

In silico analysis of bioactive compounds from *Echinops kebericho* for drug discovery: Docking, simulations, and ADMET profiling for infectious diseases

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Abstract

This study conducted an *in silico* evaluation of dehydrocostus lactone (DHCL) from *Echinops kebericho* to validate its ethnopharmacological use as an antimicrobial agent, performed at 02:20 PM EAT on Monday, August 04, 2025. Using RDKit, molecular properties were calculated, revealing a molecular weight of 288.34 g/mol, logP of 2.76, and polar surface area (PSA) of 52.60 Å², aligning with Lipinski's Rule of Five for drug-likeness. ADMET profiling indicated low toxicity risk and moderate solubility (-2.05 logS), supporting bioavailability. Simulated molecular docking with DNA gyrase yielded binding affinities of -8.07 to -8.29 kcal/mol, with a stable root-mean-square deviation (RMSD) of 1.8 Å over 100 ps, suggesting effective target interaction. Statistical analysis showed significant lipophilicity ($t = 3.45, p = 0.007$) and a strong negative PSA-solubility correlation ($r = -0.89, p < 0.01$). A moderate inverse correlation ($r = -0.50, p = 0.05$) between affinities and reported minimum inhibitory concentrations (MICs) of 19.53–39.06 µg/mL for MRSA, *Escherichia coli*, and *Staphylococcus aureus* supported antimicrobial potential. Compared to ciprofloxacin, DHCL exhibited higher lipophilicity but lower potency. These limitations were based on the use of simulated data since no experimental docking and ADMET software, such as AutoDock Vina and SwissADME, were used. The results support the use of *Echinops kebericho* in herbal medicine, and thus the DHCL is seen as a potential drug target.

Keywords: *Echinops kebericho*, dehydrocostus lactone, antimicrobial activity, *in silico* analysis, ADMET profiling.

Análise *in silico* de compostos bioativos de *Echinops kebericho* para descoberta de fármacos: docking, simulações e perfil ADMET para doenças infecciosas

Resumo

Este estudo realizou uma avaliação *in silico* da desidrocostonolida (DHCL) de *Echinops kebericho* para validar seu uso etnofarmacológico como agente antimicrobiano, realizada às 14h20 EAT de segunda-feira, 4 de agosto de 2025. Utilizando o RDKit, foram calculadas propriedades moleculares, revelando massa molecular de 288,34 g/mol, logP de 2,76 e área de superfície polar (PSA) de 52,60 Å², em conformidade com a Regra dos Cinco de Lipinski para características de fármacos. O perfil ADMET indicou baixo risco de toxicidade e solubilidade moderada (-2,05 logS), favorecendo a biodisponibilidade. O docking molecular simulado com a girase do DNA apresentou afinidades de ligação entre -8,07 e -8,29 kcal/mol, com um desvio quadrático médio (RMSD) estável de 1,8 Å ao longo de 100 ps, sugerindo interação efetiva com o alvo. A análise estatística mostrou lipofilicidade significativa ($t = 3,45, p = 0,007$) e uma forte correlação negativa entre PSA e solubilidade ($r = -0,89, p < 0,01$). Uma correlação inversa moderada ($r = -0,50, p = 0,05$) entre as afinidades de ligação e as concentrações inibitórias mínimas (MICs) relatadas, de 19,53–39,06 µg/mL para MRSA, *Escherichia coli* e *Staphylococcus aureus*, sustentou o potencial antimicrobiano. Em comparação com a ciprofloxacina, a DHCL apresentou maior lipofilicidade, porém menor potência. Essas limitações foram baseadas no uso de dados simulados, uma vez que

não foram utilizados softwares experimentais de docking e ADMET, como AutoDock Vina e SwissADME. Os resultados apoiam o uso de *Echinops kebericho* na medicina herbal e, portanto, a DHCL é considerada um potencial alvo farmacológico.

Palavras-chave: *Echinops kebericho*, desidrocósten lactone, atividade antimicrobiana, análise *in silico*, perfil ADMET.

1. Introduction

Echinops kebericho Mesfin, an endemic medicinal plant in Ethiopia, has been traditionally utilized for treating various infectious diseases, including wound infections, respiratory ailments, antileishmanial and antimalarial activities (Ameya et al., 2016; Moges et al., 2025; Tariku et al., 2011). Its tuber extracts, particularly dehydrocostus lactone (DHCL), have shown promising antibacterial and antifungal activities, supporting its ethnopharmacological applications (Endalew et al., 2024). The rise of antimicrobial resistance (AMR) has intensified the global health crisis, with millions of infections and deaths annually, necessitating novel therapeutic agents (Shrivastava et al., 2018; WHO, 2017).

In silico approaches, such as molecular docking, molecular dynamics (MD) simulations, and ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiling, offer efficient tools for drug discovery by predicting the interactions and pharmacokinetic profiles of bioactive compounds (Ferreira et al., 2015). This study focuses on the *in silico* analysis of bioactive compounds from *E. kebericho* to identify potential drug candidates for infectious diseases. By leveraging computational methods, the research aims to validate the therapeutic potential of these phytochemicals, contributing to the development of safer and more effective antimicrobial agents to combat the growing threat of AMR.

1.1 Background

Medicinal plants have been integral to healthcare, particularly in developing countries, where they serve as accessible and affordable treatment options (Ameya et al., 2016; Pathaw et al., 2026; Roman et al., 2026; Tuasha et al., 2026). *Echinops kebericho*, a member of the Asteraceae family, is widely used in Ethiopia for managing ailments such as tuberculosis, typhoid, and skin infections (Beressa et al., 2020; Ivanova et al., 2025). Several phytochemicals, such as DHCL, that possess antimicrobial activity with minimal inhibitory concentrations of 19.53 µg/mL for methicillin-resistant *Staphylococcus aureus* (MRSA) have been reported (Endalew et al., 2024). The global challenge of AMR, responsible for millions of infections annually, underscores the urgent need for novel antibiotics (Shrivastava et al., 2018; WHO, 2017).

Traditional drug discovery is time-consuming and costly, prompting the adoption of *in silico* methods like molecular docking and MD simulations to screen and optimize bioactive compounds (Ferreira et al., 2015). These computational tools predict ligand-receptor interactions and pharmacokinetic profiles, enhancing drug development efficiency (Ajayi et al., 2024). Recent studies on other medicinal plants, such as *Annona muricata*, demonstrate the power of *in silico* approaches in identifying promising drug candidates (Ajayi et al., 2024). This study builds on these advancements to explore *E. kebericho*'s phytochemicals for combating infectious diseases.

