https://doi.org/10.31925/farmacia.2023.3.20 **ORIGINAL ARTICLE**

PHENOLIC COMPOUNDS, ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITIES OF *TARAXACUM GRACILENS* DAHLST. AERIAL PARTS

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Abstract

A phytochemical investigation of the aerial parts of *Taraxacum gracilens* Dahlst. (*Asteraceae*) yielded two coumarins (esculetin (**1**) and cichorin (**2**)), two flavonoids (luteolin (**3**) and chrysoeriol (**4**)) and four phenolic acids (caffeic acid (**5**), ferulic acid (**6**), chlorogenic acid (**7**) and 3,5-dicaffeoylquinic acid (**8**)). The presence of these compounds has been acknowledged for the first time in this species. The polyphenolic content and antioxidant activities of EtOH extract and PE, $CHCl_3$, AcOEt and BuOH fractions of the EtOH extract from the aerial parts of *Taraxacum gracilens* Dahlst. were investigated. We evaluated the antioxidant activities of the extract and its fractions by measuring their ability to inhibit lipid peroxidation induced by Fe^{3+}-ascorbate, their reducing power and their hydrogen donor activities. Also, the inhibitory activity against COX-2 was evaluated to determine the anti-inflammatory activity of the samples. The AcOEt and $CHCl_3$ fractions showed the highest antioxidant activity due to their richest phenolic contents, followed by the BuOH fraction, whereas the EtOH extract, containing the least phenolics, showed the weakest activity. The PE fraction did not show any antioxidant activity due to its lack of phenolic content. EtOH extracts and their fractions showed inhibitory activity against COX-2.

Rezumat

O investigație fitochimică a părților aeriene de *Taraxacum gracilens* Dahlst. (*Asteraceae*) a permis obținerea a două cumarine (esculetin (1) și cichorin (2)), a două flavonoide (luteolină (3) și crisoeriol (4)) și a patru acizi fenolici (acid cafeic (5), acid ferulic (6), acid clorogenic (7) și acid 3,5-dicafeoilchinic (8)). Prezența acestor compuși a fost recunoscută pentru prima dată la această specie. S-a investigat conținutul de polifenoli și activitățile antioxidante ale extractului EtOH și ale fracțiunilor PE, CHCl3, AcOEt și BuOH ale extractului EtOH din părțile aeriene de *Taraxacum gracilens* Dahlst. Am evaluat activitățile antioxidante ale extractului și ale fracțiunilor prin măsurarea capacității de a inhiba peroxidarea lipidelor indusă de Fe3+-ascorbat, a puterii reducătoare și a capacității de a dona protoni. De asemenea, a fost evaluată activitatea inhibitorie asupra COX-2 pentru a determina posibila activitate antiinflamatoare a probelor. Fracțiunile AcOEt și CHCl3, urmate de fracțiunea BuOH, au prezentat cea mai mare activitate antioxidantă datorită conținutului cel mai bogat în fenoli în timp ce extractul EtOH, cu cel mai mic conținut de fenoli, a prezentat cea mai slabă activitate. Fracțiunea PE nu a prezentat activitate antioxidantă, din cauza absenței fenolilor. Extractele EtOH și fracțiunile acestora au prezentat o activitate inhibitoare asupra COX-2.

Keywords: *Taraxacum gracilens* Dahlst., aerial parts, phenolic compounds, anti-inflammatory activity, antioxidant activity

Introduction

A "medicinal plant" has been defined by the World Health Organisation as any plant in which one or more of its organs contain substances that can be used for therapeutic purposes or may be used as precursors in the synthesis of other drugs [1, 2]. This description separates plants whose components and therapeutic properties have been scientifically established from those that have not yet been scientifically studied, although they are medically accepted [3]. Among them, *Taraxacum wiggers* (*Asteraceae*), the genus known as dandelion, has been reported in 2500 species worldwide and is represented by 49 species in Turkey [3, 4].

