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# In silico analysis of *Lansium domesticum* secondary metabolites as potential antimalarial agents targeting *Plasmodium falciparum* Lactate Dehydrogenase (PfLDH)

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**ABSTRACT**. Malaria continues to be a significant global infectious illness, with *Plasmodium falciparum* primarily responsible for the most severe and lethal cases, including cerebral malaria. *P. falciparum* lactate dehydrogenase (PfLDH), an essential enzyme in the parasite's glycolytic cycle, is a viable molecular target for the development of antimalarial drugs. The deficiencies in existing therapeutics underscore the necessity for novel candidate alternative drugs. *Lansium domesticum*, a native Indonesian plant, possesses bioactive compounds with potential antimalarial effects. This work sought to assess *L. domesticum* secondary metabolites as potential antimalarial agents using an in silico methodology. A total of 47 compounds were evaluated to forecast antimalarial efficacy, thereafter, assessing their physicochemical attributes, pharmacokinetic features, and toxicity profiles. Molecular docking was used to examine the interactions between potential drugs and the PfLDH target enzyme. Four compounds—is-3-Hexen-1-ol, Aromadendrene, Isoledene, and Hexadecanoic acid—fulfilled the necessary physicochemical, pharmacokinetic, and toxicological standards. Hexadecanoic acid demonstrated the most robust interaction with PfLDH, establishing three critical amino acid connections at the active site (GLY29, THR97, and HIS195) and exhibiting a superior binding affinity compared to control and natural ligands. The data indicate that hexadecanoic acid is a promising antimalarial candidate sourced from *L. domesticum*. Additional molecular dynamics simulations, together with in vitro and in vivo investigations, are required to validate its therapeutic efficacy.

**Keywords**: antimalarial; bioinformatics; in silico; *Lansium domesticum*; PfLDH

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## INTRODUCTION

Malaria has become one of the most contagious and deadly infections worldwide, particularly impacting neonates, young children, and lactating women. Insufficient and tardy management of malaria can result in severe outcomes, including significant anaemia, organ dysfunction, and death (Widjanarko *et al*., 2022). The World Health Organisation (2024) recorded 608,000 fatalities due to malaria and 249 million new cases in 2022, with 94% of these incidents occurring in Africa. Malaria has persisted as public health concern in 107 countries until 2025 (WHO, 2024). In Indonesia, malaria prevalence increased by 56% in 2022, with around 811,636 cases documented in 2021 (Indonesian Ministry of Health, 2022). A significant obstacle in malaria management is the increasing resistance of *Plasmodium falciparum*, the species obligated to the majority of severe infections and elevated mortality rates, particularly cerebral malaria (Ramanto & Nurdiansyah, 2021; Kilo *et al*., 2024).

Malaria induces various symptoms, including fever, nausea, vomiting, headache, and chills, as well as haematological abnormalities characterised by decreased levels of platelets, leukocytes, lymphocytes, eosinophils, and haemoglobin, alongside elevated counts of monocytes and neutrophils in affected individuals (Kilo *et al*., 2024). Modern antimalarial strategies increasingly emphasise the metabolic pathways of the parasite. *Plasmodium falciparum* Lactate dehydrogenase (PfLDH) is a glycolytic enzyme in that catalyses the conversion of pyruvate to lactate while oxidising NADH to $NAD^+$, hence promoting parasite survival (Zakaria *et al*., 2020). Due to its essential role in energy production, LDH has become an attractive molecular target for antimalarial drug development, since

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its inhibition can disrupt glycolysis and obstruct metabolic pathways crucial for parasite survival (Kilo *et al*., 2024).

Despite the availability of treatments such as chloroquine, artemisinin, and artesunate–mefloquine combinations, therapeutic challenges persist. Artemisinin resistance reduces drug efficacy, highlighting the need for new antimalarial candidates (Ashley *et al*., 2014). Natural products offer promising leads for drug discovery, and *Lansium domesticum*—known in Indonesia as *duku*, *langsat*, and *kokosan*—exhibits various pharmacological activities, including antimalarial, antitumor, anticancer, antibacterial, antimelanogenesis, antimutagenic, and antioxidant properties (Hanum & Rina, 2013). The antimalarial potential of *L. domesticum* has been demonstrated by Abdallah *et al*. (2022), who reported that bark extracts disrupt the life cycle of *P. falciparum*, including chloroquine-resistant strains.

To evaluate its potential more efficiently, *L. domesticum* requires systematic assessment using advanced computational methods. In silico approaches offer cost- and time-effective alternatives to traditional in vivo studies, which typically require large numbers of animal subjects and substantial resources (Makatita *et al*., 2020; Shaker *et al*., 2021). In silico analysis enables early prediction of drug characteristics such as biological activity, physicochemical properties, pharmacokinetic behavior, toxicity, and molecular docking interactions (Sulistyowaty *et al*., 2021; Fadzillah, 2024; Karim *et al*., 2024). Furthermore, advances in pharmacogenomics and artificial intelligence enhance safety prediction and support personalized therapy (Xu *et al*., 2024).

This study provides the first comprehensive *in silico* screening of individual secondary metabolite compounds from *L. domesticum* specifically targeting the PfLDH enzyme. By integrating biological activity prediction, physicochemical filtering, pharmacokinetic and toxicity assessment, and detailed molecular docking analysis, this research identifies promising PfLDH inhibitors that have not been previously characterized at the compound level. The findings offer new insights and contribute novel potential lead molecules for antimalarial drug discovery.

