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Research Article

Phytochemical profiling of the methanolic partition of endophytic *Streptomyces* sp. SUK48 using LC-MS/MS and molecular networking

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Abstract

Antimicrobial resistance has become a global challenge due to the difficulty in controlling it and the increasing need for new drugs. *Streptomyces* species are Gram-positive bacteria recognized for producing a wide range of secondary metabolites with diverse biological functions. This study aimed to profile and characterize the phytochemicals of the methanolic partition of *Streptomyces* sp. SUK48 using liquid chromatography quadrupole time-of-flight mass spectrometry with tandem mass spectrometry (LC-QTOF-MS/MS) equipped with electrospray ionization (ESI). The analysis was conducted via the Global Natural Products Social Molecular Networking (GNPS) platform. *Streptomyces* sp. SUK48 was cultivated in a rice-based yeast medium for 8 days (SRY48-8) and sequentially partitioned into methanol and hexane fractions. The methanol fraction was analyzed using LC-QTOF-MS/MS with ESI, and the resulting data were processed through GNPS. Seventeen phytochemicals were identified, including polyketides, amino acids, lipids, pyrimidine derivatives, and fatty acids. Some identified compounds, such as tetracycline (2) and luvangetin (5), have been previously reported to exhibit antibacterial and antifungal properties. These findings emphasize the potential of *Streptomyces* sp. SUK48 is a promising candidate for future drug discovery.

Keywords: Antimicrobial resistance, Drugs discovery, Secondary Metabolites, Molecular Networking, *Streptomyces* sp.

Introduction

Antimicrobial resistance (AMR) is a major global threat due to the ability of microorganisms to resist drugs designed to treat them, leading to critical public health problems [1]. The United States Centers for Disease Control and Prevention (USCDC, 2019) reported that at least 2.8 million people in the U.S. suffered from antibiotic-resistant infections, resulting in 35,000 deaths [2]. Besides the high estimated death toll, AMR also affects the economy and can cause poverty among millions of people [3]. The World Health Organization (WHO) has emphasized the benefits of natural resources as an alternative to fill gaps in current treatments. This highlights that natural products contain bioactive compounds with diverse chemical compositions and pharmacological potential, capable of treating diseases such as microbial infections, inflammatory disorders, and cancer [4]. *Streptomyces* spp. is among the largest and most widespread actinomycetes, leading the field of drug-producing microbes. They are considered prolific producers, with over 7,600 bioactive compounds identified [5, 6]. Furthermore, *Streptomyces* spp. has shown great ability in producing secondary metabolites with a wide range of biological activities [7]. These secondary metabolites encompass diverse chemical classes such as cyclic and linear peptides, peptide derivatives, polyketides, terpenoids, polyaromatics, macrocycles, and furans, which exhibit various biological activities, including enzyme inhibition and anticancer effects. This confirms that *Streptomyces* spp. remains a significant source of natural products [8].

Streptomyces sp. SUK48 was isolated from the fruit of *Brasilia* sp., located in the Universiti Kebangsaan Malaysia reserve forest. A study by Ahmad and colleagues showed metabolites from this endophytic *Streptomyces* sp. SUK48 has high potential as an antimalarial drug, with an inhibition concentration (IC50) value of 0.1963 ng/mL [9]. Additionally, *Streptomyces* sp. SUK48, when incubated in a broth medium for 14 days, exhibited antibacterial activity against *Pseudomonas aeruginosa*, *Acinetobacter*

baumannii, and *Escherichia coli*, while showing no cytotoxicity against normal cells. This demonstrates its potential as a non-toxic antibiotic producer [10]. Previous studies have consistently shown the capacity of *Streptomyces* sp. SUK48 as an excellent antimicrobial producer.

The complexity of natural products often requires significant time and effort for compound production. Therefore, optimizing metabolite production methods and employing advanced analytical techniques for compound screening are essential [11-13]. Metabolomics analysis is a powerful tool for both qualitative and quantitative profiling of metabolites, even those at low abundance [14, 15]. Combining LC-MS and computational tools for compound prediction allows for comprehensive analysis of complex natural products [16]. A key technique in this process is molecular networking (MN), which groups compounds with similar MS/MS fragmentation patterns into clusters [17-19]. Additionally, molecular networking, when aided by the Global Natural Products Social Molecular Networking (GNPS) library, greatly improves efficiency of compound annotation, facilitating both identification and characterization [20, 21].