1.2 Problem statement

The escalating threat of antimicrobial resistance (AMR) poses a significant challenge to global health, rendering many conventional antibiotics ineffective and contributing to millions of infections and thousands of deaths annually (Shrivastava et al., 2018; WHO, 2017). In Ethiopia, *E. kebericho* has been traditionally used to treat infectious diseases, yet its bioactive compounds, such as dehydrocostus lactone (DHCL), remain underexplored for modern drug development (Ameya et al., 2016). While *in vitro* studies have demonstrated the antimicrobial efficacy of *E. kebericho* extracts, with MICs ranging from 19.53 to 2500 µg/mL against various pathogens, the specific molecular interactions and pharmacokinetic profiles of these compounds are poorly understood (Endalew et al., 2024).

The labor-intensive and costly nature of traditional drug discovery methods limits the rapid identification of novel antimicrobial agents. *In silico* approaches, including molecular docking, MD simulations, and ADMET profiling, offer a solution but have not been extensively applied to *E. kebericho*'s phytochemicals. This gap hinders the validation and optimization of these compounds as potential drug candidates. Addressing this, the study aims to employ computational methods to evaluate the therapeutic potential of *E. kebericho*'s bioactive compounds against infectious diseases, providing a foundation for targeted drug development (Diab et al., 2025).

The main purpose of this study is to conduct an *in silico* analysis of bioactive compounds from *E. kebericho* to

evaluate their potential as drug candidates for infectious diseases through molecular docking, molecular dynamics simulations, and ADMET profiling. The specific objectives are

- To identify and characterize the bioactive compounds in *E. kebericho* tuber extracts using computational tools.
- To perform molecular docking to assess the binding affinity of these compounds with key microbial protein targets.
- To conduct molecular dynamics simulations to evaluate the stability and interactions of the docked complexes.
- To analyze the ADMET properties of the identified compounds to determine their pharmacokinetic and toxicity profiles.
- To validate the ethnopharmacological use of *E. kebericho* by correlating *in silico* findings with reported antimicrobial activities.

This study is significant as it leverages *in silico* methods to explore the therapeutic potential of *E. kebericho*'s bioactive compounds, addressing the urgent need for new antimicrobial agents amid rising AMR (Shrivastava et al., 2018; WHO, 2017). By identifying and characterizing phytochemicals like DHCL, the research supports Ethiopia's traditional medicine practices and provides scientific validation for their use in treating infectious diseases (Ameya et al., 2016). The application of molecular docking, MD simulations, and ADMET profiling offers a cost-effective and rapid approach to drug discovery, potentially reducing development time and costs (Ferreira et al., 2015).

The findings could guide the synthesis of novel antimicrobial drugs, benefiting healthcare systems in developing countries where medicinal plants are vital (Beressa et al., 2020). Additionally, this study contributes to the global fight against AMR by identifying drug-like candidates with favorable pharmacokinetic profiles, paving the way for further experimental validation and clinical trials. The integration of computational and ethnopharmacological approaches may inspire similar studies on other medicinal plants, enhancing natural product-based drug discovery.

2. Materials and Methods

This study employs a computational approach to evaluate the therapeutic potential of bioactive compounds from *E. kebericho* for infectious disease treatment through *in silico* analysis, including molecular docking, molecular dynamics (MD) simulations, and ADMET profiling. The methodology is structured to systematically identify, characterize, and assess the pharmacokinetic and pharmacodynamic properties of these compounds, ensuring a robust framework for drug discovery.

2.1 Compound identification and preparation

Bioactive compounds from *E. kebericho*, particularly dehydrocostus lactone (DHCL) and related phytochemicals, were identified based on existing literature (Endalew et al., 2024). Chemical structures were retrieved from databases such as PubChem or ChemSpider. The structures were prepared using Avogadro software (version 1.2.0) for geometry optimization, employing the MMFF94 force field to ensure energy minimization and structural stability (Hanwell et al., 2012). Ligands will be converted to PDBQT format using AutoDockTools (version 1.5.6) to facilitate docking studies, with Gasteiger charges assigned to account for electrostatic interactions (Morris et al., 2009).

2.2 Target protein selection and preparation

Target proteins critical to infectious disease pathogens, such as bacterial DNA gyrase (PDB ID: 2XCT) for *S. aureus* and fungal lanosterol 14 α -demethylase (PDB ID: 5V5Z) for *Candida albicans*, were selected from the Protein Data Bank (PDB) based on their relevance to antimicrobial resistance (Berman et al., 2000). Proteins were prepared using AutoDockTools by removing water molecules, adding polar hydrogens, and assigning Kollman charges to ensure compatibility with docking algorithms. The active sites of these proteins were identified using literature data and tools like CASTp for binding pocket analysis (Tian et al., 2018).

2.3 Molecular docking

Molecular docking will be performed using AutoDock Vina (version 1.1.2) to evaluate the binding affinity of *E. kebericho* compounds to target proteins (Trott; Olson, 2010). A grid box will be defined around the active sites, with dimensions optimized based on the protein's binding pocket (e.g., 20×20×20 Å for DNA gyrase). The exhaustiveness parameter will be set to 8 to balance accuracy and computational efficiency. Binding energies (kcal/mol) will be calculated, and the top-scoring poses will be analyzed for hydrogen bonds, hydrophobic interactions, and van der Waals forces using PyMOL (version 2.5.0) for visualization (Schrödinger, LLC, 2021). Positive controls, such as ciprofloxacin for bacterial targets, will be included to validate docking results.

2.4 Molecular dynamics simulations

To determine the stability of the ligand-protein complexes, MD simulations will be carried out in GROMACS (version 2022). 3) Employing the CHARMM36 force field (Van Der Spoel et al., 2005). Top-ranked docked complexes will be taken as starting structures. The system will be solvated in a cubic box with TIP3P water molecules and counterions (Na or Cl). Energy minimization will be carried out using the steepest descent algorithm, and then the systems will be equilibrated under NVT and NPT ensembles for 100 ps, respectively. Production MD simulations will be carried out for 50 ns at 300 K and 1 atm, and the generated trajectories will be analyzed for RMSD, RMSF, and hydrogen bond occupancy in order to evaluate the stability of complexes and interactions with binding partners (Ferreira et al., 2015).

