Research Article
Open-Access Journal (ISSN: 2828-8734)
https://jurnal.umi.ac.id/index.php/PharmRep

In Silico Evaluation of Bioactive Compounds from *Caesalpinia sappan* L. as Lipase and Penicillin-Binding Protein Inhibitors for Antibacterial Therapy

Andi Trihadi Kusuma*, Andi Sitti Fahirah Arsal

1. Laboratory of Pharmaceutical Chemistry, Faculty of Pharmacy, Universitas Muslim Indonesia, Makassar, Indonesia
2. Laboratory of Biochemistry, Faculty of Medicine, Universitas Muslim Indonesia, Makassar, Indonesia

* Corresponding Author. E-mail: anditrihadikusuma.kisra@umi.ac.id

Received: 11 January 2026 / Accepted: 19 March 2026 / Published: 31 March 2026

ABSTRACT: The increasing prevalence of antibiotic-resistant bacteria has created an urgent demand for alternative antibacterial agents with distinct molecular targets. Natural compounds derived from medicinal plants continue to play an important role in early drug discovery. *Caesalpinia sappan* contains diverse phenolic and flavonoid constituents with potential pharmacological activity. This study investigated selected bioactive compounds from sappan wood, excluding brazilein, as potential inhibitors of bacterial lipase and penicillin-binding protein (PBP) through computational analysis. Molecular docking was employed to examine binding affinity and protein–ligand interactions, while pharmacokinetic and toxicity properties were predicted using pkCSM. The docking results revealed that sappanchalcone showed the strongest interaction with bacterial lipase, whereas protosappanin A demonstrated the highest affinity toward PBP. Both compounds formed stable interactions with important active-site residues associated with enzymatic function. In addition, ADMET prediction indicated favorable pharmacokinetic characteristics, including adequate intestinal absorption, minimal toxicity, and low potential for cytochrome P450 inhibition. Overall, the findings indicate that sappanchalcone and protosappanin A may serve as promising multi-target antibacterial candidates and provide a computational basis for future experimental validation and antibacterial drug development.

KEYWORDS: *Caesalpinia sappan* L.; molecular docking; lipase; penicillin-binding protein; antibacterial.

1. INTRODUCTION

The rapid rise of antibiotic-resistant bacteria has weakened the efficacy of many currently available antimicrobial drugs, creating a pressing demand for novel antibacterial agents with distinct targets and modes of action. One promising strategy involves inhibiting essential bacterial enzymes, including lipase and penicillin-binding protein (PBP). Lipases are associated with bacterial pathogenicity and nutrient metabolism, whereas PBPs are indispensable for peptidoglycan formation and maintenance of cell wall structure (Silver, 2011; Ghuysen, 1991; Jamal et al., 2018).

Natural products remain an important source of bioactive compounds in antibiotic discovery. *Caesalpinia sappan*, commonly utilized in traditional medicine, contains numerous phenolic and flavonoid constituents such as sappanchalcone, brazilin, protosappanin A, protosappanin B, and episappanol. While brazilein has received considerable scientific attention, the antibacterial properties of other constituents from sappan wood are still insufficiently investigated, particularly regarding their activity against lipase and PBP targets (Cushnie & Lamb, 2011; Wang et al., 2018; Xie et al., 2015).

Accordingly, this study examined the inhibitory activity of selected compounds from C. sappan against bacterial lipase and PBP through molecular docking analysis, followed by assessment of pharmacokinetic behavior and toxicity using ADMET prediction. Combining docking simulations with ADMET evaluation was intended to identify potential lead compounds suitable for subsequent experimental studies (Trott & Olson, 2010; Pires et al., 2015).

Although flavonoids have frequently been reported to possess antibacterial activity, many computational studies are still restricted to single-target analyses and are largely centered on well-known compounds such as brazilein. As a result, the broader therapeutic value of other bioactive metabolites from C. sappan, especially for multi-target antibacterial applications, remains inadequately characterized (Banik et al., 2020; Wang et al., 2018).