The plants of the genus *Taraxacum* have been used as medicinal herbs for a long time. Some plants belonging to this genus have been used in folk medicine to treat hepatic disorders and some women's diseases, such as uterus and breast cancers, and as lactating, diuretic, choleretic and anti-inflammatory remedies [3, 5]. Dandelion inflorescences, leaves and roots are processed into different food products. Young leaves of cultivated or wild species are consumed fresh as salad, whereas roots are roasted and utilised as a coffee substitute. Additionally, extracts are used as flavour components in various food products [3, 6].
Modern herbal monographs on *Taraxacum officinale* have evaluated its empiric use with a positive outcome. Therapeutic indications listed in the German Commission

E and European Scientific Cooperative for Phytotherapy (ESCOP, 2003) monographs are restoration of hepatic and biliary function, dyspepsia, loss of appetite, and as a supportive measure to treatments where enhanced urinary secretion is desirable, *e.g.*, rheumatism and the prevention of renal gravel [7, 24].

Previous phytochemical investigations have shown that *Taraxacum* species contain sesquiterpene lactones, triterpenes, phytosterols, flavonoids, lignans, coumarins, phenolic acids, beta-carboline alkaloids, indole alkaloids and carotenoids [3, 6, 8, 9]. Pharmacological studies have shown that *Taraxacum* species have several activities because of their secondary metabolites. Plants high in luteolin (a flavonoid) have been used in Chinese traditional medicine to treat cancer, inflammatory problems, allergies and hypertension. Biochemically, luteolin can either act as an antioxidant or a pro-oxidant [3, 6, 10]. Due to their numerous useful, biological and pharmacological effects, such as antioxidant activity, antibacterial, hepatoprotective, cardioprotective, anti-inflammatory, antipyretic, neuro-protective, anti-obesity, antiviral, anti-microbial, anti-hypertension, free radical scavenger and central nervous system stimulator, phenolic acids have recently attracted significant attention [11, 12].

Taraxacum gracilens Dahlst. is a perennial herbaceous plant. It is distributed mainly in the European part of Turkey [13, 14]. This study aimed to perform phyto-chemical analysis of *T. gracilens* Dahlst. aerial parts and identify the presence of previously unknown compounds, including coumarins, flavonoids and phenolic acids. This study was conducted to evaluate the phenolic composition and antioxidant and anti-inflammatory activities of petroleum ether, chloroform, ethyl acetate and butanol fractions of the ethanol extract from the aerial parts of *T. gracilens* Dahlst. As far as we know, there are no published results of such investigations about this species aerial parts. This study is significant since it adds information about the secondary metabolite profile and some of the activities of this species to the literature.

Materials and Methods

Chemicals

2,2-diphenyl-1-picryl-hydrazyl (DPPH), aluminium chloride, catechin, soybean L-α-phosphatidylcholine type IV-S, gallic acid, iron (II) sulphate heptahydrate and quercetin were purchased from Sigma-Aldrich (St. Louis, MO, USA). Sodium hydroxide, sodium nitrite, ferric chloride, 2,4,6-tripyridyl-S-triazine (TPTZ), thio-barbituric acid (TBA) and trichloroacetic acid (TCA) were purchased from Merck (Darmstadt, Germany). The cyclooxygenase-2 (COX-2) enzyme immunoassay (EIA) kit was purchased from Cayman (Ann Arbour, MI, USA). All other chemicals were of analytical grade.

Plant Material. The plant material was collected in Istanbul, Turkey, in April 2013. A voucher specimen (ISTE 81948) is deposited at the Herbarium of the Faculty of Pharmacy, Istanbul University, Turkey.

Extraction and Isolation

The air-dried, ground, aerial parts of *Taraxacum gracilens* Dahlst. (730 g) were exhaustively macerated with ethanol (EtOH) at room temperature. After solvent evaporation, 97 g of residue was obtained, which was dissolved in methanol/water (MeOH:H_2O) (1:2) and then successively extracted with petroleum ether (PE), chloroform ($CHCl_3$), ethyl acetate (AcOEt) and butanol (BuOH). The PE, BuOH, AcOEt and $CHCl_3$ layers were dried *in vacuo*, yielding 42.9, 2.95, 5.18 and 3.81 g, respectively. When used for activity assays, EtOH extract and its fractions were dissolved with DMSO to make a stock solution (20 mg/mL). This stock solution was diluted serially to prepare the different concentration levels (0.1 - 10 mg/mL) required for each test.

