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Antimicrobial and antioxidant activities of different extracts from *Aspergillus unguis* SPMD-EGY grown on different media

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Abstract

Background: Recently, researchers demonstrate the importance of associated microorganisms as potential sources of bioactive natural products. Especially, marine-derived fungi consider a treasure of new pharmaceutical leads due to the chemical diversity of their secondary metabolites.

Results: *Aspergillus unguis* SPMD-EGY was isolated from the soft coral *Sinularia* sp. and was cultivated on different media. Three broth media potato dextrose broth (PDB), peptone yeast extract malt extract glucose (PYMG), and Dox media in addition to one solid medium (rice medium) were used for this purpose. The fungus was grown under shake and static conditions (for broth media only). Ethyl acetate extract from both mycelia and culture supernatant and the extract from the direct extraction of rice solid medium were tested for their antimicrobial and antioxidant activities. It has been found that PYMG medium (mycelia static and culture static) exhibited the highest antimicrobial activity against all test microbes except *Aspergillus niger* followed by PDB medium (culture static and mycelia static). From the antioxidant point of view, the PDB medium showed the highest antioxidant activity (culture-shake) followed by Dox medium (culture static and mycelia static). The obtained results have been assessed and compared to the results of previous works constructed. GC/MS analysis of the fungal extracts showing high significant antimicrobial activities was evaluated.

Conclusion: Three different culture media were tested for the cultivation of the locally isolated fungus *Aspergillus unguis* isolate SPMD-EGY and were tested as antimicrobial and antioxidant agents. It has been found that growth media and growth incubation conditions have a very important role in secondary metabolites production.

Keywords: *Aspergillus* sp., Culture media, Antimicrobial, Antioxidant, DPPH

Introduction

As infectious diseases evolve to become more resistant to existing antibiotics, there is an undeniable need to discover new, safe, and effective drugs from natural sources with novel mechanisms of action to combat these pathogens. Marine environment is considered as an extremely diverse pool of life and has varied structurally unique biologically active natural products because of its extreme and rapidly changeable conditions (Zainuddin et al. 2010).

The oceans are considered as a resource for discovery of different types of bioactive compounds such as nutritional material, enzymes, cosmetics, aflatoxins, and pharmaceuticals (Park et al. 2002; El-Shafei et al. 2010; El-Neekety et al. 2016). More than 70% of the Earth is covered by oceans, and it is believed that life on Earth originated from the sea (Haefner 2003). Although the terrestrial environment has been increasingly of interest as a source of new bioactive molecules, the marine environment is considered as a unique source of a diverse array of natural products, primarily from invertebrates such as tunicates, sponges, mollusks, and bryozoans, and from marine fungi, bacteria, and cyanobacteria.

Recently, the importance of marine organisms over the past 30–40 years has been the focus of the researchers as potential sources for the discovery of chemotherapeutic

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agents (Kjer et al. 2010), more than 12,000 novel chemical structures with hundreds of new compounds still being discovered from marine plants, animals, and microbes every year (Donia and Hamann 2003). Additionally, a great percentage of marine microorganisms have not been described (Pomponi 1999). Marine associate microorganisms especially fungi were considered as an important and prolific source of biologically active metabolites (Saleem et al. 2007).

Many marine fungal strains were screened to assess their ability to produce antimicrobial, anticancer, and antiviral agents belonging to various compound classes including macrolides, terpenoids, alkaloids, or peptide derivatives (Bhadury et al. 2006). One of the most potent bioactive compound, the chlorinated benzophenone pestalone, was isolated from the marine fungus *Pestalotia* sp. and was shown to possess potent antibiotic activity against *Staphylococcus aureus* (MIC = 37 ng/ml) and *Enterococcus faecium* (MIC = 78 ng/ml), indicating that it could be evaluated further in advanced models of infectious disease (Cueto et al. 2001). Another new compound sorbicillactone A isolated from the sponge-derived fungus *Penicillium chrysogenum* exhibited promising activity against leukemia cells without exhibiting notable cytotoxicity (Zhou et al. 2018). This work has been undertaken with the aim of cultivation of the fungus on different medium in shaking and static conditions. The antimicrobial activity and the antioxidant activity, evaluated by two methods, will be investigated.

