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Predicition Molecular Docking, Pharmacokinetic, Physicochemical, Toxicity, Synthetic Accessibility Aspect of Several Compounds in *Cratoxylum glaucum* and *Cratoxylum arborescens* as Antimalarial

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Abstract: This study aims to identify potential antimalarial compounds targeting the *Plasmodium falciparum* lactate dehydrogenase enzyme (PfLDH), given the parasite's dependency on glycolysis for energy production. Considering the high similarity of LDH enzymes across Plasmodium species, developing novel PfLDH inhibitors may offer therapeutic benefits, particularly against *P. vivax, P. malariae,* and *P. ovale*. Computational approaches were employed to screen natural compounds from the Cratoxylum genus (*Cratoxylum glaucum* and *Cratoxylum arborescens*). Molecular docking was performed using Molegro Virtual Docking (MVD) to assess binding affinity. SwissADME was utilized to evaluate pharmacokinetic, physicochemical, synthetic accessibility properties, and ProTox II was used for toxicity prediction. Molecular docking results indicated that fuscaxanthone C and 3-geranyloxy-6-methyl-1,8-dihydroxyanthraquinone exhibited strong inhibitory activity against PfLDH, with rerank scores of -103.068 kcal/mol and -111.141 kcal/mol, respectively surpassing the reference ligand chloroquine (-94.307 kcal/mol). Pharmacokinetic analysis revealed that all compounds, except stigmasterol and fuscaxanthone C, met Lipinski's Rule of Five. Toxicity prediction categorized fuscaxanthone C as Class III (toxic). Additionally, synthetic accessibility predictions indicated that all compounds, except stigmasterol, are easy to synthesize. Natural compounds from the Cratoxylum genus, particularly 3-geranyloxy-6-methyl-1,8-dihydroxyanthraquinone, show promise as PfLDH inhibitors. Despite its potency, fuscaxanthone C's toxicity profile warrants caution. Further studies are needed to validate these findings through in vitro and in vivo testing.
Keywords: *Cratoxylum glaucum*; *Cratoxylum arborescens*; malaria; molecular docking

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INTRODUCTION

Malaria is a prevalent infectious disease that poses a significant risk to approximately half of the global population. The World Malaria Report 2022 estimates that approximately 247 million people worldwide were infected with malaria, which was responsible for 619 thousand deaths in 2021 (WHO, 2022). In 2021, the Ministry of Health of the Republic of Indonesia documented 304,607 cases of malaria in Indonesia. Consequently, the Annual Parasite Incidence (API) data indicates that malaria accounted for 1.1 fatalities per 1,000 individuals. Malaria-endemic regions of significant stature have been identified in Papua, East Nusa Tenggara, East Kalimantan, and West Papua (Kemenkes RI, 2023). This disease is transmitted by female Anopheles mosquitoes. Plasmodium pathogens of five distinct species are capable of infecting humans (Taek et al., 2024). Nevertheless, *Plasmodium falciparum*

stands out as the most pathogenic species, capable of causing severe malaria and potentially fatal outcomes for immunocompromised individuals (particularly children under the age of five) if left untreated (Suryanto et al., 2024).

Malaria commonly manifests as chills, muscle aches, and a high fever 10–15 days following the bite. Most of the time, infections can be cured with the proper medications, but in certain circumstances, serious illnesses can emerge and even result in death. Numerous diseases are associated with severe malaria, including anemia, metabolic changes, renal failure, liver and lung dysfunctions, and cerebral malaria (Rénia et al., 2012). Resistance to several malaria medications has been reported, such as chloroquine, sulfadoxine-pyrimethamine, and artemisinin-based combination treatment (Rahmasari et al., 2022). Novel therapeutic candidates from a variety of medicinal plant resources provide the basis for phytomedicines and antimalarials. Several antimalarial drugs are derived from natural sources, such as terpenoid compounds are utilized in the synthesis of the artemisinin medication sourced from *Artemisia annua*, while alkaloid compounds are employed in the production of quinine medication extracted from the bark of the cinchona tree (Habibi et al., 2022).

