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Research Article

Phenolic profile, antioxidant and antimicrobial activity of *Echinophora tenuifolia* L. subsp. *sibthorpiana*

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Abstract

In the present study, the phenolic profile, the antioxidant activity, and the antimicrobial activity of an aqueous-methanolic extract prepared from the aerial parts of *Echinophora tenuifolia* subsp. *sibthorpiana* growing in Bulgaria were investigated for the first time. The evaluation of the phenolic composition of the extract revealed high levels of total phenols (111.3 ± 9.1 mg GAE/g dry extract) and the presence of the phenolic acids chlorogenic acid, *p*-coumaric acid, ferulic acid, salicylic acid, rosmarinic acid, the flavonol glycoside rutin, and the flavanone glycoside hesperidin. The highest concentration was observed for rutin (29.625 mg/g). The extract demonstrated good radical scavenging activity in the DPPH assay (IC_{50} 71.3 ± 0.01 µg/mL) and antioxidant capacity in the ferric-ferrozine assay (405.1 ± 39.9 µmol/g). In addition, the extract exhibited antibacterial activity against *E. coli* (MIC 1.85 mg/mL, MBC 3.5 mg/mL) and *S. aureus* (MIC 3.7 mg/mL). In contrast, no antifungal activity against *C. albicans* was observed.

Keywords

antimicrobial activity, antioxidant activity, *Echinophora tenuifolia* subsp. *sibthorpiana*, phenolic composition, traditional medicine

Introduction

Echinophora tenuifolia L. subsp. *sibthorpiana* (Guss.) or *Echinophora sibthorpiana* (Guss.) (*E. tenuifolia* subsp. *sibthorpiana*) is a perennial aromatic plant belonging to the Apiaceae family, distributed in the countries of the Balkans and Southwest Asia, including Turkey and Iran (Ivanova et al. 2023). Different parts of the plant, usually the leaves, are used in Turkey as an herb for flavoring of different foods such as meatballs, soups, and pickles, in which the herb plays a role as a natural preservative for extending the shelf life (Kargıoğlu et al. 2008; Ghafoor et

al. 2021). In addition to flavoring, the plant is used for its nutritional properties. It is often included as a flavoring agent in the traditional fermented cereal food tarhana, in which it has been shown to improve the fermentation process and the nutritional value (Ozdemir et al. 2007; Ghafoor et al. 2021).

Echinophora tenuifolia subsp. *sibthorpiana* is associated not only with a nutritional value, but it is also regarded as a plant with a therapeutic potential. Although the studies about the biological activity of *E. tenuifolia* subsp. *sibthorpiana* are limited, different data reported that the plant was involved in the traditional medicine for the management of various medical conditions, specifically digestive disorders as an antispasmodic, digestive, and anti-ulcer agent; respiratory disorders, including shortness of breath and common cold; and also as a skin-recovery remedy (Ivanova et al. 2024).

Most of the phytochemical studies investigating *E. tenuifolia* subsp. *sibthorpiana* were focused on the essential oil (EO) isolated from the plant. Currently, data about the chemical composition of *E. tenuifolia* subsp. *sibthorpiana* extracts are quite limited. However, *Echinophora* species seem to be a source of many phenolic compounds, phytosteroids, and terpenes (Valizadeh et al. 2014; Marrelli et al. 2017; Aksit et al. 2022). Previously, some novel molecules were described from *Echinophora* species – polyacetylenes called echinophorins (Jelodarian et al. 2017). These phytochemicals demonstrated selectivity toward the transient receptor potential channels of ankyrin type-1 (Chianese et al. 2018). Echinophorins are regarded as compounds with a promising potential to become drug candidates for the management of pain and inflammation (Chianese et al. 2018).

The aim of the present study is to determine the phenolic profile of aqueous-methanolic extract of *E. tenuifolia* subsp. *sibthorpiana*, including the determination of the total phenolic content and identification of individual phenols, and to investigate the in vitro antioxidant activity and the antimicrobial activity of the extract. To the best of our knowledge, this is the first report investigating the non-volatile phytochemical composition and biological properties of *E. tenuifolia* subsp. *sibthorpiana* growing wild in Bulgaria.

