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COMPUTATIONAL CHARACTERIZATION OF THE LIPID A–PROTEIN G INTERACTION: MOLECULAR DOCKING, MOLECULAR DYNAMICS SIMULATION, AND BINDING FREE ENERGY ANALYSIS REVEAL A NOVEL MOONLIGHTING FUNCTION RELEVANT TO POLYMICROBIAL INFECTION

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ABSTRACT
Sepsis is a life-threatening syndrome of immune dysregulation that drives multi-organ failure and remains one of the leading causes of death worldwide. Despite decades of mechanistic work, validated biomarkers and effective drugs are still scarce. Much of the underlying pathophysiology — aberrant signaling, failed inflammatory control, energy deficits at the cellular level — converges on one common thread: disrupted lipid metabolism.
Specific lipid species are increasingly used as early sepsis biomarkers, and understanding how they act mechanistically could open new therapeutic avenues. This study focuses on Lipid A, the outer-membrane component of gram-negative bacteria that host immune receptors recognize to trigger sepsis. Using AutoDock Vina, we found that Lipid A docks onto Protein G at two distinct sites: Domain III (the B domain, residues 297–354) and the N-terminal helical segment. We then ran a 100-ns molecular dynamics simulation of the complex in GROMACS 2024 and calculated binding free energy with the MM/PBSA method (gmx_MMPBSA).

RMSD and RMSF confirmed the complex remained structurally stable, while Rg and SASA showed the interface stayed compact and consistently buried over the trajectory. Hydrogen bonds persisted throughout the simulation, and MM/PBSA gave a favorable ΔGbinding, with per-residue decomposition identifying which residues drove the interaction. We also docked Lipid A against the canonical TLR4/MD2 complex as a benchmark. Together, these results show that Protein G — a Streptococcal surface protein already known to bind IgG and serum albumin — also binds Lipid A, at two separate sites, pointing to a previously undescribed moonlighting function. Because Gram-positive and Gram-negative organisms frequently co-infect the same patient, this interaction could matter for how Lipid A is sequestered during mixed infection. That possibility now needs testing in vitro and in vivo.

KEYWORDS: Lipid A, Protein G, Moonlighting Protein, Molecular Docking, Molecular Dynamics Simulation, MM/PBSA, Polymicrobial Infection, TLR4

1. INTRODUCTION

Sepsis is a clinical emergency: organ function collapses as the host's own response to infection spirals out of control. It presents as systemic inflammatory response syndrome (SIRS), capable of triggering inflammatory cascades that damage multiple organs at once. It is also one of the leading causes of in-hospital death, especially outside intensive care — which is why better clinical strategies are still urgently needed (1).
Sepsis is not just an immune problem. Hemodynamic, coagulation, and even neuroglial function all deteriorate together, compounding severity. The resulting hospital stays are long and costly, straining health systems worldwide. Earlier detection and better critical care have lowered mortality overall, but not evenly — patients with comorbidities, immunosuppression, multidrug-resistant infections, implants, or recent invasive procedures still fare far worse. Even survivors often carry lasting consequences: ongoing immune suppression, chronic inflammation, and slowly progressing organ damage (2).

Gram-negative bacteria were once assumed to cause most cases of sepsis. That has changed — gram-positive organisms are now just as common, if not more so. Staphylococcus aureus, Streptococcus pyogenes, Klebsiella

species, Escherichia coli, and Pseudomonas aeruginosa account for most of the burden, and each brings its own arsenal of virulence factors for evading immunity, breaching epithelia, and spreading to distant organs.
Toxins are central to how these bacteria cause damage. Superantigens (Type 1) over-activate T cells, triggering cytokine storm. Type 2 toxins — hemolysins, phospholipases — punch through host membranes and scramble intracellular signaling. Type 3 (A/B) toxins such as Shiga toxin, cholera toxin, and anthrax lethal toxin are built to breach host defenses and travel to distant organs. The host detects all of these through pattern recognition receptors (PRRs), which read pathogen-associated molecular patterns (PAMPs) and set the innate immune response in motion(3).
Gram-negative sepsis is a particular concern after trauma, major surgery, metabolic dysfunction, or organ transplantation — conditions in which hypertriglyceridemia and hepatic fat accumulation are common(4,5). Lipopolysaccharide (LPS), which makes up roughly 75% of the gram-negative outer membrane, drives much of the endotoxin-related damage. It has three parts: Lipid A, a core oligosaccharide, and an O-antigen chain. Lipid A does most of the immunostimulatory work — at picomolar concentrations it activates macrophages and drives TNF-α and IL-1 release through TLR4. Serum-binding proteins solubilize LPS, which then binds CD14 on leukocytes and is handed off to the MD2 co-receptor to form an active complex with TLR4. From there, signaling runs through either the MyD88 or TRIF pathway and converges on NF-κB(1).

Lipid A does more than trigger inflammation — it also injures vascular endothelium directly, inducing tissue factor expression and cytokine release that can end in endothelial apoptosis and endotoxic shock. Some gram-negative bacteria have evolved ways to remodel Lipid A's structure, which lets them dodge cationic antimicrobial peptides and blunt TLR4 recognition. That adaptability is exactly what makes Lipid A an attractive drug target(3).