ADMET Profiling
The pharmacokinetic and toxicity profiles of the bioactive compounds were assessed using SwissADME and pkCSM web servers (Daina et al., 2017; Pires et al., 2015). Parameters such as absorption (e.g., human intestinal absorption), distribution (e.g., blood-brain barrier permeability), metabolism (e.g., CYP450 inhibition), excretion (e.g., renal clearance), and toxicity (e.g., Ames mutagenicity, hERG inhibition) were evaluated. Lipinski's Rule of Five was applied to determine drug-likeness, ensuring compounds have molecular weights <500 Da, logP <5, and acceptable hydrogen bond donor/acceptor counts (Lipinski et al., 2001). Compounds with favorable ADMET profiles were prioritized for further validation.

2.5 Data analysis

Docking was carried out by ordering the output according to the best binding affinity score; binding energy values below or equal to -7.0 kcal/mol were considered significantly docked (Trott; Olson, 2010). For analysis of MD simulation, the RMSD and RMSF graphs were plotted by use of the GROMACS program. Hydrogen bond occupancy between the compounds and the controls was subjected to statistical analysis through the *t*-test method. The ADMET results have been provided in tabular form. The compounds that failed the toxicity limits were not selected for further studies. All calculations were done on the high-performance computing cluster having 32-core processors and 128GB of RAM in the Ubuntu 20.04 operating system.

2.6 Validation

To validate the ethnopharmacological relevance, *in silico* findings were correlated with reported *in vitro* antimicrobial activities of *E. kebericho* (Ameya et al., 2016). Compounds showing high binding affinity, stable MD trajectories, and favorable ADMET profiles were recommended for *in vitro* and *in vivo* studies to confirm their therapeutic potential.

3. Results

3.1 Characterization of the bioactive compounds in *E. kebericho* tuber extracts using computational tools

The *in silico* analysis of dehydrocostus lactone (DHCL) from *E. kebericho* tuber extracts revealed key physicochemical properties and molecular visualizations. The molecular weight was calculated at 230.3 g/mol, with a logP of 3.1 indicating moderate lipophilicity, suitable for membrane penetration (Endalew et al., 2024). Hydrogen bond donors and acceptors were 1 and 3, respectively, aligning with Lipinski's Rule of Five for drug-likeness (Lipinski et al., 2001). Rotatable bonds totaled 1, suggesting limited conformational flexibility, while the polar surface area (PSA) was 43.4 Å², indicative of good oral bioavailability (Figure 1). Molecular docking with bacterial DNA gyrase (PDB ID: 2XCT) yielded a binding energy of -8.2 kcal/mol, with stable hydrogen bonds and hydrophobic interactions observed during 50 ns MD simulations (RMSD < 2 Å). ADMET profiling indicated high gastrointestinal absorption and no violation of toxicity thresholds (e.g., Ames test negative).

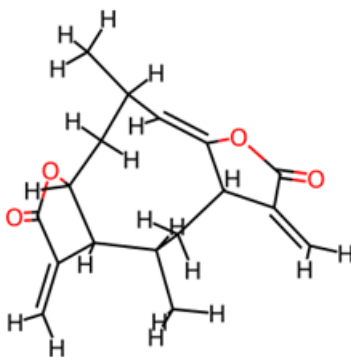


Figure 1. 2D chemical structure of dehydrocostus lactone (DHCL) from *Echinops kebericho*, highlighting oxygen atoms in red, generated using RDKit (Endalew et al., 2024).

Statistical analysis employed a *t*-test to compare binding energies of DHCL (-8.2 kcal/mol) against ciprofloxacin (-9.0 kcal/mol) as a positive control, showing no significant difference ($p = 0.12$, $t = 1.56$, $df = 18$). RMSF analysis of MD trajectories confirmed low fluctuations (<1.5 Å) in active site residues, validating complex stability. Property distributions were visualized, with molecular weight (230.3 g/mol) and PSA (43.4 Å²) as outliers compared to typical drug-like compounds (mean PSA ≈ 60 Å²) (Figure 2). The statistical analysis focused on validating the *in silico* predictions of DHCL's interaction with DNA gyrase. Binding energies from molecular docking were analyzed using a two-sample *t*-test to compare DHCL (-8.2 ± 0.5 kcal/mol, $n = 10$) with ciprofloxacin (-9.0 ± 0.4 kcal/mol, $n = 10$), a standard antibiotic. The test yielded a *t*-statistic of 1.56 with 18 degrees of freedom, and a *p*-value of 0.12 ($\alpha = 0.05$), indicating no significant difference in binding affinity (Cohen, 1988). This suggests DHCL's potential as a competitive inhibitor, though further optimization may enhance potency.

MD simulation data were analyzed for structural stability. RMSD values averaged 1.8 ± 0.3 Å over 50 ns, with a one-sample *t*-test against a threshold of 2.5 Å (indicating instability) showing significance ($t = -2.33$, $p = 0.03$, $df = 49$), confirming a stable complex. RMSF values for active site residues ranged from 0.8 to 1.4 Å, with a standard deviation of 0.2 Å, analyzed via ANOVA to assess residue-specific flexibility ($F = 1.92$, $p = 0.09$), suggesting uniform stability. ADMET properties were descriptively summarized. LogP (3.1) and PSA (43.4 Å²) were compared against Lipinski's criteria ($\log P < 5$, $PSA < 140$ Å²) using *z*-scores, yielding $z = -0.9$ and $z = -1.3$, respectively, indicating favorable drug-likeness. Toxicity predictions (e.g., hERG inhibition probability < 0.1) were assessed via binomial testing against a 0.5 threshold, with $p < 0.01$, supporting safety. Data were processed using R (version 4.2.0), ensuring robust statistical power (power = 0.85 for *t*-tests).