Materials and methods

Fungal strain and culture condition

The fungus *Aspergillus unguis* SPMD-EGY was isolated from the internal part from *Sinularia* sp. (soft coral) after cutting it into small cubes (1 cm) and using them to inoculate the isolation medium (PDA), and the fungus was previously identified by the molecular technique (18S rRNA) as previously described by Abd El-Hady et al. (2016a). *Aspergillus* sp. was cultivated on three broth media: potato dextrose broth (PDB), peptone yeast extract malt extract glucose (PYMG) broth, and Czapek-Dox (Dox) broth, in addition to the rice medium which is considered as solid medium (Abd El-Hady et al. 2016b).

Extraction of secondary metabolites

The fungi were harvested at the end of incubation period, centrifuged at 8000 rpm and subjected to extraction. The culture supernatant was extracted with ethyl acetate (× 3 or till exhaustion) and then evaporated under vacuum. On the other hand, the fungal mycelia were first extracted using acetone and evaporated till dryness. The residual part was re-extracted using a small volume of ethyl acetate (Abd El-Hady et al. 2014).

Antimicrobial activity measurement

Agar disc plate method has been established to measure the antimicrobial activities of different fungal extract samples (Collins and Lyne 1985; Youssef et al. 2014; Abdel-Aziz et al. 2015). Two bacterial test microbes: *Staphylococcus aureus* (Gram-positive) and *Pseudononas aeruginosa* (Gram-negative) and one yeast test microbe *Candida albicans* and one fungal test microbes, i.e. *Aspergillus niger*, were selected to evaluate the antimicrobial activities. The bacterial and yeast test microbes were grown on a nutrient agar medium (NA) of the following ingredients (g/l): beef extract (3), peptone (10), and agar (20). On the other hand, the fungal test microbes were cultivated on Szapek-Dox agar medium of the following ingredients (g/l): sucrose (30), $NaNO_3$ (3), $MgSO_4.7H_2O$ (0.5), KCl (0.5), $FeSO_4.7H_2O$ (0.055), K_2HPO_4 (1), and agar (20). The culture of each test microbe was diluted by distilled water (sterilized) to 10^7 to 10^8 colony-forming units (CFU)/ml then 1 ml of each was used to inoculate 1 l Erlenmeyer flask containing 250 ml of solidified agar media (Youssef et al. 2014). These media were put onto previously sterilized Petri dishes (10 cm diameter having 25 ml of solidified media). Filter paper discs (5 mm, Whatman No. 1 filter paper) were loaded with 0.2 mg of each extract. The clay discs were placed on the surface agar plates seeded with test microbes and incubated for 24 h at the appropriate temperature of each test organism. Antimicrobial activities were recorded as the diameter of the clear zones (including the film itself) that appeared around the films (Abdel-Aziz et al. 2015).

Antioxidant determination

By DPPH method

DPPH radical scavenging activity of all extracts was analyzed according to a modified procedure of Matsushige and his group (Matsushige et al. 1996). One milliliter of methanol solution for each extract (100 μg/ml) was added to 1 ml of methanol solution of DPPH (60 μM). The prepared solutions were mixed and left for 30 min at room temperature. The optical density was measured at 520 nm using a spectrophotometer (UV-1650PC Shimadzu, Japan). Mean of three measurements for each compound was calculated. Caffeic acid was used as a positive control with 80.2% scavenging activity.

By superoxide anion scavenging activity (XOD)

Superoxide anion scavenging activity was determined according to a modified method of Matsushige and his group (Matsushige et al. 1996). Reaction mixtures containing 1.4 ml of 50 mM Na_2CO_3 (pH 10.2), 100 μl of 3 mM xanthine, 100 μl of 3 mM EDTA, 100 μl of BSA (1.5 mg/ml), 100 μl of 75 mM Nitro blue tetrazolium, and 50 μl of each compound (100 μg/ml) were preincubated at 30 °C for 10 min, and 50 μl of xanthine oxidase (0.3

unit/ml) was added. After incubation at 30 °C for 20 min, 200 µl of 6 mM $CuCl_2$ was added to stop the reactions, and the absorbance was measured at 560 nm. Caffeic acid was used as a positive control with 73.5% scavenging activity.