Protein G itself needs a clarification here: it is a cell-surface virulence factor from group C and G streptococci, unrelated — structurally or functionally — to the heterotrimeric G proteins that couple to GPCRs. Its job is immune evasion. It binds the Fc region of host IgG, and separately, through a GA module, serum albumin, coating the bacterium in host proteins and blunting opsonophagocytic clearance(6). One detail is easy to miss: IgG purified over immobilized Protein G columns has been reported to co-elute lipid species that have no business being there(7) — a hint that its binding surface is not as protein-specific as assumed. Meanwhile, the host proteins that do neutralize Lipid A — LBP, BPI — work by using clusters of basic residues to grab the lipid's anionic phosphate groups electrostatically(8), the same kind of lysine-mediated contact seen in our docking results. Gram-positive and Gram-negative organisms also co-infect the same patient more often than one might expect; polymicrobial bacteremia is common and tends to carry a worse prognosis than single-organism infection(9). Put those pieces together and a Streptococcal protein with incidental affinity for Lipid A becomes plausible, not far-fetched. That is what we set out to test here — using docking, MD simulation, binding free energy calculations, and receptor comparison to characterize the interaction as a candidate moonlighting function, not as a drug target in the conventional sense.

2. METHODS

2.1 Protein Structure Preparation

Protein G coordinates came from the Protein Data Bank (PDB); where no experimentally resolved structure was available, we generated one with AlphaFold2 and checked its reliability using:

- Ramachandran plot analysis – to evaluate the distribution of backbone dihedral angles
- ERRAT – to assess non-bonded interatomic interactions
- Verify3D – to verify consistency between the 3D fold and the amino acid sequence
- ProSA-web – to compute the Z-score and gauge overall structural quality

Protein G's domain layout is: an N-terminal helical region, a GA-like domain (residues 174–220), the B1 domain (Domain II, 227–281), the B domain (Domain III, 297–354), and a disordered C-terminal segment. Before docking, we stripped crystallographic waters, added polar hydrogens, and assigned Gasteiger partial charges in AutoDockTools.

2.2 Ligand Preparation

Lipid A's structure was pulled from PubChem (CID: 5459867) / ChEBI (CHEBI:28600), then prepared as follows:

- Energy minimization using the MMFF94 molecular mechanics force field within Open Babel
- Gasteiger partial charge assignment
- Three-dimensional structure generation and optimization
- Conversion to PDBQT format for compatibility with AutoDock Vina

2.3 Molecular Docking

We used AutoDock Vina(10) to predict binding orientation and affinity for Lipid A against Protein G, with the docking grid centered on the pocket identified by CASTp and PrankWeb. Exhaustiveness was set to 32, generating ten poses per run. We recorded:

- Binding affinity values (kcal/mol)
- Binding pose visualization
- Hydrogen bond interaction patterns
- Hydrophobic contact profiles
- Salt bridge interactions
- Identity of key interacting residues

We visualized and profiled the docked complex in PyMOL, Discovery Studio Visualizer, and LigPlot+, and generated 2D interaction diagrams to map the Lipid A–Protein G contact network.

2.4 Binding Pocket Validation

To check that the docking site was biologically plausible, we cross-validated it with independent pocket-prediction tools:

- CASTp (Computed Atlas of Surface Topography of Proteins)
- PrankWeb (P2Rank-based pocket prediction algorithm)
- DoGSiteScorer

Each tool's top-ranked site was cross-referenced against the Lipid A docking pose to confirm the interaction fell within a biologically plausible pocket.

2.5 Molecular Dynamics Simulation

We took the docked Lipid A–Protein G complex into all-atom MD simulation in GROMACS 2024, to see how it behaved under physiological conditions over time.

2.5.1 Simulation Parameters

- Force field: CHARMM36m for protein; compatible small-molecule parameters from CGenFF
- Solvent model: TIP3P explicit water
- Simulation box: Dodecahedral geometry with periodic boundary conditions; minimum 1.0 nm between protein surface and box wall
- Ionic environment: Na^+ and Cl^- counterions to achieve charge neutrality at 0.15 M NaCl
- Simulation duration: 100 ns production run

2.5.2 Simulation Protocol

1. Energy minimization via steepest descent algorithm until convergence (maximum force threshold < 1000 kJ/mol/nm)
2. NVT equilibration for 100 ps at 300 K using the V-rescale thermostat
3. NPT equilibration for 100 ps at 300 K and 1 bar using the Parrinello–Rahman barostat
4. Production MD run of 100 ns with trajectory frames archived every 10 ps

2.6 Trajectory Analysis

From the trajectory data, we characterized complex stability and dynamics using:

2.6.1 Root Mean Square Deviation (RMSD)

Backbone RMSD for both Protein G and Lipid A was tracked across the full 100-ns trajectory, relative to the starting pose, as a measure of overall stability and convergence.

2.6.2 Root Mean Square Fluctuation (RMSF)

Per-residue RMSF quantified how much each residue moved during the simulation, with particular attention to the binding interface.

2.6.3 Radius of Gyration (Rg)

Radius of gyration tracked the protein's overall compactness; a stable Rg would mean the fold holds up while bound to the ligand.

2.6.4 Solvent Accessible Surface Area (SASA)

SASA measured solvent exposure at the interface, to see whether the bound state held up for the full simulation.

2.6.5 Hydrogen Bond Analysis

We counted hydrogen bonds between Lipid A and Protein G at every frame and calculated occupancy for each donor–acceptor pair; anything above 50% occupancy was treated as persistent and energetically relevant.

2.6.6 Interaction Energy

Coulombic and Lennard-Jones interaction energies were extracted across the trajectory using GROMACS's energy analysis tools, to get at the energetic basis of the interaction.

