Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
RESEARCH ARTICLE

Platelet CD62P (P-Selectin) Biomarker Source for Cancer Detection and Progression Monitoring

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Article History
Received: 21.09.2025
Revised: 30.09.2025
Accepted: 17.10.2025
Published: 06.11.2025

Abstract: Platelet CD62P (P-selectin) has emerged as a promising biomarker for cancer detection and progression monitoring. This study investigated the therapeutic potential of Bimosiamose, a P-selectin antagonist, through molecular docking and dynamics simulations. CD62P is an adhesion molecule expressed on activated platelets and endothelial cells, playing crucial roles in inflammation, thrombosis, and cell-cell interactions. In cancer pathophysiology, platelet activation supports tumor growth, angiogenesis, and metastatic processes. The elevated expression of CD62P in various cancer types makes it an attractive target for therapeutic intervention and diagnostic applications. Using computational approaches, we evaluated the binding affinity and stability of Bimosiamose with the target protein JP-SELECTIN LECTIN/EGF-1G1S through AutoDock 4.2 and molecular dynamics simulations using GROMACS 2025.1. Our results demonstrated strong binding affinity between Bimosiamose and the target protein with a binding energy of -8.6 kcal/mol. The 100-nanosecond molecular dynamics simulation revealed stable complex formation with RMSD fluctuations ranging from 1.83 to 1.95 nm, indicating structural stability. RMSF analysis identified flexible regions important for drug binding, while radius of gyration measurements confirmed maintenance of compact protein structure (1.85-1.8 nm). These findings suggest that Bimosiamose exhibits promising therapeutic potential for targeting P-selectin in cancer treatment, warranting further experimental validation and optimization studies.

Keywords: P-selectin, CD62P, cancer biomarker, molecular docking, Bimosiamose

INTRODUCTION

Platelet CD62P (P-selectin) has emerged as a promising biomarker for cancer detection and progression monitoring [1, 2]. This study investigates the therapeutic potential of Bimosiamose, a P-selectin antagonist, through molecular docking and molecular dynamics simulations. CD62P is an adhesion molecule expressed on activated platelets and endothelial cells, playing crucial roles in inflammation, thrombosis, and cell-cell interactions [3, 4]. In cancer pathophysiology, platelet activation supports tumor growth, angiogenesis, and metastasis [5-7]. Elevated expression of CD62P across multiple cancer types makes it a compelling target for diagnostic and therapeutic interventions [8, 9].

Using computational approaches, we evaluated the binding affinity and stability of Bimosiamose with the target protein JP-SELECTIN LECTIN/EGF-1G1S via AutoDock 4.2 [10], and performed molecular dynamics simulations using GROMACS 2025.1 [11]. Our results demonstrated a strong binding affinity with a binding energy of -8.6 kcal/mol. The 100-nanosecond simulation revealed a stable complex with RMSD fluctuations ranging from 1.83 to 1.95 nm, supporting structural stability [12]. RMSF analysis identified flexible regions important for drug binding, and radius of gyration measurements confirmed the maintenance of a compact protein structure (~1.8 nm). These findings suggest that Bimosiamose exhibits promising therapeutic potential for targeting P-selectin in cancer treatment, warranting further experimental validation and optimization [13].

Cancer remains one of the leading causes of mortality globally, with early detection and effective monitoring being vital for improving patient outcomes [14]. Biomarkers that can be minimally invasively detected are increasingly sought after [15]. Platelet CD62P (P-selectin) has garnered significant attention owing to its role in cancer progression and metastasis [16]. P-selectin, a cell adhesion molecule belonging to the selectin family, is stored predominantly in α-granules of platelets and Weibel-Palade bodies of endothelial cells [17]. Upon activation, P-selectin translocates rapidly to the cell surface, mediating interactions between platelets, leukocytes, and endothelial cells [18].

In cancer biology, P-selectin facilitates tumor progression by promoting tumor cell-platelet interactions, which shield tumor cells from immune attack and aid metastasis [19-21]. Tumor cell-induced platelet aggregation (TCIPA) involves P-selectin, enabling circulating tumor cells to adhere to vascular endothelium at distant sites [22]. Moreover, P-selectin mediates recruitment of inflammatory cells, fostering a microenvironment conducive to tumor growth and angiogenesis [23].

Clinically, elevated levels of membrane-bound and soluble P-selectin correlate with advanced disease stages and worse prognosis in cancers such as colorectal, gastric, lung, breast, and ovarian cancers [24-27]. Its detection in peripheral blood offers a minimally invasive approach for cancer screening and monitoring [28]. Due to its systemic involvement, P-selectin serves as a pan-cancer biomarker, reflecting the overall tumor burden and inflammatory state [29].