To address the inherent complexity of natural product mixtures, this study employed LC-QTOF-MS/MS coupled with GNPS. This integrated approach enables comprehensive profiling and sensitive detection of low-abundance metabolites, providing a reliable platform to uncover novel bioactive compounds in *Streptomyces* sp. SUK48. The utility of this strategy has been demonstrated in previous studies; for instance, Adra et al. (2023) analyzed extracts from *Streptomyces* sp. using LC-QTOF-MS/MS combined with molecular networking and identified several abundant classes of compounds, including polyketides, isoflavonoids, macrolides, coumarins, and cyclic peptides [22]. Similarly, application of the same analytical framework to *S. albidoflavus* SAC61 revealed its potential as a novel source of antimicrobial agents, with cyclopentanone-derived compounds exhibiting significant bioactivity. Notably, *S. albidoflavus* SAC61 inhibited the growth of *P. aeruginosa* and *E. coli* with MIC values of 25 µg/mL and 12.5 µg/mL, respectively [23], highlighting the power of LC-MS/MS and molecular networking in linking chemical diversity to biological function.

Given the rising threat of antimicrobial resistance, the identification of novel bioactive compounds from *Streptomyces* sp. SUK48 holds considerable promise in addressing this global health challenge. The findings of this study could pave the way for the development of new antimicrobial agents, contributing to more effective treatments and improved public health outcomes.

Materials and Methods

Preparation of *Streptomyces* sp. SUK48 sample

A stock culture of *Streptomyces* sp. strain SUK48 was obtained from the Microbiology Laboratory of Prof. Dr. Noraziah Mohd Zain at Universiti Kebangsaan Malaysia, Kuala Lumpur. This strain, originally isolated from the fruit of *Brasilia* sp., was revived by inoculation onto International *Streptomyces* Project-2 Medium (ISP-2) agar plates. Cultures were prepared in triplicate and incubated at room temperature for 10 days to ensure active growth.

Preparation of methanol partition of *Streptomyces* sp. SUK48 incubated in rice with yeast medium for 8 days (SRY48-8)

A total of 100 g of rice, 100 mL of Milli-Q water, and 200 mg of yeast extract were added to a 2 L Erlenmeyer flask and soaked overnight before autoclaving. The medium was then cooled to room temperature. A 500 µL inoculum of *Streptomyces* sp. SUK48 was pipetted into the flask and adjusted to a 0.33 McFarland standard. The mixture was homogenized thoroughly and incubated for 8 days (100 replicates). Subsequently, 1 L of ethyl acetate was added to each flask, followed by sonication for 1 hour and filtration through cotton wool. The organic extracts were concentrated under reduced pressure using a rotary evaporator (Büchi, Switzerland). Liquid–liquid extraction (LLE) was performed with hexane and methanol. The resulting hexane and methanol fractions were concentrated under vacuum with a rotary evaporator. The extracts were stored at 4 °C until further analysis.

Metabolic profiling of methanol partition of SRY48-8 using LC-QTOF-MS/MS

The methanol fraction (1 mg) was dissolved in 1 mL of methanol and analyzed by liquid chromatography–time of flight mass spectrometry (LC-QTOF-MS) using a MicroTOF QIII mass spectrometer (Bruker Daltonics, USA) equipped with electrospray ionization (ESI). Chromatographic separation was performed on a Thermo Scientific C18 column (Acclaim™ Polar Advantage II, 3 × 150 mm, 3 µm) coupled to an UltiMate 3000 UHPLC system (Dionex, USA). The mobile phases comprised (A) water containing 0.1% formic acid and (B) 100% acetonitrile. A linear gradient was applied at a flow rate of 0.4 mL/min and column temperature of 40 °C as follows: 5% B (0–3 min), 80% B (3–10 min), isocratic at 80% B (10–15 min), and re-equilibration to 5% B (15–22 min). The TOF analyzer operated in positive ion mode to produce high-resolution mass data for molecular ion detection. Data acquisition and processing were performed using Compass DataAnalysis software (Bruker Daltonik

GmbH, USA). All analyses were conducted at the Institute of Biotechnology (INBIOSIS), Universiti Kebangsaan Malaysia (UKM).

Structural annotation using GNPS-library

Raw mass spectrometry data in proprietary format (.d) were converted to the open mzML format using DataAnalysis software (Bruker Daltonics) and subsequently uploaded to the GNPS platform (GNPS, https://gnps.ucsd.edu). GNPS parameters were set: precursor ion mass tolerance of 2.0 Da and fragment ion mass tolerance of 0.5 Da. Molecular networks were constructed with a minimum of six matched fragment ions, a minimum cosine score of 0.55, and a cluster density threshold of 0.5. Spectral annotation was performed by comparing MS/MS data against the GNPS spectral library. Molecular networks were visualized and analyzed using Cytoscape (version 3.10.2, www.cytoscape.org).

