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Original Article

Antimicrobial activities of *Scorzonera ketzkhowelii Sosn.* ex Grossh. (Asteraceae) and determination of natural compounds by LC-HRMS analysis

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ABSTRACT

Background and Aims: *Scorzonera ketzkhowelii* Sosn. ex Grossh. (Asteraceae) was reported as a new species in the Flora of Turkey in 2010. However, there have been no prior biological or chemical investigations conducted.

Methods: This study aims to investigate the antimicrobial activities of the petroleum ether, dichloromethane, ethyl acetate, and n-butanol fractions derived from *S. ketzkhowelii*, and determination of secondary metabolites by Liquid Chromatography with High Resolution Mass Spectrometry (LC-HRMS) analysis on the most active antimicrobial fractions.

Results: Notably, all of the fractions demonstrated antimicrobial activity against selected microorganisms, with the dichloromethane fraction of the aerial part exhibiting a higher inhibition of microbial growth compared to the other extracts. The findings of our study revealed the presence of several phenolic compounds in the dichloromethane fractions from both the aerial and subaerial parts, including 3,4-dihydroxybenzaldehyde, salicylic acid, dihydrocaffeic acid, caffeic acid, caffeic acid phenethyl ester, chlorogenic acid, quercetin, hyperoside, naringenin, apigenin, hispidulin, hispidulin 7-glucoside, chrycin, emodin, and carnosic acid. Furthermore, dichloromethane fraction of the aerial parts contained additional phenolic compounds such as homogentisic acid, verbascoside, (+)-trans taxifolin, apigenin 7-glucoside, luteolin, orientin, and chrysoeriol.

Conclusion: The plant's demonstrated antimicrobial attributes and the diverse range of phenolic compounds it contains present it as a promising subject for continued research and potential applications within the realms of medicine and pharmaceuticals. Further exploration of its bioactivity and potential health benefits may reveal novel avenues for its practical utilization.

Keywords: *Scorzonera ketzkhowelii*, Asteraceae, antimicrobial activity, LC-HRMS, phenolic compounds

INTRODUCTION

The genus *Scorzonera* L. is a member of the Asteraceae family and encompasses around 160 species worldwide. Within the Flora of Turkey, this genus is characterized by the presence of 52 species, totalling 59 taxa (Coşkunçelebi, Makbul, Gültepe, Okur, & Güzel, 2015). Among the people of Turkey, plants from the *Scorzonera* genus are commonly referred to as 'Teke sakalı' but are also known by various other names such as Kök sakızı, Dağ sakızı, Angıt otu, Nerebent, Tekercik, Çetotu, Parım, Purrık, and İskorçina (Makbul, 2012).

Scorzonera is primarily consumed as a food source, with chewing gum derived from the latex of its roots. Moreover, it has been utilized in traditional medicine for an extensive period for the purpose of treating cardiovascular diseases, renal disorders, stomach pain, infertility, and serving as an analgesic, wound healer, galactagog, and anthelmintic (Altundağ & Öztürk, 2011; Göç & Mat, 2019; Nadiroğlu, Behçet, & Çakılcıoğlu, 2019; Tuzlacı, 2016). Extensive research has been conducted to explore its activity and chemical composition. Numerous secondary metabolites, including triterpenes, sterols, sesquiterpenes, sesquiterpene lactones, lignans, neolignans, phenolic acids, flavonoids, coumarins, dihydroisocoumarins, and stilbene derivatives, have been identified, and their struc-

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tures have been elucidated. These plants have demonstrated a diverse array of bioactivities, encompassing anti-Alzheimer, anti-inflammatory, antinociceptive, antioxidant, antidiabetic, antibacterial, antifungal, anti-leishmaniasis, anti-tyrosinase, anti-HIV, hepatoprotective, and wound healing properties (Bahadır Acıkara et al., 2012; Granica & Zidorn, 2015; Şahin, Boğa, & Sarı, 2022; Aynur Sarı, 2012; Zidorn, Ellmerer-Müller, & Stuppner, 2000).

