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Antifungal Compounds from the Rhizome and Roots of *Ferula hermonis*

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The antifungal activity of hexane, dichloromethane, methanol and aqueous extracts from the rhizome and root of *Ferula hermonis* was assayed *in vitro* by the agar disk diffusion method against a panel of human opportunistic and pathogenic fungi. Among them, the hexane and dichloromethane extracts showed the highest activity particularly against the dermatophytes *Microsporum gypseum* and *Tricophyton mentagrophytes* as well as the yeast *Candida lactis-condensi*. Activity-guided fractionation of both extracts using an agar overlay bioautographic method led to the isolation of two antifungal compounds which were identified as the daucane aryl esters jaeschkeanadiol *p*-hydroxybenzoate (ferutinin) and jaeschkeanadiol benzoate (teferidin). Determination of minimal inhibitory concentration (MIC) and minimal fungicidal concentration (MFC) values of both compounds evidenced a stronger antifungal activity for ferutinin than for teferidin. Particularly, *T. mentagrophytes* was the most sensitive strain with MIC and MFC values ranging from 8 to 256 μg/mL. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: Ferula hermonis; jaeschkeanadiol *p*-hydroxybenzoate; jaeschkeanadiol benzoate; antifungal activity; dermatophytes.

INTRODUCTION

Fungal diseases have emerged as important public health problems with a high economic cost. Fungal infections in humans, in particular those involving skin and mucosal surfaces, have increased considerably in the last decades, especially in tropical and subtropical countries, dermatophytes and *Candida* sp. being the most frequent pathogens. Furthermore, a dramatic increase of cases of immunocompromised patients which frequently develop opportunistic and superficial mycoses has been also reported in the last years (Pfaller and Diekema, 2007).

Although at present several antimycotic drugs are available, its use is limited by a number of factors such as low potency, poor solubility, drug toxicity and emergence of resistant strains due in part to their intensive prophylactic use (Bastert *et al.*, 2001). Therefore, despite the progress in human medicine, there is a distinct need for the discovery of alternative new, safer and more effective antifungal agents (Abad *et al.*, 2007).

Natural products, either as pure compounds or as standardized herbal extracts, provide unlimited opportunities for new drug leads because of the unmatched availability of chemical diversity (Cos *et al.*, 2006). In recent years, many studies on the evaluation of antifungal activities of plant extracts have been carried out, and a number of reports on new antifungal agents from plants have been reported (Lang and Buchbauer, 2012; Abad *et al.*, 2007).

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The genus *Ferula* (Apiaceae), known as a good source of biologically active compounds, comprises about 170 species widely distributed throughout the Mediterranean area and Central Asia. Many of them have been employed since antiquity as sources of scented gum-resins used either for medicinal or culinary purposes. Several species of *Ferula* are appreciated in traditional medicine for the treatment of skin infections, stomach disorders, fever, dysentery, hysterias and as aphrodisiac (Al-Yahya *et al.*, 1998; Gamal-Eldeen and Hegazy, 2010). Hormonal effects and, more recently, cytotoxic and cancer preventing properties have been also investigated in plants of this genus (Lhuillier *et al.*, 2005; Poli *et al.*, 2005). Some of these activities have been related to sesquiterpene derivatives, mainly to those of the daucane type, such as ferutinin (Zanoli *et al.*, 2005; Zavatti *et al.*, 2006), a potent phytoestrogen which acts as an agonist for both estrogen receptors, ERα and ERβ (Ikeda *et al.*, 2002).

Particularly, *F. hermonis* Boiss. (in some papers referred as *F. harmonis*), a perennial shrub that grows on the Hermon mountain, between Lebanon and Syria, commonly known as 'Shirsh-el-Zallouh' which means hairy root, is used in the Middle East to improve sexual behavior in the treatment of frigidity and impotence (Auzi *et al.*, 2008; El-Taher *et al.*, 2001; Lev and Amar, 2002). Although some papers dealing on the sesquiterpene composition of different extracts (Al-Sha'er *et al.*, 2001; Auzi *et al.*, 2008; Diab *et al.*, 2001a, 2001b; Galal, 2000; Galal *et al.*, 2001; Ibraheim *et al.*, 2011; Lhuillier *et al.*, 2005) as well as on its antibacterial and insecticidal activities (Al-Nahar *et al.*, 2006; Al-Sha'er *et al.*, 2001; Galal *et al.*, 2001; Hilan *et al.*, 2007; Ibraheim *et al.*, 2011) have been previously published, little is known about its antifungal activity.

