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Genome mining and AntiSMASH analysis of an Endophytic *Talaromyces* sp. reveal biosynthetic pathway gene clusters for novel bioactive compounds

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ABSTRACT

Medicinal plants and their endophytes are one of the efficient producers of diverse secondary metabolites with therapeutic importance. In the present study, an endophytic fungus *Talaromyces* spp. isolated from *Syzygium samarangense* was subjected to whole-genome sequencing and Antibiotics and Secondary Metabolite Analysis Shell (AntiSMASH) annotation to identify biosynthetic gene clusters (BGCs) of secondary metabolites and their biosynthetic pathways. The Funannotate results revealed that the *Talaromyces* isolate has a total of 30.5Mb genome consisting of 372 contigs, 372 scaffolds and 47.64% GC content. In addition, 114 tRNA, 12722 functional mRNA, 12721 CDS transcripts, and 12721 protein coding sequences were predicted and annotated using various BLAST databases. AntiSMASH revealed the presence of 76 BGCs, including 28 T1 Polyketide synthase (T1 PKS), 10 Nonribosomal peptide synthetases (NRPSs), 9 terpene, 1 Indole, 12 NRPs like, 4 T1 PKS and NRPs like, 2 T1 PKS Indole, 1 NRPs like terpene, 3 NRPs T1 PKS, 1 Indole NRPs, 2 betalactone, 1 phosphonate, 1 fungal-RiPP T1 PKS and 1 Other type. The analysis also predicted the occurrence of enzymes involved in the biosynthesis of some of the important secondary metabolites such as Pyranonigrin, Squalestatin -S, Azanigerone -A, Asperterpenoid -A, Napthopyrone, Clavaric acid, and Fusarin.

1. INTRODUCTION

Fungal endosymbionts are rich reservoirs for a wide variety of phytochemicals and phytohormones [1]. Endophytes residing inside plant systems contribute to the production of numerous novel compounds which have significant bioactive potential such as anti-cancerous, anti-inflammatory, anti-leishmanial, anti-microbial, and anti-malarial properties [2-4]. Several of these compounds synthesized under biotic and abiotic stress conditions during interdependent interaction between plants and their endophytes increases the survival value of both organisms. The fungus *Talaromyces* was first reported by mycologist Chester Ray Benjamin in 1955 under *Trichocomaceae*. The genus exhibits tightly interwoven hyphae with soft, cottony, yellowish fruit bodies (ascocarp) encompassing granules [5]. *Talaromyces* has been reported to synthesize several important secondary metabolites, including Huperzine A, a potent acetylcholine esterase inhibitor [6], and amestolkaloids, known for anti-inflammatory properties [7].

Whole genome sequencing (WGS) of fungi followed by genome annotation offers an attractive option for the identitification of novel and unexplored secondary metabolites and their biosynthetic genes. Bioinformatic tools such as Funannotate and SMuRF assist researchers in genome pipeline assemblies, annotations and natural product discovery through *in silico* strategies with precise, non-laborious, and rapid analysis. An important tool to identify Biosynthetic gene clusters (BGCs) in fungal genomes is Antibiotics and Secondary Metabolite Analysis Shell (AntiSMASH), which has been widely used to analyze several fungal genomes for secondary metabolites. Several compounds from *Talaromyces* spp. have been extensively studied for their bioactivities. However, genome mining of the species has not been carried out so far. In the present work, endophytic *Talaromyces* spp. isolated from *S. samarangense* was subjected to WGS and genome mining using AntiSMASH to identify any novel putative bioactive compounds.

2. MATERIALS AND METHODS

2.1. Isolation and Sub-culturing of Endophytic Fungal Strain-YS-1

The explant material (*S. samarangense*) leaves and stems were collected from Vajamangala village, Mysore district. The explant was thoroughly washed under running tap water. The leaf and stem bits were surface sterilized using 70% ethanol for 4 min, followed by

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sterile distilled water wash and treated with 1% sodium hypochlorite solution for 4 min. They were again washed with sterile distilled water for 2–3 times, and the leaf bits were placed on solidified potato dextrose agar (PDA) media supplemented with ampicillin 100 mg/mL. The Petri dishes were sealed with parafilm™ and incubated at 25 ± 2°C for 15 days with alternate light and dark cycles. Endophytic fungal mycelia which were observed on leaf and stem explants, were subcultured by point inoculation on PDA and potato dextrose broth media. Samples were monitored for further mycelial growth and were subjected to staining with lactophenol cotton blue in their sporulation state. Among the four endophytic fungal strains isolated from *S. samarangense*, strain YS-1 was selected for the present study.