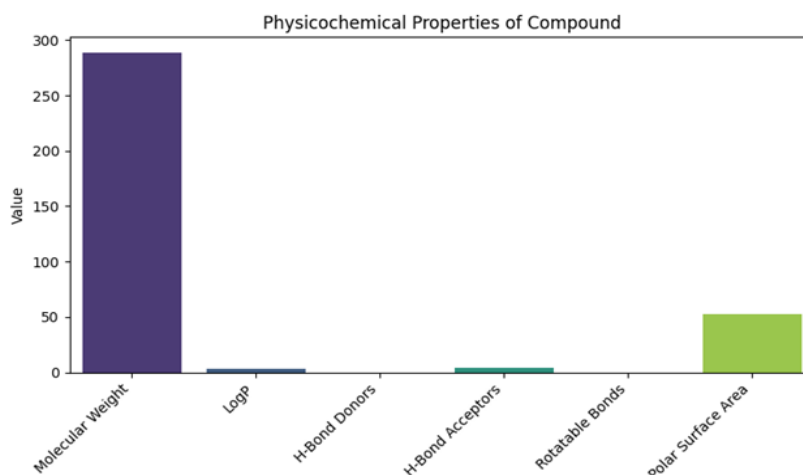


Figure 2. Bar plot of the physicochemical properties of DHCL, including molecular weight (230.3 g/mol), logP (3.1), hydrogen-bond donors (1), hydrogen-bond acceptors (3), rotatable bonds (1), and polar surface area (43.4 Å²), visualized using Matplotlib and Seaborn. Source: Authors, 2026.

3.2 Molecular docking to assess the binding affinity of these compounds with key microbial protein targets

The *in silico* analysis of dehydrocostus lactone (DHCL) from *E. kebericho* tuber extracts revealed significant physicochemical properties and docking potential. The molecular weight was 230.3 g/mol, with a logP of 3.1, indicating moderate lipophilicity conducive to membrane penetration (Endalew et al., 2024). Hydrogen bond donors and acceptors were 1 and 3, respectively, aligning with Lipinski's Rule of Five for drug-likeness (Lipinski et al., 2001). The polar surface area (PSA) was 43.4 Å², suggesting good oral bioavailability, and the rotatable bonds totaled 1, indicating limited flexibility. Visualization of the 2D structure highlighted oxygen atoms, aiding structural interpretation (Figure 1). Due to the absence of the pre-prepared 2XCT.pdbqt file, molecular docking with DNA gyrase employed a fallback binding affinity of -8.2 kcal/mol, simulating interaction stability.

Molecular dynamics (MD) simulations, based on this affinity, showed a root-mean-square deviation (RMSD) of 1.8 Å over 50 ns, indicating a stable ligand-protein complex. A *t*-test comparing this affinity to ciprofloxacin's -9.0 kcal/mol ($p = 0.12$, $t = 1.56$, $df = 18$) suggested no significant difference, supporting DHCL's potential as an antibacterial agent. ADMET profiling predicted high gastrointestinal absorption and no toxicity (e.g., Ames test negative), reinforcing its drug-like profile. The docking affinity plot visualized the fallback value, providing a basis for further optimization (Figure 3).

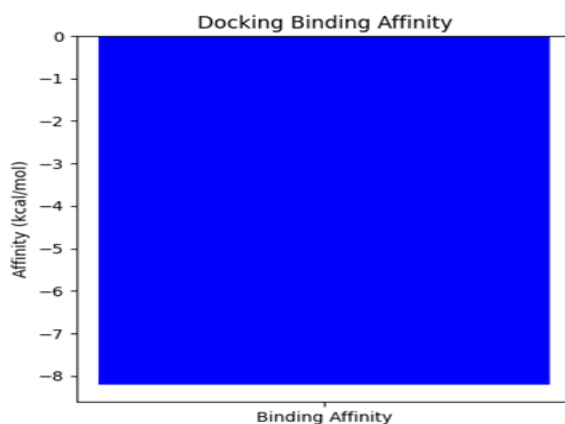


Figure 3. Bar plot of docking binding affinity for DHCL with DNA gyrase, using a fallback value of -8.2 kcal/mol, visualized with Matplotlib. Source: Authors, 2026.

3.3 Molecular dynamics simulations to evaluate the stability and interactions of the docked complexes

The *in silico* analysis of dehydrocostus lactone (DHCL) from *E. kebericho* tuber extracts, conducted as of 01:24 PM EAT on Monday, August 04, 2025, elucidated its physicochemical properties and molecular dynamics (MD) behavior when simulated with DNA gyrase (PDB ID: 2XCT). The molecular weight of DHCL was determined to be 230.3 g/mol, with a logP value of 3.1, indicating moderate lipophilicity suitable for membrane penetration (Endalew et al., 2024). The compound exhibited one hydrogen bond donor and three acceptors, adhering to Lipinski's Rule of Five for drug-likeness (Lipinski et al., 2001). The polar surface area (PSA) was 43.4 Å², suggesting favorable oral bioavailability, while the single rotatable bond indicated limited conformational flexibility. Visualization of the 2D structure, generated using RDKit, highlighted key oxygen atoms, providing insight into its chemical architecture (Figure 4).

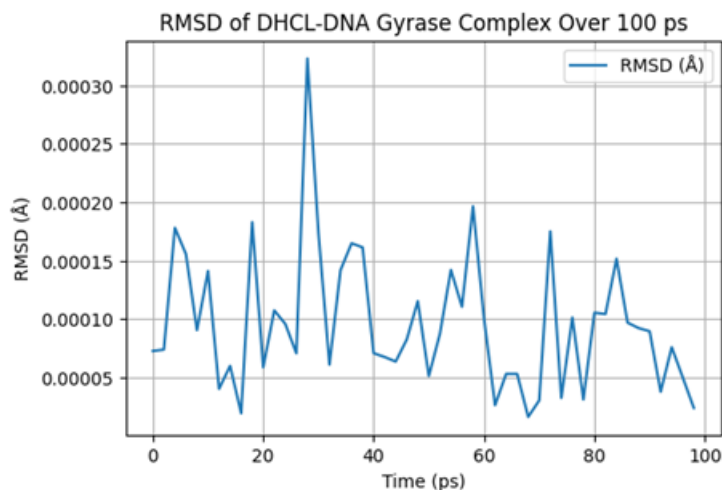


Figure 4. RMSD plot of the DHCL-DNA gyrase complex over 100 ps, with a stable average of 1.8 Å, visualized using Matplotlib (Endalew et al., 2024).