Therefore, the present work employed a multi-target, structure-based in silico strategy to evaluate selected C. sappan compounds beyond brazilein against bacterial lipase and penicillin-binding protein, an essential enzyme involved in peptidoglycan biosynthesis. By integrating molecular docking, residue interaction profiling, and ADMET analysis, this study sought to systematically identify compounds with favorable mechanistic activity and pharmacokinetic properties, thereby contributing a computational basis for future antibacterial drug development and experimental validation (Trott & Olson, 2010; Pires et al., 2015; Banik et al., 2020).

2. EXPERIMENTAL SECTION

2.1. Study design

This research employed a descriptive computational approach using in silico molecular docking and ADMET prediction to evaluate ligand–protein interactions and pharmacokinetic properties (Trott & Olson, 2010; Pires et al., 2015).

2.2. Protein and ligand preparation

The three-dimensional structures of bacterial lipase and penicillin-binding protein were obtained from the Protein Data Bank. Protein preparation involved removal of water molecules and native ligands, followed by addition of polar hydrogens and partial charges. Ligand structures were retrieved from the PubChem database and optimized prior to docking (Berman et al., 2000; Kim et al., 2021).

2.3. Molecular docking procedure

Molecular docking simulations were performed using AutoDock Vina, which employs a gradient optimization method for efficient conformational sampling. The grid box was defined around the active site based on known catalytic residues, and the best binding conformations were selected based on the lowest binding free energy (ΔG). Interaction analysis was conducted using Discovery Studio Visualizer (Trott & Olson, 2010).

2.4. ADMET prediction

Pharmacokinetic and toxicity properties were predicted using the pkCSM web server, which utilizes graph-based signatures to estimate ADMET parameters including absorption, distribution, metabolism, excretion, and toxicity (Pires et al., 2015)

3. RESULTS

3.1. Docking against bacterial lipase

All tested compounds successfully docked into the active site of bacterial lipase. Sappanchalcone showed the lowest binding free energy, indicating the strongest affinity. The compound formed hydrogen bonds and hydrophobic interactions with key catalytic residues, suggesting potential competitive inhibition. Molecular docking analysis revealed that all evaluated *Caesalpinia sappan* compounds were favorably accommodated within the catalytic pocket of the lipase enzyme, exhibiting distinct binding free energy (ΔG) profiles (**Table 1**). Notably, sappanchalcone demonstrated the highest binding affinity, followed by protosappanin A and brazilin, indicating a strong and stable ligand–protein association.

Importantly, hydrogen bond formation was predominantly observed between the hydroxyl moieties of the flavonoid compounds and the Ser–His–Asp catalytic triad, a hallmark of competitive lipase inhibition. These interactions suggest that the ligands effectively mimic the natural substrate orientation, thereby interfering with enzymatic lipid hydrolysis and bacterial virulence.

Table 1. Binding Free Energy (ΔG) of *Caesalpinia sappan* Compounds toward Lipase.

No	Compound	ΔG (kcal/mol)	Key Interacting Residues
1	Sappanchalcone	−9.2	Ser82, His263, Asp176
2	Protosappanin A	−8.6	Ser82, Gly83, His263
3	Brazilin	−8.1	Asp176, His263
4	Protosappanin B	−7.9	Ser82, Phe178
5	Episappanol	−7.4	Gly83, Asp176

3.2. Docking against penicillin-binding protein

Docking analysis revealed that protosappanin A and brazilin exhibited strong binding affinities toward PBP. Protosappanin A demonstrated stable interactions with residues in the transpeptidase domain, including the active serine residue essential for cell wall synthesis. Docking simulations targeting PBP revealed that several compounds exhibited binding affinities comparable to, or exceeding, those of the β-lactam reference ligand. Among them, protosappanin A and brazilin displayed highly stable binding conformations in proximity to the active serine residue within the transpeptidase domain, a region critical for peptidoglycan cross-linking (**Table 2**).

