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Original Article

MOLECULAR DOCKING INSIGHTS INTO PROBIOTICS AS POTENTIAL INHIBITORS OF THE PI3K PATHWAY FOR COLON CANCER THERAPY

MOHD ABDUL BAQI[1], KOPPULA JAYANTHI[2], RAMAN RAJESHKUMAR[1*]

[1]Department of Pharmaceutical Biotechnology, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty, Nilgiris, Tamil Nadu, India. [2]Department of Pharmaceutical Chemistry, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty, Nilgiris, Tamil Nadu, India

*Corresponding author: Raman Rajeshkumar; *Email: bathmic@jssuni.edu.in

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ABSTRACT

Objective: This study investigates the interactions of probiotics-derived bacteriocins with Phosphoinositide 3-kinases (PI3Ks), a key enzyme involved in cell growth and survival pathways, with a focus on the cancer-associated PI3K pathway (PDB ID: 1E8X). The aim is to explore the anti-cancer potential of these bacteriocins as inhibitors of the PI3K catalytic subunit.

Methods: Using the Glide module, the study first involved molecular docking of bacteriocins. Next, an Absorption, Distribution, Metabolism, and Excretion (ADME) study was conducted using Qikprop. The Prime Molecular Mechanics Generalised Born Surface Area (MM-GBSA) method was used to calculate binding free energy.

Results: Five bacteriocins demonstrated significant binding affinity and interactions, including hydrogen and hydrophobic bonds, with key residues such as Tyr867, Trp812, Asp950, Asn951, Lys802, Lys890, Lys833, Val882, Ser806, Thr886, and Gln893 in the PI3K catalytic subunit (PDB ID: 1E8X). Among these, *Plantaricin D* exhibited an excellent XP-docking score of-7.47 kcal/mol, indicating strong binding potential. Prime MM-GBSA analysis revealed promising binding affinities with ΔBind (-92.85 kcal/mol), ΔLipo (-65.81 kcal/mol), and ΔVdW (-47.34 kcal/mol). The ligand consistently interacted with residues Asp950, Lys890, Gln893, Ser894, Thr887, Ala885, Tyr757, Asp758, Lys802, and Val759.

Conclusion: *Plantaricin D* bacteriocin, characterized by functional groups including the primary amine (NH_2), carbonyl (C=O), hydroxide (OH), and oxygen (O), demonstrates significant potential as a PI3K inhibitor. This suggests its promising application as an anti-cancer agent, particularly for colon cancer.

Keywords: Phosphoinositide 3-kinases (PI3Ks), Molecular docking, MM-GBSA, ADME, Cancer, Probiotics, Bacteriocins, Anti-cancer agents

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INTRODUCTION

Phosphoinositide 3-kinase (PI3K) is an essential pathway that controls many cellular functions, including as growth, survival, metabolism, and proliferation. Three primary components make up this pathway: mechanistic target of *rapamycin* (mTOR), protein kinase B (Akt), and PI3K. Phosphorylation of inositol lipids is caused by PI3K activation, and this in turn activates Akt. Akt promotes cell cycle progression and inhibits pro-apoptotic proteins, controlling several downstream pathways necessary for cell survival and proliferation [1]. Cancer typically exhibits deregulation of the PI3K/AKT/mTOR pathway, which contributes to unchecked cell proliferation and resistance to apoptosis. Mutations or amplifications in PI3K, or alterations in its downstream effectors, can lead to hyperactivation of the pathway. This aberrant signaling is implicated in many cancers, including breast, lung, and prostate [2]. As a result, focussing on the PI3K pathway has become a viable approach for cancer treatment, with the goals of regaining normal cellular regulation and preventing tumour development. Probiotics, live microorganisms that confer health benefits to the host, have garnered attention for their role in gut health and their potential in cancer prevention and therapy. Certain probiotic strains produce bacteriocins, antimicrobial peptides that can inhibit the growth of pathogenic bacteria. Recent research has expanded the focus to include the anti-cancer properties of these bacteriocins. In addition to inducing cancer cells to undergo apoptosis and inhibiting tumour development, bacteriocins also modify the immune system [3]. Bacteriocins from probiotics have demonstrated potential in targeting cancer cells through different mechanisms. For instance, they can interact with cell membranes, leading to cell lysis or altered cellular functions. Additionally, bacteriocins may impact signaling pathways associated with cancer, such as the PI3K pathway. By affecting these pathways, bacteriocins might help in controlling tumor progression and enhancing the efficacy of existing therapies [4, 5]. In this study, we explore the interactions of bacteriocins derived from probiotic strains with the PI3K pathway, specifically focusing on the PI3K catalytic domain (PDB ID: 1E8X). By employing docking studies, we aim to elucidate how these bacteriocins might bind to and inhibit the PI3K pathway, providing insights into their potential role in colon cancer therapy.

MATERIALS AND METHODS

Molecular docking

Using molecular docking, the binding affinities and interaction processes between ligands and PI3K were predicted. The goal was to identify the best-docked conformations based on e-model, energy, and score values. Schrödinger Suite 2021-4 was used to generate the X-ray crystal structure of PI3K (PDB ID: 1E8X, 1.65 Å resolution), which was obtained [6] and prepared using Schrödinger Suite 2021-4. This preparation involved adding hydrogens, optimizing protonation states, and ensuring structural readiness for docking (Schrödinger, 2021-4). Crystallographic water molecules were removed to avoid interfering interactions [7] and missing side chains were completed using the Prime module [8]. Ligand structures were prepared with LigPrep, which generated various conformations and tautomers for Five Bacteriocin compounds [9]. Docking simulations employed the Optimized Potentials for Liquid Simulations (OPLS)3-2005 force field, known for its precision in modeling non-covalent interactions while maintaining computational efficiency [10]. The active site was defined using a 10 Å grid box centred on the co-crystallized ligand, which helped with the docking calculations [11]. The docking simulations were performed using Glide XP, which offers a thorough assessment of ligand binding conformations [12]. The most advantageous docked conformations were identified by evaluating the docking findings using Glide energy, score, and e-model values (Schrödinger, 2021-4). The protein-ligand complexes were visualized to analyze the interactions and conformations, as illustrated in fig. 1.