Materials and methods

Plant material and extract preparation

The aerial parts (stems, leaves, and flowers) of *E. tenuifolia* subsp. *sibthorpiana* were collected during the flowering stage in August 2022 in Southeastern Bulgaria. The aerial parts were air-dried at room temperature and protected from sunlight and subsequently cut and freeze-dried. The freeze-dried plant material was ground and extracted with 50% aqueous methanol for 60 min using ultrasound-assisted extraction. The obtained extract was filtered and concentrated with a rotary vacuum evaporator and further freeze-dried and stored at -20 °C before use.

Spectrophotometric determination of total phenolic content

The total phenolic content of the extract was determined spectrophotometrically according to the Folin–Ciocalteu colorimetric method using gallic acid as a standard (Latimer 2023). Briefly, 100 µL of extract (1 mg/mL) solution was added to 500 µL diluted commercial Folin–Ciocalteu reagent (1:9). After 5 min, 400 µL of a 7.5% Na_2CO_3 solution was added, and the mixture was left at room temperature for 60 minutes. Afterwards, the absorbance was measured at 765 nm against a blank sample. The results were expressed as milligrams of gallic acid equivalents per gram of dry extract (mg GAE/g dry extract).

HPLC analysis

The extract was analyzed using high-performance liquid chromatography (HPLC) with UV detection by a previously validated and published method according to Krasteva et al. (Krasteva et al. 2022). Briefly, the analytical conditions include a Supelco Discovery HS C18 column (5 µm, 250 mm × 4.6 mm), mobile phase, consisting of 1% acetic acid in water (Solvent A) and methanol (Solvent B) in gradient elution, and a detection wavelength of 280 nm for gallic acid, protocatechuic acid, (+)-catechin, vanillic acid, syringic acid, (-)-epicatechin, *p*-coumaric acid, salicylic acid, hesperidin, and 360 nm for chlorogenic acid, caffeic acid, ferulic acid, rutin, rosmarinic acid, quercetin, and kaempferol (Krasteva et al. 2022).

Antioxidant activity

DPPH assay

The DPPH free radical scavenging activity of the extract was determined according to the procedure described by Paun et al. (Paun et al. 2016). The assay was based on the discoloration of violet DPPH (2,2-diphenyl-1-picrylhydrazyl radical) solution in the presence of an antioxidant. The aliquots of plant extract were mixed with a methanolic solution of DPPH (60 mM). The reactive mixture was allowed to stand at room temperature in the dark for 20 min, and the absorbance was measured at 517 nm. The experiment was carried out in triplicate. The results were expressed as IC_{50}, which was defined as the concentration (in µg/mL) of the extract required to scavenge 50% of DPPH radicals.

Ferric-ferrozine assay

The total antioxidant capacity of plant extract was evaluated by monitoring the reduction of the Fe(III)-ferrozine agent to a stable Fe(II)-ferrozine complex according to the method proposed by Berker et al. (Berker et al. 2010). Different quantities of the extract, 0.3 mL ferric-ferrozine solution, and 0.4 mL sodium acetate buffer at pH 5.5 (0.2 M CH_3COOH/CH_3COONa) were mixed, and the absorbance of the reaction mixture against a reagent blank was measured at 562 nm after 30 min. The standard curve was constructed

using solutions of Trolox (50–250 µM) in methanol, and the results were expressed as Trolox Equivalents (TE), i.e., µmol Trolox causing the same reduction of the ferric-ferrozine complex as 1 g dry extract. All the measurements were taken in triplicate, and the mean values were calculated.

Antibacterial and antifungal activity

The antimicrobial activity of *E. tenuifolia* subsp. *sibthorpiana* extract was tested against *Escherichia coli* ATCC25922, *Staphylococcus aureus* ATCC25713, and *Candida albicans* ATCC10231. The tested strains (MicroSwab, Ridacom, Bulgaria) were activated for the purposes of this study through initial plating on blood agar (HiMedia, Ridacom, Bulgaria).

