THE POTENTIAL AGAINST METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* OF JATROPHONE FROM *JATROPHA PODAGRICA* THROUGH MOLECULAR DYNAMIC INTERACTION WITH PENICILLIN-BINDING PROTEIN 2A: INSIGHTS FROM COMPUTATIONAL CHEMISTRY ANALYSIS

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ABSTRACT

Jatropha podagrica Hook (Bottle tree) demonstrates antimicrobial activity against various bacteria, particularly strains of the ESKAPEE pathogens, though the mechanisms underlying compounds of the plant remain unclear. This research employs molecular docking and dynamics simulations to investigate the interaction between Jatrophone, a compound derived from this plant, and Penicillin-binding Protein 2a, a protein found in Methicillin-resistant *Staphylococcus aureus*. Analysis based on Root Mean Square Deviation and Root Mean Square Fluctuation indicated that Jatrophone bound strongly to the active site of Penicillin-binding Protein 2a, involving several key residues such as LYS644, ASP654, ILE648, SER581, and GLU583. The protein-ligand complex was highly stable, with Jatrophone displaying flexibility that enabled it to effectively fit into the binding pocket of the protein pocket, especially with residues crucial to β-lactam resistance. These findings highlight Jatrophone as a promising candidate for developing novel anti-methicillin-resistant *Staphylococcus aureus* therapies, offering a strong basis for further optimization and experimental validation.

TIỀM NĂNG CHỐNG LẠI TỤ CẦU VÀNG KHÁNG METHICILLIN CỦA JATROPHONE TỪ *JATROPHA PODAGRICA* THÔNG QUA TƯƠNG TÁC ĐỘNG LỰC PHÂN TỬ VỚI PROTEIN LIÊN KẾT PENICILLIN 2A: NHỮNG HIỂU BIẾT TỪ PHÂN TÍCH HÓA HỌC TÍNH TOÁN

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TỪ KHÓA

Jatropha podagrica Hook
Jatrophone
Kháng khuẩn
Phân tích hoá học tính toán
Protein liên kết Penicillin 2a

TÓM TẮT

Jatropha podagrica Hook (cây bình rượu) thể hiện hoạt tính kháng khuẩn chống lại nhiều loại vi khuẩn, đặc biệt là các chủng vi khuẩn gây bệnh ESKAPEE, mặc dù các cơ chế tác động của các hợp chất từ cây này vẫn chưa rõ ràng. Nghiên cứu này sử dụng mô phỏng gắn kết phân tử và động lực học phân tử để điều tra sự tương tác giữa Jatrophone, một hợp chất chiết xuất từ cây này, và Protein liên kết Penicillin 2a, một protein có trong tụ cầu vàng kháng methicillin. Phân tích dựa trên độ lệch căn bậc hai trung bình và dao động căn bậc hai trung bình cho thấy Jatrophone gắn kết mạnh mẽ với vị trí hoạt động của Protein liên kết Penicillin 2a, liên quan đến một số vị trí quan trọng như LYS644, ASP654, ILE648, SER581 và GLU583. Phức hợp protein-ligand rất ổn định, với Jatrophone thể hiện tính linh hoạt cho phép nó dễ dàng khớp vào vị trí gắn của protein, đặc biệt là với các vị trí quan trọng đối với khả năng kháng thuốc β-lactam. Những phát hiện này cho thấy Jatrophone như một ứng cử viên đầy hứa hẹn cho việc phát triển các liệu pháp mới chống lại tụ cầu vàng kháng methicillin, cung cấp cơ sở vững chắc để tiếp tục tối ưu hóa và kiểm chứng bằng thực nghiệm.

