Nig. J. Biotech. Vol. 41(2): 95-107 (June 2025)
ISSN: 0189 1731
Available online at
http://www.ajol.info/index.php/njb/index
and https://bsn.org.ng
DOI: **10.5281/zenodo.15732233**

NIGERIAN JOURNAL OF BIOTECHNOLOGY

In Silico Evaluation of the Anti-Malaria Potential of *OLAX SUBSCORPIOIDEA* Leaf Extract

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Abstract

Malaria continues to pose a serious threat to world health, especially in sub-Saharan Africa, where medication resistance makes traditional treatments less effective.The study aims at ascertaining the antimalarial potential of *Olax subscorpioidea* leaf extract. The antimalarial potential of *Olax subscorpioidea* leaf extract was determined following ethanol extraction, compound identification and *in silico approach* **where the identified phytochemicals were subjected to** molecular docking**. According to the research findings, naringin (−7.608 kcal/mol), catechin (−7.102 kcal/mol), and resveratrol (−6.326 kcal/mol) demonstrated substantial binding affinities, whereas chloroquine, the reference medication, had a binding affinity of −10.673 kcal/mol. Like chloroquine, these chemicals formed important hydrogen bonds and hydrophobic interactions with the enzyme's active site, according to pharmacophore modeling result. According to ADMET result, the majority of the substances exhibited good water solubility (catechin and epicatechin at 1.74 mg/ml) and high oral bioavailability scores (0.55–0.56). According to toxicity profile result, substances such as naringin and flavan-3-ol were categorized as Class 5 (LD_{50} = 2300–2500 mg/kg) with low toxicological concerns, whereas epicatechin and catechin belonged to toxicity Class 6 (LD_{50} = 10,000 mg/kg), suggesting good safety. These results support *Olax subscorpioidea's* traditional use in the treatment of malaria and confirm its promise as a source of safe and efficient antimalarial drugs.**

Keywords: *Plasmodium falciparum*, *O subscorpioidea*, antimalarial, molecular docking, and drug development

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Introduction

Plasmodium falciparum is the cause of the deadliest type of malaria, which continues to be one of the biggest risks to global public health (Kant et al., 2021). The World Health Organization reports that each year, especially in sub-Saharan Africa, malaria results in more than 200 million illnesses and hundreds of thousands of fatalities (WHO, 2023). The rise of drug-resistant strains, particularly those resistant to artemisinin-based and chloroquine-based medicines, is undermining the efficacy of current treatments despite significant eradication efforts (Conrad and Rosenthal, 2019; Kant et al., 2021). The pressing need for new therapeutic medicines with unique molecular targets and modes of action is highlighted by the growing resistance dilemma.

To overcome these obstacles, in silico methods have emerged as a key component of contemporary drug discovery (Tung et al., 2022). Without the immediate need for laboratory testing, these computational methods—such as

molecular docking, pharmacophore modeling, and ADMET profiling—make it easier to predict ligand-receptor interactions, drug-likeness, and pharmacokinetic behaviors (Tung et al*.,* 2022; Kant et al., 2021). A first indicator of biological activity is provided by molecular docking, which models the binding affinity between candidate drugs and target proteins. The key elements that contribute to receptor binding, such as hydrogen bond donors, acceptors, and hydrophobic interactions, are further clarified using pharmacophore modeling. Early in the discovery phase, drugs with poor pharmacological profiles are filtered out using ADMET profiling, which assesses absorption, distribution, metabolism, excretion, and toxicity factors (Dong et al., 2020; Adeoye et al., 2019). These techniques are perfect for screening intricate phytochemical libraries since they are scalable and reasonably priced. There is good reason for the growing interest in plant-based medicine discovery around the world. As evidenced by the discovery of antimalarials like quinine from Cinchona spp. and artemisinin from Artemisia annua, natural products have long been abundant sources of therapeutic compounds (Newman and Cragg, 2020).

Many of the secondary metabolites found in medicinal plants, such as flavonoids, alkaloids, terpenes, and phenolics, have bioactivities against malarial targets such as ATPase enzymes, PfDHFR, and falcipain-2 (Ntie-Kang et al., 2020; Mojab, 2019). These phytochemicals are useful in the early stages of the antimalarial drug pipeline because, according to computational studies, they frequently exhibit favorable docking profiles and ADMET properties. *Olax subscorpioidea* has become a strong contender in this context. The herb is widely used in West African traditional medicine and is said to be effective in treating fevers, inflammatory diseases, and malaria (Dike et al., 2018; Idu et al., 2020). Its hepatoprotective, antioxidant, and antiplasmodial properties have been confirmed by recent experimental results (Ezeokonkwo et al., 2019; Odeyemi et al., 2021). However, little molecular evidence exists to explain how its bioactive components work against malaria. Therefore, to examine the binding interactions, pharmacophoric properties, and pharmacokinetic profiles of phytochemicals extracted from *O. subscorpioidea* leaves, this study used thorough in silico analysis. To confirm the plant's ethnopharmacological significance and find possible lead compounds for antimalarial drug development, this research aims to validate the plant's ethnopharmacological role and identify potential lead compounds for antimalarial drug development (Kant et al*.,* 2021; Ntie-Kang et al*.,* 2020).