2.2. Genomic DNA isolation and WGS of YS1 strain

DNA was isolated from the fungal mycelia by CTAB method [8]. Isolated DNA was eluted with 50 µL of TE buffer and stored at −20°C. The purity of isolated DNA was determined using NanoDrop™ 2000C spectrophotometer (Thermo Fisher Scientific). Genomic DNA samples were electrophoresed on 1% agarose gel to check purity and integrity. The high-quality DNA of strain YS1 was sent for whole genome sequence analysis to Hi-Gx360® Himedia Laboratories Pvt. Ltd., Mumbai, India. The sample analysis was as follows: 250 ng of total DNA was used as input for library preparation using QIASeq FX DNA kit to fragment and obtain adapter ligated and indexed library as per manufacturer's instructions. The indexed library was sequenced on an Illumina Miseq by paired-end chemistry of 300 cycles. The parameters used to check the raw data quality are included in a MultiQC report and are used to understand the quantity of data obtained for each of the paired read files for an individual sample [9]. The fastp tool (v0.12.4) was used to remove adapter contamination [10].

2.3. Genome Assembly and Annotations

A *de novo* de-brujin graph-based assembly was carried out to assemble the short reads into larger stretches of DNA called contigs. These contigs are the starting material used for executing a genome annotation that assigns functions to various regions of the genome of the organism in question. Quality assessment for genome assemblies generated by Spades, bioSpades, and Megahit assemblers was performed using the Quast tool [11-13]. It was noticed that the assembly generated by the megahit assembler had a comparatively higher number of contigs with sizes >10kb. Hence, assembly generated in bioSpades mode used for phylogenomics analysis and assembly generated using megahit assembler was masked and further used for annotations and natural product discovery.

A new pipeline carried out fungal gene structural and functional annotation, Funannotate, which uses several gene predictors such as glimerHMM, Augustus, SNAP, and Coding-Quarry to improve its prediction [14]. Proteins, transcripts, and nucleic acid annotation were executed by using software such as MEROPS (version 12), UniProt (version 2022_03), dbCAN (version 11), Pfam (version 35), RepeatsDB (version 1), GO (version 2022-07-01), MIBiG (version 1.4), InterPro (version 90), gene2product (version 1.8).

2.4. Phylogenomic Analysis

The Phylogenomic analysis was carried out by using the Benchmarking Universal Single-Copy Orthologs (BUSCO) quantitative genome analysis tool which basically compares different genomic data sets containing whole, identical and disintegrated genes based on gene prediction strategies [15].

2.5. Genome Mining for Natural Product Discovery

AntiSMASH tool: Fungal version 6.1.1 pipeline was used for the identification of potent secondary metabolite BGCs [16].

3. RESULTS AND DISCUSSION

3.1. YS-1 Strain Identification

The cultured fungal organism showed yellow-colored cottony mycelial mat with white dots covering the entire plate after being incubated for 15 days at 25 ± 2°C. Annotation and phylogenetic analysis results showed that the organism belongs to *Talaromyces* spp. and the stereomicroscopic view of strain YS-1 was examined [Figure 1a and b].

