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Targeting p75NTR, NGF, and NOTCH Signaling: Network Pharmacology Insights into Neurodegenerative and Mental Health Therapies from *Salinispora* and *Streptomyces* Actinobacteria

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Abstract

Marine Actinobacteria, notably *Salinispora* and *Streptomyces* species, are emerging as promising sources of bioactive compounds with therapeutic potential for neurodegenerative and mental health disorders. This study employs a network pharmacology approach to investigate how compounds from these marine microbes interact with key genes in the p75 Neurotrophin receptor (p75NTR), nerve growth factor (NGF), and NOTCH signaling pathways, all of which are crucial in neurodegenerative processes. A comprehensive screening pipeline, involving absorption, distribution, metabolism, and excretion (ADME) evaluation (drug-likeness, oral bioavailability, blood-brain barrier permeability) and in silico toxicity profiling across five major toxicity categories**,** was conducted to identify bioactive compounds with favorable pharmacokinetic properties and non-toxic profiles. Top candidates were selected based on their significant interactions with genes related to the aforementioned signaling pathways. Notably, Salinosporamide A (NPI-0052 and its fused-lactam-lactone form) from *Salinispora*, and Bonactin, Azamerone, and Methoxyneihumicin from *Streptomyces*, were identified as key compounds. These showed interactions with genes such as MAPK1, NCSTN, APH1A, AR, JAK2, and PSENEN, which are crucial in regulating p75NTR-mediated, NGF, and NOTCH signaling. The p75NTR pathway is involved in neuronal survival, apoptosis, and synaptic function; its disruption contributes to neurodegeneration. NGF signaling supports neuronal differentiation and survival, with its dysregulation linked to Alzheimer's and similar diseases. The NOTCH pathway governs neurodevelopment, cell communication, and synaptic plasticity, with perturbations associated with schizophrenia and neurodegenerative disorders.

Keywords

Network pharmacology, Neurodegeneration, Drug discovery

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1. Introduction

Neurodegenerative and mental health disorders pose a significant global health burden, with conditions such as Alzheimer's disease, Parkinson's disease, depression, and schizophrenia affecting millions worldwide [1]. These disorders are characterized by progressive neuronal dysfunction, synaptic loss, and neuroinflammation, ultimately leading to cognitive decline and behavioral impairments [2,3]. Despite extensive research, effective treatment options remain limited, primarily focusing on symptomatic relief rather than halting or reversing disease progression [4]. Key signaling pathways such as p75 Neurotrophin receptor (p75NTR), nerve growth factor (NGF), and NOTCH are critically involved in the regulation of neuronal survival, apoptosis, synaptic plasticity, and neurodevelopment. Disruptions in these pathways have been directly linked to the onset and progression of Alzheimer's disease, schizophrenia, and other neurodegenerative and psychiatric disorders. Therefore, targeting these core pathways offers a promising strategy for multi-modal intervention in complex neurological conditions [5-7].

Emerging evidence highlights the interconnected nature of neurodegenerative and metabolic disorders. For instance, Alzheimer's disease shares key pathological mechanisms with Type 2 Diabetes, such as insulin resistance, amyloid aggregation, and oxidative stress. Similarly, estrogen dysregulation is implicated in both Alzheimer's disease and breast cancer, linking hormonal imbalances with neuronal vulnerability [8-10]. Depression, another major mental health disorder, exhibits molecular and genetic overlaps with breast cancer, underscoring the need for integrative approaches in disease management. These interconnections suggest that targeting common molecular pathways could provide broader therapeutic benefits across multiple disorders [11,12].

Despite significant advancements in drug discovery, the current pharmaceutical pipeline faces major challenges in developing effective therapies for neurodegenerative diseases. The conventional reductionist approach, which focuses on single-target drug development, often fails to address the multifactorial nature of these diseases. Many promising drug candidates, including those targeting amyloid plaques and tau pathology, have failed in clinical trials, emphasizing the limitations of this approach [13-15]. In contrast, systems biology-based methodologies offer a more comprehensive framework by integrating multi-target strategies, enabling a deeper understanding of disease networks and facilitating drug repurposing opportunities.

Natural products have long been explored as alternative and complementary therapies for neurodegenerative and mental health disorders. Bioactive compounds derived from medicinal plants, fungi, and microbial sources possess diverse pharmacological properties, including neuroprotection, anti-inflammatory activity, and neurotransmitter modulation. However, their widespread therapeutic application is hindered by challenges such as poor bioavailability, multitargeted mechanisms, and the complexity of extracting and standardizing bioactive components. To overcome these limitations, systems biology and network pharmacology approaches have emerged as powerful tools for decoding the complex interactions between natural compounds and disease networks [16,17].

Among natural sources, marine Actinobacteria–particularly the genera *Salinispora* and *Streptomyces*–have gained attention for their prolific production of structurally diverse and pharmacologically active secondary metabolites. Recent studies have identified neuroprotective, anti-inflammatory, and antioxidant properties in compounds derived from these marine microbes, indicating their potential for treating central nervous system (CNS) disorders. *Salinispora*, a rare obligate marine Actinobacterium, is notable for producing novel compounds such as Salinosporamide A, a potent proteasome inhibitor with CNS activity. *Streptomyces*, well-known for its wide biosynthetic repertoire, has yielded neuroactive compounds like Bonactin and Azamerone. These species differ from terrestrial sources by thriving in high-pressure, saline environments, which drive unique biosynthetic gene clusters and metabolite novelty [18-21].

In our previous work on marine-derived Actinobacteria, we identified promising lead compounds with potential neuroprotective properties. Separately, our study on a traditional herbal formulation involved an extensive integrative analysis combining systems pharmacology, molecular docking, and molecular dynamics simulations to elucidate its therapeutic mechanisms. Together, these studies highlight the effectiveness of computational approaches in identifying and characterizing bioactive compounds for neurodegenerative disorders, reinforcing the need for a systematic exploration of natural product-based interventions [22,23].

In this study, we apply an integrative network pharmacology approach to investigate the therapeutic potential of bioactive compounds derived from *Salinispora* and *Streptomyces* species. By screening and analyzing key interactions between these compounds and molecular targets, we aim to elucidate their roles in modulating critical neurodegenerative pathways, specifically p75(NTR)-mediated signaling, NGF signaling, and NOTCH signaling. These pathways are known to play crucial roles in neuronal survival, synaptic plasticity, and neuroinflammation, making them attractive therapeutic targets. Through comprehensive pathway analysis and systems-level insights, this study provides a framework for leveraging natural product-derived compounds as potential therapeutic candidates for neurodegenerative and mental health disorders. Therefore, the central hypothesis of this study is that bioactive compounds derived from marine Actinobacteria can modulate key neurodegenerative signaling pathways (p75NTR, NGF, and NOTCH) through multi-target mechanisms, offering therapeutic potential for complex CNS disorders. The primary research objective is to systematically identify, screen, and characterize these compounds using an integrative bioinformatics and systems biology approach, thereby laying the groundwork for their future preclinical validation.

2. Methodology

2.1 Exploration of Actinomycetes Strains and Bioactive Compounds

To specifically identify Actinomycetes strains and their associated bioactive metabolites derived from the Indian Ocean ecosystem, a focused and systematic literature mining approach was employed. Using keywords such as "Actinomycetes", "marine-derived bacteria", "Indian Ocean", and "bioactive metabolites", we conducted comprehensive searches across reputable academic databases including PubMed, Scopus, and Web of Science. Only original research articles were considered, with inclusion strictly limited to studies that explicitly isolated Actinomycetes strains from Indian Ocean samples–such as sediment, seawater, marine invertebrates, or deep-sea sources. Furthermore, selected studies were required to report the structural characterization or pharmacological evaluation of the isolated metabolites, ensuring both geographic and functional relevance. All identified compounds were then cross-validated through secondary sources and annotated based on their documented therapeutic activities. This refined selection process ensured that the final list of 91 compounds was both scientifically robust and geographically representative of the Indian Ocean biosphere, offering unique insights into the metabolic diversity and therapeutic promise of regional marine Actinomycetes.