The plant genus with potential for further development as an antimalarial agent is Cratoxylum. Chemotaxonomic studies report that plants within this genus contain major secondary metabolites from the polyphenol group (xanthones, flavonoids, quinones, anthraquinones, and phenols) (Son, 2019). Additionally, reports on the in vitro antimalarial activity of *C. maingayi*, *C. cochinchinense*, and *C. sumatranum* exist (Laphookhieo et al., 2009; Tumewu et al., 2021). Interestingly, *Cratoxylum glaucum* and *Cratoxylum arborescens* have not been reported as antimalarial. Sim et al (2011) in their research succeeded in isolating several compounds from the bark of *C. glaucum* and *C. arborescens* which showed antioxidant activity, such as 5'-demethoxycadensin G (alkaloid), fuscaxanthone C (xanthone), β-mangostin (xanthone), 3-geranyloxy-6-methyl-1,8-dihydroxyanthraquinone (antrakuinon), vismiaquinone (antrakuinon), 1,8-dihydroxy-3-methoxy-6-methylanthraquinone (antrakuinon), and stigmasterol (sterol) (Sim et al., 2011).

It is critical to thoroughly evaluate the safety of a drug candidate derived from natural compounds with regard to contraindications, adverse effects, toxicity, and treatment duration throughout the registration or authorization process. Prior to clinical studies, the drug candidate compound must be subjected to comprehensive evaluations of carcinogenicity, reproductive and developmental toxicity, in silico, in vitro, and in vivo genotoxicity, as well as studies assessing the impact on drug metabolizing enzymes (Habibi et al., 2022). Molecular docking has become an indispensable element in the realm of in silico drug discovery. Predicting atomic interactions between a minuscule chemical and a protein is necessary for this method. In molecular docking, the ligand-receptor complex is predicted through the use of computer-based methods. The docking procedure consists of two fundamental stages: ligand sampling and scoring function utilization (Das et al., 2020; Agu et al., 2023).

For the purpose of identifying a potential molecular target for a malaria drug, molecular docking will be implemented. It has been suggested that the *Plasmodium falciparum* lactate dehydrogenase enzyme (PfLDH) could serve as a molecular therapeutic target. Although quinoline pharmaceuticals primarily inhibit heme polymerization, other molecular targets have been recognized as crucial in improving their biological effectiveness against *P. falciparum* (Penna-Coutinho et al., 2011; Chaniad et al., 2021). Enzyme LDH catalyzes the transformation of pyruvate to lactate, signifying the final stage of glycolysis, which is essential for cellular energy production.

During the degradation of hemoglobin, malarial parasites generate ferriprotoporphyrin IX (hematin), which competes with NADH for the active site of PfLDH and induces parasite intoxication. Penna-Coutinho et al. (2011) state that the parasite's decline is the result of hematin polymerization into hemozoin within its food vacuole, which is critical to its survival. Therefore, this research aims to identify potential antimalarial compounds from *C. glaucum* and *C. arborescens* through molecular docking analysis targeting the PfLDH enzyme, and to evaluate their pharmacokinetic, physicochemical, synthetic accessibility, and toxicity profiles.

METHOD

PfLDH and Chloroquine Structure Preparation

The molecular interaction experiment was performed utilizing a Lenovo laptop operating on Windows 11, 64-bit. It features 16 GB of RAM, a 512 GB SSD, and an AMD Ryzen 5,000 series processor. Among the applications utilized are ChemDraw version 17 and Molegro Virtual Docker (MVD). The 3D structure of PfLDH, which serves as the receptor (PDB ID: 1LDG), was acquired in pdb format from the RCSB PDB. Concurrently, the three-dimensional conformation of chloroquine (molecule 3) was acquired via PubChem.

Ligand Molecule Preparation

We drew the structures of compounds of the stem bark of *Cratoxylum glaucum* and *Cratoxylum arborescens* (Sim et al., 2011): 3-geranyloxy-6-methyl-1,8 dihydroxyanthraquinone (molecule 1), fuscaxanthone C (molecule 2), 1,8-dihydroxy-3-methoxy-6-methylanthraquinone (molecule 4), vismiaquinone (molecule 5), 5'-demethoxycadensin G (molecule 6), β-mangostin (molecule 7), and stigmasterol (molecule 8) using ChewDraw Ultra 12 in MDL.mol format. We then optimized them using Avogadro tools to achieve the minimum energy state.

