Tropical Journal of Pharmaceutical Research February 2026; 25 (2): 193-203
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
https://dx.doi.org/10.4314/tjpr.v25i2.7

Original Research Article

Identification of *Alstonia boonei*-derived Phytocompounds as Promising Drug Candidates against Plasmodium falciparum Dihydroorotate Dehydrogenase Protein in Malaria Treatment

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Sent for review: 21 October 2025 *Revised accepted: 16 February 2026*

Abstract

Purpose: *To evaluate phytocompounds from Alstonia boonei as promising anti-malarial drug candidates and determine their interactions with a key Plasmodium falciparum protein.*
Methods: *Gas chromatographic-mass spectrometry (GC-MS) was used to obtain Alstonia boonei compounds and a computational approach was utilized. Maestro Schrodinger Suite was used to perform molecular docking, prediction of absorption, distribution, metabolism and excretion (ADME) properties, molecular mechanics/generalized born surface area (MM/GBSA) estimation, induced-fit docking, and AutoQSAR analysis. These methods were employed to predict the binding efficacy and stability of Alstonia boonei-derived phytocompounds against Plasmodium falciparum dihydroorotate dehydrogenase protein using artemether as standard drug.*
Result: *The results identified five phytocompounds: Sweroside (-10.152 kcal/mol), 7-Deoxyloganic acid (-10.066 kcal/mol), Swertiamarin (-9.611 kcal/mol), Secologanoside methyl ester (-9.013 kcal/mol), and Caffeic acid (-8.178 kcal/mol) with superior binding stability compared to the standard drug, artemether. These compounds also demonstrated a better induced fit docking score, indicating more favorable and stable interactions with the target protein.*
Conclusion: *This work suggests that the five (5) identified phytocompounds from Alstonia boonei are effective potential inhibitors of Plasmodium falciparum dihydroorotate dehydrogenase and represent promising candidates for further development as anti-malarial treatments.*

Keywords: *Alstonia boonei, Phytocompounds, Molecular docking, Plasmodium falciparum, Malaria treatment*

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INTRODUCTION

Malaria is a life-threatening disease caused by *Plasmodium* parasites, with symptoms including cyclical fever, chills, and potential severe complications, commonly treated with Artemisinin-based Combination Therapies (ACTs); risk factors centre on geographic

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exposure to endemic regions, and the most vulnerable populations are children under five, pregnant women, and non-immune individuals, its commonly referred to as the king of diseases mainly because this disease is endemic to about 100 countries in the world. About 40% of the world's population is said to have malaria, which is a life-threatening illness caused by *Plasmodium* parasites, and remains a major global health concern. In 2020, 84 endemic countries reported 247 million cases and approximately 627,000 deaths [1]. In 2024, World Health Organization (WHO) reported an estimated 263 million malaria cases in malaria-endemic countries, with Nigeria accounting for 25.9% of these cases, reflecting an 11 million increase from the previous year's report [2].

Malaria parasite is transmitted by about 30 varying species of the *Anopheles* mosquito. Due to causes like increasing parasites' resistance to drugs and decreasing attention to malaria control, malaria cases are on the rise. Rainfall, high humidity, stagnant waters, and consistent high temperatures are predisposing factors to malaria. Malaria cases are more common in rural areas than in urban areas. In sub-Saharan Africa, approximately $12 billion is lost yearly due to malaria [3]. There have also been reported cases where two or more parasites like Plasmodium falciparum and Plasmodium vivax combine to cause malaria, especially in endemic regions of Africa [4].