GC/MS analyses

One milligram of the dried extract was prepared for chromatography by derivatization for 30 min at 85 °C with 20 µl pyridine + 30 µl N,O, bis-(trimethylsilyl)trifluoroacetamide (BSTFA) and analyzed by GC/MS (Abd El-Hady et al. 2016a). A Finnigan MAT SSQ 7000 mass spectrometer was coupled with a Varian 3400 gas chromatograph. DB-1 column, 30 m × 0.32 mm (internal diameter), was employed with helium as carrier gas (He pressure, 20 Mpa/cm^2), injector temperature, 310 °C; and GC temperature program, 85–310 °C at 3 °C/min (10 min initial hold). The mass spectra were recorded in electron ionization (EI) mode at 70 eV. The scan repetition rate was 0.5 s over a mass range of 39–650 amu.

Statistical analysis

Data were presented as mean ± standard deviation of triplicates ($n = 3$) according to Annegowda et al. 2010 using SPSS 13.0 program (SPSS Inc. USA) (Annegowda et al. 2010).

Results

Ethyl acetate extracts from the fungus SPMD, previously identified as *Aspergillus unguis* isolate SPMD-EGY (accession no. KM203833) and was cultivated on different culture media, i.e., potato dextrose broth (PDB), peptone yeast extract malt extract glucose (PYMG), Czapek-Dox (Dox), and rice (solid) media, were evaluated for their antimicrobial activities. It has been found that the antimicrobial activities were higher when the fungus was grown on PYMG broth medium (culture static and mycelia static) against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*. Potato dextrose broth (culture static and mycelia static) exhibited slightly higher antimicrobial activities against all tested microbes (Fig. 1). All the produced extracts from the different medium by this fungus (*Aspergillus unguis* SPMD-EGY) did not exhibit any antifungal activity against *Aspergillus niger* (test microbe). Results in Fig. 2 distinguish the antimicrobial activity of our previous work of the same fungus grown on the same broth medium with the only differences are the utilization of different glucose concentration and seawater (Abd El-Hady et al. 2016a). It has been found that the produced extracts exhibited nearly the same results with the only difference is that there is an antimicrobial activity against the fungus *Aspergillus niger*. Results in Fig. 3 revealed that the antioxidant activity from *Aspergillus unguis* SPMD-EGY grown on potato dextrose broth (PDB) medium exhibited the promising activity measured by both DPPH and X-XOD under shake conditions from culture supernatant ethyl acetate extract. Also, PDB exhibited reasonable antioxidant activity (DPPH) under shake and static conditions from

