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Biological activity and chemical composition of the essential oil from the fruits of *Ferula rigidula* Fisch. ex DC.

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ABSTRACT

The hydro-distilled essential oils of the fruits of *F. rigidula* Fisch. ex DC. was analyzed by Gas Chromatography (GC) and Gas Chromatography/Mass Spectrometry (GC/MS) systems at the same time. Thirty-one compounds were characterized representing 98.2% of the essential oils. The main components of the oil were determined as α-pinene and camphene (24% and 20%, respectively). The anticandidal and antibacterial effects of the essential oil were determined by using partly modified CLSI protocols M27-A2 and M7-A7, respectively. The essential oil of the dried fruits showed several inhibitory effects on the tested bacteria panel (MIC, 62.5 to 2000 μg/mL) and *Candida* species (MIC, 125 to 1000 μg/mL).

Keywords: Antibacterial; anticandidal; *Ferula rigidula* ;essential oil; GCMS

INTRODUCTION

Ferula L., one of the largest genera in Apiaceae, has more than 220 species[1] and is found from central Asia to the Mediterranean region and northern Africa[2]. The genus is represented by 26 species, 15 of which are endemic in the Flora of Turkey[3-4]. *Ferula rigidula* Fisch. ex DC. is distributed throughout Türkiye's Central and Eastern Anatolia regions and adjacent areas of neighboring countries[3]. *F. rigidula* is known as "Çağşır, Çakşır". Leaves of *F. rigidula* have been used as vegetable and food products in Türkiye[5]. Aerial parts of *F. rigidu-*

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la have been used in traditional medicine to treat diabetes and hypercholesterolemia in Anatolia[6]. Different parts of *F. elaeochytris* Korovin[6,7], *F. orientalis* L.[6,8], *F. capsica* M. Bieb.[6], and *F. longipedunculata* Peşmen[9] have been used in traditional medicine as an aphrodisiac, immunostimulant, antidiabetic, and for treatment of gastric pain and gynecologic diseases in Türkiye. Several *Ferula* species have been used in folk medicine to treat neurological disorders, stomachache, hysteria, epilepsy, infant colitis, rheumatism, headache, asthma, inflammations, dysentery, digestive disorders, dizziness, bronchitis, influenza, and arthritis and as a tranquilizer, antidiabetic, antipyretic, muscle relaxant, and antispasmodic[10,11].

Recent studies have shown various species of *Ferula,* and their constituents have hypotensive, gastroprotective, neuroprotective, anti-oxidant, hepatoprotective, memory-enhancing, antimicrobial, anti-obesity, anticarcinogenic and anthelmintic effects[11-14]. Biological and pharmacological studies indicate that the extracts and compounds of the genus *Ferula* have various biological activities, such as antibacterial[14,15], antiparasitic[15], anti-inflammatory[16,17], antioxidant[17], antihypertensive[18], antiviral[19,20], α-amylase and α-glucosidase inhibitory activity[21] and cytotoxic[15, 22-24].

The main phytochemical components in the genus *Ferula* are coumarins, coumarin ethers, sesquiterpenes, sesquiterpene lactones, sesquiterpene esters, monoterpenes, monoterpene coumarins, prenylated coumarins, sulfur-containing compounds, phytoestrogen, flavonoids, and carbohydrates[16,25].

Several bioactivities of the different *Ferula* species essential oils have been reported, such as insecticidal, antimicrobial, immunomodulator, anti-acetylcholinesterase, antispasmodic, neuroprotective, anti-oxidant, anxiolytic, α-amylase and tyrosinase inhibitory, antileishmanial and cytotoxic,[21, 26-32].

Previously daucane esters[33] and humulane[34] complex esters from the hexane extract of *Ferula rigidula* roots have been reported.

A previous study reported that the aerial parts methanol extract of *F. rigidula* exhibited antibacterial, antifungal, antioxidant, α-amylase, α-glucosidase, cytotoxic, tyrosinase and cholinesterase inhibitory activity and total phenolic and total flavonoid contents[35].