The protozoan parasite known as *Plasmodium* is responsible for the disease, malaria. Malaria parasites are generally host-specific and there are over 200 species of the parasite infecting mammals, reptiles, and birds. Out of these species, there are 5 species that cause malaria in humans, with *Plasmodium falciparum* causing the most severe form of malaria with variable clinical features such as fever, cold, headache, vomiting, cough, diarrhoea, abdominal pain, muscular aching and weakness [4]. Malaria caused by *Plasmodium falciparum* is responsible for about one million deaths yearly. This has necessitated the identification of novel targets against *Plasmodium* species. Pyrimidines are essential metabolites that are precursors for DNA and RNA biosynthesis. *Plasmodium falciparum* needs pyrimidine for its cell growth, metabolism, and replication, but it does not have pyrimidine salvage enzymes and therefore cannot recover pyrimidine from its host. *Plasmodium falciparum*, therefore, relies on the de novo biosynthesis route for pyrimidine [5]. Since the rate-limiting phase of this process is facilitated by dihydroorotate dehydrogenase (a flavin-dependent enzyme that facilitates the oxidation of dihydroorotate to orotic acid), dihydroorotate dehydrogenase is now considered a good target against malaria. Dihydroorotate dehydrogenases are in two forms that can be found in prokaryotes and eukaryotes. In prokaryotes, a cytosolic family uses various soluble molecules as electron sinks, while respiratory quinones are exclusively used as the distal electron receptor by a membrane-associated family found in eukaryotes [6].

The increase in cost of anti-malaria drugs such as Artemisinin-based Combination Therapies (ACTs), resistance of parasite to available drugs and saturation of the market with fake and unregistered drugs have led to an increase in the use of plant parts to cure and manage malaria even in urban areas. One of such plants used in Nigeria is *Alstonia boonei*, more commonly known as cheese wood or stool wood [7]. This is a tropical medicinal plant that originates from West Africa and belongs to the Apocynaceae family. *Alstonia boonei* leaf is used ethnomedicinally in the treatment of various diseases such as malaria, hypertension, toothache, arthritis, sore throat, snake bites, jaundice, rheumatism, cough, and ulcer [8]. This plant has been reported to contain several phytochemicals, among which are the alkaloids that have also been reported by different studies to contribute to its antimalarial properties [9]. Therefore, this study aims to identify phytochemicals of *Alstonia boonei* with potential in the treatment of malaria using in *silico* approach.

EXPERIMENTAL

Protein preparation

The 3D structure of *Plasmodium falciparum* dihydroorotate dehydrogenase with Protein Data Bank (PDB) ID 6I55 was downloaded from PDB and subsequently imported into the Maestro Schrodinger suite (2025). Using the protein preparation wizard, the imported protein was pre-processed and refined [10]. The pre-processing phase was used to add missing hydrogen atoms, remove water molecules and fill loops to complete missing segments. The refining phase allowed for the optimization of hydrogen bonds, aiding the enhancement of structural stability. This was followed by minimization to achieve an average root mean square deviation (RMSD) of 0.3 Å [10].

Receptor Grid Generation

For molecular docking to take place, a glide grid file needs to be generated. This glide grid file represents the receptor's active sites gotten

through the x, y and z coordinates located on the co-crystallized ligand of the *Plasmodium falciparum* dihydroorotate dehydrogenase protein [19]. For this study, the x, y, and z coordinates are 16.95, 21.93 and 34.82, respectively.

Ligand preparation

Phytocompounds identified from *Alstonia boonei* were sourced from literature, the 2D structures were downloaded and imported into Maestro Schrodinger suite (2025), after which they were grouped. Energy minimization and protonation at physiological pH were done as a means to process the phytocompounds using the LigPrep panel. The Ligprep panel also enables the conversion of structures and the generation of structural variations after stereoisomer computation, which was allowed to produce a maximum of 1 per ligand, and the output format was allowed to remain as a maestro [11].

Molecular extra precision docking

The prepared phytocompounds were docked into the protein's (6I55) active site using extra precision docking. GLIDE, a Maestro Schrodinger tool designed to predict the binding region between the phytocompounds and protein, was used to carry out this process. Exploring various phytocompound poses, GLIDE ranks the phytocompounds based on their docking scores, calculated using shape complementarity, interaction energy and binding affinities [10].

ADME predictions

To assess the physicochemical profiles and pharmacokinetics of phytocompounds, so as to gain knowledge on how a phytocompound will behave within a human body, ADME (Absorption, Distribution, Metabolism, and Excretion) prediction is carried out [12]. The QikProp panel of the Maestro Schrodinger was used to determine key parameters related to pharmacokinetics and drug-likeness of the phytocompounds, such as Lipinski's rule of five [19].