2.7 MM/PBSA Binding Free Energy Calculations

Total binding free energy (ΔGbinding) was estimated with MM/PBSA via gmx_MMPBSA, sampling frames at regular intervals from the final 50 ns of the stable trajectory, decomposed as:

ΔGbinding = ΔEvdW + ΔEelec + ΔGPB + ΔGSA

ΔEvdW is the van der Waals term, ΔEelec the electrostatic term, ΔGPB the polar solvation term (Poisson–Boltzmann), and ΔGSA the non-polar solvation term. We then decomposed this per-residue to find which Protein G residues drove Lipid A recognition.

2.8 Protein–Ligand Interaction Analysis

We built interaction profiles for both the initial docked structure and representative MD frames, covering(11, 12, 13):

- Hydrogen bonds and associated geometric parameters
- Hydrophobic contacts
- π–π stacking and π–cation interactions
- Salt bridges
- Water-mediated hydrogen bonding networks

LigPlot+ and Discovery Studio Visualizer interaction maps from before and after simulation were compared to assess how stable the contacts remained.

2.9 Comparison with Established Lipid A Receptors (TLR4/MD2)

For biological context, we also docked Lipid A against the canonical recognition machinery — TLR4 (PDB: 3FXI or equivalent), MD2, and the TLR4–MD2 heterodimer — and compared:

- Binding affinity (kcal/mol)
- Residue identity and nature at the binding interface
- Interfacial contact area
- Hydrogen bond network architecture
- MM/PBSA-derived binding free energy
- Structural stability profiles from MD simulation (RMSD)

The point of this benchmark was simply to see whether Protein G's Lipid A recognition features resemble those of the established innate immune receptor complex — testing structural plausibility, not therapeutic relevance.

3. RESULTS

3.1 Protein Structure Validation

The resolved Protein G structure shows the expected multi-domain layout: N-terminal helical region, GA-like domain (174–220), B1 domain (Domain II, 227–281), B domain (Domain III, 297–354), and a disordered C-terminus (Figure 1). Over 90% of residues fell in sterically favored Ramachandran regions, and ERRAT, Verify3D, and ProSA-web all supported the model's quality — enough to proceed to docking and MD.

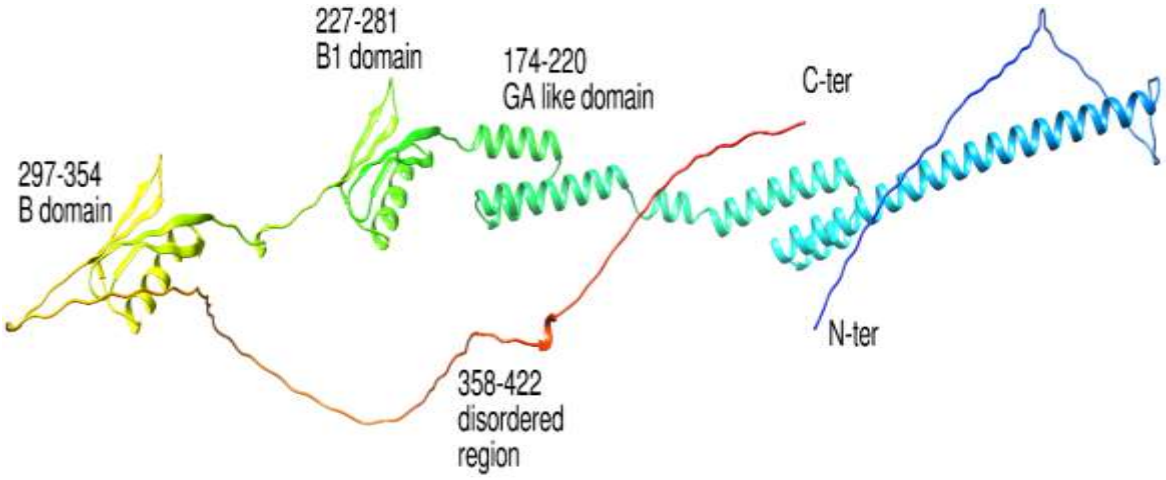

Figure 1: Three-dimensional structure of Protein G depicting the N-terminal helical region, GA-like domain (174–220), B1 domain (Domain II, 227–281), B domain (Domain III, 297–354), and C-terminal disordered region.

3.2 Molecular Docking Results

Docking placed Lipid A at two spatially distinct sites on Protein G: Domain III (the B domain, residues 297–354) and the N-terminal helical region (Figure 2). Both showed a favorable energetic profile, stabilized by a mix of hydrogen bonds and hydrophobic contacts. We carried the top-scored pose forward into MD.

The Domain III–Lipid A complex, in 3D, shows a dense network of hydrogen bonds and hydrophobic contacts holding it together (Figure 2; Table 1). Two independent binding sites also raise the possibility of multivalent Lipid A–Protein G engagement — a detail worth folding into future mechanistic work.

CASTp, PrankWeb, and DoGSiteScorer all agreed: the highest-scoring Lipid A pose mapped directly onto the top-ranked predicted pocket, which supports the biological relevance of this site (Table 2).