## MATERIALS AND METHODS

**Research design.** This research employed an *in silico* experimental approach (Shaker *et al*., 2021) to identify *L. domesticum* secondary metabolites with potential inhibitory activity against *P. falciparum* Lactate Dehydrogenase (PfLDH). The study was conducted from October to December 2024 at the Genetics and Biotechnology Laboratory, Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Sriwijaya, Indralaya.

**Research requirements.** All computational analyses were performed using Biovia Discovery Studio Visualizer 2024, PyRx with AutoDock Vina, ChemSketch, and online databases including PDB, PubChem, KNApSAck, IMPPAT, PASS Online, SwissADME, ADMETlab, and pkCSM, running on a Windows 10 system equipped with an Intel® Celeron® N3060 processor and 4 GB RAM. A total of 159 secondary metabolite compounds of *L. domesticum* and one compound (chloroquine) as control were compiled from the KNApSAck and IMPPAT databases as well as from Abdallah *et al*. (2022) and Mayanti *et al*. (2022). Canonical SMILES or 3D structures were obtained from PubChem, and compounds lacking 3D structures were modelled in ChemSketch. Energy minimization of all ligands was conducted using the Open Babel feature in PyRx to generate optimized structures for docking (Thandra *et al*., 2020). The PfLDH enzyme structure (PDB ID: 1LDG) (Tahghighi *et al*., 2020) was retrieved from the PDB and prepared by removing water molecules and native ligands, while retaining the active-site residues GLY29, MET30, ASP53, THR97, PHE100, ASN140, TYR85, and HIS195 (Coutinho *et al*., 2011).

**Ligand preparation.** Ligand preparation involved standardizing compound structures from *L. domesticum* using canonical SMILES and 3D models. Structures obtained from PubChem were downloaded in .sdf format, while compounds without available structures were generated in ChemSketch using SMILES identifiers. All compounds were converted to 3D format and subjected

to energy minimization in PyRx, followed by export in .pdb format for docking simulations (Thandra *et al*., 2020; Heikal *et al*., 2023).

**Receptor preparation.** The PfLDH crystal structure (1LDG) was prepared using Discovery Studio Visualizer by removing crystallographic water molecules, natural ligands, and unrelated residues. The cleaned receptor structure was saved in .pdb format for docking. The validated active site included amino acids GLY29, MET30, ASP53, THR97, PHE100, ASN140, TYR85, and HIS195 (Coutinho *et al*., 2011).

**Biological activity prediction.** All 160 compounds were predicted using PASS Online, based on canonical SMILES input. Compounds were screened quantitatively according to Pa–Pi values, where Pa > 0.70 was classified as high predicted activity, 0.50 ≤ Pa ≤ 0.70 as moderate activity, and Pa < 0.50 as low activity (Lagunin *et al*., 2018). Compounds with Pa > Pi and Pa ≥ 0.50 proceeded to the next evaluation stage. This screening produced 48 active compounds: 47 secondary metabolites and 1 control compound.

**Prediction of physicochemical properties.** Physicochemical evaluation of the 48 active compounds was performed using SwissADME. Compounds were assessed according to Lipinski's Rule of Five, including molecular weight < 500 g/mol, LogP < 5, hydrogen bond acceptors < 10, hydrogen bond donors < 5, and molar refractivity 40–130 (Fadzillah *et al*., 2024). Compounds violating two or more criteria were excluded, yielding 35 compounds that fully complied with drug-likeness guidelines.

**Pharmacokinetic prediction.** ADME profiles of the 35 compounds were predicted using ADMETlab and pkCSM (Fadzillah *et al*., 2024). Parameters included human intestinal absorption, volume of distribution (VDss), blood–brain barrier permeability (BBB), CYP2D6 and CYP3A4 inhibition, total clearance, and renal excretion. Compounds with poor HIA (<30%), strong CYP inhibition, or extreme clearance values were excluded. This step resulted in nine pharmacokinetically acceptable compounds.

**Prediction of toxicity.** Toxicity predictions for the eight remaining compounds were generated using ADMETlab (Sulistyowaty *et al*., 2021). Hepatotoxicity, AMES mutagenicity, and rat oral acute toxicity (LD50) were evaluated. Only compounds that were non-hepatotoxic, non-mutagenic, and exhibited LD50 > 300 mg/kg were retained. Four compounds met all toxicity criteria.

**Ligand and receptor docking stages.** Molecular docking was conducted using PyRx with AutoDock Vina (Heikal et al., 2023). The PfLDH protein (1LDG) served as the receptor, while *L. domesticum* compounds functioned as test ligands. Chloroquine acted as the reference ligand, and oxamate (OXM) as the natural ligand. A docking grid was positioned to cover the conserved active site (GLY29, MET30, ASP53, THR97, PHE100, ASN140, TYR85, HIS195). Each ligand generated nine conformations, and the model with the lowest binding affinity (kcal/mol) and acceptable RMSD was selected for further analysis (Kilo *et al*., 2024).

**Visualization of docking results.** The best docking conformations (lowest binding affinity) were visualized using Biovia Discovery Studio Visualizer (Bahi *et al*., 2023; Uzzaman *et al*., 2023). Hydrogen bonds, hydrophobic interactions, interacting residues, and interaction distances were examined to characterize ligand–receptor binding stability (Kinasih *et al*., 2023).