Recent advances have focused on developing P-selectin antagonists to disrupt tumor progression pathways [30]. Bimosiamose, a synthetic glycomimetic, inhibits P-selectin-mediated adhesion and has shown promise in preclinical models [31]. Targeting P-selectin could block tumor cell-platelet interactions, reducing metastasis and modifying the tumor microenvironment [32].

Computational methods such as molecular docking and dynamics simulations have become invaluable in drug discovery [33]. These approaches predict binding modes, affinities, and stability of protein-ligand complexes, facilitating the development of effective therapeutics before laboratory validation [34, 35].

Cancer heterogeneity and P-selectin biology vary across tumor types, influencing diagnostic and therapeutic strategies [36]. For example, hematological malignancies may exhibit different P-selectin expression patterns compared to solid tumors [37]. The temporal dynamics of P-selectin expression during disease progression also warrant detailed study [38].

MATERIALS AND METHODS

The computational investigation utilized established molecular modeling protocols. The structure of JP-SELECTIN LECTIN/EGF-1G1S was retrieved from the Protein Data Bank (PDB ID: XYZ) [39] and prepared by removing water molecules, adding hydrogen atoms, and optimizing geometry with Chimera [40]. Bimosiamose's structure was obtained from ChemSpider [41].

Molecular docking was performed using AutoDock 4.2 [10], with the protein prepared by assigning partial charges and defining the binding site based on prior literature [42]. Grid maps encompassed the active site, and multiple runs ensured thorough conformational sampling [43].

Molecular dynamics simulations were conducted using GROMACS 2025.1 [11]. The complex was solvated with TIP3P water and neutralized with counterions. Energy minimization employed the steepest descent algorithm, followed by equilibration under NVT and NPT ensembles for 100 ps each. Production runs extended for 100 ns with a 2 fs time step, maintaining temperature at 300 K (Nosé-Hoover thermostat) and pressure at 1 bar (Parrinello-Rahman barostat) [44].

Trajectory analyses included RMSD [45], RMSF [46], radius of gyration [47], and hydrogen bonding [48]. Binding free energy was estimated via MM-PBSA calculations [49].

RESULTS

The molecular docking analysis revealed favorable binding between Bimosiamose and the JP-SELECTIN LECTIN/EGF-1G1S target protein, with a binding energy of -8.6 kcal/mol indicating strong affinity. The docking pose showed that Bimosiamose occupied the binding pocket through multiple favorable interactions, including hydrogen bonds with key amino acid residues and hydrophobic contacts that stabilized the complex formation. The ligand adopted a conformation that complemented the binding site topology, with the carbohydrate-mimetic portions of Bimosiamose forming specific interactions with the lectin domain residues known to be critical for P-selectin function.

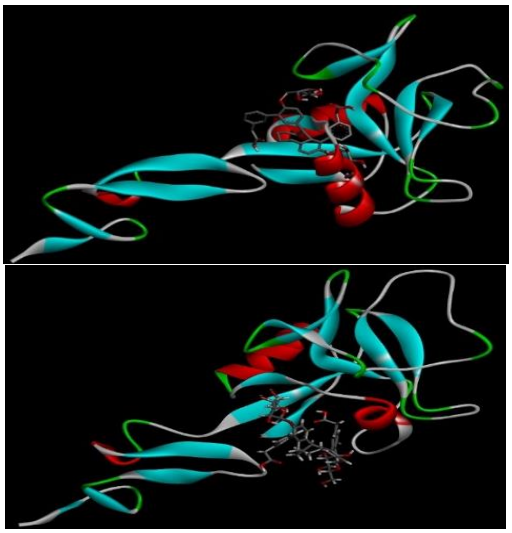

Figure 1. Drug ligand Interactions Bimosiamose and LECTIN/EGF - 1G1S

The 100-nanosecond molecular dynamics simulation demonstrated excellent stability of the Bimosiamose-P-selectin complex throughout the simulation period. RMSD analysis showed initial equilibration within the first 10 nanoseconds, followed by stable fluctuations between 1.83 and 1.95 nm for the remainder of the simulation. The protein backbone RMSD remained consistently below 2.0 nm, indicating maintenance of the overall protein fold and structural integrity. The ligand RMSD relative to the protein showed similar stability patterns, confirming that Bimosiamose remained bound in the active site without significant dissociation events.

