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Original Research

Network Pharmacology and Molecular Docking of the Marine Peptide FVKVEVLPQ: A Computational Exploration of Putative Breast Cancer Targets

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Abstract

Background: FVKVEVLPQ from *Arbacia lixula* has previously been studied computationally in triple-negative breast cancer. This study explored its putative targets in breast cancer more broadly using network pharmacology and molecular docking.

Methods: Peptide-associated targets were predicted using SwissTargetPrediction and SEA. Breast cancer-associated genes were obtained from DisGeNET and GeneCards. Shared genes underwent protein interaction and enrichment analyses. ADMET properties and toxicity were predicted using ADMETlab 3.0 and ProTox-III. Six proteins prioritized by network analysis were examined by molecular docking in MOE v2022.02.

Results: The analysis identified 247 putative peptide targets and 3,431 breast cancer-associated genes, including 89 shared genes. The protein interaction network contained 87 nodes and 521 edges. FVKVEVLPQ had low predicted Caco-2 permeability (−6.565), plasma protein binding of 1.0%, and an estimated acute oral LD_{50} of 836 mg/kg. Docking S-scores ranged from −9.08 to −10.77 across STAT3, CASP3, ERBB2, CCND1, ABL1, and IGF1R.

Discussion: Enrichment analysis identified biological processes involving PDGF and VEGF receptor signaling. Docking indicated possible contacts with the six selected proteins, without establishing their biological effects.

Conclusion: The findings generate testable hypotheses about FVKVEVLPQ interactions with breast cancer-associated proteins. Experimental studies are needed to assess target engagement, biological activity, and safety.

Keywords: Breast cancer; Molecular Docking; Network Pharmacology; Peptides

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1. INTRODUCTION

Breast cancer remains one of the most frequently diagnosed malignancies and a leading cause of cancer-related mortality among women worldwide. In 2020, approximately 2.3 million new cases and 685,000 deaths were reported globally.[1] Although treatment has improved, systemic toxicity remains a concern for agents such as doxorubicin.[2] Identifying additional molecular interactions may help guide early research into breast cancer therapeutics.

Marine organisms are recognized as sources of structurally diverse bioactive compounds. In vitro experiments have shown that cell-free coelomic fluid extracts from the sea urchin *Arbacia lixula* alter mitochondrial function and stimulate autophagic activity in MDA-MB-231 breast cancer cells.[3] These findings concern the extracts and do not establish the activity of an individual peptide. FVKVEVLPQ, a peptide sequence identified from *A. lixula*, was subsequently evaluated in an *in silico* study of triple-negative breast cancer. That study examined predicted toxicity and allergenicity and docked the peptide against GSK3B, CDK2, and VEGFR2.[4]

The earlier analysis focused on selected proteins involved in cell-cycle progression and angiogenesis in triple-negative breast cancer. A broader breast cancer gene set offers a way to explore additional putative targets across the disease's molecular context. Peptides are of interest as therapeutic candidates, although limited membrane permeability and stability can constrain their development.[5] Computational methods can help prioritize molecular hypotheses for subsequent testing.[6] Accordingly, this study combined target prediction, network and enrichment analyses, ADMET prediction, and molecular docking to examine FVKVEVLPQ against breast cancer-associated targets beyond those investigated previously.

2. METHODS

2.1 Ligand Preparation

The initial three-dimensional structure of FVKVEVLPQ was generated from its amino acid sequence using the peptide-building function in UCSF Chimera v1.17.1. The peptide was initialized using α-helical backbone dihedral angles ($\varphi = -57°$ and $\psi = -47°$). Tamoxifen (PubChem CID: 2733526) was used as an exploratory ligand. Both ligands were optimized and energy-minimized using MOE v2022.02 with an RMS gradient of 0.001 kcal/mol/Å².

2.2 ADMET Prediction

The pharmacokinetic profile of FVKVEVLPQ was predicted using ADMETlab 3.0, including absorption, distribution, metabolism, and excretion parameters.[7] Toxicity prediction was performed using ProTox-III to estimate LD_{50} and potential

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hepatotoxicity, carcinogenicity, mutagenicity, and cytotoxicity.[8]

2.3 Network Pharmacology Analysis

Breast cancer-associated genes were retrieved from DisGeNET and GeneCards using the search terms “breast cancer” and “breast carcinoma”.[9,10] Peptide-associated targets were predicted using SwissTargetPrediction and the Similarity Ensemble Approach (SEA), with the organism restricted to *Homo sapiens*. Target identifiers from each source were standardized to human gene symbols before the lists were combined. Duplicate entries were removed within and across sources, and the intersection of the peptide-associated and breast cancer-associated gene sets was identified using InteractiVenn.

2.4 Protein–Protein Interaction and Hub Gene Analysis

The overlapping targets were submitted to STRING v12.0 to construct a protein–protein interaction network using a minimum confidence score of 0.4. The network was visualized and analyzed in Cytoscape v3.10.0. Hub proteins were ranked using the Maximal Clique Centrality (MCC) algorithm in the CytoHubba plugin. The six highest-ranked proteins were selected for subsequent molecular docking analysis.