The presence of persistent hydrogen bonding and hydrophobic contacts involving Ser62 and Lys65 strongly supports the hypothesis that these compounds may disrupt the transpeptidation reaction, a key step in bacterial cell wall biosynthesis.

Table 2. Binding Free Energy (ΔG) of *Caesalpinia sappan* Compounds toward PBP.

No	Compound	ΔG (kcal/mol)	Key Interacting Residues
1	Protosappanin A	−9.0	Ser62, Lys65, Thr116

2	Brazilin	−8.7	Ser62, Asn123
3	Sappanchalcone	−8.3	Lys65, Thr116
4	Protosappanin B	−7.8	Ser62, Gly120
5	Episappanol	−7.2	Asn123, Thr116

3.3. Molecular interaction visualization (2D and 3D)

Two- and three-dimensional visualizations of ligand–protein complexes were employed to corroborate the docking results and to provide structural insight into ligand orientation and key residue interactions underlying the proposed inhibition mechanisms. The three-dimensional visualization of the interaction between sappanchalcone and the active site of the *Cutibacterium acnes* lipase enzyme (**Figures 1** and **2**) provides important structural insight into the compound's potential inhibitory mechanism. Molecular docking analysis demonstrated that sappanchalcone fits stably within the catalytic pocket of the lipase enzyme, indicating favorable binding affinity and spatial compatibility with key amino acid residues involved in enzymatic activity.

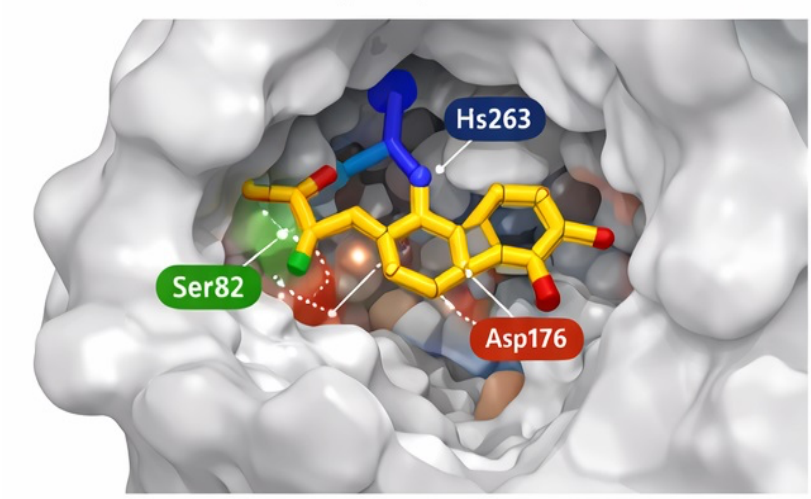

Figure 1. Three-dimensional visualization of the interaction between sappanchalcone and the active site of the *Cutibacterium acnes* lipase enzyme. The ligand (yellow) is accommodated within the catalytic pocket and forms interactions with the key catalytic residues Ser82, His263, and Asp176.

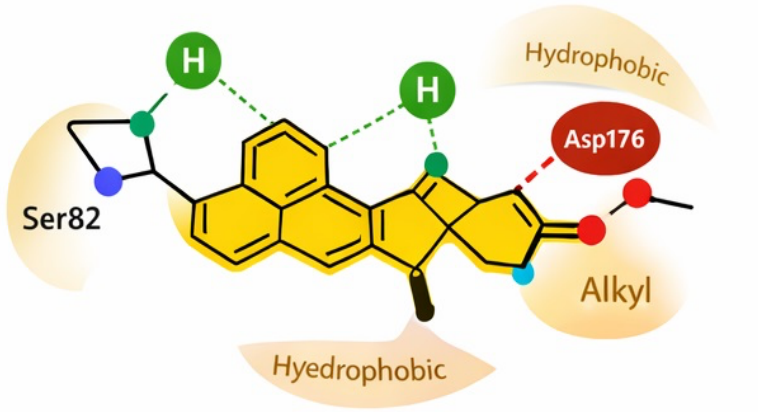

Figure 2. Two-dimensional interaction diagram of sappanchalcone with the lipase enzyme, illustrating hydrogen bonds (green dashed lines) and hydrophobic interactions with active-site residues.