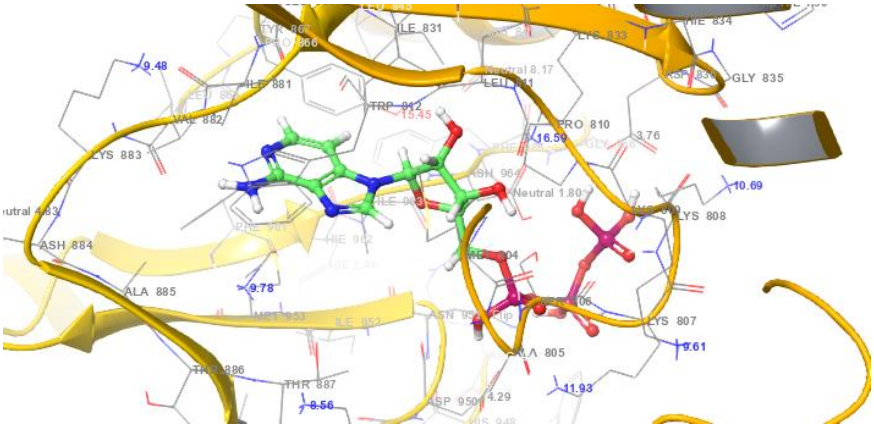


Fig. 1: Protein-ligand interaction complex (PDB id: 1E8X) in molecular docking

Binding free energy calculations using prime MM-GBSA

Each protein-ligand complex's binding free energy was determined by applying the Prime MM-GBSA technique from Schrödinger Suite 2021-4. By combining different contributions to the binding free energy, this approach offers a thorough assessment of binding affinity. To calculate the binding free energy, Prime MM-GBSA blends implicit solvation models with molecular mechanics energies. The procedure entails a number of crucial phases, one of which is the energy minimisation of every protein-ligand combination. This is accomplished by applying the OPLS3e force field, a sophisticated force field that is specifically made for modelling biomolecular interactions with great accuracy [10]. An implicit solvation model, Variable Dielectric Generalized Born 2.0 (VSGB 2.0), was used to account for solvation effects, offering a detailed treatment of hydrogen bonding, self-contact interactions, and hydrophobic effects [13]. The Surface Area Term (which accounts for the hydrophobic effect), Generalised Born Solvation Energy (which represents implicit solvation), and Molecular Mechanics Energy (which accounts for Van der Waals and electrostatic interactions) are the main components that the MM-GBSA method adds up to determine binding free energy. The total free energies of the individual proteins and ligands are subtracted from the free energy of the protein-ligand complex to provide the binding energy, which is an estimate of the ligand's binding affinity to the target protein. The result of this computation sheds light on the stability and strength of the ligand-target interaction. The MM-GBSA approach also includes physics-based corrections to enhance accuracy, addressing interaction effects not fully captured by basic energy terms.

ADME calculation

The ADME properties for each protein-ligand complex were assessed using Schrödinger Suite 2021-4. This evaluation involved protein-ligand systems where protein structures were sourced from experimental data or modelled as necessary, and ligands were prepared using standard molecular modeling protocols. The ADME predictions were made using the Prime QIKPROP method in Schrödinger Suite. The OPLS3-2005 force field was used, which is an improved version of the OPLS force field. This force field is well-known for its improved performance in modelling protein-ligand interactions and its accuracy in predicting molecular properties [14]. Accurate solvation energy estimations were obtained by using the VSGB 2.0 solvation model, which successfully addressed the dynamic character of the solvent environment in protein-ligand complexes [15].

Protein and ligand structures were prepared with Schrödinger's tools, including energy minimization and protonation state assignment at physiological pH. Each complex underwent further energy minimization using the OPLS3-2005 force field to ensure accurate low-energy conformations. The Prime QIKPROP tool then estimated ADME properties, predicting absorption, distribution, metabolism, and excretion characteristics with high accuracy based on empirical models.

Probiotic compounds used

The study involved several bacteriocins derived from probiotic strains of lactic acid bacteria, which are antimicrobial peptides that inhibit the growth of similar or closely related bacterial strains. The compounds included *Plantaricin D*, produced by *Lactobacillus plantarum*, a common probiotic bacterium used in fermented foods with a history of safe use [16]. *Bacteriocin 28b*, from *Lactobacillus sakei*, is known for its antimicrobial activity and application in food preservation [17]. *Plantaricin BN*, also from *Lactobacillus plantarum*, shares similarities with *Plantaricin D* and helps maintain a healthy microbial balance by inhibiting pathogenic bacteria [18]. *Enterocin A*, produced by *Enterococcus faecium*, is noted for its potent antimicrobial effects and role in intestinal health. *Sakacin P*, another bacteriocin from *Lactobacillus sakei*, is valued for its strong antimicrobial activity and use in food preservation [19]. All bacteriocins structures present in fig. 2.

RESULTS

Docking results and analysis

Docking studies were conducted using the Phosphoinositide 3-kinase (PI3K) crystal structure (PDB ID: 1E8X) with Schrödinger Suite 2021-4. The virtual screening method based on ligands guaranteed that ligand conformations had a 1.5 Å root mean square deviation (RMSD) in relation to the co-crystallized structure. To weed out functional groups that could have a detrimental interaction with the ligands, Lipinski's rule of five was used. Many Glide XP-docking metrics, such as the glide score, e-model, Van der Waals energy (E_vdw), Coulomb energy (E_coul), and the overall docking energy (E_energy), were taken into account in order to assess the screening findings.

