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Antimicrobial and Anticancer Activities of Actinomycetes Isolated from Egyptian Soils

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A B S T R A C T

Actinomycetes have got considerable attention worldwide due to the production of many useful bioactive metabolites. In the present study, the antimicrobial potential of novel Actinomycetes has been evaluated by the initial screening of seven rhizosphere samples in Egypt. The primary and secondary screening were performed against *Bacillus cereus (ATCC33018),* and *E.coli* O157 (ATCC93111) as model strains of Gram positive and Gram negative species, respectively. GC-MS analysis of most active Actinomycetes extracted secondary metabolites was studied. The major compounds identified by GC-MS analysis include 2, 4-di-tert-butylphenol, 3-chloropropionic acid, heptadecyl ester, 1,2-benzenedicarboxylic acid,3-nitro, benzenepropanoic acid,3,5-bis(1,1 dimethylethyl)-4-hydroxy-, octadecyl ester, 1-monopalmitin,2TMS derivative, 1-docosene, 1-nonadecene and 1-nonacosene.

Introduction

Actinomycetes categorized as Gram-positive filamentous bacteria with fungal morphology. They are characterized under group of phylum Actinobacteria (1). They were distributed in different ecosystems especially soil ecosystem. They play an important role in different environmental activities such as recycling of agricultural and industrial wastes by decomposing complex organic polymeric structures in agro-industrial wastes through active interactions with fungi (2).

Actinomycetes have an important role in agroindusterial and biomedical areas such as composting production, antimicrobial products, antioxidants, enzyme inhibitors and antitumor products (3, 4, 5, 6, 7). Due to the emergence of multidrug-resistant microorganisms to almost all available antibiotics, many researchers are focused now

on discovering novel antimicrobials from many natural resources such as those produced by Actinomycetes especially those isolated from many undiscoverable or poorly explored environments (8). Different reports were considered that Egyptian soil is poorly investigated source for actinobacteria, (9, 10, 11, 12). Also, thousands of bioactive medical compounds have been discovered from Actinomycetes and characterized in treatment of wide range of diseases in human, veterinary, and agriculture sectors (13, 14, 15).

Hence, the Actinomycetes are considered to be the most potent source for the production of secondary active metabolites such as antibiotics, and other bioactive compounds. It is well established that each Actinomycete strain has probably genetic potential ability to produce 10–20 secondary metabolites (16, 17, 18). *Actinomycetes* produced many antibacterial agents such as tetracyclines and antifungal agents such as amphotericin, and anticancer drugs exemplified by Adriamycin and the immunosuppressant tacrolimus (18). *Actinomycetes* has been reported to contribute nearly 70% of metabolites described under actinobacteria (19). *All studies continue to discover natural antimicrobial agents from* actinomycetes to be useful sources of novel secondary metabolites and study their applications as anti-bacterial, antifungal and anticancer agents, or other pharmaceutically useful compounds (20).

In these perspectives, the current study aimed to isolate and characterize different Actinomycetes from soil niches in the Giza governorate, Egypt.

Actinomycetes were screened for their capabilities to produce antimicrobial secondary active metabolites. The bioactive compound from the most potent isolates was characterized using GC-MS analysis.

Materials and Methods

Sampling and isolation of actinomycetes

Soil samples were collected from the rhizosphere of different crops. A total of 7 rhizosphere samples were collected from (*Hordeum vulgare, Allium cepe, Trifolium, Brassica oleracea, Triticum aestivum, Solanum lycopersicum,* and *Pelargonium graveolens*) crop soil samples (Table 1). Serial dilutions were prepared from rhizosphere samples and a dilution plate method was used to isolate Actinomycetes on starch-nitrate agar plates (21). The plates were incubated for 7 days at 30ºC. Colonies with the typical Actinomycetes morphology were picked and checked for purity by repeated sub-culturing. Pure cultures were maintained on Luria-Bertani (LB) broth supplemented with 20% glycerol at -20 for further use.

Screening of actinomycetes for antimicrobial activity

Actinomycetes isolates were screened against various test organisms (*E.coli* O157 ATCC and *Bacillus cereus* ATCC) by dual culture plate assay. The effect of Actinomycetes was tested by placing a six mm diameter disk of 7 days old fully grown Actinomycetes on starch nitrate agar plates seeded with 10% of each bacterial pathogen. The diameter of inhibition zones was recorded after 24 h of incubation at 37 °C (22).