Materials and Methods

Collection and Identification of Plant Material

The taxonomist (Dr. Nwankwo) of applied biology department of Ebonyi State University identified the plant *Olax subscorpioidea* after it was collected from the Mgbalukwu community in the Abakaliki Local Government Area, Ebonyi state.

Plant Material Preparation

The *Olax subscorpioidea* plant's leaves were gathered and allowed to dry completely at room temperature in the shade for three to five days. They were then ground into a smooth powder and used for extraction. 250 g of *Olax subscorpioidea* were placed in a conical flask with 500 ml of ethanol, and the flask was sealed with foil to prevent the ethanol from evaporating. A rotary evaporator was used to filter and dry the mixture after 48 hours. A sterile vial is used to hold the dried sample.

Ethanol Leaf Extraction of Olax subscorpioidea

In a sterile glass container, 250 g of the powdered leaf material was weighed and soaked in 95% ethanol at a 1:5 (w/v) ratio for the multiple downstream analyses. For 48–72 hours, the mixture was left at room temperature and stirred periodically to maximize the extraction of bioactive components. After the extraction period, the mixture was filtered first using muslin cloth to remove coarse particles and then through Whatman No. 1 filter paper to achieve a clean filtrate. To eliminate the ethanol solvent, the filtrate was concentrated using a rotary evaporator set at 40–50°C at low pressure. The resulting semi-solid extract was then dried further at 40°C in a hot-air oven until its weight remained constant. Until it was needed, the dried extract was kept at 4°C in an airtight container or a desiccator. (Ezeokonkwo, 2029; Eluu et al., 2019)

In silico Studies
Protein preparation

The protein Data Bank (PDB) repository provided the crystal structure of the human NADH kinase domain. The Glide protein preparation wizard's pane (Schrodinger Suite 2021-2) was used to prepare the protein. Bond orders were assigned, hydrogen was added, disulfide bonds were formed, and prime was used to fill in the loop and missing side chains. After removing water molecules that exceeded 3.0 A of the heteroatoms, the structure was optimized using PROPKA and reduced using OPLS2005. The receptor grid was then created to specify the ligands' binding pocket. (Sastry et al., 2013)

Ligand Preparation

The Ligprep module (Schrodinger Suite 2021-2) was used to prepare the lead compounds of Olax subscorpiodea (which were already extracted with their phytochemical identified and validated using PubChem database) for molecular docking. Correct chiralities were produced in low-energy 3D structures. At a physiological pH of 7.2 ± 0.2, the potential ionization states for every ligand structure were produced. Each ligand's stereoisomers were calculated by maintaining certain chairalities while varying others (Sastry et al., 2013).

Receptor grid generation

Receptor grid development allows determining the position and size of the protein's active site for ligand docking. Using Schrodinger Maestro 12.5's receptor grid generating tool, the scoring grid was established based on the co-crystallized ligand NADH. Nonpolar receptor atoms have a partial charge cut off 0.25 and a van der Waals (vdW) radius scaling factor of 1.0.

Protein-Ligand Docking

Molecular docking investigations were conducted utilizing the produced receptor grid file and the Protein-Ligand Docking Glide tool of Schrodinger Maestro12.8. Standard precision (SP) was used to dock the produced ligands with ligand sampling set to flexible and none (refine only). The partial charge cut-off for ligand atoms was set at 0.15, and the vdW (Van de Waals) radius scaling factors were scaled at 0.80.(Friesner et al., 2004)

Pharmacological analysis

Using insilico integrative model predictions at the SwissADME and PROTOX-II servers, the lead compounds of *Olax subscorpiodea* leaf extract were utilized by this software for the prediction of their drug-like properties such as: absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics were ascertained (Halgren et al., 2004).