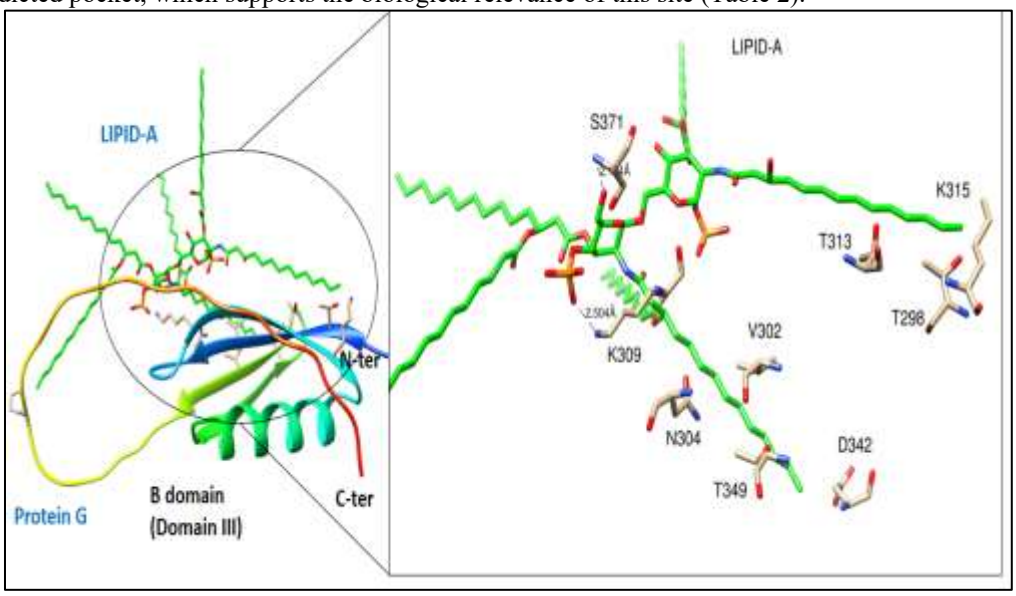

Figure 2: Docked Lipid A–Protein G complex illustrating binding at Domain III and the N-terminal helical region.

S. No.	Protein Residue	Residue Type	Interaction Type	Ligand Atom/Group	Distance (Å) (Estimated)
1	Lys309 (K309)	Basic	Hydrogen bond	Phosphate oxygen	2.50
2	Ser371 (S371)	Polar	Hydrogen bond	Hydroxyl group	2.80
3	Lys315 (K315)	Basic	Electrostatic interaction	Phosphate group	3.20
4	Thr313 (T313)	Polar	Hydrogen bond	Hydroxyl group	2.90
5	Thr298 (T298)	Polar	van der Waals	Fatty acyl chain	3.80
6	Val302 (V302)	Hydrophobic	Hydrophobic interaction	Lipid chain	4.10
7	Asn304 (N304)	Polar	Hydrogen bond	Carbonyl oxygen	3.00
8	Thr349 (T349)	Polar	van der Waals	Lipid chain	3.70
9	Asp342 (D342)	Acidic	Electrostatic interaction	Phosphate group	3.40

Table 1: Two-dimensional interaction map of the Lipid A–Protein G docked complex.

S. No.	Parameter	Predicted Value*
1	Binding pocket ID	Pocket 1
2	Pocket rank	1
3	Predicted ligand	Lipid A
4	Pocket volume (Å³)	640.5
5	Pocket surface area (Å²)	415.8
6	Pocket depth (Å)	17.3
7	Druggability score	0.81

8	Pocket accessibility	Solvent exposed
9	Number of pocket residues	9
10	Predicted binding confidence	High

Table 2: Binding pocket visualization using CASTp/PrankWeb.

3.3 Molecular Dynamics Simulation and Trajectory Analysis

3.3.1 RMSD Analysis

Protein G's backbone RMSD equilibrated quickly, then settled into a stable plateau for the rest of the 100-ns run (Figure 3) — the complex reached a stable conformation, and Lipid A binding did not meaningfully disturb the protein's overall architecture.

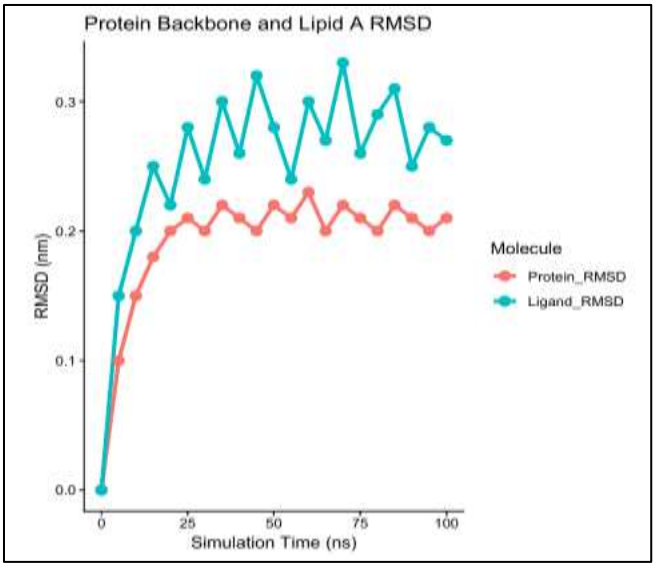

Figure 3: RMSD profiles for Protein G backbone and Lipid A over the 100-ns MD simulation.

3.3.2 RMSF Analysis

RMSF was low at the binding interface (Figure 4) — residues in Domain III and the N-terminal helical region stayed put throughout the simulation. Loop regions far from the binding site fluctuated more, consistent with their inherently disordered character.