Table 1: The XP-docking scores for bacteriocins in PI3K's catalytic pocket (PDB ID: 1E8X)

S. No.	Compound code	[a]G_{score}	[b]G_{vedw}	[c]G_{ecou}	[d]G_{energy}	[e]G_{emodel}
1	*Plantaricin D*	-7.478	-40.347	-14.824	-55.171	-31.587
2	*Enterocin A*	-7.478	-40.347	-14.824	-55.171	-31.587
3	*Plantaricin BN*	-7.235	-46.058	-22.370	-68.429	-28.271
4	*Bacteriocin 28b*	-5.724	-36.078	-15.434	-51.513	-0.514
5	*Sakacin P*	-3.837	-22.584	-9.956	-32.541	-41.304
6	Co-crystal	-8.698	-41.005	-35.327	-76.333	-114.537
7	*Doxorubicin*	-6.222	-40.492	-6.676	-47.169	-61.760

[a]Glide Score, [b]Glide E-model, [c]Glide Van der Waals Energy, [d]Glide Coulomb Energy, [e]Glide Energy

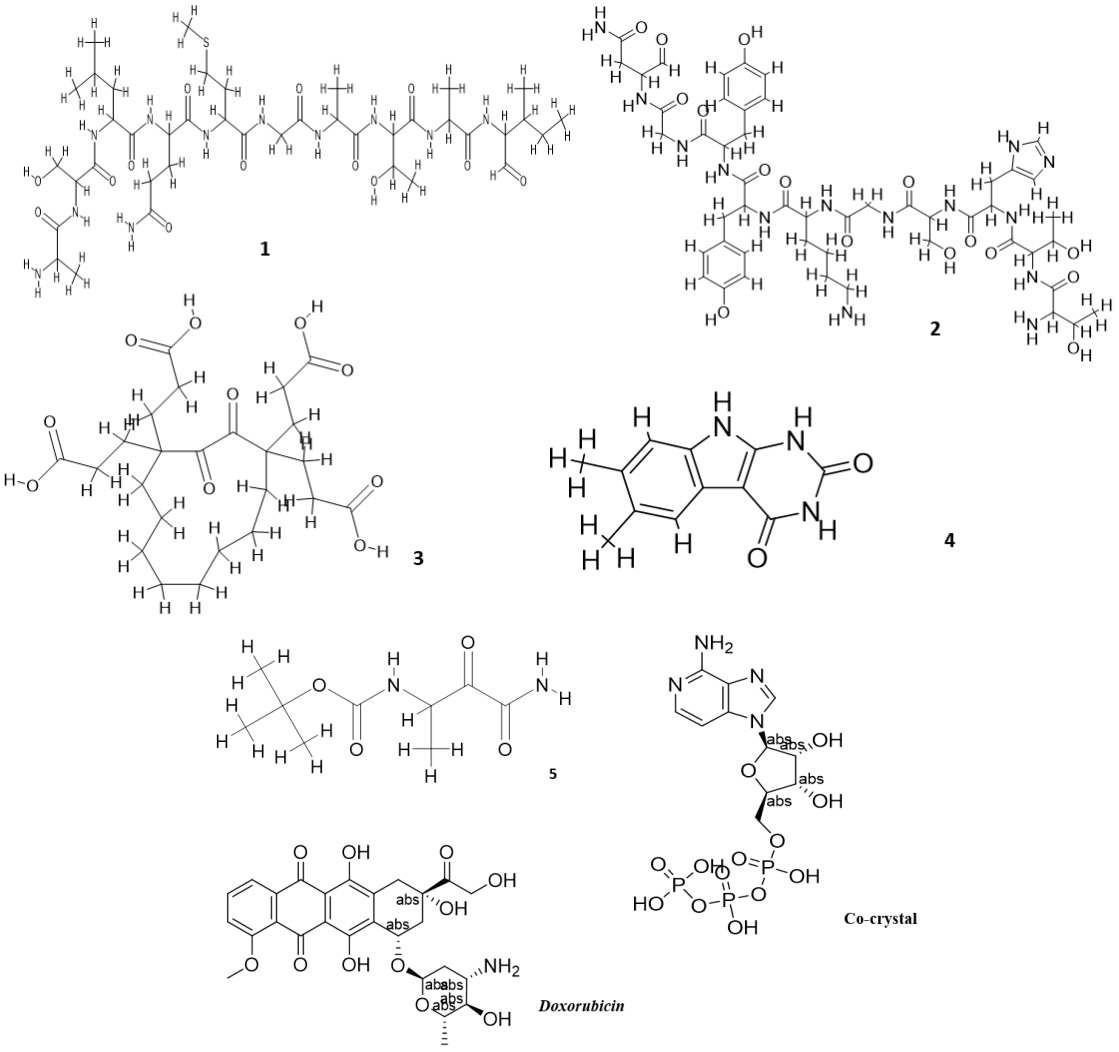


Fig. 2: Bacteriocins structures (1). *Plantaricin D*, (2). *Enterocin A*, (3). *Plantaricin BN*, (4). *Bacteriocin 28b*, (5). *Sakacin P*

Docking analysis revealed that all bacteriocins showed favorable binding activity compared to *Doxorubicin*, with *Plantaricin D* and *Enterocin A* achieving the highest glide scores of-7.478 kcal/mol, indicating strong binding affinity. Although *Plantaricin BN* had a little lower glide score of-7.235 kcal/mol than *Plantaricin D* and *Enterocin A*, which indicated great binding affinities, it nevertheless demonstrated a substantial binding potential. Nonetheless, poorer binding interactions were indicated by the glide scores of-5.724 kcal/mol for *Bacteriocin 28b* and-3.837 kcal/mol for *Sakacin P*. A Glide score of-8.698 kcal/mol for the co-crystal structure and-6.222 kcal/mol for *Doxorubicin* indicated the maximum binding affinity. Notably, *Plantaricin D* also exhibited robust interaction metrics, including Van der Waals energy (E_vdw) of-40.347 kcal/mol, Coulomb energy (E_coul) of-14.824 kcal/mol, total docking energy (E_energy) of-55.171 kcal/mol, and e-model (Gemodel) of-31.587 kcal/mol. These findings highlight *Plantaricin D* as the most promising bacteriocin, showing binding affinity comparable to the co-crystal structure and superior to *Doxorubicin*, making it a strong candidate for further research targeting PI3K.