Free energy calculation

Molecular docking accuracy can be improved by a post-docking refinement method that uses their energetic profile to re-evaluate docked poses. This process is known as free energy calculation or prime MM-GBSA (Molecular Mechanics/Generalized Born Surface Area) [12]. The prime MM-GBSA calculates the difference in energy between the minimised protein-ligand complex and the unbound protein and ligand [13]. The prime MM-GBSA on Maestro was used to determine the binding free energy for the ligand-receptor complex.

Induced fit docking

Induced fit docking (IFD) is an advanced molecular docking technique that allows the protein to rotate upon binding to a ligand (phytocompound) so as to enable the accuracy of a binding affinity prediction [14]. The IFD panel on Maestro Schrodinger allows the protein to adjust properly to ligand binding when it combines GLIDE for initial docking with Prime for refining the protein. For targets with flexible binding sites, IFD is a valuable tool.

Quantitative Structure-Activity Relationship (QSAR)

QSAR is a powerful machine-learning tool that leverages biological activity metrics such as IC_{50} values and structural data to develop accurate models [15]. The FASTA sequence of 6I55 was queried and compound dataset with their corresponding IC_{50} was obtained from ChEMBL. The compounds with no pChEMBL value were deleted on Microsoft Excel and the file was moved to data-warrior were it was converted to a structural data file format. This format was then imported into the Maestro Schrodinger 14.3. The AutoQSAR panel of Maestro Schrodinger was used to build QSAR models based on the inhibitors' structural data and their respective pIC_{50} values (pIC_{50} is a predictive value generated using the QSAR model, while IC_{50} is an experimental value that can be obtained during *in vitro* or *in vivo* analysis).

RESULTS

Table 1 shows the result of the promising compounds of *Alstonia boonei* and their docking scores ranked based on their interaction with the *Plasmodium falciparum* Dihydroorotate Dehydrogenase Protein. It also shows the number of hydrogen bonds present in the interaction and the amino acids involved in the hydrophobic interaction. Two-dimensional (2D) structures of 7-Sweroside (Figure 1), 7-Deoxyloganic acid (Figure 2), Swertiamarin (Figure 3), Secologanoside methyl ester (Figure 4), and Caffeic acid (Figure 5) indicate promising compounds of *Alstonia boonei* with good docking scores and artemether (Figure 6), which has been used in this study as a standard drug. The number of hydrogen bonds and amino acids involved in the hydrophobic interactions is also shown in the 2D structures.

Table 1: Molecular Docking, Number of Hydrogen Bonds (H-Bond) with Interacting Amino Acid Residue and Hydrophobic Interactions Results of the Promising Phytocompounds of *Alstonia boonei* and the Standard Drug against *Plasmodium falciparum* Dihydroorotate Dehydrogenase Protein

S/n	Phytocompound	Docking score (kcal/mol)	No of H-bond	Hydrophobic interaction
1	Sweroside	-10.152	5 (HIE185, HIE185, GLY181, ARG265, ARG265)	PHE227, LEU187, PHE188, CYS184, TYR528, LEU531, VAL532, MET536, TYR168, PHE171, LEU172, CYS175, LEU176
2	7-Deoxyloganic acid	-10.066	2(ARG265, TYR168)	PHE227, PHE188, CYS184, LEU531, VAL532, MET536, LEU172, LEU176, CYS175, PHE171, TYR168, LEU191, LEU187
3	Swertiamarin	-9.611	3(HIE185, GLY181, ARG265)	PHE227, LEU187, PHE188, CYS184, TYR528, LEU531, VAL532, MET536, TYR168, PHE171, LEU172, CYS175, LEU176, LEU191, ILE263
4	Secologanoside methyl ester	-9.013	2(ARG265, TYR168)	PHE227, LEU187, PHE188, CYS184, TYR528, LEU531, VAL532, MET536, TYR168, PHE171, LEU172, CYS175, LEU176, LEU191, ILE272, ILE263
5	Caffeic acid	-8.178	1(LEU531)	PHE227, PHE188, CYS184, LEU531, VAL532, MET536, LEU172, LEU176
6	Artemether	-2.652	0	LEU187, PHE171, CYS175, TYR168, PRO198, LEU197, ILE196, LEU191