Results

Docking Scores

Table 1 shows the docking scores of the standard drug (Chloroquine) and the selected compounds of *Olax subscorpiodea* leaf extract. Naringin, Catachin, Reseratrol, Naringenin, Flavan-3-ol, Opicatechir, Ribalinidine, Anthocyanin, Humulone and Cohumulor are the top-scoring compounds, with docking scores ranging from -7.608 kcal/mol to -4.852 kcal/mol

Table 1: The binding affinity (kcal/mol) of the top ten ranked bioactive compounds of *Olax subscorpiodea* against NADH targe

Names	**Pubchem Compound ID**	Binding affinity
Chloroquine	439153	-10.673
Naringin	442428	-7.608
Catachin	9064	-7102
Reseratrol	445154	-6.326
Naringenin	439246	-6.185
Flavan-3-ol	37072443	-6.116
Opicatechir	72276	-5.756
Ribalinidine	336322	-5.4
Anthocyani	145858	-4.952
Humulone	442911	-4.856
Cohumulor	196915	-4.852

Receptor-ligand complex pharmacophore modelling

Figures 1 through 7 display the pharmacophore models of the standard ligand and five chosen

compounds. A: hydrogen acceptor, D: hydrogen donor, H: hydrophobic contact, N: and R: aromatic ring are examples of interactions depicted in the models. The compounds from *Olax subscorpiodea* occupied the assigned bonding position and interacted with the identical amino acid residues that the reference drug interacted with, according to the two-dimensional images of proton ligand interactions. The chemicals established hydrophobic contacts with multiple amino acid residues of the ATP binding site in addition to one or more hydrogen bond interactions. Most malaria cycle inhibitors are said to target molecular interactions with these amino acid residues.

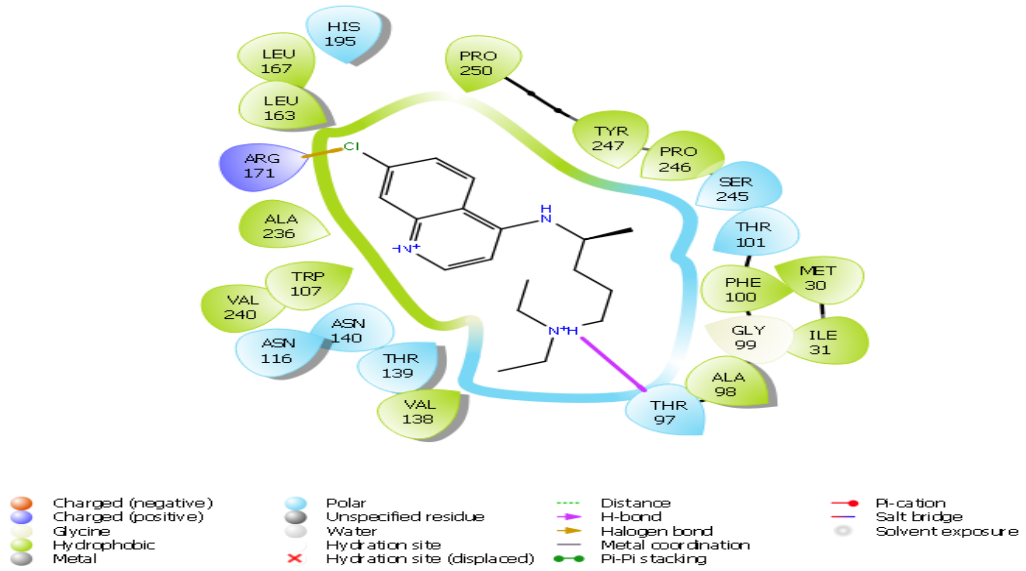


Fig 1: Two Dimensional Molecular Docking structure of standard drug and Biological target

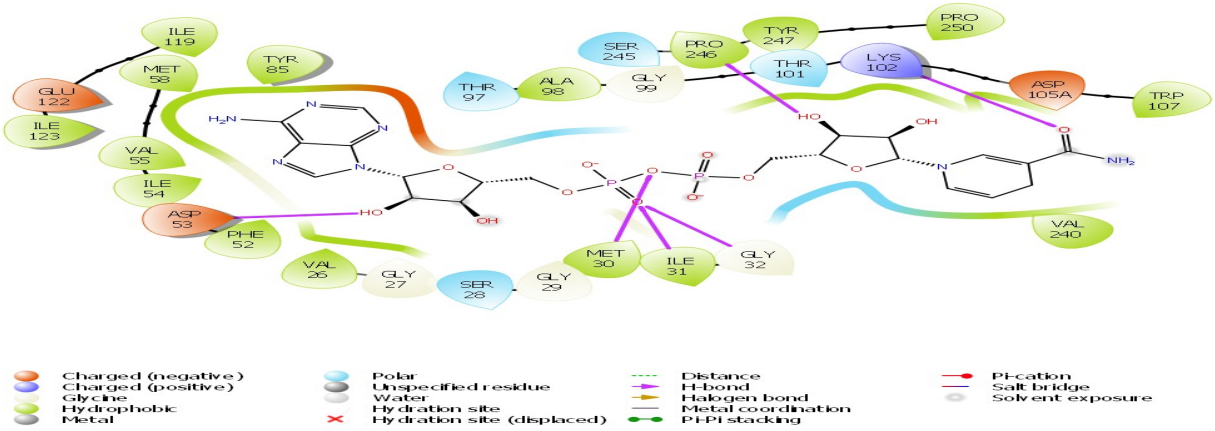


Fig 2: Two Dimensional Molecular Docking structure of NADH.

