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Genome mining of secondary metabolites from marine *Streptomyces* spp. as potent therapeutics for RET-specific non-small-cell lung cancer

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ABSTRACT

The rearranged during transfection (RET) gene encodes a tyrosine kinase oncogene implicated in various cancers, including non-small-cell lung cancer (NSCLC). Till now, multiple kinase inhibitors are commonly used to treat RET-positive NSCLC. However, these inhibitors often exhibit significant toxicity and demonstrate reduced efficacy and specificity toward RET. Recently, bioactive compounds derived from marine sources have shown promising anticancer properties. Therefore, this study aimed to identify effective bioactive compounds from marine *Streptomyces* species using a virtual screening approach to address these limitations. A literature search identified 20 marine *Streptomyces* species as potential sources of bioactive compounds. The antibiotics and secondary metabolite analysis shell (antiSMASH) online tool were used to analyze the gene clusters of these marine *Streptomyces* species, revealing 7,251 metabolites. A total of 661 distinct metabolites were analyzed through a comprehensive array of virtual screening methodologies. The molecular docking and pharmacokinetic analysis resulted in the identification of four metabolites with better binding scores and pharmacological properties than pralsetinib. Collectively, we hypothesize that the identified bioactive compounds could be considered as potent leads for further analysis.

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1. INTRODUCTION

The prevalence of lung cancer in the world has been estimated to 2.4 lakh cases in 2023. The incidence of lung cancer in India continues to grow exponentially with every passing year, thus making it essential to develop new and effective therapeutics for its treatment. Notably, 85% of lung cancer cases accounts for non-small cell lung cancer (NSCLC) [1]. Targeted therapies utilizing specific inhibitors against oncogenic kinases have revolutionized the treatment of cancer, including NSCLC [2]. Nevertheless, the development of acquired resistance to these therapeutics has emerged as a substantial obstacle in developing more effective and specific inhibitors [3].

One of the recurrent mutations found in NSCLC is RET gene fusions caused by the integration of two juxtaposed genes that were otherwise functioning independently of each other. Rearranged during transfection (RET), a tyrosine kinase receptor, which plays a crucial role in the central and peripheral nervous systems, has been identified to exhibit overexpression in 1%–2% of patients with NSCLC [4]. Out of the 45 RET fusion partners that have been identified in NSCLC, the most common ones that have been studied are

KIF5B, CCDC6, and NCOA4. Multiple kinase inhibitors (MKIs) such as vandetanib and cabozantinib are the first-line therapeutics for treating patients with RET-positive NSCLC. Some of the other class of drugs include agerafenib, selpercatinib, and pralsetinib [5], [6]. Nonetheless, these MKIs exhibited off-target adverse effects and limited efficacy [7]. Therefore, it is imperative to develop more potent targeted kinase inhibitors, specifically against RET to overcome acquired resistance.

In recent years, marine organisms have emerged as a significant source of chemically active molecules with beneficial bioactive properties, including anticancer effects [8]. It is worth mentioning that numerous natural compounds obtained from marine sources have been used as therapeutics to treat ovarian cancer, metastatic breast cancer, leukemia and soft tissue sarcoma [9], [10]. For instance, Natarajan *et al.* [11], employing a virtual screening method, identified six compounds derived from marine algae as strong inhibitors of Akt1 and Akt2 in oral cancer. Similarly, Alamri *et al.* [12] employed a structure-based virtual screening approach to identify potent marine compounds as inhibitors for estrogen receptor alpha (ERα). The study screened 450 marine-derived compounds and reported seven compounds as potential leads for ERα-positive breast cancer. Particularly, the genus *Streptomyces* constitutes the most extensive taxon within the phylum Actinobacteria and holds paramount importance for the pharmaceutical sector [13]. This gram-positive bacteria is the producer of active secondary metabolites, including antitumor, immunosuppressive agents, antimalarial, and antibiotic. Interestingly, *Streptomyces* is also the source of anticancer antibiotics, including doxorubicin, anthracycline, and the glycopeptide bleomycin [14].

Virtual screening plays a pivotal role in the discovery and advancement of anticancer therapeutics by facilitating the efficient identification of potential drug candidates from vast chemical libraries. Moreover, it accelerates the drug discovery process, reduces costs, and enhances the precision of targeting specific cancer-related proteins or pathways [15]. A plethora of studies have been carried out to screen anti-cancer agents using computational approaches. For instance, Patel *et al.* [16] virtually screened PubChem database to identify potential VEGFR-2 kinase inhibitors. The studied identified four compounds with better binding affinity, absorption, distribution, metabolism, and excretion (ADME) properties, and scaffold similar to AG-013736 as VEGFR-2 inhibitors. In another study, Murali and Karuppasamy [17] screened 1574 natural compounds to identify potent mIDH2 inhibitor for the management of glioma. The reported squalene as the lead molecule with high binding affinity alongside good brain penetrating potential for the management of glioma in the near future. Similarly, Krishnamoorthy and Karuppasamy [18] virtually screened FDA approved molecules to identify potential PD-L1 inhibitor for the management of triple-negative breast cancer. They identified DB01238 as potent lead molecule with better binding affinity, pharmacokinetic properties and conformational stability than BMS-1166.

