmacia.2026.4.7 **ORIGINAL ARTICLE**

SIYABU (*DIPLOTAENIA TURCICA*) - TRADITIONAL FOOD PLANT FROM EASTERN ANATOLIA: ANTIANGIOGENIC, ANTICANCER, ANTIOXIDANT, AND ENZYME INHIBITORY ACTIVITIES

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Abstract

Diplotaenia turcica Pimenov & Kljuykov (siyabu), an endemic species from Eastern Anatolia, is traditionally used as food and medicine by local communities. This study evaluated the biological activities of solvent-based extracts and traditional preparations from the root and leaf parts of *D. turcica*. The ethanolic extract and infusion demonstrated potent antioxidant activity in the FCR, FRAP, and ORAC assays and inhibited digestive enzymes in α-glucosidase and pancreatic lipase assays. Hexane extracts exhibited selective effects against the MDA-MB-231 breast cancer cell line, with GI50 values of 19.6 ± 0.68 µg/mL, fourfold lower than for normal endothelial cells (EA.hy926) at 85.4 ± 3.4 µg/mL. CAM assay results showed that ethanolic and hexane extracts of *D. turcica* inhibited vascular formation. The ethanolic leaf extract showed a vascular inhibition score of 1.28 ± 0.45, the leaf infusion 1.06 ± 0,37, and the leaf hexane extract 0.937 ± 0.11, confirming antiangiogenic potential. Collectively, these findings underscore the multifaceted biological activities of *D. turcica* extracts. Further in vivo and clinical studies are needed to validate therapeutic potential and safety for nutraceutical and food applications targeting angiogenesis-related diseases.

Rezumat

Diplotaenia turcica Pimenov & Kljuykov (siyabu), o specie endemică din Anatolia de Est, este utilizată tradițional ca aliment și medicament de către comunitățile locale. Studiul a evaluat activitățile biologice ale extractelor și ale preparatelor tradiționale din rădăcină și frunză ale *D. turcica*. Extractul etanolic și infuzia au demonstrat o activitate antioxidantă puternică în testele FCR, FRAP și ORAC și au inhibat enzimele digestive în testele de α-glucozidază și lipază pancreatică. Rezultatele testului CAM au arătat că extractele etanolice și hexanice din *D. turcica* au inhibat formarea vasculară. Extractul etanolic din frunză a prezentat un scor de inhibare vasculară de 1.28 ± 0.45, infuzia din frunză de 1.06 ± 0.37, iar extractul hexanic din frunză de 0.937 ± 0.11, confirmând potențialul antiangiogenic. Aceste rezultate evidențiază spectrul larg de activități biologice al extractelor din *D. turcica* și sugerează un potențial promițător pentru utilizarea acestora în domeniul nutraceutic și alimentar. Cu toate acestea, sunt necesare studii suplimentare *in vivo* și investigații clinice pentru a confirma eficacitatea terapeutică, profilul de siguranță și aplicabilitatea lor în prevenirea și managementul afecțiunilor asociate proceselor de angiogeneză.

Keywords: *Diplotaenia turcica*, antiangiogenic, anticancer, antioxidants, enzyme inhibition, phenolics

Introduction

The utilization of plants as food has long and deep roots in the history, tradition, and culture of Eastern Anatolia, which was earlier confirmed by the fossil records found in the Shanidar cave, including 8 plant species commonly used from the Middle Paleolithic period (approximately 60 thousand years ago) in the region (1). The rich biodiversity, high rates of endemic and/or rare plants, unique microclimatic characteristics, and the presence of various cultures and civilizations have contributed to a rich cultural heritage of plant-based food knowledge, which has been passed down orally from generation to generation for centuries and acquired through diverse experiences. Plant samples are collected from the wild and dried in the shade for later use as food in rural areas because of the region's harsh climatic and geographical conditions and the lack of marketing facilities (2).

Of these significant plant sources, *Diplotaenia turcica* Pimenov & Kljuykov, belonging to the *Apiaceae*

family, is one of the most used taxa for food and medicine, known as "Siyabu", "Siyabo", or "Köseotu" in the region. It is an endemic and vulnerable plant species grown in Eastern Anatolia and was formerly known as *Diplotaenia cachrydifolia* until 2011 (3). It is very popular among tribal and nomadic local people and is used as a flavor, vegetable, and herbal agent in cheese because of its aromatic taste. Therefore, it is sold as a vegetable at stalls during the vegetation period. Also, omelets and sauces are prepared for lunch or dinner. Moreover, infusions or decoctions obtained from the leaves, roots, and stem parts are used to treat diabetes, cancer, hypertension, gastric pain, and rheumatism (2).