2.5 GO and KEGG Enrichment Analysis

The 89 shared genes were submitted to DAVID 2022 for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses. GO biological process, molecular function, and cellular component terms were examined separately from KEGG pathways. Terms with a false discovery rate-adjusted *p* value below 0.01 were considered significant for the reported enrichment results. Selected terms and their associated genes were visualized using SRplot.

2.6 Molecular Docking Analysis

Molecular docking was performed in MOE v2022.02 using structures of STAT3 (6NJS), CASP3 (3GJQ), ERBB2 (3PP0), ABL1 (4TWP), CCND1 in complex with CDK4 (2W96), and IGF1R (2OJ9) obtained from the Protein Data Bank. Water molecules, heteroatoms, and co-crystallized ligands were removed, and the proteins were energy-minimized using Amber10:EHT. Predicted binding sites are presented in Supplementary Table S1. Docking used Triangle Matcher placement with 30 poses and London dG scoring, followed by rigid receptor refinement of five poses and GBVI/WSA dG rescoring. Final poses and residue interactions were examined using two-

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dimensional and three-dimensional visualizations.

3. RESULTS

3.1 ADMET Prediction

FVKVEVLPQ showed low predicted intestinal permeability, with a Caco-2 permeability value of −6.565, and was classified as having poor human intestinal absorption. It was not predicted to inhibit P-glycoprotein. The predicted plasma protein binding was 1.0%, and blood–brain barrier penetration was not predicted. The peptide was not predicted to be a substrate or inhibitor of the evaluated CYP isoenzymes, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, and CYP2B6. Predicted plasma clearance was 2.897 mL/min/kg, with an elimination half-life of 1.185 h. ProTox-III estimated an acute oral LD_{50} of 836 mg/kg, corresponding to toxicity class IV. Hepatotoxicity, carcinogenicity, mutagenicity, and cytotoxicity were classified as inactive by the prediction model (Table 1).

Table 1. Predicted ADMET Properties of The Marine-Derived Peptide FVKVEVLPQ Based on In Silico Pharmacokinetic and Toxicity Analysis

Category	Parameter	Predicted Value / Interpretation
Absorption	Caco-2 permeability (log Papp)	–6.565 (low permeability)
	P-gp inhibitor	No
	Human intestinal absorption (HIA)	Poor
Distribution	Plasma protein binding (PPB)	1.0 % (low)
	Blood–brain barrier (BBB) penetration	No
Metabolism	CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, and CYP2B6 (substrate/inhibitor)	No
Excretion	Plasma clearance (CL)	2.897 mL/min/kg (low)
	Half-life (T½)	1.185 (h) (short)
Toxicity	LD50 (Class)	836 mg/kgBW (Class IV)
	Hepatotoxicity	Inactive
	Carcinogenicity	Inactive
	Mutagenicity	Inactive
	Cytotoxicity	Inactive

3.2 Potential Targets of FVKVEVLPQ in Breast Cancer

A total of 247 predicted peptide-associated targets and 3,431 breast cancer-associated genes were identified after combining the respective sources and removing duplicate entries. The two sets shared 89 genes (Figure 1A). The remaining 158 peptide-associated targets and 3,342 breast cancer-associated genes were not

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included in the subsequent PPI and enrichment analyses.