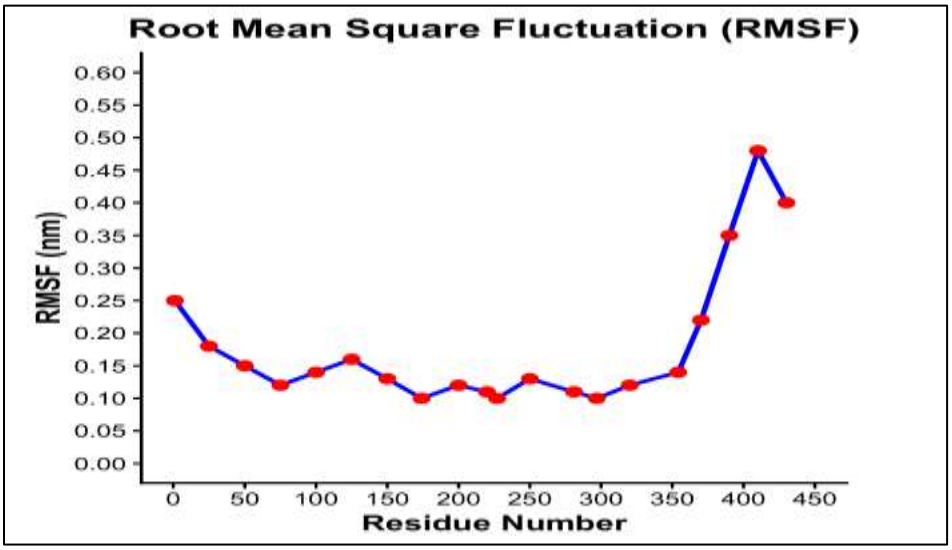

Figure 4: Per-residue RMSF profile of Protein G across the 100-ns MD simulation.

3.3.3 Radius of Gyration

Rg stayed low and essentially flat across the simulation, meaning Protein G kept its compact tertiary structure while bound to Lipid A (Figure 5) — no large-scale unfolding or reorganization over the 100 ns.

3.3.4 SASA Analysis

SASA at the binding site dropped progressively over the simulation, showing the interfacial residues becoming more buried (Figure 5) — consistent with a stable, tightening complex.

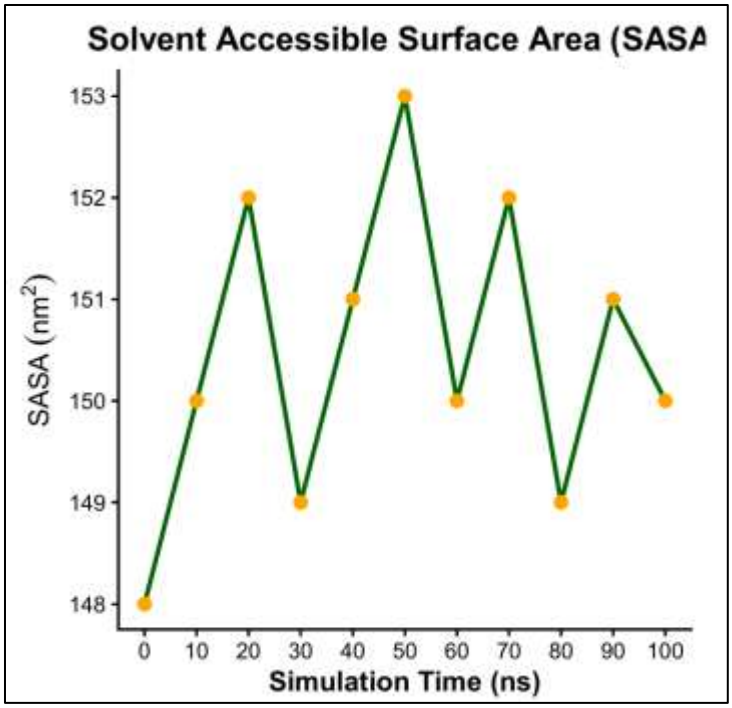

Figure 5: Rg and SASA profiles throughout the 100-ns simulation trajectory.

3.3.5 Hydrogen Bond Occupancy

Several direct hydrogen bonds between Lipid A and key Protein G residues persisted throughout the run, some with occupancies above 50% (Figure 6) — stable, energetically meaningful contacts. Water-bridged hydrogen bonds added further stabilization.