**Data analysis.** Final data analysis integrated Pa–Pi values, physicochemical properties, pharmacokinetic behavior, toxicity predictions, and molecular docking results. Compounds meeting all criteria—Pa > 0.70, complete drug-likeness compliance, favourable ADME predictions, safe toxicity profiles, and strong PfLDH binding affinity—were identified as the most promising PfLDH inhibitor candidates (Sulistyowaty *et al*., 2021; Fakih *et al*., 2022; Bahi *et al*., 2023; Fadzillah *et al*., 2024).

## RESULTS AND DISCUSSION

**Biological activity prediction.** A total of 159 secondary metabolites of *Lansium domesticum* were compiled from literature and phytochemical databases (Abdallah *et al*., 2022; Mayanti *et al*.,

2022). PASS Online analysis identified 47 compounds with Pa > Pi, indicating potential antimalarial activity (Lagunin *et al*., 2018). Chloroquine, used as the control, exhibited a high Pa value (0.898). Octadecanoic acid showed the strongest predicted activity (Pa = 0.742), consistent with reported bioactivity of fatty acids (Anjuwon *et al*., 2023). Other compounds such as oleic acid, gallic acid, and citric acid displayed moderate predicted activity (Pa 0.50–0.60), suggesting weaker but notable antimalarial potential (Ikhtira *et al*., 2023). The Pa and Pi values of the active compounds are presented in Table 1.

**Table 1.** Biological activity prediction results of *L. domesticum* compounds

| Num. | Compunds | Pa | Pi | Potential Activity |
|---|---|---|---|---|
| 1. | Chloroquine (Control) | 0.898 | 0.002 | antimalarial |
| 2. | Octadecanoic acid | 0.742 | 0.001 | antimalarial |
| 3. | Palmitic acid | 0.742 | 0.001 | antimalarial |
| 4. | Azadiradione | 0.619 | 0.004 | antimalarial |
| 5. | Oleic acid | 0.574 | 0.002 | antimalarial |
| 6. | Gallic acid | 0.554 | 0.002 | antimalarial |
| 7. | Citric acid | 0.527 | 0.002 | antimalarial |
| 8. | Rutin | 0.507 | 0.004 | antimalarial |
| 9. | Lamesticumins F | 0.397 | 0.006 | antimalarial |
| 10. | Quercetin | 0.365 | 0.008 | antimalarial |
| 11. | Dukunolides F | 0.298 | 0.014 | antimalarial |
| 12. | Dukunolide E | 0.298 | 0.014 | antimalarial |
| 13. | Catechin | 0.284 | 0.016 | antimalarial |
| 14. | Dukunolides D | 0.279 | 0.017 | antimalarial |
| 15. | 3-Oxo-24-cycloarten-21-oic acid | 0.275 | 0.172 | antimalarial |
| 16. | Dukunolides C | 0.249 | 0.026 | antimalarial |
| 17. | cis-3-Hexen-1-ol | 0.247 | 0.004 | antimalarial |
| 18. | trans-3-Hexen-1-ol | 0.247 | 0.004 | antimalarial |
| 19. | P-Coumaric acid | 0.239 | 0.005 | antimalarial |
| 20. | Dukunolides B | 0.236 | 0.032 | antimalarial |
| 21. | Dukunolides A | 0.225 | 0.038 | antimalarial |
| 22. | 2-Hexen-1-OL | 0.218 | 0.005 | antimalarial |
| 23. | 1,3,5-Trioxane | 0.213 | 0.005 | antimalarial |
| 24. | Kokosanolide B | 0.2 | 0.058 | antimalarial |
| 25. | 3-Hydroxy-8,14-secogammacera-7,14-dien-21-one | 0.192 | 0.065 | antimalarial |
| 26. | 2-Hexenal | 0.176 | 0.009 | antimalarial |
| 27. | Lamesticumins C | 0.172 | 0.087 | antimalarial |
| 28. | Kokosanolide A | 0.168 | 0.093 | antimalarial |
| 29. | Methyl angolensate | 0.167 | 0.094 | antimalarial |
| 30. | Aromadendrene | 0.167 | 0.095 | antimalarial |
| 31. | 21alpha-Hydroxyonocera-8(26),14-dien-3-one | 0.165 | 0.098 | antimalarial |
| 32. | 3beta-Hydroxyonocera-8(26),14-dien-21-one | 0.165 | 0.098 | antimalarial |
| 33. | Isoledene | 0.164 | 0.099 | antimalarial |
| 34. | Viridiflorene | 0.162 | 0.102 | antimalarial |
| 35. | 7,14(27)-Onoceradiene-3,21-dione | 0.161 | 0.103 | antimalarial |
| 36. | β-Sitosterol | 0.159 | 0.106 | antimalarial |
| 37. | Kokosanolide C | 0.145 | 0.132 | antimalarial |
| 38. | α-Copaene | 0.145 | 0.132 | antimalarial |
| 39. | Ellagic acid | 0.143 | 0.004 | antimalarial |
| 40. | Ethyl oleate | 0.133 | 0.015 | antimalarial |
| 41. | Scopoletin | 0.093 | 0.017 | antimalarial |
| 42. | Hexadecanoic acid | 0.085 | 0.026 | antimalarial |
| 43. | 4-Hydroxy-N-methylproline | 0.079 | 0.034 | antimalarial |
| 44. | Humulene | 0.073 | 0.042 | antimalarial |
| 45. | δ-Cadinene | 0.068 | 0.06 | antimalarial |
| 46. | Aphanamol II | 0.026 | 0.004 | antimalarial |
| 47. | δ-Selinene | 0.025 | 0.005 | antimalarial |
| 48. | α-Calacorene | 0.016 | 0.003 | antimalarial |

**Prediction of physicochemical properties.** Lipinski-based screening using SwissADME revealed that 34 of the 47 compounds possessed acceptable physicochemical properties (Table 2). Molecular weight, LogP, HBD, HBA, and MR values indicated suitable drug-like properties for a majority of compounds. High LogP and excessive hydrogen-bonding groups were the most common reasons for exclusion, as both characteristics may impair cell permeability (Klara et al., 2023; Naufa *et al*., 2022). Compounds violating multiple Lipinski parameters were excluded (Ekawasti *et al*., 2022), resulting in 34 candidates eligible for pharmacokinetic evaluation.