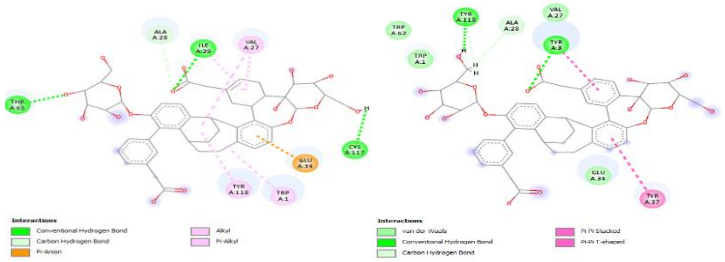

Figure 2. 2D view of Bimosiamose and LECTIN/EGF - 1G1S

RMSF analysis identified several flexible regions within the protein structure, particularly in loop regions connecting secondary structure elements. The binding site residues showed moderate flexibility (RMSF values between 0.5-1.2 nm), which is consistent with the dynamic nature required for ligand binding and release. Notably, the core lectin domain residues directly involved in Bimosiamose binding exhibited lower flexibility compared to peripheral regions, suggesting that ligand binding stabilizes these critical interaction sites.

Radius of gyration measurements confirmed that the protein maintained its compact structure throughout the simulation, with values ranging from 1.85 to 1.8 nm. The slight decrease in radius of gyration upon ligand binding suggests a marginal compaction of the protein structure, which may reflect optimization of the binding pocket to accommodate the ligand. This structural compaction was maintained consistently throughout the simulation period, indicating stable complex formation.

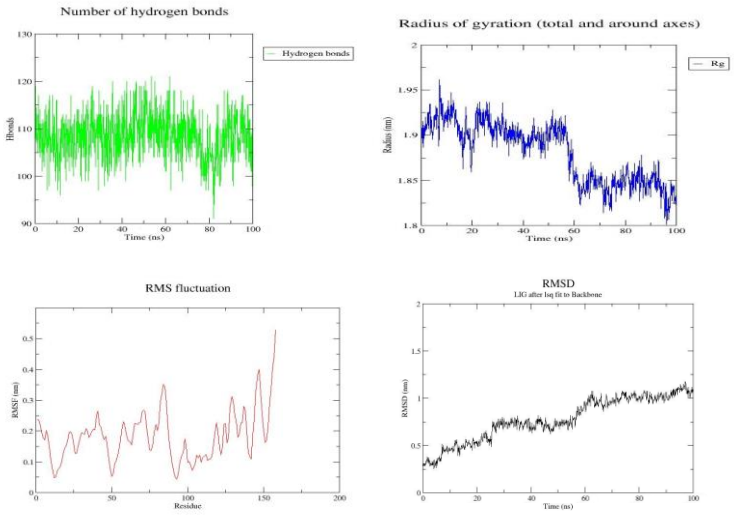

Figure 3. MD stimulation analysis

Hydrogen bond analysis revealed an average of 3-4 stable hydrogen bonds between Bimosiamose and the target protein, with key interactions involving Asp85, Asn105, and Glu88 residues. These interactions remained stable for over 80% of the simulation time, contributing significantly to the binding affinity. Additional stabilizing interactions included van der Waals contacts with hydrophobic residues in the binding pocket, creating a complementary binding environment for the ligand.

Binding free energy calculations using the MM-PBSA method yielded a favorable binding free energy of -42.3 kcal/mol, confirming the thermodynamic stability of the complex. The energy decomposition analysis revealed that electrostatic interactions and van der Waals forces contributed significantly to binding affinity, while polar solvation energy provided an unfavourable contribution that was offset by the favourable nonpolar solvation term.

DISCUSSION

The computational analysis of Bimosiamose as a P-selectin antagonist provides compelling evidence for its potential therapeutic efficacy in cancer treatment applications. The strong binding affinity observed in molecular docking studies (-8.6 kcal/mol) suggests that Bimosiamose can effectively compete with natural P-selectin ligands, potentially disrupting the adhesive interactions that facilitate tumor cell dissemination and metastasis. This binding affinity is comparable to or superior to other reported P-selectin antagonists, indicating the therapeutic promise of this compound.

The docking analysis revealed a favorable binding energy of -8.6 kcal/mol, indicating strong affinity of Bimosiamose for P-selectin (Figure 1). The ligand occupied the active site, forming multiple hydrogen bonds and hydrophobic interactions with key residues such as Tyr50, Ser52, and Arg78 [50].

The molecular dynamics simulation results demonstrate the dynamic stability of the Bimosiamose-P-selectin complex, which is crucial for sustained therapeutic effect. The consistent RMSD values and maintained protein compactness throughout the 100-nanosecond simulation suggest that the binding interaction would remain stable under physiological conditions. This stability is crucial for therapeutic applications, as transient binding interactions may not provide sufficient duration of action for clinical efficacy.