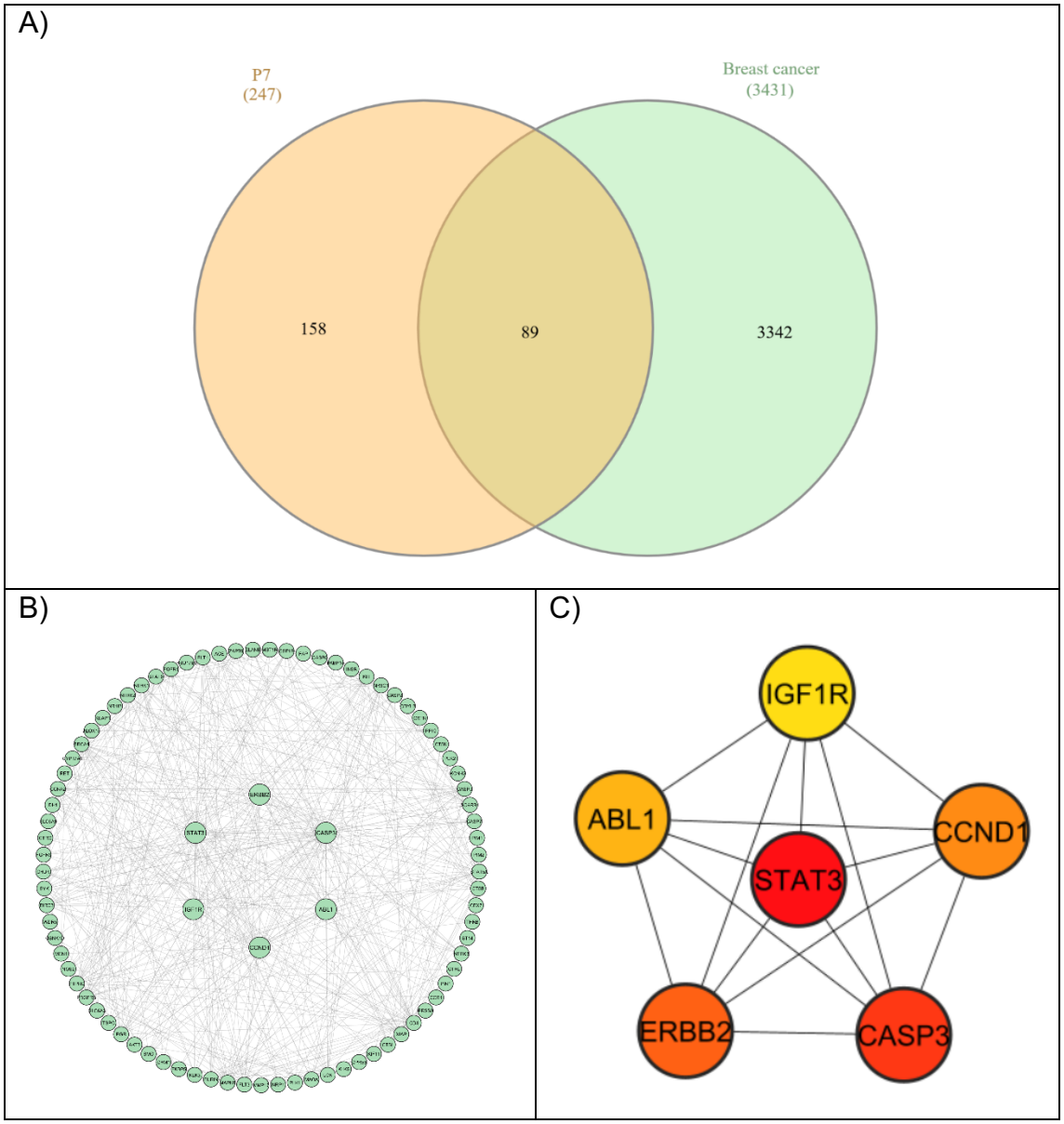

Figure 1. Network pharmacology analysis of FVKVEVLPQ against breast cancer. (A) Venn diagram showing 89 overlapping targets between FVKVEVLPQ and breast cancer. (B) PPI network of the overlapping targets constructed using STRING and visualized in Cytoscape. (C) Hub gene network identified using CytoHubba based on MCC and centrality parameters.

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Table 2. Top Hub Genes Identified from the PPI Network of FVKVEVLPQ target Proteins Based on Network Topology Parameters.

Name	MCC
STAT3	1,463,296
CASP3	1,430,958
ERBB2	1,257,962
CCND1	1,207,221
ABL1	1,159,728
IGF1R	812,430

3.3 Protein–Protein Interaction Network and Hub Gene Analysis

The 89 shared targets were submitted to STRING using a minimum interaction confidence score of 0.4. The resulting network contained 87 nodes and 521 edges. Two submitted targets were not represented in the interaction network. MCC analysis ranked STAT3, CASP3, ERBB2, CCND1, ABL1, and IGF1R as the six highest-scoring proteins (Figure 1C and Table 2). STAT3 had the highest MCC score (1,463,296). These scores describe network topology and were used to prioritize proteins for docking (Table 2).

3.4 GO and KEGG Pathway Enrichment Analysis

GO analysis of the 89 shared targets identified 142 terms at FDR < 0.01, comprising 78 biological process, 28 cellular component, and 36 molecular function terms. Reported biological process terms included platelet-derived growth factor receptor signaling, vascular endothelial growth factor receptor-1 signaling, and positive regulation of T cell proliferation. Cellular component terms included receptor complex, cell surface, and external side of the plasma membrane. Molecular function terms included neurotrophin receptor activity and transmembrane receptor protein tyrosine kinase activity (Figure 2). KEGG analysis identified 115 pathways under the reported significance criterion. Figure 3 shows the positions of selected shared genes, including ERBB2, AKT1, MAPK1, PIK3R1, CCND1, BRCA1, and BRCA2, on the KEGG breast cancer pathway map. This mapping describes pathway membership and does not by itself establish enrichment of other pathways.