In addition to their ethnobotanical significance, the phytochemical and the pharmacological potential of the *Apiaceae* species has been widely documented. Members of this family contain a variety of biologically active compounds, including flavonoids, phenolic acids, coumarins, furanocoumarins, and terpenoids; many of which have been associated with antioxidant, anti-inflammatory, anticancer, and enzyme inhibitory activities (4-6). Studies on related genera such as *Cachrys*, *Prangos*, and *Ferula* have shown that these compounds significantly contribute to their biological activity profiles, particularly by modulating mechanisms related to oxidative stress, apoptotic pathways, and angiogenesis (6-10). However, phytochemical and pharmacological data on *Diplotaenia* species, which are classified as a subcategory of various *Apiaceae* species, remain limited. While previous studies have reported the presence of total phenolics and flavonoids and indicated their potential biological activities, a comprehensive characterization of the chemical composition and its direct relationship with biological activity remains lacking (11). Moreover, most available studies focus on a single extraction method or specific plant parts, limiting the broader understanding of how different extraction approaches affect bioactive compound profiles and their biological effects (11, 12). However, the leaf part of *D. turcica* is more commonly used in food and medicinal culture in Eastern Anatolia and is generally used as an infusion or decoction (2).

Therefore, a clear research gap exists regarding the comparative evaluation of different extraction methods and their influence on the biological activity of *D. turcica*. In particular, the relationship between solvent polarity, extract composition, and selective anticancer or antiangiogenic activity has not been systematically investigated. Addressing this gap is essential for a deeper understanding of the pharmacological potential of this plant, which is traditionally used. In this study, we aimed to comprehensively investigate the biological activity (antioxidant, enzyme inhibitory, anticancer, and antiangiogenic properties) of different organic solvent-based extracts (n-hexane, acetone, and ethanol) and traditional preparations (infusion and decoction) of the root and leaf parts of *D. turcica* using appropriate methodologies.

Materials and Methods

Plant materials

Multiple root and leaf samples of *D. turcica* Pimenov & Kljuykov were collected from rocky slopes in the villages of Konalga, Catak, Van, Turkey, on May 29th, 2020 (Global Positioning System (GPS) coordinates 37°49'081" N, 43°12'402" E; 2209 m) and transferred to the laboratory. Taxonomic identification and nomenclature of the plant samples were performed at Van Pharmaceutical Herbarium (VPH), Faculty of Pharmacy, Van Yuzuncu Yil University, Turkey, and the voucher specimens were stored at VPH (Herbarium code: VPH-53, Collector Code: DM-24). After cleaning, the plant materials were dried at room temperature. Subsequently, root and leaf samples were powdered using a grinding mill and stored at -20°C.

Cell Culture and Chemicals

Unless otherwise stated, all the chemicals were purchased from Sigma-Aldrich, Inc. (St. Louis, MO, USA) and were of analytical or HPLC grade. EA.hy926 and MDA-MB-231 cells were purchased from the American Type Culture Collection (Manassas, VA, USA). Immortalized human vascular endothelial cells (EA.hy926) were developed by fusing human umbilical vascular endothelial cells (HUVEC) with A549/8 cells (13). The MDA-MB-231 is a highly aggressive, invasive, and poorly differentiated triple-negative breast cancer (TNBC) cell line (14). EA.hy926 cells were cultured in DMEM supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin at 37°C in a humidified atmosphere containing 5% CO_2. MDA-MB231 cells were cultured in RPMI supplemented with 5% fetal bovine serum, 2 mM L-glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin at 37°C in a humidified atmosphere containing 5% CO_2. Hexane, acetone, and ethanol extracts of *Diplotenia turcica* root were dissolved in dimethyl sulfoxide (DMSO) to prepare stock solutions (50 mg/mL). The other *D. turcica* extracts were dissolved in normal saline to prepare stock solutions (10 mg/mL). The n-hexane leaf extract did not dissolve well in natural saline and DMSO; therefore, this extract was excluded from the cell viability analysis.

Extraction

Organic solvent-based extracts were used to obtain phytochemicals from the matrix of *D. turcica* root and leaf parts. Briefly, 10 g of pulverized ground plant materials were mixed with 100 ml of n-hexane (1/10 ratio; g/ml) for 2 h at 24°C and then centrifuged at 15.300 × g (10000 rpm in a Beckman JA14 (137 mm) rotor, Sorvall RC-5B centrifuge, Wilmington, DE, USA) at 4°C for 20 min to obtain the super-

natant. Subsequently, the residues of the plant materials were treated using the same extraction procedure: acetone (80%) and ethanol (80%, obtained from 95%) individually. Each extraction was performed in triplicate. n-Hexane, acetone, and ethanol-based supernatants were concentrated using a rotary evaporator (Rotavapor R-205, Buchi, Flawil, Switzerland) at 37°C and subsequently freeze-dried using a lyophilizer (Alpha 1-2 LDplus, Christ, Osterode am Harz, Germany) under vacuum at -51°C. The samples were stored at -20°C for a maximum of 4 weeks until analyzed. The extraction % yield was calculated using the following formula:

% yield = (final weight × 100)/(initial weight).

Traditional preparations of D. turcica are used in folk medicine

Herbal infusion and decoction. Infusion or decoction was prepared as described previously by Baytop (1999) (1). The powdered crude extracts were moistened with pre-boiled distilled water and incubated for 10 min. After filtration, the mixture was evaporated and freeze-dried. For the preparation of the decoction, powder of the same plant material was mixed with a 10-fold volume (g/mL) of cold distilled water and boiled for 3 min. After cooling for 10 min, the mixture was filtered.