Results and Discussion

Metabolite profiling of the methanol partition of SRY48-8 was conducted using LC-MS/MS in positive ionization mode. Compound identification relied on high-resolution full MS and MS/MS spectra obtained under these conditions. The total ion chromatogram (TIC) shows the summed ion intensities of the detected metabolites (**Figure 1**). Seventeen metabolites were annotated through molecular networking on the GNPS platform, each assigned a unique cluster index. Detailed information on these metabolites is presented in **Table 1**.

The partition included various chemical classes, such as polyketides, amino acids, lipids, pyrimidine derivatives, and fatty acids—compound families known for their antifungal and antibacterial properties. Among the annotated metabolites, five were identified as polyketides: 8-hydroxy-6-methoxy-7-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxy methyl)oxan-2-yl]oxychromen-2-one (1), tetracycline (2),(1S,4aS,7aR)-7-methyl-1-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-4a [(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxy-1,7a-dihydrocyclopenta[c]pyran-5-one(4), luvangetin (5), and nanaomycin E (9).

The identification of these structurally diverse and bioactive compounds in the methanolic extract of *Streptomyces* sp. SUK48 highlights its potential as a source of novel antimicrobial agents. Specifically, polyketides such as tetracycline (2), luvangetin (5), and nanaomycin E (9) are well-known for their broad-spectrum antibacterial and antifungal activities [24–26]. Tetracycline, originally isolated from *Streptomyces aureofaciens* and *S. rimosus*, acts against clinically relevant pathogens including *Staphylococcus aureus*, *E. coli*, and *Candida albicans* [27, 28]. Luvangetin has shown antifungal activity, especially against *Fusarium verticillioides* [29–31], while *nanaomycin* E selectively inhibits Gram-positive bacteria [32].

In addition to polyketides, several fatty acids and lipid compounds were annotated via the GNPS spectral library, including 12S-hydroxy-5Z,8E,10E-heptadecatrienoic acid (14), 9S-hydroxy-10E,12Z,15Z-octadecatrienoic acid (15), and 2-stearoyl-sn-glycero-3-phosphocholine (3). Fatty acids of this class are recognized for their antimicrobial and anti-inflammatory effects [33–37]. Compounds 14 and 15, along with vanillyl mandelic acid (16), have demonstrated inhibitory effects against pathogenic strains such as S. aureus and E. coli [20, 38, 39]. The co-occurrence of bioactive polyketides and structurally diverse lipids in the methanol partition suggests possible synergistic interactions that may enhance antimicrobial effectiveness [40].

Structural assignment of the annotated metabolites was confirmed by spectral matching against reference entries in the GNPS library, with several compounds showing mirror-image spectral similarity. Annotation confidence was evaluated using the GNPS class-level scoring system: gold (high similarity), silver (moderate), and bronze (low). Compounds including luvangetin (5), nanaomycin E (9), (E)-(Dimethylamino)methylidene amino phenyl methylcarbamate hydrochloride (11), and vanillyl mandelic acid (16) achieved gold-level annotations, demonstrating high structural congruence between experimental and reference MS/MS spectra (**Figure 2**)

Table 1. Compounds from the methanol partition of *Streptomyces* sp. SUK48 day 8 (SRY48-8) annotated by the GNPS library