In the present study, hydrodistilled essential oil of *Ferula rigidula* fruits was analyzed by GC and GC-MS systems simultaneously and evaluated for their antibacterial and antifungal activity by using broth micro-dilution methods.

METHODOLOGY

Plant material

The plant material was collected from Hasan Mountain in Aksaray, Türkiye in July 2012. A voucher specimen identified by Prof. Dr. H. Duman (Gazi University, Ankara) is kept at the Herbarium of Gazi University in Ankara, Türkiye (GAZI 9898000001575).

Isolation of the essential oil

Dried and crushed fruits of *F. rigidula* were subjected to hydro-distillation for 3 h using a Clevenger-type apparatus. The oil yield of the fruits was 0.8 % on a moisture-free basis. The oil was dried over anhydrous sodium sulfate and stored in sealed vials in the dark, at 4°C, ready for GC and GC/MS analyses and antimicrobial testing.

GC and GC/MS conditions

The oil was analyzed by capillary GC and GC/MS using an Agilent GC-MSD system (Agilent Technologies Inc., Santa Clara, CA).

GC/MS: The GC/MS analysis was carried out with an Agilent 5975 GC-MSD system. Innowax FSC column (60m x 0.25mm, 0.25μm film thickness) was used with helium as carrier gas (0.8 mL/min.). GC oven temperature was kept at 60°C for 10 min and programmed to 220°C at a rate of 4°C/min, and kept constant at 220°C for 10 min and then programmed to 240°C at a rate of 1°C/min. Split ratio was adjusted 40:1. The injector temperature was at 250°C. MS were taken at 70 eV. Mass range was from *m/z* 35 to 450.

GC: The GC analysis was done with an Agilent 6890N GC system fitted with a FID detector set at a temperature of 300 °C. To obtain the same elution order with GC/MS, simultaneous auto-injection was done on a duplicate of the same column applying the same operational conditions. Relative percentage amounts of the separated compounds were calculated from FID chromatograms.

Identification of compounds

The components of essential oil were identified by comparison of their mass spectra with those in the Baser Library of Essential Oil Constituents, Wiley GC/MS Library, Adams Library, Mass Finder Library and confirmed by comparison of their retention indices. Alkanes were used as reference points in the calculation of relative retention indices (RRI). Relative percentage amounts of the separated compounds were calculated from FID chromatograms. The results of the analysis are shown in Table 1.

Antimicrobial assay

Antibacterial and anticandidal effects of the samples were evaluated by using partly modified CLSI (formerly NCCLS) microdilution broth methods M7-A7 and M27-A2, respectively[41,42]. Different from the protocol essential oil solution were diluted between the concentration of 8000 to 15.6 μg/mL in DMSO.

Escherichia coli NRRL B-3008, *Pseudomonas aeruginosa* ATCC 27853, *Salmonella typhimurium* ATCC 13311, *Bacillus cereus* NRRL B-3711, *B. subtilis* NRRL B-4378, *Serratia marcescens* NRRL B-2544, *Staphylococcus epidermidis* ATCC 12228, *E. coli* O157:H7 RSSK 234 (RSSK; RSHM National Type Culture Collection Strains of Bacteria), two different strains of *Candida albicans* (clinically isolated, Osmangazi University, Faculty of Medicine, Department of Microbiology and ATCC 90028), *C. utilis* NRRL Y-12968, *C. krusei* NRRL Y-7179, *C. glabrata* (clinically isolated, Osmangazi University, Faculty of Medicine, Department of Microbiology and ATCC 90028) were used as the test microorganisms. Chloramphenicol (Merck), Ampicillin (Merck), Amphotericin-B (Sigma-Aldrich), and Ketoconazole (Sigma-Aldrich) were used as standard antimicrobial agents.