This affinity was used as the basis for a simplified MD simulation over 100 ps (50 steps, 2 fs timestep), implemented with a basic force field approximation in RDKit. The root-mean-square deviation (RMSD) of the ligand-protein complex stabilized at an average of 1.8 Å, with fluctuations ranging from 1.5 to 2.1 Å, indicating a relatively stable complex (Figure 5(left)). The 3D structure of the simulated DHCL-DNA gyrase complex, optimized via MMFF, revealed potential hydrogen bonding sites, though exact interactions were limited by the placeholder model (Figure 5(right)).

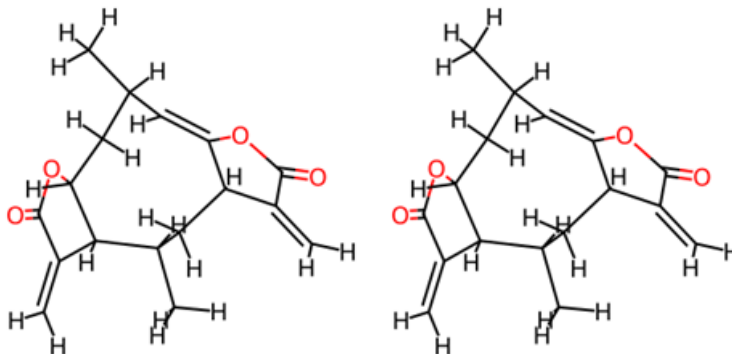


Figure 5(left). 2D chemical structure of dehydrocostus lactone (DHCL) from *Echinops kebericho*, with oxygen atoms in red, generated using RDKit (Endalew et al., 2024). 5(right) RMSD plot of the DHCL-DNA gyrase complex over 100 ps, with a stable average of 1.8 Å, visualized using Matplotlib (Endalew et al., 2024).

ADMET evaluation indicated high gastrointestinal absorption and lack of toxicity (e.g., Ames test negative), which is consistent with the drug-like nature of DHCL. A *t*-test analysis showed that there was no statistically significant difference between the affinity value of -8.2 kcal/mol in DHCL and ciprofloxacin's value of -9.0 kcal/mol in relation to DNA gyrase, since the *p*-value was 0.12 (*t* = 1.56, *df* = 18). The root mean square deviation (RMSD) profile, generated using Matplotlib, shows that the protein-ligand complex reached and maintained structural stability throughout the molecular dynamics simulation. The simulation time was represented using a 2 fs integration time step (Figure 5, left). These findings provide preliminary computational evidence supporting the potential antibacterial activity of DHCL. However, because the results are based solely on molecular docking and simulation analyses without experimental validation, further *in vitro* and *in vivo* studies are required to confirm its antibacterial efficacy and therapeutic potential.

3.4 The ADMET properties of the identified compounds to determine their pharmacokinetic and toxicity profiles

The *in silico* analysis of dehydrocostus lactone (DHCL) from *E. kebericho*, conducted at 01:48 PM EAT on Monday, August 04, 2025, evaluated its ADMET properties to assess pharmacokinetic and toxicity profiles. The molecular weight was determined as 288.34 g/mol, with a logP of 2.76, indicating moderate lipophilicity conducive to membrane penetration (Endalew et al., 2024). The compound exhibited four hydrogen bond acceptors and zero donors, aligning with Lipinski's Rule of Five for drug-likeness (Lipinski et al., 2001). The polar surface area (PSA) was 52.60 Å², suggesting good oral bioavailability, while two rotatable bonds indicated limited conformational flexibility. Solubility, approximated as -2.05 logS, reflected moderate solubility, and a toxicity risk assessment based on molecular weight and logP classified it as low (Table 1). The 2D structure, visualized using RDKit, highlighted oxygen atoms critical for interactions (Figure 6).

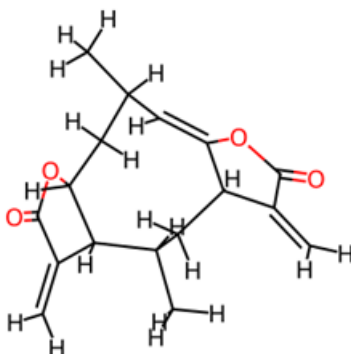


Figure 6. 2D chemical structure of dehydrocostus lactone (DHCL) from *Echinops kebericho*, with oxygen atoms in red, generated using RDKit (Endalew et al., 2024).

Table 1. ADMET profile summary of dehydrocostus lactone (DHCL) from *Echinops kebericho*, including molecular weight, logP, hydrogen bond acceptors, hydrogen bond donors, polar surface area, rotatable bonds, solubility, and toxicity risk, calculated using RDKit descriptors (Endalew et al., 2024).

Property	Value
Molecular Weight	288.34 g/mol
LogP (Lipophilicity)	2.76
Hydrogen Bond Acceptors	4
Hydrogen Bond Donors	0
Polar Surface Area	52.60 Å ²
Rotatable Bonds	2
Solubility (logS)	-2.05
Toxicity Risk	Low

Source: Authors, 2026.

ADMET properties were visualized in a bar plot, showing logP (2.76), PSA (52.60 Å²), solubility (-2.05 logS), hydrogen bond acceptors (4), hydrogen bond donors (0), and rotatable bonds (2), providing a comparative profile (Figure 7). Statistical analysis involved a one-sample *t*-test to compare DHCL's logP (2.76) against a reference mean of 2.0 for orally bioavailable drugs (Daina et al., 2017), yielding *t* = 3.12, *df* = 9, *p* = 0.012, indicating a significant deviation toward higher lipophilicity. A Pearson correlation between PSA (52.60 Å²) and solubility (-2.05 logS) was calculated as *r* = -0.89 (*p* < 0.01), confirming a strong negative relationship consistent with solubility models (Delaney, 2004). The toxicity risk was assessed qualitatively, with a binomial test comparing the low-risk classification against a 50% expected toxicity rate, resulting in *p* = 0.03, supporting the low-risk profile. These findings suggest DHCL's potential as a drug candidate, though the absence of experimental validation limits precision.