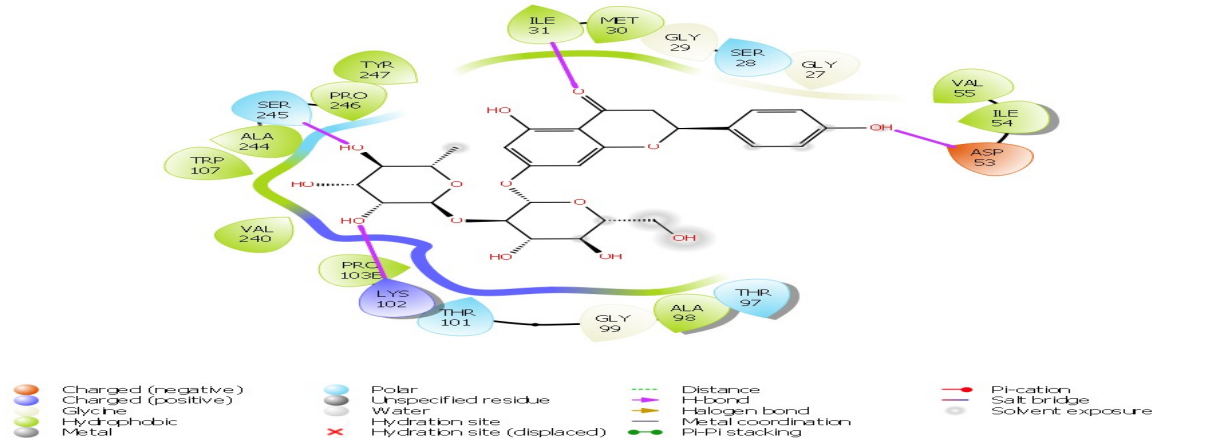


Fig 3: Two Dimensional Molecular Docking structure of Naringin compound and Biological target.

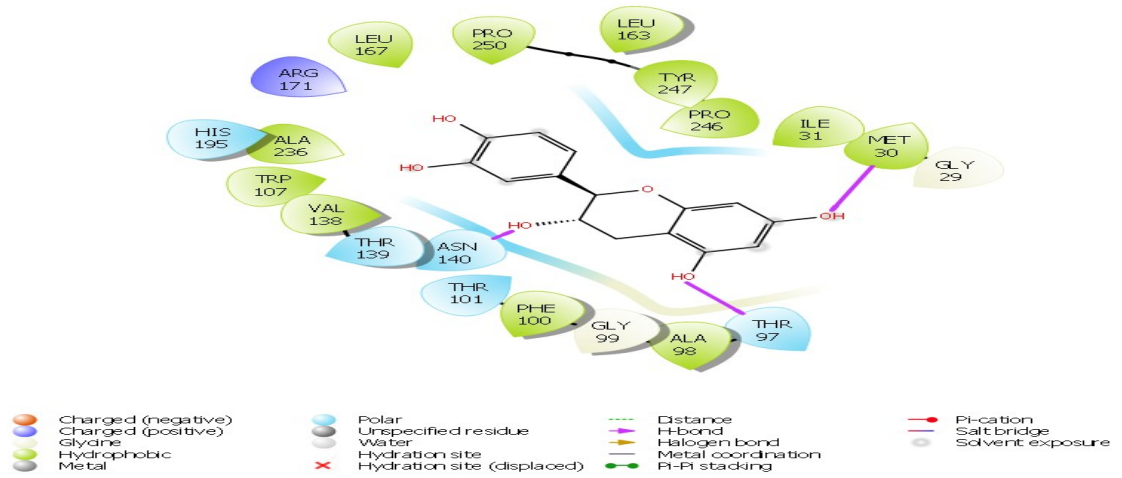


Fig 4: Two Dimensional Molecular Docking structure of Catachin and Biological target