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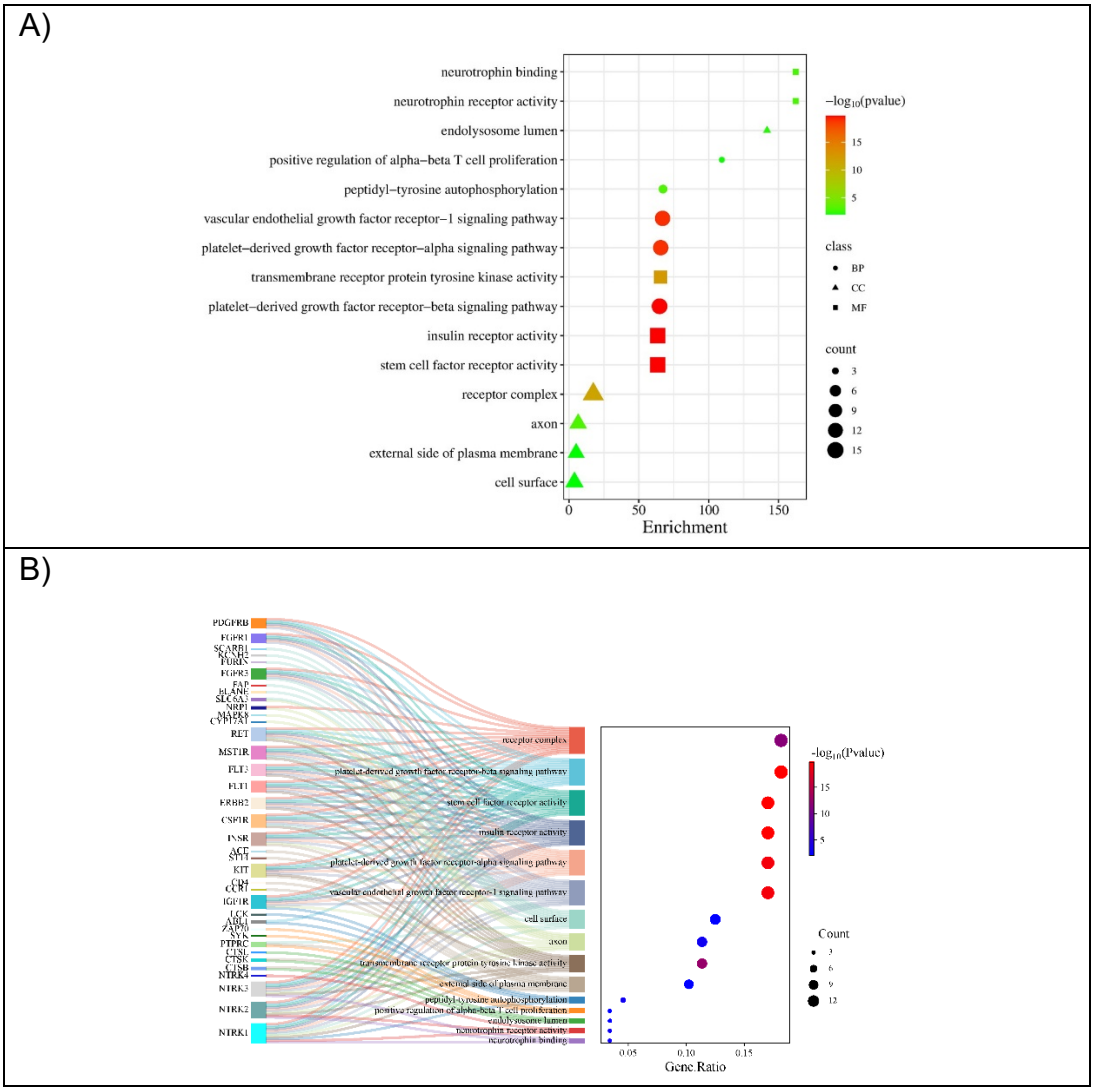

Figure 2. GO enrichment analysis of shared targets. (A) Enriched GO terms. (B) Sankey plot linking shared genes to GO terms.

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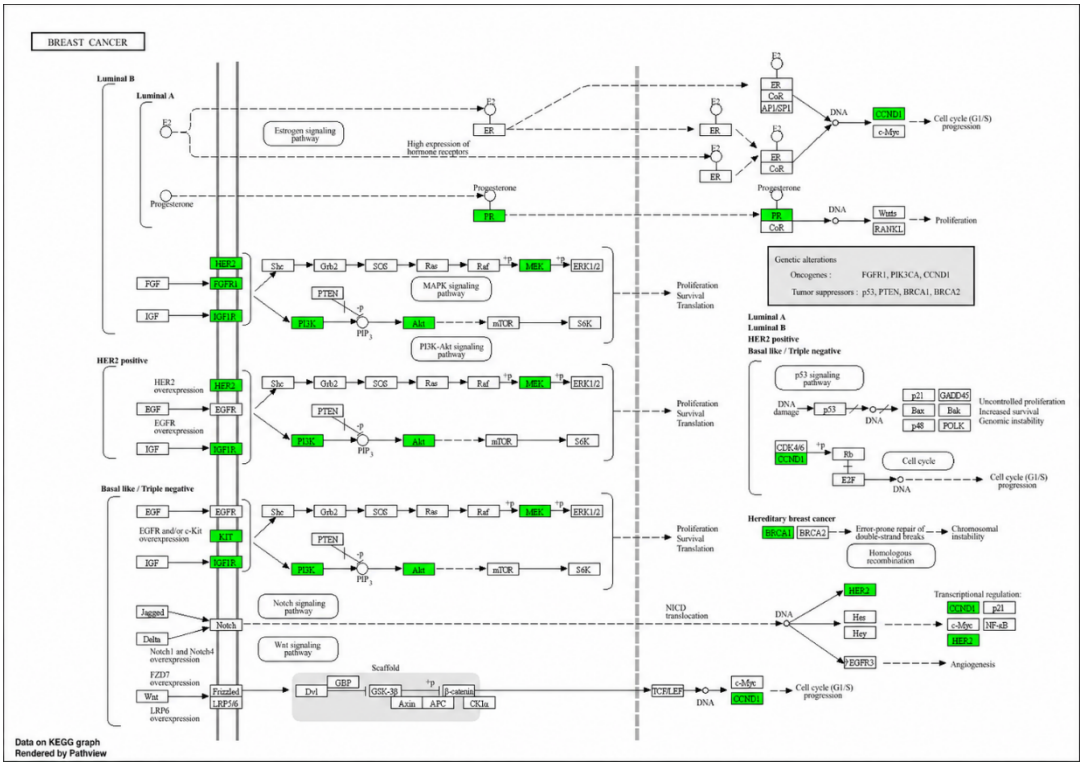

