Antioxidant and Anti-Growth Properties of Selected Anatolian Plant Species: Exploring the Potential of *Heracleum humile*, *Doronicum reticulatum*, *Centaurea drabifolia*, and *Senecio olympicus*

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ABSTRACT

This study investigated the anti-growth and antioxidant properties of four plant species native to the Anatolian region: *Heracleum humile*, *Doronicum reticulatum*, *Centaurea drabifolia*, and *Senecio olympicus*. Plant materials were collected, authenticated, and extracted using a Soxhlet apparatus. The growth inhibitory activities of the extracts were evaluated in human breast cancer cell lines MCF-7 and MDA-MB-231, and the nonmalignant immortalized human breast cell line MCF-10A, using the sulforhodamine B (SRB) assay. Antioxidant capacities were assessed via DPPH and CUPRAC assays. The results demonstrated that *C. drabifolia* extract exhibited potent cytotoxic effects, while *D. reticulatum* displayed selective toxicity and the most pronounced antioxidant activity among the evaluated species. These findings contribute to our understanding of the therapeutic potential of these indigenous plant species in addressing various public health issues, including cancer.

Keywords: Cytotoxicity, antioxidant, *Heracleum humile*, *Doronicum reticulatum*, *Centaurea drabifolia*, *Senecio olympicus*

Seçilen Anadolu Bitki Türlerinin Antioksidan ve Anti-Büyüme Özellikleri: *Heracleum humile*, *Doronicum reticulatum*, *Centaurea drabifolia* ve *Senecio olympicus*'un Potansiyelini Keşfetme

ÖZET

Bu çalışma, Anadolu bölgesine özgü dört bitki türünün anti-büyüme ve antioksidan özelliklerini incelemiştir: *Heracleum humile*, *Doronicum reticulatum*, *Centaurea drabifolia* ve *Senecio olympicus*. Bitki materyalleri toplanmış, doğrulanmış ve bir Soxhlet aygıtı kullanılarak ekstrakte edilmiştir. Ekstrelerin büyüme inhibe edici aktiviteleri, insan meme kanseri hücre hatları MCF-7 ve MDA-MB-231 ve malignan olmayan ölümsüzleştirilmiş insan meme hücre hattı MCF-10A üzerinde sülfarodamin B (SRB) testi kullanılarak değerlendirildi. Antioksidan kapasiteler DPPH ve CUPRAC testleri ile değerlendirildi. Sonuçlar, *C. drabifolia* ekstresinin güçlü sitotoksik etkilere sahip olduğunu gösterirken, *D. reticulatum* seçici toksisite sergiledi ve değerlendirilen türler arasında en belirgin antioksidan aktiviteye sahipti. Bu bulgular, söz konusu yerli bitki türlerinin, kanser de dâhil olmak üzere çeşitli halk sağlığı sorunlarına yönelik terapötik potansiyellerini anlamamıza katkı sağlamaktadır.

Anahtar kelimeler: sitotoksisite, antioksidan, *Heracleum humile*, *Doronicum reticulatum*, *Centaurea drabifolia*, *Senecio olympicus*

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INTRODUCTION

In recent years, there has been growing recognition of the potential of plants to provide unique compounds for addressing a wide array of public health challenges, including cancer. However, it is important to note that only a fraction of higher plant species has undergone thorough investigation to uncover their diverse biological properties (Fabricant & Farnsworth, 2001). The Anatolian region, renowned for its rich floral diversity, stands out with an impressive inventory of over ten thousand plant species, with a remarkable endemism rate exceeding 30% (Türe & Böcük, 2010).

Numerous efforts are underway to investigate the biological activities of plant species indigenous to Anatolia. In this context, we have selected four plant species, namely *Heracleum humile* Sm. [Syn.: *Heracleum massyciticum* Stapf & Wettst. ex Stapf, *Pastinaca humilis* Calest.], *Doronicum reticulatum* Boiss. [Syn.: *Doronicum bithynicum* J.R. Edmondson, *Doronicum bithynicum* subsp. *bithynicum*, *Doronicum bracteatum* J.R. Edmondson, *Doronicum thirkei* Sch.Bip. ex Boiss.], *Centaurea drabifolia* subsp. *drabifolia* Sm. [Syn.: *Chartolepis drabifolia*, *Cheirolepis drabifolia*, *Phaeopappus drabifolius*] and *Senecio olympicus* Boiss.