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1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is primarily determined by Penicillin-binding Protein (PBP) family, especially PBP2a, which confers β-lactam resistance [1]. The *mec*A gene encodes the presence of this particular peptidoglycan transpeptidase included in the genetic element of the staphylococcal chromosomal cassette (SCC) mec [2]. Generally, the production of PBP2a enables bacteria to synthesize cell walls despite the presence of β-lactam, eventually conserving bacterial survival [3]. *Staphylococcus aureus* exhibits two mechanisms to resist against β-lactam via β-lactamase or PBP2a. Specifically, when β-lactams are absent, *Bla*I and *mec*I transcriptional repressors function as dimers and prevent the transcription of Blaz and *mec*A. Otherwise, the presence of β-lactams acylates *Bla*R1 and *mec*R1, activating a zinc protease. This phenomenon cleaves *Bla*I and *mec*I, triggering the transcription of Blaz and *mec*A, which leads to the synthesis of PBP2a and β-lactamase. β-lactamase then hydrolyzes the β-lactam ring, generating inactive derivatives. PBP2a, with its retained transpeptidase activity and a low affinity for several β-lactam antibiotics, ensures continued cell wall synthesis despite the presence of β-lactam antibiotics [4]. This enables MRSA to evade treatment, making it a severe health threat, associated with conditions such as pneumonia, bloodstream infections, surgical site infections, sepsis, and even mortality. Targeting PBP2a offers a promising strategy to combat MRSA, potentially through the use of natural products alongside existing antibiotics to restore or enhance their efficacy [4], [5].

In our screening for the anti-bacterial agents from Vietnamese natural and medicinal plants, it has been found that *Jatropha podagrica* Hook collected in Vietnam shows very potential against S. *aureus* and MRSA. The Jatropha species, belonging to the tribe Joanneasiae of Crotonoideae within the family Euphorbiaceae, have long been used in traditional medicine across Asia and Africa to treat a range of ailments [6]. *Jatropha podagrica*, a species within the genus Jatropha, is particularly renowned for its therapeutic applications in treating conditions such as gout, paralysis, gonorrhea, skin infections, jaundice, and fever. Extracts from various parts of *J. podagrica* have demonstrated significant medicinal properties [7]. Specifically, extracts from the stem and stem bark, prepared in chloroform, methanol, and hexane, have shown strong inhibitory effects against clinical isolates of *S. aureus*, *E. coli*, *Candida albicans*, and several Gram-positive bacteria, highlighting the potential of plant as both an antimicrobial and antifungal agent. Among extracted compounds from *J. podagrica*, jatrophone is a common macrocyclic diterpene. Its derivatives have exhibited a range of biological activities, including the ability to suppress insulin, inhibit lymphocyte activation, impede tumor cell growth, display molluscicidal properties, and offer gastroprotective benefits [8].

Although several bioactive compounds have been isolated from various parts of *J. podagrica*, investigation of its antibacterial properties, particularly against *S. aureus* and MRSA strains remains limited. Therefore, this study aims to identify the anti-bacterial properties of jatrophone, a main diterpenoid in *J. podagrica*, based on the molecular dynamic interaction with penicillin-binding protein 2a (PBP2a) using computational chemistry methods.

2. Materials and Methods

2.1. Chemical data preparation

A data mining method from PubMed database was used to build a dataset of compounds extracted from *J. podagrica*. A list of 41 compounds from *J. podagrica* was prepared for the molecular docking process (Table 1). The 3D structures of the compounds were obtained from PubChem, and prepared by MarvinSketch (ChemAxon, Cambridge, MA, USA).

Table 1. *List of selected compounds from J. podagrica* [7]

No.	Compound name	No.	Compound name
1	Rutin	22	Japodagrone
2	Sikkimenoid A	23	Acacetin
3	Jatrointelon B	24	4E-jatrogrossidentadion
4	15-Epi-4E-jatrogrossidentadion	25	15-Epi-4Z-jatrogrossidentadion
5	Isovitexin	26	Isojatrogrossidion
6	Jatropodagrene	27	Jatrointelon G
7	Jatrophone	28	Jatropodagin A
8	Sikkimenoid B	29	7,4'-dimethoxyflavone
9	Luteolin	30	Jatrodagricaine A
10	4Z-jatrogrossidion	31	Quercetin
11	4Z-jatrogrosidentadion	32	16-hydroxyphorbol
12	Jatropodagin B	33	Jatrointelon F
13	Apigenin	34	Labda-8,13E-diene-3,15-diol
14	Vitexin	35	Japodagricanone A
15	Japodagrin	36	8α,15,16-trihydroxy-labd-13E-ene
16	Jatrogricaine A	37	Japodagricanone B
17	2-epihydroxyisojatrogrossidion	38	Kayadiol
18	2-hydroxyisojatrogrossidion	39	Fraxetin
19	2-epi-isojatrogrossidion	40	Fraxidin
20	Flavone-5-hydroxy	41	Scoparone
21	Jatrocurcasenon D		