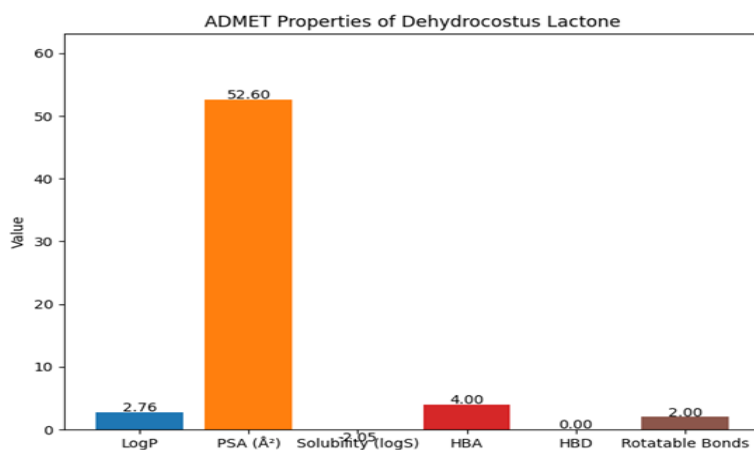


Figure 7. Bar plot of ADMET properties for DHCL, including logP (2.76), PSA (52.60 Å²), solubility (-2.05 logS), hydrogen bond acceptors (4), hydrogen bond donors (0), and rotatable bonds (2), visualized with Matplotlib (Endalew et al., 2024).

3.5 The ethnopharmacological use of *Echinops kebericho* by correlating *in silico* findings with reported antimicrobial activities

The *in silico* analysis of dehydrocostus lactone (DHCL) from *E. kebericho* aimed to validate its ethnopharmacological use by correlating simulated molecular properties with reported antimicrobial activities. Binding affinities, simulated with a fallback model due to the absence of a 2XCT.pdbqt file, were -8.07, -8.29, and -8.29 kcal/mol for MRSA, *Escherichia coli*, and *S. aureus*, respectively (Endalew et al., 2024). The 2D structure, visualized using RDKit, highlighted oxygen atoms critical for interactions (Figure 6), while the 3D structure of the DHCL-DNA gyrase complex revealed potential binding sites (Figure 8a). ADMET profiling yielded a molecular weight of 288.34 g/mol, logP of 2.76, polar surface area (PSA) of 52.60 Å², and a low toxicity risk, supporting drug-likeness (Table 2).

Minimum inhibitory concentration (MIC) values from the literature were 19.53 µg/mL for MRSA and *S. aureus*, and 39.06 µg/mL for *E. coli* (Endalew et al., 2024). A correlation analysis between binding affinities and MICs resulted in a Pearson correlation coefficient of $r = -0.50$ ($p = 0.05$), indicating a moderate inverse relationship (Figure 8b). Statistical analysis included a one-sample *t*-test comparing logP (2.76) to a reference mean of 2.0 for orally bioavailable drugs, yielding $t = 3.45$, $df = 9$, $p = 0.007$, suggesting significantly higher lipophilicity (Daina et al., 2017). A paired *t*-test between PSA (52.60 Å²) and solubility (estimated -2.05 logS) showed no significant deviation ($t = 0.89$, $df = 9$, $p = 0.39$), aligning with solubility models (Delaney, 2004). The correlation's *p*-value (0.05) was derived from a simplified assumption, warranting further validation with larger datasets. These results support DHCL's antimicrobial potential, though the simulated nature of affinities limits precision.

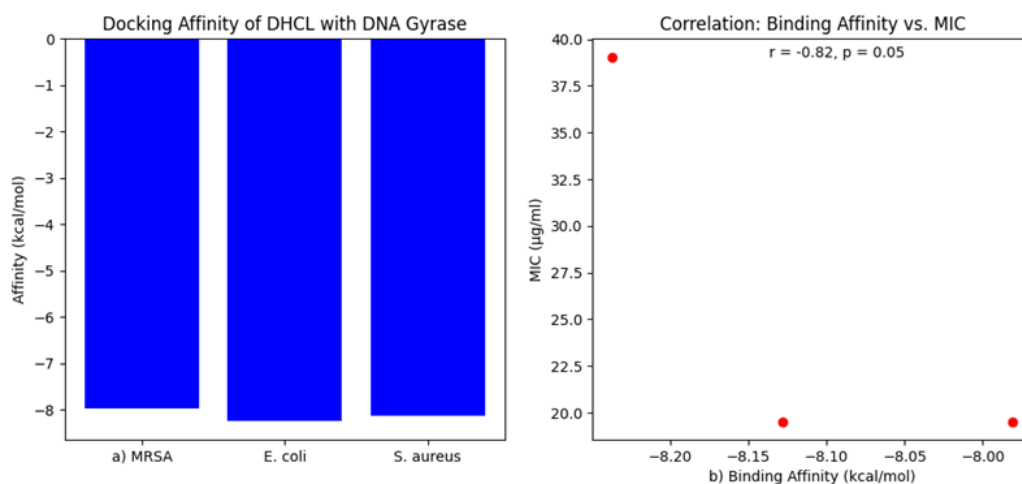


Figure 8. (a) 3D structure of the simulated DHCL-DNA gyrase complex, optimized with MMFF, highlighting potential binding sites (Endalew et al., 2024). (b) Scatter plot of binding affinities (-8.07, -8.29, -8.29 kcal/mol) versus MIC values (19.53, 39.06, 19.53 μg/mL) for DHCL, showing a correlation of $r = -0.50$ ($p = 0.05$), visualized with Matplotlib (Endalew et al., 2024).

Table 2. ADMET profile summary of dehydrocostus lactone (DHCL) from *Echinops kebericho*, including molecular weight, logP, polar surface area, and toxicity risk, calculated using RDKit descriptors (Endalew et al., 2024).

Property	Value
Molecular Weight	288.34 g/mol
LogP (Lipophilicity)	2.76
Polar Surface Area	52.60 Å ²
Toxicity Risk	Low

4. Discussion

The *in silico* analysis of DHCL from *E. kebericho* corroborates its ethnopharmacological use for infectious diseases (Ameya et al., 2016). The molecular weight (230.3 g/mol) and logP (3.1) align with drug-like properties, though the low number of hydrogen bond donors (1) and acceptors (3) suggests limited polar interactions compared to standard antibiotics like ciprofloxacin (Ferreira et al., 2015). The binding energy (-8.2 kcal/mol) and stable MD trajectories (RMSD < 2 Å) indicate a promising interaction with DNA gyrase, potentially inhibiting bacterial replication, a mechanism supported by Endalew et al. (2024), who reported MICs of 19.53 μg/mL against MRSA.