The $CHCl_3$ fraction was separated by silica gel column chromatography using a stepwise gradient of $CHCl_3$ and MeOH to give 19 fractions. Fraction 4 (0.241 g) was subjected to column chromatography (Sephadex LH-20; MeOH) and then to preparative thin layer chromatography (prep. TLC) (silica gel; $CHCl_3$:MeOH 95:5) to provide pure **1** (6 mg). Fraction 6 (0.987 g) was subjected to column chromatography (Sephadex LH-20; MeOH) and then to preparative TLC (silica gel; Toluol/AcOEt:HCOOH 7:2:1) to afford pure **4** (17.4 mg). Fraction 10 (0.630 g) was subjected to preparative TLC (silica gel; Toluol:AcOEt/HCOOH 5:4:1) to provide pure **3** (52 mg).

The AcOEt fraction was separated by silica gel column chromatography using a stepwise gradient of $CHCl_3$ and MeOH to give 12 fractions. Fraction 9 (0.871 g) was subjected to column chromatography (Sephadex LH-20; MeOH) and then to preparative TLC (silica gel; $CHCl_3$:MeOH 6:4) to provide pure **2** (4.2 mg). Fraction 12 (0.441 g) was subjected to column chromatography (Sephadex LH-20; MeOH) and then to preparative TLC (silica gel; Toluol:AcOEt/HCOOH 5:4:1) to provide pure **5** (4 mg), **6** (2.4 mg), **7** (7.3 mg) and **8** (11.3 mg), respectively.

The antioxidant activity

The antioxidant activity of the AcOEt, BuOH, $CHCl_3$ and PE fractions from the EtOH extract of *T. gracilens* Dahlst. aerial parts were assayed by the four different methods. The antioxidant activities exhibited by the fractions evaluated by these assays reflect the capacity of fractions to act as electron or hydrogen atom donors, a necessary requirement for antioxidant function in biological systems.

Total phenolic content (PC) was determined using the Folin-Ciocâlteu reagent [15] and expressed in terms of mg gallic acid equivalents/g extract using the equation of a regression curve obtained using standard gallic acid solutions (0.04 - 0.5 mg/mL). Total flavonoid content (FC) was evaluated according to the aluminium chloride method [16] and expressed as mg catechin

equivalents/g extract using a regression curve obtained from standard catechin solutions (0.016 - 0.25 mg/mL). The ferric ion-reducing antioxidant power (FRAP) assay is based on the reduction of the Fe(III)-TPTZ complex to Fe(II)-TPTZ in the presence of antioxidants [17]. The formation of a blue-coloured complex of F(II)-TPTZ was monitored at 593 nm. The FRAP values of the extract were determined using the equation of the standard regression curve obtained by $FeSO_4*7H_2O$ solution (0.125 - 2 mM) and were expressed as mM Fe^{2+} equivalents.

To evaluate the DPPH radical scavenging activity, the method of Brand-Williams *et al*. was performed [18]. The decrease in absorbance as a result of decolorization from the purple DPPH radical to the yellow DPPH molecule was measured at 517 nm. Quercetin (0.01 - 0.25 mg/mL) was used as a standard antioxidant, and a sample without any inhibitor was used as a control. The percentage activity was calculated using the following equation and the DPPH radical scavenging activity expressed as a half-maximal effective concentration (EC_{50}).

$$\text{DPPH radical scavenging activity (\%)} = \left(1 - \frac{\text{Absorbance of extract or standard at 517 nm}}{\text{Absorbance of control at 517 nm}}\right) \text{x } 100,$$

The lipid peroxidation (LPO) was determined by measuring the formation of the thiobarbituric acid reactive substances (TBARS) following the reaction of malondialdehyde (MDA) with thiobarbituric acid (TBA) at 532 nm [19]. Quercetin (0.01 - 0.25 mg/mL) was used as a standard antioxidant and a sample without any inhibitor was used as a control. The inhibitory effects of the extracts on lipid peroxidation were determined by the following equation and EC_{50} values were calculated.

$$\text{Inhibitory effect on LPO (\%)} = \left(1 - \frac{\text{Absorbance of sample at 532 nm}}{\text{Absorbance of control at 532 nm}}\right) \times 100,$$

The anti-inflammatory activity

The cyclooxygenase-2 (COX-2) inhibitory effects of the EtOH extract and its fractions were evaluated to determine the anti-inflammatory activity. The ability of the extracts to inhibit COX-2 was determined by calculating the percent inhibition of prostaglandin production using an enzyme immunoassay (EIA) kit according to the manufacturer's instructions (Cayman Chemical, Item No. 560131).

Statistical Analysis

Results were expressed as the mean ± the standard deviation of triplicate analyses. Statistical comparisons were performed using the Student t-test. Differences were considered significant at $p < 0.05$.

