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Genome Report

Complete Whole-Genome Sequence of *Streptomyces* sp. MUM 178J, a Potential Anti-*Vibrio* Agent

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Abstract: *Streptomyces* sp. is a group of filamentous, Gram-positive bacteria well known for their capabilities in producing bioactive compounds that have been used as novel drugs and lead in drug development. The *Streptomyces* sp. MUM 178J was isolated from a mangrove forest in Malaysia. This isolate was found to harbor anti-*Vibrio* properties as its crude extract inhibited the growth of multidrug-resistant *Vibrio parahaemolyticus*. Therefore, the strain was subjected to whole genome sequencing to unearth its genomic potential. The genome of *Streptomyces* sp. MUM 178J consists of 6,699,249 bp with a G+C content of 71.3%. 66 tRNA genes and 18 rRNA genes were also predicted to be present within the genome. Further analysis with the bioinformatics tool, antiSMASH (antibiotics & Secondary Metabolite Analysis Shell), detected nine biosynthetic gene clusters displaying more than 70% similarity to known gene clusters, including one associated with melanin production. Melanin has demonstrated antagonistic activity against the growth of members of the *Vibrio* family, including *V. parahaemolyticus*. This indicates the potential correlation between the production of melanin and the anti-*Vibrio* properties of MUM 178J. The availability of the whole genome sequence of *Streptomyces* sp. MUM 178J allows for future in-depth investigation and potential exploitation of MUM 178J to harvest useful bioactive compounds.

Keywords: *Streptomyces* sp. MUM178J; genome; anti-*Vibrio*; melanin; mangrove; SDG 3 Good health and well-being

1. Introduction

Streptomyces sp. are a group of filamentous, Gram-positive bacteria that belong to the phylum *Actinobacteria* [1, 2]. Members of the genus *Streptomyces* remain captivating subjects in the realm of microbiology and drug discovery as they can produce a plethora of bioactive secondary metabolites [3, 4]. These metabolites are produced to prevent the growth of competing microorganisms when essential nutrients are depleted [5-7]. This is part of the developmental process in the complex life cycle of *Streptomyces* sp., which ensures the survival of species [8, 9]. Since the discovery of the first aminoglycoside, streptomycin, from *Streptomyces griseus* [10], decades of research ensued to extract bioactive compounds from streptomycetes [11]. Extensive research has proven that this filamentous bacteria acts as a reservoir for bioactive secondary metabolites that have the potential for numerous applications in developing drugs and therapeutics [12-17]. In recent years, research on *Streptomyces* has shifted to isolating novel species from underexplored environments such as mangroves, deserts, oceans, and even the Arctic to search for novel bioactive compounds [18-27]. For example, the secondary metabolites from *Streptomyces* sp. derived from these unchartered territories have exhibited interesting bioactivities such as anticancer, antifungal, antimicrobial, cytotoxic, and antioxidant properties [21, 23-25, 28-34]. These findings underscore the substantial potential of the undiscovered *Streptomyces* species in these unique environments.

In an effort to explore the diversity of *Streptomyces* species in dynamic environments, our previous study isolated *Streptomyces* sp. MUM 178J from soil sampled from mangrove forests in East Malaysia [35]. Upon further investigation, it was found that the fermentative extract of MUM 178J inhibited the growth of a multidrug-resistant (MDR) *Vibrio parahaemolyticus* strain RP0132. The minimum inhibitory and minimum bactericidal concentrations were 12.5mg/mL and 50mg/mL, respectively. This interesting finding shows the potential of MUM 178J to be harnessed as an anti-*Vibrio* agent to control MDR *V. parahaemolyticus* in aquatic environments. MDR *V. parahaemolyticus* remains prevalent in our surrounding environment, evidenced by various studies worldwide reporting on its prevalence in clinical, environmental, and seafood samples [36-47]. This pathogen can be easily transmitted to humans by consuming contaminated seafood and water, causing gastroenteritis or wound infections [48-51]. The high prevalence of MDR *V. parahaemolyticus* in the environment is concerning as these bacteria will propagate and further spread antibiotic resistance (AMR) intra- and interspecies [52-58]. This jeopardizes the sanctity of public health as infections caused by MDR bacteria are more difficult to treat and could ultimately result in longer durations of hospitalization and higher mortality rates [59, 60]. As reports of MDR *V. parahaemolyticus* continue to surge, it is imperative to develop alternatives to antibiotics to manage this pressing issue [61]. Hence, discovering anti-*Vibrio* properties in MUM 178J provides an optimistic outlook for developing an anti-*Vibrio* agent that can manage MDR *V. parahaemolyticus* populations. This, in turn, will reduce the spread of AMR in the environment, thereby preserving the efficacy of the antimicrobial agents that are currently available for use. To better understand the underlying mechanisms of the anti-*Vibrio* properties of *Streptomyces* sp. MUM 178J, the isolate was subjected to complete whole genome sequencing. This aims to identify the biosynthetic gene clusters (BGC) responsible for the production of the bioactive compound(s) associated with its anti-*Vibrio* activity through genome mining and to gain insight into the genomic characteristics of MUM 178J [62-66].