2.2 ADME Profiling and Computational Toxicity Assessment

To systematically evaluate the pharmacokinetic properties and safety profile of bioactive metabolites derived from Actinomycetes strains isolated from the Indian Ocean, we performed an integrated Absorption, Distribution, Metabolism, and Excretion (ADME) analysis followed by in silico toxicological screening. Pharmacokinetic Screening: The SwissADME web tool (http://www.swissadme.ch/index.php) [24] was utilized to predict essential drug-like properties, including drug-likeness (DL≥30%), oral bioavailability (OB≥18%), and blood-brain barrier permeability (BBBp between -0.3 and 3). Additionally, the specific numerical cutoffs for key ADME descriptors were applied to ensure reproducibility: log P≤5 (as per Lipinski's rule), molecular weight ≤500 Da, topological polar surface area ≤ 140 Å² for optimal absorption, number of hydrogen bond donors ≤5, and number of hydrogen bond acceptors ≤ 10. Structural and physicochemical data were compiled from established databases and literature sources, ensuring the inclusion of highly bioactive compounds. To maintain analytical accuracy, duplicate structures were carefully removed, leading to a refined dataset. Ultimately, from an initial pool of 91 bioactive compounds, 43 met the predetermined ADME criteria, signifying their potential for oral administration and CNS penetration. Computational Toxicity Evaluation: Following ADME analysis, shortlisted compounds were subjected to toxicity prediction using the ProTox-II platform (https://toxnew.charite.de/protox_II/) [25]. Toxicity profiling was performed using ProTox-II (v2.0, 2024 release), which integrates structure-activity relationship-based classification models and machine-learning algorithms. The evaluation covered a broad spectrum of toxicity endpoints, including hepatotoxicity, immunotoxicity, carcinogenicity, mutagenicity, and cytotoxicity, along with cardiotoxicity endpoints such as hERG channel inhibition potential and oral acute toxicity (LD_{50} classification). Additionally, endocrine disruption potential and Tox21 stress pathway activation were also assessed to provide a comprehensive safety overview. Bioactive metabolites demonstrating no predicted toxic effects across all five categories were prioritized, ensuring a higher safety margin for further preclinical evaluations. This strategic selection process was instrumental in minimizing potential risks while identifying promising drug candidates for subsequent research and therapeutic exploration.

2.3 Target Identification and Disease Association Mapping

To systematically identify potential therapeutic targets for the bioactive metabolites derived from Actinomycetes, we employed a dual-platform approach using SwissTargetPrediction (http://www.swisstargetprediction.ch/) [26] and BindingDB (https://www.bindingdb.org/bind/index.jsp) [27]. These platforms leverage machine learning-based predictive models to establish target-protein interactions based on the structural features of input compounds in .sdf format. Predictive Target Screening: SwissTargetPrediction ranked the top fifteen most likely protein targets for each compound, while BindingDB assigned confidence scores ranging from 0.9 to 1 to indicate highly probable interactions. To ensure robustness, we prioritized targets common across both platforms while eliminating redundancies. Additionally, targets associated with multiple bioactive compounds were given precedence, aligning with a polypharmacological strategy for drug discovery. Disease Association Analysis: The finalized target list was subjected to disease association mapping via the DisGeNET database (https://www.disgenet.org/) [28], a curated repository of Gene-disease association (GDA). Target proteins were evaluated based on their GDA scores, enabling the identification of high-confidence disease correlations. This workflow provided key insights into the therapeutic relevance of the predicted targets, facilitating the identification of potential intervention points for further drug development.

2.4 Protein-Protein Interaction Network Construction

To gain deeper insights into the molecular interactions of the predicted targets, we conducted a Protein-Protein Interaction (PPI) analysis using the STRING v11.5 database (https://string-db.org/) [29]. This platform integrates data from multiple sources, including experimental evidence, computational predictions, and text mining, to construct a comprehensive interaction network. Network Construction and Filtering: We identified first-degree interactors of the target proteins, focusing exclusively on high-confidence interactions (score≥0.7) to ensure network reliability. Redundant edges were systematically removed to eliminate noise and improve interpretability. Modular Analysis and Centrality Assessment: To reveal functionally significant clusters within the PPI network, we applied the Markov Cluster (MCL) algorithm, which groups proteins based on connectivity strength and shared biological functions. The finalized interaction map was imported into Cytoscape (https://cytoscape.org/) [30] for network visualization and further computational analysis. Using the degree centrality metric, we identified key regulatory hubs—proteins exhibiting the highest number of direct interactions. These hubs play crucial roles in molecular signaling and may serve as potential therapeutic targets. By integrating PPI mapping with functional clustering, our approach provided a structured framework to understand target protein behavior, interaction dynamics, and their broader implications in disease networks. In addition to degree centrality, we incorporated complementary network topology measures to enhance robustness. Specifically, betweenness centrality was used to identify "bottleneck" nodes—critical intermediaries that regulate information flow across the network. We computed the average degree (AD) and standard deviation (SD) for each network, designating as hubs those nodes exceeding (2SD+AD). Simultaneously, the top 5% of nodes ranked by betweenness centrality were defined as bottlenecks. Proteins meeting both criteria were categorized as "hub-bottlenecks," representing the most influential regulators in the system. The method used for identifying hub-bottlenecks was followed based on a previous study [31]. Using Cytoscape, we then extracted hubs, hub-bottlenecks, and their direct neighbors, enabling precise identification of the genes most pivotal to network stability and disease-related signaling.

2.5 Functional Annotation and Pathway Analysis

Gene Ontology (GO)-Based Functional Characterization: To systematically analyze the biological roles of disease-associated genes, we performed GO enrichment analysis using FunRich 3.1.3 [32]. This AI-powered tool categorizes genes based on their involvement in biological processes, cellular components, and molecular functions, enabling a deeper understanding of their relevance to disease mechanisms. Pathway Mapping and Enrichment Study: To uncover the molecular pathways influenced by these genes, we conducted pathway enrichment analysis with FunRich 3.1.3. This computational approach helped identify significantly enriched signaling pathways, revealing critical regulatory mechanisms associated with disease pathology. The integration of AI-driven pathway analysis provided key insights into the therapeutic potential of bioactive compounds in targeting disease-related pathways. By combining functional annotation and pathway mapping, we established a comprehensive framework for understanding GDAs, aiding in the identification of promising therapeutic targets.

3. Results

3.1 Screening of Bioactive Compounds from Marine Actinomycetes

Following an extensive review of available literature, we compiled a diverse library of bioactive compounds derived from marine Actinomycetes, initially comprising 91 candidates (Supplementary Table 1). To narrow down this collection, we applied a stringent ADME analysis, which enabled us to assess pharmacokinetic properties such as (DL≥30%), oral (OB≥18%), and (BBBp between -0.3 and 3). This careful evaluation resulted in the identification of 43 compounds that met the required criteria (Supplementary Table 2). Subsequently, these 43 compounds were subjected to a rigorous toxicological screening to evaluate their safety profile across critical toxicity categories, including hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity (Supplementary Table 3). Based on this analysis, we identified 20 compounds that showed no adverse effects in any of the five toxicity categories (Supplementary Table 4). To prioritize the most promising candidates for further investigation, we ranked these 20 compounds according to their bioavailability, an essential parameter for effective therapeutic use and drug delivery. This refined selection of compounds provides a robust foundation for ongoing research into their therapeutic potential, particularly for neurodegenerative diseases and mental health disorders, offering new prospects for drug development from marine Actinomycetes. The top-ranked compounds, according to their bioavailability, are highlighted in Table 1, representing a crucial step toward identifying viable drug candidates.

Table 1. ADMET screening of bioactive compounds.

S No.	AC ID	Name	PubChem ID	Species	BA	GI	Ro5	BBBp	DL	Targets	Ref.
1	AC06	Helquinoline	10466080	*Janibacter limosus*	0.85	H	Y	Y	-0.15	22	[33]
2	AC02	Bonactin	11741721	*Streptomyces sp., Streptomyces sp.* BD21-2	0.56	H	Y	N	0.10	20	[33]
3	AC14	Azamerone	11684910	*Streptomyces sp.*	0.56	H	Y	N	0.85	21	[34]
4	AC25	Arcyriaflavin A	5327723	Z (2)0392	0.55	H	Y	N	-1.50	71	[35]
5	AC09	Salinosporamide A (NPI-0052)	138113779	*Salinispora tropica*	0.55	H	Y	N	-0.02	27	[33]
6	AC42	Salinosporamide A (fused - lactam--lactone)	11347535	*Salinispora tropica*	0.55	H	Y	N	-0.02	27	[33]
7	AC26	Streptokordin	11579160	*Streptomyces sp.* KORDI-3238, *Streptomyces sp.*	0.55	H	Y	Y	-0.32	20	[36]
8	AC28	Methoxyneihumicin	9949544	Nicardiopsis alba SCSIO 03039	0.55	H	Y	Y	-0.79	22	[37]
9	AC29	Diketopiperazines	7817	*Streptomyces fungicidicus*	0.55	L	Y	N	-1.42	20	[38]
10	AC31	Streptopyrrolidine	25033126	*Streptomyces sp.*	0.55	H	Y	N	-0.67	22	[39]
11	AC33	Strepsesquitriol	73603988	*Streptomyces sp*. SCSIO 10355	0.55	H	Y	Y	-0.92	20	[40]
12	AC37	Xiamenmycin C	139588672	*Streptomyces xiamenesis* M1-94P	0.55	H	Y	Y	0.54	23	[36]
13	AC38	Xiamenmycin D	139588677	*Streptomyces xiamenesis* M1-94P	0.55	H	Y	N	0.41	21	[41]
14	AC39	2-Allyloxyphenol	70772	*Streptomyces sp.*	0.55	H	Y	Y	-1.16	20	[30]
15	AC04	3,6-disubstituted indole	21577159	*Streptomyces sp.*	0.55	H	Y	Y	-0.76	14	[33]
16	AC18	Butenolide	10341	*Streptoverticillium luteoverticillatum, Streptomyces sp*. TP-A0873	0.55	H	Y	N	-1.42	7	[33]
17	AC36	Champacyclin	139587727	*Streptomyces strain* C42	0.17	L	N	N	0.00	20	[31]
18	AC30	Benzoxacystol	53327671	*Streptomyces sp*.	0.11	L	Y	N	-0.41	20	[32]
19	AC32	Ahpatinin F	139589300	*Streptomyces sp.* ACT232	0.11	L	N	N	-0.28	28	[42]