2.2. Protein structure preparation

The crystal structure of Penicillin-binding protein 2a (PDB ID: 1VQQ) – Chain A was obtained from the Research Collaboratory for Structural Bioinformatics Protein Data Bank. Existing ligands and water molecules were removed using Discovery Studio. Polar hydrogen and Kollman charges were added to the protein using Autodock tools (v. 1.5.6). Finally, the protein was converted to pdbqt format for molecular docking analysis.

2.3. Molecular docking study

The selected compound was virtually screened bound to PBP2a proteins using AutoDock Vina 1.1.2. The grid box covering the active site of protein was selected from the interactive site of the crystal ligand. Docking scores, reported in kcal/mol, were used to rank the potential compounds. Finally, the molecular interactions between proteins and selected ligands were visualized by Discovery Studio Visualizer 2020, and their 3D and 2D interaction plots were derived [9].

2.4. Molecular dynamics simulations (MD)

MD simulations were performed using the Desmond package (Schrödinger 2020-1, New York, NY, USA) [10], [11]. The protein-ligand complex was prepared in a 10.0 × 10.0 × 10.0 Å orthorhombic box (simple point-charge solvation model). Next, a 0.15 M NaCl solution and counter-ions were added to the system for neutralization. The solvated system was energy-minimized, and its position was restrained with the OPLS3e force field. The minimized system was implemented in an NPT ensemble at 300 K and 1 atm. Finally, MD simulation was conducted to run for 100 ns, and 1000 frames were generated, with a recording interval of 100 ps [12].

3. Results and Discussion

3.1. Molecular docking analysis

The binding affinity values of bioactive compounds isolated from *J. podagrica* were promising, with jatrophone (Pubchem CID 6325446) showing a value of -8.447 kcal/mol in the top ten of the best binding affinities to PBP2a (Table 2).

Table 2. *Best docking scores of top ten compounds from J. podagrica and PBP2a*

No.	Compound	Binding energy (kcal/mol)	No.	Compound	Binding energy (kcal/mol)
1	Rutin	-8.88	6	Jatropodagrene	-8.455
2	Sikkimenoid A	-8.658	7	Jatrophone	-8.447
3	Jatrointelon B	-8.483	8	Sikkimenoid B	-8.41
4	15-Epi-4E-jatrogrossidentadion	-8.483	9	Luteolin	-8.308
5	Isovitexin	-8.477	10	4Z-jatrogrossidion	-8.303
			Reference	Ampicillin	-7.674

Based on these results, jatrophone was selected for further experiments in this study. Molecular docking simulations between jatrophone and PBP2A protein are shown in Figure 1.

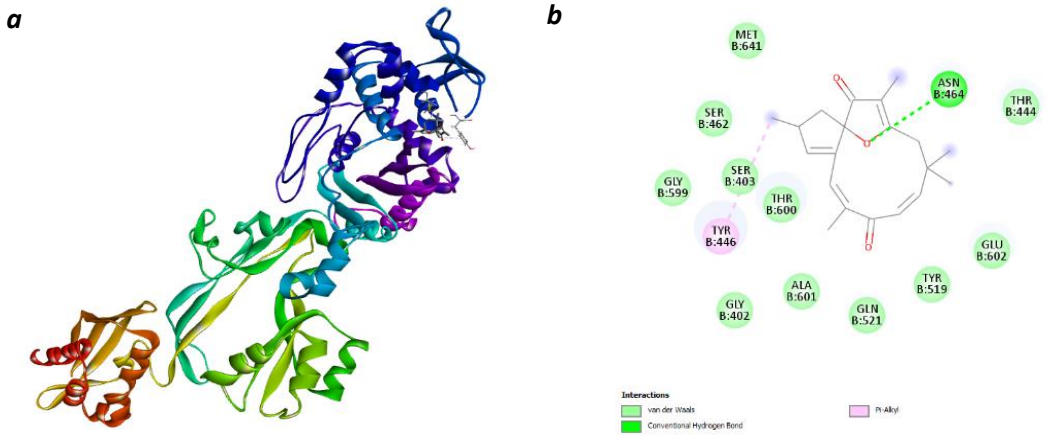

Figure 1. *Binding diagram at the active site (a) and the molecule interactions (b) of jatrophone with PBP2a (1VQQ)*