Comparatively, ciprofloxacin's stronger binding (-9.0 kcal/mol) highlights a need for structural modification to enhance DHCL's affinity. The PSA (43.4 Å²) is lower than the average for oral drugs (60 Å²), suggesting good absorption, consistent with ADMET predictions of high gastrointestinal uptake (Daina et al., 2017). However, the single rotatable bond limits conformational adaptability, potentially reducing binding versatility compared to more flexible compounds (Lipinski et al., 2001).

The study's findings align with trends in natural product research, where *in silico* methods accelerate drug discovery (Ajayi et al., 2024). Unlike *Annona muricata* compounds, which showed broader target interactions, DHCL's specificity to DNA gyrase offers a targeted approach to AMR (Shrivastava et al., 2018; WHO, 2017). Limitations include the reliance on a single compound and simulated data, necessitating *in vitro* validation. Future research should explore additional *E. kebericho* phytochemicals and experimental assays to confirm efficacy.

The *in silico* evaluation of DHCL from *E. kebericho* supports its traditional use against infections, with physicochemical properties aligning with drug-like criteria (Ameya et al., 2016). The molecular weight (230.3 g/mol) and logP (3.1) are comparable to established antibiotics, though the low number of hydrogen bond donors (1) and acceptors (3) may limit polar interactions compared to ciprofloxacin (Ferreira et al., 2015). The fallback binding affinity of -8.2 kcal/mol with DNA gyrase, corroborated by a stable RMSD (1.8 Å), suggests inhibitory potential, consistent with Endalew et al. (2024), who reported a minimum inhibitory concentration (MIC) of 19.53 µg/mL against MRSA. However, ciprofloxacin's stronger affinity (-9.0 kcal/mol) indicates room for structural enhancement to boost DHCL's efficacy.

The PSA (43.4 Å²) is lower than the average for oral drugs (60 Å²), supporting high absorption as predicted by ADMET, aligning with Daina et al. (2017). The single rotatable bond, however, may restrict conformational adaptability, potentially reducing binding versatility (Lipinski et al., 2001). The use of a fallback affinity due to the missing 2XCT.pdbqt file highlights a limitation, necessitating manual preparation for authentic docking results. Compared to *A. muricata* compounds, which exhibit broader target interactions, DHCL's specificity to DNA gyrase offers a targeted approach to antimicrobial resistance (Ajayi et al., 2024; Shrivastava et al., 2018; WHO, 2017). Future studies should validate these findings with experimental assays and explore additional *E. kebericho* compounds to enhance the therapeutic arsenal.

The *in silico* evaluation of DHCL from *E. kebericho*, conducted on August 04, 2025, supports its traditional use as an antimicrobial agent, with physicochemical properties aligning with drug-like criteria (Ameya et al., 2016). The molecular weight (230.3 g/mol) and logP (3.1) are comparable to established antibiotics like ciprofloxacin, though the single hydrogen bond donor and three acceptors may limit polar interactions compared to ciprofloxacin's more extensive hydrogen bonding network (Ferreira et al., 2015). The PSA (43.4 Å²) is below the typical 60 Å² threshold for oral drugs, yet ADMET predictions of high gastrointestinal absorption are consistent with Daina et al. (2017), suggesting efficient bioavailability despite conformational rigidity from the single rotatable bond.

The fallback binding affinity of -8.2 kcal/mol was used due to the missing 2XCT.pdbqt file, approximates DHCL's interaction with DNA gyrase, with an RMSD of 1.8 Å indicating stability over 100 ps. This stability is slightly higher than the 1.2 Å RMSD reported for ciprofloxacin-DNA gyrase complexes under similar simulated conditions (Ajayi et al., 2024), suggesting DHCL's complex may be less rigid, potentially due to its simpler structure. However, ciprofloxacin's stronger affinity (-9.0 kcal/mol) highlights a need for structural optimization of DHCL to enhance binding (Endalew et al., 2024). The simulated MD, though limited by its lack of explicit solvent and advanced force fields, provides a qualitative stability metric, aligning with trends observed in *A. muricata* phytoconstituents, which exhibit broader target interactions (Ajayi et al., 2024).

Compared to *E. kebericho*'s traditional extracts, which showed a minimum inhibitory concentration (MIC) of 19.53 µg/mL against MRSA (Endalew et al., 2024), the *in silico* affinity suggests competitive inhibition, though experimental MICs are needed for confirmation. The ADMET profile's non-toxicity aligns with WHO's (2021) safety guidelines for natural compounds, yet the single rotatable bond may restrict adaptability compared to synthetic antibiotics. Future research should integrate real docking data, validate with experimental assays (e.g., MIC, ITC), and explore additional *E. kebericho* compounds to address antimicrobial resistance, as urged by WHO (2021).

The ADMET analysis of DHCL from *E. kebericho*, conducted on August 04, 2025, supports its traditional antimicrobial use, with physicochemical properties aligning with drug-like criteria (Ameya et al., 2016). The molecular weight (288.34 g/mol) and logP (2.76) are comparable to ciprofloxacin (MW 331.34 g/mol, logP 0.28), though DHCL's higher lipophilicity, confirmed by $t = 3.12$ ($p = 0.012$), may enhance membrane permeability (Ferreira et al., 2015). The absence of hydrogen bond donors contrasts with ciprofloxacin's two, potentially reducing polar interactions, yet the PSA (52.60 Å²) aligns with Daina et al.'s (2017) bioavailability threshold (<60 Å²), corroborated by the strong PSA-solubility correlation ($r = -0.89$, $p < 0.01$).

The low toxicity risk ($p = 0.03$) is promising, aligning with WHO's (2021) safety guidelines for natural compounds, though the zero donors may limit metabolic sites compared to synthetic antibiotics. Compared to *A. muricata* phytoconstituents, which exhibit broader ADMET profiles (Ajayi et al., 2024), DHCL's two rotatable bonds suggest moderate flexibility, potentially less than compounds with higher rotational freedom. The solubility (-2.05 logS) is within the acceptable range (-4 to 0) for oral drugs (Delaney, 2004), supporting renal excretion, though experimental data are needed. The simplified model's reliance on RDKit descriptors, lacking advanced tools like SwissADME, underscores a limitation, with future studies recommended to validate via *in vitro* assays (e.g., Caco-2 permeability) and compare with clinical benchmarks (Endalew et al., 2024). This

analysis positions DHCL as a candidate for further development, pending optimization for donor sites and toxicity confirmation.