Antioxidant capacity

Folin-Ciocalteu Reducing (FCR). FCR levels, formerly known as total phenolic content, were measured as described previously (Dalar and Konczak, 2013).

Ferric reducing antioxidant power (FRAP). FRAP values of the extracts were measured as described previously (15) and the reducing capacities of the extracts were expressed as mmol of iron (Fe^{2+})/g dry weight based on an iron sulfate standard (Fe_2SO_4) curve against a blank control.

Oxygen radical absorbance capacity (ORAC). The ORAC assay was performed as previously described (15). Briefly, samples were placed in a 96 well microplate, inserted into the microplate reader, and incubated at 37°C for 20 min. Subsequently, 20 µL AAPH was added to each well, and fluorescence measurements were initiated immediately. Fluorescence (excitation wavelength 495 nm and emission wavelength 515 nm) was measured every min until the fluorescence reached zero and a kinetic curve was obtained using Mars data analysis software (POLARstar Omega, BMG Labtech, Offenburg, Germany). The antioxidant capacity of the coffee formulations was expressed as millimoles of Trolox equivalents per gram of dry weight (dw) based on a Trolox standard curve.

Enzyme inhibitory activities

The α-Glucosidase inhibitory activity. α-Glucosidase inhibition was measured as previously described (Dalar and Konczak, 2013) using sucrose (2 g in 100 mL of maleic acid buffer) as a substrate. Absorbance was measured at 505 nm. Relative α-glucosidase inhibition was calculated using the following formula:

% Inhibition = [((ACB - AC) - (ASB - AS))/ (ACB - AC)] x 100,

where AS and AC are the absorbance of the sample and negative control, respectively, and ASB and ACB are the absorbance of the sample blank and control blank, respectively.

Pancreatic lipase inhibitory activity. The lipase inhibitory activity was determined as described previously (15), using 4-methylumbelliferyl oleate (4-MuO, 0.1 mmol) as a substrate. The relative lipase inhibition activity was calculated using the formula:

% Inhibition = (1 - (FS - FSB)/(FC - FCB)) x 100,

where FS and FC were the values of samples and negative control measured fluorometrically at an emission wavelength of 460 nm and excitation of 320 nm with slit widths of 5 nm using the microplate reader, and where FSB and FCB were the fluorescence readings of the sample blank and control blank, respectively.

Cell viability

EA.hy926 cells and MDA-MB-231 were seeded in triplicate in 96-well plates at a density of 10×10^3 and 5×10^3 cells *per* well, respectively, and incubated overnight. The cells were treated with extracts (0.5 - 500 µg/mL) for 48 h (16-18). The highest vehicle concentration (1% DMSO), which was used for the 500 µg/mL hexane, acetone, and ethanol extracts, was used as the negative control. All other dilutions contained less than 0.1% DMSO to minimize the potential effects of solvents. The sulforhodamine B (SRB) cytotoxicity assay was performed as described previously (19). Absorbance was measured at 540 nm using a BioTek EL311 microplate reader. GI50 (50% cell growth inhibition), TGI (total growth inhibition), and LC50 (50% lethal concentration) were determined. Growth inhibition of 50% (GI50) was calculated as follows:

((Ti-Tz)/(C-Tz)) × 100 = 50.

The drug concentration resulting in total growth inhibition (TGI) was calculated as Ti = Tz. The LC50 indicates a net loss of cells after treatment, which is calculated as:

((Ti-Tz)/(C-Tz) × 100 = 0.

Tz represents the cell population for each cell line at the time of drug administration, Ti represents the growth of cells in the presence of a given concentration of the sample, and C represents the control cells at the end of the 48-hour incubation. The GI50, TGI, and LC50 values were calculated based on this normalization, ensuring that the observed inhibitory effects were attributable to the hexane, acetone, and ethanol extracts rather than solvent-related interference. Each parameter for all extracts was calculated based

on at least three independent experiments, each performed in triplicate.

Antiangiogenic activity

The antiangiogenic potential of *D. turcica* extracts was determined using a chick embryo chorioallantoic membrane (CAM) assay. The *in vivo* CAM assay was performed as previously described (20). The CAM assay did not require approval from the Animal Ethics Committee. In most countries, chick embryos are not considered live animals until the 15th day of hatching and, therefore, cannot experience pain (21, 22). Fertilized eggs were supplied by the Mudurnu Piliç-Pak Tavuk Company (Istanbul, Turkey). All extracts were examined at a concentration of 5 mg/mL. A positive control of (±) thalidomide (Sigma-Aldrich, Germany) at 5 mg/mL and a negative control of 2.5% (w/v) agarose (UltraPure Agarose, Invitrogen) were used. All extracts were dissolved in 2.5% (w/v) agarose. Extract pellets (10 µL) were prepared for application onto the CAM. The experiment was conducted by incubating fertilized chicken eggs at 36.5°C and a relative humidity of 80%. Eggs were collected at 0 days post-fertilization and incubated for 72 h. Albumin was extracted from the eggs (8 - 10 mL). Briefly, the eggs were opened from the top of the eggshell, covered, and incubated for 72 h. On the sixth day, pellets (1 pellet/egg) were applied to the CAM and incubated for 24 h to evaluate the anti-angiogenic effects of the extracts. Vascular formation in the CAM area was assessed using a Leica stereomicroscope and Leica Application Suite, Las V4.7 (Leica). All experiments were performed independently with 15 eggs and in triplicate for each extract, with 45 eggs in each. The anti-angiogenic effects of extracts were evaluated using a scoring system (Table I) (14, 15), and scores were calculated using the following formula (23, 24):

Average score = [Number of eggs (score > 1) × 2 + number of eggs (score > 0.75 - 1) × 1]/ (total number of eggs scored).