**Table 2.** Physicochemical prediction outcomes

| Num. | Test Ligand | MW (<500/mol) | LogP (<4,15) | HBD (<5) | HBA (<10) | MR (40-130) |
|---|---|---|---|---|---|---|
| 1. | Chloroquinone (Control) | 319.87 | 3.20 | 1 | 2 | 97.41 |
| 2. | Octadecanoic acid | 284.48 | 4.67 | 1 | 2 | 90.41 |
| 3. | Palmitic acid | 256.42 | 4.19 | 1 | 2 | 80.80 |
| 4. | Azadiradion | 450.57 | 3.28 | 0 | 5 | 123.48 |
| 5. | Oleic acid | 282.46 | 4.57 | 1 | 2 | 89.94 |
| 6. | Gallic acid | 170.12 | -0.16 | 4 | 5 | 39.47 |
| 7. | Citric acid | 192.12 | -1.48 | 4 | 7 | 37.47 |
| 8. | Rutin | 610.52 | -3.89 | 10 | 16 | 141.38 |
| 9. | Lamesticumins F | 458.72 | 4.82 | 2 | 3 | 142.72 |
| 10. | Quercetin | 302.24 | -0.56 | 5 | 7 | 78.03 |
| 11. | Dukunolides F | 484.50 | 0.59 | 2 | 9 | 117.27 |
| 12. | Dukunolide E | 632.82 | 3.42 | 3 | 9 | 173.38 |
| 13. | Catechin | 290.27 | 0.24 | 5 | 6 | 74.33 |
| 14. | Dukunolides D | 468.50 | 1.29 | 2 | 8 | 117.79 |
| 15. | 3-Oxo-24-cycloarten-21-oic acid | 454.68 | 5.73 | 1 | 3 | 135.95 |
| 16. | Dukunolides C | 540.52 | 0.12 | 1 | 11 | 127.70 |
| 17. | cis-3-Hexen-1-ol | 100.16 | 1.39 | 1 | 1 | 31.64 |
| 18. | trans-3-Hexen-1-ol | 100.16 | 1.39 | 1 | 1 | 31.64 |
| 19. | *P*-Coumaric acid | 164.16 | 1.28 | 3 | 2 | 45.13 |
| 20. | Dukunolides B | 498.48 | -0.18 | 2 | 10 | 116.28 |
| 21. | Dukunolides A | 482.48 | 0.51 | 2 | 9 | 116.80 |
| 22. | 2-Hexen-1-OL | 100.16 | 1.39 | 1 | 1 | 31.64 |
| 23. | 1,3,5-Trioxane | 90.08 | -1.09 | 0 | 3 | 17.68 |
| 24. | Kokosanolide B | 456.70 | 4.91 | 1 | 3 | 137.95 |
| 25. | 3-Hydroxy-8,14-secogammacera-7,14-dien-21-one | 430.71 | 5.60 | 1 | 2 | 137.18 |
| 26. | 2-Hexenal | 98.14 | 1.28 | 0 | 1 | 30.68 |
| 27. | Lamesticumins C | 454.68 | 4.82 | 1 | 3 | 137.44 |
| 28. | Kokosanolide A | 500.54 | 1.20 | 1 | 9 | 124.04 |
| 29. | Methyl angolensate | 470.55 | 2.36 | 0 | 7 | 123.61 |
| 30. | Aromadendrene | 204.35 | 5.65 | 0 | 0 | 67.14 |
| 31. | 21alpha-Hydroxyonocera-8(26),14-dien-3-one | 440.70 | 5.79 | 1 | 2 | 137.24 |
| 32. | 3beta-Hydroxyonocera-8(26),14-dien-21-one | 440.70 | 5.79 | 1 | 2 | 137.24 |
| 33. | Isoledene | 204.35 | 5.65 | 0 | 0 | 67.14 |
| 34. | Viridiflorene | 204.35 | 5.65 | 0 | 0 | 67.14 |
| 35. | 7,14(27)-Onoceradiene-3,21-dione | 438.69 | 5.70 | 0 | 2 | 136.28 |
| 36. | β-Sitosterol | 414.71 | 6.73 | 1 | 1 | 133.23 |
| 37. | Kokosanolide C | 720.89 | 3.08 | 2 | 10 | 192.35 |
| 38. | α-Copaene | 204.35 | 5.65 | 0 | 0 | 67.14 |
| 39. | Ellagic acid | 302.19 | 0.14 | 4 | 8 | 75.31 |
| 40. | Ethyl oleate | 310.51 | 6.98 | 0 | 2 | 99.06 |
| 41. | Scopoletin | 192.17 | 0.76 | 1 | 4 | 51.00 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 42. | Hexadecanoic acid | 254.41 | 4.09 | 1 | 2 | 80.32 |
| 43. | 4-Hydroxy-N-methylproline | 145.16 | -0.85 | 2 | 4 | 38.59 |
| 44. | Humulene | 204.35 | 4.53 | 0 | 0 | 70.42 |
| 45. | δ-Cadinene | 204.35 | 4.63 | 0 | 0 | 69.04 |
| 46. | Aphanamol II | 236.35 | 2.63 | 1 | 2 | 70.62 |
| 47. | δ-Selinene | 204.35 | 4.63 | 0 | 0 | 68.78 |
| 48. | *α*-Calacorene | 200.32 | 5.36 | 0 | 0 | 68.39 |