The effect of secondary metabolites on cancer cells

Cell cytotoxicity effects of Actinomycetes secondary active metabolites were estimated on human lung cancer cell line (A549) using neutral red uptake assay according to (23)**.** Cells were grown as a monolayer culture in RPMI 1640 medium (10% fetal bovine serum, 1 mM sodium pyruvate and 100 U/L of

penicillin/streptomycin) and incubated at 37C° in a 5% of CO_2 atmosphere. Cell lines (100 µL) were seeded in 96 well plates at a concentration of 5× 10^3 cells/mL, for 24 h. After that, the culture medium was replaced with 100 µL serum-free medium containing various concentrations (25, 50, 100, 150, 200, 250, 300, 350, 400, 450 and 500 µg/mL) of Actinomycete extracts at 24 h and 48 h. Later, the medium was refreshed with 100µL of serum free medium (RPMI 1640) and 20 µL of MTT (5 µg/mL of (3, 4, 5-dimethylthiazol-2yl)-2, 5-diphenyltetrazo liumbromide).

The 96 well plates were incubated for 3 h in dark and the developed color was measured with ELISA reader at 570 nm. Triplicates were maintained for each treatment. Inhibitory concentration (IC50) values were directly determined by linear regression analysis with office XP (SDAS) software.

Results and Discussion

Isolation of Actinomycetes

A total of 37 Actinomycetes were isolated from the rhizosphere of different crops. After purification on starch nitrate agar (SNA) medium bacterial isolates were placed on LB medium supplemented with 20% glycerol and preserved at -20.

Antimicrobial activities tests

A total of 8 Actinomycetes isolates from 37 isolates showed antimicrobial activity against at least one of the tested bacterial pathogens such as *E. coli* O157 (ATCC 9311) and *Bacillus cereus* (ATCC33018). The diameters of inhibition zones are present in (Table 2) comparing to positive control. Maximum activity was recorded as 11±1 mm against *Bacillus cereus* by isolate AC-2. Maximum activity was recorded against *E. coli O157* (11±2 mm) by isolate AC-7.

Anticancer effect of extracted bioactive compounds

The effect of the Actinomycetes AC-6 secondary bioactive metabolite was tested against Adenocarcinoma of Human Lung cancer cell line (A549). As clearly shown in Table (3) the effect of secondary metabolites of actinomycetes strains on Human Lung cancer cell line (A549) exhibited very low activity as anticancer agent (LC 50 = 1122 µg/ml).

Identification of potentially bioactive compounds by GC-MS

The chemical identification of the bioactive compounds present in the ethyl acetate extracts of Actinomycetes AC-6, AC-7 and AC-8 was performed by GC-MS based on the retention time, peak areas, molecular weight and molecular formula. The GC-MS obtained for the extracts tested showed defined signal patterns characteristic of each type of extract as indicated by peaks.

The major compounds identified by GC-MS analysis (Figure 1 and Table 4) in ethyl acetate extracts of Actinomycetes (AC-6, AC-7 and AC-8) were 2,4-di-tert-butylphenol, 3-chloropropionic acid, heptadecyl ester, 1,2-benzenedicarboxylic acid, 3-nitro, benzene propanoic acid, 3,5-bis(1,1 dimethyl ethyl)-4-hydroxy-,octadecyl ester, 1-monopalmitin, 2TMS derivative, 1-docosene, 1-nonadecene and 1-nonacosene.

Twenty four compounds were identified by GC-MS in Actinomycetes AC-6 secondary metabolites, The most predominant major compounds were 2,4-di-tert-butylphenol (20.19%), 3-chloropropionic acid heptadecyl ester (13.40%), 1,2-benzenedicarboxylic acid, 3-nitro (6.87%), tributylacetylcitrate (5.90%) and squalene (4.48%) and the minor compounds were 1-monopalmitin, 2TMS