Figure 3. Mapping of selected shared genes to the KEGG breast cancer pathway. Green nodes indicate overlapping target genes associated with FVKVEVLPQ and breast cancer.

3.5 Molecular Docking Analysis

FVKVEVLPQ yielded more negative docking S-scores than tamoxifen across the six examined structures, ranging from −9.08 for STAT3 to −10.77 for ABL1 (Table 3). The predicted STAT3 pose contacted Lys557, Lys591, and Ser636. The CASP3 pose contacted Met61, Arg64, Gly122, and Tyr204. Predicted contacts in ERBB2 involved Lys762, Arg844, Arg868, Lys883, and Arg897. The CCND1 pose contacted Glu69, His181, and Arg218. The ABL1 pose contacted Tyr253, Thr277, Arg367, Asn368, and Asp381. The IGF1R pose contacted Leu975, Gln977, and Met982 (Figure 4). The available results identify contacted residues but do not establish the types of interaction.

Table 3. Comparative docking S-score (kcal/mol) of the marine peptide FVKVEVLPQ and Tamoxifen against selected breast cancer–related target proteins.

Protein	Docking S-score (kcal/mol)	
	FVKVEVLPQ	Tamoxifen
STAT3	-9.08	-6.00
CASP3	-9.92	-6.28
ERBB2	-9.58	-6.93
ABL1	-10.77	-6.98
CCND1	-9.51	-6.59
IGF1R	-9.18	-7.96

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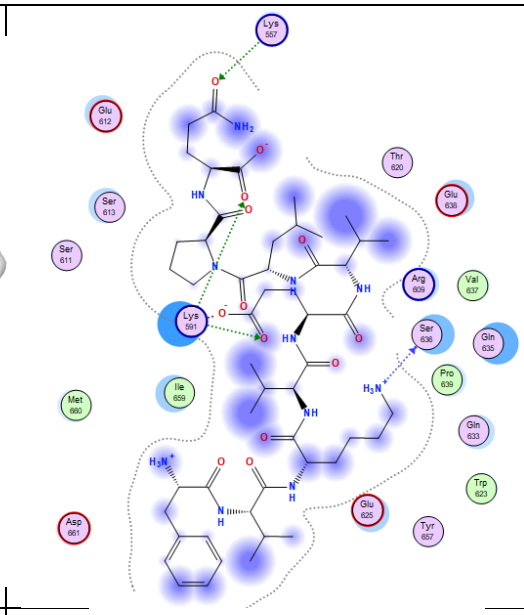
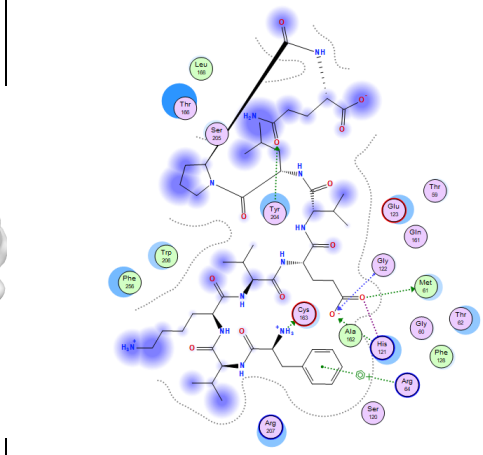
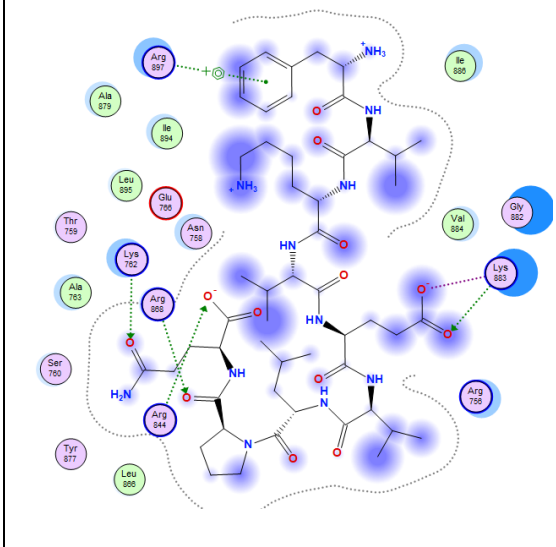
A) STAT3	
B) CASP3	
C) ERBB2	
D) CCND1	