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With the aim of searching for new antifungal agents and to potentiate the use of natural resources, we recently report on the composition and antifungal activity of its essential oil against several yeasts and filamentous fungi. Particularly, a purified fraction with 73% of jaeschkeanadiol benzoate and the constituent 3,5-nonadiyne evidenced strong antifungal activity against the dermatophyte *T. mentagrophytes* (Al-Ja'fari *et al.*, 2011).

In order to further investigate on the antimycotic constituents of this species, the activity of different extracts from the rhizome and roots of *F. hermonis* was assayed against a panel of human opportunistic and pathogenic fungi, and a bioguided fractionation was performed to characterize the active fractions and/or constituents.

MATERIALS AND METHODS

General experimental procedures. Silica gel 60 (35–70 μm, SDS, France) and Sephadex® LH-20 (Pharmacia Biotech, Sweden) were used for preparative column chromatography. Precoated silica gel 60 F_{254} plates were used for analytical thin layer chromatography (TLC) (SDS, France) and for preparative TLC (20 × 20 cm; 2 mm thickness; Merck, Germany).

NMR spectra of **1** and **2** were recorded in $CDCl_3$, on a Varian VNMRS 400 MHz spectrometer using tetramethylsilane (TMS) as internal standard. MS were obtained with Agilent Technologies 5973 and 5975 Inert XL mass spectrometers.

Sabouraud dextrose agar (Panreac, Spain) and Sabouraud dextrose broth (Adsa, Spain) were used as culture media for the antifungal assays. Sterile paper disks were provided by Difco (diameter: 13 mm, ref. 1571–33). Nystatin, amphotericin B, ketoconazole and clotrimazole were purchased from Sigma Chemical (USA).

Plant material. Air-dried rhizome and roots of *Ferula hermonis* Boiss. (Apiaceae) were provided by The Jordanian Pharmaceutical Manufacturing Co. (Naor, Jordan). Voucher specimens were identified and deposited at the Herbarium of the University of Barcelona under No. BCN 51579.

Preparation of extracts. Powdered air-dried plant material was successively submitted to extraction with increasing polarity solvents: hexane, dichloromethane, methanol and water. Additionally, an aqueous decoction was also obtained.

The hexane extract was obtained by maceration of the plant material (25 g) in hexane at room temperature, shaking for 18 h. The extract was filtered and the dried plant residue submitted to dichloromethane extraction in a Soxhlet apparatus over 12 h. Once the extract was filtered, the extracted plant material was dried and later left to soak in methanol 95% at room temperature and shaked over 18 h. Then, the crude methanol extract was filtered, and the plant residue was dried and extracted with boiling water for 3 h.

All the filtered extracts were concentrated in vacuum to dryness. Methanol and aqueous extracts were subsequently lyophilized.

An additional aqueous extract was obtained by decoction of the plant material (25 g) in distilled water over 3 h. The solution was filtered, evaporated and lyophilized.

Fractionation of the hexane and dichloromethane extracts. Preparative TLC performed with the hexane extract (265 mg) on five precoated silica gel plates using hexane:EtOAc (75:25) as mobile phase gave eight fractions: F-1 to F-8. Subsequent fractionation of F-5 (131 mg) by column chromatography on Sephadex® LH-20 (column size 80 × 1 cm) using Cl_2CH_2:MeOH (1:1) as mobile phase and on silica gel 60 (column size 85 × 1.4 cm) eluting with hexane:EtOAc (80:20) finally afforded 61.7 mg of compound **1**.

2 g of the dicloromethane extract was submitted to preparative flash-chromatography (column size 60 × 4.5 cm) on silica gel 60 eluted with a gradient of petroleum ether:EtOAc:MeOH from (95:5:0) to (35:55:10) giving 18 fractions. Fraction 2 (130 mg) further submitted to column chromatography on Sephadex® LH-20 (column size 85 × 1.4 cm), using Cl_2CH_2:MeOH (1:1) as mobile phase, allowed the isolation of compound **2** (27 mg). Final purification of fraction 6 (921 mg) through Sephadex® LH-20 gave 915 mg of pure compound **1**.