Molecular Docking Analysis

Using molecular docking, we determined the interaction between compounds from *C. glaucum* and *C. arborescens* with PfLDH using the Molegro Virtual Docker (MVD) program. The Molegro Virtual Docker (MVD) software is utilized for determining the interaction energies between ligands and macromolecular systems, employing the 3D structures of both the protein and ligands (Penna-Coutinho et al., 2011). In short, the docking process began by downloading the receptor from the Protein Data Bank (PDB), preparing the ligands stored in SDF format, conducting docking and amino acid analysis using MVD, detecting the receptor position and interaction sites, inserting the 3D compound structures into the selected cavity through alignment, predicting the interaction positions between the compound and receptor, and identifying the pharmacophore groups of the formed bonds.

Pharmacokinetic, Physicochemical, Synthetic Accessibility, And Toxicity Characteristics Prediction

The SMILES code is utilized by researchers to input the synthetic accessibility, pharmacokinetic, and physicochemical characteristics of each compound onto the SwissADME website (http://www.swissadme.ch/index.php). ADME characteristics consist of solubility, absorption in the digestive tract, blood-brain barrier traversal, bioavailability, and synthesis capability (Daina et al., 2017; Ononamadu & Ibrahim, 2021). The Protox II website (https://tox-new.charite.de/protox_II) is used to obtain predictions of toxicity properties. The classification of toxicity classes is based on the value of the lethal dose or LD_{50} (mg/kg body weight) (GHS): Class I: indicates fatality

upon ingestion (LD50 ≤ 5 mg/kg); Class II: signifies fatality if ingested (5 mg/kg < LD_{50} ≤ 50 mg/kg); Class III: reflects toxicity if swallowed (50 mg/kg < LD_{50} ≤ 300 mg/kg); Class IV: denotes harm if ingested (300 mg/kg < LD_{50} ≤ 2,000 mg/kg); Class V: suggests potential harm if swallowed (2,000 mg/kg < LD_{50} ≤ 5,000 mg/kg) (Gadaleta et al., 2019).

RESULTS AND DISCUSSION

Molecular Docking Analysis

Molecular docking, based on MolDock Scoring functions, was used to assess how well the selected compounds could fit into the active site of PfLDH. The MolDock Score reflects the estimated free energy required for ligand binding, with more negative values indicating stronger interactions. In this context, to evaluate the antimalarial potential of secondary metabolites from *C. arborescens* and *C. glaucum*, a molecular docking study was conducted targeting the PfLDH enzyme

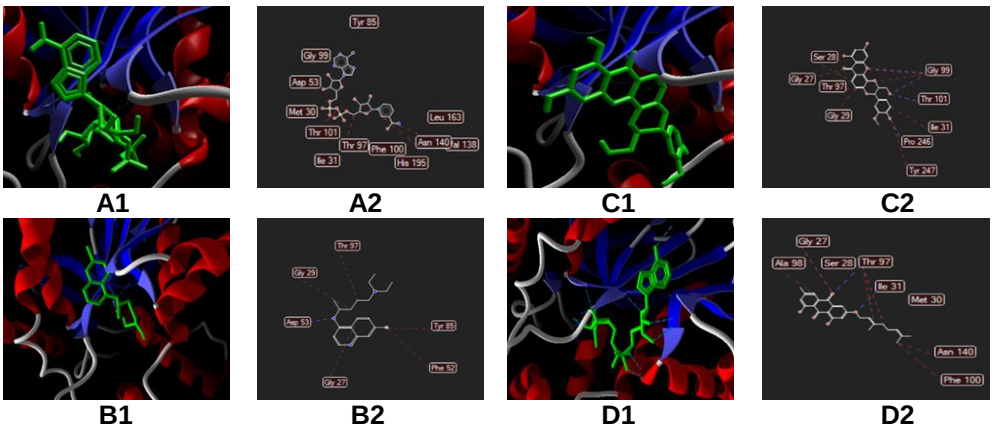

Figure 1. The interaction of ligands with amino acids (A. native ligand; B. chloroquine; C. fuscaxanthone C; D. 3-geranyloxy-6-methyl-1,8 dihydroxyanthraquinone; 1. 3Dimention; 2. 2Dimention)