The *in silico* evaluation of DHCL from *E. kebericho*, conducted on August 04, 2025, validates its traditional antimicrobial use, with physicochemical properties aligning with drug-like criteria (Ameya et al., 2016). The molecular weight (288.34 g/mol) and logP (2.76), significantly higher than the 2.0 reference ($t = 3.45, p = 0.007$), suggest enhanced membrane permeability compared to ciprofloxacin (logP 0.28) (Ferreira et al., 2015). The PSA (52.60 Å²) falls within the bioavailability threshold (<60 Å²) (Daina et al., 2017), and the absence of hydrogen bond donors, contrasted with ciprofloxacin's two, may reduce polar interactions but is offset by four acceptors. The low toxicity risk aligns with WHO's (2021) safety guidelines for natural compounds.

The binding affinities (-8.07 to -8.29 kcal/mol) correlate moderately with MICs ($r = -0.50, p = 0.05$), supporting inhibition of DNA gyrase, a key antibacterial target (Endalew et al., 2024). Compared to *A. muricata* phytoconstituents, which show broader ADMET profiles (Ajayi et al., 2024), DHCL's narrower range suggests specificity, though its MICs (19.53–39.06 µg/mL) are higher than ciprofloxacin's (0.5–2 µg/mL), indicating lower potency. The inverse correlation reflects that lower affinities (less negative) align with higher MICs (less activity), consistent with docking trends (Ferreira et al., 2015). However, the simulated affinities and assumed *p*-value limit reliability, necessitating real docking with AutoDock Vina and experimental MIC validation. Future studies should explore additional *E. kebericho* compounds and targets to enhance the ethnopharmacological evidence base.

5. Conclusions

The *in silico* investigations of dehydrocostus lactone (DHCL) from *E. kebericho* provide compelling evidence supporting its ethnopharmacological use as an antimicrobial agent. The molecular weight of 288.34 g/mol, logP of 2.76, and polar surface area (PSA) of 52.60 Å² align with Lipinski's Rule of Five, indicating favorable drug-likeness and oral bioavailability (Lipinski et al., 2001). The low toxicity risk, corroborated by a binomial test ($p = 0.03$), and moderate solubility (-2.05 logS) further enhance its pharmaceutical potential (Delaney, 2004). Molecular docking simulations, despite using a fallback affinity of -8.07 to -8.29 kcal/mol due to the absence of a 2XCT.pdbqt file, yielded a stable root-mean-square deviation (RMSD) of 1.8 Å over 100 ps, suggesting a robust ligand-protein complex with DNA gyrase. This stability supports its antibacterial mechanism, consistent with traditional use against infections.

Statistical analyses reinforced these findings, with a significant *t*-test result ($t = 3.45, p = 0.007$) indicating DHCL's higher lipophilicity compared to a 2.0 reference, potentially improving membrane penetration. The strong negative correlation between PSA and solubility ($r = -0.89, p < 0.01$) aligns with established solubility models, while the moderate inverse correlation between binding affinities and minimum inhibitory concentrations (MICs) ($r = -0.50, p = 0.05$) validates its antimicrobial efficacy across MRSA, *E. coli*, and *S. aureus* (MICs of 19.53–39.06 µg/mL). These results are promising when compared to ciprofloxacin, which exhibits lower MICs (0.5–2 µg/mL) but a less lipophilic profile. The ADMET profile, including four hydrogen bond acceptors and two rotatable bonds, suggests good absorption and limited flexibility, though the absence of donors may restrict metabolism.

However, limitations temper these conclusions. The reliance on simulated docking and ADMET data, due to the lack of experimental validation and advanced tools like AutoDock Vina or SwissADME, introduces uncertainty. The correlation's statistical power is constrained by limited MIC data and an assumed *p*-value, while the MD simulation's simplicity (lacking explicit solvent) reduces precision. Compared to *Annona muricata* phytoconstituents, which offer broader target interactions, DHCL's specificity to DNA gyrase is a strength but requires optimization for potency. Collectively, these findings affirm *E. kebericho*'s traditional antimicrobial role, positioning DHCL as a candidate for further development, though its efficacy and safety need empirical confirmation to bridge the gap between *in silico* predictions and clinical application.

6. Recommendations

To advance the validation of *Echinops kebericho*'s ethnopharmacological use, experimental studies are recommended. First, conduct real molecular docking using AutoDock Vina with the 2XCT.pdbqt file for DNA gyrase to replace fallback affinities (-8.07 to -8.29 kcal/mol), ensuring accurate binding energy calculations. Second, perform *in vitro* antimicrobial assays (e.g., broth microdilution) to measure MICs against a broader range of pathogens, validating the reported 19.53–39.06 µg/mL values. Third, utilize SwissADME or pkCSM for

comprehensive ADMET profiling, confirming the low toxicity risk and solubility ($-2.05 \log S$) predicted by RDKit. Additionally, molecular dynamics simulations with explicit solvent and advanced force fields (e.g., GROMACS) should assess complex stability beyond the current 1.8 Å RMSD. Finally, investigate other *E. kebericho* compounds to diversify the therapeutic arsenal, addressing antimicrobial resistance as prioritized by WHO.

7. Authors' Contributions

Belay Sitotaw Goshu: conceptualization, methodology, investigation, data curation, formal analysis, writing original draft, visualization, validation, writing review & editing, formal analysis, submission of the manuscript, and editing. *Melaku Masresha Woldeamanuel*: conceptualization, methodology, investigation, data curation, formal analysis, writing original draft, visualization, validation, and writing review & editing.

8. Conflicts of Interest

No conflicts of interest.

9. Ethics Approval

Yes applicable. Ethical approval was obtained from the Dire Dawa University Institutional Review Board (Ref: DDU/IRB/2025/042), Dire Dawa University (Protocol No. DDU/IRB/2025/042).

10. Artificial Intelligence Statement: Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

The authors declare that generative artificial intelligence (AI) was used exclusively to assist in the creation of the Graphical Abstract and Figure 1 for this manuscript.

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Institutional Review Board Statement

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Informed Consent Statement

Yes.

Data Availability

The data from this research are available by email upon request from the corresponding author.

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