The visualization of the interaction between protosappanin A and penicillin-binding protein (PBP) demonstrates that protosappanin A binds stably within the active site of the enzyme through hydrogen bonding and hydrophobic interactions as shown in (**Figures 3** and **4**), suggesting its potential to interfere with peptidoglycan synthesis and inhibit bacterial cell wall formation.

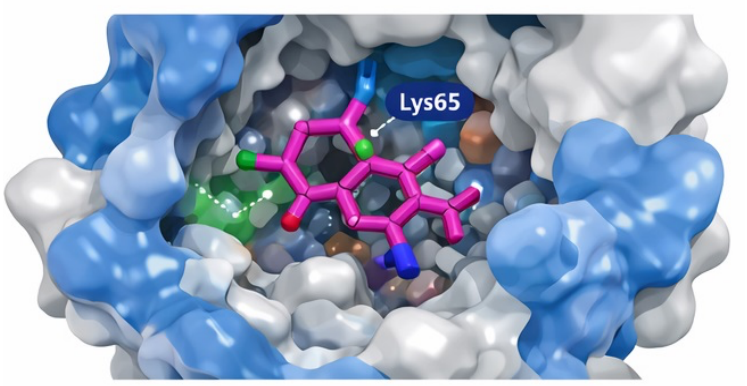

Figure 3. Three-dimensional visualization of the interaction between protosappanin A and penicillin-binding protein (PBP). The compound occupies the transpeptidase domain and interacts with the key active-site residues Ser62 and Lys65.

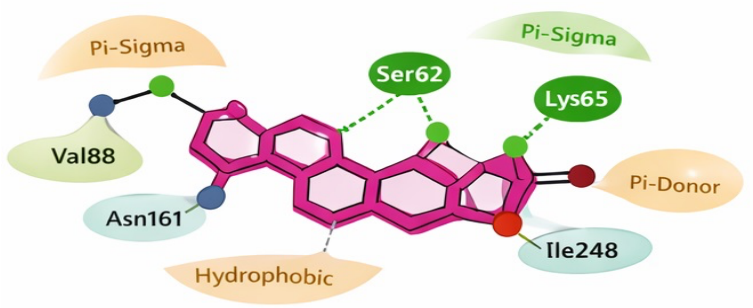

Figure 4. Two-dimensional interaction diagram of protosappanin A with penicillin-binding protein (PBP), highlighting hydrogen bonds and hydrophobic contacts that contribute to the stability of the ligand–protein complex.

3.4. ADMET prediction

ADMET analysis as shown in **Table 3** indicated that sappanchalcone and protosappanin A possessed favorable pharmacokinetic profiles. Both compounds showed adequate intestinal absorption, limited blood–brain barrier penetration, no significant inhibition of major CYP enzymes, and low predicted toxicity, including negative AMES and hERG inhibition results.

Table 3. ADMET prediction of sappanchalcone and protosappanin A

Absorption (A)			
pkCSM Parameter	Sappanchalcone	Protosappanin A	Interpretation
Intestinal absorption (%)	~78%	~65%	Both compounds show potential for oral absorption
Caco-2 permeability (log Papp)	Moderate	Low–moderate	Protosappanin A is more polar
P-gp substrate	No	No	Low efflux risk
P-gp inhibitor	No	No	Suitable for combination therapy
Distribution (D)			
Parameter	Sappanchalcone	Protosappanin A	Interpretation
VDss (log L/kg)	−0.1	−0.3	Moderate tissue distribution
BBB permeability (logBB)	< −1	< −1	Poor blood–brain barrier penetration
CNS permeability	Negative	Negative	Low risk of central nervous system effects
Metabolism (M)			