Table 1. Results of MolDock Scores (MVD) values

Compound	Rerank score (kcal/mol)	Activity Prediction
3-geranyloxy-6-methyl-1,8-dihydroxyanthaquinone	-111.141	Active
Fuscaxanthone C	-103.068	Active
Chloroquine	-94.307	Active
1,8-dihydroxy-3-methoxy-6-methylanthraquinone	-88.961	Inactive
Vismiaquinone	-87.899	Inactive
5'-demethoxycadensin G	-87.676	Inactive
β-mangostin	-41.064	Inactive
Stigmasterol	74.270	Inactive

Table 2. The interaction of ligands with amino acids

Comp.	Interaction of amino acid residues	
	Hydrogen bonds	Other bonds
NR	Tyr 85, **Asp 53***, Gly 99, **Met 30***, **Ile 31***, Phe 100, His 195, Leu 163, Val 138, Asn 140	Thr 101, **Thr 97***, **Asn 140***, Val 138

Comp.	Interaction of amino acid residues	
	Hydrogen bonds	**Other bonds**
Mol 1.	Thr 97, **Ile 31***	Gly 25, Ser 28, **Thr 97***, Ala 98, Ile 31, Met 30, **Asn 140***, Phe 100
Mol. 2	Thr 97, **Met 30***	Asp 53, Phe 52, Gly 99, Ala 98, **Thr 97***, Met 30
CQ	**Asp 53***	**Thr 97***, Gly 29, Asp 53, Gly 27, Phe 52, Tyr 85

Explained: *(Similarity of amino acid interactions with native ligand); NR (native ligand); molecule 1 (3-geranyloxy-6-methyl-1,8dihydroxyanthaquinone); molecule 2 (fuscaxanthone C); CQ (chloroquine).

Table 1 provides a summary of the outcomes of the molecular docking investigation employing MolDock Scores (MVD) to ascertain the inhibitory effects of seven compounds derived from *C. arborescens* and *C. glaucum* on PfLDH. The rerank score value of the comparative ligand (chloroquine) is documented to be -94.307 kcal/mol, whereas the rerank score values of the seven compounds demonstrate considerable variation. The rerank scores for the compounds 3-geranyloxy-6-methyl-1,8-dihydroxyanthraquinone and stigmasterol, which has the lowest score, vary from -111.141 kcal/mol to 74.270 kcal/mol, respectively. The rerank score of the MolDock Scores provides insight into the energy required to establish a bond with the receptor, thereby offering a potential predictor of the computational simulation activity of a compound. Shah et al. (2021) state that a stronger affinity between the ligand and the receptor is indicated by a lower rerank score. According to the outcomes of the docking simulation, it is possible to predict that among the seven compounds derived from the *C. arborescens* and *C. glaucum* plants, only two (geranyloxy-6-methyl-1,8-dihydroxyanthraquinone and fuscaxanthone C) possess significantly greater potency in inhibiting the PfLDH receptor in comparison to chloroquine.

Molecular docking results on the interaction of amino acid residues on the active ligand show hydrogen bonding and several hydrophobic interactions at the PfLDH binding site responsible for antimalarial activity (**Figure 1** and **Table 2**). The main objective in understanding the interaction of amino acid residues is to comprehend the interactions involved in the pharmacological effects of inhibiting the PfLDH target protein. The hydrogen bonds and other hydrophobic interactions between the derivative and the receptor may be responsible for the derivative's high binding affinity (Ibrahim et al., 2022). An amino acid residue close to the enzyme's surface creates a binding groove. Several of these amino acids, including ALA98, ILE54, and ILE119, are identical to those that bind NADH to its binding site (Zakaria et al., 2020). Compounds 3-geranyloxy-6-methyl-1,8-dihydroxyanthaquinone and fuscaxanthone C also interact specifically at the PfLDH binding site.

