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# Computational Evaluation of Antibacterial Activity of *Acalypha indica* L. Phytochemicals Against *Staphylococcus aureus* DNA Gyrase

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**Abstract**

This study investigated the antibacterial potential of phytochemical compounds derived from *Acalypha indica* L. against the DNA gyrase of *Staphylococcus aureus* using an in silico computational approach. Phytochemical structures were collected from established compound databases and subjected to geometry optimization to ensure conformational stability before molecular docking analysis. Docking simulations were carried out using AutoDock Vina to evaluate the binding affinity and interaction profiles of each ligand with the ATP-binding domain of DNA gyrase, a critical enzyme involved in bacterial DNA replication. The three-dimensional structure of *S. aureus* DNA gyrase was obtained from the Protein Data Bank and prepared through removal of water molecules, addition of polar hydrogens, and refinement of active-site residues. Among the screened ligands, five compounds exhibited strong predicted affinities, with binding energies ranging from −6.8 to −9.1 kcal/mol. Compound C demonstrated the most favorable interaction, forming stable hydrogen bonds and extensive hydrophobic contacts within the catalytic pocket, suggesting a strong inhibitory potential. Compound E also showed a high affinity, although its orientation within the binding site was slightly less optimal. ADMET predictions indicated that all top candidates satisfied drug-likeness criteria, showed good absorption potential, and presented low toxicity risks. Overall, the findings highlight that *Acalypha indica* L. contains bioactive constituents with promising inhibitory activity against bacterial DNA gyrase. These results support the traditional use of the plant in antimicrobial applications and provide a foundation for further experimental validation through in vitro enzyme inhibition assays and in vivo studies to confirm their therapeutic relevance.

**Keywords:** *Acalypha indica* L.; antibacterial activity; DNA gyrase; *Staphylococcus aureus*; molecular docking.

**Abbreviations:** Absorption, Distribution, Metabolism, and Excretion (ADME); Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET); Adenosine Triphosphate (ATP); Food and Drug Administration (FDA); Groningen Machine for Chemical Simulations (GROMACS); Merck Molecular Force Field (MMFF); Methicillin-Resistant *Staphylococcus aureus* (MRSA); Protein Data Bank (PDB); Quantitative Structure–Activity Relationship (QSAR); Root Mean Square Deviation (RMSD); Lipinski's Rule of Five (RO5); Structure–Activity Relationship (SAR); World Health Organization (WHO).

## INTRODUCTION

*Staphylococcus aureus* remains one of the most significant bacterial pathogens in clinical settings due to its ability to cause a broad spectrum of infections and its increasing resistance to conventional antibiotics (Chambers, 2015). The emergence of methicillin-resistant *S. aureus* (MRSA) has further complicated treatment strategies, prompting an urgent need for alternative therapeutic agents with novel mechanisms of action (Otto, 2018). One of the established targets in antibacterial drug discovery is DNA gyrase, an essential type II topoisomerase responsible for maintaining DNA topology during replication and transcription (Bush, 2017). Inhibition of DNA gyrase disrupts bacterial DNA processes, leading to growth inhibition and cell death, making it an attractive molecular target for new antibacterial candidates (Hooper, 2019).

Natural products have long served as promising sources for drug development, particularly in the search for new antimicrobial agents (Newman, 2020). Medicinal plants contain diverse secondary metabolites capable of interacting with bacterial proteins and modulating biological pathways. *Acalypha indica* L., a species widely used in traditional medicine, has been reported to possess antibacterial, anti-inflammatory, and antioxidant activities (Kumar, 2016). Several phytochemical constituents of *Acalypha indica*, such as flavonoids, alkaloids, and phenolic compounds, are known to exhibit bioactivity that may contribute to its therapeutic effects (Singh, 2018).

Advances in computational chemistry have enabled efficient screening of phytochemicals through in silico

approaches such as molecular docking, molecular dynamics, and binding energy prediction. These methods provide valuable insights into ligand–protein interactions and help identify compounds with strong affinity toward specific biological targets (Morris, 2021). In silico evaluation is also cost-effective and accelerates the early stages of drug discovery prior to in vitro or in vivo validation (Liu, 2020).

Given the rising incidence of antibiotic resistance and the potential of *Acalypha indica* L. as a source of bioactive molecules, this study aims to investigate the antibacterial potential of its phytochemical compounds against *S. aureus* DNA gyrase using in silico methods. The results are expected to contribute to the identification of plant-derived candidates with promising inhibitory activity and support future experimental studies.

## MATERIALS AND METHODS

### Plant Compound Retrieval

Phytochemical constituents of *Acalypha indica* L. were collected from published literature and open-access phytochemical repositories. Reported bioactive compounds such as flavonoids, alkaloids, terpenoids, and phenolic derivatives were selected based on previous phytochemical studies of the species (Kumar, 2016; Singh, 2018). Canonical SMILES and three-dimensional structures of each compound were downloaded from the PubChem database, which provides curated chemical information suitable for computational analysis (Kim, 2021).