Note: BA: Bioavailability probability predicted by SwissADME; GI: Gastrointestinal absorption (H: High, L: Low); Ro5: Lipinski's rule-of-five compliance (Y: Yes, N: No); BBBp: Blood-brain barrier permeability (predicted value); DL: Drug-likeness score; Targets: Number of predicted protein targets. BA values represent the probability of oral bioavailability (range: 0-1). All abbreviations are defined at first use for clarity.

3.2 Identification of Potential Targets and Disease Relevance

Target identification is a crucial phase in understanding the therapeutic potential of bioactive compounds. Each compound, based on its structural features, may interact with specific proteins to offer protective effects against pathogenic processes. To identify potential targets, the structures of the active compounds were submitted to online prediction systems. After removing duplicates, a total of 290 predicted targets were obtained (Supplementary Table 5). These targets were then analyzed using the DisGeNET server, which revealed genes associated with neurodegenerative and mental health disorders. These insights are invaluable for understanding the therapeutic applications of the compounds and their relevance to the associated diseases.

3.3 Construction and Analysis of Interaction Networks

To explore the complex dynamics between bioactive compounds, their molecular targets, and their implications for mental health disorders, we utilized network analysis. Two critical datasets were employed: the Bioactive-Target interaction data (Supplementary Table 6) and the Target-Disease association data (Supplementary Table7). These

datasets served as the foundation for creating two informative bipartite networks using Cytoscape v3.7.1. The first network, referred to as the Bioactive-Target interaction map (Figure 1), visually represents the engagement between bioactive compounds and their molecular targets. Through this network, we identified the bioactive compounds responsible for significant modulation of specific biological activities and the targets they interact with. To examine the importance of these interactions, we employed the degree centrality network parameter, allowing us to identify pivotal nodes within the network. The second network (Figure 2) expanded our analysis to include predicted targets and their connections to mental health disorders, providing insights into the potential therapeutic relevance of the compounds. Again, the degree centrality parameter was applied to uncover the network's structural nuances, highlighting bioactive compounds, their targets, and the mental health disorders they may impact. Using the 'Network Analyzer' tool in Cytoscape, we rigorously analyzed the network, identifying key nodes with high centrality that may play crucial roles in mental health contexts. For a more comprehensive understanding, topological analyses of the Bioactive-Target interactions are summarized in Table 2, Notably, compounds such as Arcyriaflavin A (AC25, degree=70, BC=0.3414) and Ahpatinin F (AC32, degree=28, BC=0.1412) emerged as dominant network hubs, indicating their strong multi-target potential. Several kinase targets, including GSK3B, EGFR, and MAPK14, also displayed high centrality, underscoring their regulatory significance in neuropsychiatric pathways. A holistic overview of the network analysis, including key network parameters and metrics, is presented in Table 3, offering a deeper perspective on the relationships between bioactive compounds, their targets, and mental health disorders.

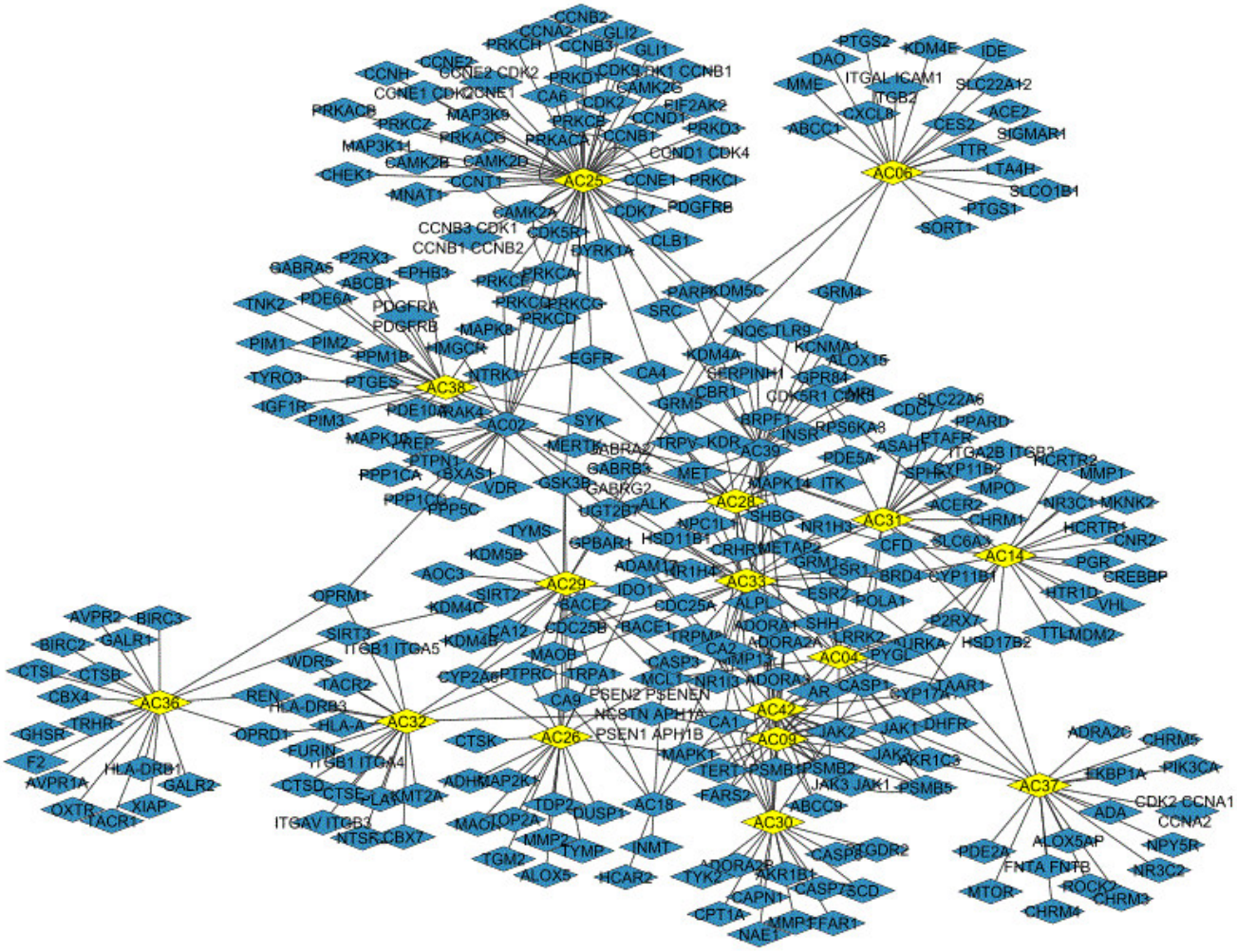

Figure 1. Bioactive-target interaction network. This figure illustrates the complex interaction landscape between bioactive metabolites derived from marine *Actinomycetes* and their predicted molecular targets, constructed using network pharmacology approaches. The network highlights the polypharmacological nature of the compounds and potential key targets relevant to therapeutic intervention. Yellow nodes represent bioactive compounds, while dark blue nodes indicate their associated protein targets. Node size is proportional to degree centrality (number of connections), and edge thickness reflects the strength of compound-target associations. This visualization provides a systems-level perspective on drug-target interactions, aiding in the identification of critical molecular nodes for further experimental validation.