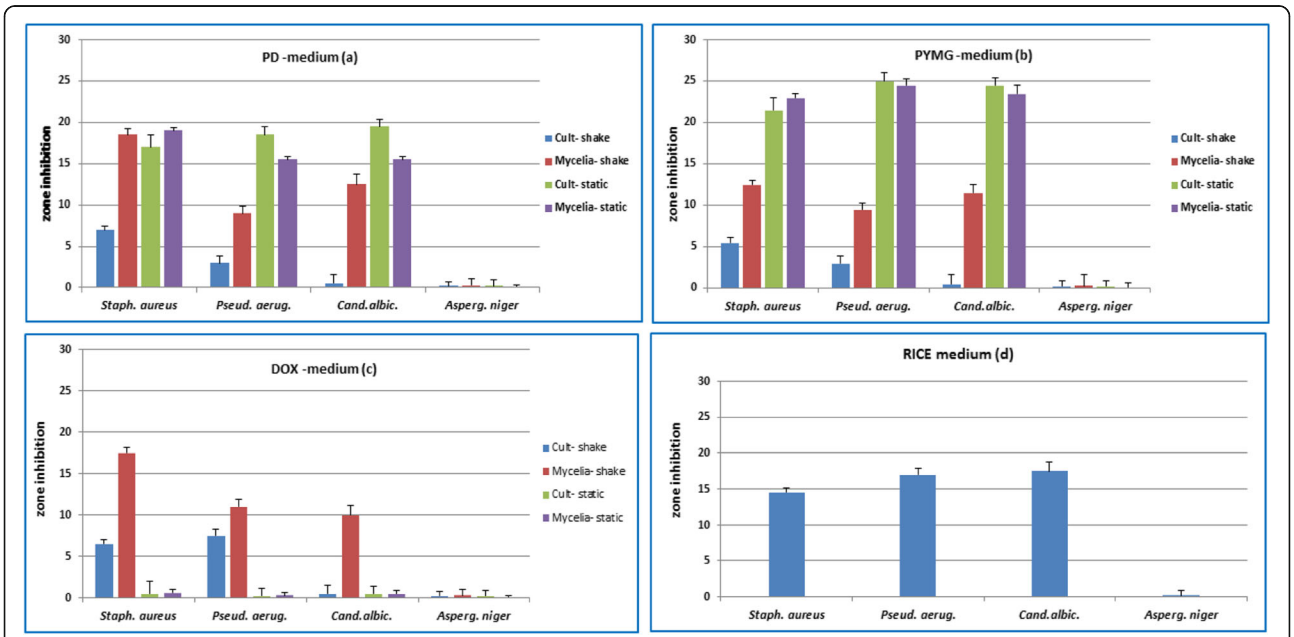

Fig. 1 Antimicrobial activity of secondary metabolite extracts from culture and mycelia (static and shake) of different media. Values are expressed as mean ± SD, $n = 3$ (200 µg/ml for all tested extracts

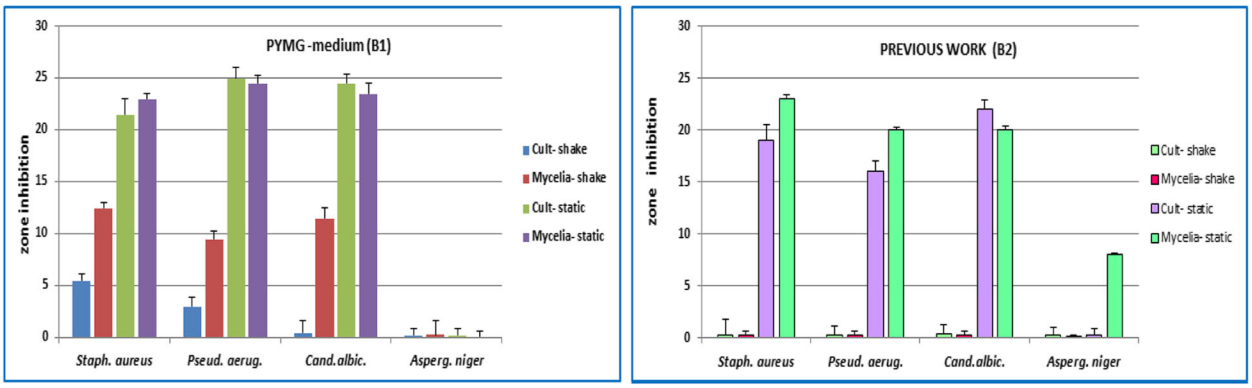

Fig. 2 Demonstrative antimicrobial comparison between PYMG medium (5% glucose, distilled water) and previous work medium (10% glucose, seawater)

culture supernatant and mycelia extracts, respectively, Czapek-Dox (Dox) broth medium followed PDB medium for antioxidant activity. It has been investigated that the DPPH and X-XOD activities were noticed under static conditions for both culture supernatant and mycelia ethyl acetate extracts. On the other hand, PYMG broth medium and rice solid medium showed restricted antioxidant activities (for DPPH only). The free radical scavenging activities measured by DPPH and X-XOD were compared to that have been previously done (Abd El-Hady et al. 2016a) and illustrated in Fig. 4. It has been found that the scavenging activities measured by DPPH showed approximately the same results, but X-XOD exhibited the highest differences for both.

The GC/MS analysis for fungal extracts showing highly significant antimicrobial activities (mycelia static and culture static of PYMG and PD media) was done. A total of 63 compounds were identified. Table 1 revealed the complete variation in the chemical composition of the four fungal extracts.