Binding free energy contributions using MM-GBSA

The binding free energy (ΔG_bind) contributions for every bacteriocin in complex with phosphoinositide 3-kinase (PI3K) (PDB ID: 1E8X) are compiled in table 2 and are determined using the MM-GBSA technique. Coulombic energy (ΔG_Coul), hydrophobic energy (ΔG_Lip), hydrogen bonding energy (ΔG_HB), and Van der Waals energy (ΔG_VdW) are among the constituents.

Table 2: Binding free energy (MM-GBSA) contribution (kcal/mol) for bacteriocins 1–6 in PI3K complexes

S. No.	Compound code	[a]ΔGBind	[b]ΔGCoul	[c]ΔGHB	[d]ΔGLip	[e]ΔGVdW
1	*Plantaricin D*	-92.857	-48.425	2.372	-65.811	-47.340
2	*Enterocin A*	-92.668	-61.813	-0.369	-10.645	-45.731
3	*Plantaricin BN*	-58.139	1.040	6.732	43.198	-7.845
4	*Bacteriocin 28b*	-28.857	-48.425	2.372	-65.811	-47.340
5	*Sakacin P*	-39.725	-17.091	-2.814	-12.797	-22.269
6	Co-crystal	-40.646	-33.837	-4.155	8.187	-22.484
7	*Doxorubicin*	-23.620	-13.080	6.749	4.934	-22.128

[a]Free Energy of Binding, [b]Coulomb Energy, [c]Hydrogen Bonding Energy, [d]Hydrophobic Energy (non-polar contribution estimated by solvent accessible surface area), [e]Van der Waals Energy.

With major contributions from Coulombic energy (-48.425 kcal/mol), hydrophobic energy (-65.811 kcal/mol), and Van der Waals energy (-47.340 kcal/mol), *Plantaricin D* exhibited the greatest binding free energy of-92.857 kcal/mol, indicating considerable binding potential. With a large Coulombic energy of-61.813 kcal/mol and a smaller hydrophobic contribution of-10.645 kcal/mol, *Enterocin A* exhibited a binding free energy of-92.668 kcal/mol that was comparable. With a positive coulombic energy of 1.040 kcal/mol, a high hydrophobic energy of 43.198 kcal/mol, a lower Van der Waals energy of-7.845 kcal/mol, and a binding free energy of-58.139 kcal/mol, *Plantaricin BN* has notable characteristics. Positive Coulombic energy (18.183 kcal/mol) and a moderate hydrophobic contribution (30.684 kcal/mol). The binding free energy of *Bacteriocin 28b* was found to be greater at-28.857 kcal/mol in comparison to *Plantaricin D*, which exhibited a binding free energy of-48.425 kcal/mol, suggesting weaker binding interactions. The hydrophobic energy (-12.797 kcal/mol) and Coulombic energy (-17.091 kcal/mol) contributed very little to the lowest binding free energy of *Sakacin P*, which was-39.725 kcal/mol. On the other hand, the binding free energy of the co-crystal structure was recorded at-40.646 kcal/mol, whereas the binding free energy of *Doxorubicin*, a regularly used medicine, was measured at-23.620 kcal/mol, which was much greater.

Hydrogen bonding and amino acid interactions

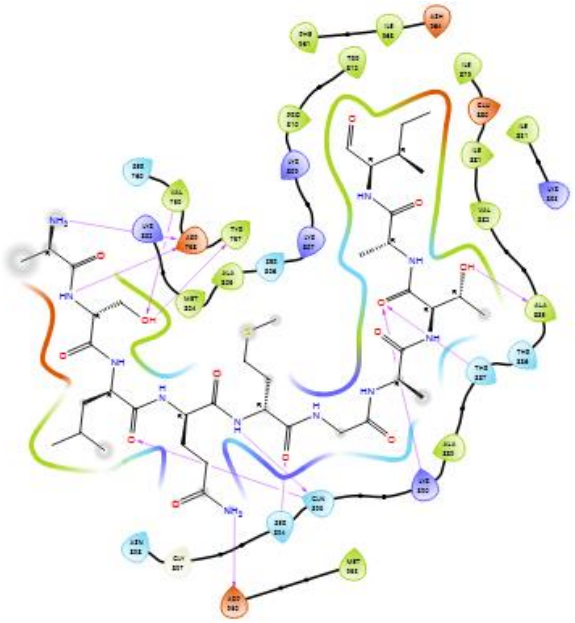
Table 3 presents a comprehensive overview of the hydrogen bonds that are established between every bacteriocin and the amino acid residues found in the catalytic pocket of PI3K (PDB ID: 1E8X). Since they have a substantial impact on both the overall molecular interactions and the potential inhibitory efficacy of the bacteriocins, these interactions are essential for the binding affinity and stability of the corresponding protein-ligand complexes.