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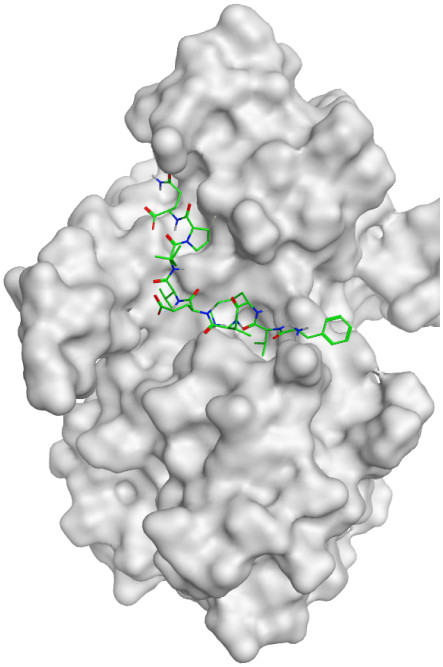
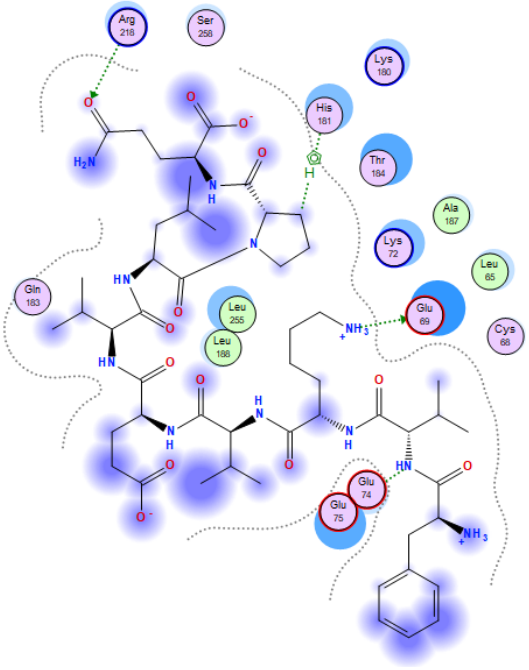
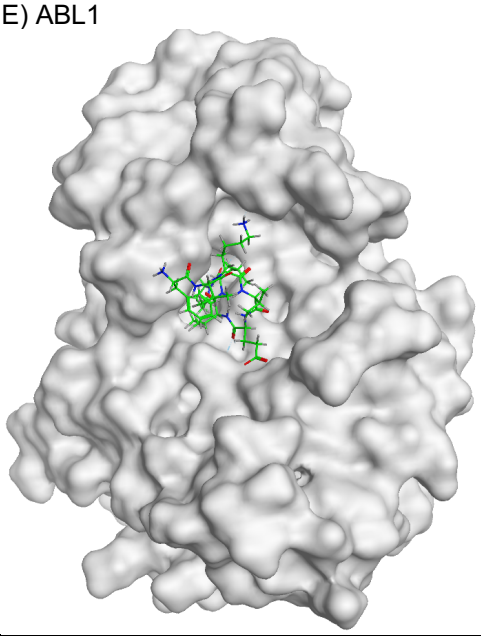
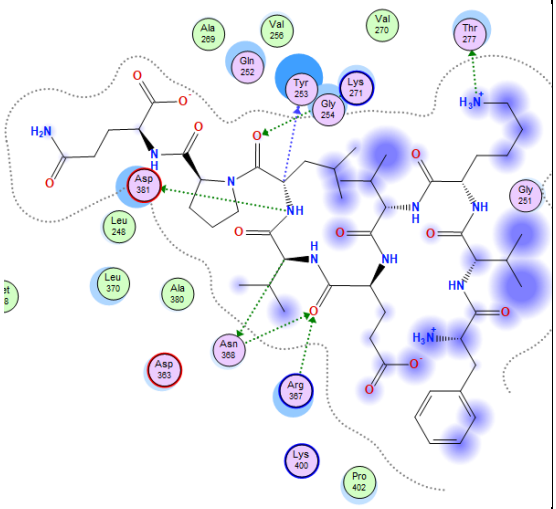