With these conceptual frameworks, the current investigation aimed to ascertain potent bioactive compounds from marine *Streptomyces* by adopting a virtual screening strategy for combating the oncogenic RET modifications in NSCLC patients. The complete metabolome of 20 marine *Streptomyces* spp. was explored against RET protein. Interestingly, this is the first study of its kind to be conducted with the goal of utilizing the complete metabolome.

2. METHOD

2.1. Acquisition of genome sequences

In the current investigation, the genomic sequences of marine *Streptomyces* species were procured from the National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/), a comprehensive database that provides access to biological sequences and annotations pertaining to a wide range of taxa [19]. Initially, we used the keyword "*Streptomyces*" to retrieve the sequences from the NCBI "Genome" database. Then, to identify the marine-related species from the array of genomes, an extensive literature survey was conducted. The search yielded 20 whole genome assemblies, which were downloaded and utilised for further genome mining analysis.

2.2. Identification of genetic determinants involved in biological activities

The antibiotics and secondary metabolite analysis shell (antiSMASH) is a web interface designed for genomic exploration, which enhances the identification and characterization of biosynthetic gene clusters (BGCs) within microbial organisms (https://antismash.secondarymetabolites.org) [20]. Therefore, this study utilized antiSMASH 6.1.1 bacterial version to extract the potent secondary metabolites from marine *Streptomyces* spp. Initially, in the data input tab the 20 genome sequences in FASTA format was uploaded. Then, the detection strictness was set to "relaxed," and the extra features such as "Known Cluster Blaster," "MIBiG Cluster Comparison," "TFBS Analysis," "ActiveSiteFinder," and "SubCluster Blaster" were enabled and submitted for prediction of gene clusters. Ultimately, a graphical output depicting compounds identified as secondary metabolites will be displayed.

2.3. Binding affinity assessment through molecular docking

To ascertain the binding affinity between the protein and ligand molecular docking analysis was carried out [21]. The crystal structure of human RET protein with PDB ID: 2IVU was extracted from the protein data bank (PDB). The obtained PDB file was refined and pre-processed using the AutoDock tools. First, the working directory was set in the preference option in AutoDock. Then, the protein PDB file was loaded, and the properties like Kollaman and Gasteiger chargers were added to estimate the partial charges on atoms within proteins [21]. Next, we added the polar hydrogen atoms using the edit option. The AD4 atom type that is crucial in calculating the interaction energies between protein and ligand was also assigned through the edit option. Finally, the prepared protein file was saved in the protein data bank, partial charge (Q), and t orsions (T) ("PDBQT") format for docking. Similarly, the 3D conformers of the obtained secondary metabolites in structure data file (SDF) format were retrieved from the Pubchem database. The Open Babel software was employed to convert the SDF files into PDBQT format for the purpose of molecular docking. In this study, the PyRx 0.8 virtual screening tool was used for docking. Initially, the RET protein and the ligand molecules were loaded into the PyRx workspace. To perform blind docking, a grid box covering the entire protein was generated under the Vina search space. Lastly, the "forward" button under the Vina wizard was clicked to run Vina. The docking parameters were carefully refined to ensure the reliability and precision of the simulation outcomes.

2.4. Assessing the drug-like properties of the bioactive compounds

Drug-likeliness is an essential step in the development of successful small-molecule drugs. It is determined by analyzing the physiochemical and structural characteristics of the compounds that can be used to predict their behavior in biological systems [22]. Interestingly, computational techniques allow for the efficient refinement of the pharmacokinetic properties and toxicity of drug candidates. Therefore, in this study, the absorption, distribution, metabolism, and excretion (ADME) features were evaluated using the ADMET lab 2.0 (https://admetmesh.scbdd.com/) to ensure the efficacy of the secondary metabolites. To calculate the properties the SMILES formula of the molecules was given as input to the ADMET lab server.