Jatrophone fits into the active site of PBP2A (Figure 1a), interacting with various amino acid residues through different bonds (Figure 1b). Van der Waals forces (green) stabilize jatrophone in the binding pocket, indicating its good fit with the hydrophobic regions. Conventional hydrogen bonds (green dashed lines) with ASN464 suggest stabilizing interactions essential for binding affinity. Pi-Alkyl interactions (pink) with TYR446 help with hydrophobic stabilization. Key residues like ASN464, TYR446, SER and GLY at several residues contribute to hydrogen bonding and Van der Waals interactions, highlighting the importance of the hydrophobic environment. The bicyclic and enone groups of jatrophone play a key role in these interactions, with oxygen atoms facilitating hydrogen bonding.

3.2. Molecular dynamic of jatrophone with Penicillin-binding protein 2a-Chain A

The Root Mean Square Deviation (RMSD) plot (Figure 2a) shows that the 1VQQ Cα atoms (blue line) rapidly increase between 0 to 10 ns, then stabilize from 10 ns to 100 ns, indicating initial structural adjustments before equilibrium. During the stable phase, the RMSD fluctuates between 4 and 7 Å, typical for large proteins. The RMSD of jatrophone (red line) also increases initially, then stabilizes with minor fluctuations, suggesting the ligand found its binding site and remained relatively stable. The ligand's average RMSD is around 15-20 Å, indicating some mobility. Overall, the RMSD plot shows the interaction between jatrophone and PBP2a reached stability after 10 ns, with no significant structural changes afterward.

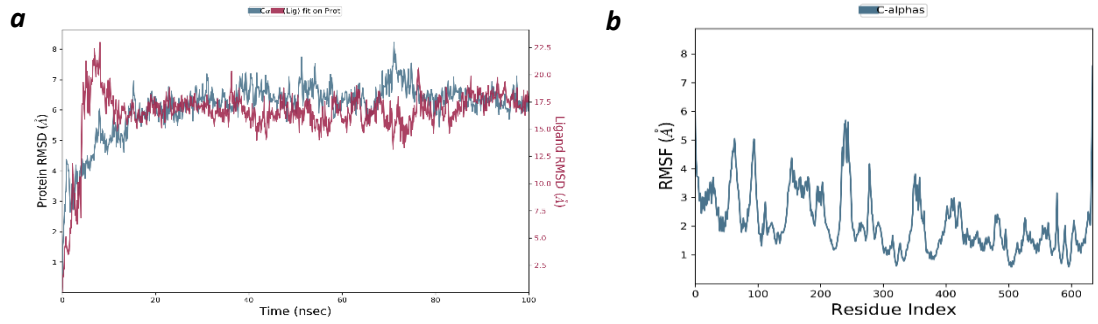

Figure 2. *RMSD (a) and RMSF (b) values of complex jatrophone and PBP2a (1VQQ)*

The Root Mean Square Fluctuation (RMSF) plot (Figure 2b) shows per-residue fluctuations of PBP2a when interacting with jatrophone. Residues with higher RMSF values (6-8 Å) are more flexible, typically at the termini or within flexible loops. Lower RMSF values (2-3 Å) indicate more stable regions, such as α-helices or β-sheets, which maintain the structure of protein. Regions with high RMSF values may be involved in ligand or molecular interactions, while stable areas form the protein's core, crucial for its function. Overall, most of PBP2a remains stable, with only a few flexible regions showing higher fluctuations.