For the determination of the minimum inhibitory concentrations (MICs), the serial two-fold dilution method was used. Two-fold serial dilutions of the *E. tenuifolia* subsp. *sibthorpiana* extract in Mueller Hinton broth (MHB) (HiMedia, Ridacom, Bulgaria) at concentrations of 29.6–0.925 mg/mL were prepared and added to six wells, each containing 0.2 mL suspension. In each well, 0.02 mL of densitometer-standardized 0.5 MF microbial suspension of the test strain was added. Positive control was considered the sample with 0.2 mL of MHB and 0.02 mL of microbial suspension, while the negative control was the highest test concentration of the *E. tenuifolia* subsp. *sibthorpiana* (29.6 mg/mL) in 0.2 mL of MHB. The samples were cultured under aerobic conditions at 37 °C for 24 hours for *E. coli* ATCC25922 and *S. aureus* ATCC25713, and at 35 °C for 48 hours – for *C. albicans* ATCC 10231. After the cultivation period, the suspension with the lowest concentration of *E. tenuifolia* subsp. *sibthorpiana* extract, at which no visual turbidity was recorded, was determined as the MIC against the respective strain.

For the determination of minimum bactericidal concentration (MBC)/minimum fungicidal concentration (MFC), an equal amount of each sample was seeded on blood agar plates and cultivated under the same incubation conditions as described above. The lowest concentration of *E. tenuifolia* subsp. *sibthorpiana* extract, at which microbial growth was inhibited by 99.9%, was reported as MBC.

In addition, the antimicrobial activity was assessed by the agar diffusion method (cup-plate technique). Mueller-Hinton agar (MHA) plates (HiMedia, Ridacom, Bulgaria) were seeded with each of the test microbes. In the center of each agar plate, a well with a 7 mm diameter was made, in which a 200 µL suspension of *E. tenuifolia* subsp. *sibthorpiana* extract (11.84 mg/mL) was placed, and then the plates were incubated under the same conditions described above. DMSO (5%) was used as a negative control. After the incubation period, the resulting inhibition zones were measured (d = mm). All the assays were performed in triplicate.

Results

Phenolic content

Since the antioxidant activity of plant extracts is often related to their phenolic content, the total phenolic content (TPC) of the extract was determined spectrophotometrically using the Folin-Ciocalteu method. The TPC was calculated using the equation of the standard curve for gallic acid (R^2 = 0.9759). The TPC of the extract was 111.3 ± 9.1 mg GAE/g dry extract.

HPLC analysis

HPLC analysis was carried out for the identification and quantification of sixteen phenolic compounds, including the phenolic acids gallic acid, protocatechuic acid, chlorogenic acid, vanillic acid, caffeic acid, syringic acid, *p*-coumaric acid, ferulic acid, salicylic acid, rosmarinic acid, and the flavonoids (+)-catechin, (-)-epicatechin, rutin, hesperidin, quercetin, and kaempferol. A total of seven phenolic compounds were identified in the extract, namely the phenolic acids chlorogenic acid, *p*-coumaric acid, ferulic acid, salicylic acid, and rosmarinic acid; the flavonol glycoside rutin (or quercetin-3-*O*-rutinoside); and the flavanone glycoside hesperidin (or hesperitin-7-*O*-rutinoside). The results of the HPLC analysis also showed that rutin was the most abundant compound identified in the extract with a concentration of 29.625 mg/g extract, followed by salicylic acid with a concentration of 12.22 mg/g extract. The concentration of the other identified compounds was lower with concentrations of 6.182, 4.474, 3.998, 3.481, and 0.364 mg/g extract for rosmarinic acid, hesperidin, ferulic acid, chlorogenic acid, and *p*-coumaric acid, respectively. Gallic acid, protocatechuic acid, vanillic acid, caffeic acid, syringic acid, (+)-catechin, (-)-epicatechin, quercetin, and kaempferol were not found in the extract.