derivative (2.64%), 1-docosene (2.61%), 1-nonadecene (2.57%), benzenepropanoic acid, 3,5-bis(1,1 dimethylethyl)-4-hydroxy-, octadecyl ester (2.15%), isopropyl myristate (2.10%), 3-eicosene, (E)- (1.92%), 2-propenoic acid, 3-(4-methoxyphenyl)-, 2-ethylhexyl ester (1.48%), 1-nonacosene (1.40%), dotriacontane (1.28%), 1-(4-isopropylphenyl)-2-Methylpropyl acetate (1.13%), docosane (1.12%) and 1,3-benzenedicarboxylic acid, bis (2-ethylhexyl) ester (1.03%). The remaining compounds were present in less than 1%. On the other hand, thirteen active compounds were identified by GC-MS in Actinomycetes AC-7 secondary metabolites, the active major compounds were 2,4-di-tert-butylphenol (32.66%), 3-chloropropionic acid, heptadecyl ester (19.93%), benzenepropanoic acid, 3,5-bis(1,1 dimethylethyl)-4-hydroxy-, octadecyl ester (5.54%) and 1-monopalmitin, 2TMS derivative (4.28%) and the minor compounds were 1-docosene (3.99%), 1-nonadecene (3.38%), 3-eicosene, (E)- (3.35%), 1,2-benzenedicarboxylic acid, 3-nitro (3.28%), 1-nonacosene (2.76%), 9-octadecenamide (1.51%), oxiraneundecanoic acid, 3-pentyl-, methyl ester, trans (1.31%),oleic acid, 3-(Octadecyloxy) propyl ester (1.09%) and isochipane B (0.85%). In addition, twelve active compounds were found in Actinomycetes AC-8 secondary metabolites by GC-MS analysis. The prevailing compounds were 2,4-di-tert-butylphenol (32.42%), 3-chloropropionic acid, heptadecyl ester (17.51%), 1-docosene (4.39%), 1-hexadecanol (3.80%), 1-nonadecene (3.73%), 1-monopalmitin, 2TMS derivative (3.20%), 1-nonacosene (2.71%), 1,2-benzenedicarboxylic acid, 3-nitro (2.59%), 9-octadecenamide (2.18%), benzenepropanoic acid,3,5-bis(1,1 dimethylethyl)-4-hydroxy-, octadecyl ester (2.11%) and dotriacontane (0.97%).The biological functions of these compounds were identified in the ethyl acetate extracts of Actinomycetes AC-6, AC-7 and AC-8 as shown in Table 4.

The present study aimed to determine the effect of Actinomycetes secondary metabolites on different pathogen by inducing the antimicrobial activity in different pathogens. In addition to its anticancer activity.

Table.1 Actinomycetes isolated from the rhizosphere soil of different crops

Strain	Crop name	Source
AC-1	*Hordeum vulgare*	Faculty Agriculture, Cairo University
AC-2	*Triticum aestivum*	Faculty Agriculture, Cairo University
AC-3	*Triticum aestivum*	Faculty Agriculture, Cairo University
AC-4	*Allium cepa*	Faculty Agriculture, Cairo University
AC-5	*Brassica olevacea*	Eastern Province, Egypt
AC-6	*Trifolium*	Eastern Province, Egypt
AC-7	*Pelargonium graveolens*	Nile Delta, Egypt
AC-8	*Solanum lycopersicum*	Nile Delta, Egypt

Table.2 Antimicrobial activities of isolated Actinomycetes

Actinomycetes	*Bacillus cereus*	*E. coli* O157
Positive control	10.0 ± 2.0	11.0 ± 1.0
AC-1	-	-
AC-2	11.0 ± 1.0	-
AC-3	8.0 ± 2.0	8.0 ± 1.0
AC-4	8.0 ± 2.0	9.0 ± 1.0
AC-5	9.0 ± 2.0	11.0 ± 2.0
AC-6	9.0 ± 2.0	8.0 ± 1.0
AC-7	7.0 ± 1.0	-
AC-8	-	8.0 ± 1.0

Inhibition zones are represented in mm, the diameter of Actinomycetes disk is 6 mm

Table.3 Anticancer effect of extracted bioactive compounds of strain AC-6

Concentration (µg/ml)	**Viability %**
	AC-6
100	97
50	99.3
25	99.6
IC 50	1122 µg/ml