3.3. Protein and ligand contacts histogram and timeline

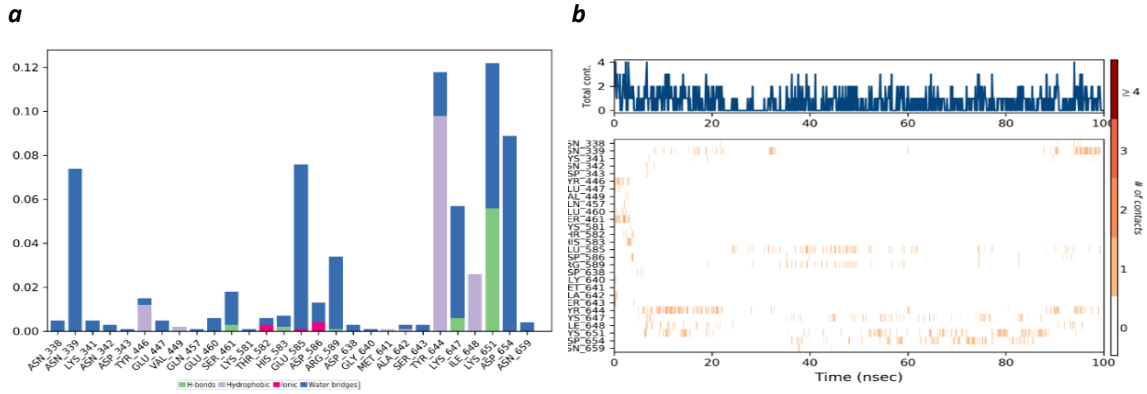

Figure 3. *Protein and ligand contacts histogram (a) and timeline (b) of jatrophone and 1VQQ*

Figure 3a shows a histogram of interactions between jatrophone and specific amino acids in PBP2a. Blue bars represent water bridges, purple bars indicate hydrophobic interactions, green bars show hydrogen bonds, and red bars reflect ionic interactions. LYS644 and ASP654 have the highest bars, indicating strong and frequent interactions with jatrophone, including water bridges, hydrophobic interactions, and hydrogen bonds, highlighting their role in stabilizing the complex. ILE648 shows significant hydrophobic interactions, while ASN338 and GLU583 have fewer interactions. SER581 and THR582 show minimal interactions, mainly through water bridges.

Figure 3b shows the total number of contacts between jatrophone and PBP2a over the 100-nanosecond simulation, with fluctuations indicating changes in interaction strength. Peaks suggest periods of strong ligand-protein binding. The "Timeline of Specific Contacts" plot highlights key amino acids like SER581, GLU583, and LYS644, which frequently interact with jatrophone, suggesting their critical role in binding. Other residues, such as TYR647 and ASP654, show fewer, more transient contacts. Stable interactions at sites like SER581 and LYS644 highlight their importance for the inhibitory activity of jatrophone, while the absence of stable contacts at some sites may indicate protein conformational changes.

3.4. Ligand and protein properties in the dynamic action

The L-RMSF plot of jatrophone (Figure 4a) shows the average fluctuation of each atom during binding to the protein. High peaks indicate less stable regions with greater variability, while low RMSF values suggest stable areas that help stabilize ligand-protein interactions.