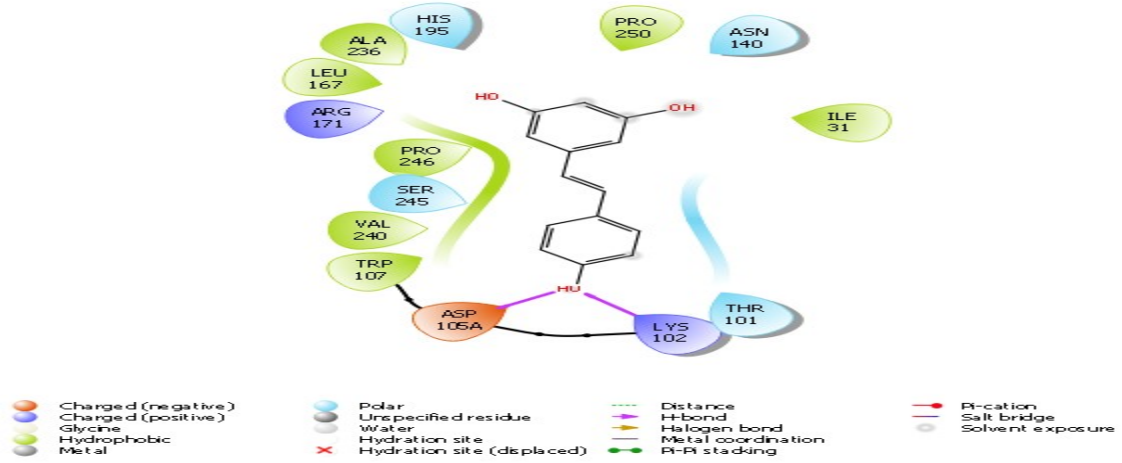


Fig 5: Two Dimensional Molecular Docking structure of Reseratrol and Biological target

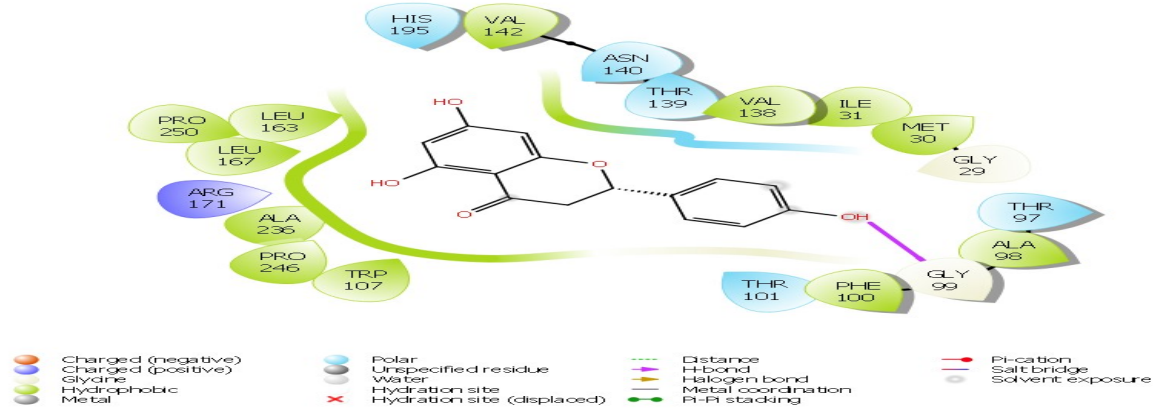


Fig 6: Two Dimensional Molecular Docking structure of Naringenin and Biological target

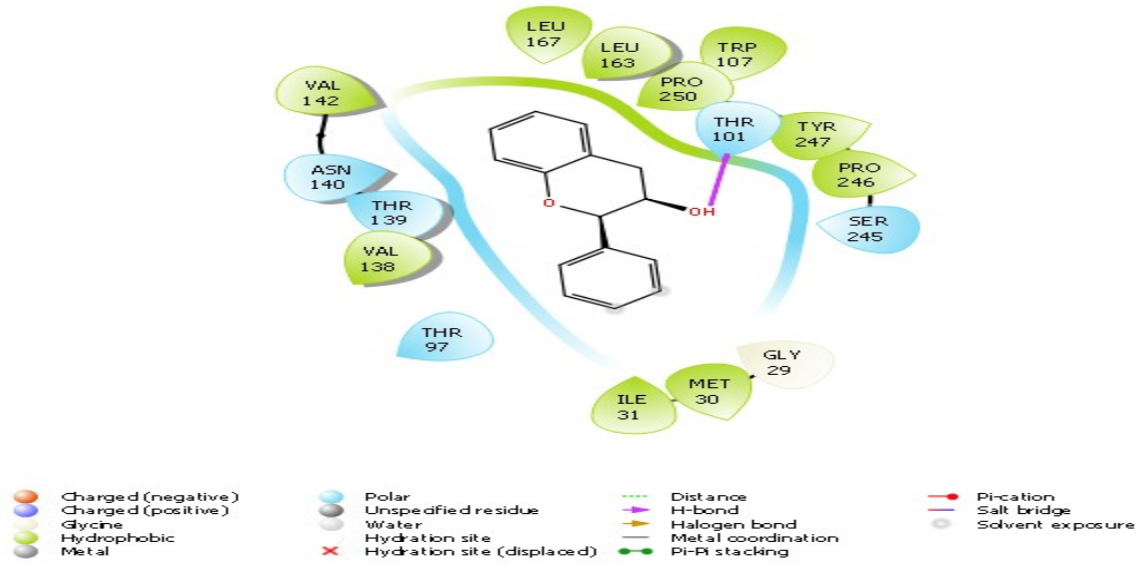


Fig 7: Two Dimensional Molecular Docking structure of Flavan-3-ol and Biological target.