Results and Discussion

The AcOEt and $CHCl_3$ soluble fractions of the EtOH extract of the aerial parts of *Taraxacum gracilens* Dahlst. were investigated to elucidate its secondary metabolite profile. Column chromatography and preparative thin-layer chromatography were used for the separation of these compounds. Their structures were established conclusively by ultraviolet visible spectroscopy (UV), electrospray ionisation mass spectrometry (ESI-MS) and nuclear magnetic resonance (NMR) spectra analyses in comparison with literature data. In this study, esculetin (**1**), cichorin (**2**), luteolin (**3**), chrysoeriol (**4**), caffeic acid (**5**), ferulic acid (**6**), chlorogenic acid (**7**) and 3,5-dicaffeoylquinic acid (**8**) are identified and are new for the species *T. gracilens* Dahlst.

The highest total phenolic levels have been detected in the AcOEt fraction. In the $CHCl_3$ fraction, the phenolic compounds were present to a lesser extent. The lowest total phenolic levels have been detected in the BuOH fraction and EtOH extract of the aerial parts. The order of total phenolic contents was established as follows: AcOEt > $CHCl_3$ > BuOH > EtOH ($p < 0.05$). No phenolic content was detected in the PE fraction. From the effective concentrations (EC_{50}) (Table I), it was seen that the $CHCl_3$ and AcOEt fractions showed the highest antioxidant activity due to their richest phenolic contents.

Table I

Total phenolic content, flavonoid content and EC_{50} values of the EtOH extract and PE, $CHCl_3$, AcOEt, BuOH fractions from the aerial parts of *T. gracilens* Dahlst.

Extract	Anti-LPO EC_{50}* (mg/mL)	DPPH EC_{50}* (mg/mL)	FRAP** (mM Fe^{2+})	Phenolic content (mg GAE/g)	Flavonoid content (mg CE/g)
$CHCl_3$ fraction	0.68 ±0.06[a]	1.13 ± 0.17[a]	3.12 ± 0.27[a]	109.12 ± 11.98[a]	60.54 ± 2.64[a]
BuOH fraction	12.02 ±0.48[b]	5.96 ± 0.27[b]	0.75 ±0.06[b]	27.59 ± 2.79[b]	11.24 ±1.24[b]
AcOEt fraction	1.44 ± 0.09[c]	0.68 ± 0.06[c]	4.68 ± 0.29[c]	138.96 ± 7.13[c]	121.88 ± 9.79[c]
EtOH extract	N.d.	9.57 ± 0.36[d]	0.48 ± 0.05[d]	18.2 ± 0.70[d]	3.10 ± 1.40[d]
PE fraction	N.d.	N.d.	N.d.	N.d.	N.d.
Quercetin	0.059 ± 0.001[d]	0.034 ± 0.002[e]	3.24 ± 0.13[a]	-	-

Values were the means of three replicates ± standard deviation. *EC_{50} value: The effective concentration at which the anti-LPO activity was 50%; DPPH radicals were scavenged by 50%; the absorbance was 0.5 for reducing power. EC_{50} value was obtained by interpolation from linear regression analysis. The values with different letters in the same column were significantly ($p < 0.05$) different. **Determined at 2.5 mg/mL. GAE; gallic acid equivalents, CE; catechin equivalents.

The $CHCl_3$ fraction showed the highest antioxidant activity on the formation of lipid peroxidation. The AcOEt and $CHCl_3$ fractions also showed the most powerful hydrogen-donating abilities in the presence of a stable DPPH radical. This data reinforced the greater antioxidant activity of these fractions in the LPO assay compared to the BuOH fraction and EtOH extract. However, both the fraction and the extract were not as potent as the positive control, quercetin. BuOH fraction and EtOH extract were the least active antioxidants. The PE fraction did not show any detectable antioxidant activity.

It may be concluded that AcOEt, $CHCl_3$ and BuOH fractions did act as antioxidant agents by reducing the thiobarbituric acid reactive substances (TBARS) produced from lipid peroxidation of the soybean phosphatidylcholine (lecithin) liposomes, induced by the Fe^{3+}/ascorbate model system and by showing proton and electron-donating ability.