H. humile is native to Turkey, Syria, and Lebanon (POWO, 2023). The *Heracleum* genus encompasses 90-120 species, with 24 of them found in Turkey (Logacheva et al., 2008). Traditionally, these species have been utilized for medicinal and dietary applications (Bahadori et al., 2016). Ethnobotanical applications of *H. humile* include treatments for snakebites, fever, neurological disorders, and abdominal cramps induced by intestinal worms (Arnold et al., 2015).

D. reticulatum is indigenous to Turkey, Iraq, and Iran (POWO, 2023). The *Doronicum* genus has been reevaluated to include 30 taxa, 10 of which are distributed in Anatolia with a 30% endemism rate (Güven et al., 2020). Previous research investigated the antioxidant and anti-inflammatory properties of *Doronicum austriacum* root extract and several fractions of *Doronicum pardalianches* methanol extract for their efficacy against Alzheimer's disease (Marzocco et al., 2017; Manayi et al., 2021). Other *Doronicum* species have been traditionally employed in antimicrobial treatments for animal injuries (Kargıoğlu et al., 2010).

C. drabifolia's distribution encompasses Turkey, Iran, Syria, and Lebanon, according to the POWO, Plants of the World Online database (POWO, 2023). *Centaurea* genus comprises 181 species within the Turkish flora, 112 of them being endemic, making it one of the most diverse genera (Candan et al., 2016). *Centaurea* has a long-standing history of traditional applications, including wound healing, common cold treatment, diabetes management, hypertension control, abdominal pain relief, ulcer treatment, and malaria therapy (Khammar & Djeddi, 2012). *C. drabifolia* subsp. *cappadocica* chloroform extract has been previously documented to possess significant antimicrobial effects (Uğur et al., 2009).

The diverse genus of *Senecio* is comprises over 1500 distinct species, with 39 of them endemic to the Anatolian region (Doral & Wink, 2002; Uğur et al., 2006). *S. olympicus* is a species exclusive to

Turkey, specifically confined to Mount Uludag (Kirmizi et al., 2011). Throughout history, various *Senecio* species have been employed in an array of traditional practices, encompassing food sources, wound healing agents, and integral components in anti-emetic, anti-inflammatory, and vasodilator formulations (Kargıoğlu et al., 2010; Khammar & Djeddi, 2012; Albayrak et al., 2014). Despite their extensive historical utilization, the existing literature on the plant's biological effects remains sparse, with a solitary report on the antibacterial and antioxidant properties of *S. olympicus* (Albayrak et al., 2014).

The objective of this study is to assess the anti-growth and antioxidant properties of a select group of indigenous plant species native to Anatolia. Our results demonstrate that *C. drabifolia* possesses a potent cytotoxic effect, while *D. reticulatum* exhibits selective toxicity and the most pronounced antioxidant activity among the assessed species.

Aim

This research aimed to determine the cytotoxic and antioxidant properties of four plants native to the Anatolian region: *Heracleum humile*, *Doronicum reticulatum*, *Centaurea drabifolia*, and *Senecio olympicus*. The study involved the collection, authentication, and extraction of bioactive compounds from these plants. Their anti-growth potentials were determined by using malignant breast cells, while antioxidant capacities were assessed using the DPPH and CUPRAC assays. The findings aimed to offer insights into the therapeutic value of these indigenous plants, highlighting the importance of conserving Anatolia's rich floristic diversity for potential medical applications.

MATERIALS AND METHODS

Plant material and extraction

Four plant species were collected, namely *H. humile*, *D. reticulatum*, *C. drabifolia*, and *S. olympicus*, from Mt. Uludag. Plants were authenticated, and voucher specimens were deposited in Bursa Uludag University herbarium to ensure their accuracy and consistency. Prior to extraction, the plants were carefully inspected for any signs of contamination or foreign materials, which were removed by hand. The unwanted plant parts were separated and discarded. The residual plant specimens were air-dried under natural shade conditions, safeguarding the integrity of their chemical constituents.

Plant materials, after being dried, were subsequently pulverized into a fine powder, and 30 g of the powdered material was extracted via a Soxhlet apparatus using 150 ml of methanol. The extracts were then concentrated in a rotary vacuum evaporator to obtain a more concentrated solution. The resulting extracts were subsequently lyophilized and stored at -80 °C for following experiments. Prior to their use in experiments, the lyophilized extracts were dissolved in DMSO to obtain a stock solution with 100 mg/ml concentration. Further dilutions were made by using respective cell culture medium.