3.2. Genome Assembly and Sequencing

The genome sequence of strain YS-1 was deposited in the NCBI GenBank database (Accession No. PRJNA953512), and the Genome assembly of *Talaromyces* spp. was accessed by assemblers such as Biosynthetic spades, Spades, and Megahit. These assemblers were compared and analyzed using Quast (Quality assessment tool for genome assemblies). Megahit was found to be an effective assembler that provided data on an organism's complex metagenomic assemblies. The whole genome size of *Talaromyces* spp. was found to be 30.5Mb, consisting of 605 contigs (≥0 bp), 372 contigs (≥1000 bp), 208 contigs (≥5000 bp), 168 contigs (≥10000 bp), 149 (≥25000 bp), 125 contigs (≥50,000 bp) and the largest contig was found to be 1112360. The GC content was 46.74%, N50 was 3.33Mb, N75 was 1.86Mb. L50 value was 30 and the L75 value was 65. The Funannotate analysis indicated the presence of 114tRNA, 12722 functional mRNA, 12721 CDS transcripts, and 12721 protein-coding sequences in *Talaromyces* spp. YS-1 strain. The completeness of genome assembly, as measured by BUSCO, gave a score of 92.9%.

3.3. Phylogenetic Analysis and Phylogenomic Tree

The phylogenetic analysis of the *Talaromyces* spp. sequenced in the present study (YS-1 Strain) was compared with the isolates available in the database. Three groups could be identified in the phylogenetic

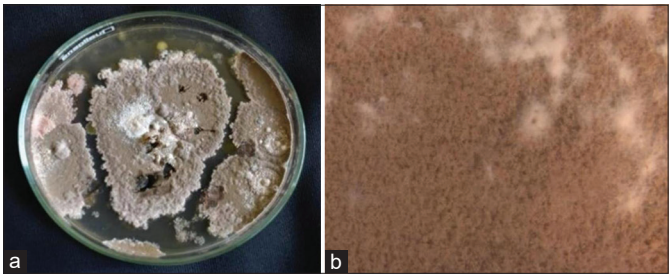

Figure 1: (a) Mycelial growth on potato dextrose agar plate. (b) Stereomicroscopic view of YS-1 strain.

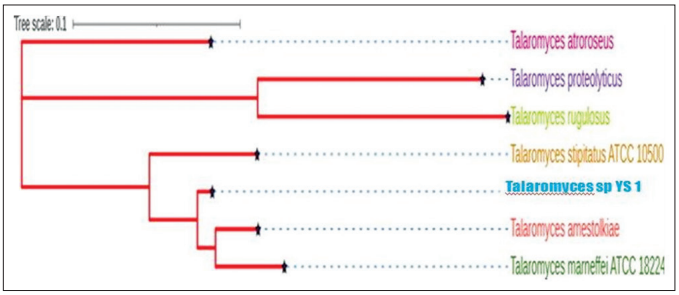

Figure 2: Phylogenomic tree of fungal *Talaromyces* strain YS-1.

tree, with the *Talaromyces* YS-1 strain forming a close relationship with *Talaromyces amestolkiae*, *Talaromyces marneffei,* and *Talaromyces stipitatus* in the first group. The second group consisted of *Talaromyces proteolyticus* and *Talaromyces rugulosus*. The other species *Talaromyces atroroseus*, formed a separate group [Figure 2].

3.4. Genome Mining for Natural Product Discovery

AntiSMASH provides information about the secondary metabolite genes by comparing the query gene cluster with the BGC library. Potential gene clusters of certain secondary metabolites such as terpenes, alkaloids, and phenolic compounds having industrial applications in pharmaceuticals and drug discovery can be analyzed using this comprehensive analysis tool for the fungal genome.

AntiSMASH analysis showed the presence of 76 secondary metabolite BGCs, which include 28 T1Polyketide synthases, 10 Nonribosomal peptide synthetases (NRPSs), 9 terpene, 1 Indole, 12 NRPs like 4 T1 Polyketide synthase (T1 PKS) and NRPs like, 2 T1 PKS Indole, 1 NRPs like terpene, 3 NRPs T1 PKS, 1 Indole NRPs, 2betalactone 1 phosphonate, 1 fungal-RiPP T1 PKS and 1 Other type [Table 1]. Over 40% of these BGCs indicated gene homologies with known clusters in the MIBiG database. Several clusters responsible for coding bioactive compounds such as Pyranonigrin-A, Alternariol, Asperterenoid-A,