Antioxidant activity

The antioxidant activity of the extract was evaluated by two spectrophotometric assays in terms of its free radical scavenging properties (DPPH assay) and its total antioxidant capacity (Ferric-ferrozine assay) (Table 1). The DPPH radical scavenging activity expressed by IC_{50} was 71.3 ± 0.01 µg/mL, whereas the total reducing capacity determined by the ferric-ferrozine assay and expressed as Trolox equivalents was 405.1 ± 39.9 µmol/g.

Table 1. Antioxidant and antimicrobial activity of *E. tenuifolia* subsp. *sibthorpiana* extract.

Antioxidant activity		
DPPH assay	IC_{50} 71.3 ± 0.01 µg/mL	
Ferric-ferrozine assay	405.1 ± 39.9 µmol/g Trolox equivalents	
Antimicrobial activity		
Strain	MIC	MBC
E. coli ATCC25922	1.85 mg/mL	3.5 mg/mL
S. aureus ATCC25713	3.7 mg/mL	–
C. albicans ATCC10231	–	–

Antibacterial and antifungal activity

The results of the serial dilution of *E. tenuifolia* subsp. *sibthorpiana* extract for determining the MIC showed the highest antimicrobial activity against *E. coli* ATCC 25922

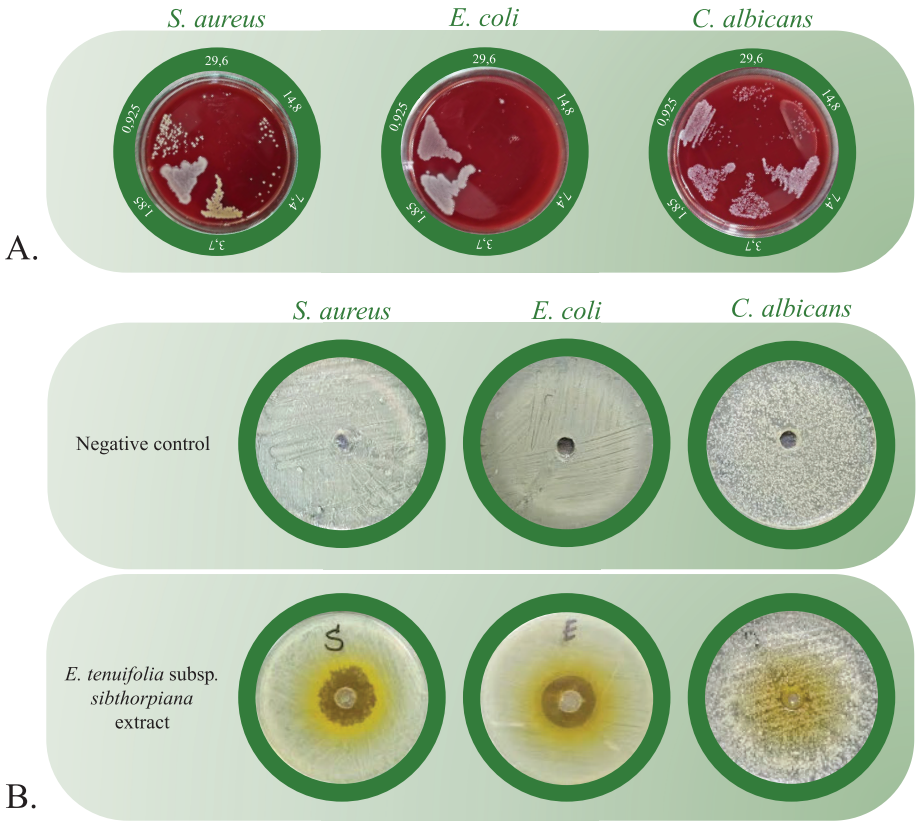

Figure 1. Antibacterial activity of *E. tenuifolia* subsp. *sibthorpiana*: **A.** Seeds of different concentrations of the extract (0.925–29.6 mg/mL) on blood agar and **B.** Inhibition zones of the extract (11.84 mg/mL) against tested microorganisms. 5% DMSO was used as a negative control.