Abbreviation: MW: Moleculer Weight, LogP: solubility of a chemical in octanol and water solvents, HBD: Hydrogen Bond Donor, HBA: Hydrogen Bond Acceptor, MR: Molar Refractivity, and Red tag: Fails to comply with Lipinski's rule

Table 2 indicates that molecular weight is the primary parameter assessed under Lipinski's rule, requiring it to be below 500 g/mol. Compounds with lower molecular weights demonstrate enhanced diffusion across biological membranes, while those exceeding 500 g/mol typically show diminished permeability, decreased interaction with target enzymes, heightened toxicity, and prolonged elimination (Wulandari *et al*., 2023). The subsequent parameter, LogP, which quantifies solubility in octanol and water, must remain below 4.15. The analysis indicated that 28 compounds satisfied this criterion, whereas 19 surpassed it. Compounds exhibiting lower LogP values demonstrate enhanced ability to traverse lipid bilayers, while those with higher LogP values signify increased hydrophobicity and a higher likelihood of toxicity resulting from extended retention within lipid membranes (Klara *et al*., 2023). Lipinski's rule stipulates a maximum of five hydrogen bond donors (HBD) and fewer than ten hydrogen bond acceptors (HBA) for hydrogen bonding parameters. Three compounds, Rutin, Quercetin, and Catechin, surpassed the hydrogen bond donor threshold, whereas four compounds, Rutin, Dukunolide C, Dukunolide B, and Kokosanolide C, exceeded the hydrogen bond acceptor limit. An increased number of hydrogen bonds decreases membrane permeability and impedes target interaction (Naufa *et al*., 2022).

The final parameter, molar refractivity (MR), indicates a compound's steric properties and is expected to fall within the range of 40 to 130. Twenty-seven compounds satisfied this criterion, whereas twenty did not. Elevated MR values suggest enhanced steric hindrance, potentially diminishing binding interactions with target enzymes (Suherlan *et al*., 2021). A total of 12 *L. domesticum* compounds adhere completely to Lipinski's rule, 22 violate one parameter, and 13 violate multiple parameters. The control compound, chloroquine, satisfies all Lipinski criteria and is deemed pharmacologically appropriate for in silico analysis. Ekawasti et al. (2022) indicate that compounds violating multiple Lipinski rules are improbable candidates for effective drugs. Consequently, 34 test compounds along with one control compound were chosen for further evaluation of pharmacokinetic properties.

**Prediction of pharmacokinetic properties.** Pharmacokinetic predictions using ADMETlab and pkCSM identified eight compounds with favorable ADME profiles (Table 3). Most compounds showed excellent intestinal absorption (HIA > 70%), though gallic acid, citric acid, and catechin demonstrated poor absorption. Distribution analysis revealed appropriate VDss ranges for most compounds, while only six indicated limited tissue distribution. Fourteen compounds showed BBB permeability, which is undesirable unless CNS targeting is intended (Sagitasa *et al*., 2021). Metabolic profiling indicated that most metabolites did not inhibit CYP2D6 or CYP3A4, whereas 11 predicted CYP3A4 inhibitors were removed due to the risk of metabolic interference (Aprilia *et al*., 2022). No compounds inhibited renal OCT2, and total clearance values were within appropriate physiological ranges (Ikhtira *et al*., 2023). Based on these criteria, eight compounds were advanced to toxicity screening.