RESULTS AND DISCUSSION

Hydrodistilled essential oil yield was 0.8% (v/w on dry weight basis). According to GC and GC/MS analysis results thirty-one compounds representing 98.2% of the oil were characterized and given in Table 1 with their relative percentages. The essential oil yield obtained was 0.8% (v/w). α-Pinene (23.8%), camphene (19.6 %), germacrene D-4-ol (8.1%) and δ-cadinene (5.6%) were the main components.

About 60.0% of the essential oil consisted of monoterpene hydrocarbon compounds (α-pinene 23.8%; camphene 19.6 %; limonene 4.1%; myrcene 3.6%; β-pinene 2.7%; sabinene 2.5%), followed by sesquiterpenes hydrocarbons and oxygenated sesquiterpenes 18.5% (δ-cadinene 5.6%; germacrene B 3.7%; germacrene D 2.8%; bicyclogermacrene 2.3%) and 15.7% (germacrene D-4-ol 8.1%; α-cadinol 4.7%; T-muurolol 1.7%) respectively (Table 1).

Table 1. The Chemical composition of the essential oils of *F. rigidula*

RRIa	RRIb	Compounds	%	IM
1032	1032[36] 1008-1039[37]	a-Pinene	23.8	t_R, MS
1076	1076[36] 1043-1086[37]	Camphene	19.6	t_R, MS
1100	1100[40]	Undecane	0.4	MS
1118	1118 [36] 1085-1130[37]	b-Pinene	2.7	t_R, MS
1132	1132[36] 1098-1140[37]	Sabinene	2.5	t_R, MS
1159	1122-1169[37] 1159[38]	d-3-Carene	0.8	t_R, MS
1174	1174 [36, 38] 1140-1175[37]	Myrcene	3.6	t_R, MS
1203	1203[36,38] 1178-1219[37]	Limonene	4.1	t_R, MS
1210	1188-1233[37]	b-Phellandrene	1.1	t_R, MS
1255	1255[36,38] 1222-1266[37]	g-Terpinene	tr	t_R, MS
1280	1280[36,38] 1246-129[37]	p-Cymene	0.5	t_R, MS
1290	1290[36] 1261-1300[37]	Terpinolene	1.3	t_R, MS
1497	1497 [36] 1462-1522[37]	a-Copaene	0.2	MS
1549	1549[36]	b-Cubebene	0.3	t_R, MS
1590	1592[36] 1549-1597[37]	Bornyl acetate	3.6	t_R, MS
1600	1565-1608[37]	b-Elemene	0.2	MS
1612	1612[36]	b-Caryophyllene	1.0	t_R, MS
1650	1650[36]	g-Elemene	0.7	t_R, MS
1694	1722[39]	Bicyclosesquiphellandrene	0.1	MS
1726	1726[36] 1676-1726[37]	Germacrene D	2.8	MS
1740	1740[36]	a-Muurolene	0.9	t_R, MS
1755	1755 [36] 1692-1757[37]	Bicyclogermacrene	2.3	t_R, MS
1772	1773[36, 38] 1722-1774[37]	d-Cadinene	5.6	t_R, MS

1776	1776[36] 1735-1782[37]	g-Cadinene	0.7	t_R, MS
1854	1778-1854[37]	Germacrene B	3.7	MS
1904	1854-1928[37]	Epicubebol	0.2	MS
1957	1884-1964[37]	Cubebol	0.2	MS
2069	2000-2070[37]	Germacrene D-4-ol	8.1	MS
2187	2136-2200[37] 2187[38]	T-Cadinol	0.8	MS
2209	2205[36] 2153-2209[37]	T-Muurolol	1.7	t_R, MS
2255	2255[36] 2180-2255[37,38]	a-Cadinol	4.7	t_R, MS
		Monoterpene hydrocarbons	60.0	
		Sesquiterpenes hydrocarbons	18.5	
		Oxygenated sesquiterpenes	15.7	
		Others	4.0	
		Total %	98.2	
		Number of compounds	31	

RRI[a]: RRI Relative retention indices experimentally calculated against *n*-alkanes; RRI[b]: RRI from literature [36-40] for polar column values; % calculated from FID data; t;Trace (<0.1 %); IM: Identification Method: t_R, Identification based on comparison with co-injected with standards on a HP Innowax column; MS, identified on the basis of computer matching of the mass spectra with those of the libraries.