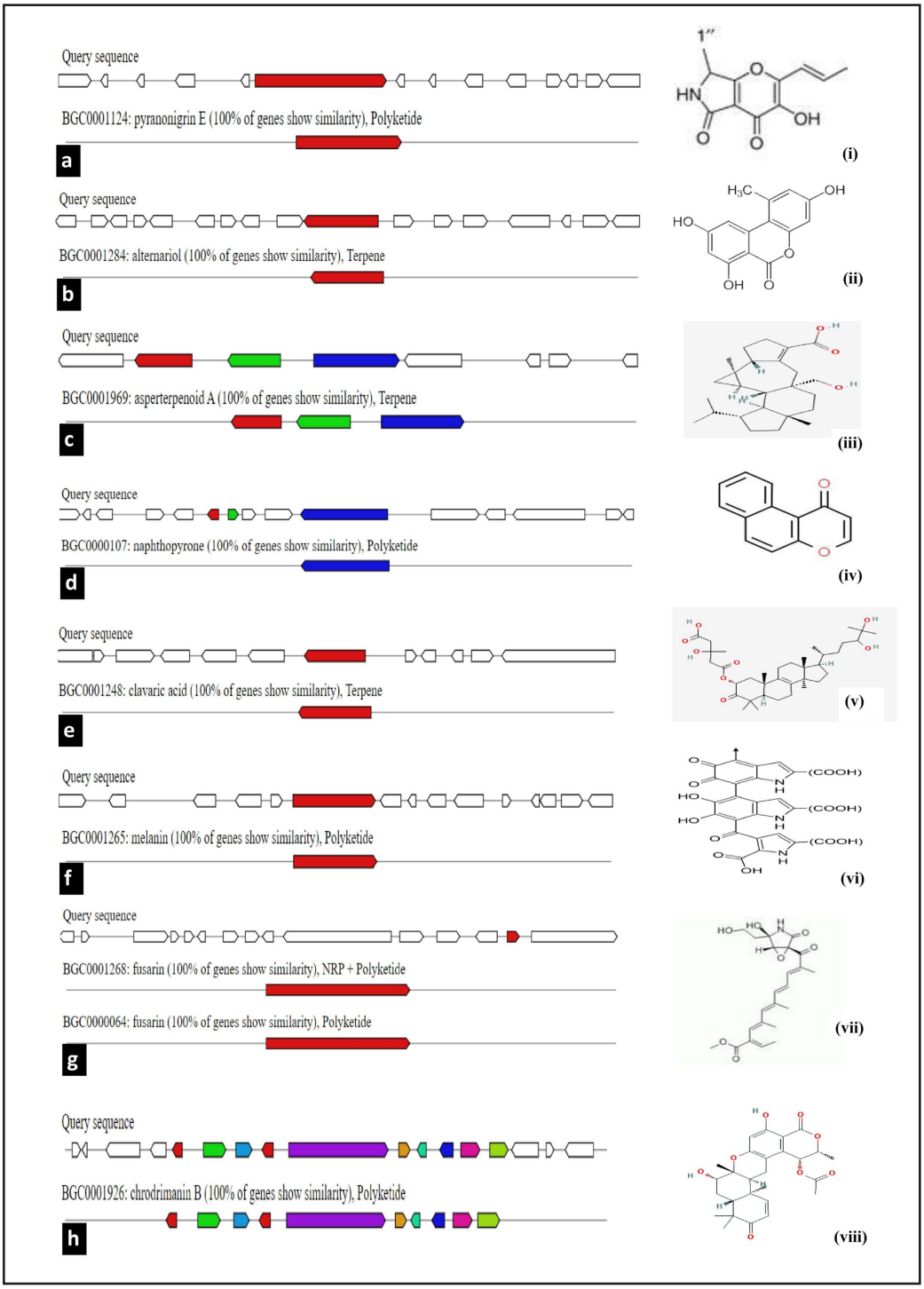

Figure 3: Comparison of BGCs in *Talaromyces* spp. YS-1 (a-h) with identified BGCs for biosynthesis of various bioactive compounds (i-viii).

Table 1: Predicted secondary metabolite biosynthetic gene clusters of strain YS-1.