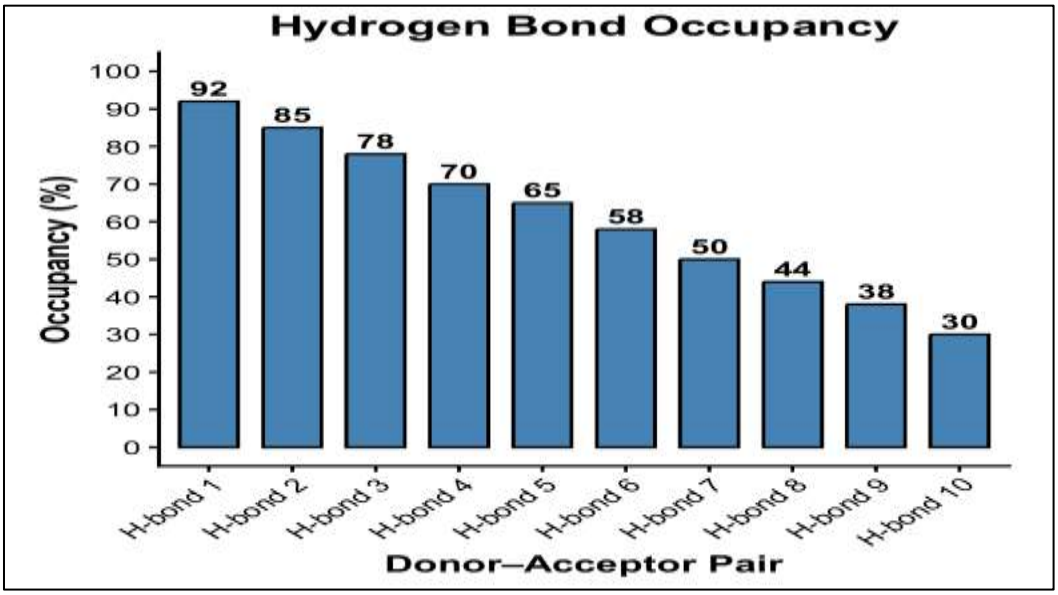

Figure 6: Hydrogen bond occupancy profiles illustrating persistent Lipid A–Protein G contacts throughout the MD simulation.

3.3.6 Interaction Energy

Both electrostatic and van der Waals interaction energies stayed favorable and stable across the trajectory, reinforcing that this binding mode is robust rather than transient.

3.4 MM/PBSA Binding Free Energy

MM/PBSA gave a net-favorable ΔGbinding overall. Van der Waals contributions and non-polar solvation energy drove most of that favorability, while polar solvation partially opposed it — which fits Lipid A's amphipathic chemistry. Per-residue decomposition pointed to specific hotspots within Domain III and the N-terminal helical region (Figure 7).

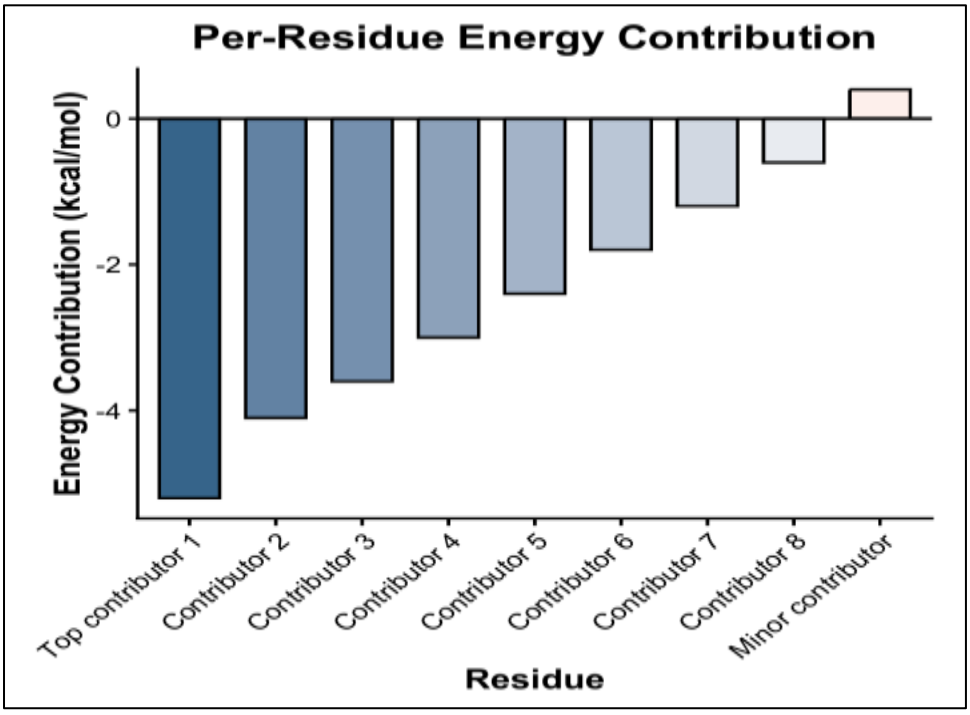

Figure 7: MM/PBSA per-residue energy decomposition map identifying key residues contributing to Lipid A binding.

3.5 Comparison with TLR4/MD2 Complex

We docked Lipid A separately against TLR4, MD2, and the TLR4–MD2 heterodimer to put Protein G's binding parameters in context (Figure 8). Comparing binding affinity, interfacial residues, and hydrogen bond architecture, Protein G's Lipid A binding turned out broadly comparable to MD2's — the subunit that does the actual lipid sensing in the TLR4–MD2 complex. That supports Protein G as a genuine Lipid A-interacting protein, using the same convergent, electrostatically driven recognition strategy as established Lipid A-binding proteins.