Data analysis

Before performing one-way ANOVA, the normality of the data distribution was assessed using the Shapiro-Wilk test to ensure its suitability for parametric analysis. One-way analysis of variance (ANOVA) followed by Tukey's *post-hoc* test was conducted using GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA) for SRB and CAM assays. Differences were considered statistically significant at $P < 0.05$. The mean values were calculated from at least three independent measurements (n = 3). Half-maximal inhibitory concentration (IC_{50}) values were derived from dose–response curves based on the best-fit modeling of the corresponding reaction points using GraphPad Prism. All results are presented as mean ± SD, with 95% confidence intervals indicating the precision of the estimates.

Table I

Antiangiogenic effects on the CAM were quantified using the scoring system outlined below

Scale	Anti-angiogenic effect	Effects observed on CAM after treatment
< 0.5	Inactive	No change (normal embryo growth).
0.50 - 0.75	Weak	The pellet was not surrounded by a capillary-free region; any reduction in capillary density around the pellet did not surpass the pellet's dimensions
> 0.75 - 1	Strong	The pellet was surrounded by either a small capillary-free area or a region of substantially reduced capillary density, with effects limited to no more than twice the pellet diameter
> 1	Very strong	The capillary-free area surrounding the pellet was at least twice the size of the pellet

Results and Discussion

Antioxidant activities

Traditional preparations, such as infusions or decoctions, are unable to extract most chemical compounds from the plant matrix because of their polarity and solubility limitations. The use of various solvents with different polarities has been recommended for the comprehensive extraction of phytochemicals (25). Therefore, solvent-based extracts selected according to polarity, along with traditional preparations (infusion and decoction), were employed to maximize the extraction yield and efficiency from *D. turcica* root and leaf samples. Under normal conditions, free radicals and the anti-oxidant defense system are in balance, and various mechanisms regulate this balance. Pathological and environmental conditions cause excessive reactive oxygen species and free radicals, which may result in neurological and metabolic diseases (26). There is a need for antioxidant compounds of natural origin that prevent the formation of free radicals, delay or prevent oxidative stress, and have tolerable side effects (27). Phenolic compounds are among the most characteristic chemical compounds of plant-based sources that can prevent the formation of free radicals (28, 29). Infusions exhibited superior activity compared to decoctions in both hydrogen atom transfer (HAT) and single electron transfer (SET) mechanisms. Regarding the reagent-based extractions, ethanol and acetone exhibited similar patterns (Table II). Our findings are consistent with those of previous studies that have reported the antioxidant capacity of the roots of *D. turcica* (11, 12) but not that of the leaves. Hexane fractions exhibited the lowest antioxidant activity, indicating the dominance of the hydrophilic characteristics of *D. turcica* (Table II).

Table II

Extraction yields and antioxidant activities of *D. turcica* root and leaf extracts

			Root	Leaf
Extraction yield (%)		n-Hexane	5.5	1.6
		Acetone	3.3	3.5
		Ethanol	20.2	16.5
		Infusion	15.8	27.2
		Decoction	15.9	22.9
Antioxidant activity	FCR (mg Gallic acid Eq./g extract)		**Root**	**Leaf**
		n-Hexane	70 ± 2a	67 ± 3a
		Acetone	139 ± 8b	139 ± 6b
		Ethanol	138 ± 5b	234 ± 7a
		Infusion	223 ± 12a	151 ± 6b
		Decoction	194 ± 12a	62 ± 1b
	FRAP (µl Fe^{2+}/g extract)		**Root**	**Leaf**
		n-Hexane	2223 ± 37a	2202 ± 74a
		Acetone	4673 ± 30a	4033 ± 46a
		Ethanol	4584 ± 71b	6097 ± 48a
		Infusion	7516 ± 88a	5562 ± 92b
		Decoction	6469 ± 62a	2411 ± 94b
	ORAC (µl Trolox Eq./g extract)		**Root**	**Leaf**
		n-Hexane	14455 ± 249a	10186 ± 180b
		Acetone	20806 ± 109a	19317 ± 144b
		Ethanol	17488 ± 190b	22102 ± 243a
		Infusion	20332 ± 248a	18151 ± 208b
		Decoction	19569 ± 297a	11295 ± 156b

Means with different letters in the same row are significantly different at $p < 0.05$. Data are presented as mean ± SD (n = 3)

Enzyme inhibitory activities

The enzyme inhibitory potential of the extracts showed that they could successively suppress the activity of digestive enzymes, including α-glucosidase and pancreatic lipase. This activity is generally linked to the ability of phytochemical compounds to bind to enzymes (30). Similar to antioxidant findings, ethanol (or acetone) extract and infusion preparation had superior inhibitory activities. The lowest activity was observed in the hexane fractions (Table III). Belhan *et al*. (2020) reported that a 100 mg/kg dose of *D. turcica* root extract effectively regulated triglyceride levels *in vivo* (12). Ozdek *et al*. reported that *D. turcica* had minimal toxicity and side effects despite its pronounced antioxidant activity in STZ-induced pancreatic damage.