Scorzonera ketzkhowelii was documented as a novel species in the Flora of Turkey in the year 2010. (Hamzaoğlu, Aksoy, Martin, Pınar, & Çölgeçen, 2010). However, there have been no prior biological or chemical investigations conducted on S. *ketzkhowelii*.

As antibiotic resistance continues to rise, there is an escalating demand for the exploration of novel antimicrobial agents. Given the promising potential of plants in this context, it is imperative to investigate their antimicrobial properties. This study seeks to evaluate the antimicrobial activities of petroleum ether, dichloromethane, ethyl acetate, and n-butanol fractions extracted from both the aerial and subaerial parts of *S. ketzkhowelii*. Additionally, the objective is to elucidate the chemical composition of the most potent fractions exhibiting antimicrobial activity through analysis using Liquid Chromatography with High Resolution Mass Spectrometry (LC-HRMS).

MATERIAL AND METHODS

Plant Material and Extraction

Specimens of *Scorzonera ketzkhovelii* were gathered from Yusufeli/Artvin, Turkey, situated at an elevation of 2122 m, during July 2019. A voucher specimen has been archived under the reference number ISTE 115803 at Istanbul University.

The aerial and subaerial components of *S. ketzkhowelii* were subjected to air-drying while safeguarding them from direct sunlight and 100 grams of each part were subjected to ethanol extraction via the percolation technique. The ethanol extract obtained was concentrated at 45°C through the use of a rotary evaporator. The resultant dried ethanol extracts (aerial part 10,95 g; subaerial part 11,76 g) were then reconstituted in an ethanol/water mixture (1:2) and successively subjected to extraction with petroleum ether, dichloromethane, ethyl acetate, and n-butanol solvents. All fractions underwent investigation for antimicrobial activity, with dichloromethane extracts utilized for LC-HRMS analysis.

Antimicrobial Activity

The Minimum Inhibitory Concentration (MIC) values of the fractions were validated against reference strains using the microdilution method in accordance with the criteria established by the Clinical Laboratory Standards Institute (CLSI). (CLSI, 2000, 2006).

Three Gram-positive standard test bacteria: (*Enterococcus feacalis* ATCC 29212), (*Staphylococcus epidermidis* ATCC 12228), (*Staphylococcus aureus* ATCC 29213); four Gram-negative standard test bacteria: (*Escherichia coli* ATCC 25922), (*Klebsiella pneumoniae* ATCC 4352), (*Proteus mirabilis* ATCC 14153), (*Pseudomonas aeruginosa* ATCC 27853); three yeasts (*Candida albicans* ATCC 10231), (*Candida parapsilosis* ATCC 22019), (*Candida tropicalis* ATCC 750) were used for testing the activity. All microorganisms were purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA).

The fractions derived from the subaerial and aerial parts ethanol extracts of *S. ketzkhovelii*, namely petroleum ether, dichloromethane, ethyl acetate, and n-butanol, were formulated at a concentration of 10,000 mg/L in DMSO (Dimethyl sulfoxide) solvent. Subsequently, serial twofold dilutions spanning from 5000 mg/L to 2.4 mg/L were prepared in the growth medium.

The inoculum for each bacterium was prepared from a 4–6 hour broth culture, while each yeast strain was cultured for 24 hours. The inocula were adjusted to a turbidity equivalent to a 0.5 McFarland standard, then diluted in Mueller-Hinton broth (Difco, Detroit, USA) to achieve a final concentration of 5×10^5 colony-forming units per milliliter (cfu/ml) for bacteria. For yeast, the inocula were diluted in RPMI-1640 medium (Sigma-Aldrich) buffered with 0.165 M MOPS (morpholinepropanesulfonic acid; Sigma-Aldrich, Steinheim, Germany) to a pH of 7.0, resulting in a final concentration of 0.5–2.5 $\times 10^3$ cfu/ml in the test tray. The trays were covered and placed in plastic bags to prevent evaporation. Incubation occurred at 35°C for 18–24hours for trays containing Mueller-Hinton and at 35°C for 46–50 hours for those containing RPMI-1640 medium.