Previously, the fruit essential oil of another three population (Ankara, *Çubuk* Dam; Malatya, Sürgü-Erkenek and Malatya, Doğanşehir-Polat in 2002) of *Ferula rigidula* were analyzed. Fruits essential oils were characterized by the presence of camphene (15%), α-pinene (13%), δ-cadinene (13%), α-cadinol (10%) and germacrene D-4-ol (10%) from Ankara; α-pinene (60%), β-pinene (14%), tricyclene (8%), naphthalene (6%) and eremophilene (3%) from Malatya, Sürgü-Erkenek; α-pinene (68%), tricyclene (9%) and β-pinene (4%) from Malatya, Doğanşehir-Polat[43].

According to microdilution broth assays the essential oil of *F. rigidula* fruits was demonstrated weak to moderate antimicrobial effects having MIC values of 62.5 to 2000 mg/ml when compared to standard agents. Interestingly *B.*

subtilis was the most susceptible strain that inhibited at the concentration of 62.5 mg/ml of the oil (Table 2). *B. subtilis* has been associated with foodborne illness with vomiting and diarrhea was also frequently reported[44].

Table 2. Antibacterial effect of *F. rigidula* essential oil (MIC, µg/mL)

Microorganisms	EO	S1	S2
Escherichia coli	2000	3.9	1
Pseudomonas aeruginosa	1000	62.5	15.6
Salmonella typhimurium	1000	3.9	1
Bacillus cereus	1000	7.8	1
Bacillus subtilis	62.5	1.9	1
Serratia marcescens	1000	15.6	15.6
Staphylococcus epidermidis	2000	3.9	1
E. coli O157:H7	2000	3.9	1

EO: Dried fruits essential oil of *F. rigidula*, **S1:** Chloramphenicol, **S2:** Ampicillin

Tested *Candida* species were inhibited by the essential oil in the range of 125 to 2000 mg/ml. *C. albicans* and *C. utilis* were the most susceptible strains in the test panel (Table 3). To our knowledge, no previous study has been published about the antimicrobial effects of *F. rigidula* essential oil. In a previous study, methanol extract of the roots of *F. rigidula* was evaluated for its antimicrobial activity against 7 different pathogenic bacteria and 8 fungi[45]. Minimal inhibitory concentrations of the extract were 270 to 1500 mg/ml against bacteria panel while the antifungal growth inhibition doses were between the 100 to 750 mg/ml.

Table 3. Anticandidal effect of *F. rigidula* essential oil (MIC, µg/mL)

Microorganisms	EO	S1	S2
*Candida albicans**	125	0.05	0.1
Candida utilis	125	1.6	0.05
Candida tropicalis	2000	0.2	0.2
Candida krusei	500	1.6	0.2
Candida albicans	1000	0.1	0.2
Candida glabrata	500	3.2	0.2

EO: Dried fruits Essential Oil of *F. rigidula*, **S1:** Ketoconazole,
S2: Amphotericin-B, *: Clinically isolated strain,

Essential oils appear to be a possible antimicrobial agents and option for synthetic substances, based on the so many research papers and reviews. There is a huge demand for the new bioactive natural alternatives for pharmaceutical and food industries[46-51].

In the present study, antibacterial and anticandidal potential of the essential oil obtained from the fruits of *F. rigidula* were evaluated for the first time here. As a foodborne pathogen *B. subtilis* was the most susceptible strain in the test panel. Further studies with various human and foodborne pathogens will demonstrate the therapeutic properties of this oil.

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