Cell culture

Cultures of MCF-7, MDA-MB-231, and MCF-10A cells were maintained at 37 °C in an environment with 5% CO_2. Specifically, MCF-7 and MDA-MB-231 human breast cancer cells were nurtured in RPMI 1640 medium enriched with 5% FBS (fetal bovine serum) and 1% mixture of penicillin-G and streptomycin. Meanwhile, MCF-10A, a nonmalignant immortalized human breast cell line, was sustained in a DMEM:Ham's F12 (1:1) medium that included 5% FBS, 1% penicillin-G/streptomycin, 20 ng/ml epidermal growth factor, 10 ng/ml cholera toxin B subunit, and 0.12 IU/ml insulin.

Determination of the growth inhibitory potential

The sulforhodamine B (SRB) assay was employed to assess the anti-growth properties of the extracts as described previously (Sarimahmut & Celikler, 2023). MCF-7, MDA-MB-231, and MCF-10A cell lines in exponential growth were pipetted in 96-well microplates at 5×10^3 cells/well. The cells were treated 48 h with 2-fold serial dilutions of the extract solutions, producing a concentration range between 3.13 and 200 µg/ml. At the end of the treatment, ice-cold trichloroacetic acid solution was pipetted to yield a 10% (w/v) final concentration. The cells were washed with deionized water and stained with SRB (0.4%, w/v in 1% v/v acetic acid solution). Then, the bound dye was dissolved using 10 mM Tris base. Absorbance was recorded at a wavelength of 564 nm. The reported data represent the mean results obtained from three separate experiments each conducted in triplicate. Calcusyn version 2.1 (Biosoft) software was used for determination of IC_{50} values of the extracts.

Determination of the antioxidant capacity

The antioxidant capacity of the extracts was evaluated using two methods: the DPPH radical scavenging and cupric reducing antioxidant capacity (CUPRAC) assays, as described previously (Molyneux, 2004; Apak et al., 2005). Both assays were conducted in 96-well microplates, with a range of extract concentrations from 0.49-500 µg/ml prepared in a 1:1 v/v mixture of EtOH:H_2O. A 1 mg/ml stock solution was prepared from each extract. All solutions were prepared freshly. The microplates were placed on a plate shaker at 600 rpm and kept at 37 °C for 30 min. The absorbance was recorded at respective wavelengths for both assays. The results were reported as the IC_{50} value for DPPH radical scavenging and Trolox equivalents (mg TE/g extract) for CUPRAC antioxidant activity.

4. RESULTS AND DISCUSSION

Growth inhibitory activity of the four plants

Exploring the anticancer activities of plant extracts that distributed to a limited geography contributes to the conservation and untapped potential of these species. In this study, we selected *H. humile, D. reticulatum, C. drabifolia,* and *S. olympicus* species and assessed their growth inhibitory activities using the SRB assay, with the outcomes illustrated in Figure 1 and Table 1. Notably, *C. drabifolia* extract exhibited potent cytotoxic activity, whereas the other plant extracts displayed weaker

cytotoxicity. *C. drabifolia* extract demonstrated dose-dependent growth inhibitory activity across various cell lines. In a related study, the ethyl acetate fraction of a dichloromethane extract from *Centaurea fenzlii*, a species belonging to the same genus, induced growth inhibitory activity against MCF-7 cells with apoptotic cell death and a comparably lower IC_{50} value of 45.77 µg/ml (Yirtici et al., 2017). Hispidulin, a flavone, was identified as the major constituent of the ethyl acetate fraction. In another investigation, a nonpolar organic extract of *Centaurea drabifolia* subsp. *detonsa* from aerial parts yielded seven sesquiterpene lactones, which were tested against sensitive and resistant acute lymphoblastic leukemia cell lines, resulting in IC_{50} values between 0.47 and 25.36 µM in the drug-sensitive CCRF-CEM cell line (Formisano et al., 2017).

Table 1. IC_{50} values following 48 h treatment of the studied plant extracts were determined by the SRB assay.

Plant	**IC_{50} (µg/ml)**		
	MCF-7	**MDA-MB-231**	**MCF-10A**
C. drabifolia	80.26 ± 10.92	47.58 ± 9.34	52.31 ± 11.51
D. reticulatum	390.08 ± 60.85	289.26 ± 32.40	N/A*
*H. humile**	N/A	N/A	N/A
S. olympicus	716.39 ± 37.34	104.63 ± 18.42	554.16 ± 53.39

*: Not calculated due to low cytotoxicity.