3. RESULTS AND DISCUSSION

3.1. Secondary metabolite gene cluster distribution among genomes

AntiSMASH 6.1.1 was used in the study to assess the secondary metabolites synthesized by bacteria. The significant types of gene clusters implicated in their biosynthesis are non-ribosomal peptide synthetases (NRPS), polyketide synthetases (PKS), terpene, linaridin, and butyrolactone. Evidence from literature suggests that NRPS, PKS, and terpenes exhibit a wide range of applications, which include clinically relevant metabolites for the treatment of cancer and microbial infections [23]. Figure 1 demonstrates the distribution of secondary metabolites produced by the different isolates. The comprehensive genomic evaluation of various marine *Streptomyces* species yielded an aggregate of 7251 bioactive secondary metabolites. From the figure, it can be observed that *Streptomyces* sp. NA02950 (523 compounds) produced the highest number of metabolites, followed by *Streptomyces* sp. SCSIO ZS0520 (484 compounds) and *Streptomyces* sp. 3025 (430 compounds). In addition, most of the metabolites were dominated by T1PKS, NPRS, and terpenes, as shown in Figure 2.

Of the 7251 metabolites, compounds with incomplete structure conformations and overlapping metabolites were eliminated. Finally, a total of 661 distinct and bioactive metabolites were considered. These were used for virtual screening purposes.

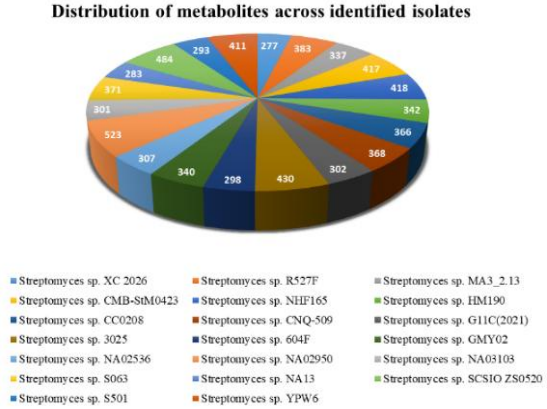

Figure 1. Distribution of secondary metabolites across identified isolates

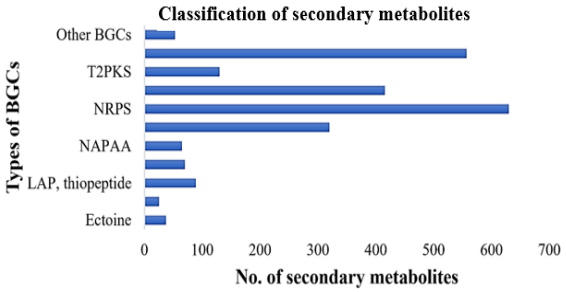

Figure 2. Classification of bioactive compounds into different biosynthetic gene cluster type

3.2. Molecular docking against RET protein

To gain a better understanding of the protein-ligand binding interactions, molecular docking analysis was performed [24]. In the present study, the predicted array of secondary metabolites alongside the reference compound (pralsetinib) was preprocessed and subjected to docking analysis via PyRx 0.8 software. The binding affinity score calculated through the PyRx algorithm proved to be effective in differentiating between binders and non-binders [25]. Binding affinities exhibiting a higher negative value (kcal/mol) signify an enhanced affinity for the target protein [26]. The findings showed that 366 molecules with binding energies ranging from -16.1 kcal/mol to -7.8 kcal/mol had a higher binding affinity than pralsetinib (-7.79 kcal/mol). Thus, these potent molecules were further considered for pharmacokinetic and toxicity analysis. Table 1 represents the docking scores of the top ten lead molecules.

The docked pose and the 4 Å interacting residues between the protein and ligand molecules are depicted in Figure 3. From Figure 3 it can be seen that all four lead molecules interacted in the same region with the RET protein. Collectively, the findings suggest that these compounds may serve as promising inhibitors targeting the RET protein.

3.3. Drug like properties of the lead molecules

Assessing the ADME profile of the lead molecules is crucial in understanding their pharmacological effect [18]. We used the ADMET lab web interface to analyze the pharmacokinetic and toxicity properties of the lead molecules in this study. The findings are tabulated in Table 2. It is evident from the findings that only four compounds, namely, semivioxanthin, endophenazine B, phenylnannolone A, and phenylnannolone B, satisfied the pharmacokinetic properties.

According to the results, all four lead molecules had log p-values in the range of 3 to 5. Similarly, plasma clearance, an important pharmacokinetic parameter, was also assessed, and all four compounds showed better clearance than the reference. More importantly, they all exhibited lower molecular weight than pralsetinib. Overall, the findings demonstrate that the compounds satisfy Lipinski rule of five and could be potent inhibitors of the RET protein.