Region	From	To	Type	Most similar known cluster
Region 1.1	27,682	357,538	T1PKS	Pyranonigrin E (100%)
Region 1.2	710,748	273,103	T1PKS	Unknown
Region 2.1	126,776	425,900	T1PKS	Terretonin (50%)
Region 2.2	498,524	46,806	NRPS-like	Unknown
Region 2.3	681,748	149,220	T1PKS, NRPS-like	Zearalenone (18%)
Region 3.1	291,287	267,110	T1PKS, indole	Trypacidin (35%)
Region 3.2	454,298	424,526	T1PKS	Viriditoxin (22%)
Region 3.3	736,454	271,795	T1PKS	Tricholignan A (50%)
Region 4.1	5,132	141,371	T1PKS	Unknown
Region 5.1	169,403	349,214	T1PKS	Alternariol (100%)
Region 5.2	358,147	224,543	NRPS-like, terpene	Squalestatin S1 (60%)
Region 5.3	689,574	171,848	NRPS-like	Unknown
Region 6.1	641	74,424	NRPS	Unknown
Region 6.2	316,319	122,148	T1PKS	Unknown
Region 6.3	605,092	179,953	NRPS, T1PKS	Emericellamide A/emericellamide B (40%)
Region 7.1	86,321	155,050	T1PKS, indole	Unknown
Region 8.1	108,656	127,159	T1PKS	Unknown
Region 8.2	429,656	35,955	indole	Fumigaclavine C (45%)
Region 9.1	117,817	133,974	NRPS-like	Unknown
Region 10.1	114,007	51,896	NRPS-like	Unknown
Region 10.2	208,461	48,783	NRPS-like	Unknown
Region 10.3	531,819	174,717	NRPS-like	Unknown
Region 10.4	598,279	61,197	other	Unknown
Region 11.1	257,617	139,510	NRPS-like	Unknown
Region 11.2	491,748	72,951	T1PKS	Azanigerone A (26%)
Region 13.1	268,179	210,071	Terpene	Asperterpenoid A (100%)
Region 14.1	64,395	71,552	NRPS	Unknown
Region 14.2	515,735	185,810	Betalactone	Unknown
Region 15.1	350,690	147,843	Terpene	Unknown
Region 16.1	411,349	176,667	NRPS	Unknown
Region 17.1	277,101	48,170	NRPS	Unknown
Region 18.1	1	154,701	NRPS	Unknown
Region 18.2	113,116	43,527	T1PKS	Unknown
Region 20.1	152,443	119,563	NRPS, T1PKS	curvupallide-B (11%)
Region 20.2	298,332	19,116	T1PKS	Griseofulvin/epidechlorogriseofulvin/norlichexanthone/ dehydrogriseofulvin/4-desmethylgriseofulvin/griseoxanthone B (14%)
Region 21.1	225,214	49,633	T1PKS	Citrinin (31%)
Region 21.2	382,522	82,811	Indole, NRPS	Clapurines (27%)
Region 22.1	1613	76,023	T1PKS	Unknown
Region 22.2	87,957	45,887	T1PKS	Azanigerone A (26%)
Region 22.3	219,037	48,863	T1PKS	Ankaflavin/monascin/rubropunctatine/monascorubrin (29%)
Region 22.4	390,717	46,696	NRPS	Unknown
Region 24.1	206,270	31,408	T1PKS	Unknown
Region 28.1	99,615	357,538	T1PKS	Fujikurin A/fujikurin B/fujikurin C/fujikurin D (66%)
Region 29.1	302,469	273,103	T1PKS	Unknown
Region 31.1	179,642	425,900	NRPS	Pyranonigrin E (100%)
Region 33.1	123,646	46,806	T1PKS	Unknown

(Contd...)