Phytochemical Properties of Ten Selected leadCompounds

Table 2 shows the phytochemical properties of ten selected hit compounds, demonstrating their lipophilicity, water solubility, druglikeness bioavailability, toxicity as well as other parameters.

Table 2: The lipophilicity profile of the top 12 ranked phytochemical constituents of *Olax subscorpiodea*.

Molecule	**MW**	**iLOGP**	**XLOGP3**	**WLOGP**	**MLOGP**	**Silicos-IT Log P**	**Consensus Log P**
Naringin	580.53	2.38	-0.44	-1.49	-2.77	-1.64	-0.79
Catechin	290.27	1.47	0.36	1.22	0.24	0.98	0.85
Resveratrol	228.24	1.71	3.13	2.76	2.26	2.57	2.48
Naringenin	272.25	1.75	2.52	2.19	0.71	2.05	1.84
Flavan-3-ol	226.27	2.52	2.84	2.4	2.54	2.98	2.66
Epicatechin	290.27	1.47	0.36	1.22	0.24	0.98	0.85
Ribalinidine	275.3	2.06	1.57	1.32	0.89	1.91	1.55
Anthocyanin	207.25	-0.76	3.51	4.38	3.28	2.79	2.64
Humulone	362.46	3.18	4.18	4.25	1.13	4.19	3.39
Cohumulone	348.43	3.07	3.95	3.86	0.91	3.77	3.11
Sparteine	234.38	3.12	2.54	1.58	2.88	1.69	2.37
Adhumulone	579	5.86	9.22	8.7	2.97	4.17	6.18

The water solubility profile of the top 12 ranked phytochemical constituents of Olax subscorpiodea.

With very few exceptions, the majority of the phytochemicals from *Olax subscorpiodea* are categorized as soluble, according to the water solubility profile of the top-ranked phytochemicals. The following compounds have good water solubility: naringin, catechin, resveratrol, naringenin, flavan-3-ol, epicatechin, ribalinidine, and sparteine. Their ESOL Log S values range from -2.22 to -3.62, and their

corresponding solubility levels are above 0.05 mg/ml. The highest solubility is exhibited by epicatechin and catechin (1.74 mg/ml), followed by naringin (0.604 mg/ml). Adhumulone had an ESOL Log S of -8.38 and a very low solubility of 2.41E-06 mg/ml, while anthocyanin, humulone, and cohumulone had ESOL Log S values ranging from -4.01 to -4.26 and solubility levels between 0.020 mg/ml and 0.028 mg/ml (Table 3).

Table 3: The water solubility profile of the top 12 ranked phytochemical constituents of *Olax subscorpiodea*.

Molecule	ESOL Log S	ESOL Solubility (mg/ml)	ESOL Class
Naringin	-2.98	6.04E-01	Soluble
Catechin	-2.22	1.74E+00	Soluble
Resveratrol	-3.62	5.51E-02	Soluble
Naringenin	-3.49	8.74E-02	Soluble
Flavan-3-ol	-3.49	7.35E-02	Soluble
Epicatechin	-2.22	1.74E+00	Soluble
Ribalinidine	-2.91	3.42E-01	Soluble
Anthocyanin	-4.01	2.02E-02	Moderately soluble
Humulone	-4.26	2.00E-02	Moderately soluble
Cohumulone	-4.09	2.81E-02	Moderately soluble
Sparteine	-2.89	3.00E-01	Soluble
Adhumulone	-8.38	2.41E-06	Poorly soluble

The drug-likeness properties of the top 10 ranked phytochemical constituents of Olax subscorpiodea.

Most of the top phytochemicals from Olax subscorpoidea, such as catechin, resveratrol, naringenin, flavan-3-ol, epicatechin, ribalinidine, anthocyanin, humulone, cohumulone, and sparteine, demonstrated no rule violations and a bioavailability score of 0.55 to 0.56, indicating good oral drug-likeness and moderate absorption potential, according to Lipinski's rule of five and bioavailability scoring. Naringin, on the other hand, has a lower bioavailability score of 0.17 and three Lipinski violations (Table 4).

Table 4: The drug-likeness properties of the top 12 ranked phytochemical constituents of *Olax subscorpiodea*.