**Table 3.** Prediction Results of Pharmacokinetic Properties

| Num. | Compounds | Absorption | Distribution | | Metabolism | | Excretion | |
|---|---|---|---|---|---|---|---|---|
| | | HIA (%) | VDss | BBB | *2D6 | *3A4 | Renal OCT2 | CLT OT |
| 1. | Chloroquine (Control) | 89.95 | 0.448 | 0.349 | No | No | No | 0.777 |
| 2. | Octadecanoic acid | 91.317 | 0.775 | -0.195 | No | No | No | 1.832 |
| 3. | Palmitic acid | 92.004 | 0.592 | -0.111 | No | No | No | 1.763 |
| 4. | Azadiradione | 99.914 | 0.348 | -0.203 | No | Yes | No | 0.154 |
| 5. | Oleic acid | 91.823 | 0,259 | -0.168 | No | No | No | 1.884 |
| 6. | Gallic acid | 43.374 | 0.3 | -1.102 | No | No | No | 0.518 |
| 7. | Citric acid | 0 | -0.461 | -1.017 | No | No | No | 0.895 |
| 8. | Quercetin | 77.207 | -0.879 | -1.098 | No | Yes | No | 0.407 |
| 9. | Dukunolides F | 90.461 | 0.269 | -0.823 | No | No | No | -0.056 |
| 10. | Catechin | 68.829 | 0.069 | -1.054 | No | No | No | 0.183 |
| 11. | Dukunolides D | 91.412 | 0.1 | -0.566 | No | Yes | No | 0.014 |
| 12. | cis-3-Hexen-1-ol | 93.765 | 0.758 | 0.16 | No | No | No | 0.452 |
| 13. | trans-3-Hexen-1-ol | 93.765 | 0.443 | 0.16 | No | No | No | 0.452 |
| 14. | *P*-Coumaric acid | 93.494 | -0.695 | -0.225 | No | No | No | 0.662 |
| 15. | Dukunolides B | 100 | 0.286 | -0.931 | No | Yes | No | -0.103 |
| 16. | Dukunolides A | 100 | 0.226 | -0.764 | No | Yes | No | -0.003 |
| 17. | 2-Hexen-1-OL | 93.765 | 0.517 | 0.16 | No | No | No | 0.382 |
| 18. | 1,3,5-Trioxane | 100 | -0.173 | -0.042 | No | No | No | 0.453 |
| 19. | 2-Hexenal | 96.295 | 0.262 | 0.175 | No | No | No | 0.325 |
| 20. | Kokosanolide A | 94.577 | 0.063 | -0.942 | No | No | No | 0.173 |
| 21. | Methyl angolensate | 100 | 0.1 | -0.699 | No | No | No | 0.288 |
| 22. | Aromadendrene | 95.302 | 2.622 | 0.822 | No | No | No | 0.926 |
| 23. | Isoledene | 96.328 | 0.304 | 0.789 | No | No | No | 0.909 |
| 24. | Viridiflorene | 94.735 | 2.186 | 0.805 | No | Yes | No | 0.91 |
| 25. | α-Copaene | 96.221 | 0.466 | 0.887 | No | Yes | No | 0.95 |
| 26. | Ellagic acid | 86.684 | 0,444 | -1.272 | No | No | No | 0.537 |
| 27. | Ethyl oleate | 91.735 | -0.468 | 0.786 | No | Yes | No | 2.03 |
| 28. | Scopoletin | 95.277 | 0,376 | -0.299 | No | No | No | 0.73 |
| 29. | Hexadecanoic acid | 92.51 | 0,217 | 0.184 | No | No | No | 1.817 |
| 30. | 4-Hydroxy-N-methylproline | 78.362 | -0.409 | -0.292 | No | No | No | 0.436 |
| 31. | Humulene | 94.682 | 2.015 | 0.663 | No | Yes | No | 1.282 |
| 32. | δ-Cadinene | 96.128 | 0.505 | 0.773 | No | No | No | 1.182 |
| 33. | Aphanamol II | 94.653 | 0.254 | 0.073 | No | No | No | 1.207 |
| 34. | δ-Selinene | 96.177 | 0.368 | 0.763 | No | Yes | No | 1.139 |
| 35. | *α*-Calacorene | 95.296 | 0.308 | 0.497 | No | Yes | No | 0.14 |

Abbreviation: HIA: Human Intestinal Absorption, VDss: Volume of Distribution, BBB: Blood-Brain Barrier, 2D6: Cytochrome CYP2D6, 3A4: Cytochrome CYP3A4, OCT2: Renal Organic Cation Transporter, CLTOT: Total Clearance, and Red tag: Low and fail to comply with ADME Parameter Value

**Prediction of toxicity.** Toxicity analysis (Table 4) revealed that cis-3-hexen-1-ol, aromadendrene, isoledene, and hexadecenoic acid displayed safe or moderate toxicity levels. Compounds such as 2-hexenal were predicted to be mutagenic (Krihariyani *et al*., 2021). Rat oral $LD_{50}$ values indicated that hexadecenoic acid and cis-3-hexen-1-ol were within safe toxicity thresholds (Astuty & Noer, 2022). These four compounds proceeded to molecular docking.

**Tabel 4.** Prediction results of toxicity properties of *L. domesticum* Compounds

| Num. | Compound Name | Hepatotoxicity | AMES Toxicity | Rat Oral Acurrate Toxicity |
|---|---|---|---|---|
| 1. | Chloroquine (Control) | 0.727 | 0.512 | 0.796 |
| 2. | cis-3-Hexen-1-ol | 0.237 | 0.412 | 0.155 |
| 3. | trans-3-Hexen-1-ol | 0.833 | 0.254 | 0.07 |
| 4. | 2-Hexen-1-ol | 0.878 | 0.215 | 0.05 |
| 5. | 2-Hexenal | 0.766 | 0.885 | 0.111 |
| 6. | Aromadendrene | 0.611 | 0.213 | 0.131 |
| 7. | Isoledene | 0.649 | 0.151 | 0.282 |
| 8. | Hexadecanoic acid | 0.232 | 0.095 | 0.083 |
| 9. | δ-Cadinene | 0.708 | 0.202 | 0.223 |

Abbreviations:

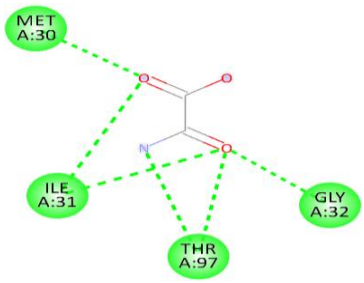
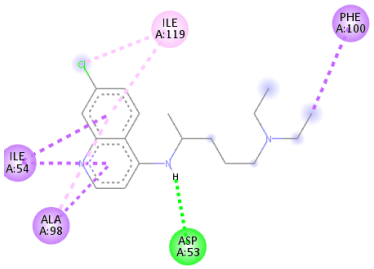
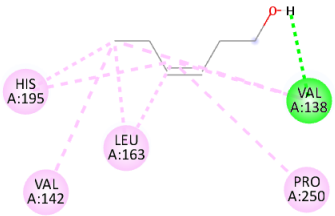
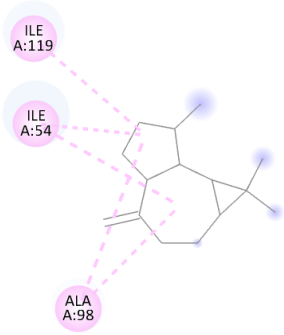
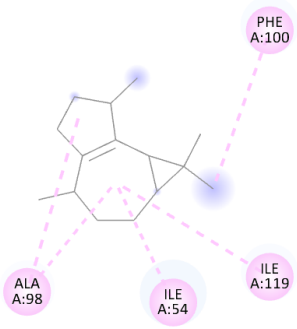
| | | |
|---|---|---|
| 0.00 – 0.30 | (Colorless) | = Safe |
| 0.31 – 0.71 | (Yellow) | = Moderate |
| 0.71 – 1.0 | (Red) | = Toxic |