Table 2. ADME properties of the lead molecules

S. No	Compound name	Mol. wt (< 500 Da)	nHA	nHD	Log P (3-5)	Clearance (> 5)	BBB (+ve)	CYPA34 & CYPD26 inhibitor
1	Pralsetinib	533.270	11	3	3.006	2.981	Yes	No
2	Semivioxanthin	274.080	5	2	3.884	12.095	Yes	No
3	Endophenazine B	322.130	5	1	3.321	6.251	Yes	No
4	Phenylnannolone A	278.130	2	0	4.114	8.588	Yes	No
5	Phenylnannolone B	264.120	2	0	3.401	5.104	Yes	No

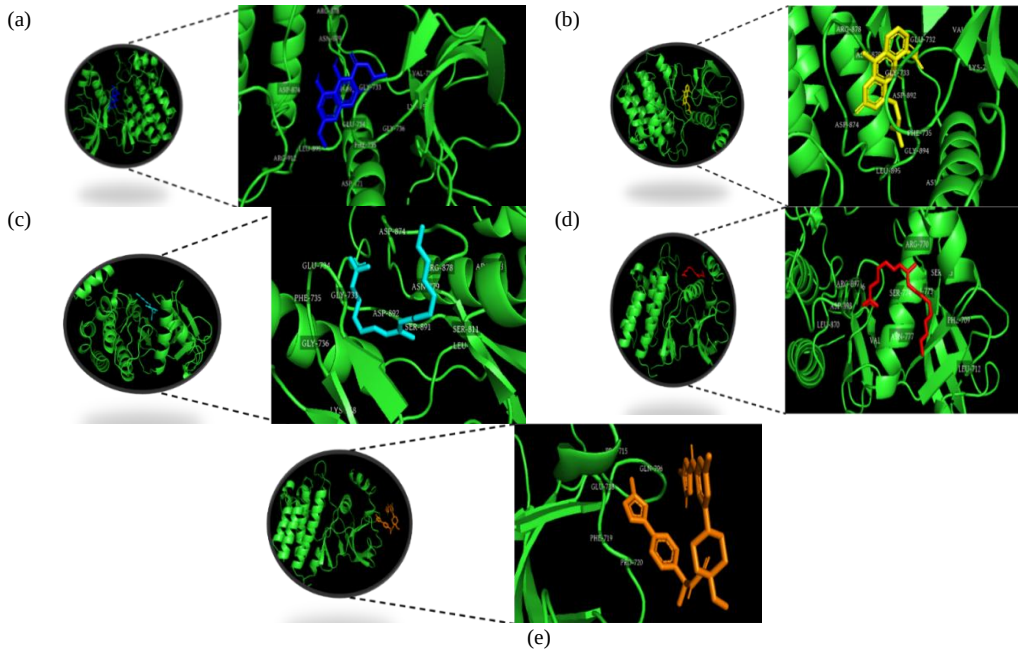

Figure 3. Interacting residues between RET protein and the lead molecules: (a) semivioxanthin, (b) endophenazine B, (c) phenylnannolone A, (d) phenylnannolone B, and (e) pralsetinib (reference)

Table 1. Docking score of top ten lead molecules in comparison with pralsetinib

S. No	PubChem ID	Compound name	Binding score (kcal/mol)
1	129073603	Pralsetinib (Reference)	-7.79
2	124080859	Moomysin	-16.1
3	145720625	Jessenipeptin	-12.8
4	443590	Telomestatin	-11.9
5	167993978	Hormaomycin	-11.4
6	6446886	Micrococcin P1	-10.6
7	132494535	Naseseazine C	-10.5
8	125349	Corynebactin	-10.5
9	248000	Dinactin	-10.3
10	24900170	Xenematide	-10.1
11	5281394	Chartreusin	-10.1

4. CONCLUSION

The current study focuses on the identification of potent drug molecules against RET using virtual screening strategies. Notably, the secondary metabolites from marine organisms act as promising anti-cancer agents. Thus, the antiSMASH online platform was employed to predict and identify BGCs from marine *Streptomyces*, aiming to discover potent anti-cancer metabolites targeting RET for the treatment of NSCLC. The genome mining analysis indicated that most metabolites were associated with the T1PKS, terpene, and NRPS gene clusters. Subsequently, the molecular docking and pharmacokinetic property analysis resulted in four potential compounds against the RET protein. The resultant lead molecules exhibited better binding affinity and a satisfactory pharmacological activity than pralsetinib. Overall, our finding will play a key role in developing new potent molecules for the management of RET-specific NSCLC in the near future. With the growing progress in computational biology, similar research utilizing other *Streptomyces* spp. bioactive compounds can be explored. Moreover, the activity of the marine compounds can be studied for other disease types in the near future.

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