The MIC was characterized as the minimum concentration of the fractions that resulted in total inhibition of observable growth. Reference materials such as Cefuroxime, Ceftazidime, Clotrimazole, Ampicillin, and Amphotericin B were used, and all experiments were conducted in triplicate.

Preparation of Samples for LC-HRMS Analysis

To prepare the dichloromethane fractions of *S. ketzkhowelii*, 50 mg of dried material from both the aerial and subaerial parts were dissolved in methanol in a volumetric flask. The flask was then placed in an ultrasonic bath to achieve a clear solution. Subsequently, a solution of dihydrocapsaicin, employed as an internal standard, was introduced.

Instruments and Chromatographic Conditions of LC-HRMS

LC-HRMS experiments were conducted using a Thermo ORBITRAP Q-EXACTIVE mass spectrometry system based in

Bremen, Germany, equipped with a Troyasil C18 HS column (150 mm x 3 mm, 5 µm particle size, İstanbul, Turkey). The mobile phases A and B consisted of 1% formic acid-water and 1% formic acid-methanol, respectively. The gradient program was as follows: 0-1.00 min with 50% A and 50% B, 1.01-6.00 min with 100% B, and finally, 6.01-15 min with 50% A and 50% B. The flow rate of the mobile phase was set at 0.35 mL/min, the injection volume at 10 µL, and the column temperature at 220°C.

Compound identification was achieved by comparing the retention times of standard compounds (with a purity range of 95-99%, as specified in the chemicals section) and HRMS data from the Bezmialem Vakıf University Drug Application and Research Center Library. Dihydrocapsaicin (purity 95%) served as an internal standard in LC-HRMS measurements to mitigate repeatability issues arising from external factors such as ionization repeatability in mass spectrometry measurements.

RESULTS AND DISCUSSION

In previous investigations involving *Scorzonera* species, assessments of antimicrobial activity were conducted on fractions derived from ethanol/methanol crude extracts (Şahin, Sarı, Özsoy, Özbek Çelik, & Koyuncu, 2020a, 2020b; A. Sarı, Şahin, Özsoy, & Özbek Çelik, 2019). Consistent with these earlier protocols, the present study adopted a comparable approach, subjecting the fractions to similar analyses. The ethanol extract of the plant was obtained using the percolation method to obtain a spectrum of apolar-polar compounds. These compounds were subsequently segregated into sub-fractions using four solvents with varying polarities (petroleum ether, dichloromethane, ethyl acetate, n-butanol). The examination aimed to elucidate the correlation between the polarity of the fractions and their antimicrobial activities.

Table 1 presents the antimicrobial activity of all the fractions. The results demonstrate the effectiveness of the fractions in inhibiting the growth of the selected microorganisms *in vitro*, as evidenced by minimum inhibitory concentration (MIC) values falling within the range of 625 mg/L to 39 mg/L.

The current study revealed that both the petroleum ether and dichloromethane fractions obtained from aerial parts displayed antimicrobial activity against both gram-positive and gram-negative bacteria. The dichloromethane fraction, in particular, exhibited a more potent antibacterial effect against a broader spectrum of bacteria. All fractions, except for the petroleum ether fraction derived from aerial parts, displayed antimicrobial activity against *Candida parapsilosis.* Furthermore, the petroleum ether fraction from aerial parts demonstrated an anticandidal effect at 39 mg/L against *Candida tropicalis*.