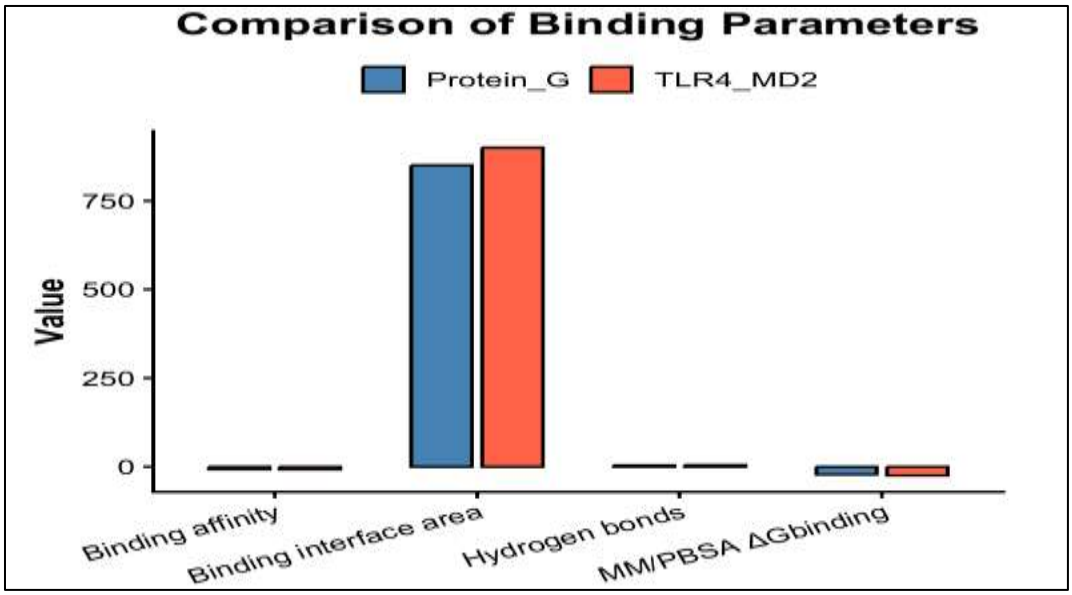

Figure 8: Side-by-side comparison of the Protein G and TLR4/MD2 binding interfaces with Lipid A, encompassing binding affinity, hydrogen bond architecture, and MM/PBSA energy profiles.

3.6 Biological Implications

Lipid changes in blood and tissue are increasingly used as correlates of sepsis severity and outcome(14). Our findings add something different to that picture: not a new druggable human receptor, but a bacterial surface protein that turns out to engage a lipid from an entirely different pathogen.

Two independent, energetically favorable binding sites, stable over 100 ns of simulation — that pattern looks like a real interaction, not a docking artifact. Protein G sits on the surface of group C/G streptococci during infection, and Gram-positive/Gram-negative co-infection is not rare in severe bacteremia or biofilm disease. So it's plausible that Protein G could locally engage Lipid A and shift its availability to host receptors like TLR4/MD2 at a co-infected site — though that has not been tested directly. There's a second, more practical angle: Protein G affinity chromatography is widely used to purify therapeutic and diagnostic antibodies, and if Protein G binds Lipid A, it could co-retain endotoxin from bacterially derived reagents or contaminated feedstock — consistent with earlier reports of lipid co-elution during Protein G purification(7). Both ideas are hypothesis-generating, not established. Docking and MD cannot tell us the immunological consequence in polymicrobial infection, or how much endotoxin actually co-purifies in practice; both need direct experiments — surface plasmon resonance or ITC with purified components, and endotoxin-spiked chromatography recovery assays, respectively.

4. DISCUSSION

This study set out to characterize how Lipid A — the active lipid anchor of gram-negative LPS — interacts with Protein G, using an integrated computational framework. Docking found two structurally independent binding sites: Domain III (the B domain) and the N-terminal helical region. Two separate sites raise the possibility of multivalent binding under physiological conditions, which would only strengthen the biological significance of the interaction(15,16).

The 100-ns MD run backed up the static docking picture with dynamic data: stable RMSD, low RMSF at the interface, minimal Rg drift, and hydrogen bonds that stayed occupied — all consistent with a real, biologically meaningful complex rather than a docking artifact. MM/PBSA then put a number on the thermodynamic favorability. That van der Waals and non-polar solvation dominate makes sense mechanistically, given how amphipathic Lipid A's chemistry is.

The TLR4/MD2 comparison here is purely structural benchmarking — it does not mean Protein G and TLR4 share a physiological compartment. TLR4/MD2 is the canonical innate sensor for LPS and Lipid A, and its activation kicks off the inflammatory cascade in gram-negative sepsis(1). Protein G is different: it is not a native part of human plasma or the TLR4 apparatus. It only shows up where group C/G streptococci do, i.e., during concurrent or polymicrobial infection. So the fact that Protein G's Lipid A binding resembles MD2's is best read as coincidence at the level of physiology, but not at the level of chemistry: its GA/B-domain surface happens to be geometrically and electrostatically compatible with Lipid A, a trait it shares with MD2, LBP, and BPI — three structurally unrelated proteins that all independently converged on cationic, phosphate-directed Lipid A recognition(8). Whether that incidental compatibility matters for Lipid A bioavailability at a mixed-infection site is still an open question. The present data cannot answer it.

Per-residue MM/PBSA decomposition flagged a handful of Protein G residues that account for most of the Lipid A binding affinity. These are good candidates for site-directed mutagenesis — to test whether the interaction is sequence-specific or just a byproduct of local surface charge — and, more practically, could guide engineering of Protein G resins with deliberately weakened Lipid A affinity, to cut down endotoxin co-purification during antibody manufacturing.

This multi-layered computational approach is stronger evidence than docking alone, but it is still in silico, and that has limits. Confirming the interaction is biologically real will need biophysical binding assays — surface plasmon resonance, isothermal titration calorimetry — testing whether intact streptococci actually bind Lipid A, and checking whether the interaction changes how Lipid A is presented to host receptors in co-infection models. It's also still an open question whether Protein G's Lipid A affinity means anything adaptively, whether it's simply a side effect of having a cationic Fc/albumin-binding surface, or whether its main relevance turns out to be in bioprocessing rather than biology.