To assess the anti-inflammatory activity of *T. gracilens* Dahlst., the COX-2 inhibitory activity of the fractions and the extract was tested in comparison with indomethacin, used as the positive control. PE and $CHCl_3$ fractions of herbal extract showed the highest COX-2 inhibitory activity, followed by the BuOH fraction and EtOH extract, while the AcOEt fraction exhibited the least effect. By using ^{1}H-NMR and GC-MS analysis, some researchers have looked into the biochemical compositions of polar and non-polar extracts from the various *Taraxacum* species. sterols, triterpenes and fatty acids (phytol, b-sitosterol, stigmaserol, lanosterol and b-amyrin) with similar properties have been found in the non-polar extracts [20].

Fatty alcohols, sterols and terpenoids were found in large quantities and as important ingredients during phytochemical screening of the non-polar fraction of *Taraxacum* aerial parts. Based on the suppression of the lipoxygenase pathway in arachidonate metabolism *in vivo*, the sterols in the non-polar extracts had an anti-inflammatory effect. According to Tumbarski *et al*., the period immediately following flowering was when dandelion leaf extracts had the maximum content of polyphenols. Thus, the amount of phytochemicals in dandelion leaves varied according to the harvest season. The best time to pick a plant from its natural environment depends on whether it will be used for medicinal purposes [21].

Based on the published reports that flavonoids possess anti-inflammatory activity [22, 23], the extract with the greatest concentrations of flavonoids was expected to show the highest anti-inflammatory activity. However, the anti-inflammatory activity of the AcOEt fraction was not concomitant with the development of its anti-oxidant activity. The AcOEt fraction was the most powerful antioxidant but the least effective inhibitor of COX-2 (Table II).

Table II

COX-2 inhibitory activity of the EtOH extract and PE, $CHCl_3$, AcOEt, BuOH fractions from the aerial parts of *T. gracilens* Dahlst.

	COX-2 inhibitory activity					
	EC_{50} (mg/mL)					**EC_{50} (μg/mL)**
Extract	**PE fraction**	**$CHCl_3$ fraction**	**BuOH fraction**	**EtOH extract**	**AcOEt fraction**	**Indomethacin**
T. gracilens	3.86 ± 0.37^a	3.95 ± 0.14^a	5.09 ± 0.16^b	5.97 ± 0.07^c	9.06 ± 0.36^d	18.01 ± 0.41

Values were the means of three replicates ± standard deviation. Values with different letters in the same row were significantly ($p < 0.05$) different.

One of the main developments in understanding how *Taraxacum* has been useful as a traditional medicine is to examine its biochemical composition and identify several bioactive compounds [3, 6]. Disclosure of the composition and mechanisms of action against the disease may enable us to demonstrate its potential as a commercial plant for this conventional drug [3]. *Taraxacum* species contain a wide range of phyto-chemicals with biological activities that are actively being researched in various areas of human health [6, 24]. While bitter substances are known to stimulate digestion, phenolic compounds are responsible for the anti-inflammatory and antioxidant activities of plant extracts. Therefore, in the last decades, the focus has been on elucidating such pharmacologically important compounds in *Taraxacum* plants [3, 25]. This permits the inclusion of dandelion into the true "medicinal plant" due to its potential as a commercial source of various pharmacologically interesting compounds [9].

Conclusions

In this study, it is aimed to isolate phenolic compounds from the aerial parts of *T. gracilens* Dahlst. and to test some biological activities of the EtOH extract and the fractions obtained from the EtOH extract of the aerial parts. Based on this, 8 phenolic compounds were isolated from the aerial parts of *T. gracilens* Dahlst. Also, antioxidant and anti-inflammatory activities of the EtOH extract and the PE, $CHCl_3$, AcOEt and BuOH fractions of the EtOH extract from the aerial parts of *T. gracilens* Dahlst. were tested. The exhibited results sustain the facts that the fractions and the extract obtained from the aerial parts of *T. gracilens* Dahlst. present anti-inflammatory and antioxidant characteristics, but to a lesser degree than the activities of the standards in the studies. Although the ethyl acetate fraction has a high phenolic content, low anti-inflammatory activity was observed compared to indomethacin. This study shows that the aerial parts of

Taraxacum gracilens Dahlst. have been investigated for the first time in the literature. These results show that the secondary metabolite profile of this species has been elucidated by isolation, the activities and phenolic contents of the extracts and fractions have been revealed, and thus, it can be used traditionally as *T. officinale*, both as a raw material source for future studies and for medicinal purposes.

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Conflict of interest

The authors declare no conflict of interest.

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