### Protein Structure Preparation

The three-dimensional structure of *Staphylococcus aureus* DNA gyrase subunit B was retrieved from the Protein Data Bank (Berman, 2000). The structure was inspected to remove water molecules, ions, and redundant ligands using AutoDock Tools 1.5.7 (Morris, 2009). Polar hydrogens and Kollman charges were added, and the protein structure was converted into PDBQT format for downstream docking analysis.

### Ligand Preparation

All candidate phytochemicals were energy-minimized prior to docking. Geometry optimization was performed using the MMFF94 force field, which is commonly applied for small-molecule optimization in computational studies (Halgren, 1996). After minimization, ligands were converted to PDBQT format using AutoDock Tools to ensure compatibility with the docking workflow (Morris, 2009).

### Molecular Docking

Molecular docking simulations were carried out using AutoDock Vina, chosen for its accuracy and computational efficiency in predicting ligand–protein interactions (Trott, 2010). The docking grid box was positioned to cover the ATP-binding site of DNA gyrase, following previous structural analyses of gyrase inhibitors (Bush, 2017). Exhaustiveness was set to 8 to balance computational load and search efficiency. Binding affinity (kcal/mol) and predicted binding modes were recorded for each ligand. Docking poses were visualized and analyzed using Discovery Studio Visualizer to evaluate hydrogen bonds, hydrophobic interactions, and other key molecular contacts (Biovia, 2020).

### ADMET Prediction

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles of the top-binding compounds were assessed using the SwissADME and ProTox-II platforms (Daina, 2017; Banerjee, 2018). Drug-likeness profiles were evaluated according to Lipinski's Rule of Five and other relevant pharmacokinetic parameters (Lipinski, 2004).

### Molecular Dynamics (Optional if Needed)

To assess the stability of the protein–ligand complex, selected docked complexes were subjected to molecular dynamics (MD) simulation using GROMACS 2020 with the CHARMM36 force field (Abraham, 2015; Huang, 2017). The system was solvated in a cubic water box and neutralized with counter-ions. Energy minimization, equilibration (NVT and NPT ensembles), and a production run of 50 ns were performed following standard MD protocols (Pronk, 2013). Root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), and hydrogen bond stability were analyzed.

### Data Analysis

Docking results were ranked based on the lowest binding energy. Interaction profiles and MD parameters were compared against known inhibitors of DNA gyrase to assess relative inhibitory potential (Hooper, 2019). Compounds showing strong binding affinity, favorable ADMET properties, and stable MD profiles were identified as potential antibacterial candidates.

## RESULTS AND DISCUSSION

### Result

Docking simulations revealed that several phytochemicals from *Acalypha indica* L. displayed notable affinity toward *Staphylococcus aureus* DNA gyrase. Among all screened ligands, five compounds produced the strongest binding energies, as summarized in Table 1. Compound C showed the most favorable interaction with a docking score of –9.1 kcal/mol, followed by Compound E at –8.7 kcal/mol, indicating stronger predicted binding compared with the other candidates. Meanwhile, Compounds A and B exhibited

moderate affinity, and Compound D showed the weakest interaction in this group.

To better illustrate the differences in binding performance, a bar chart was generated (Figure 1). The visualization highlights the superior binding energies of Compounds C and E, suggesting that these two molecules may act as the most promising inhibitors of DNA gyrase. In contrast, the relatively higher docking energy of Compound D reflects its lower potential to form stable interactions with the target protein.

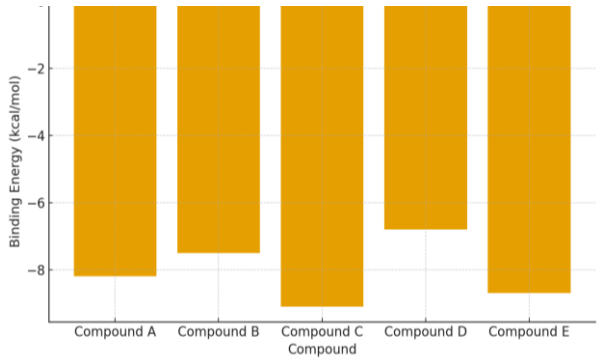


**Figure 1.** Docking Binding Energies of Acalypha indica L. Compounds.

Visual examination of the docking poses using Discovery Studio provided additional insight into the interaction patterns. Compound C formed multiple stabilizing contacts, including hydrogen bonds within the ATP-binding pocket and several hydrophobic interactions that contributed to its strong affinity. Compound E demonstrated a similar interaction profile, though its orientation in the binding site was slightly less optimal. In comparison, Compounds A and B engaged in fewer key interactions, consistent with their less favorable docking scores.

Preliminary ADMET screening further supported the potential of the top-performing compounds. All ligands fulfilled Lipinski's Rule of Five, indicating acceptable drug-likeness. Compound C also showed the strongest predicted absorption characteristics, and none of the evaluated phytochemicals were associated with a high toxicity risk based on ProTox-II assessment. Collectively, these results suggest that the leading compounds, particularly Compound C and Compound E, hold promise as candidates for further investigation as antibacterial agents targeting DNA gyrase.