Pharmacokinetic, physicochemical, and synthetic accessibility prediction

To further assess the pharmacokinetic profiles of the selected compounds, a Boiled-Egg plot analysis was performed to predict human intestinal absorption (HIA) and blood-brain barrier (BBB) permeability based on cLogP and TPSA values. The values of the Topological Polar Surface Areas (TPSA) vary between 20.23 and 138.82 Ω². Compounds with water solubility (cLogS) values between -3.87 and -7.46 are considered soluble to moderately soluble. **Figure 2** illustrates the relationship between the cLogP and TPSA values of these compounds and their predicted human intestinal absorption (HIA) and blood-brain barrier (BBB) access. They are separated into three categories in the boiled-egg plot: the grey area (no HIA or BBB access), the white area (HIA access), and the yellow area (BBB access). Molecule 3, chloroquine, is

anticipated to traverse the BBB. The white area (HIA) contains the following compounds: fuscaxanthone C (molecule 2), 3-geranyloxy-6-methyl-1,8-dihydroxyanthraquinone (molecule 1), 1,8-dihydroxy-3-methoxy-6-methylanthraquinone (molecule 4), vismiaquinone (molecule 5), and β-mangostin (molecule 7). Chedik et al. (2017) utilized Human Absorption Simulation (HAS) measurements to investigate pharmacokinetic studies pertaining to oral administration.

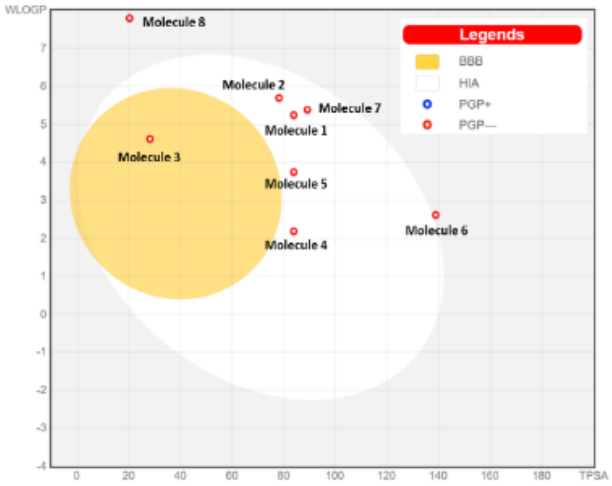

Figure 2. The boiled-egg plot of compounds

Table 3. Pharmacokinetic, physicochemical, and synthetic accessibility prediction

Comp.	MW <500 g/mol	Log P <5	HBA <10	HBD <5	SA
Mol. 1	406.47	4.87	5	2	3.73
Mol. 2	438.51	5.36	6	1	4.19
Mol. 3	319.87	4.15	2	1	2.76
Mol. 4	284.26	2.27	5	2	2.69
Mol. 5	352.38	3.66	5	2	3.49
Mol. 6	438.38	2.30	9	4	4.53
Mol. 7	424.49	4.97	6	2	4.07
Mol. 8	412.69	6.97	1	1	6.21

The pharmacokinetic and physicochemical characteristics of compounds derived from *C. arborescens* and *C. glaucum* are compared to those of the reference drug, chloroquine, in **Table 3**. To assess these properties, parameters derived from Lipinski's Rule of Five (RO5) were utilized. It is predicted that all compounds derived from this plant, including the reference drug chloroquine, will satisfy the RO5 criteria, with the exception of stigmasterol and fuscaxanthone C, which have a log P value below 5 (Lipinski et al., 2001). RO5 criteria are valuable for predicting the similarity of a drug in a chemical compound with a specific biological activity intended for oral administration. Sub-500 g/mol molecular weight, log P value <5 (indicating hydrophobicity), hydrogen bond donor (HBD) values >5, and hydrogen bond acceptor (HBA) values not exceeding >10 are the minimum requirements for drug compounds according to RO5 (Chagas et al., 2018; Huang et al., 2019; Ma'arif et al., 2022). It is hypothesized that if a compound satisfies the five principles of RO5, its pharmacokinetic properties will improve, thereby increasing its bioavailability within the organism. Excluding drug molecule screening that fails to comply is critical for initial compound screening as a

candidate drug; doing so can result in cost savings for research and drug development. The RO5 guidelines may also be utilized as a benchmark or reference for compound synthesis in the context of clinical trial requirements and the construction of drug databases (Chen et al., 2020).