Molecule	Lipinski violations	Bioavailability Score
Naringin	3	0.17
Catechin	0	0.55
Resveratrol	0	0.55
Naringenin	0	0.55
Flavan-3-ol	0	0.55
Epicatechin	0	0.55
Ribalinidine	0	0.55
Anthocyanin	0	0.55
Humulone	0	0.56
Cohumulone	0	0.56
Sparteine	0	0.55
Adhumulone	1	0.85

The toxicity profile of *Olax subscorpiodea's* top ten phytochemical ingredients. Different levels of safety were demonstrated by *Olax subscorpoidea* according to toxicity classifications and LD_{50} values. With the highest LD_{50} values of 10,000 mg/kg, epicatechin and catechin were classified as toxicity Class 6 and showed outstanding safety profiles by being inactive for all toxicity indicators. Despite naringin's immunotoxicity and anthocyanin's potential for both carcinogenesis and mutagenesis, compounds such as naringin (2300 mg/kg), flavan-3-ol (2500 mg/kg), and anthocyanin (2500 mg/kg) were classified as Class 5 substances, indicating low toxicity. Both naringenin (2000 mg/kg) and resveratrol (1560 mg/kg) belonged to Class 4, with naringenin exhibiting cytotoxicity but both being inert in other toxicity markers. Class 3 compounds included humulone (100 mg/kg), sparteine (220 mg/kg), and ribalinidine (150 mg/kg), the latter of which exhibited both mutagenic and immunotoxic effects. Despite having an LD_{50} of 100 mg/kg, cohumulone was classified as Class 4 and did not exhibit any toxicity indications. With an LD_{50} of 28 mg/kg, adhumulone was the most dangerous compound. It was classified as Class 2, indicating a high level of toxicity, however it was inactive for all toxicity endpoints. Most of the chemicals were categorized as either benign or mildly toxic, indicating the necessity for dose-controlled uses while also bolstering *Olax subscorpoidea's* medicinal potential (Table 5).

Table 5: The toxicity profile of the top 10 ranked phytochemical constituents of *Olax subscorpiodea*

Compound	LD50 (mg/kg)	Toxicity class	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
Naringin	2300	5	Inactive	Inactive	Active	Inactive	Inactive
Catechin	10000	6	Inactive	Inactive	Inactive	Inactive	Inactive
Resveratrol	1560	4	Inactive	Inactive	Inactive	Inactive	Inactive
Naringenin	2000	4	Inactive	Inactive	Inactive	Inactive	Active
Flavan-3-ol	2500	5	Inactive	Inactive	Inactive	Inactive	Inactive
Epicatechin	10000	6	Inactive	Inactive	Inactive	Inactive	Inactive
Ribalinidine	150	3	Inactive	Inactive	Active	Active	Inactive
Anthocyanin	2500	5	Inactive	Active	Inactive	Active	Inactive
Humulone	100	3	Inactive	Inactive	Inactive	Inactive	Inactive
Cohumulone	100	4	Inactive	Inactive	Inactive	Inactive	Inactive
Sparteine	220	3	Inactive	Inactive	Inactive	Inactive	Inactive
Adhumulone	28	2	Inactive	Inactive	Inactive	Inactive	Inactive

Discussion

A crucial enzyme in *Plasmodium falciparum,* NADH oxidoreductase, was the target of molecular docking investigations. Although natural substances like naringin, catechin, and resveratrol also demonstrated great binding affinities, the docking data revealed that chloroquine, which was utilized as a control, had the highest binding affinity. For antimalarial leads, binding affinity ratings below -6.0 kcal/mol are regarded as promising (Kant et al., 2021). As a result, *Olax subscorpoidea* components such naringin and catechin exhibit great promise as new antiplasmodial drugs. The plant's traditional effectiveness in treating malaria may be explained by the high binding scores, which imply that these chemicals may efficiently suppress parasite metabolism.

To forecast the pharmacokinetic characteristics and safety of the discovered drugs, the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling was assessed. Good membrane permeability was shown by the lipophilicity profile, which showed acceptable LogP values for the majority of substances. The bulk of the compounds were categorized as soluble by water solubility analysis, which is advantageous for oral bioavailability. Lipinski's rule for drug-likeness study revealed that the majority of compounds had no infractions, indicating that they had good drug-like qualities. Because of its enormous molecular weight and high number of hydrogen bond donors/acceptors, which are characteristics of glycosylated flavonoids, only naringin broke the three criteria. According to the toxicity profiles, the majority of the compounds had acceptable LD_{50} values and were neither mutagenic, carcinogenic, or hepatotoxic. Interestingly, substances like epicatechin and catechin were classified by the GHS as Toxicity Class 6, which means they are essentially non-toxic. These outcomes are in line with research by Ntie-Kang et al. (2020), which found that a large number of natural compounds derived from flavonoids had reduced toxicity concerns and favorable ADMET profiles, making them more suitable for therapeutic development. Together, the study's findings show that *Olax subscorpoidea* leaf extract has substantial *in silico* antiplasmodial actions, powerful bioactive components, important antioxidant qualities, and excellent pharmacokinetic profiles. These results establish the plant as a prospective source of novel antimalarial medication candidates and scientifically support its ethnomedicinal use to treat malaria