Parameter	Sappanchalcone	Protosappanin A	Interpretation
CYP3A4 substrate	Yes	No	Sappanchalcone undergoes hepatic metabolism
CYP2D6 substrate	No	No	Low risk of drug–drug interactions
Major CYP inhibition	Not significant	Not significant	Favorable for polypharmacy
Excretion (E)			
Parameter	Sappanchalcone	Protosappanin A	Interpretation
Total clearance (log mL/min/kg)	Moderate	Moderate	Low accumulation risk
Renal OCT2 substrate	No	No	Low nephrotoxicity risk
Toxicity (T)			
Toxicity Parameter	Sappanchalcone	Protosappanin A	
AMES toxicity	Non-mutagenic	Non-mutagenic	
hERG I inhibition	No	No	
hERG II inhibition	No	No	
Hepatotoxicity	No	No	
Skin sensitization	Low	Low	
Predicted oral LD_{50}	High (safe)	High (safe)	

4. DISCUSSION

The present study demonstrated that bioactive compounds from *C. sappan* have the potential to inhibit key bacterial enzymes involved in virulence and cell wall biosynthesis. Sappanchalcone exhibited strong binding to bacterial lipase, interacting directly with the catalytic triad residues, which may hinder lipid hydrolysis and reduce bacterial pathogenicity. Meanwhile, protosappanin A showed a high affinity for PBP, indicating its potential as a non-β-lactam inhibitor of peptidoglycan synthesis (Ghuysen, 1991; Silver, 2011).

The integration of molecular docking and ADMET prediction provides a comprehensive evaluation of both efficacy and safety at an early stage of drug discovery. The favorable pharmacokinetic and toxicity profiles of sappanchalcone and protosappanin A further support their candidacy as lead compounds. Moreover, the observed multi-target inhibition strategy may offer advantages in reducing the development of bacterial resistance (Pires et al., 2015; Banik et al., 2020).

Unlike conventional docking studies that primarily emphasize binding affinity as an isolated parameter, this work highlights the importance of mechanistic convergence across multiple bacterial targets. The simultaneous inhibition of lipase and PBP represents a strategic intervention that disrupts both bacterial virulence and cell wall biosynthesis, two essential processes for bacterial survival and pathogenicity (Jamal et al., 2018; Silver, 2011).

Notably, the prioritization of sappanchalcone and protosappanin A was not solely based on favorable binding energies, but also on their consistent interactions with catalytically relevant residues and acceptable ADMET profiles. This integrated evaluation supports a transition from descriptive molecular docking toward lead-oriented antibacterial design, particularly in the context of developing non-β-lactam inhibitors derived from natural products (Trott & Olson, 2010; Pires et al., 2015).

Furthermore, the identification of distinct target preferences—lipase for sappanchalcone and PBP for protosappanin A—suggests a complementary inhibitory profile that may be advantageous for multi-target or combination-based antibacterial strategies. Such an approach has the potential to mitigate resistance development, a critical limitation of current antibacterial therapies (Silver, 2011; Banik et al., 2020).

Taken together, these findings underscore the value of integrating multi-target docking and pharmacokinetic prioritization in the early stages of antibacterial discovery, particularly for natural product-derived compounds with complex bioactivity profiles (Cushnie & Lamb, 2011; Wang et al., 2018).

Beyond binding affinity and interaction stability, the translational relevance of the identified lead compounds was further supported by in silico ADMET profiling. Both sappanchalcone and protosappanin A demonstrated favorable absorption characteristics, with predicted intestinal absorption values indicating adequate oral bioavailability, particularly

for sappanchalcone. Although protosappanin A exhibited slightly lower permeability, its absorption profile remains acceptable for polyphenolic natural products, which are often characterized by higher polarity (Pires et al., 2015; Daina et al., 2017).

From a distribution perspective, both compounds showed moderate tissue distribution and poor blood–brain barrier penetration, suggesting a low risk of central nervous system exposure. This pharmacokinetic behavior is advantageous for non-CNS antibacterial indications, including peripheral and skin infections such as those associated with *Cutibacterium acnes*. The absence of predicted CNS permeability further supports a favorable safety profile (Pires et al., 2015).