H-bond: Hydrogen-bond

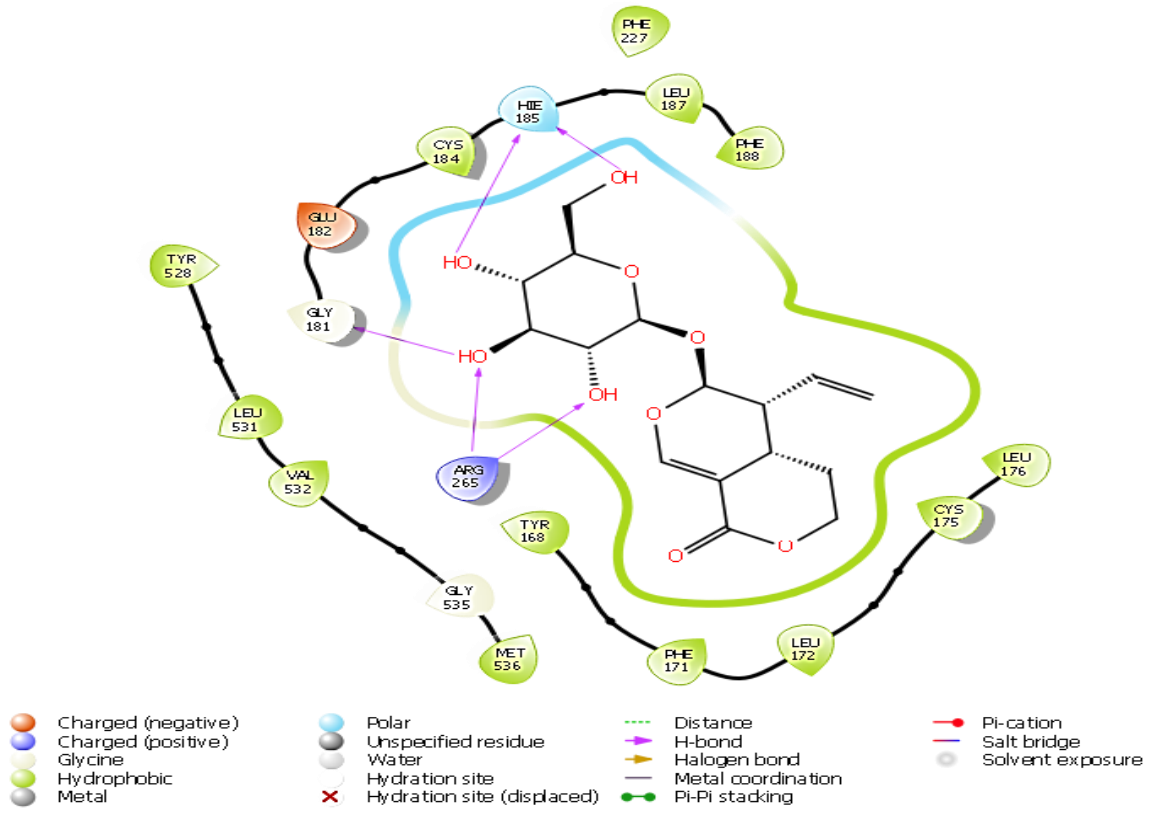


Figure 1: 2D Interaction of Sweroside with amino acid residue within the binding site of *Plasmodium falciparum* dihydroorotate dehydrogenase protein