Table 3: Number of hydrogen bonds and specific amino acid residues involved in bacteriocin interactions within the PI3K catalytic pocket (PDB ID: 1E8X)

S. No.	Compound code	Number of hydrogen bonds	Interacting amino acid residues
1	*Plantaricin D*	10	Asp950, Lys890, Gln893, Ser894, Thr887, Ala885, Tyr757, Asp758, Lys802, Val759
2	*Enterocin A*	8	Asp950, Gln893, Lys890, Lys802, Thr886, Glu814, Lys883, Ala889
3	*Plantaricin BN*	5	Lys890, Val882, Ser806, Asn951, Lys833
4	*Bacteriocin 28b*	0	0
5	*Sakacin P*	2	Ser806, Asn831
6	Co-crystal	8	Asa964, Val882, Asp836, Asp950, Asn951, Lys833, Ser806, Lys807
7	*Doxorubicin*	4	Lys 802, Ser806, Lys890, Thr886

Each compound's hydrogen bond count and interacting amino acid residues are included in the table.

Table 3 outlines the interactions between each bacteriocin and the PI3K catalytic pocket. *Plantaricin D* formed the most hydrogen bonds, with 10 interactions involving residues such as Asp950, Lys890, Gln893, Ser894, Thr887, Ala885, Tyr757, Asp758, Lys802, and Val759. This extensive bonding indicates *Plantaricin D's* strong binding affinity and potential effectiveness as a PI3K inhibitor. *Enterocin A* established 8 hydrogen bonds with key residues including Asp950, Gln893, Lys890, Lys802, Thr886, Glu814, Lys883, and Ala889, showcasing significant binding potential, though slightly fewer than *Plantaricin D*. *Plantaricin BN* formed 5 hydrogen bonds with Lys890, Val882, Ser806, Asn951, and Lys833. Despite having fewer hydrogen bonds, both maintain notable interactions with the catalytic pocket. *Bacteriocin 28b* did not form any hydrogen bonds, suggesting a weaker interaction with PI3K compared to other bacteriocins. *Sakacin P* formed 2 hydrogen bonds with Ser806 and Asn831, indicating limited but still significant interactions. For comparison, the co-crystal structure showed 8 hydrogen bonds with residues such as Asn964, Val882, Asp836, Asp950, Asn951, Lys833, Ser806, and Lys807, reflecting well-optimized binding. *Doxorubicin*, the standard drug (STD), had 4 hydrogen bonds with Lys802, Ser806, Lys890, and Thr886, demonstrating a moderate level of interaction.



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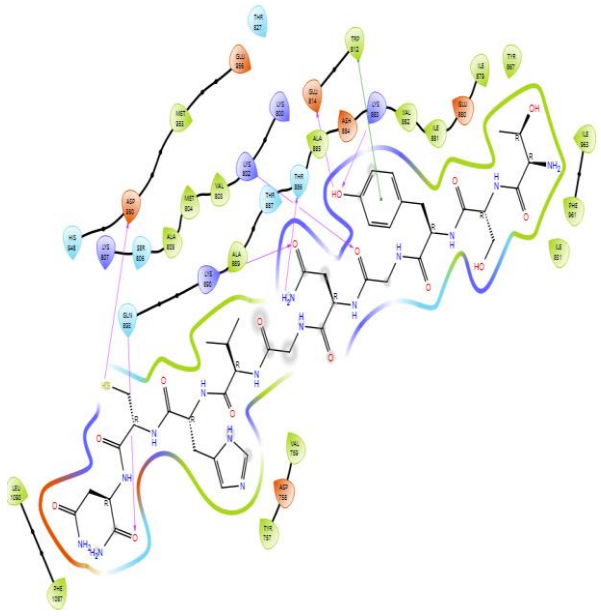

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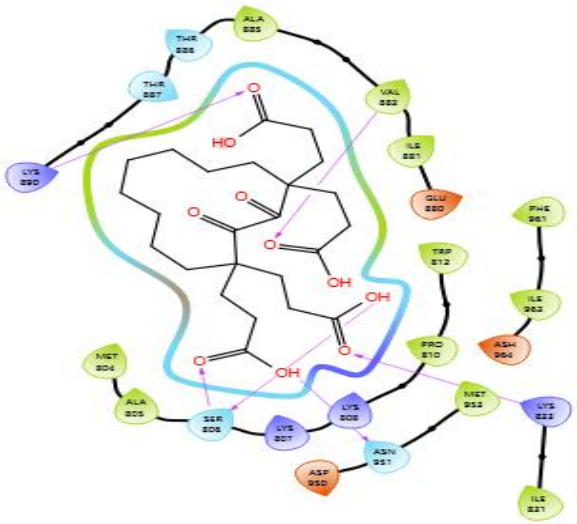

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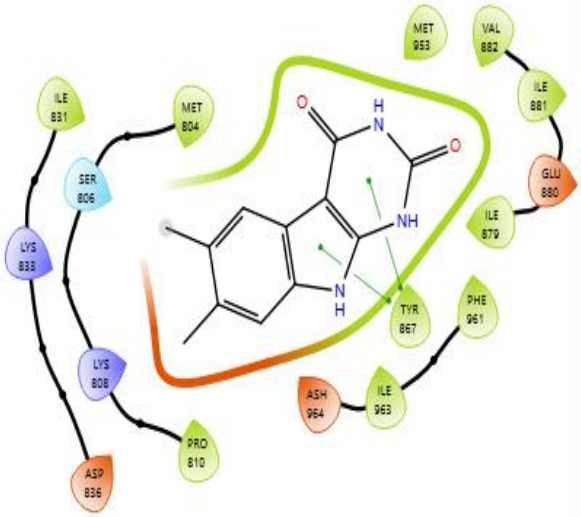