Interestingly, *D. reticulatum* exhibited selective cytotoxicity against cancer cells with 3-fold selectivity at the highly growth-inhibitory concentration of 200 µg/ml. No data regarding the selective cytotoxicity or anticancer effects of *D. reticulatum* currently exists. Species from the *Doronicum* genus are known to contain pyrrolizidine alkaloids, flavonoids, essential oils as hydrocarbon sesquiterpenes, and primarily thymol derivatives with ester groups, which may contribute to both cytotoxic effects and selective cytotoxicity (Badalamenti et al., 2021).

S. olympicus showed weak cytotoxicity (IC_{50} > 100 µg/ml) across all cell lines, although relatively higher cytotoxic activity was observed against MDA-MB-231 cells. The current study represents the initial investigation into the cytotoxic activity of *S. olympicus*. Research on other *Senecio* species has uncovered that *Senecio stabianus* exerted cytotoxic activity against MCF-7 cells, with IC_{50} values of 91.1, 87.2, and >100 µg/ml from methanol, *n*-hexane, and ethyl acetate extracts, respectively (Tundis et al., 2009). Additional species within the *Senecio* genus are known to contain bioactive compounds, such as the cytotoxic quinone molecule jacaranone, its derivatives, and pyrrolizidine alkaloids, which have the potential to induce hepatotoxicity (Loizzo et al., 2007; Wang et al., 2010; Acito et al., 2022).

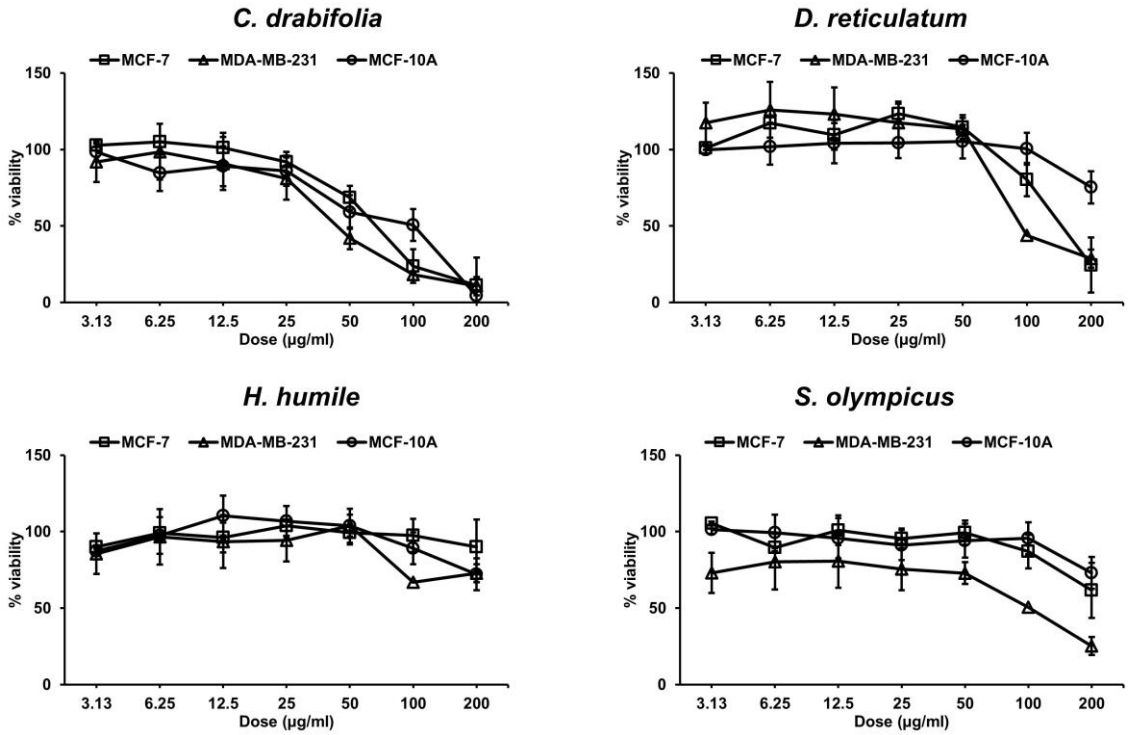

Figure 1. Dose response curves of *H. humile*, *D. reticulatum*, *C. drabifolia*, and *S. olympicus* extract treated cell lines for 48 h.