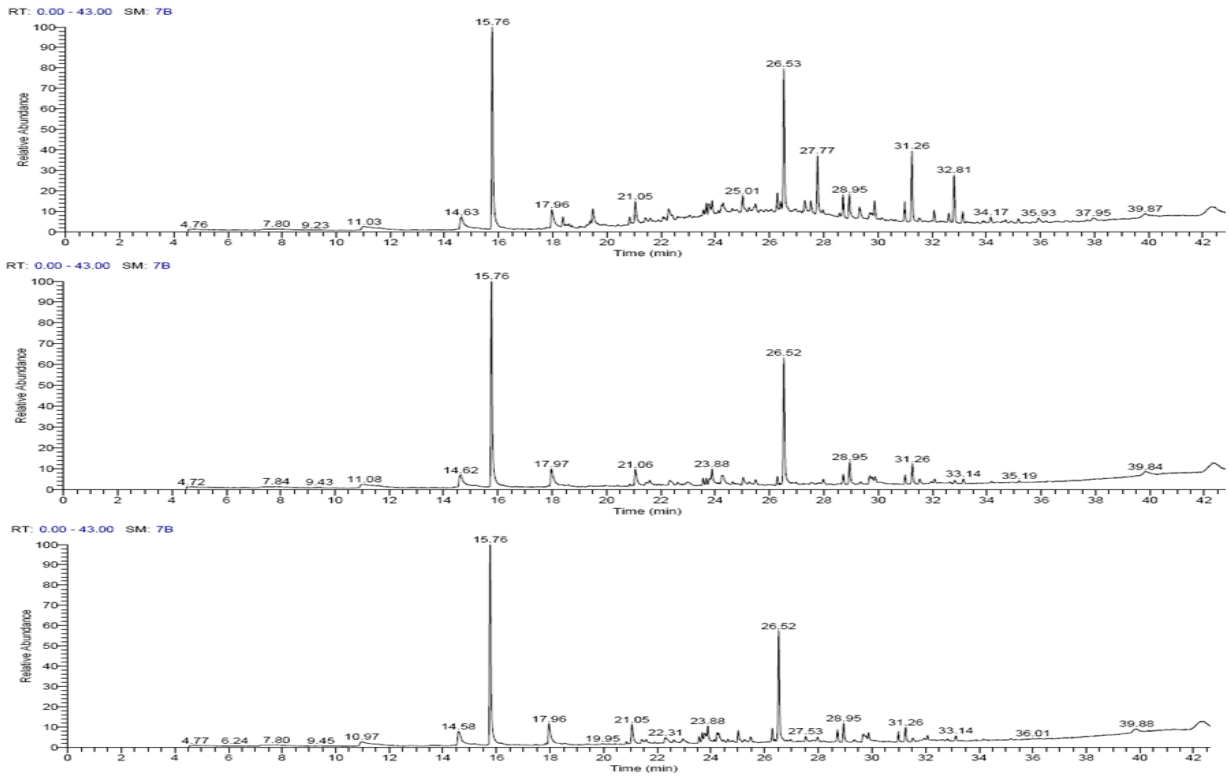
Table.4 GC-MS analysis of the ethyl acetate extracts of AC-6, Ac-7and Ac-8)

RT	**Percentage area**			**Compound name**	**Molecular formula**	**Molecular weight**	**Proposed function**
	AC-6	**AC-7**	**AC-8**				
14.58	-	-	3.8	1-Hexadecanol	$C_{14}H_{34}O$	242	Antibacterial (35)
14.62	1.92	3.35	-	3-Eicosene, (E)-	$C_{20}H_{40}$	280	Antimicrobial, Antihyperglycemic , Cytotoxic Activity , Antioxidant, Insecticidal activity (36)
15.76	20.19	32.66	32.42	Phenol, 2,4-Bis(1,1-dimethyl ethyl)	$C_{14}H_{22}O$	206	Antioxidant, Analgesic, Anticancer **(37)**
17.96	2.61	3.99	4.39	1-Docosene	$C_{22}H_{44}$	308	Antibacterial, Anti-inflammatory (38)
18.37	1.13	-	-	1-(4-IsoPropylPhenyl)2-Met-Hylpropyl Acetate	$C_{15}H_{22}O_2$	234	Anti-inflammatory, antiheistamanial and antitrypanosoma (39)
19.38	0.05	-	-	Pentacosane	$C_{25}H_{52}$	352	Major component of essential oils (40)
19.47	2.10	-	-	Isopropyl Tetradecanoate	$C_{17}H_{34}O_2$	270	Anti-inflammatory (41)
20.84	0.76	-	-	Methoxyacetic acid, 2-tetradecyl Ester	$C_{17}H_{34}O_3$	286	Anti-microbial (35)
21.05	2.57	-	3.73	1-Docosene	$C_{22}H_{44}$	308	Antibacterial (38)