Table III

Enzyme inhibitory activities of *D. turcica* root and leaf extracts

			Root	Leaf
Enzyme inhibitory activity	Pancreatic lipase (IC_{50}-µg/ml)	n-Hexane	21 ± 1a	30 ± 1b
		Acetone	12 ± 2a	13 ± 1a
		Ethanol	18 ± 1b	9 ± 1a
		Infusion	11 ± 1a	17 ± 1b
		Decoction	13 ± 1a	23 ± 2b
	α-Glucosidase (IC_{50}-µg/ml)		**Root**	**Leaf**
		n-Hexane	50 ± 3a	47 ± 1a
		Acetone	18 ± 1a	22 ± 1b
		Ethanol	27 ± 1b	13 ± 1a
		Infusion	19 ± 1a	28 ± 1b
		Decoction	18 ± 1a	50 ± 2b

Means with different letters in the same row are significantly different at $p < 0.05$. Data are presented as mean ± SD (n = 3)

Antiproliferative, cytostatic, and cytotoxic effects

Tumorigenesis is a multistep process regulated by multiple signaling pathways. Herbal extracts, particularly those rich in phenolic compounds, have been extensively studied for their multitargeted potential in cancer therapy (31-34). This This study evaluated the *in vitro* antiproliferative efficacy of *D. turcica* root and leaf extracts on EA.hy926 (endothelial) and MDA-MB-231 (breast cancer) cell lines. Dose-response curves were generated after 48 h of treatment with various extract concentrations (0.5 - 500 µg/mL) (Figure 1 and Figure 2).

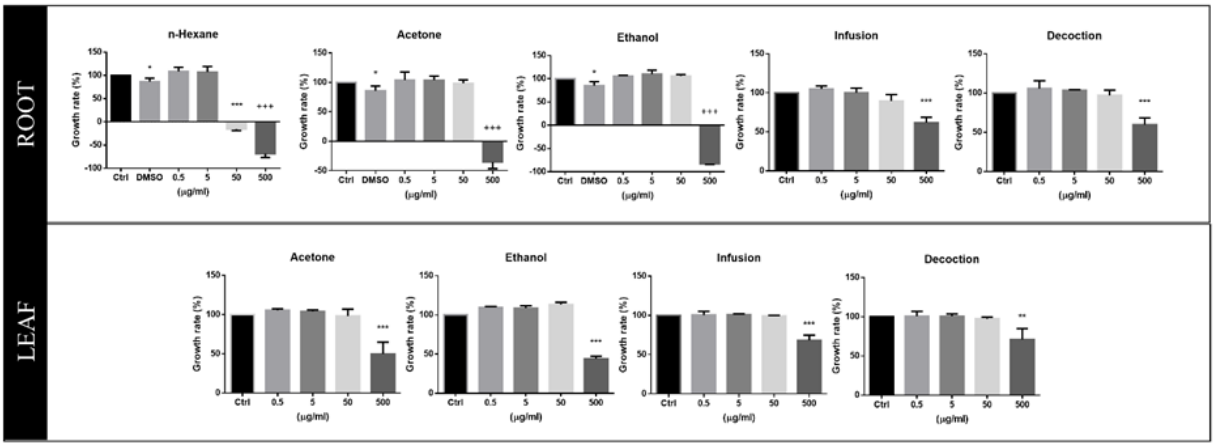

Figure 1.

Dose-response effect of the extracts on EA.hy926 cells. Cells were exposed to different concentrations of the compounds for 48 h, and growth rates were calculated using the sulforhodamine B (SRB) assay.

All extracts were tested at four concentrations (0.5, 5, 50, 500 µg/mL). Bars show the average of three independent experiments, each performed in triplicate, ± SD. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ compared to untreated control; +++ $p \leq 0.001$ compared to 1% DMSO