An important source of information about the nature of interactions between ligands and their biological targets is pharmacophore modeling. Like the common antimalarial medication chloroquine, the chosen bioactive compounds from *Olax subscorpoidea*—naringin, catechin, resveratrol, naringenin, and flavan-3-ol—were able to occupy the ATP binding site of the NADH oxidoreductase enzyme as evident in pharmacophore modeling results in the figures , according to the receptor-ligand complex analysis conducted in this study. Essential chemical characteristics including hydrophobic contacts (H), hydrogen bond donors (D), hydrogen bond acceptors (A), and aromatic ring interactions were detected in the pharmacophore models that were produced. These characteristics are essential for effective ligand binding and enzymatic activity suppression. The chosen substances established substantial hydrophobic contacts and hydrogen bonds with important amino acid residues in the NADH oxidoreductase active site, both of which are known to improve binding affinity and stabilize the receptor-ligand complex. The observed hydrogen bond interactions are especially significant since they support the ligand's stability and specificity at the active site. By allowing the ligands to properly align within the binding pocket, hydrogen bonds guarantee that the enzyme's catalytic or allosteric sites are properly engaged. In the meantime, hydrophobic interactions help the complex remain thermodynamically stable by lowering binding-induced desolvation penalties and promoting a tighter molecular fit (Tung et al., 2022).

Crucially, *Olax subscorpoidea's* bioactive compounds exhibited a comparable binding mechanism to chloroquine by interacting with the same amino acid residues as shown in the receptor-ligand complex pharmacophore modelling. This finding is significant because the compounds may be used to produce antimalarial drugs since they can directly affect parasite metabolism by binding to conserved residues crucial in NADH oxidoreductase function. According to earlier research, Plasmodium falciparum's intraerythrocytic growth can be successfully inhibited by drugs that target redox metabolism pathways, specifically NADH and mitochondrial enzymes (Dong et al., 2020). Naringin and catechin, two of the chosen chemicals, showed especially good pharmacophore profiles, creating several hydrophobic and hydrogen bonding interactions. These flavonoid structures tend to exhibit robust receptor binding and good pharmacodynamics because of their planar aromatic systems and hydrogen-bonding hydroxyl groups, according to literature publications by Kant et al. (2021) and Ntie-Kang et al. (2020). *Olax subscorpoidea* is further supported as a promising source of antimalarial agents by the successful mapping of pharmacophoric features across the chosen compounds, which indicates that the phytochemicals have the bare minimum of chemical requirements for activity against the NADH target.

The multi-interaction patterns, shown in the receptor-ligand complex pharmacophore modelling, exhibited by these compounds are similar to those of synthetic inhibitors being studied for resistant strains of malaria when compared to current pharmacophore-based drug development investigations in work of Conrad and Rosenthal (2019). Therefore, the bioactive compounds from *Olax subscorpoidea* may not only be effective inhibitors but also be able to overcome the resistance limitations commonly associated with single-target therapies due to their multifunctional pharmacophoric attributes (hydrophobicity, hydrogen bond formation, and aromatic stacking). The potential of specific phytochemicals from *Olax subscorpoidea* to function as potent antimalarial drugs by interacting with crucial enzyme targets is clearly supported by the pharmacophore modeling analysis.

Conclusion

Bioactive chemicals from *Olax subscorpoidea* shown substantial binding affinities against Plasmodium falciparum's NADH oxidoreductase target, according to molecular docking studies. Comparable to conventional medications, compounds like catechin and naringin demonstrated outstanding anticipated antimalarial efficacy. According to ADMET profiling, most of the compounds found had low projected toxicity, favorable lipophilicity, acceptable solubility, and good oral bioavailability. The majority of the compounds were categorized as non-carcinogenic, non-hepatotoxic, and non-mutagenic by toxicity analysis, and they all adhered to Lipinski's rule of five.

Recommendations

It is recommended that more in vitro and in vivo research be carried out to confirm the antimalarial activity of the identified bioactive chemicals from *Olax subscorpioidea* in light of the research findings. Also it is recommended to explore additional molecular targets involved in malaria pathogenesis, such as falcipain-2, dihydrofolate reductase (PfDHFR), and the Kelch13 propeller domain, in order to gain a broader understanding of the therapeutic range of these compounds. Conducting multi-target screening can help identify compounds with dual or synergistic mechanisms, thereby increasing their effectiveness and potentially overcoming resistance.

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