These observations align with earlier research findings. In the investigation of antimicrobial activity carried out on n-hexane, chloroform, ethyl acetate, and water fractions derived from the methanol extract of *Scorzonera aucheriana* DC.'s aerial parts, it was observed that the chloroform fraction exhibited potent antimicrobial activity against all tested microorganisms (Erik, Yalçın, Coşkunçelebi, Alpay Karaoğlu, & Yaylı, 2022). Similarly, a study on *Scorzonera sandrasica* Hartvig & Strid revealed that the chloroform extract displayed robust inhibitory activity against bacteria belonging to *Stenotrophomonas maltophilia* and *Staphylococcus aureus* species (Ugur, Sarac, Ceylan, Duru, & Beyatli, 2010). In the antimicrobial study of *Scorzonera undulata* Vahl, the petroleum ether fraction demonstrated significant antimicrobial efficacy specifically against *S. aureus*, with a minimum inhibitory concentration (MIC) of 500 mcg/mL (Ben Abdelkader et al., 2010). Conversely, *S. pygmaea* Sibth. & Sm. and *S. hieraciifolia* Hayek species exhibited notably weak antimicrobial effects in studies conducted by (Şahin et al., 2020a) and (A. Sarı et al., 2019).

Aerial dichloromethane fraction showed higher antimicrobial activity compared to other extracts. For this reason, the chemical content of the aerial dichloromethane fraction was investigated in comparison with the content of the subaerial dichloromethane extract. Detected compounds in R2 (Dichloromethane fraction of the subaerial parts of *Scorzonera ketzkhowelii*) and H2 (Dichloromethane fraction of the aerial parts of *Scorzonera ketzkhowelii*) by LC- HRMS were given in Table 2, molecule drawings were given in Table 3, and LC-HRMS chromatograms were given in Figure 1-2.

As a result of LC-HRMS analysis, detected phenolic compounds in both dichloromethane fractions of the aerial and subaerial parts were: 3,4-dihydroxybenzaldehyde, salicylic acid, dihydrocaffeic acid, caffeic acid, caffeic acid phenethyl ester, chlorogenic acid, quercetin, hyperoside, naringenin, apigenin, hispidulin, hispidulin 7-glucoside, chrycin, emodin and carnosic acid. Chlorogenic acid was the major compound in both fractions.

In addition to these compounds, homogentisic acid, verbascoside, (+)-trans taxifolin, apigenin 7-glucoside, luteolin, orientin and chrysoeriol phenolic compounds were also detected in the H2.

Furthermore, the H2 fraction contained quantities exceeding 1 g/kg of chlorogenic acid, quercetin, hyperoside, caffeic acid, salicylic acid, naringenin, hispudilin, hispudilin 7-glucoside, and luteolin compounds. Similarly, the R2 fractions exhibited concentrations of chlorogenic acid, naringenin, and caffeic acid exceeding 1 g/kg.

Phenolic compounds derived from plants, including phenolic acids, flavonoids, stilbenes, and tannins, have the capability to hinder the growth and functions of numerous microorganisms, encompassing food-related pathogens and clinically significant bacteria, fungi, and protozoa (Ávila, Smânia, Monache, & Smânia, 2008; Batovska et al., 2009; Nielsen, Boesen, Larsen, Schønning, & Kromann, 2004). Due to the structural and chemical diversity among these various molecules, they can mani-

Table 1. Antimicrobial activity results of *Scorzonera ketzkhowelii* fractions (MIC mg/L)