with a MIC of 1.85 mg/mL. Against *S. aureus* ATCC 25913, visual growth was suppressed at the lowest concentration of 3.7 mg/mL, while no activity was observed against *C. albicans* ATCC 10231. All suspensions from the serial dilution for determining the MBC/MFC were subcultured in agar media (Fig. 1A). The *E. tenuifolia* subsp. *sibthorpiana* extract demonstrated the highest antimicrobial effect against *E. coli* ATCC 25922, as microbial growth was completely inhibited with MBC 3.7 mg/mL. Against *S. aureus* ATCC 25913 and *C. albicans* ATCC 10231, a strong reduction in microbial growth was also observed, but no total bactericidal/fungicidal effect was reported at the concentrations set in the study.

Using the cup plate technique, however, stronger antimicrobial effects were observed against *S. aureus* ATCC 25913 (Fig. 1B). In this method, *S. aureus* ATCC25913 was the most sensitive strain, demonstrating a zone of inhibition of 25 mm at a concentration of 11.84 mg/mL, while that of *E. coli* ATCC 25922 was 21 mm. No antifungal activity was observed against *C. albicans* ATCC 10231.

Discussion

The results from the current study suggest that *E. tenuifolia* subsp. *sibthorpiana* extract is associated with good antibacterial and antioxidant activities, which are an important factor for the future evaluation of this plant species as a natural preservative for the food industry (Fig. 2). The plant is characterized by a non-toxic and safe profile and is traditionally used as a spice and a flavoring agent in different foods, including for the improvement of shelf life (Kargıoğlu et al. 2008, Ghafoor et al. 2021). Moreover, our findings suggest that *E. tenuifolia* subsp. *sibthorpiana* extract could possess significant therapeutic potential and could be a valuable source of novel compounds with biological activity for the pharmaceutical industry. However, more comprehensive studies, including phytochemical studies and in vivo studies for the evaluation of pharmacological activities, are required.

Previously, two studies have examined the phenolic composition and the antibacterial and antioxidant activities of *E. tenuifolia* subsp. *sibthorpiana* extracts. Aydin and Sümbül determined the TPC, antioxidant activity, and antibacterial activity of two extracts (acetone and ethyl acetate) from commercial samples of *E. tenuifolia* subsp. *sibthorpiana* from Turkey (Aydin and Sümbül 2022). The phenolic content of the ethyl acetate extract (141.6 ± 0.006 µg GAE/mL) was higher than that of the acetone extract (46.97 ± 0.001 µg GAE/mL). In addition, the ethyl acetate extract showed the highest total antioxidant capacity (373.50 ± 0.033 µg AAE/mL) and cupric reducing antioxidant capacity (373.50 ± 0.033 µg AAE/mL) among the tested extracts, while the acetone extract demonstrated higher DPPH radical scavenging activity. The two extracts demonstrated the highest antibacterial activity against