Hexadecanoic acid (18%), 9,12-Octadecadienoic acid, 9-Octadecenoic acid, 8-Methoxy-2,3-dihydro-1 h-benzazepin-2-one-5-acetic acid, and diisooctyl phthalate were

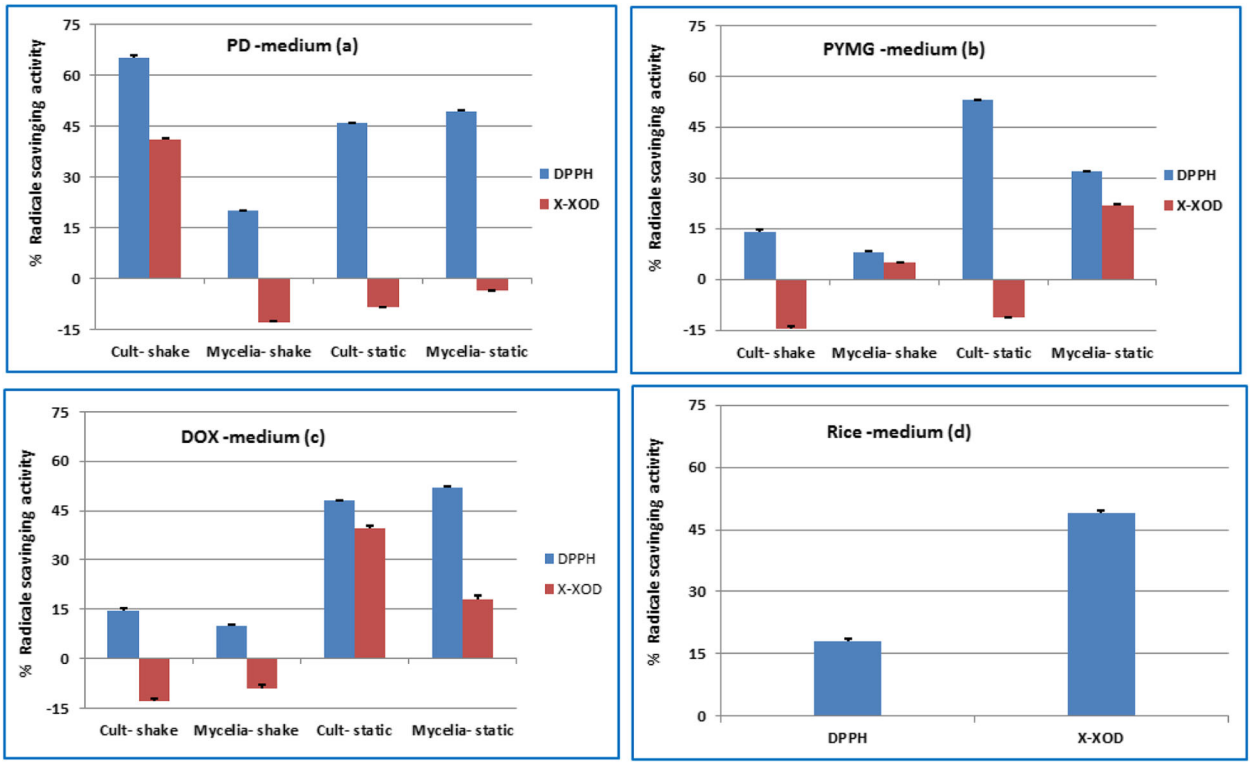

Fig. 3 Free radical scavenging activity of secondary metabolite extracts from culture and mycelia (static and shake) of different media in the DPPH radical and xanthine-XOD assays. Values are expressed as mean ± SD, $n = 3$, at a concentration of 200 μg/ml for all tested extracts