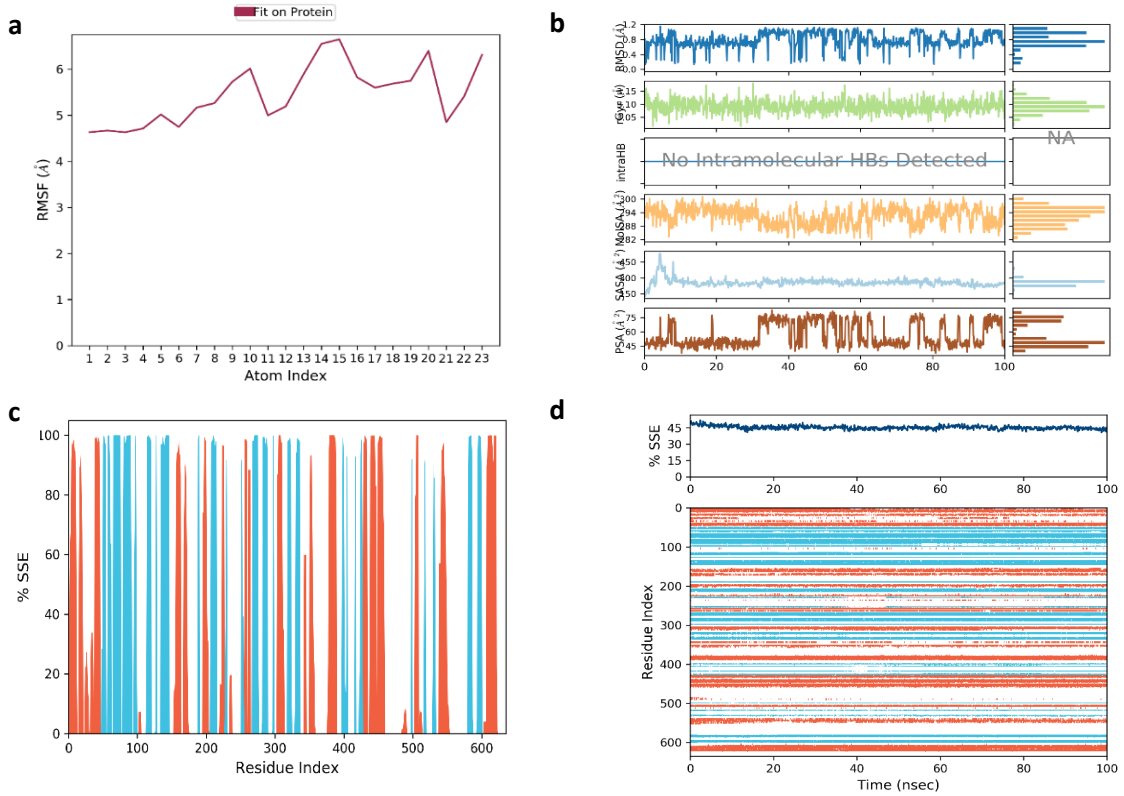

Figure 4. *L-RMSF (a), Ligand Properties (b), P-SSE Histogram (c), and P-SSE Timeline (d) of jatrophone*

Figure 4b shows various properties of jatrophone during the molecular dynamics simulation. The RMSD (blue line) indicates the stability of ligand, with minor fluctuations suggesting it remains stable when bounding to the protein. The radius of gyration (rGyr, green line) reflects the compression or expansion of ligand. The intraHB plot shows that jatrophone forms few internal hydrogen bonds, affecting its mobility. The MolSA (orange line) shows slight changes in surface exposure, while SASA (light blue line) reveals the interaction of ligand with the solvent. The PSA (brown line) remains stable, indicating consistent polarity during the simulation.

Figure 4c shows the percentage of secondary structure elements (SSE) in PBP2a over time, highlighting the occurrence of alpha-helices and beta-sheets. Segments with high SSE percentages (near 100%) indicate stable secondary structures, while low or fluctuating percentages suggest flexible, unstable regions, often in loops. The alternating colors reflect transitions between alpha-helices and beta-sheets. Long uniform stretches indicate stable sections, while significant SSE changes may point to flexible segments or structural adjustments during ligand binding. Figure 4d tracks SSE changes in PBP2a during the simulation. The color-coded timeline shows beta-sheets in blue and alpha-helices in red. Stable color segments indicate regions with consistent secondary structures, while color transitions highlight flexible areas. Overall, the protein maintains a stable secondary structure throughout the simulation, reflecting its structural integrity.