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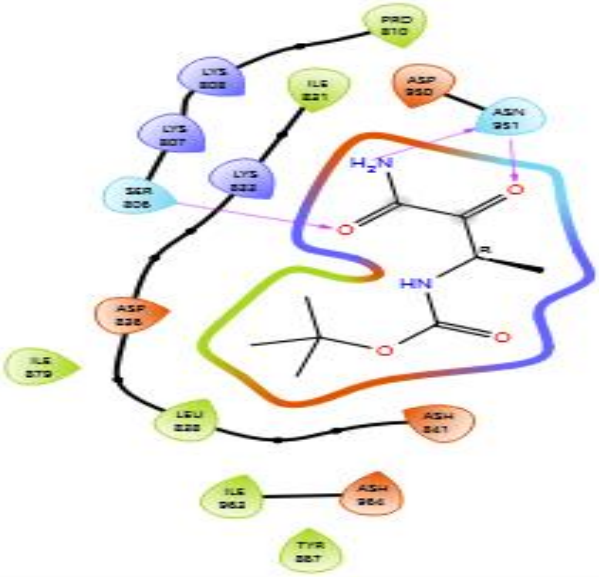

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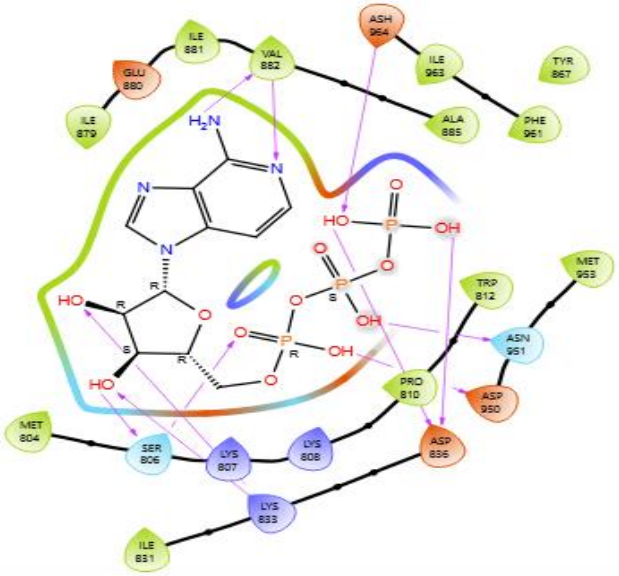
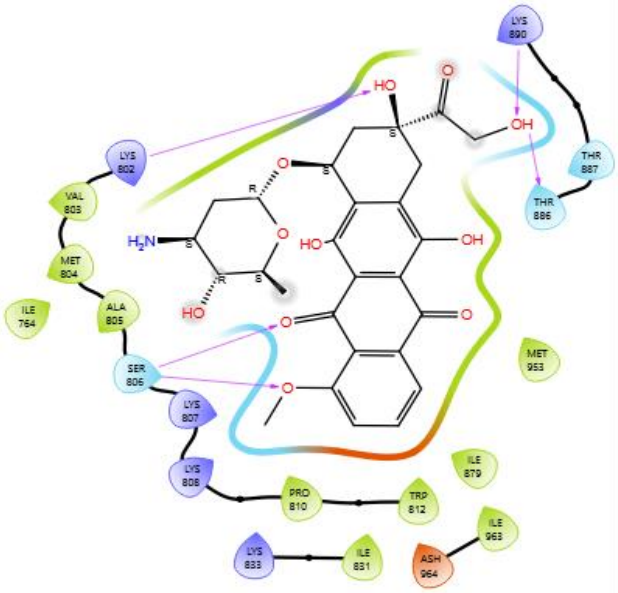


Co-crystal



Doxorubicin

Fig. 3: Bacteriocins 2D interaction diagrams in the PI3K catalytic pocket. (1). *Plantaricin D*, (2). *Enterocin A*, (3). *Plantaricin BN*, (4). *Bacteriocin 28b*, (5). *Sakacin P*