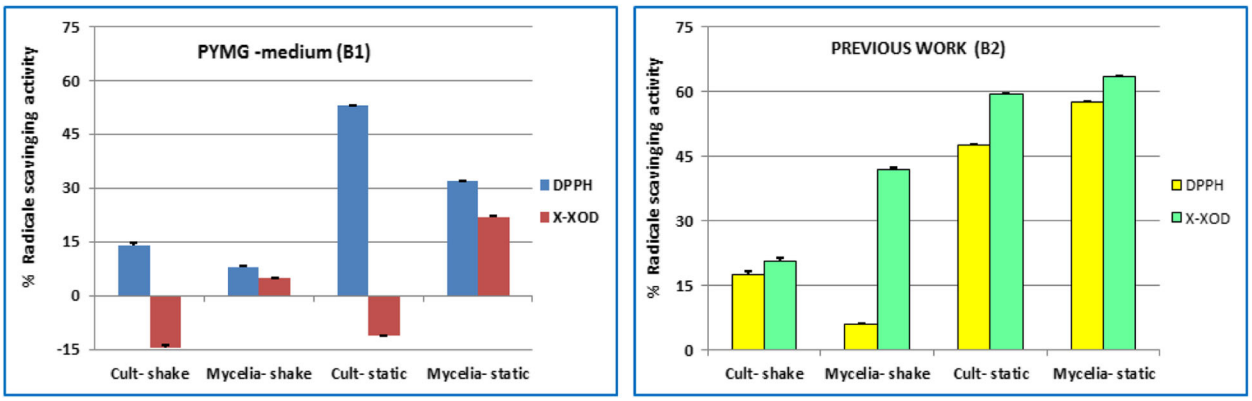

Fig. 4 Demonstrative antioxidant comparison between PYMG medium (5% glucose, distilled water) and previous work medium (10% glucose, seawater)

present in PYMG mycelia static (M.st.) extract with high concentrations. 2,2′-Dihydroxy-chalcone (33.6%), D-Friedoolean-14-en-3-one (39.8%), 1,6,7-Trimethyl-3-phenyl-9H-xanthen-9-one, and 2,4,4′-Trihydroxy-chalcone were present in PYMG culture static (C.st) extract with high concentration. Dodecanoic acid and 2,4-Dihydroxybenzoic acid were mainly found in PD mycelia static (M.st) extract, while in its culture static (C.st) extract, hexadecanoic acid (11.6%) and Acetamide-2,2,2-trifluoro (19.3%) were present in high concentrations.

Discussion

Growth media and growth incubation conditions have a strong effect on secondary metabolite production, and there is no compromise on which culture media are optimal for specific metabolite production (Mathan et al. 2013). Several culture media like Czapek-Dox broth, Sabourod broth, potato dextrose broth, malt extract broth, and nutrient broth were used to investigate the antimicrobial activities from *Aspergillus terreus* KC582297. Potato dextrose broth was found to be a potent medium for the production of bioactive antimicrobial metabolites (Mathan et al. 2013). Noaman et al. (2004) studied the effect of different concentrations of glucose on growth and antimicrobial activity from *Synochococcus leopoliensis*. It has been found that maximum antimicrobial activity was reported at a glucose concentration of 0.6 g/l. On the other hand, antimicrobial activity from the fungus *Arthrinium* c.f. *saccharicola* was higher after cultivating it on medium with higher glucose concentration (Miao et al. 2006). The bioactivity from this fungus was also increased with increasing salinity (up to 3 ppm). It has been reported that the antioxidant activity is species- and culture medium-dependent (Dulay et al. 2015a). Antioxidant activities from *Penicillium antillarium* grown on different broth media exhibited the highest scavenging activity with potato broth medium (Dulay et al. 2015b). Moreover, ethyl acetate extract from different broth media including rice bran, coconut water, corn grit, and potato broth and all cultivated with *Lentinus* spp. were tested for their antioxidant activities. It has been found that rice bran exhibited the highest scavenging activities for both *Lentinus* spp. (Dulay et al. 2015a). Ethyl acetate extract from Czapek-Dox medium cultivated with *Chaetomium madrasense* exhibited the highest antioxidant activity (Abo-Elmagd 2015).

It was reported that free fatty acids showed antimicrobial activities against 12 oral pathogens which cause dental caries, stomatitis, periodontitis, and gingivitis (Choi et al. 2013). Long-chain unsaturated fatty acids, such as linoleic acid, show antibacterial activity. Additional unsaturated fatty acids including palmitoleic acid, oleic acid, linolenic acid, and arachidonic acid also exhibited antibacterial activity (Zheng et al. 2005). Lauric, palmitic, linolenic, linoleic, oleic, stearic, and myristic acids are known to have potential antibacterial and antifungal agents (Agoramoorthy et al. 2007). Investigation of in vitro synergism between several chalcones substituted in combination with oxacillin, an antibiotic used conventionally against *S. aureus* ATCC 43 300 that is resistant to meticillin, using the kinetic turbidimetric method developed earlier. The results were satisfactory for all assayed combinations and in accordance with the mechanism of bacteriostatic inhibition previously proposed, except for 2′,4′-dihydroxy-3′--methoxychalcone – oxacillin (Talia et al. 2011).