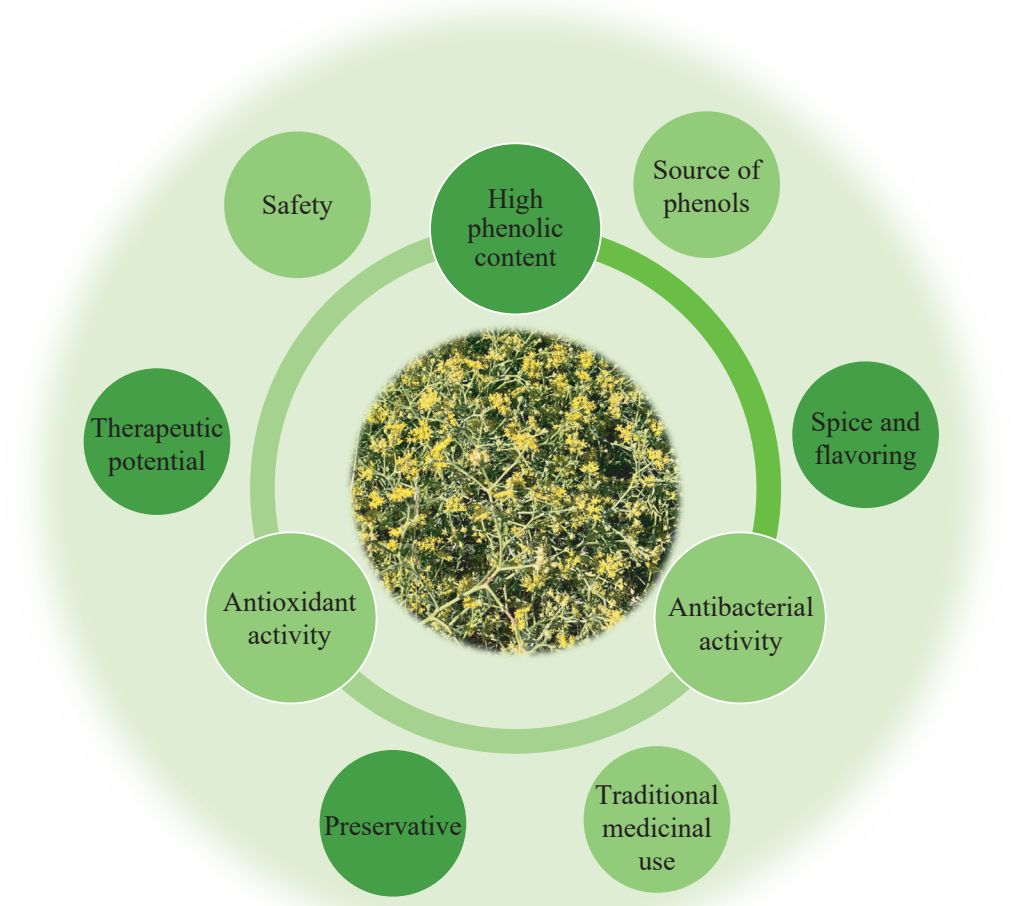

Figure 2. Relationship between traditional uses and potential applications of *E. tenuifolia* subsp. *sibthorpiana*.

Gordonia rubripertincta, in addition to activity against *S. aureus* subsp. *aureus* (Aydin and Sümbül 2022).

Mileski et al. examined the phenolic content and antioxidant antimicrobial activities of methanolic, ethanolic, and aqueous extracts from different parts (roots and aerial parts) of wild-grown *E. tenuifolia* subsp. *sibthorpiana* from Macedonia (Mileski et al. 2014). The highest phenolic content was observed in the methanolic extract from the aerial parts of the plant (60.72 ± 0.012 mg GE/g of dry extract), while the highest antioxidant activity showed the aqueous extract from the aerial parts in the DPPH radical scavenging assay (IC_{50} 1.67 mg/mL) and the ethanolic extract of the aerial parts in the ABTS scavenging assay (1.11 ± 0.016 mg vit. C equivalents/g dry extract) (Mileski et al. 2014). The strongest antibacterial effects demonstrated the roots ethanolic extract (highest activity against *Bacillus cereus* with MIC 0.45 mg/mL and MBC 0.75 mg/mL) and aerial parts methanolic extract (highest activity against *B. cereus*, *Enterobacter cloacae*, and *S. aureus* with MIC 3.00 mg/mL and MBC 4.00 mg/mL for each strain) (Mileski et al. 2014).