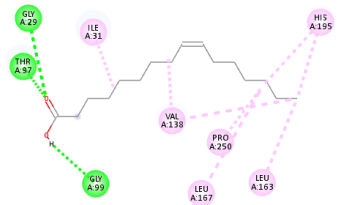
Source: ADMETlab Database

The first metric considered in the toxicity study, as shown in Table 4, is hepatotoxicity, which indicates a compound's ability to cause liver damage. The predictions showed that the control chemical chloroquine, as well as the test substances cis-3-Hexen-1-ol, Aromadendrene, Isoledene, and Hexadecanoic acid, were non-toxic, implying no negative effects on liver health. In contrast, numerous test substances were found to have potential hepatotoxic effects. According to Novianty *et al*. (2024), depending on the dose, hazardous chemicals might cause liver abnormalities such as hepatocyte enlargement, fatty degeneration, inflammation, and steatosis. The second metric, AMES toxicity, assesses the mutagenicity of substances. Table 4 shows that 2-Hexenal is mutagenic and carcinogenic. The AMES test predicts a compound's ability to produce genetic changes using bacterial models (Krihariyani *et al*., 2021). The Rat Oral Acute Toxicity ($LD_{50}$) measure determines the fatal dose of a chemical taken orally. In Table 4, the control chemical chloroquine has a high $LD_{50}$ value, indicating low toxicity and a larger tolerance threshold. Astuty and Noer (2022) found that substances with greater $LD_{50}$ values are less harmful, while lower $LD_{50}$ values indicate increased toxicity and danger. Four of the eight L. domesticum test compounds were found to have safe to moderate toxicity levels. Among these, cis-3-Hexen-1-ol, Aromadendrene, and Isoledene were somewhat hazardous, necessitating strict dosage control, although Hexadecanoic acid was deemed safe. As a result, these four compounds were moved to the molecular docking stage to determine their interactions with the target enzyme PfLDH.

**Molecular docking.** The test compounds that successfully passed previous evaluations proceeded to the molecular docking phase to examine the interaction of *L. domesticum* compounds in inhibiting the growth and development of *Plasmodium falciparum* through the target enzyme PfLDH *in silico*. This docking analysis involved four test ligands, one control ligand (chloroquine), and one natural ligand (oxamate, OXM) as the receptor reference. The molecular docking process generated binding affinity values and visualized 2D and 3D interaction profiles, as presented in Tables 5 and 6. According to Table 5, the natural ligand OXM exhibited a binding affinity of −4.3 kcal/mol, while the control ligand chloroquine showed a stronger interaction with a binding affinity of −6.4 kcal/mol. Among the test ligands, Hexadecanoic acid and Isoledene demonstrated more negative binding affinity values than OXM, indicating stronger binding potential, whereas only Aromadendrene showed a lower binding affinity than chloroquine.

**Table 5.** Docking results

| Ligand | Binding Affinity | Hydrogen Bond Distance | Hydrogen Bonds | Hydrophobic Bonds | Van Der Waals Bond | 2D Image |
|---|---|---|---|---|---|---|
| OXM (Native) | -4,3 | 3.1<br>2.8<br>3.2<br>3.1 | MET30,<br>GLY32,<br>ILE31,<br>THR97. | - | - |  |
| Chloroquine (Control) | -6,4 | 2.1<br>3.2 | ASP53, | ILE54.<br>ALA98,<br>PHE100<br>ILE119 | - |  |
| cis-3-Hexen-1-ol | -4,1 | 2.0 | VAL138 | VAL142,<br>HIS195,<br>LEU164,<br>PRO250 | - |  |
| Aromadendrene | -7,2 | - | - | ILE54,<br>ALA98,<br>ILE119 | - |  |
| Isoledene | -6,3 | - | - | PHE100,<br>ILE119,<br>ILE54,<br>ALA98 | - |  |

| | | | | | | |
|---|---|---|---|---|---|---|
| Hexadecanoic acid | -6 | 3.1<br>3.1<br>2.4 | GLY29,<br>THR97,<br>GLY99 | ILE31,<br>VAL138,<br>PRO250,<br>HIS195,<br>LEU167,<br>LEU163 | - |  |

Note: Amino acid residues in bold are the same amino acid as the active site

The binding affinity values of the test compounds ranged from −7.2 to −4.1 kcal/mol. Among these, Aromadendrene exhibited the strongest interaction with PfLDH, exceeding the control ligand chloroquine (−6.4 kcal/mol). As shown in Table 5, Aromadendrene produced the most negative binding energy, suggesting high stability and strong interaction with the enzyme. This pattern aligns with the principle that more negative docking scores indicate stronger ligand–enzyme interactions (Chaniad *et al*., 2021) and that stable ligand binding enhances potential biological activity (Kinasih *et al*., 2023).