In contrast, *H. humile* extract did not exhibit significant cytotoxic activity against any of the breast cell lines (IC_{50} > 200 µg/ml). A recent study analyzed three *H. humile* extracts acquired via an ultrasound-assisted extraction method and tested them against MDA-MB-231 and MCF-7 cells using the MTT cell viability test (Ocal et al., 2022). Consistent with our findings, the methanol extract of the plant did not display substantial growth inhibitory activity at 125 µg/ml concentration. However, the ethyl acetate extract displayed more potent cytotoxicity, with IC_{50} values of 97.94 and 103.9 µg/ml against MCF-7 and MDA-MB-231 cells, respectively. Numerous *Heracleum* species are utilized in culinary practices worldwide, and the majority of previous studies report weak to moderate cytotoxicity from various *Heracleum* species (Bahadori et al., 2016). The essential oil of common hogweed (*Heracleum sphondylium* L. subsp. *ternatum*) displayed weak cytotoxic activity against MDA-MB-231 and the glioblastoma multiforme cell line T98G (IC_{50} > 200 µg/ml), while it demonstrated moderate activity against a melanoma (A375, IC_{50} = 48.69 µg/ml) and a colon carcinoma (HCT116, IC_{50} = 95.83 µg/ml) cell line. with IC_{50} values of and 95.83 µg/ml, respectively (Maggi et al., 2014). Furthermore, it was discovered that treatment with the ethanolic extract of *Heracleum persicum* led to a 60% reduction in human lymphocyte viability at 250 µg/ml and resulted in DNA damage at the same concentration (Amani et al., 2019).

Antioxidant potential of the four plants

We determined the antioxidant capacities of the plant extracts through the employment of DPPH and CUPRAC assays (Table 2). The most potent antioxidant activity was observed in *D. reticulatum*,

followed sequentially by *S. olympicus*, *C. drabifolia* and *H. humile* extracts. The outcomes of both DPPH and CUPRAC assays exhibited consistency in evaluating antioxidant activity.

Table 2. The results of the assessment of antioxidant activity in the selected plants, conducted via the DPPH and CUPRAC assays.

Plant extracts	**DPPH radical scavenging activity (IC_{50}) (µg/ml)**	**CUPRAC (mg TE/g extract)**
C. drabifolia	210.60 ± 29.51	83.04 ± 5.10
D. reticulatum	97.39 ± 1.48	148.71 ± 7.37
H. humile	257.84 ± 30.66	78.02 ± 1.32
S. olympicus	171.35 ± 0.85	137.74 ± 14.79
Ascorbic acid	5.01 ± 0.06	1817.83 ± 39.86
Gallic acid	1.29 ± 0.04	3924.71 ± 185.29

CUPRAC: Cupric reducing antioxidant capacity; DPPH: 2,2-Diphenyl-1-picrylhydrazyl; TE: Trolox equivalent.

Concurring reports highlight the antioxidant capacity of various *Doronicum* species. CUPRAC reducing power of an ethanol/water (7:3, v/v) extract of *Doronicum orientale* showed 151.15 mg TE/g extract; while the IC_{50} value for DPPH scavenging activity of *Doronicum hookeri* methanol extract was reported as 217 µg/ml (Gupta et al., 2011; Zengin et al., 2022). 3- and 5-caffeoylquinic acid were detected as the predominant compounds in the ethanol/water extract of *Doronicum orientale* (Zengin et al., 2022).

Antioxidant activity of *C. drabifolia* methanolic extract was previously measured as 102.35 mg TE/g extract using the CUPRAC assay, which aligns with our findings (Zengin et al., 2018). Phenolic compounds, namely protocatechuic, caffeic, monocaffeoylquinic acids, monoferuloylquinic acid, and flavonoids, have been identified as likely contributors to the antioxidant activity (Zengin et al., 2022). The *H. humile* methanolic extract demonstrated an antioxidant capacity of 47.15 mg TE/g extract in CUPRAC assay (Ocal et al., 2022). Additionally, the DPPH radical scavenging activity of *S. olympicus* methanol extract was reported to have 46.81 µg/ml IC_{50} value (Albayrak et al., 2014). Observed discrepancies in the antioxidant capacities of *H. humile* and *S. olympicus*, when compared to our study's findings, may be attributed to variations in extraction methods as well as seasonal and ontogenetic factors.

CONCLUSION

Our study examined the cytotoxic and antioxidant properties of four plants native to Mt. Uludag. Our findings reveal that *C. drabifolia* extract displayed potent cytotoxic activity against breast cancer cells, while *D. reticulatum* extract demonstrated selective cytotoxicity towards cancer cells at relatively elevated concentrations. Moreover, *D. reticulatum* possessed the highest antioxidant capacity among

the investigated plants. This research contributes to the understanding of the biological importance of Anatolia's floristic diversity and emphasizes the necessity of preserving these species within the region.

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Conflict of Interest

None declared.

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