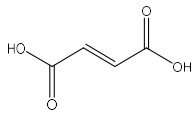
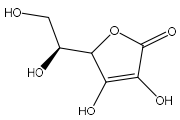
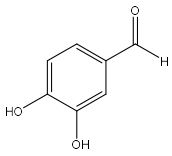
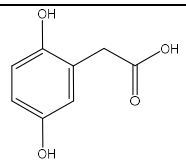
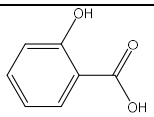
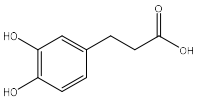
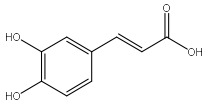
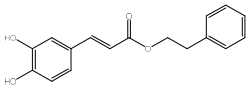
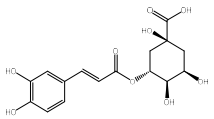
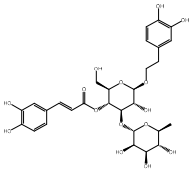
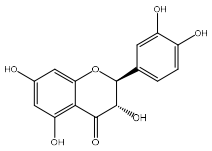
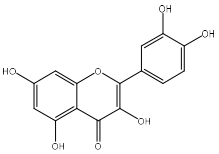
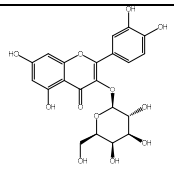
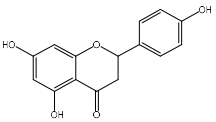
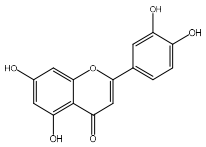
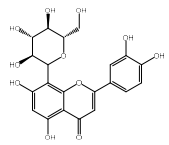
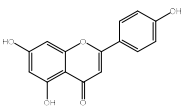
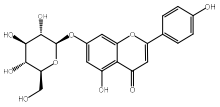
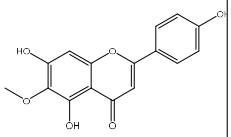
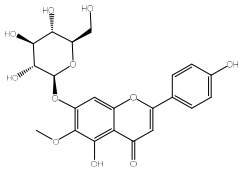
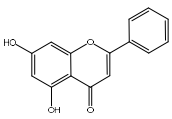
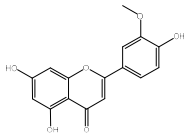
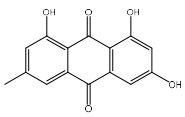
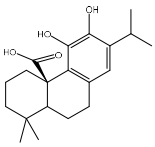
	P. aeruginosa ATCC 27853	*E. coli* ATCC 25922	*K. pneumoniae* ATCC 4352	*P. mirabilis* ATCC 14153	*E. faecalis* ATCC 29212	*S. epidermitidis* ATCC 12228	*S. aureus* ATCC 29213	*C. albicans* ATCC 10231	*C. parapsilosis* ATCC 22019	*C. tropicalis* ATCC 750
H1	625	-	-	-	312.5	625	312.5	-	-	39.06
H2	-	312.5	625	625	625	625	312.5	-	312.5	-
H3	-	-	-	-	-	-	-	-	312.5	-
H4	-	-	-	-	-	-	-	-	312.5	-
R1	-	-	-	-	-	-	-	-	312.5	-
R2	-	-	-	-	-	-	-	-	312.5	-
R3	-	-	-	-	-	-	-	-	312.5	-
R4	-	-	-	-	-	-	-	-	312.5	-
Standarts	Seftazidim pentahidrat	Sefuroksim Na	Sefuroksim Na	Sefuroksim Na	Ampisilin Na	Sefuroksim-Na	Sefuroksim-Na	Klotrimazol	Amfoterisin B	Amfoterisin B
	2.4	4.9	4.9	2.4	8.0	9.8	1.2	4.9	0.5	1

H1: Petroleum ether fraction of aerial part, H2: Dichloromethane fraction of aerial part, H3: Ethyl acetate fraction of aerial part, H4: n-Butanol fraction of aerial part R1: Petroleum ether fraction of subaerial part R2: Dichloromethane fraction of subaerial part, R3: Ethyl acetate fraction of subaerial part, R4: n-Butanol fraction of subaerial part. The antimicrobial activity results of fractions are expressed as the MIC (Minimum Inhibitory Concentration) determined by the microdilution method.