Structure elucidation. Structure elucidation of **1** and **2** was achieved using standard spectroscopic techniques: ^{1}H NMR, ^{13}C NMR, DEPT, EI-MS and CI-MS. For complete assignments of ^{1}H and ^{13}C NMR signals, COSY, HMBC and HSQC 2D-NMR methods were applied.

Antifungal activity. The antifungal activity of the extracts as well as of its fractions and major constituents was assayed against eight yeasts and filamentous fungi strains.

Microorganisms, growth conditions, and preparation of fungal inocula. *Aspergillus fumigatus* CECT 2071, *A. niger* CECT 2574, *Candida albicans* CECT 1394, *C. lactis-condensi* CECT 1075, *Microsporum gypseum* CECT 2908, *Penicillium purpurogenum* CECT 20436, *Saccharomyces cerevisiae* CECT 1324 *and Trichophyton mentagrophytes* CECT 2795 were provided by the Colección Española de Cultivos Tipo (CECT), Valencia, Spain. Strains were grown on Sabouraud dextrose agar plates for 24 h at 30°C. Cell suspensions of yeasts in sterile NaCl 0.9% were adjusted at 0.5 McFarland to obtain approximately 10^6 CFU/mL. Spore suspensions of filamentous fungi were adjusted at 10^6 CFU/mL by plating 10 μL of four- and five-times serially diluted suspensions and counting germinated spores/dilution.

Paper disk-agar diffusion method. Antimycotic activities of the hexane, dichloromethane, methanol and aqueous extracts from the rhizome and roots of *F. hermonis* were first evaluated by the paper disk-agar diffusion method (Barry and Thornsberry, 1991). Test plates (diameter: 15 cm) were prepared with Sabouraud dextrose agar medium and inoculated in surface with cells and spores suspensions of yeasts and filamentous fungi.

Sterile paper disks impregnated with 100 μL of extract dilutions at concentrations of 50 and 100 mg/mL, as

previously reported (Portillo *et al*., 2001), or with 20 μL of a solution of 1 mg/mL of amphotericin B or nystatin as active reference compounds, were applied over the test plates. The diameters of the growth inhibition zones around each disk were measured after incubation at 30 °C for 48 h. For each extract, three replicate trials were conducted against each fungus.

Overlay bioautographic method. A bioautographic agar overlay method was used for the detection of the antifungal activity of the fractions of the extracts (Rahalison *et al*., 1991). Developed TLC plates of each fraction on precoated silica gel 60 F_{254} plates eluted with hexane-EtOAc (6:4) and (9:1) or CH_2Cl_2:MeOH (98:2) were placed over an inoculated Sabouraud dextrose agar medium (test plates dimensions: 12 x 12 cm), for 1 h at 4 °C. After removing TLC, test plates were incubated at 30 °C for 48 h to visualize growth inhibition. Assays were performed against the dermatophytes *T. mentagrophythes* and *M. gypseum* and the yeasts *C. albicans*, *C. lactis-condensi* and *S. cerevisiae*.

Minimal inhibitory concentration. The minimal inhibitory concentration (MIC) was determined by a standard two-fold dilution technique (Murray *et al*., 1999). Sabouraud dextrose broth was used as medium for yeasts and dermatophytes.

Samples were first dissolved in dimethylformamide (2.56 mg/mL) and the fungistatic activity was determined by measuring the MIC from diluted aqueous samples of 256, 128, 64, 32, 16, 8, 4, 2, 1, 0.5, 0.25 and 0.125 μg/mL. All the experiments were performed in triplicate and the results expressed as mean values. Nystatin, amphotericin B, ketoconazole and clotrimazole were included (at an initial concentration of 0.8 mg/mL) as active reference substances. MIC values ≤ 256 μg/mL were considered active.

Minimal fungicidal concentration. The minimal fungicidal concentration (MFC) was established technically by extending the MIC (microdilution method) (Balows *et al*., 1991). Mixtures of the fungus with samples which in MIC studies showed no visible growth in the last three wells after 48 h of incubation were subcultured onto Sabouraud dextrose agar medium plates using an inoculum of 0.01 mL. Plates were incubated at 37°C for 48 h. The MFC was regarded as the lowest concentration that prevented the growth of any fungal colony on the solid medium.