Table 1: *(Continued).*

Region	From	To	Type	Most similar known cluster
Region 34.1	52,652	149,220	Terpene	Unknown
Region 37.1	78,840	267,110	NRPS-like	Unknown
Region 38.1	128,355	424,526	NRPS, T1PKS	Unknown
Region 39.1	111,254	271,795	NRPS-like	Unknown
Region 40.1	105,708	141,371	Terpene	Unknown
Region 41.1	1	349,214	Phosphonate	Unknown
Region 41.2	90,852	224,543	NRPS-like	Unknown
Region 47.1	27,647	171,848	Betalactone	Unknown
Region 48.1	2189	74,424	T1PKS	Naphthopyrone (100%)
Region 49.1	67,645	122,148	fungal-RiPP, T1PKS	Ankaflavin/monascin/rubropunctatine/monascorubrin (20%)
Region 54.1	13,165	179,953	T1PKS	Pyranonigrin E (100%)
Region 54.2	116,565	155,050	Terpene	Unknown
Region 57.1	19,253	127,159	T1PKS, NRPS-like	Unknown
Region 59.1	196,661	35,955	Terpene	Unknown
Region 60.1	49,877	133,974	Terpene	Sordarin (11%)
Region 63.1	163,422	51,896	Terpene	Clavaric acid (100%)
Region 67.1	92,953	48,783	T1PKS	Chrysoxanthone A/chrysoxanthone B/chrysoxanthone C (8%)
Region 68.1	132,828	174,717	NRPS-like	Unknown
Region 69.1	4601	61,197	T1PKS	Melanin (100%)
Region 69.2	105,785	139,510	T1PKS	Fusarin (100%)
Region 71.1	502	72,951	NRPS	Unknown
Region 71.2	73,873	210,071	NRPS	Unknown
Region 73.1	1	71,552	Terpene	Unknown
Region 97.1	1	185,810	T1PKS	Sorbicillin (71%)
Region 98.1	21,324	147,843	T1PKS, NRPS-like	Shearinine D (9%)
Region 107.1	27,684	176,667	T1PKS	Chrodrimanin B (100%)
Region 127.1	3370	48,170	NRPS-like	Unknown
Region 129.1	3888	154,701	T1PKS	Depudecin (33%)
Region 130.1	1	43,527	NRPS	Unknown
Region 139.1	1	119,563	T1PKS, NRPS-like	Fusarin (100%)

Naphthopyrone, Clavaric acid, Melanin, and Fusarin showed 100% similarity.

AntiSMASH analysis of *Talaromyces* spp. strain YS-1indicated that the gene clusters in the regions 1.1, 31.1, and 54.1 has significant similarity with the BGCs of Pyranonigrin E from *Aspergillus niger* ATCC 1015 (GenBank: ACJE01000019.1.) [Figure 3a]. Pyranonigrin- E, isolated from *Aspergillus niger*, is a pyranopyrrole having effective anti-oxidant and radical scavenging activities [17]. BGC region 5.1 noted significant BLAST hits with Alternariol from *Parastagono sporanodorum* SN15 (GenBank: KP941080.1) [Figure 3b]. Alternariol is reported to be an effective anti-cancerous and antibacterial metabolite [18]. BGC 13.1 exhibited high similarity with known clusters implicated in the synthesis of Asperterpenoid-A from *Talaromyces wortmannii* (GenBank: MK140602.1) [Figure 3c]. Asperterpenoid-A has effective anti-inflammatory and antibacterial activities [19]. BGCs found in region 48.1 of the YS-1 strain showed similarity with Naphthopyrone BGC from *Aspergillus nidulans* FGSC A4 (Gen Bank: BN001302.1) [Figure 3d]. Li *et al.* [20] have reported that naphthopyrone is a potential antiproliferative compound produced from *A. niger*. A notable BLAST hit for the BGC region 63.1 was similar to BGC from *Hypholomas ublateritium* (Gen Bank EU665687.1) for synthesis of Clavaric acid, a potential anti-tumor compound [21] [Figure 3e]. Biosynthetic cluster region 69.1 showed homology with Melanin BGC [Figure 3f]. Melanin is found predominantly in PKS clusters of Fungi and is useful for adjusting to different environmental conditions [22]. The fungal YS-1 strain in regions 69.2 and 139.1 encodes BGC with BLAST hits for Fusarin BGC from *Fusarium fujikuroi* (Gen Bank: JX308619.1) [Figure 3g]. Fusarin BGCs were been identified in *Fusarium* spp., along with different polyketide gene clusters [23]. BGC region 107.1 of fungal YS-1 strain presented 100% similarity with BGC from *Talaromyces verruculosus* (Gen Bank: LC422696.1) meant for biosynthesis of secondary metabolite chrodrimanin B [Figure 3h]. Different classes of secondary metabolites and a new monoterpenoid Chrodrimanin-T have been reported from *T. amestolkiae* [24]. Chrodrimanin-B- B isolated from *Talaromyces funiculosus* showed a broad range of anti-bactericidal activity against *Staphylococcus aureus*, *Mycobacterium smegmatis*, *Mycobacterium phlei*, *Micrococcus tetragenus* and *Escherichia coli* [25]. In addition, several other bioactives and Antibiotics such as Terretonin, Zearalenone, Trypacidin, Viriditoxin, Tricholignan -A, Squalestatin -S, Emericellamide -A,B, Fumigaclavine -C, Azanigerone -A, Curvupallide -B, Griseofulvin,