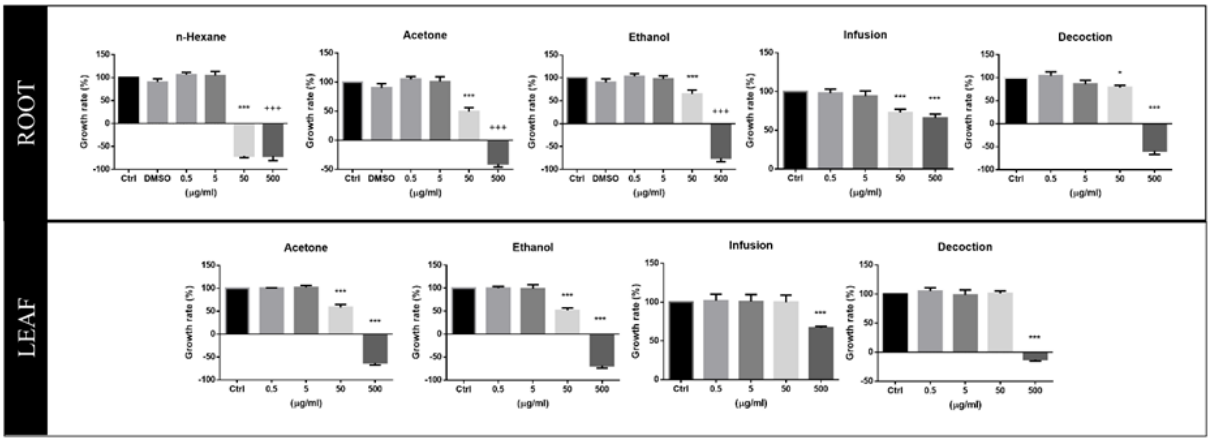

Figure 2.

Dose-response effect of the extracts on MDA-MB-231 cells. Cells were exposed to different concentrations of the compounds for 48 h, and growth rates were calculated using the sulforhodamine B (SRB) assay.

All extracts were tested at four concentrations (0.5, 5, 50, 500 µg/mL). Bars show the average of three independent experiments, each performed in triplicate, ± SD. * $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$ compared to untreated control; +++ $p \leq 0.001$ compared to 1% DMSO

Based on these results, we were able to determine the GI50 (growth inhibition 50%), TGI (total growth inhibition), and LC50 (lethal concentration 50%) values. These were used to assess and compare the antiproliferative, cytostatic, and cytotoxic effects, respectively (35) (Table IV). Among the tested extracts, the hexane extract of *D. turcica* roots exhibited the most potent antiproliferative, cytostatic, and cytotoxic effects on the cells. In contrast, the infusion extracts of *D. turcica* leaves and roots showed no significant antiproliferative, cytostatic, or cytotoxic activity in either cell line (Table IV).

Table IV

GI50 (50% cell growth inhibition), TGI (total cell growth inhibition), and LC50 (50% lethal concentration), parameters for EA.hy926 and MDA-MB-231 cells after a 48 h incubation with the extracts

		EA.hy926			MDA-MB-231		
		GI50	**TGI**	**LC50**	**GI50**	**TGI**	**LC50**
ROOT	Hexane	85.4 ± 3.4	204.4 ± 1.6	323.4 ± 2.9	19.6 ± 0.68	32.4 ± 0.75	45.3 ± 0.01
	Acetone	213 ± 22.2	379 ± 28.1	> 500	141 ± 2.7	322.2 ± 3.84	> 500
	Ethanol	182.7 ± 4	301.2 ± 0,9	419.7 ± 1,7	98.1 ± 2.3	256.5 ± 19.8	414.8 ± 13.05
	Infusion	> 500	> 500	> 500	> 500	> 500	> 500
	Decoction	> 500	> 500	> 500	146.3 ± 15.3	306.8 ± 19.9	467.4 ± 25.6

		EA.hy926			MDA-MB-231		
		GI50	**TGI**	**LC50**	**GI50**	**TGI**	**LC50**
LEAF	Acetone	> 500	> 500	> 500	86.6 ± 4.3	267.5 ± 10.1	448.5 ± 7.4
	Ethanol	468.2 ± 11.3	> 500	> 500	50.4 ± 2.7	239.5 ± 9.9	428.6 ± 19.7
	Infusion	> 500	> 500	> 500	> 500	> 500	> 500
	Decoction	> 500	> 500	> 500	251.3 ± 13.1	450.3 ± 11	> 500

Data are presented as mean ± SD (n = 3)

The hexane, acetone, and ethanol extracts of *D. turcica* roots and the ethanol extract of *D. turcica* leaves exhibited antiproliferative effects at higher concentrations on EA.hy926 cells. However, only the hexane and ethanol extracts of *D. turcica* roots exhibited cytotoxic effects on EA.hy926 cells. For the MDA-MB-231 cell line, all extracts (except the infusion extracts) demonstrated dose-dependent inhibition of proliferation (Figure 2). However, only the hexane and ethanol extracts of *D. turcica* roots and the acetone and decoction extracts of *D. turcica* leaves exhibited cytotoxic effects (Table IV and Figure 1 and Figure 2). The results of the cell viability assay suggest that these extracts were more effective against cancer cell lines than endothelial cells, which may also underscore the lower toxicity of the tested extracts against normal cells compared to tumor cells (except the root ethanol extracts). The observed activity may be partially associated with phenolic and flavonoid constituents previously reported in related species of the *Apiaceae* family (36, 37). Based on these observations, our study revealed that specific extracts of *D. turcica* roots and leaves exhibited cytotoxic effects, with the hexane extract of *D. turcica* roots demonstrating the highest potency against tumor cells without affecting the EA.hy926 cells to the same extent. Notably, the hexane extract exhibited a four-fold higher antiproliferative effect, sixfold higher cytostatic effect, and sevenfold higher cytotoxic effect on MDA-MB-231 cells compared to EA.hy926 cells (Table IV). The different solvent methods, including hexane, ethanol, acetone, and decoctions, were responsible for the selective toxicity observed in this study. For instance, hexane extracts of *D. turcica* roots may be rich in highly hydrophobic compounds (38, 39), resulting in selective toxicity against MDA-MB-231 breast cancer cells.