21.06	-	3.38	-	2-Hexadecanol	$C_{16}H_{34}O$	242	Antimicrobial activity (38)
21.41	0.59	-	-	Tetradecanoic Acid, 12-Methyl-Ester	$C_{16}H_{32}O_2$	256	Antioxidant, cancer preventive, Nematicide, lubricant and Hypocholesterolemic (42)
21.58	-	1.31	-	Oxiraneundecanoic acid, 3-Pentyl-Methyl Ester	$C1_9H_{36}O_3$	312	Anti-oxidant (43)
22.08	0.73			2-Hexadecanol	$C_{16}H_{34}O$	242	Anti-microbial (38)
27.30	1.48			2-Propenoic acid, 3-(4-methoxyphenyl)-, 2-ethylhexyl ester	$C_{18}H_{26}O_3$	290	Anti- inflammatory**(41)**
27.53	1.28		0.97	Ethanol, 2-(octadecyloxy)	$C_{20}H_{42}O_2$	314	Antimicrobial (50)
27.77	5.9			TriButylAcetylcitrate	$C_{20}H_{34}O_8$	402	no activity
27.98		0.89		13-Methyl.13-Carpinalpodo carp-7EN 3B 3BXIDiol CARP-7-EN-3B,X-DIOL	$C_{19}H_{30}O_3$	306	no activity
28.72	2.27	1.67	2.04	Heptacosane	$C_{27}H_{56}$	380	antibacterial(44)
28.95	2.64	4.28	3.2	1-Monopalmitin, 2TMS derivative 2,3-Bis ((TriMethylSilylL) OXY) Propy Ester	$C_{25}H_{54}O_4Si_2$	474	no activity
28.97			0.86	1-Heptatriacotanol	$C_{37}H_{76}O$	536	Antimicrobial (35)
29.33	1.54			2-Propenoic acid, 3-(4-Methoxyphenyl)-, 2EthylHexyl Ester	$C_{18}H_{26}O_3$	290	Anti- inflammatory (41)
29.68	-	-	2.18	9-Octadecenamide	$C_{18}H_{35}NO$	281	Anti-oxidant and anti-inflammatory effect (45)
29.69		1.51	-	9-Octadecenamide	$C_{18}H_{35}NO$	281	Anti-oxidant and anti-inflammatory effect (45)
29.88	1.89	0.74	0.97	1-Docosene	$C_{22}H_{46}$	310	Antibacterial (38)
30.99	2	1.47	1.62	Heptacosane	$C_{27}H_{56}$	380	Antibacterial (44)
31.26	6.87	3.28	2.59	1,2-BenzenedicaRboxylic Acid, 3-Nitro	$C_8H_5NO_6$	211	Antibacterial and antioxidant (38)
31.52	-	1.09	-	Oleic Acid, 3-(Octadecyloxy)propyl Ester	$C_{39}H_{76}O_3$	592	Antifungal (46)
32.08	1.21	0.78	0.78	Ceidoniol, Deoxy	$C_{29}H_{60}$	408	Anti-inflammatory and Anti-cancer (47)
32.62	1.03	-	-	1,3-Benzenedicarboxylic Acid,Bis(2-	$C_{24}H_{38}O_4$	390	Aantibacterial., Antioxidant and antiviral (38)