D-Friedoolean-14-en-3-one was demonstrated in vitro antileishmanial and antitumor activities (Moulisha et al. 2009). 2,4-Dihydroxybenzoic and protocatechuic acids were the phenolic compounds with higher activity against the majority of Gram-negative and Gram-positive bacteria. Furthermore, phenolic compounds inhibited more MRSA than methicillin-susceptible *Staphylococcus aureus*. MRSA was inhibited by 2,4-dihydroxybenzoic, vanillic, syringic acids. The presence of carboxylic acid (COOH), two hydroxyl (OH) groups in para- and ortho positions of the

Table 1 Chemical composition assessed by GC/MS analysis for fungal extracts with high antimicrobial activities from different media for *Aspergillus unguis* SPMD-EGY

No.	Compound	PYMG medium		PD medium	
		M. st.[a]	CC. st.[b]	M. st.[c]	CC. st.[d]
		*TIC%			
	Saturated fatty acids				
1	Butanedioic acid	1.0			
2	Butanoic acid-2-methyl			0.78	
3	Butanoic acid-4-hydroxy			0.05	
4	Azelaic acid	0.8			
5	Propanoic acid, 2,3-dihydroxy			0.22	
6	2-Isopropyl-2-hydroxy succinic acid			0.04	
7	Dodecanoic acid (lauric acid)			7.13	
8	Tetradecanoic acid (myristic acid)	0.4			
9	Pentadecanoic acid	0.4			
10	Hexadecanoic acid (palmitic)	18.0		1.63	11.64
11	Heptadecanoic acid	0.3			
12	Octadecanoic acid (stearic acid)	3.1		0.41	0.73
	Unsaturated fatty acids				
13	Cis-9-hexadecenoic acid (oleic acid)	0.6			
14	Heptadecenoic acid	0.3			
15	9,12-Octadecadienoic acid (linoleic acid)	3.4			
16	9-Octadecenoic acid	3.5		1.11	0.96
17	11-Octadecenoic acid	0.3			
	Fatty acid esters				
18	5-Keto-2,2-dimethyl-heptanoic acid, propyl ester	0.6			
19	Hexadecanoic acid-2,3-dihydroxy propyl ester	0.6			
20	9,12-Octadecadienoic acid-2-hydroxy-ethyl ester	0.3			
21	Octadecanoic acid- 2,3-dihydroxy- propyl ester			0.16	
22	Docosanoic acid,1,2,3-propanetriyl ester			0.11	
	Phenolic acids				
23	Benzoic acid			0.14	
24	Benzeneacetic acid-α-4-dihydroxy			0.13	
25	Benzeneacetic acid-2-hydroxy			0.17	
26	Benzenepropanoic acid-α-hydroxy			0.09	
27	2,4-Dihydroxybenzoic acid			2.65	
28	Caffeic acid			0.64	
	Nitrogenous compounds				
29	8-Methoxy-2,3-dihydro-1 h-benzazepin-2-one-5-acetic acid	6.2			
30	Acetamide-2,2,2-trifluoro				19.3
31	Morpholine				2.7
32	*N*,*N*-diethylamine				0.20
33	*N*-Acetyl-*N*-methyl alanine	3.1			
34	*N*-l-valyl-l-valinate			0.12	
35	3-Pyridine-carboxylic acid			0.1	
36	2,6-Ditbutyl-4-hydroxy-4-phenyl-1-imino-2,5-cyclohexadiene	0.4			

Table 1 Chemical composition assessed by GC/MS analysis for fungal extracts with high antimicrobial activities from different media for *Aspergillus unguis* SPMD-EGY *(Continued)*