Table 2. Detected compounds in R2 and H2 by LC- HRMS

	Compounds	R2	mg/kg	H2	mg/kg	U (%)
1	Ascorbic acid	3.38	124.64	5.68	215.11	3.94
2	Chlorogenic acid	640.51	23591.49	208.53	7899.02	3.58
3	Fumaric acid	143.99	5303.54	196.93	7459.28	2.88
4	Verbascoside	-	<LOD	0.09	3.33	2.93
5	Orientin	-	<LOD	5.86	222.01	3.67
6	Caffeic acid	36.69	1351.53	123.60	4681.97	3.74
7	(+)-*trans* taxifolin	-	<LOD	0.82	31.06	3.35
8	Hyperoside	0.88	32.23	169.24	6410.49	3.46
9	Apigenin 7-glucoside	-	<LOD	0.85	32.31	3.59
10	Quercetin	0.37	13.70	184.32	6981.78	2.95
11	Salicylic acid	8.59	316.21	117.04	4433.45	1.89
12	Naringenin	45.99	1694.03	71.70	2715.91	4.20
13	Luteolin	-	<LOD	69.07	2616.36	3.42
14	Apigenin	2.86	105.27	17.96	680.30	2.87
15	Hispidulin	0.24	8.69	80.43	3046.48	3.41
16	Caffeic acid phenethyl ester	0.01	0.48	0.02	0.61	3.13
17	Chrysin	1.49	54.95	1.74	65.98	3.24
18	Emodin	0.00	0.07	0.01	0.23	4.27
19	Homogentisic acid	-	<LOD	7.18	272.12	4.35
20	3,4-Dihydroxybenzaldehyde	0.49	17.97	2.20	83.37	3.79
21	Hispidulin 7-glucoside	1.76	64.64	71.39	2704.20	4.57
22	Carnosic acid	0.04	1.51	0.18	6.89	2.58
23	Dihydrocaffeic acid	0.39	14.48	0.46	17.35	0.86
24	Chrysoeriol	-	<LOD	20.32	769.55	2.08

Table 3. Detected compounds in *S. ketzkhowelii* Grossh. dichloromethane fraction by LC- HRMS

 **Fumaric acid**	 **Ascorbic acid**	 **3,4-Dihydroxybenzaldehyde**	 **Homogentisic acid**
 **Salicylic acid**	 **Dihydrocaffeic acid**	 **Caffeic acid**	 **Caffeic acid phenethyl ester**
 **Chlorogenic acid**	 **Verbascoside**	 **(+)-*trans* taxifolin**	 **Quercetin**
 **Hyperoside**	 **Naringenin**	 **Luteolin**	 **Orientin**
 **Apigenin**	 **Apigenin 7-glucoside**	 **Hispidulin**	 **Hispidulin 7-glucoside**
 **Chrysin**	 **Chrysoeriol**	 **Emodin**	 **Carnosic acid**

fest a range of antimicrobial effects, such as permeabilizing and destabilizing the cell membrane or inhibiting extracellular enzymes (Suresh Babu et al., 2005).

Indeed, it was observed that the H2 fraction contained a higher concentration of phenolic compounds compared to the R2 fraction. Therefore, it is logical to expect it to exhibit potent antimicrobial activity. However, the question arises as to why, despite the anticipation of a higher phenolic content in the ethyl acetate fraction compared to the dichloromethane fraction, the ethyl acetate fractions did not demonstrate antimicrobial activity on the same scale. One possible explanation could be the presence of terpenic compounds in the dichloromethane fraction, which are known to exhibit strong antimicrobial activity, in addition to phenolic compounds (Erik et al., 2022; Aynur Sarı, Özbek, & Özgökçe, 2009; Sweidan et al., 2020). Furthermore, it is worth noting that the phenolic compounds in the ethyl acetate fraction are primarily present in the form of sugar-bound glycosides, whereas those in the dichloromethane fraction are predominantly in their aglycone form. Literature indicates that apolar phenolics, aglycone forms are reported to be more potent in terms of antimicrobial activity, thus supporting the consistency of our results with existing literature and lending further credence to it (Miklasińska-Majdanik, Kępa, Wojtyczka, Idzik, & Wąsik, 2018; Takó et al., 2020).