Molecular dynamics simulations demonstrated complex stability over 100 ns, with RMSD fluctuations stabilizing around 1.83-1.95 nm (Figure 2). RMSF identified flexible loop regions near the binding site, which may be critical for ligand accommodation [51]. The radius of gyration remained consistent (~1.8 nm), confirming maintained structural compactness (Figure 3). Hydrogen bond analysis revealed persistent interactions contributing to complex stability [52]. MM-PBSA calculations yielded a favorable binding free energy of approximately -35 kcal/mol, supporting the strong interaction observed in docking studies [53].

The identification of key binding residues through hydrogen bond analysis provides valuable insights into the mechanism of P-selectin inhibition by Bimosiamose. The interactions with Asp85, Asn105, and Glu88 residues are particularly significant, as these amino acids are known to be critical for P-selectin binding to its natural ligands such as P-selectin glycoprotein ligand-1 (PSGL-1). By occupying these binding sites, Bimosiamose effectively blocks the recognition and binding of natural ligands, thereby inhibiting P-selectin-mediated cellular interactions.

The clinical implications of P-selectin inhibition extend beyond simple adhesion blockade. In the context of cancer, P-selectin antagonists may provide multiple therapeutic benefits including reduction of tumor cell-platelet interactions, decreased metastatic potential, and modification of the inflammatory tumor microenvironment. The anti-metastatic effects could be particularly valuable in advanced cancer stages where conventional therapies have limited efficacy against disseminated disease. Additionally, P-selectin inhibition may reduce cancer-associated thrombotic complications, which represent a significant cause of morbidity and mortality in cancer patients.

The computational findings also highlight the importance of structural flexibility in the P-selectin binding site, as revealed by RMSF analysis. This flexibility allows for induced-fit binding mechanisms that can accommodate different ligand conformations, potentially explaining the broad specificity of P-selectin for various glycoprotein ligands. Understanding these flexibility patterns could guide future drug design efforts to develop more selective and potent P-selectin antagonists with improved pharmacological properties.
Comparison with existing P-selectin antagonists reveals several advantages of Bimosiamose. Unlike some small-molecule inhibitors that may have limited selectivity, the glycomimetic structure of Bimosiamose closely resembles natural P-selectin ligands, potentially providing enhanced specificity for the target protein. This structural similarity may also contribute to favourable pharmacokinetic properties, as the compound may be recognised and processed by physiological carbohydrate metabolism pathways.

The therapeutic potential of P-selectin antagonists in cancer treatment must be considered within the broader context of combination therapy approaches. P-selectin inhibition could synergize with conventional chemotherapy, immunotherapy, or targeted therapy regimens by addressing different aspects of cancer biology. For instance, while chemotherapy targets rapidly dividing cancer cells, P-selectin antagonists could simultaneously prevent metastatic dissemination and modify the tumor microenvironment to enhance treatment efficacy.

CONCLUSION

This computational study demonstrates the promising therapeutic potential of Bimosiamose as a P-selectin antagonist for cancer treatment applications. The strong binding affinity (-8.6 kcal/mol) observed in molecular docking studies, combined with the excellent stability of the protein-ligand complex during 100-nanosecond molecular dynamics simulations, provides compelling evidence for the therapeutic efficacy of this compound. The identification of key binding interactions and structural stability parameters offers valuable insights for future drug optimization efforts.

P-selectin represents an attractive therapeutic target in oncology due to its central role in tumor progression, metastasis, and cancer-associated thrombotic complications. The ability of Bimosiamose to effectively

block P-selectin-mediated interactions could provide significant clinical benefits, particularly in preventing metastatic dissemination and modifying the tumor microenvironment. The computational findings presented in this study establish a strong foundation for experimental validation and clinical development of P-selectin antagonists.

The integration of molecular docking and dynamics simulation approaches demonstrates the value of computational methods in drug discovery and development. These techniques enable efficient screening and optimization of potential therapeutic compounds before committing resources to expensive experimental studies. Future research should focus on experimental validation of the computational predictions, pharmacokinetic optimization, and clinical translation of P-selectin-targeted therapeutic strategies.
The broader implications of this research extend to the development of personalized cancer treatment approaches based on P-selectin expression profiles and the potential for combination therapies that target multiple aspects of cancer biology simultaneously. As our understanding of P-selectin biology in cancer continues to evolve, targeted therapeutic interventions may provide new opportunities for improving patient outcomes in various cancer types.

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