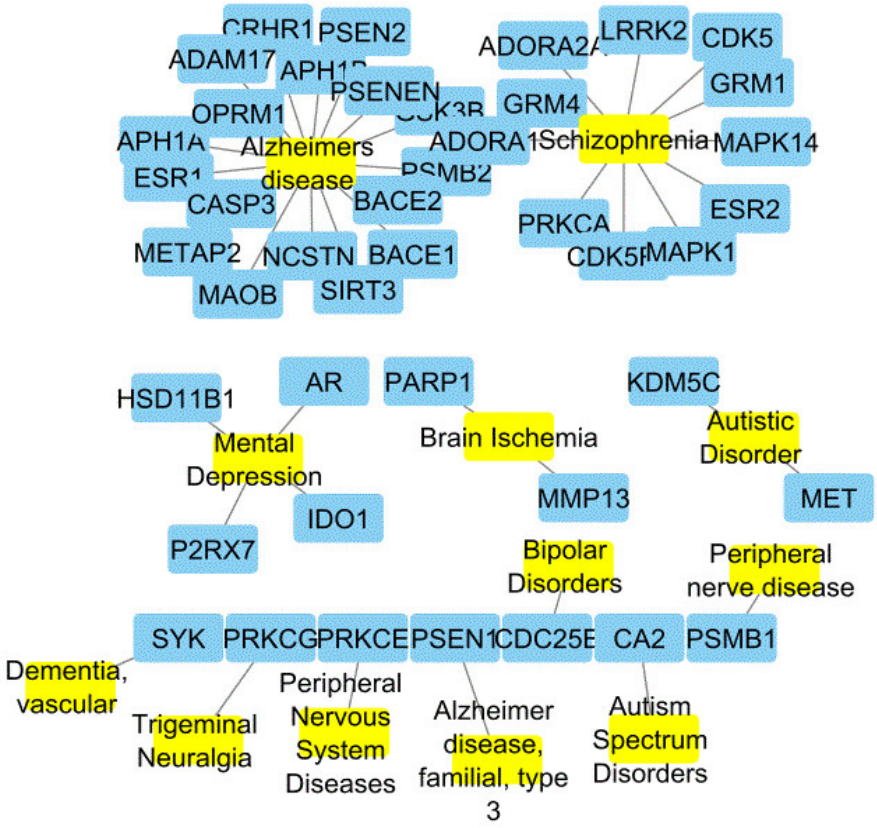

Figure 2. GDA network. This figure illustrates the complex interactions between predicted target genes and their associated diseases, providing a systems-level perspective on the genetic underpinnings of disease mechanisms. The network highlights how multiple genes may converge on common disease pathways and how individual genes can be implicated in multiple pathological conditions, offering valuable insights for biomarker discovery and therapeutic target prioritization. Yellow nodes represent disease entities, while light blue nodes denote the associated genes. Node size corresponds to degree centrality (connectivity within the network), and edge thickness indicates the strength or confidence level of the gene-disease association. This integrative view facilitates the identification of critical genetic drivers and shared molecular pathways across diseases.

3.4 Mapping Protein-Protein Interactions

Based on the GDA scores, we identified 75 targets classified as disease-regulating targets (DRTs). Using these DRTs, we constructed a PPI network consisting of 75 nodes and 355 edges. The network analysis revealed an average node degree of 9.5 and an average local clustering coefficient of 0.540. Additionally, the PPI enrichment p-value (<1.0e-16) confirmed the biological relevance of the network. The PPI network was imported from the STRING database into Cytoscape software for further analysis to identify potential regulatory targets (PRTs). Hub genes were identified based on a minimum degree cutoff of ≥3, while bottleneck nodes were screened using a bottleneck cutoff score above 7.32×10^{-6}. These hub-bottleneck genes represent highly connected and topologically critical nodes within the network, playing a pivotal role in information flow and regulatory control. The identified PRTs form the core network of genes modulated by the bioactives in the context of mental health disorder treatment, as illustrated in Figure 3. Further details of bioactives interacting with highly modulated core targets via PPI are provided in Table 4, MAPK1, MAPK14, ESR1, CASP3, NCSTN, APH1A, AR, JAK2, and PSENEN emerged as top hub-bottleneck nodes, with several being directly modulated by bioactives such as Salinosporamide A (NPI-0052) and its analogs, as well as Streptokordin, Bonactin, and diketopiperazines. The recurrent interaction of Salinosporamide A with multiple core targets highlights its broad regulatory influence within the PPI network.

Table 2. Topological overview of the bioactive-target interaction network.

Node	Degree	BC	Node	Degree	BC	Node	Degree	BC
AC25	70	0.341410266	CCNE1	3	0	CDK7	2	0
AC32	28	0.141190294	GSK3B	3	0.078479744	PTPRC	2	0.001862588
AC09	25	0.116713067	PRKCB	3	0	MAOB	2	0.001862588
AC42	25	0.107854783	PRKACA	3	0	CYP2A6	2	0.001862588
AC37	23	0.109728186	EGFR	3	0.050595266	MET	2	0.011049029
AC06	22	0.1136358	CDC25B	3	0.020230397	MMP13	2	0.006267921
AC28	22	0.123002577	IDO1	3	0.017574041	MERTK	2	0.007446069
AC31	22	0.118874325	PRKCD	2	0.011518364	ADORA3	2	0.006267921
AC14	21	0.094954612	PRKCA	2	0.011518364	SYK	2	0.007446069
AC38	21	0.101629643	UGT2B7	2	0.008278323	AURKA	2	0.009381333
AC02	20	0.131719528	PRKCG	2	0.011518364	SIRT3	2	0.042628399
AC26	20	0.086041047	PRKCE	2	0.011518364	CASP3	3	0.018869342
AC29	20	0.146628493	PRKCQ	2	0.011518364	CASP1	2	0.016667586
AC30	20	0.09671574	ESR1	3	0.001954281	BACE1	2	0.008743078
AC33	20	0.097208954	ESR2	2	0.001954281	BACE2	2	0.008743078
AC36	20	0.107824928	METAP2	2	0.005082581	ITGB3	2	0.008743078
AC39	20	0.159661065	CRHR1	2	0.0041423	REN	2	0.011618466
AC04	14	0.060059653	P2RX7	2	0.005587463	ITGB1	2	0
AC18	7	0.016945356	GRM1	2	0.0041423	OPRD1	2	0.011618466
ADORA1	5	0.062559134	KDM4A	2	0.024352473	HMGCR	1	0
MAPK14	4	0.056482179	GRM4	2	0.066338701	PPP1CC	1	0
MCL1	4	0.027537988	KDM5C	2	0.024352473	PTPN1	1	0
JAK3	4	0.023922971	PSMB2	2	7.32E-06	PPP1CA	1	0
JAK1	4	0.023922971	PSMB1	2	7.32E-06	PPM1B	1	0
PSMB5	4	7.32E-06	ABCC9	2	7.32E-06	PPP5C	1	0
CYP17A1	4	0.028189976	TERT	2	7.32E-06	VDR	1	0
ADORA2A	4	0.033387115	FARS2	2	7.32E-06	MAPK10	1	0
CA2	4	0.026640363	PSENEN	3	7.32E-06	PTGES	1	0
HSD11B1	3	0.019188274	NCSTN	3	0.010918113	PREP	1	0
OPRM1	3	0.073942786	BRD4	2	0.010052719	TBXAS1	1	0
JAK2	3	0.003934134	CFD	2	0.005212298	TAAR1	1	0
PYGL	3	0.011266782	CDK5	2	0.012986835	AKR1C3	1	0
ADAM17	3	0.037994724	CA9	2	0.001559696	DHFR	1	0
AR	3	0.016770038	CDK2	2	0	PTGS2	1	0
APH1A	3	0.02224667	CCNB3	2	0	PTGS1	1	0
PSEN1	3	0.02224667	PARP1	2	0.024043729	DAO	1	0
APH1B	3	0.02224667	CCNB1	2	0	ITGAL	1	0
MAPK1	3	0.02934555	PDGFRB	2	0.022202699	ICAM1	1	0
LRRK2	3	0.017837862	SRC	2	0.024043729	ITGB2	1	0
ALPL	3	0.016921159	CA4	2	0.022387808	KDM4E	1	0
HSD17B2	3	0.016437625	CDK2	2	0.01816925	ACE2	1	0
CDK5R1	3	0.051963054	CCNT1	2	0	ABCC1	1	0
CA1	3	0.010501204	CAMK2A	2	0	SIGMAR1	1	0
TRPA1	3	0.004872729	CCNA2	2	0.01816925	SORT1	1	0

Note: Represents either a bioactive compound (AC IDs) or a target protein. Degree: Number of direct connections (edges) each node possesses in the interaction network. BC (Betweenness Centrality): A measure of the node's importance in facilitating interactions and information flow within the network. Higher degree and BC values indicate greater topological significance and potential biological relevance. Network parameters were calculated using Cytoscape v3.9.1.

Table 3. Summary of network analysis.