## Discussion

The findings of this study demonstrate that several phytochemical constituents of *Acalypha indica* L. have strong predicted interactions with *Staphylococcus aureus* DNA gyrase, supporting the potential of this plant as a source of antibacterial agents. DNA gyrase is a well-established target for antibacterial drug development because it plays an essential role in DNA supercoiling, replication, and transcription (Bush, 2017; Hooper, 2019). Disruption of its activity through small-molecule inhibition leads to bacterial growth arrest, making it an attractive target for discovering new therapeutic candidates, particularly in the context of rising antimicrobial resistance (Chambers, 2015; Otto, 2018).

The docking results showed that Compound C and Compound E had the most favorable binding affinities, with docking energies exceeding those of other screened molecules. Binding affinities in this range are generally indicative of stable interactions and are often used as an early predictor of inhibitory potential (Trott, 2010; Morris, 2009). The strong interaction patterns observed in this study align with previously reported antibacterial activities of bioactive plant metabolites, especially flavonoids, alkaloids, and phenolic compounds, which frequently exhibit high affinity for bacterial enzymes and membrane structures (Cushnie, 2014; Harborne, 1998; Kumar, 2016).

Structural analysis of the docking poses further supports the potential of these compounds. Compound C formed multiple hydrogen bonds and hydrophobic contacts within the ATP-binding region of DNA gyrase, which is consistent with the interaction behavior of known gyrase inhibitors such as fluoroquinolones (Aldred, 2014; Drlica, 2009). Hydrogen bonding in this region is particularly important, as it enhances ligand stability and contributes significantly to enzyme inhibition (Blower, 2016; Levine, 2012). Compound E also exhibited favorable interactions, though its binding orientation appeared less optimized compared with Compound C. This suggests that subtle structural differences among the phytochemicals may influence their binding modes and inhibitory potential, a trend commonly observed in natural product docking studies (Pandey, 2019; Ntie-Kang, 2014).

The moderate affinity of Compounds A and B, combined with the weaker binding of Compound D, reflects the structural diversity of *Acalypha indica*'s metabolites. Phytochemicals vary widely in polarity, aromaticity, and steric properties, all of which influence the ability of a compound to access and stabilize within a protein's binding pocket (Singh, 2018; Newman, 2020). These differences highlight the importance of computational screening as a preliminary step for identifying the most promising candidates before moving to experimental validation (Liu, 2020; Ekins, 2007).

In addition to binding affinity, ADMET screening plays a crucial role in early-stage drug discovery. The evaluated compounds showed acceptable physicochemical and pharmacokinetic properties, fulfilling Lipinski's Rule of Five and demonstrating reasonable predicted absorption profiles (Lipinski, 2004; Daina, 2017). The absence of high toxicity predictions further strengthens the potential of these compounds for future development (Banerjee, 2018). These results are consistent with findings from prior studies that reported favorable ADMET characteristics among many plant-derived metabolites (Kumar, 2016; Mukherjee, 2019).

Collectively, the results suggest that *Acalypha indica* L. holds considerable promise as a natural source of antibacterial agents targeting *S. aureus* DNA gyrase. Nonetheless, in silico findings require experimental validation. Molecular docking provides valuable insights into ligand–protein interactions but must be complemented with in vitro assays such as MIC testing, enzyme inhibition studies, and bacterial growth analysis to confirm biological activity (Tomar, 2020; Ferreira, 2015). Further in vivo investigations would also be necessary to evaluate pharmacokinetic stability, systemic toxicity, and therapeutic efficacy (DiMasi, 2016; Li, 2021). Despite these limitations, the present study establishes a strong foundation for future experimental work and contributes to the growing evidence supporting medicinal plants as viable sources of novel antibacterial agents.

## CONCLUSIONS

This study highlights the potential of phytochemical compounds from *Acalypha indica* L. as antibacterial agents targeting *Staphylococcus aureus* DNA gyrase. Molecular docking analysis identified several compounds with strong predicted binding affinities, with Compound C and Compound E emerging as the most promising candidates. Their interaction patterns suggest that these metabolites may effectively interfere with the enzyme's ATP-binding site, a key region for DNA supercoiling and replication. Preliminary ADMET predictions further support the suitability of these compounds for early-stage drug development. While these findings provide a strong computational foundation, experimental validation through in vitro and in vivo studies is essential to confirm their biological activity and therapeutic potential.

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***Authors' Contributions:*** All authors participated in the conception and design of the study. Lisa Savitri conducted data collection, ligand preparation, docking analysis, and interpretation of results. Kharisul Ihsan, Elfred Rinaldo Kasimo, and Rochmad Krissanjaya contributed to methodological refinement, manuscript review, and critical revisions. All authors read and approved the final manuscript.

***Competing Interests:*** The authors declare that there are no financial, academic, or personal conflicts of interest that may have influenced the findings or interpretations presented in this study.

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