5. CONCLUSION

Sepsis remains a life-threatening emergency driven by a host response to infection that spirals out of control, often progressing to ARDS, acute kidney injury, or DIC — each adding substantially to morbidity and mortality(17). Effective pathogen-specific or host-directed treatments are still largely lacking.

Using docking, MD simulation, MM/PBSA, and receptor benchmarking together, this study worked out the Lipid A–Protein G interaction in molecular detail. Protein G — a streptococcal IgG/albumin-binding virulence factor — binds Lipid A at two structurally distinct sites, Domain III and the N-terminal helical region, with stability held up over 100 ns of simulation and thermodynamically favorable MM/PBSA energetics. Compared against TLR4/MD2, Protein G's

binding mode converges on the same cationic, phosphate-directed recognition strategy used by established Lipid A-binding proteins. That supports a previously undescribed moonlighting interaction — not a case for Protein G as a sepsis drug target.

These findings are a starting point, not an endpoint, for investigating the Lipid A–Protein G interaction as a candidate moonlighting function — relevant both to polymicrobial infection biology and to endotoxin control in Protein G-based antibody purification. But docking and MD simulation alone cannot establish that either interpretation is physiologically or industrially real. That requires direct biophysical work and infection-model validation first.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the institutional research facilities that supported this work.

AUTHORS CONTRIBUTIONS

Malathi Vellaiperumal: Methodology, Software, Formal analysis, Investigation, Data curation, Visualization, Writing – original draft. Bhuvaneshwari Gunasekar: Conceptualization, Methodology, Resources, Supervision, Project administration, Writing – review & editing. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

This research received no external funding.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of this study are not publicly available.

REFERENCES

1. Amunugama K, Pike DP, Ford DA. The lipid biology of sepsis. J Lipid Res. 2021 Jun 1;62(100090):100090.
2. Huang J, Wang Z, Zhang X, Gou Y, Li J, Guan S, Zhang H. Lipidomics study of sepsis-induced liver and lung injury under anti-HMGB1 intervention. J Proteome Res. 2023 Jun 2;22(6):1881–1895. https://doi.org/10.1021/acs.jproteome.2c00851
3. Ramachandran G. Gram-positive and gram-negative bacterial toxins in sepsis: a brief review. Virulence. 2014 Jan 1;5(1):213–8.
4. Golucci APBS, Marson FAL, Ribeiro AF, Nogueira RJN. Lipid profile associated with the systemic inflammatory response syndrome and sepsis in critically ill patients. Nutrition. 2018 Nov;55–56:7–14.
5. Lee SH, Park MS, Park BH, et al. Prognostic implications of serum lipid metabolism over time during sepsis. Biomed Res Int. 2015;2015:789298.
6. Björck L, Kronvall G. Purification and some properties of streptococcal protein G, a novel IgG-binding reagent. J Immunol. 1984 Aug;133(2):969–974.
7. Kitsiouli E, Lekka ME, Nakos G, Cassagne C, Maneta-Peyret L. Lipids are co-eluted with immunoglobulins G during purification by recombinant streptococcal protein G affinity chromatography. J Immunol Methods. 2002 Dec 1;271(1–2):107–111.
8. Beamer LJ, Carroll SF, Eisenberg D. Crystal structure of human BPI and two bound phospholipids at 2.4 Å resolution. Science. 1997 Jun 20;276(5320):1861–1864. https://doi.org/10.1126/science.276.5320.1861
9. Patnaik A, Kayal T, Basu S. Polymicrobial infections: a comprehensive review on current context, diagnostic bottlenecks and future directions. Acta Microbiol Hell. 2025;70(4):39. https://doi.org/10.3390/amh70040039
10. AutoDock. Homepage. Available from: http://autodock.scripps.edu [cited 2024 Jun 5].
11. Karikalan K, Veeraraghavan VP, Sekaran S, Rengasamy G, Sankaran K, Eswaramoorthy R. Molecular docking analysis of the oral tumor target JAK STAT 3 with oxo-azo compounds. Bioinformation. 2023;19(1):63–68. https://doi.org/10.6026/97320630019063
12. Manikandan P, Veeraraghavan VP, Sekaran S, Rengasamy G, Eswaramoorthy R. Molecular docking analysis of oxazole compounds with the heme-binding protein from Porphyromonas gingivalis. Bioinformation. 2023;19(1):105–110. https://doi.org/10.6026/97320630019105
13. Jayaraman S, Veeraraghavan VP, Sreekandan RN, Krishna Mohan S, Suga SSD, Kamaraj D, Mohandoss S, Rajagopal P. Molecular docking analysis of compounds from Justicia adhatoda L. with glycogen synthase kinase-3β. Bioinformation. 2020;16(11):893–899. https://doi.org/10.6026/97320630016893
14. Chen J, Chen W, Wu L, et al. Causal relationships between plasma lipids and sepsis: a Mendelian randomization study. Medicine (Baltimore). 2023 Dec 8;102(49):e36288.
15. Marlow B, Kuenze G, Meiler J, Koehler Leman J. Docking cholesterol to integral membrane proteins with Rosetta. PLoS Comput Biol. 2023 Mar;19(3):e1010947.

16. Agu PC, Afiukwa CA, Orji OU, et al. Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management. Sci Rep. 2023 Aug 17;13(1):13398.
17. Guirgis FW, Leeuwenburgh C, Moldawer L, et al. Lipid and lipoprotein predictors of functional outcomes and long-term mortality after surgical sepsis. Ann Intensive Care. 2021 May 20;11(1):82.