E) ABL1





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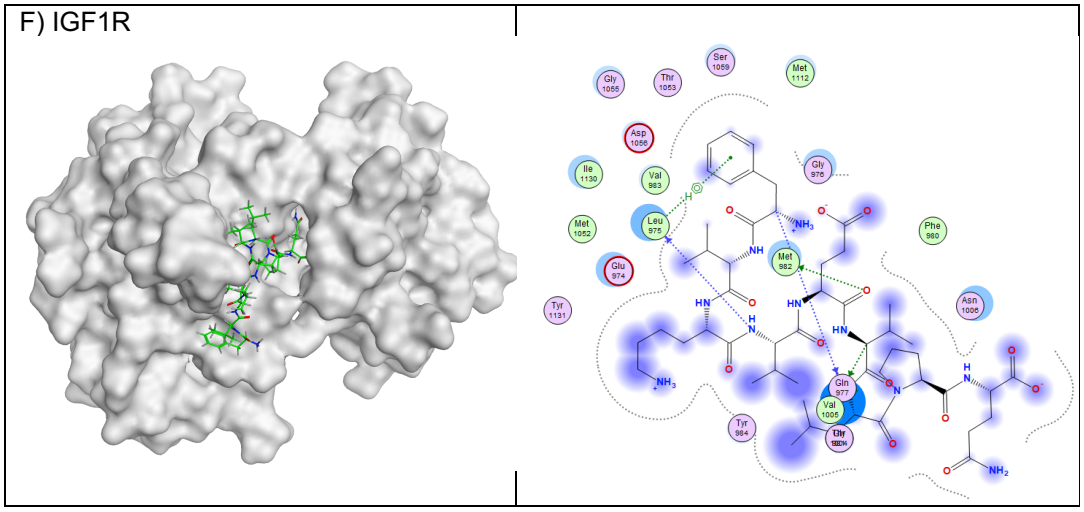

Figure 4. Two-dimensional and three-dimensional molecular docking visualization of FVKVEVLPQ with: A) STAT3, B) CASP3, C) ERBB2, D) CCND1, E) ABL1, F) IGF1R proteins.

4. DISCUSSION

Breast cancer remains one of the most common malignancies worldwide despite advances in detection and treatment. Conventional therapies continue to face limitations, including systemic toxicity and treatment resistance.[11] Marine organisms provide structurally diverse compounds for therapeutic research.[12] FVKVEVLPQ was previously evaluated computationally against proteins related to the cell cycle and angiogenesis in the context of triple-negative breast cancer.[4] The present study extends that work by examining predicted targets across breast cancer-associated genes and prioritizing six proteins for structural analysis. This broader scope allows the peptide's predicted target profile to be explored beyond a single breast cancer subtype, although the analysis does not establish activity in any subtype.

GO analysis identified biological processes involving PDGF and VEGF receptor signaling, alongside terms related to receptor activity and the cell surface. The KEGG breast cancer pathway map placed several shared genes within signaling and cell-cycle components. These findings describe associations among predicted targets and annotated pathways. They do not show that FVKVEVLPQ changes pathway activity. PI3K–Akt signaling has an established role in cancer cell survival, while ERBB2 is relevant to the biology of HER2-positive breast cancer.[13,14] The biological importance of these pathways provides context for interpreting the target network, rather than evidence of a peptide-induced effect.[15,16]

FVKVEVLPQ produced more negative docking S-scores than tamoxifen for all six examined structures, with the most negative score observed for ABL1 (−10.77). Tamoxifen was an exploratory comparator and is not a target-specific reference ligand for these proteins. The predicted residue contacts support the possibility of structural interactions, but the available output does not establish their interaction types or whether binding occurs under experimental conditions. Docking scores also cannot be compared as direct measures of affinity or biological efficacy, particularly for ligands of different sizes. Molecular modelling remains useful for generating testable peptide–protein interaction hypotheses.[17]

The six proteins have distinct biological functions, which makes the direction of any peptide-related effect especially important to establish experimentally. For example, ABL1 and CASP3 have documented roles in tumor-related signaling and apoptosis, respectively.[18,19] A predicted contact with either protein does not establish kinase inhibition or caspase activation. Likewise, docking to STAT3, ERBB2, CCND1, or IGF1R cannot demonstrate altered transcription, receptor signaling, or cell-cycle progression. Tumor heterogeneity and drug resistance provide a rationale for studying multiple targets, but a therapeutic advantage cannot be inferred from the present target network.[20]

Several limitations affect the interpretation of these findings. SwissTargetPrediction and SEA rely on ligand similarity, and their applicability to a nonapeptide requires caution. The ADMET and acute toxicity outputs are model predictions rather than measurements of safety. Future work should verify the computational protocol, examine complex stability, and test peptide uptake, stability, cytotoxicity, target engagement, and pathway responses in relevant breast cancer models.[17]

5. CONCLUSION

This computational study identified 89 shared genes between predicted FVKVEVLPQ targets and breast cancer-associated genes. Network analysis prioritized STAT3, CASP3, ERBB2, CCND1, ABL1, and IGF1R for docking, which yielded peptide S-scores ranging from −9.08 to −10.77. The enrichment and docking results provide hypotheses about potential peptide–protein interactions. Experimental studies are needed to determine whether these interactions occur and affect breast cancer cells.

6. RECOMMENDATION

Further in vitro, in vivo, and molecular dynamics studies are needed to validate the biological activity, complex stability, safety, and therapeutic potential of FVKVEVLPQ as a marine peptide-based candidate for breast cancer treatment.