No.	Compound	PYMG medium		PD medium	
		M. st.[a]	CC. st.[b]	M. st.[c]	CC. st.[d]
		*TIC%			
37	4(4-Methoxyphenyl)-4-(1H-pyrrolo[2,3b]pyridin-3-yl)butan-2-one	0.8			
38	7,8-Dihydroxy-benzo(5,6 g)1H,3H-quinazoline-2,4-dione	0.7			
39	1-Imino6(4-methylphenyl)3-oxo-2,5dipheny-l1,2,3,5,6-pentahydro-imidazo[1,5a]pyrazine-8-carboxamide			2.5	
40	4,6-Dimethoxy-7(5-methyl-1-pyrrolin-2-yl)2,3-diphenylindole	0.22			
41	2,2-Dichloro-1,1-bis(4-diethylaminophenyl)ethylene	0.8			
42	1,1,3-Trifluoro-3,3-bis[ethylamino]1-phenyldisiloxane	3.5			
	Others				
43	Glycerol	2.3			
44	Methyl -7(2,4,6-trimethylphenyl)-5H-furo[2,3c] thiopyran-4-carboxylate	0.5			
45	Tridecanol	0.62			
46	L-Threitol	2.0			
47	6(4 t-Butylphenyl)1,3,5-hexatriynyl)trimethylsilane	1.5			
48	Arabitol	3.4			
49	1,1,4,4-Tetramethyl-2,3-diphenyl-1,4-disilacyclohex-2ene	0.93			
50	1,1,4,4Tetramethyl2,3diphenyl1,4di-silacyclohex2ene (isomer)	0.89			
51	4,4′-Dihydroxy-chalcone	1.3			
52	3-Deoxyglucitol	0.45			
53	Sorbitol	6.1			
54	2,2′-Dihydroxy-chalcone		33.6		
55	Methyl 2{2[3(methoxycarbonyl)phenyl]-1-ethynyl}5-hydroxy-ethynyl)benzoate	0.8			
56	Erythrose			0.07	
57	Glucose oxime				0.50
58	D-Gluconic acid				2.45
59	D-Galactonic acid-α-lactone			0.11	
60	D-Friedoolean-14-en-3-one		39.8		
61	1,6,7-Trimethyl-3-phenyl-9H-xanthen-9-one and		3.1		
62	2,4,4′-Trihydroxy-chalcone		3.2		
63	Diisooctyl phthalate	13.8		0.16	0.30

**TIC* the ion current generated depends on the characteristics of the compound concerned and it is not a true quantitation, *M. st.* mycelia static, *C. st.* culture static

[a]Data previously mentioned (Abd El-Hady et al. 2016a); [b,d](Abd El-Hady et al., 2016c);[c](Abd El-Hady et al. 2016d)

benzene ring and also a methoxyl (OCH3) group in the meta position seems to be important for anti-MRSA activity (Alves et al. 2013). *N*-benzyl-2,2,2-trifluoroacetamide was assessed for its antimicrobial and antioxidant. It showed good antifungal activity against tested fungi, specially *C. albicans* and moderate antibacterial activity. *N*-benzyl-2,2,2-trifluoroacetamide showed high antioxidant activity. Cupric ion reducing the antioxidant capacity of *N*-benzyl-2,2,2-trifluoroacetamide was dependent on the concentration (Balachandran et al. 2015). The antibacterial and antifungal activities of ethyl acetate extract, di-(2-ethylhexyl) phthalate (compound 1) and compound 2 were measured using the disc diffusion method. Ethyl acetate extract and compound 1 presented better results than anhydrosophoradiol-3-acetate (compound 2).

Conclusion

The utilization of different growth media exhibited a prolific role in the production of unique bioactive secondary metabolites with a unique chemical skeleton. Three different culture media, namely potato dextrose broth (PDB), peptone yeast extract malt extract glucose (PYMG), and Czapek-Dox (Dox) and rice (solid) media were used for the cultivation of the locally isolated fungus *Aspergillus unguis* isolate SPMD-EGY (accession no. KM203833), and the produced ethyl acetate extract from

each medium were tested as antimicrobial and antioxidant agents. Diverse results have been obtained and varied from medium to another medium.

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Availability of data and materials
Data are available on request from the authors.

Authors' contributions
MA-A, FAEH, and AH contributed to the design and implementation of the research, analysis of the results, writing of the manuscript. FAEH, AH, and MAA performed the experiments. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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