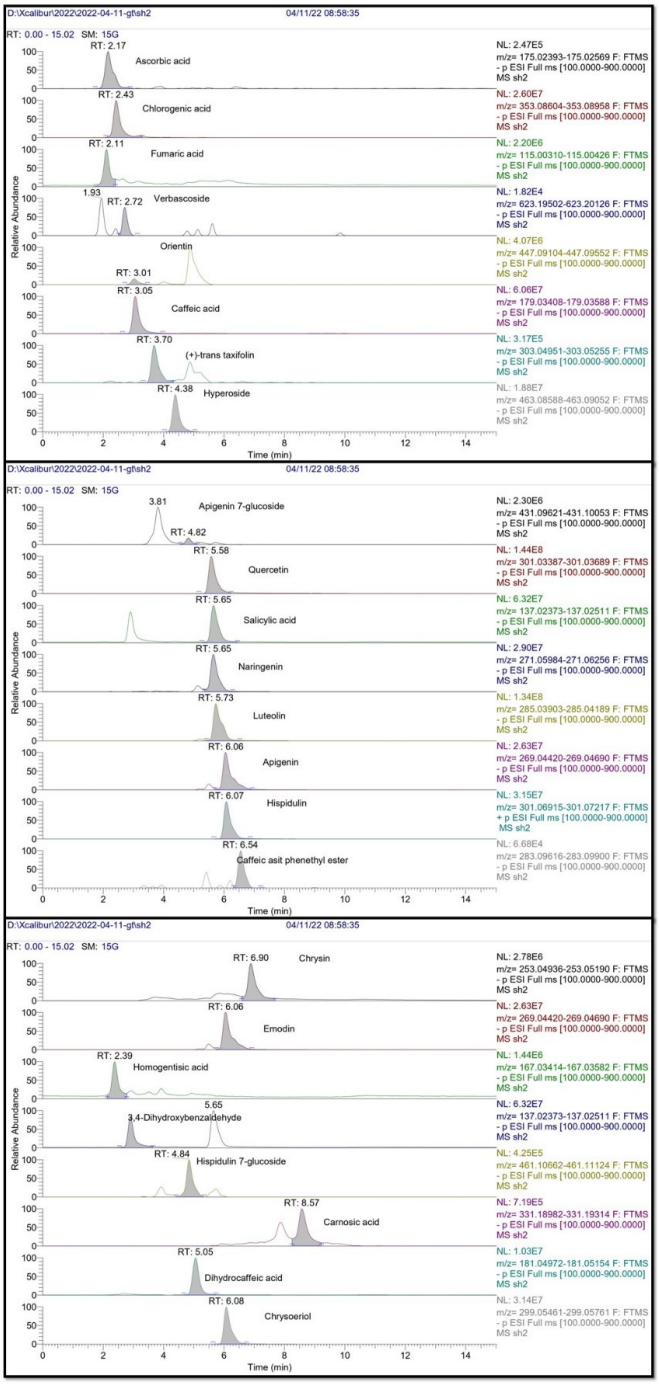


Figure 1. LC-HRMS chromatogram of H2 (Dichloromethane fraction of the aerial part)

CONCLUSION

In this study, which was carried out for the first time on the *Scorzonera ketzkhowelii* species, the antimicrobial activities of petroleum ether, dichloromethane, ethyl acetate and n-butanol fractions obtained from the ethanol extract of the plant were revealed. As a result of the study, dichloromethane fractions of the plant exhibited strong antimicrobial activity. Based on this, the phenolic chemical contents of these dichloromethane