The Synthetic Accessibility (SA) score is a metric utilized in virtual screening to assess the accessibility of drug-like compounds. It is associated with organic chemistry concepts such as molecular docking and QSAR, both of which are computational approaches to compound design. The SA values span from 1 to 10, where a value approaching 1 indicates a simpler synthesis process and a value approaching 10 indicates a more difficult synthesis process (Daina et al., 2017). We predict compound synthesis of *C. arborescens* and *C. glaucum* to be straightforward, with the exception of stigmasterol, which has a SA value of 6 and is approaching 10.

Toxicity properties prediction

Organ toxicity, more precisely hepatotoxicity, as predicted by ProTox-II, was not observed in any of the examined compounds. Hepatotoxicity, which is also referred to as organ toxicity, denotes the impairment or operation of the liver. The liver is often the organ that sustains damage in the presence of substances or pharmaceuticals (Björnsson, 2016). However, it was expected that every compound would demonstrate immunotoxic characteristics, as ascertained by the toxicity endpoint. Substance-induced modifications to the functionality of the systemic and local immune systems are the defining characteristics of immunotoxicity. Immunotoxicity can be caused by synthetic molecules, pharmaceuticals, and natural contaminants alike. The detection of immunotoxicity may pose difficulties as different medications have the potential to elicit unique effects on immune function (Abdollahi & Behboudi, 2014). Mutagenic properties were observed in chloroquine, 1,8-dihydroxy-3-methoxy-6-methylanthraquinone, and vismiaquinone. Mutagenicity pertains to the capacity of a pharmaceutical product or chemical agent to induce injury to DNA or chromosomes, also known as mutation. Substances with this characteristic are known as mutagens (Hsu et al., 2016).

Table 4. Results of toxicity prediction

Comp.	Classification					
	Organ Toxicity		Toxicity Endpoint			LD50 (mg/kg)
Mol. 1	Inactive	Inactive	Active	Inactive	Inactive	IV (1,560)
Mol. 2	Inactive	Inactive	Active	Inactive	Inactive	III (150)
Mol. 3	Inactive	Inactive	Active	Active	Inactive	IV (750)
Mol. 4	Inactive	Inactive	Active	Active	Inactive	V (5,000)
Mol. 5	Inactive	Inactive	Active	Active	Inactive	V (5,000)
Mol. 6	Inactive	Inactive	Active	Inactive	Inactive	IV (650)
Mol. 7	Inactive	Inactive	Active	Inactive	Inactive	IV (1,500)
Mol. 8	Inactive	Inactive	Active	Inactive	Inactive	IV (890)

The toxicity prediction, which is predicated on the median lethal dose (LD_{50}), denotes the dose at which 50% of the animal population under investigation succumbs to death. Acute toxicity assessment is often the preliminary screening method employed to examine and appraise the potentially deleterious attributes of a drug. Compounds exhibiting an oral LD_{50} ranging from 0 to 50 mg/kgBW are considered to be exceedingly hazardous, while those surpassing 2,000 mg/kgBW are considered to have low toxicity (Morris-Schaffer & McCoy, 2021). The LD_{50} values for all compounds

indicated that they belonged to classes IV and V, with the exception of fuscaxanthone C, which belonged to toxicity Class III (toxic if ingested) (chloroquine, LD_{50} Class IV).

CONCLUSION

The results of molecular docking analysis revealed that among the seven compounds obtained from *C. arborescens* and *C. glaucum*, only fuscaxanthone C and 3-geranyloxy-6-methyl-1,8-dihydroxyanthraquinone demonstrated inhibitory activity against PfLDH in comparison to the reference ligand, chloroquine. Nevertheless, the pharmacokinetic and physicochemical forecasts for fuscaxanthone C fail to satisfy the RO5 criteria and indicate the potential for toxicity. Consequently, additional investigation is required.

RECOMMENDATION

Further research through molecular dynamic observations and in vivo or in vitro tests is needed to optimize its development as an antimalarial drug candidate.

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