The studies regarding the chemical composition of individual non-volatile phytochemicals, including phenolic compounds, in the genus *Echinophora* are limited. However, our results regarding the phenolic composition of *E. tenuifolia* subsp. *sibthorpiana* comply with earlier studies. Quercetin and rutin were identified in the polar ethyl acetate fraction of the methanolic extract of *E. tenuifolia*, while ferulic acid was identified in the dichloromethane fraction of the same extract (Marrelli et al. 2017). In addition, the polar ethyl acetate fraction of the extract demonstrated high antioxidant activity in the DPPH assay and β-carotene bleaching test (Marrelli et al. 2017). The flavonol glycosides quercetin-3-*O*-β-D-glucopyranoside and kaempferol-3-*O*-β-D-glucopyranoside were successfully isolated from *E. cinerea* hydroalcoholic extract (Shokoohinia et al. 2017). The isolated compound quercetin-3-*O*-β-D-glucopyranoside demonstrated good cytoprotective effects in cisplatin-induced neurotoxicity and H_2O_2-induced cytotoxicity (Shokoohinia et al. 2015, 2017). Thirty-three flavonoids and organic acids were identified in *E. chrysantha* hydroalcoholic extract, in which rutin, quercetin-3-O-glucoside, hesperidin, quinic acid, and chlorogenic acid were the most abundant (Aksit et al. 2022).

Phenolic compounds are the most widely distributed secondary metabolites in plants and include many structurally diverse classes such as phenolic acids, flavonoids, and tannins (Dai and Mumper 2010; Zhang et al. 2022). Polyphenols are defined by the presence of two or more phe-

nolic groups and are compounds with relatively complex structures and high molecular weights. However, simple phenols like phenolic acids, which could serve as polyphenol precursors, are also classified within this category (Hano and Tungmunnithum 2020). Dietary plant polyphenols are present in a variety of foods and beverages such as fruits, vegetables, wine, tea, and coffee, as well as in many aromatic and medicinal plants (Pandey and Rizvi 2009; Oreopoulou et al. 2019). Plant polyphenols are associated with a variety of health benefits due to their diverse biological activities, such as antioxidant, antimicrobial, and anti-inflammatory effects (Zhang et al. 2022), and could possess beneficial effects on different conditions, including cardiovascular diseases (Iqbal et al. 2023), diabetes (Guasch-Ferré et al. 2017), obesity (Boccellino and D'Angelo 2020), anxiety and depression (Dias et al. 2012; Pathak et al. 2013), and aging-related disorders (Luo et al. 2021).

Many of the health benefits of polyphenols can be attributed to their antioxidant effects. Polyphenols are the most common naturally occurring antioxidants (Luo et al. 2021). The molecular mechanisms by which polyphenols exhibit their antioxidant properties include direct reaction with free radicals by donation of hydrogen atoms or electrons and chelation of metal ions (Leopoldini et al. 2011; Zhang and Tsao 2016). These activities are associated with the chemical structure of polyphenols, which is composed of planar aromatic rings, allowing conjugation and delocalization of π-electrons, and numerous hydroxyl groups (Leopoldini et al. 2011; Zhang and Tsao 2016).

Conclusion

Studies regarding the phytochemistry of plants and their extracts play a significant role in the more comprehensive understanding of their biological and pharmacological effects. This is the first report on the non-volatile phytochemical profile and the antioxidant and antimicrobial activities of Bulgarian *E. tenuifolia* subsp. *sibthorpiana*. Our results revealed high phenolic content of the extract and the presence of individual phenolic compounds, including rutin, salicylic acid, rosmarinic acid, hesperidin, ferulic acid, chlorogenic acid, and *p*-coumaric acid. The extract demonstrated good antioxidant activity in terms of its radical scavenging properties and total antioxidant capacity, in addition to antibacterial activity against *E. coli* and *S. aureus*. The results of this study reveal *E. tenuifolia* subsp. *sibthorpiana* as a potential source of phenolic compounds for the food and pharmaceutical industries and could serve as a basis for the evaluation of different pharmacological activities of this species. Further investigations are needed for the more extensive determination of the phytochemical profile of this plant and its correlation to its biological effects.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Author contributions

Conceptualization, S.D., S.I. and K.I.; methodology, S.D., I.S., N.E., E.M. S.S.; investigation, S.D., I.S., N.E., E.M. S.S.; writing – original draft preparation, S.D. and S.I.; writing – review and editing S.D., S.I., I.S. and S.S.; visualization S.D. and S.I.; supervision, S.I., K.I. and M.B.

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Data availability

All of the data that support the findings of this study are available in the main text.

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