RESULTS AND DISCUSSION

The rhizome and roots of *Ferula hermonis* submitted to an extraction with increasing polarity solvents and to an aqueous decoction afforded five different crude extracts whose yields are given in Table 1, on basis of dried plant material.

A first screening of the antifungal activity of the extracts by the paper disk-agar diffusion method against a panel of human opportunistic and pathogenic fungi evidenced antimycotic activity against some of them, which was confirmed by determination of the MIC values, ranging from 32 to 256 μg/mL (Table 2). The strongest activity was obtained against dermatophytes, particularly *T. mentagrophytes*, which showed equal MIC and MFC values (32 μg/mL) for the dichloromethane extract and an MFC value about two-fold the MIC value in the case of the hexane extract (64 and 32 μg/mL, respectively). *M. gypseum* showed for both extracts MIC values of 128 μg/mL and MFC values of 256 μg/mL. MIC and MFC values for methanol and aqueous extracts were ≥256 μg/mL, being *T. mentagrophytes* the most sensitive strain.

Bioguided fractionation of the hexane extract by preparative TLC afforded eight fractions from which the major one (F-5, 131 mg) showed the strongest activity in the agar overlay bioautographic assay, which was directly related to a dark blue-colored spot detected at Rf 0.75 in the TLC (silica gel; hexane:EtOAc (6:4)) chromatogram after spraying with vanillin-sulphuric acid reagent. Repeated alternate fractionation of F-5 by means of silicagel 60 and Sephadex™ LH-20 column chromatography allowed the isolation of the active compound **1**.

Fractionation of the dichloromethane extract by flash-chromatography on silicagel afforded 18 fractions, F-2 (130 mg) and particularly F-6 (921 mg) being the major ones. Further fractionation of F-2 through Sephadex® LH-20 led to the isolation of compound **2**, whereas final purification of F-6 resulted in compound **1**.

The structures of compounds **1** and **2** were elucidated by standard spectroscopic techniques as jaeschkeanadiol *p*-hydroxybenzoate and jaeschkeanadiol benzoate, two known daucane aryl esters called ferutinin and teferidin, respectively (Fig. 1) (Diab *et al*., 2001a; Galal *et al*., 2001). Ferutinin, for which a weak activity against *Aspergillus niger* has been previously reported (Al-Shae'r *et al*., 2001), was isolated for the first time from the roots of *Ferula ovina* (Saidkhozhaev and Nikonov, 1974). Teferidin was described from the fruits of *Ferula tenuisecta* (Saidkhozhaev and Nikonov, 1976), and we did not find any antimycotic activity previously reported in the literature.

Results on the antifungal activity of both compounds are shown in Table 2. Ferutinin evidenced strong antimycotic activity against *T. mentagrophytes*, *M. gypseum* and *C. lactis-condensi*. Its MFC value against *T. mentagrophytes* was about two-fold the MIC value (16 and 8 μg/mL, respectively), whereas in the case of the other two strains, equal values were obtained for MIC and MFC: 16 μg/mL for *M. gypseum* and 32 μg/mL for *C. lactis-condensi*. In the case of teferidin, a weaker activity in front of *T. mentagrophytes* was found (MIC 128 μg/mL; MFC 256 μg/mL). These results suggest that the presence of a phenolic hydroxyl in the acidic moiety of the ester, in the case of jaeschkeanadiol *p*-hydroxybenzoate, enhances the antifungal activity.

Table 1. Extract yields from the rhizome and root of *Ferula hermonis*

Extract	Yield (%, wt/wt)
Hexane	13.2
Dichloromethane	10.5
Methanol	11.5
Aqueous	7.3
Decoction	22.7

Table 2. Antifungal activity of extracts, ferutinin and teferidin from the rhizome and roots of *Ferula hermonis*