No.	Compound Name	Library Class	Cluster Index	Cosine	MZ Error/ PPM	Spectral m/z Library m/z	Instrument	Data Source
1	8-hydroxy-6-methoxy-7-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] oxychromen-2-one	Bronze	311	0.59	2287	371.946/371.10	ESI-QFT	MoNA
2	Tetracycline	Bronze	360	0.59	449	445.36/445.16	Hybrid FT	Massbank
3	2-Stearoyl-sn-glycero-3-phosphocholine	Gold	376	0.70	66	524.337/524.37	CID; Velos	Thomas Metz
4	(1S,4aS,7aR)-7-methyl-1-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] oxy-4a-[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl] oxy-1,7a-dihydrocyclopenta[c]pyran-5-one	Bronze	372	0.62	3694	487.354/489.16	ESI-QFT	MoNA
5	Luvangetin	Gold	247	0.51	6752	279.182/281.08	Orbitrap	BMDMS-NP
6	2-(4-fluoro-N-propan-2-ylanilino)-2-oxoethanesulfonic acid	Bronze	244	0.61	4056	277.119/276.07	qTof	Massbank
7	Monoethylglycinexylidide|N-(2,6-dimethylphenyl)-2-(ethylamino)acetamide	Bronze	43	0.83	9350	209.086/207.15	qTof	Massbank
8	9-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl) oxolan-2-yl]-2-(methylamino)-3H-purin-6-one	Bronze	255	0.91	6658	296.13/298.12	qTof	Massbank
9	Nanaomycin E	Gold	283	0.51	5126	334.385/336.11	Maxis II HD Q-TOF Bruker	Jadhav/Dorrestein
10	N-Hydroxypentadecanoylphenylalanine	Bronze	341	0.66	4878	404.312/406.29	Orbitrap	de Pascale/Della Sala
11	(E)-(Dimethylamino) methylidene amino phenyl methylcarbamate hydrochloride	Gold	80	0.68	9004	224.123/222.12	Maxis HD Q-TOF	Dorrestein/Touboul
12	Phe-C15:1	Silver	324	0.66	5101	386.304/388.29	qTof	Dorrestein
13	1,2-Dilinoleoyl-sn-glycero-3-phosphocholine	Bronze	427	0.96	0	782.563/782.56	HCD	Data from Pieter C. Dorrestein
14	12S-Hydroxy-5Z,8E,10E-heptadecatrienoic acid	Bronze	41	0.83	369	203.175/203.10	IT/ion trap	Data from Dorrestein/Knight
15	9S-Hydroxy-10E,12Z,15Z-octadecatrienoic acid	Bronze	248	0.65	7199	279.226/277.23	Ion trap	Data from Valerie J Paul
16	Vanillyl mandelic acid	Gold	37	0.79	9848	195.105/197.05	Orbitrap	PI
17	2-(4-methyl-6-(2-naphthyloxy) pyrimidin-2-ylthio)-1-phenylethan-1-one	Bronze	327	0.59	154	387.175/387.12	Orbitrap	Trent Northen