Antiangiogenic activity

Pathological angiogenesis, defined as the formation of new blood vessels from pre-existing ones, is a hallmark of various pathological conditions, including cancer. Recently, there has been significant interest in plant-derived phenolic compounds as potential antiangiogenic agents (40-42). Several studies have demonstrated the efficacy of various plant species belonging to the *Apiaceae* family in inhibiting angiogenesis; it has been shown that extracts derived from these plants can inhibit tumor-induced blood vessel formation by suppressing the expression of VEGF-A and VEGFR-2 (43, 44). In the present study, we investigated the antiangiogenic effects of *D. turcica* extracts using the CAM assay (Tables V and Figure 4). No toxic effects were observed in the eggs at the doses used. The positive control, thalidomide, demonstrated a strong antiangiogenic effect (score: 0.82 ± 0.2) on CAM. The antiangiogenic effects of the extracts (50 µg/pellet) were compared with those of thalidomide. The ethanolic extract and infusion preparation of the leaf part significantly disturbed vascular structure, at least doubling the size of the pellet, thus exhibiting a very strong antiangiogenic effect (score: 1.28 ± 0.45; 1.06 ± 0.37, $p < 0.001$). Hexane and infusion extracts of the root, along with decoction extracts of the leaf part, significantly reduced the density of capillaries in the pellet area, displaying a strong antiangiogenic effect (scores: 0.85 ± 0.25; 0.8 ± 0.3; 0.937 ± 0.11; 0.83 ± 0.12, respectively) compared to the positive control thalidomide. In contrast, the acetone and ethanol extracts and the decoction of the root demonstrated weak anti-angiogenic activity, indicating a weak effect on reducing capillary density in the pellet area. Finally, the acetone leaf extract did not affect the CAM area or angiogenesis (Table V and Figure 3).

The suppressive effects of various herbal extracts on angiogenesis have been reported in several studies. (45-47). The present study suggests that the antiangiogenic effects of *D. turcica* leaf and root extracts are influenced by the solvent type, extraction method, and the phytochemical composition of the extracts. It is crucial to note that the use of diverse extraction methods and solvents results in variations in the concentration and type of bioactive compounds in the extracts. These differences in phyto-chemical composition lead to various effects when comparing root and leaf extracts (48-50) Our results are consistent with these reports; *D. turcica* extracts, particularly those from leaves, exhibited higher anti-angiogenic activity. Hexane extracts frequently contain high concentrations of terpenoids, fatty acids, sterols, and phenolic compounds, among other substances. These compounds exhibit a variety of biological activities, including antioxidant, anti-inflammatory, and antiangiogenic properties (38, 51, 52). Consequently, the potent antiangiogenic effect observed in the hexane extracts in the present study may be due to the presence of lipophilic substances in their composition.

Table V

Average scores of anti-angiogenic effect of *D. turcica* root and leaf extracts in the CAM assay

			Root			Leaf		
Antiangiogenic activity		**Conc. (µg/pellet)**	**Average score**	**Anti-angiogenic effect**	**Tox (%)**	**Average score**	**Anti-angiogenic effect**	**Tox (%)**
	n-Hexane	50	0.85 ± 0,25	Strong effect	-	0.937 ± 0,11	Strong effect	-
	Acetone	50	0.56 ± 0,22	Weak effect	-	0,25 ± 0,36	No effect	-
	Ethanol	50	0.625 ± 0,24	Weak effect	-	1,28 ± 0,45***	Very strong effect	-
	Infusion	50	0.8 ± 0,3	Strong effect	-	1,06 ± 0,37***	Very strong effect	-
	Decoction	50	0.67 ± 0,32	Weak effect	-	0,83 ± 0,12	Strong effect	-
Controls		**Conc (µg/pellet)**	**Average score**			**Anti-angiogenic effect**	**Tox (%)**	
+	Thalidomide	50	0,82 ± 0,12			Strong effect	-	
-	Agarose	%2.5, w/v	0.2 ± 0.2			No effect	-	

A total of 45 eggs were used for each extract and control group (negative and positive). ***, $p < 0.001$ compared to thalidomide; Conc: Concentration, Tox: Toxicity. Data are presented as mean ± SD (n = 45 for extracts and n = 30 for controls)