Fungi strains[a]		Extracts[b]					Compounds[c]		Active reference substances[d]			
		H	DCL	MeOH	W	D	1	2	A	N	K	C
C.a.	MIC[e]	>256	>256	>256	>256	>256	>256	>256	1	4	>8	4
	MFC[f]	>256	>256	>256	>256	>256	>256	>256	1	4	>8	4
C.l.	MIC	256	256	>256	>256	>256	32	>256	0.5	2	0.5	0.125
	MFC	256	256	>256	>256	>256	32	>256	0.5	2	0.5	0.125
S.c.	MIC	>256	>256	>256	>256	>256	>256	>256	4	8	0.25	0.125
	MFC	>256	>256	>256	>256	>256	>256	>256	8	8	1	0.5
T.m.	MIC	32	32	256	256	256	8	128	2	4	0.25	0.125
	MFC	64	32	256	256	256	16	256	2	4	0.5	0.125
M.g.	MIC	128	128	>256	>256	>256	16	>256	4	8	8	0.25
	MFC	256	256	>256	>256	>256	16	>256	4	8	8	0.5
A.n.	MIC	>256	>256	>256	>256	>256	>256	>256	4	8	>8	4
	MFC	>256	>256	>256	>256	>256	>256	>256	4	8	>8	4
A.f.	MIC	>256	>256	>256	>256	>256	>256	>256	4	8	8	1
	MFC	>256	>256	>256	>256	>256	>256	>256	4	8	8	1
P.p.	MIC	>256	>256	>256	>256	>256	>256	>256	8	8	4	2
	MFC	>256	>256	>256	>256	>256	>256	>256	8	8	4	2

[a]Fungi strains: *C.a.: Candida albicans; C.l.: C. lactis-condensi; S.c.: Saccharomyces cerevisiae; T.m.: Tricophyton mentagrophytes; M.g.: Microsporum gypseum; A.n.: Aspergillus niger; A.f.: A. fumigatus; P.p.: Penicillium purpurogenum*.

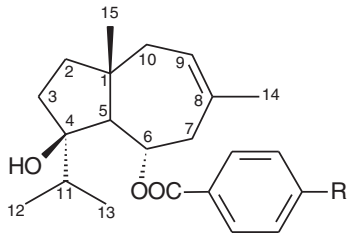
[b]Extracts: **H**: Hexane extract; **DCL**: Dichloromethane extract; **MeOH**: Methanolic extract; **W**: Aqueous extract; **D**: Decoction.

[c]Compounds: **1**: Ferutinin; **2**: Teferidin.

[d]Active reference substances: **A**: amphotericin B; **N**: nistatyn; **K**: ketoconazole; **C**: clotrimazole.

[e]MIC: Minimal inhibitory concentration (μg/mL).

[f]MFC: Minimal fungicidal concentration (μg/mL).



1 R = -OH

2 R = -H

Figure 1. Structure of jaeschkeanadiol *p*-hydroxybenzoate (ferutinin, **1**) and jaeschkeanadiol benzoate (teferidin, **2**).

This would be consistent with the fact that compounds with phenolic structures, like carvacrol, eugenol and thymol show stronger antimicrobial activities than those lacking a phenol group, as for example *p*-cymene (Dorman and Deans, 2000; Ultee *et al.*, 2002; Lang and Buchbauer, 2012).

Thus, it can be stated that hexane and dichloromethane extracts of the rhizome and roots of *F. hermonis* have antifungal activity mainly against *T. mentagrophytes*, *M. gypseum* and *C. lactis-condensi*, and that ferutinin and teferidin are active constituents of these extracts. In an earlier paper, the activity against plant pathogenic fungi was reported for different crude extracts of *F. hermonis*, the ethyl acetate extract showing the highest inhibitory effect against all fungi tested (Al Mughraby and Aburjai, 2003). It should be noted that some daucane sesquiterpene derivatives have been previously identified in the essential oil of *F. hermonis*, in particular: jaeschkeanadiol (ferutinol), jaeschkeanadiol benzoate (teferidin) and jaeschkeanadiol angelate. Both the volatile oil and the two latter compounds exhibited a remarkable antimycotic activity against the human pathogenic dermatophytes *T. mentagrophytes* and *M. gypseum* (Al-Ja'fari *et al.*, 2011).

In conclusion, results obtained from this study together with those previously reported (Al-Ja'fari *et al.*, 2011) evidence that the rhizome and roots of *F. hermonis* have outstanding antifungal activity against human opportunistic pathogenic fungi, which at least is partly due to the presence of daucane sesquiterpene esters, such as jaeschkeanadiol *p*-hydroxybenzoate (ferutinin) and jaeschkeanadiol benzoate (teferidin). These compounds, together with the essential oil of this species, could be of interest for the pharmaceutical industry for developing new antimycotic agents particularly useful in the treatment of dermatophyte infections.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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