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REFERENCES

1. World Health Organization. Cancer Today, Global Cancer Observatory. Lyon: International Agency for Research on Cancer. 2020. Available from: https://gco.iarc.fr/today/online-analysis-multi-bars.
2. Lee J, Choi MK, Song IS. Recent advances in doxorubicin formulation to enhance pharmacokinetics and tumor targeting. *Pharmaceuticals (Basel).* 2023;16:802. doi:10.3390/ph16060802.
3. Luparello C, Ragona D, Asaro DML, Lazzara V, Affranchi F, Arizza V, et al. Cell-free coelomic fluid extracts of the sea urchin *Arbacia lixula* impair mitochondrial potential and stimulate autophagic activity in MDA-MB231 breast cancer cells. *J Mar Sci Eng.* 2020;8:261. doi:10.3390/jmse8040261.
4. Arisanty D, Cuandra KN, Putra AE, Rita RS, Ilmiawati C, Anggraini FT. Exploring the potential of *Arbacia lixula* coelomic fluid peptides as cell cycle and angiogenesis inhibitor for triple-negative breast cancer therapy: In silico study. *J Pharm Pharmacogn Res.* 2025;13(1):242–253. doi:10.56499/jppres24.1991_13.1.242.
5. Wang L, Wang N, Zhang W, Cheng X, Yan Z, Shao G, et al. Therapeutic peptides: current applications and future directions. *Signal Transduct Target Ther.* 2022;7:48. doi:10.1038/s41392-022-00904-4.
6. Agamah FE, Mazandu GK, Hassan R, Bope CD, Thomford NE, Ghansah A, et al. Computational/in silico methods in drug target and lead prediction. *Brief Bioinform.* 2020;21:1663–1675. doi:10.1093/bib/bbz103.
7. Fu L, Shi S, Yi J, Wang N, He Y, Wu Z, et al. ADMETlab 3.0: an updated comprehensive online ADMET prediction platform. *Nucleic Acids Res.* 2024;52:W422–W431. doi:10.1093/nar/gkae236.
8. Banerjee P, Kemmler E, Dunkel M, Preissner R. ProTox 3.0: a webserver for the prediction of toxicity of chemicals. *Nucleic Acids Res.* 2024;52:W513–W520. doi:10.1093/nar/gkae303.

9. Hu Y, Guo X, Yun Y, Lu L, Huang X, Jia S. DisGeNET: a disease-centric interaction database among diseases and associated genes. *Database (Oxford).* 2025;2025:baae122. doi:10.1093/database/baae122.
10. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, et al. The GeneCards suite: from gene data mining to disease genome sequence analyses. *Curr Protoc Bioinformatics.* 2016;54:1.30.1–1.30.33. doi:10.1002/cpbi.5.
11. Zafar A, Khatoon S, Khan MJ, Abu J, Naeem A. Advancements and limitations in traditional anti-cancer therapies: a comprehensive review. *Discov Oncol.* 2025;16:607. doi:10.1007/s12672-025-02198-8.
12. Zhang J. Marine-derived compounds: a new horizon in cancer, renal, and metabolic disease therapeutics. *Mar Drugs.* 2025;23:283. doi:10.3390/md23070283.
13. He Y, Sun MM, Zhang GG, Yang J, Chen KS, Xu WW, et al. Targeting PI3K/Akt signal transduction for cancer therapy. *Signal Transduct Target Ther.* 2021;6:425. doi:10.1038/s41392-021-00828-5.
14. Li YW, Dai LJ, Wu XR, Zhao S, Xu YZ, Jin X, et al. Molecular characterization and classification of HER2-positive breast cancer inform tailored therapeutic strategies. *Cancer Res.* 2024;84:3669–3683. doi:10.1158/0008-5472.CAN-23-4066.
15. Yang X, Yang D, Qi X, Luo X, Zhang G. Endocrine treatment mechanisms in triple-positive breast cancer: from targeted therapies to advances in precision medicine. *Front Oncol.* 2025;14:1467033. doi:10.3389/fonc.2025.1467033.
16. Samad MA, Ahmad I, Khan MR, Suhail M, Zughaibi TA, Al-Abbasi FA, et al. Breast cancer: molecular pathogenesis and targeted therapy. *MedComm.* 2025;6:e70404. doi:10.1002/mco2.70404.
17. Agoni C, Fernández-Díaz R, Timmons PB, Adelfio A, Gómez H, Shields DC. Molecular modelling in bioactive peptide discovery and characterisation. *Biomolecules.* 2025;15:524. doi:10.3390/biom15040524.
18. Dong Q, Wang D, Song C, Gong C, Liu Y, Zhou X, et al. ABL1-mediated phosphorylation promotes FOXM1-related tumorigenicity by increasing FOXM1 stability. *Cell Death Differ.* 2024;31:1285–1301. doi:10.1038/s41418-024-01339-w.
19. Dou H, Yu PY, Liu YQ, Zhu Y, Li FC, Wang YY, et al. Recent advances in caspase-3, breast cancer, and traditional Chinese medicine: a review. *J Chemother.* 2024;36:370–388. doi:10.1080/1120009X.2023.2278014.

20. Fu YC, Liang SB, Luo M, Wang XP. Intratumoral heterogeneity and drug resistance in cancer. *Cancer Cell Int.* 2025;25:103. doi:10.1186/s12935-025-03734-w.