Following the docking process, molecular interactions were visualized to analyze hydrogen bonding, hydrophobic interactions, and residue contacts. Hydrogen bond distances between 2.2–2.5 Å indicate strong interactions, 2.5–3.2 Å indicate moderate strength, and values >3.2 Å indicate weak bonds (Kai *et al*., 2021). The *L. domesticum* metabolites formed hydrogen bonds ranging from 2.0 to 3.1 Å, representing moderate-to-strong interactions. Aromadendrene and isoledene did not form hydrogen bonds, implying that their binding strength arises predominantly from hydrophobic interactions.

**Mechanism of PfLDH inhibition and interaction interpretation.** The PfLDH plays a critical role in *P. falciparum* glycolysis by converting pyruvate to lactate and regenerating $NAD^+$, enabling ATP production under anaerobic conditions (Zakaria *et al*., 2020). Inhibitors typically act by occupying the active-site loop, thereby blocking substrate access and disrupting catalytic turnover. Residues such as GLY29 and THR97 are essential for substrate positioning, while HIS195 serves as a proton-transfer residue. Disrupting the interactions at these positions interferes with pyruvate reduction and consequently hinders energy production in the parasite. Among the test ligands, hexadecanoic acid formed the greatest number of hydrogen bonds, specifically with GLY29, THR97, and GLY99. Its interaction with GLY29 and THR97 suggests interference with substrate orientation, while hydrophobic contact near HIS195 may disrupt proton transfer. These interactions indicate strong occupancy of the catalytic region and support its potential as a PfLDH inhibitor (Astuty & Noer, 2022).

Aromadendrene and isoledene, although lacking hydrogen bonds, displayed extensive hydrophobic interactions—particularly with ILE54, ALA98, and ILE119. Their sesquiterpenoid structures allow deep insertion into the hydrophobic PfLDH pocket, explaining their strong binding affinities despite the absence of polar contacts. Hydrophobic packing is a well-recognized mechanism for stabilizing inhibitor binding in PfLDH and other glycolytic enzymes. The natural ligand oxamate interacted with MET30, GLY32, ILE31, and THR97, consistent with its role as a substrate analog, while chloroquine interacted through hydrogen bonding at ASP53 and hydrophobic interactions at PHE100. Hexadecanoic acid sharing key residues—especially GLY29, THR97, and HIS195—with the catalytic site reinforces its mechanistic plausibility as an inhibitor.

The binding affinity of chloroquine (−6.4 kcal/mol) is consistent with values previously reported for PfLDH docking study (−6.0 to −6.6 kcal/mol) Khan *et al*. (2025), confirming the reliability of the docking protocol. Fatty acids such as palmitic and palmitoleic acid have been reported to exhibit antimalarial properties through membrane disruption and enzyme interaction (Bickii *et al*., 2007; da Silva Ferreira *et al*., 2018). Sesquiterpenes—including aromadendrene—are known for cytotoxic and antimalarial activities (Afoulous *et al*., 2011; Abu-Izneid *et al*., 2020), which supports the strong docking performance observed in the present study.

Collectively, the docking results indicate that the four *L. domesticum* metabolites—cis-3-hexen-1-ol, aromadendrene, isoledene, and hexadecanoic acid—possess potential inhibitory activity against PfLDH. Hexadecanoic acid demonstrates the strongest mechanistic fit due to its direct engagement with multiple catalytic residues, while aromadendrene shows the highest binding affinity, driven by hydrophobic complementarity within the PfLDH active site. These findings support *L. domesticum* as a promising source of natural antimalarial lead compounds targeting the glycolytic pathway of *P. falciparum*.

**Study limitations and future prospects.** This investigation was conducted exclusively in silico, hence restricting the capacity to validate chemical action under physiological circumstances. Molecular docking yields significant predictions; yet it neglects protein flexibility, solvent dynamics, and metabolic reactions. The PfLDH structure utilised (PDB ID: 1LDG) depicts a static conformation, while genuine protein–ligand interactions entail dynamic variations. Moreover, ADME and toxicity predictions depend on computational models that may inadequately represent biological complexity. Subsequent research should incorporate molecular dynamics simulations to evaluate the durability of receptor-ligand interactions over time (Pieroni *et al*., 2023), specifically for hexadecanoic acid and aromadendrene. Subsequent *in vitro* enzyme inhibition studies and cell-based antiplasmodial evaluations are crucial to confirm anticipated action, then promising compounds must thereafter undergo i*n vivo* pharmacokinetic and toxicology assessments (Adebayo *et al*., 2024). Examining chemical derivatives or structural alterations of the lead compounds may further improve binding affinity, specificity, and safety.

## CONCLUSION

This study identified four *Lansium domesticum* metabolites—cis-3-hexen-1-ol, aromadendrene, isoledene, and hexadecanoic acid—as promising antimalarial candidates based on integrated in silico screening. These compounds fulfilled physicochemical, pharmacokinetic, and toxicity criteria, and molecular docking revealed favorable interactions with the PfLDH enzyme. Among them, hexadecanoic acid showed the strongest mechanistic potential through direct engagement with key catalytic residues of PfLDH. While the findings highlight *L. domesticum* as a potential source of antimalarial lead molecules, further validation is required. Future studies should include molecular dynamics simulations to confirm binding stability, followed by *in vitro* and *in vivo* assays to evaluate biological activity and therapeutic feasibility.

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