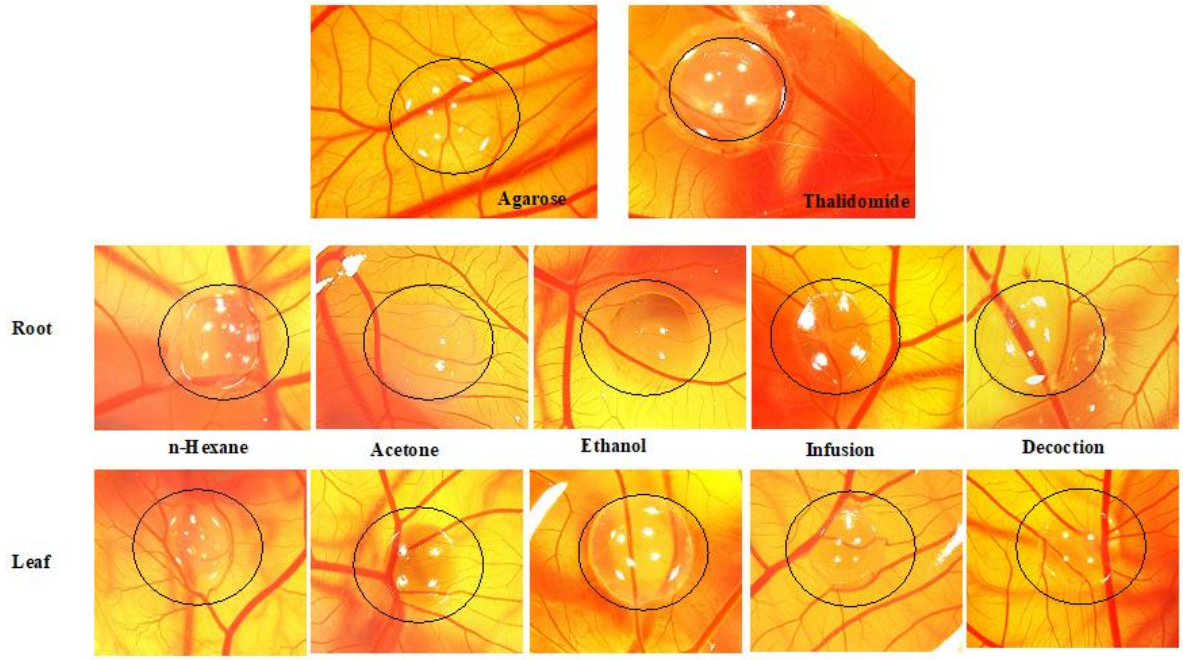

Figure 3.

Antiangiogenic effects of different concentrations of *D. turcica* extracts on branching blood vessels in the chick chorioallantoic membrane (CAM) test. All extracts were examined at a concentration of 5 mg/mL. A positive control of (±) thalidomide (Sigma-Aldrich, Germany) at 5 mg/mL and a negative control of 2.5% (w/v) agarose (UltraPure Agarose, Invitrogen) were used. All extracts were dissolved in 2.5% (w/v) agarose

The selective antiproliferative and antiangiogenic activities observed in this study may involve multiple interconnected mechanisms. Phenolic compounds and other secondary metabolites reported in *Apiaceae* species have been associated with the modulation of oxidative stress, induction of apoptosis, suppression of pro-survival signaling pathways, and inhibition of angiogenic mediators such as VEGF and VEGFR-2 (43, 44, 53, 54). In particular, lipophilic compounds enriched in hexane extracts may more readily interact with cellular membranes and intra-cellular targets (55), thereby contributing to the stronger cytotoxic effects observed against MDA-MB-231 cells. Furthermore, the higher sensitivity of MDA-MB-231 cells compared to that of EA.hy926 endothelial cells may indicate partial selectivity toward highly proliferative tumor cells. Previous studies have also demonstrated that phenolics, flavonoids, and terpenoid derivatives can suppress endothelial cell migration, capillary tube formation, and vascular remodeling processes associated with pathological angiogenesis (56-58). Therefore, the potent antiangiogenic effects observed in the CAM assay may be partially associated with these mechanisms. However, further molecular

and phytochemical studies are required to clarify the exact signaling pathways and active constituents responsible for these effects.

Conclusions

This study provides the first comprehensive assessment of the biological potential of *D. turcica*, an endemic and vulnerable species from Eastern Anatolia, demonstrating significant antioxidant, digestive enzyme inhibitory, antiproliferative, and antiangiogenic activities. The results indicate that both plant organ and extraction method strongly influence bio-activity, with leaf ethanol extracts and infusion preparations showing the most promising overall effects. Their pronounced antioxidant, antiangiogenic, and antiproliferative properties, combined with relatively low toxicity toward normal-like endothelial cells, highlight the therapeutic relevance of these preparations and support their traditional ethnomedicinal use. Moreover, the notable activity observed for the hexane extract suggests that both hydrophilic and lipophilic constituents contribute to the biological effects of the species. Overall, *D. turcica* emerges as a promising source of bioactive compounds with potential applications in the prevention and management of angio-genesis-related and metabolic disorders. Nevertheless, further phytochemical investigations, including bioactivity-guided fractionation and LC-MS/MS and GC-MS analyses, together with molecular and *in vivo* studies, are required to identify the active constituents and confirm their efficacy and safety.

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Availability of data and materials

All data generated and/or analyzed during this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

AI use disclosure

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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