Parameters	*Salinispora sp.*	*Streptomyces sp.*	*Nocardia sp.*	Common	Combined
Bioactive	5	17	4	4	22
High Scoring Bioactive	2	4	2	4	8
High scoring bioactive names	Salinosporamide A (NPI-0052), Salinosporamide A (fused - lactam--lactone)	Azamerone, Streptopyrrolidine, Ahpatinin F, Xiamenmycin C	Helquinoline, Arcyriaflavin A,	Bonactin, Cyclomarin A, Streptokordin, Butenolide	-
Targets	54	249	115	7	425

Note: This table summarizes the results of the compound-target network analysis performed for bioactive metabolites derived from different marine actinomycete genera. “Bioactive” indicates the total number of bioactive compounds identified for each genus, while “High Scoring Bioactive” refers to those exhibiting the highest network centrality or pharmacological relevance based on topological metrics. “High scoring bioactive names” lists representative lead compounds identified in the analysis. “Targets” represents the number of predicted protein targets associated with each group. “Common” denotes overlapping bioactives and targets shared among multiple genera, and “Combined” represents the total number across the integrated network.

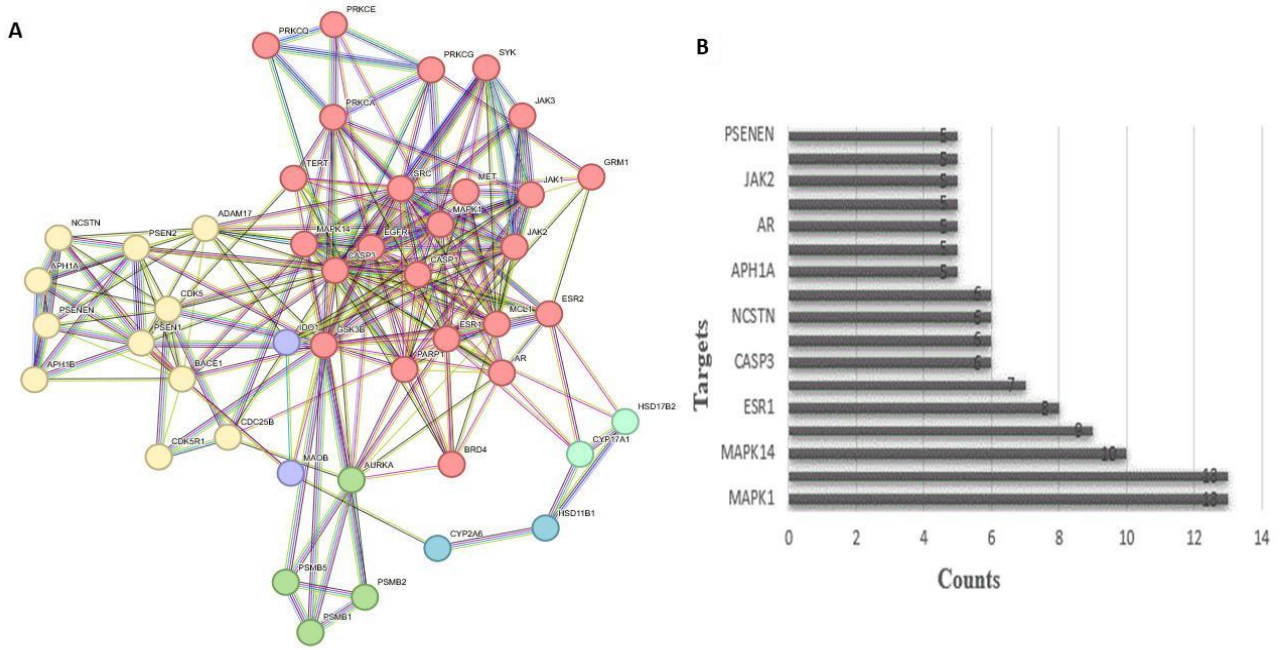

Figure 3. Compound-disease target interaction network and degree centrality analysis. (A) This network depicts the interaction landscape between bioactive compounds and disease-associated gene targets, comprising 73 target nodes and 344 edges. Network topology analysis revealed an average node degree of 9.42 and an average local clustering coefficient of 0.531, indicating a moderately interconnected network structure. Node size is proportional to degree centrality, highlighting the relative importance of each gene in the network. (B) Notable hub targets with higher degrees include MAPK1, MAPK14, ESR1, CASP3, NCSTN, APH1A, AR, JAK2, and PSENEN, which may play key regulatory roles in disease-related signaling pathways. Edges represent predicted interactions between compounds and their associated targets. Degree statistics for all nodes were calculated and analyzed using Microsoft Excel. This visualization facilitates the identification of high-priority gene targets for subsequent functional validation and therapeutic exploration.

Table 4. Bioactives interacting with the core targets.

Targets	Degree	Betweenness Centrality	H-B	Bioactives			
				Salinispora sp.	***Streptomyces sp.***	**Others**	**Common**
MAPK1	3	0.02934555	Yes	Salinosporamide A (NPI-0052), Salinosporamide A (fused - lactam--lactone)	Streptokordin	-	-
MAPK14	4	0.056482179	Yes	-	Bonactin, Azamerone, Methoxyneihumicin, Streptopyrrolidine	-	-
ESR1	3	0.001954281	Yes	-	3,6-disubstituted indole, Strepsesquitriol	-	-
CASP3	3	0.018869342	Yes	-	Diketopiperazines, Benzoxacystol	-	-
NCSTN	3	0.010918113	Yes	Salinosporamide A (NPI-0052), Salinosporamide A (fused - lactam--lactone)	Ahpatinin F	-	-
APH1A	3	0.02224667	Yes	Salinosporamide A (NPI-0052), Salinosporamide A (fused - lactam--lactone)	Ahpatinin F	-	-
AR	3	0.016770038	Yes	Salinosporamide A (NPI-0052), Salinosporamide A (fused - lactam--lactone)	Ahpatinin F	-	-
JAK2	3	0.003934134	Yes	Salinosporamide A (NPI-0052), Salinosporamide A (fused - lactam--lactone)	3,6-disubstituted indole	-	-
PSENEN	3	7.32E-06	Yes	Salinosporamide A (NPI-0052), Salinosporamide A (fused - lactam)	Ahpatinin F	-	-

Note: This table summarizes the key bioactive compounds interacting with core protein targets identified through network topology analysis. “Degree” indicates the number of direct interactions (edges) each target node possesses within the network, while “Betweenness Centrality” reflects the node’s centrality and influence on network communication. “H-B” refers to hub-bottleneck genes, which are highly connected and topologically critical nodes playing a central role in network stability and signal integration. Bioactives are categorized based on their source—*Salinispora sp.*, *Streptomyces sp.*, or Others—and “Common” denotes bioactives shared across multiple genera. These hub-bottleneck interactions highlight potential key regulatory targets for therapeutic intervention.

3.5 Enrichment Analysis of GO and Biological Pathways

Through a detailed GO enrichment analysis, we systematically categorized the DRTs according to their involvement in three key areas: cellular components, biological processes, and molecular functions. The results revealed significant enrichment across all categories, highlighting the fun ctional roles of the DRTs. In the cellular component category, "Integral to Plasma Membrane" emerged as the most enriched term, with a noteworthy gene fold of 5.1. This suggests a strong connection between the DRTs and the structural components of the plasma membrane. As shown in Table 5 & Figure 4, the top five enriched cellular components include "Integral to Plasma Membrane", "Plasma Membrane", "Endoplasmic Reticulum", "Golgi Apparatus" and "Cytoplasm", with fold changes of 5.1, 2.5, 4.0, 4.2, and 1.7, respectively. These findings highlight the significant roles of DRTs in various essential cellular processes. For example, DRTs in the endoplasmic reticulum and Golgi apparatus indicate their involvement in protein synthesis, modification, and trafficking, while DRTs in the plasma membrane play crucial roles in cell signaling and transport. The presence of DRTs in the cytoplasm suggests their participation in other intracellular activities. This comprehensive analysis provides valuable insights into how DRTs are linked to cellular components and their functional roles in cellular processes.

Table 5. GO analysis of cellular components.

Sr No.	Cellular component	Percentage	-log10(p-value)	Fold
1	Integral to Plasma membrane	32.6%	3.71	5.1
2	Plasma membrane	60.5%	3.58	2.5
3	Endoplasmic reticulum	30.2%	2.07	4
4	Golgi apparatus	25.6%	1.48	4.2
5	Cytoplasm	67.4%	0.93	1.7

Note: This table presents the results of GO enrichment analysis for cellular components associated with the predicted target genes. "Percentage" represents the proportion of total genes localized to each cellular compartment. "-log10(p-value)" indicates the statistical significance of enrichment, where higher values denote stronger confidence in the association. "Fold" refers to the fold enrichment compared to the expected background frequency. The results suggest that a majority of target proteins are associated with membrane-related components (e.g., plasma membrane and integral membrane proteins), followed by endoplasmic reticulum, Golgi apparatus, and cytoplasmic localization, indicating their potential involvement in signaling, trafficking, and intracellular regulatory processes.