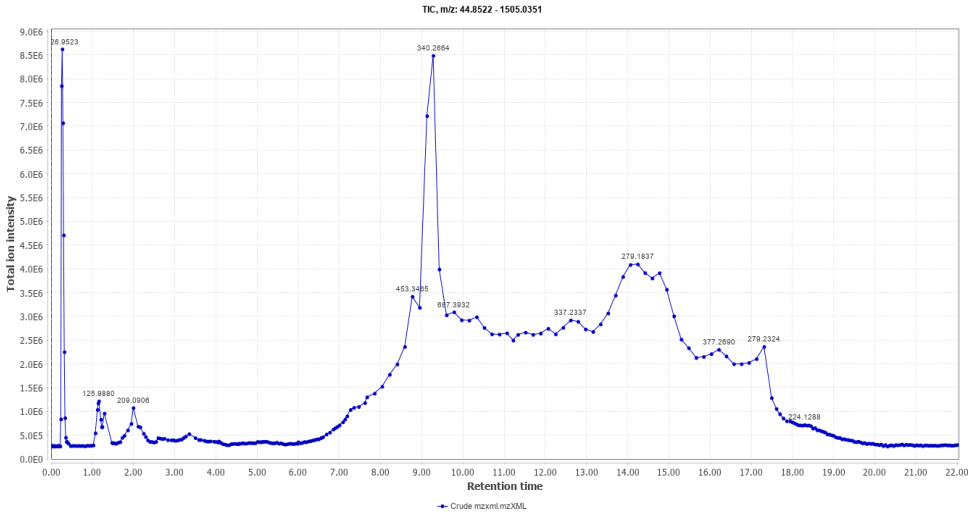

Figure 1. The total of ion chromatogram (TIC) of the SRY48-8 methanol partition

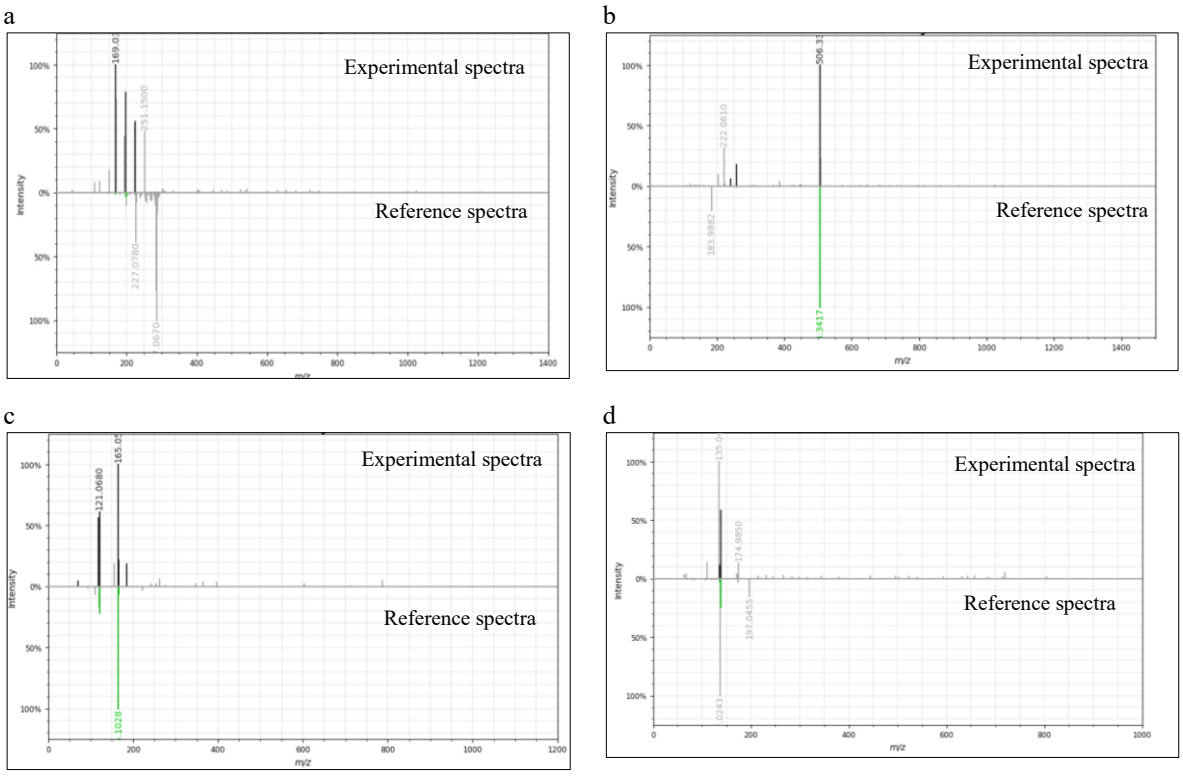

Figure 2. (a) Mirror match of compound 5 with the reference spectra, showing a gold library class and a cosine value of 0.59; (b) Mirror match of compound 9 with the reference spectra, showing a gold library class and a cosine value of 0.51; (c) Mirror match of compound 11 with the reference spectra, showing a gold library class and a cosine value of 0.68; (d) Mirror match of compound 16 with the reference spectra, showing a gold library class and a cosine value of 0.79

While the LC-MS/MS analysis allowed the annotation of several bioactive metabolites, the absence of in vitro bioactivity assays in this study restricts the confirmation of their functional properties. Future research should prioritize the isolation and purification of these compounds to assess their antimicrobial and cytotoxic activities. Furthermore, mechanistic investigations are required to clarify their modes of action and evaluate their therapeutic potential. The findings of this study expand the current understanding of microbial natural products and emphasize the importance of *Streptomyces* sp. SUK48 as a valuable source of bioactive metabolites. By revealing a diverse range of annotated compounds, this work provides a basis for developing novel antimicrobial agents in response to the increasing global challenge of antimicrobial resistance.

Conclusion

This study successfully profiled the methanolic extract of *Streptomyces* sp. SUK48 using LC-QTOF-MS/MS combined with GNPS-based molecular networking led to annotating 17 metabolites. These compounds represent diverse chemical classes, including polyketides, fatty acids, lipids, amino acids, and pyrimidine derivatives. Notably, several annotated compounds such as tetracycline, luvangetin, and nanaomycin E are known for their broad-spectrum antibacterial and antifungal activities, emphasizing the strain's potential as a source of bioactive natural products. The co-occurrence of multiple antimicrobial-associated compound classes indicates possible synergistic interactions, although this hypothesis requires further experimental validation. These findings highlight the metabolic richness of *Streptomyces* sp. SUK48 and support its role in the discovery of novel agents to combat antimicrobial resistance. Future studies should focus on the isolation and purification of these metabolites for in vitro testing of antimicrobial and cytotoxic activities. Mechanistic investigations will further clarify their modes of action and therapeutic applicability. Using advanced metabolomics approaches, this work contributes to the expanding knowledge of microbial natural products and supports ongoing efforts to address one of the most pressing global health challenges.

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