3.5. Jatrophone torsion analysis

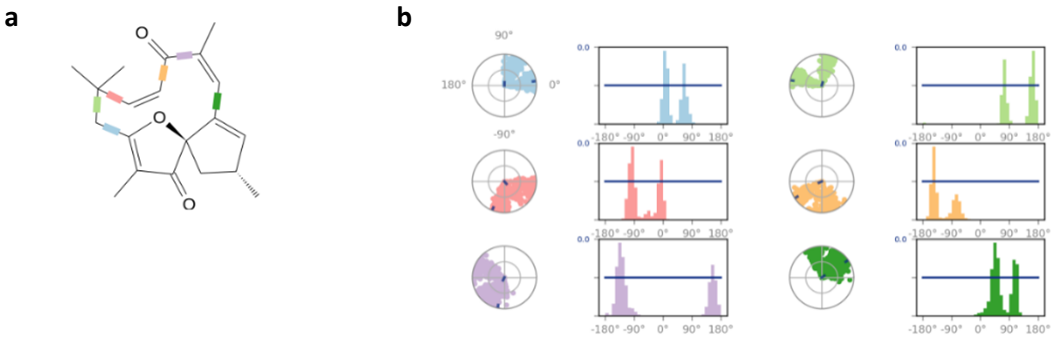

Figure 5. *Jatrophone torsion properties at backbone (a) and side chain (b)*

Figure 5 shows the 2D structure of jatrophone, with colored bonds representing key torsion angles that influence its flexibility or stability. Polarization plots illustrate bond rotation angles over time, with histograms showing rotation frequency. High peaks indicate stable rotations, while broader distributions suggest greater flexibility. Kinetic analysis shows jatrophone forms stable interactions with PBP2a through hydrogen bonds, hydrophobic interactions, and water bridges, with amino acids like LYS644, ASP654, and ILE648 playing significant roles. PBP2a's secondary structure remains stable, indicating that jatrophone does not disrupt its function, supporting its potential as a candidate against drug-resistant bacteria.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a global health threat due to its resistance to β-lactam antibiotics, including methicillin. This resistance is driven by the mecA gene, which encodes penicillin-binding protein 2a (PBP2a), a protein with low affinity for β-lactams. PBP2a allows MRSA to continue cell wall synthesis even in the presence of these drugs. Its expression is regulated by mecR1 and mecI in response to β-lactam exposure. Structural and allosteric mutations in PBP2a further reduce β-lactam binding, enhancing resistance. Understanding PBP2a-mediated resistance is key for developing new therapies against MRSA infections. Molecular dynamics (MD) simulations provide key insights into the interaction between jatrophone and PBP2A, supporting its potential as an anti-MRSA agent. The results show the stability of the jatrophone-PBP2A complex, with RMSD values stabilizing after ~10 ns, indicating equilibrium. The RMSD of protein (4–7 Å) and the RMSD of ligand (~15–20 Å) suggest stability with some ligand mobility due to flexibility within the binding pocket. RMSF analysis reveals high fluctuations in flexible protein loops and stable regions in α-helices and β-sheets, essential for function. Key residues like LYS644, ASP654, and ILE648 plays vital roles in stabilizing the complex through hydrogen bonds, ionic, and hydrophobic interactions. Water-mediated contacts with residues like SER581 and GLU583 highlighted dynamic nature of the binding site. The L-RMSF analysis shows that stable regions of jatrophone are involved in critical interactions, while flexible regions adapt for binding. The compactness (rGyr) and solvent-accessibility (SASA and PSA) of jatrophone reflect its stable conformation. PBP2A's secondary structure remains mostly intact, with flexible regions identified as potential regulatory hotspots. Torsional analysis indicates that stable torsions correlate with strong interactions, while flexible torsions provide rotational freedom.

4. Conclusion

The molecular docking and dynamics simulations of jatrophone with penicillin-binding protein 2a (PBP2A) provide valuable insights into the ligand-protein interaction dynamics, highlighting its potential as a lead compound for combating methicillin-resistant *Staphylococcus aureus* (MRSA). Initial docking reveals that jatrophone fits well into the active site of PBP2A,

forming critical interactions with key residues. During the simulation, PBP2A and jatrophone reach stable conformations, with RMSD values indicating that the ligand-protein complex had achieve equilibrium. The stabilization of Jatrophone within the binding pocket reflects its favorable binding properties and compatibility with PBP2A, involving several key residues such as LYS644, ASP654, ILE648, SER581, and GLU583. The ligand-protein interaction profile demonstrates a well-balanced combination of hydrophobic interactions, hydrogen bonds, ionic interactions, and water-mediated contacts, all contributing to forming a stable and robust complex. The docking and MD simulations results show that jatrophone establishes strong, stable interactions with PBP2A, particularly with residues critical to β-lactam resistance. These findings position jatrophone as a promising candidate for developing novel anti-MRSA therapies, providing a solid foundation for further optimization and experimental validation.

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