2. Data description

MUM 178J was grown routinely on International *Streptomyces* Project (ISP) 2 medium at 28˚C. Genomic DNA of MUM 178J was extracted using MasterPure Gram Positive DNA Purification Kit (LGC Biosearch Technologies) according to the manufacturer's instructions [56, 67]. The DNA quality and quantity were checked using agarose gel electrophoresis and Qubit 2.0 Fluorometer (Life Technologies, Carlsbad, CA, USA). SMRTbell DNA libraries were generated according to standard protocols and checked with Qubit for quantification and bioanalyzer for size distribution detection. The whole genome of MUM 178J was sequenced on PacBio Sequel II/IIe systems. Upon sequencing, the raw reads were assembled using Falcon, which is based on the hierarchical genome assembly process (HGAP). BUSCO assessment was also done to assess the genome assembly and annotation completeness with single-copy orthologs. Assembled genome was annotated by NCBI Prokaryotic Genome Annotation Pipeline (PGAP) v6.6. Ribosome RNA (rRNA) genes were analyzed by the RNAmmer and transfer RNA (tRNA) genes were predicted by the tRNAscan-SE. The whole genome of MUM 178J consists of 1 contig with G+C content

of 71.3%, the genome size of 6,699,249 bp, and a genome coverage of 300-fold. A total of 5,952 predicted genes and 5,693 protein-coding genes were detected in the genome. Based on the predictions, 69 tRNA genes, 18 rRNA genes, and 171 pseudogenes were present in the whole genome of MUM 178J (Table 1).

Table 1. Genomic features of *Streptomyces* sp. MUM 178J.

Streptomyces sp. MUM 178J	
Genome size (bp)	6,699,249
Total number of contigs	1
Contigs N_{50} (bp)	6,699,249
G+C content (%)	71.3
Genome coverage	300x
Number of chromosomes	1
Total number of predicted genes	5,952
Total number of protein coding genes	5,693
Total number of tRNA-coding genes	68
Total number of rRNA-coding genes	18
Total number of pseudogenes	171

Furthermore, analysis based on antibiotics & Secondary Metabolite Analysis SHell (antiSMASH version 7.0) database was performed on the whole genome to detect the presence of BGC in MUM 178J [68, 69]. This aimed to detect the presence of BGCs related to the production of secondary metabolites MUM 178J, which elicits anti-*Vibrio* properties. From the antiSMASH analysis, the BGC associated with the production of melanin was detected within the genome of MUM 178. Interestingly, studies have shown that melanin produced from *Streptomyces* sp. can exhibit anti-*Vibrio* properties. For instance, the melanin compound dihydroxyphenylalanine (DOPA), is produced from *Streptomyces* sp. MVSC6, isolated from marine sediments, elicited antagonistic activity against *V. parahaemolyticus* [70]. Moreover, marine *Streptomyces* have been reported to produce melanin pigments, which have antibacterial effects against Gram-negative bacteria, including members of the *Vibrio* family, such as *Vibrio cholerae* [71]. In addition, melanin pigments produced by marine-derived *Streptomyces* sp. MVCS13 was reported to inhibit fish pathogens such as *Vibrios* [72]. Therefore, the anti-*Vibrio* properties of MUM 178J could be attributed to the presence of melanin BGCs in its whole genome. These findings indicate the potential of MUM 178J as an anti-*Vibrio* agent that can be useful in managing MDR *V. parahaemolyticus* in the environment in efforts to reduce AMR. The availability of the whole genome sequence of MUM 178J also allows for further studies on the strain, including genomic manipulation to produce beneficial bioactive compounds.

The whole genome sequence of MUM 178J has been deposited at DDBJ/EMBL/GenBank under accession number CP140097. The data are publicly available

at NCBI GenBank under the BioProject accession number PRJNA679911, and the BioSample accession number SAMN16862319.

Author Contributions: K-YL conducted the laboratory research work, data analysis and manuscript writing. K-OC, JW-FL and L-HL provided support on the data analysis and data management. LT-HT, JW-FL, PP, K-GC, L-HL and VL provided resources, supervision, proofreading and technical support. VL, JW-FL and L-HL conceptualized and founded this writing project. All authors have read and agreed to the published version of the manuscript.

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