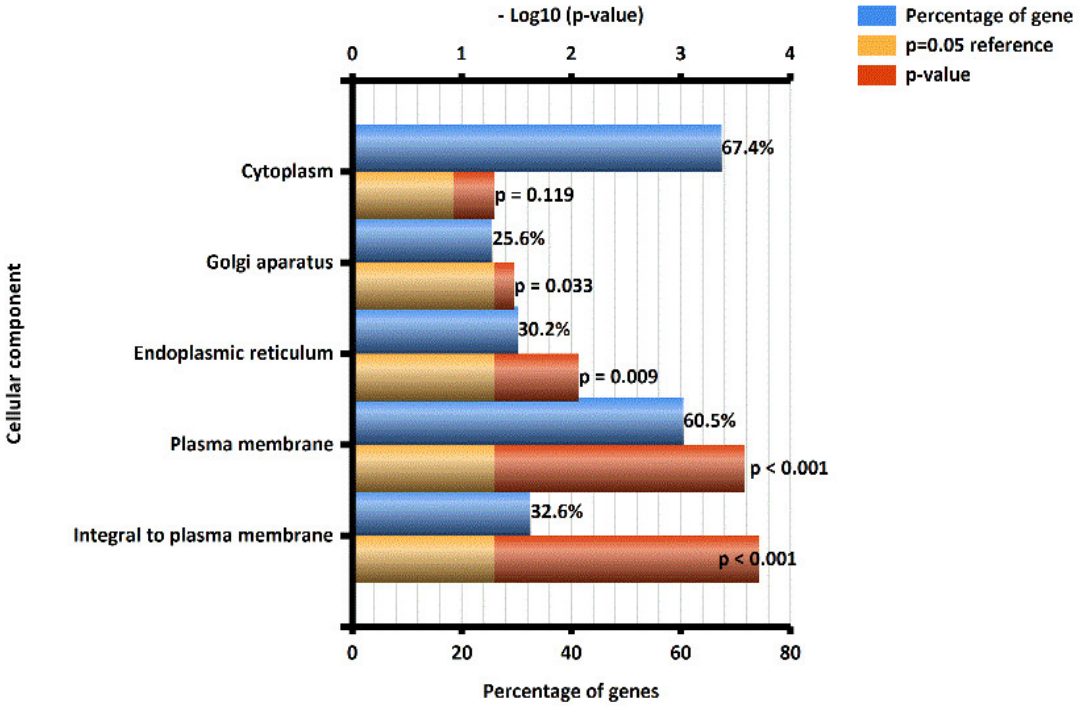

Figure 4. GO enrichment analysis of DRTs—cellular component category. This figure presents the top five significantly enriched cellular component terms associated with the predicted DRTs, including "Integral to Plasma Membrane", "Plasma Membrane", "Endoplasmic Reticulum", "Golgi Apparatus" and "Cytoplasm". These enriched components highlight the primary subcellular localizations where target proteins are likely to function, reflecting their structural roles in membrane dynamics, intracellular trafficking, and signal transduction. Fold enrichment values represent the magnitude of overrepresentation compared to background expectations, providing insights into the spatial distribution and potential functional significance of these targets within the cellular environment.

Continuing from our analysis of cellular components, our investigation extended to biological processes, shedding light on the functional characteristics of the DRTs. In terms of biological processes, the DRTs exhibited extraordinary enrichment, and the most remarkably enriched process was "Gene Silencing", with a remarkable gene fold of 141.4. This intriguing finding underscores the pivotal role of DRTs in processes related to gene silencing, indicating their potential significance in regulating gene expression. Additionally, as demonstrated in Table 6 & Figure 5, the top 5 enriched biological processes include "Gene Silencing", "Apoptosis", "Signal Transduction", "Protein Metabolism" and "Cell Communication" with fold changes of 141.4, 5.8, 2.0, 3.2, and 1.9, respectively. These enrichments provide a comprehensive view of the DRTs' involvement in critical biological processes, offering valuable insights into their functional implications in cellular regulation and signaling pathways.

Table 6. GO analysis of biological process.

Sr No.	Biological Process	Percentage	-log10(p-value)	Fold
1	Signal transduction	44.2%	0.84	2
2	Protein metabolism	23.3%	0.81	3.2
3	Cell Communication	39.5%	0.23	1.9
4	Gene silencing	2.3%	0.00	141.4
5	Apoptosis	7%	0.00	5.8

Note: This table summarizes the GO enrichment analysis of biological processes associated with the predicted target genes. "Percentage" indicates the proportion of genes involved in each process relative to the total annotated targets. "-log10(p-value)" represents the statistical significance of enrichment, where higher values correspond to stronger associations. "Fold" denotes the fold enrichment compared to background levels. The analysis highlights a dominant involvement of targets in key biological processes such as signal transduction, protein metabolism, and cell communication, while highly enriched but less frequent processes like gene silencing and apoptosis suggest specialized regulatory roles with potential therapeutic significance.

Expanding on molecular functions, our analysis identified a striking overrepresentation of "Ligand-Gated Ion Channel Activity" with an exceptional gene fold of 141.4. This highlights the crucial involvement of DRTs in modulating ligand-gated ion channels, which are fundamental to cellular signaling and neurotransmission. As summarized in Table 7 & Figure 6, the top five enriched molecular functions include "Ligand-Gated Ion Channel Activity", "Protein Serine/Threonine Kinase Activity", "Protein Binding", "Catalytic Activity", and "Peptidase Activity", with fold enrichments of 141.4, 9.8, 7.0, 4.0, and 14.6, respectively. These findings underscore the integral role of DRTs in diverse cellular functions, offering deeper insights into their mechanistic impact on biological pathways and processes.

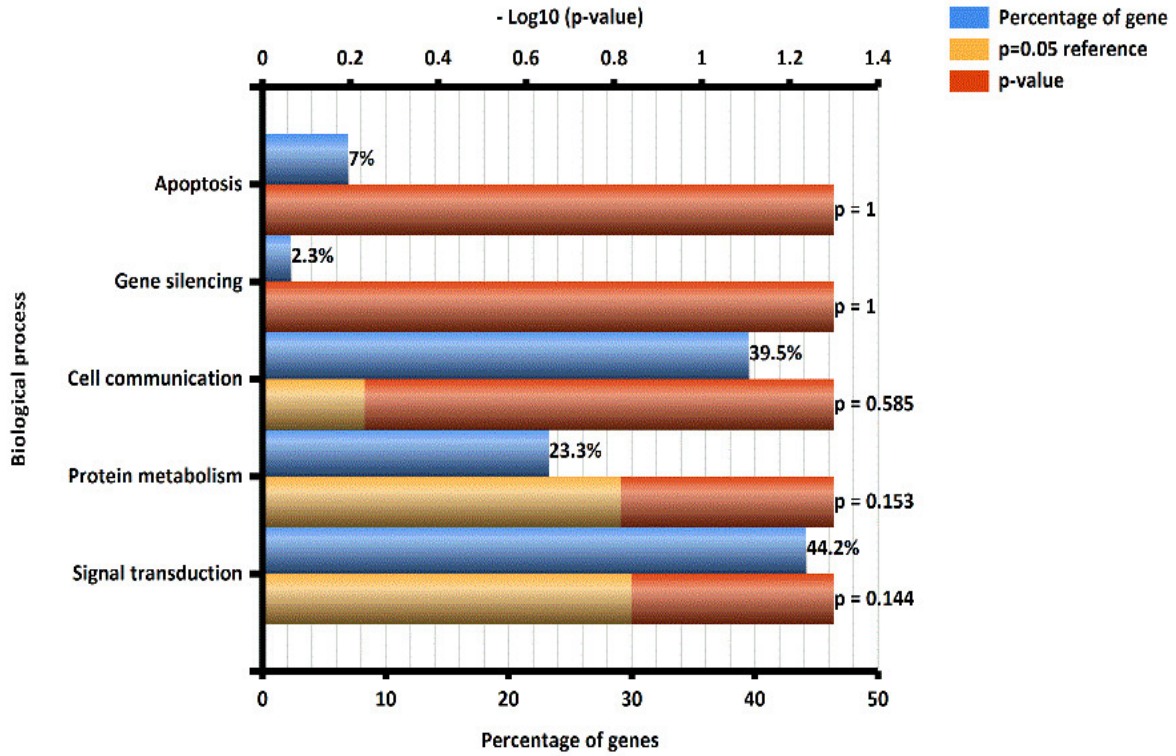

Figure 5. GO enrichment analysis of DRTs–biological process category. This figure illustrates the top five significantly enriched biological processes associated with the predicted DRTs, including "Gene Silencing", "Apoptosis", "Signal Transduction", "Protein Metabolism", and "Cell Communication". These processes reflect the functional diversity of target genes, encompassing key regulatory mechanisms such as transcriptional and epigenetic control, programmed cell death, intracellular signaling cascades, metabolic regulation, and intercellular communication. Fold enrichment values represent the degree of overrepresentation relative to background, providing insight into the functional prominence of each process in disease modulation.