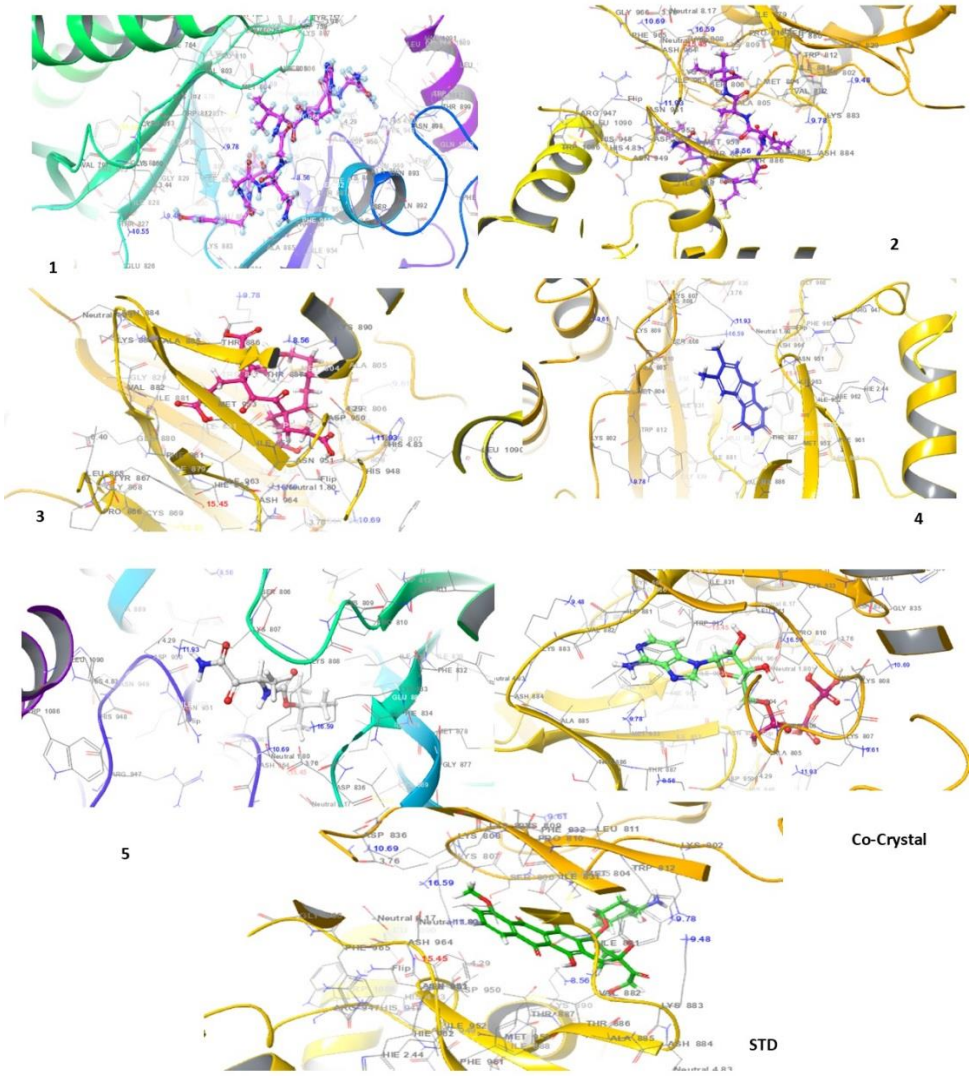


Fig. 4: 3D Interaction diagrams of bacteriocins in the PI3K catalytic pocket. (1). *Plantaricin D*, (2). *Enterocin A*, (3). *Plantaricin BN*, (4). *Bacteriocin 28b*, (5). *Sakacin P*, STD (*Doxorubicin*)

Fig. 4 illustrates the 3D interaction diagrams for the five bacteriocins within the PI3K catalytic pocket (PDB ID: 1E8X). The diagrams show the spatial arrangement of each bacteriocin's binding, including the binding orientation and fit within the receptor's active site. They detail how functional groups, such as carbonyls (C=O), amines (NH_2, NH), and hydroxyls (OH), interact with receptor residues through hydrogen bonds, hydrophobic contacts, and potential π-π stacking. This 3D view provides insights into the molecular contacts and overall stability of the ligand-receptor complex, illustrating how these interactions influence binding and receptor function.

ADME study results

The ADME properties of the five bacteriocins were evaluated to assess their pharmacokinetic profiles and safety profiles. The results are summarized in table 4, and the following detailed explanation interprets these findings.

Table 4: ADME properties of bacteriocins and standard drug

S. No.	Compound code	CNS	SASA	Donor HB	Accept HB	QPlog P o/w	QPP Caco	QPlog HERG	PSA	QPlog BB	Human oral absorption	Rule of five
1	*Plantaricin D*	-2	651.62	2	6.25	2.60	156.50	-6.17	105.23	-2.07	3	0
2	*Enterocin A*	-2	611.45	2	5.5	2.42	145.02	-6.21	96.79	-1.99	3	0
3	*Plantaricin BN*	-2	686.93	2	7	2.65	134.76	-6.13	114.98	-2.25	2	0
4	*Bacteriocin 28b*	-1	764.43	0	5	5.16	1026.1	-6.99	71.00	-0.93	1	1
5	*Sakacin P*	-2	709.17	1	9.25	2.68	527.63	-5.77	105.57	-1.13	3	0
6	Co-crystal	0	694.64	0	5	5.28	909.92	-5.09	70.65	-0.39	1	1
7	*Doxorubicin*	0	620.14	0	5	3.83	1143.36	-5.21	69.29	-0.53	3	0

CNS: Central Nervous System Penetration (values ≤-2 indicate low CNS penetration). SASA: Solvent Accessible Surface Area (in $Å^2$), indicative of molecular surface interaction. Donor HB/Acceptor HB: Number of hydrogen bond donors and acceptors. QPlog P o/w: Octanol-water partition coefficient, indicating lipophilicity. QP Caco: Permeability across Caco-2 cell monolayers (nm/s), reflecting intestinal absorption. QPlog HERG: Potential for interaction with the HERG channel (negative values indicate lower risk of cardiotoxicity). PSA: Polar Surface Area (in $Å^2$), affecting drug permeability. QPlog BB: Blood-brain barrier permeability (negative values indicate low permeability). Human Oral Absorption: Predicted oral absorption potential. Rule of Five: Compliance with Lipinski's Rule of Five.

The ADME analysis reveals that all bacteriocins exhibit minimal central nervous system (CNS) penetration, with values of-2 or less, indicating a lower risk of CNS side effects. Solvent Accessible Surface Area (SASA) values range from 611.45 to 764.43 $Å^2$, suggesting good surface interactions and potential for effective absorption. The number of hydrogen bond donors ranges from 0 to 2, and acceptors range from 5 to 9, with *Plantaricin D* and *Enterocin A* showing optimal hydrogen bonding for target interaction. Lipophilicity (QPlog P) varies from 2.42 to 5.28, indicating balanced properties for absorption. Caco-2 permeability values range from 134.76 to 1447.23 nm/s, with higher values suggesting better intestinal absorption. All bacteriocins show low cardiotoxicity risk (QPlog HERG), and negative QPlog BB values indicate low potential for crossing the blood-brain barrier. Most bacteriocins comply with Lipinski's Rule of Five, supporting good oral bioavailability. Overall, the ADME profiles suggest these bacteriocins are promising candidates for further development as safe and effective therapeutic agents.