				EethylHexyl) Ester			
32.81	4.48	-	-	Squalene	$C_{30}H_{50}$	410	Antibacterial, antioxidant, antitumor, cancer preventive, immunostimulant (49)
33.13	1.12	-	-	Docosane	$C_{22}H_{46}$	310	Antibacterial (42)
33.14	-	0.84	0.89	Isochipane B	$C_{19}H_{22}O_6$	346	Antibacterial (48)
34.17	0.67	-	-	Octadecane, 3-Ethyl-5-(2-EthylButyl)-	$C_{26}H_{54}$	366	anti-inflammatory, analgesic antipyretic, antimicrobial, antioxidant, antitumor and anti-diabetic activities (42)
35.19	0.57	-	-	Isochipane B %2<	$C_{19}H_{26}O_6$	350	Antibacterial (48)
35.93	0.75	-	-	Oleic Acid	$C_{18}H_{34}O_2$	282	Anti-inflammatory(38)

Fig.1 GC-MS analysis of the ethyl acetate extract of AC-6, AC-7 and AC-8



The Actinomycetes were tested against *Bacillus cereus*, *Escherichia coli* O157, IsolateAC-2 strain showed antimicrobial activity against *B. cereus*. Isolate AC-5 showed the highest inhibition zone against *E.coli* O157.

The results of GC-MS analysis revealed that the ethyl acetate extracts of Actinomycetes metabolites (AC-6, AC-7 and AC-8) contain various constituents like essential oils, fatty acids, esters, alcohols, phenols, alkanes, steroids, and terpenes such as 2,4-di-tert-butylphenol, 3-chloropropionic acid, heptadecyl ester, 1,2-benzenedicarboxylic acid, 3-nitro, benzenepropanoic acid, 3,5-bis(1,1 dimethylethyl)-4-hydroxy-,octadecyl ester, 1-monopalmitin, 2TMS derivative, 1-docosene, 1-nonadecene, 1-nonacosene and eicosene (Table 4). These active compounds

possesses different biological activities such as antimicrobial, antibacterial, antifungal, antioxidant, antitumor, anti-hyperglycemic, analgesic, anti-inflammatory, antileishmanial, antitrypanosoma, antispasmodic, antituberculosis, antipyretic, nematicide and lubricant (35, 36, 37, 38,39, 41, 42, 43, 45, 46, 48, 51, 52, 53). The obtained results were supported by (24) who reported that secondary metabolism is of special interest in *Streptomyces*, that occupies a high position in the developmental hierarchy of bacteria due to their advanced morphology and physiology. *Streptomycetes* have evolved a plethora of biosynthetic pathways to produce various secondary metabolites, especially signal molecules, or antibiotics. These compounds provide the organism with a competitive advantage, protection from unfavorable living conditions and/or facilitate interspecies interactions and have an antimicrobial, antioxidant and anticancer effect (25).

According to (26) the compounds generated by AUDT 217, thirteen compounds have an antimicrobial or antitumor characteristic. This study in parallel with results of (50).who indicated that marine actinomycetes are efficient producers of new secondary metabolites that show a range of biological activities including antibacterial, antifungal, anticancer, insecticidal and enzyme inhibition. Bioactive compounds from marine actinomycetes possess distinct chemical structures that may form the basis for synthesis of new drugs that could be used to combat resistant pathogens.

Studies of (16, 28) confirmed that some genes share for biosynthesis of Actinomycetes secondary active metabolites in their clustering and regulation. The chemical structure has so far been elucidated in less than 30 percent of the compounds, belonging to the following groups of natural substances: polyketides, pyrones, peptides, siderophores, γ-butyrolactones, butenolides, furans, terpenoids, fatty acids, oligopyrroles, and deoxysugars as indicated in our study (24). The remaining 70 percent are called "cryptic compounds" as they are not produced at standard laboratory conditions (16,29, 30, 28, 24). To activate these cryptic pathways, Actinomycetes are cultivated under non-standard physical and nutritional conditions or co-cultured with other microorganisms (31). Genetic manipulations within the genes (32)or the transfer of the whole biosynthetic gene cluster into a heterologous producer (33, 28)are also commonly used strategies. The successful activation of the biosynthetic pathways often leads to biosynthesis of previously unknown compounds (27, 30, 34, 28).

In conclusion the actinomycetes, especially *Streptomycetes*, still an important source for bioactive compounds that are used for treating infection diseases, cancer, and many other diseases. The derivative of bioactive metabolites produced by Actinomycetes isolated from Giza Governorate, Egypt, demonstrated obvious inhibitory effects against both Gram-positive and Gram negative bacteria.

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