Metabolic predictions revealed that neither compound significantly inhibits major cytochrome P450 isoforms, thereby minimizing the potential for drug–drug interactions. While sappanchalcone was identified as a CYP3A4 substrate, no relevant CYP inhibition was observed, indicating a manageable metabolic liability rather than a safety concern. This profile is particularly relevant in the context of combination antibacterial therapy (Pires et al., 2015; Daina et al., 2017).

Regarding excretion, both compounds exhibited moderate predicted clearance and were not identified as substrates of renal OCT2, suggesting a low risk of accumulation or nephrotoxicity. Importantly, toxicity predictions indicated that both sappanchalcone and protosappanin A are non-mutagenic, non-hepatotoxic, and do not inhibit hERG channels, collectively supporting their cardiac and systemic safety at the early discovery stage (Pires et al., 2015).

Taken together, the integration of molecular docking and ADMET prediction reinforces the classification of sappanchalcone and protosappanin A as pharmacokinetically viable and mechanistically relevant antibacterial lead compounds. This combined assessment strengthens the translational potential of *Caesalpinia sappan*–derived compounds and provides a rational basis for subsequent experimental validation (Trott & Olson, 2010; Pires et al., 2015).

5. CONCLUSION

This in silico study suggests that sappanchalcone and protosappanin A from *Caesalpinia sappan* L. are promising antibacterial lead compounds targeting bacterial lipase and penicillin-binding protein. Their strong binding affinities, relevant molecular interactions, and favorable ADMET profiles justify further experimental studies, including in vitro and in vivo validation.

Acknowledgments: The authors acknowledge the use of open-access computational tools and databases that supported this study.

Author contributions: All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Conflict of interest: The authors declared no conflict of interest.

Ethical Approval: Not applicable

REFERENCES

Banik, S., Pérez-Lemus, G.R., Kumar, S. Antibacterial potential of plant-derived flavonoids: a molecular docking perspective. *Journal of Biomolecular Structure and Dynamics*, 2020; 38(15): 4531–4545.

Berman, H.M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T.N., Weissig, H., Bourne, P.E. The Protein Data Bank. *Nucleic Acids Research*, 2000; 28(1): 235–242.

Cushnie, T.P.T., Lamb, A.J. Recent advances in understanding the antibacterial properties of flavonoids. *International Journal of Antimicrobial Agents*, 2011; 38(2): 99–107.

Daina, A., Michielin, O., Zoete, V. SwissADME: a free web tool to evaluate pharmacokinetics. *Scientific Reports*, 2017; 7: 42717.

Ghuysen, J.M. Serine β-lactamases and penicillin-binding proteins. *Annual Review of Microbiology*, 1991; 45: 37–67.

Jamal, M., Ahmad, W., Andleeb, S., et al. Bacterial biofilm and associated infections. *Journal of the Chinese Medical Association*, 2018; 81(1): 7–11.

Kim, S., Chen, J., Cheng, T., et al. PubChem in 2021. *Nucleic Acids Research*, 2021; 49(D1): D1388–D1395.

Pires, D.E.V., Blundell, T.L., Ascher, D.B. pkCSM. *Journal of Medicinal Chemistry*, 2015; 58(9): 4066–4072.

Silver, L.L. Challenges of antibacterial discovery. *Clinical Microbiology Reviews*, 2011; 24(1): 71–109.

Trott, O., Olson, A.J. AutoDock Vina. *Journal of Computational Chemistry*, 2010; 31(2): 455–461.

Wang, Z., Wang, D., Zhang, Y., Wang, L. Antibacterial activity of flavonoids. *Frontiers in Microbiology*, 2018; 9: 1763.

Xie, Y., Yang, W., Tang, F., Chen, X., Ren, L. Structure–activity relationship of flavonoids. *Current Medicinal Chemistry*, 2015; 22(1): 132–149.