Citrinin, Clapurines, Fujikurin A,B,C,D, Ankaflavin, Sordarin, Chrysoxanthone -A,B,C, Sorbicillin, Shearinine -D, and Depudecin have been identified in the present study.

Earlier reports have indicated that *Talaromyces* species produce several important bioactive compounds. Quinoid compounds such as erythroskirin, islandicin, skyrin, luteoskyrin, regulosin and anthroquinone exhibiting antitumor and antioxidant activities were identified in *Talaromyces islandicus* [26]. This species also produces mycotoxins and cyclochlorotine, with hepatotoxic and mutagenic activities. Several isocoumarin derivatives and benzofurones identified in the endophytic fungus *T. amestolkiae* exhibited antibacterial and α-glucosidase inhibitory activities [27,28].

Genome fungiSMASH analysis of *T. islandicus* detected 19 different types 1 PKS, anthrol reductase BGCs involved in the synthesis of potent alkaloid anthroquinone [29]. Talaropeptins A&B synthesizing NRPs gene cluster was identified in a marine isolate of *Talaromyces purpureogenus* CX11 [30]. These compounds had antifungal activity. Li *et al.* [31] have reported the presence of Talaromycolides in *Talaromyces pinophilus*, which showed antibacterial activity toward *S. aureus* resistant to methicillin**.**

In the present study, *S. samarangense*, a medicinal plant with known pharmacological activities such as anti-oxidant, anti-inflammatory, anti-ulcer, anti-trypanosomal, and hepatoprotective activity, was used as a source for isolation of fungal endophytes [32]. It is suggested that mutualistic interaction between medicinal plants and their endophytes may lead to the development of highly diverse metabolomes with compounds such as alkaloids, terpenoids, flavonoids, coumarins, and tannins [33]. Endophytic *Talaromyces* spp. was shown to be a reservoir of many bioactive compounds. The systematically organized gene annotation and prediction of BGCs revealed the presence of novel bioactives like clapurines and pyranonigrins, which were reported for the first time in *Talaromyces* species. The collection of different genes reported in the present analysis provides information about several known, unknown secondary metabolites for drug discovery. Identification of secondary metabolite pathways and their corresponding key gene clusters through *in silico* analysis assists in developing strategies for targeting these genes through cloning and expression studies. This approach will result in the production of novel metabolites with pharmacological significance.

4. CONCLUSION

Endophyte *Talaromyces* isolated from medicinal plants is a fascinating reservoir of various metabolites with diverse bioactivities. WGS followed by AntiSMASH analysis indicated the presence of 76 BGCs for the production of like several classes of terpenoids, alkaloids, PKS-NRPSs, and antibiotics. A diverse congregate of genes reported in the present analysis provides information about known and unrevealed metabolites, which can be used further for gene targeting and drug discovery.

5. ACKNOWLEDGMENT

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6. AUTHOR CONTRIBUTIONS

SS and KRK conceptualized and designed the study. MM, LMP and GN collected and isolated the samples. PSN and SB carried out the experiments and collected the data. PSN, SB, SS and KRK analysed the data and finalized the manuscript. All authors have read and approved the final manuscript.

7. CONFLICT OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

8. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

9. DATA AVAILABILITY

The data generated and analyzed are included within this research article.

10. PUBLISHER'S NOTE

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