Table 7. GO analysis of molecular function.

Sr No.	Molecular Function	Percentage	-log10(p-value)	Fold
1	Protein serine/threonine kinase activity	16.3%	2.85	9.8
2	Ligand-gated ion channel activity	2.3%	0.00	141.4
3	Catalytic activity	11.6%	0.00	4
4	Peptidase activity	4.7%	0.00	14.6
5	Protein binding	7%	0.00	7

Note: This table presents the GO enrichment analysis of molecular functions associated with the predicted target genes. "Percentage" represents the proportion of genes annotated with each molecular function relative to the total target set. "-log10 (p-value)" indicates the statistical significance of enrichment, with higher values reflecting stronger confidence in functional association. "Fold" denotes the fold enrichment compared to background occurrence. The results highlight significant involvement of target proteins in catalytic and signaling-related functions, particularly protein serine/threonine kinase activity, peptidase activity, and protein binding. Additionally, highly enriched but less frequent functions such as ligand-gated ion channel activity suggest potential roles in synaptic transmission and signal modulation.

The investigation of PRTs revealed substantial enrichment in key biological pathways, as detailed in Table 8 & Figure 7. The top five pathways influenced by these PRTs encompass essential cellular functions and provide insights into their mechanistic roles. These pathways are not only relevant to Alzheimer's disease but also extend to other neurodegenerative and mental health disorders such as Parkinson's disease, schizophrenia, and depression. Among them, "Regulated proteolysis of p75NTR" exhibited an exceptional gene fold of 97.1, emphasizing its critical role in these conditions. These pathways regulate fundamental processes, making them central to understanding the molecular mechanisms impacted by PRTs. For instance, "Signaling by NGF" and "p75(NTR)-mediated signaling" contribute to neurotransmitter clearance and synaptic regulation, key elements in Parkinson's disease and depression management. The "NOTCH" signaling pathway, essential for neurodevelopment and intercellular communication, has been linked to schizophrenia. Disruptions in these pathways can lead to neurodegeneration and pathological accumulation of toxic molecules, hallmarks of many neurological disorders. This enrichment analysis provides valuable insights into the broader disease landscape, offering a deeper understanding of their role in disease pathogenesis and potential therapeutic strategies. Figure 4 visually represents these enriched pathways, illustrating their significance in a broader neurological context.

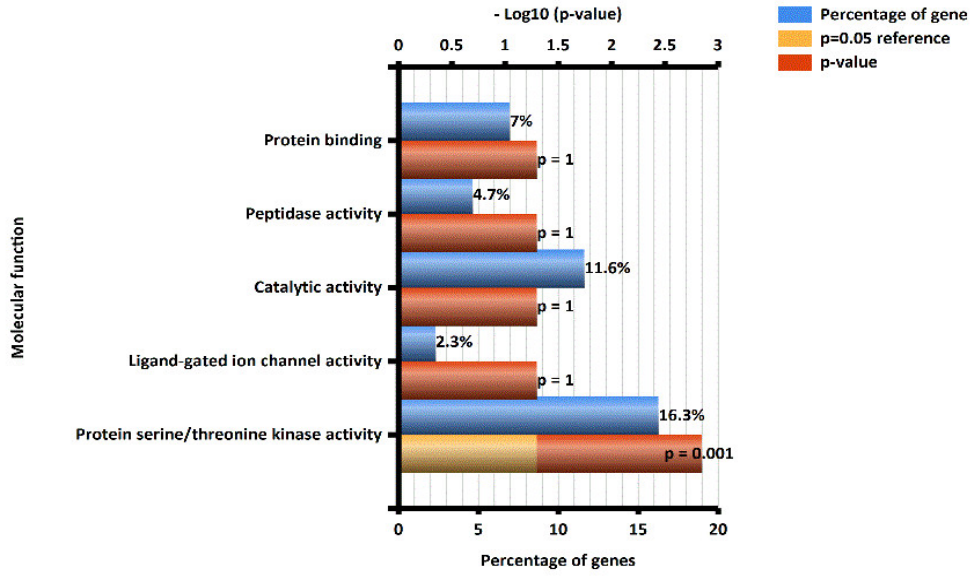

Figure 6. GO enrichment analysis of DRTs–molecular function category. This figure depicts the top five significantly enriched molecular functions associated with the predicted DRTs, including "Ligand-Gated Ion Channel Activity", "Protein Serine/Threonine Kinase Activity", "Protein Binding", "Catalytic Activity" and "Peptidase Activity". These enriched functions highlight the multifaceted roles of target proteins in modulating cellular signaling, enzymatic regulation, substrate processing, and protein-protein interactions—key mechanisms underlying disease pathophysiology. Fold enrichment values indicate the degree of functional overrepresentation relative to the genomic background, underscoring the biological significance of these molecular activities in disease modulation.

Table 8. Top 5 enriched pathways.

Sr No.	Biological Pathway	Percentage	-log10(p-value)	Fold
1	p75(NTR)-mediated signaling	38.9%	9.33	13.7
2	Signaling by NGF	30.6%	6.45	13.4
3	Regulated proteolysis of p75NTR	13.9%	6.02	97.1
4	NOTCH	22.2%	5.95	24.5
5	Presenilin action in Notch and Wnt signaling	19.4%	5.08	26.6

Note: This table summarizes the top five significantly enriched biological pathways associated with the predicted target genes. "Percentage" represents the proportion of target genes participating in each pathway relative to the total number of annotated targets. "-log10(p-value)" denotes the statistical significance of enrichment, where higher values indicate stronger associations, and "Fold" represents the fold enrichment compared to the expected background. The results highlight critical neurobiological signaling cascades, including p75(NTR)-mediated signaling, NGF signaling, and regulated proteolysis of p75NTR, which are essential for neuronal survival, differentiation, and apoptosis. Additionally, enrichment of the NOTCH pathway and presenilin-related signaling underscores the potential involvement of these targets in neurodegenerative disease mechanisms such as Alzheimer's pathology.

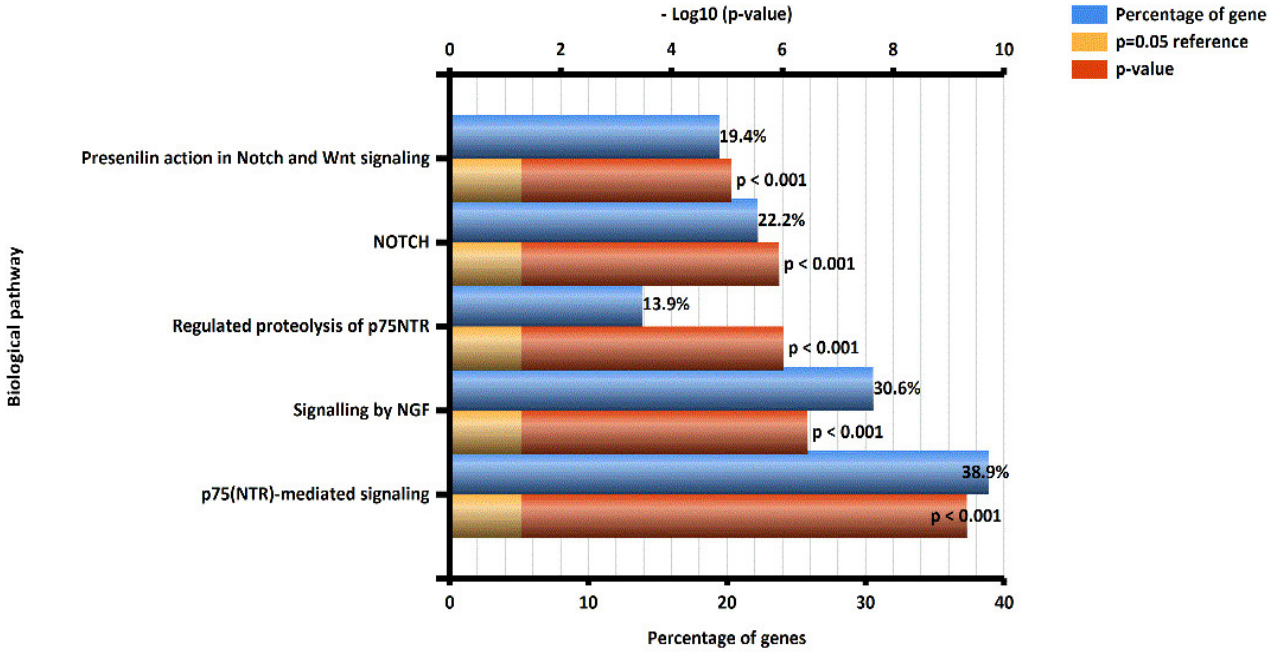

Figure 7. Pathway enrichment analysis of PRTs. This figure presents the top five significantly enriched signaling pathways associated with the predicted regulatory targets, including "Regulated Proteolysis of p75NTR", "Signaling by NGF", "p75(NTR)-Mediated Signaling", "NOTCH Signaling", and "Neurotrophin Signaling". These pathways collectively underscore the mechanistic roles of PRTs in the molecular pathogenesis of Alzheimer's disease and other neurodegenerative or psychiatric disorders, particularly in processes related to neuronal survival, synaptic plasticity, and cell fate determination. Fold enrichment values indicate the extent of pathway overrepresentation relative to background, providing insights into the relative contribution and regulatory influence of these targets across disease-relevant signaling cascades.