Comparative analysis of bacteriocins and standard drug

The comparative analysis of five bacteriocins against Phosphoinositide 3-kinases (PI3Ks), benchmarked against *Doxorubicin* and a co-crystal structure, reveals their potential as therapeutic agents. Docking studies show *Plantaricin D* and *Enterocin A* with the highest binding affinities (-7.478 kcal/mol), outperforming others. *Plantaricin D* also demonstrates the strongest binding free energy (-92.857 kcal/mol) and forms the most hydrogen bonds i. e., 10 with key PI3K residues, indicating robust interactions. ADME properties reveal that all bacteriocins exhibit minimal CNS penetration and low cardiotoxicity risk, with *Plantaricin D* and *Enterocin A* showing favorable profiles for oral absorption and lipophilicity. Despite variations in hydrogen bonding and binding free energies, these bacteriocins, especially *Plantaricin D*, display promising attributes for further development as effective PI3K inhibitors.

DISCUSSION

The molecular docking and ADME analyses underscore the potential of bacteriocins, particularly *Plantaricin D* and *Enterocin A*, as novel therapeutic agents targeting Phosphoinositide 3-kinases (PI3Ks), which are crucial in cancer progression. These bacteriocins exhibit strong binding affinities to PI3K, with docking scores of-7.478 kcal/mol, comparable to the co-crystal (-8.698 kcal/mol) and superior to *Doxorubicin* (-6.222 kcal/mol) [20]. Binding free energy calculations further validate their potential, with *Plantaricin D* and *Enterocin A* showing free energies of-92.857 kcal/mol and-92.668 kcal/mol, respectively, indicating robust and stable interactions [21]. The extensive hydrogen bonding with key residues such as Asp950 and Lys890 enhances their binding efficiency and suggests strong inhibition of PI3K [22].

ADME profiling reveals favorable pharmacokinetic properties for these bacteriocins, including minimal CNS penetration and good oral absorption potential [23]. The low cardiotoxicity risk associated with these natural compounds further supports their safety relative to conventional synthetic drugs. Notably, the probiotic origin of these bacteriocins provides an added advantage, particularly in the context of colon cancer. Probiotics play a beneficial role in maintaining gut health and modulating the gut microbiota, which can be crucial in preventing and managing colon cancer. Unlike synthetic drugs, which often come with significant side effects and toxicity, probiotics and their derived bacteriocins offer a more targeted and safer approach to treatment. They not only interact directly with cancer cells but also contribute to a healthier gut environment, potentially enhancing overall therapeutic outcomes.

The ability of bacteriocins to target the PI3K pathway could complement existing cancer treatments, especially for colon cancer, where maintaining a healthy gut microbiome is vital. Synthetic drugs may lack this holistic approach and can sometimes exacerbate gut issues, whereas probiotics can offer additional benefits by promoting gut health and preventing disease recurrence.

The novelty of this study lies in its innovative exploration of bacteriocins derived from probiotics as inhibitors of the PI3K pathway, a key target in cancer therapy, particularly for colon cancer. While much of the research in this area has focused on synthetic compounds, this study shifts attention to naturally occurring molecules, presenting a fresh perspective on therapeutic options. The identification of *Plantaricin D* and *Enterocin A* as candidates with significant binding affinity to the PI3K catalytic domain is a ground-breaking finding that bridges the gap between microbiology and oncology. The rationality of the study is anchored in its scientific foundation; targeting the PI3K pathway is crucial, given its role in cancer progression, and the use of molecular docking to assess binding affinities provides a robust methodology for identifying potential inhibitors. Additionally, the favorable pharmacokinetic properties of these bacteriocins, coupled with their low toxicity profiles, support their viability as safer alternatives to traditional therapies, addressing the pressing need for effective treatments with fewer side effects. This combination of novelty and a well-reasoned approach underscores the potential of probiotic-derived bacteriocins in advancing cancer therapy.

Future research should focus on validating these findings through detailed studies, including binding affinity assays using Surface Plasmon Resonance (SPR) or Isothermal Titration Calorimetry (ITC), molecular dynamics simulations, and comprehensive *in vitro* and *in vivo* efficacy evaluations in colon cancer models [24, 25]. Furthermore, comprehensive toxicity testing and ADME profiling will be necessary to guarantee the security and efficacy of these bacteriocins as therapeutic agents [26-28]. By integrating these bacteriocins into therapeutic regimens, particularly for colon cancer, there is potential to leverage their natural origin and multifaceted benefits, offering a promising alternative or adjunct to synthetic drugs.

CONCLUSION

This study emphasizes the potential of bacteriocins derived from probiotics as inhibitors of the PI3K pathway, which is a crucial target in cancer therapy. Our docking studies identified several bacteriocins, especially *Plantaricin D* and *Enterocin A*, with significant binding affinity to the PI3K catalytic domain. These compounds demonstrated strong inhibitory potential through favorable docking scores and binding free energies. *Plantaricin D*, in particular, showed the highest affinity and extensive hydrogen bonding, suggesting it as a potent inhibitor. According to Lipinski's Rule of Five, these bacteriocins have favourable pharmacokinetic qualities and minimal CNS toxicity, as shown by the ADME investigation. This safety profile suggests that probiotic-derived bacteriocins could be a safer alternative to synthetic drugs, reducing side effects. Importantly, considering the role of the PI3K pathway in colon cancer, these bacteriocins offer a novel and potentially safer approach to targeting this pathway in colon cancer therapy. In summary, our findings support the use of these natural compounds in colon cancer therapy, highlighting their promise as effective and safer alternatives to traditional synthetic drugs. To verify the therapeutic effectiveness and safety of these findings, more research should be conducted both in *in vitro* and *in vivo*.

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AUTHORS CONTRIBUTIONS

Mohd Abdul Baqi-Conceptualization, validation, writing-original draft preparation and Data curation. Koppula Jayanthi-Data curation, methodology, writing-Review and Editing. Raman Rajeshkumar-Conceptualization, Formal analysis, validation, and supervision.

CONFLICT OF INTERESTS

Declared none

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