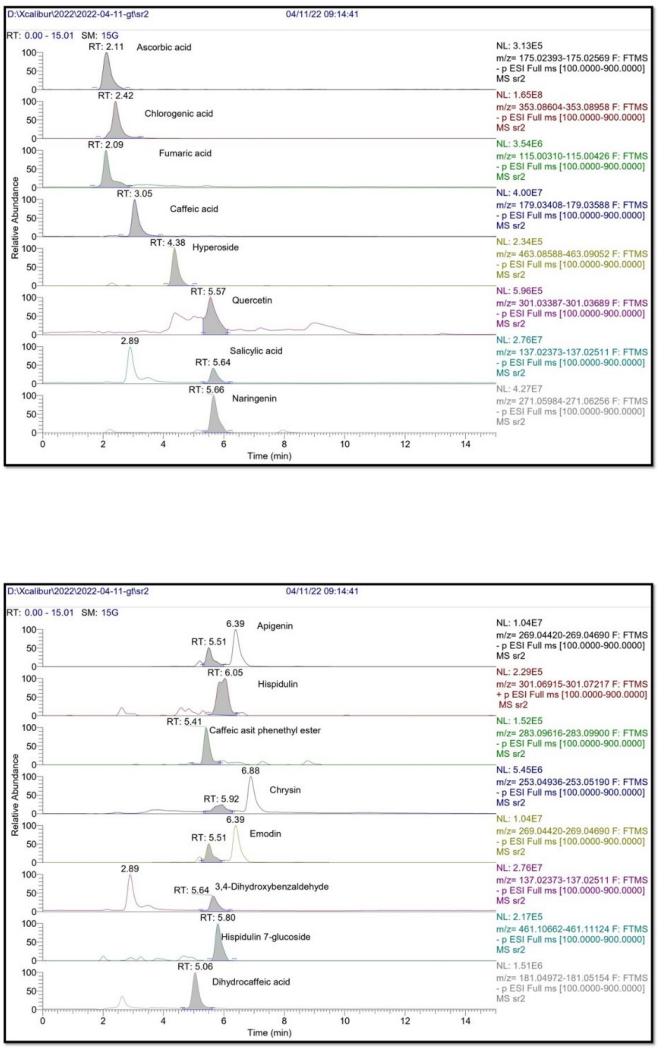


Figure 2. LC-HRMS chromatogram of R2 (Dichloromethane fraction of the subaerial part)

fractions were determined by the LC-HRMS method and their relationship with antimicrobial activity was explained. Studies have demonstrated that phenolic compounds derived from natural origins display robust antimicrobial activity against a range of clinically significant pathogens linked to microbial infections. Moreover, they enhance the susceptibility of multi-drug resistant strains to bactericidal or bacteriostatic antibiotics.

The antimicrobial activity study results of the *Scorzonera ketzkhowelii* species confirm each other with previous studies showing that phenolic compounds obtained from natural sources exhibit potent antimicrobial activity against a number of clinically important pathogens associated with microbial infections. Moreover, in this study, it is thought that the dichloromethane fraction exhibits stronger antimicrobial activity than the ethylacetate fraction, and that the nonpolar phenolic compounds found in the plant may exhibit stronger antimicrobial activity than the polar phenolic compounds, and that the antimicrobial effect of the phenolic compounds with other, es-

pecially terpenic compounds, found in the dichloromethane fraction may be strengthened with a synergistic effect.

These findings not only provide valuable insights into the antimicrobial potential of *Scorzonera ketzkhowelii* but also expand our knowledge of its chemical composition. The plant's antimicrobial properties and the presence of diverse phenolic compounds make it a promising candidate for further research and potential applications in the field of medicine and pharmaceuticals. Further investigations into its bioactivity and potential health benefits may uncover new avenues for its utilization.

This is the first chemical composition analysis and antimicrobial activity report for the *Scorzonera ketzkhowelii*. This plant could be evaluated for further phytochemical and other biological activity search.

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