3.6 Gene-Pathway Interaction Network

Figure 8 presents the Gene-Pathway Interaction Network, illustrating the complex associations between key regulatory genes–MAPK1, MAPK14, ESR1, CASP3, NCSTN, APH1A, AR, JAK2, and PSENEN–and the significantly enriched pathways identified in our study. This network visualization highlights the molecular interconnections that drive neurodegenerative and mental health disorders, offering crucial insights into their underlying mechanisms. By deciphering these associations, we enhance our understanding of disease pathology, paving the way for precision-targeted therapeutic interventions and future research directions.

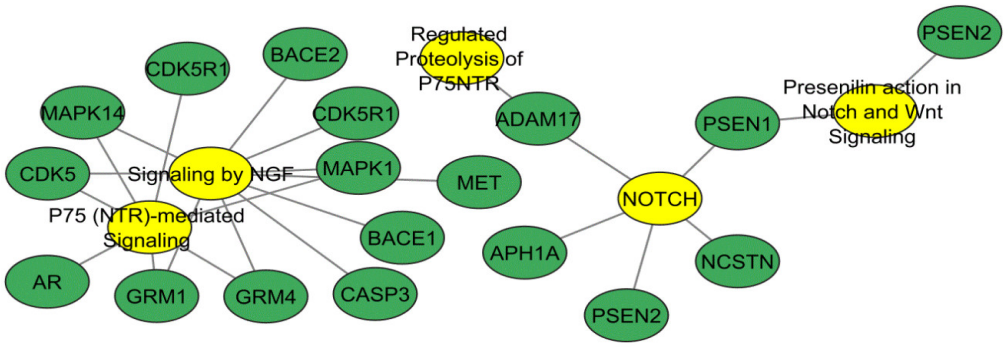

Figure 8. Gene-pathway interaction network. This figure illustrates the associations between core regulatory genes—MAPK1, MAPK14, ESR1, CASP3, NCSTN, APH1A, AR, JAK2, and PSENEN—and the significantly enriched biological pathways they modulate. Green nodes represent genes, while yellow nodes denote associated pathways. The network reveals the intricate molecular crosstalk underlying the pathophysiology of neurodegenerative and psychiatric disorders, highlighting how multiple signaling cascades are coordinated through shared regulatory nodes. This visualization underscores the importance of these genes as central hubs within the signaling landscape and suggests their potential as therapeutic targets for disease intervention.

4. Discussion

The integration of network pharmacology and AI has emerged as a transformative approach in drug discovery, particularly for identifying therapeutic compounds from natural sources. In this study, we explored the potential of marine Actinomycetes, an underexplored reservoir of bioactive compounds, for treating neurodegenerative and mental health disorders. Through an extensive literature survey, we initially identified 91 bioactive compounds, which were systematically refined using ADME screening to 43 compounds with favorable pharmacokinetics, followed by toxicological assessments, further narrowing them to 19 promising candidates with optimal safety profiles. These compounds were mapped to regulatory gene targets, revealing strong associations with key pathways implicated in neurological disorders.

To unravel the molecular mechanisms, we constructed a PPI network and performed GO and pathway enrichment analyses using an AI-powered tool. This highlighted crucial biological functions such as Ligand-Gated Ion Channel Activity (gene fold: 141.4), Gene Silencing (141.4), Integral to Plasma Membrane (5.1), and Regulated Proteolysis of p75NTR (97.1) [43]. These pathways are essential in the context of neurodegeneration. For instance, *Signaling by NGF* and p75(NTR)-mediated signaling influence neurotransmitter clearance and synaptic integrity, with implications in Parkinson's disease and depression. Moreover, the NOTCH signaling pathway, a key regulator of neurodevelopment, has been linked to schizophrenia when dysregulated [44].

While traditional tools such as DAVID offer similar mapping capabilities, we reinforced the validity of our findings through a comprehensive cross-validation with experimental studies. This triangulation supports the robustness of the predicted mechanisms despite the limited prior characterization of many marine-derived compounds. This study lays the groundwork for a systems-level understanding of marine actinomycete-derived bioactives in neurological therapeutics. However, future studies demand experimental validation—such as transcriptomic profiling, Western blotting for key pathway proteins, and functional cell-based assays—to confirm the mechanistic predictions and pharmacological efficacy of the candidate compounds. Such validations are crucial steps in translating computational insights into clinically viable neurotherapeutics.

However, it is important to acknowledge that many marine-derived natural products face inherent bioavailability challenges, particularly when targeting the CNS. Factors such as poor aqueous solubility, low gastrointestinal absorption, high molecular weight, and limited blood-brain barrier (BBB) permeability may restrict their therapeutic efficacy in neurological applications [45]. To address these limitations, advanced drug delivery strategies are essential. One promising approach is the development of nanoformulation-based optimized delivery systems—such as lipid nanoparticles, polymeric nanocarriers, or solid lipid nanoparticles—which can enhance solubility, stability, targeted delivery, and BBB penetration of marine bioactive compounds. These formulations not only improve oral bioavailability but also enable controlled release and targeted CNS delivery, thereby increasing therapeutic effectiveness while minimizing systemic toxicity [46,47]. We have incorporated the development of such nanoformulation strategies as a key component of our future experimental pipeline to improve the translational viability of these compounds for neurological disorders.

Future investigations should follow a phased trajectory to ensure clinical translation of computational findings. While the present study concentrated on the identification of marine actinomycete strains, therapeutic targets, and associated pathways, subsequent efforts will require rigorous in silico validation using approaches such as molecular docking and molecular dynamics to evaluate binding affinity and stability of candidate compounds. Beyond computational studies, experimental confirmation through *in vitro* assays—including transcriptomic profiling, protein expression analyses, and

functional cellular models–will be critical to verify mechanistic predictions. As a prioritized roadmap, initial experimental phases should focus on BBB permeability assays (e.g., PAMPA-BBB or transwell-based endothelial co-culture models) to validate CNS accessibility, followed by neuronal cell viability and neuroprotection studies using human-derived neuronal or glial cell lines to assess cytotoxicity and functional efficacy. Subsequent stages should incorporate target engagement assays and pathway modulation analyses to confirm biological relevance. In parallel, in vivo pharmacokinetic and brain distribution evaluations, particularly with advanced delivery systems such as nanoformulations, will be necessary to optimize bioavailability and therapeutic potential. Ultimately, long-term studies involving animal models of neurodegenerative disease should be undertaken to evaluate efficacy, safety, and dose-response relationships prior to clinical translation**.** Collectively, these steps represent essential components for bridging computational insights with clinically viable neurotherapeutics.

5. Conclusion

Marine Actinomycetes represent an untapped frontier in the search for novel therapeutics, particularly for complex neurological and psychiatric disorders. By combining systems biology with AI-driven analytics, this study demonstrates the feasibility of moving beyond reductionist approaches to capture the multifaceted interactions between bioactive compounds and disease networks. Rather than isolating single targets, our framework underscores how marine-derived molecules can simultaneously modulate interconnected pathways that govern neuronal health, resilience, and repair. Importantly, this integrative approach positions marine Actinomycetes as not only a source of promising leads but also as a model for how computational tools can accelerate the discovery pipeline. The true impact of this work lies in establishing a translational bridge–wherein computational predictions can be systematically funneled into experimental pipelines to shorten the path from natural product discovery to clinical application. Looking ahead, the convergence of marine natural product research, precision pharmacology, and AI is poised to redefine therapeutic innovation for brain disorders, setting the stage for the next generation of multi-targeted, mechanism-informed interventions.

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Data Availability Statement

Data available in the article's supplementary material.

Author Contributions

MRC was responsible for the study design, data acquisition, computational and statistical analysis, and manuscript preparation. VSD supervised the research process, provided critical feedback, and contributed to manuscript revision.

Conflict of Interest

The authors declare no conflict of interest.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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