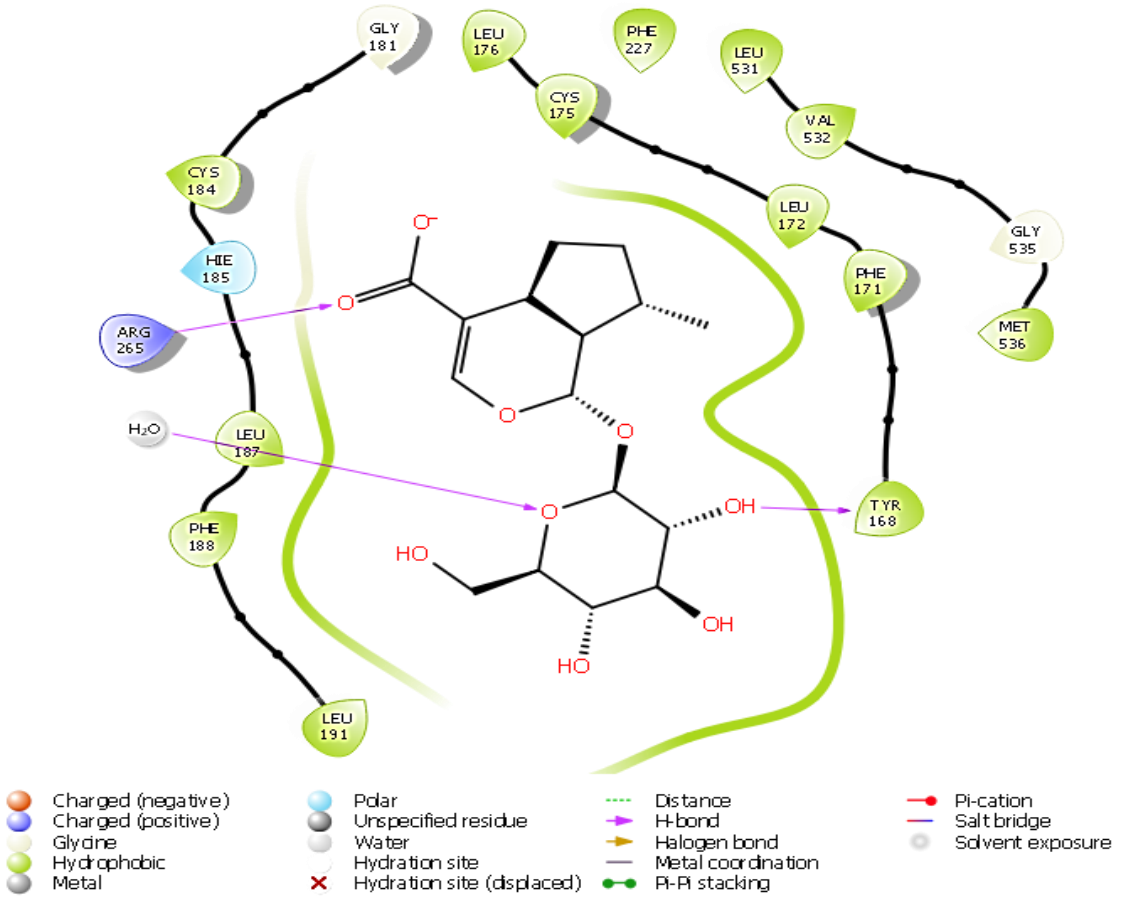


Figure 2: 2D Interaction of 7-Deoxyloganic acid with amino acid residue within the binding site of *Plasmodium falciparum* dihydroorotate dehydrogenase protein

Table 2 shows the result of the promising compounds of *Alstonia boonei,* stating Lipinski's rule of 5, indicated by the molecular weight, hydrogen bond donor (HB donor), hydrogen bond acceptor (HB acceptor), and the water partition coefficient. The rule of 5 column is also shown. A "0" score indicates compliance with all of Lipinski's rules of 5.

Table 3 shows the result of the promising compounds of *Alstonia boonei,* listing the binding free energy score (MMGBSA), induced fit docking (IFD) score and the negative base-10 logarithm of the half-maximal inhibitory concentration (pIC_{50}) score.

DISCUSSION

The key proteins in *Plasmodium falciparum* are primarily to enable host cell invasion, facilitate immune evasion, drive lifecycle progression, or confer drug resistance. Pyrimidine production is essential to the survival and growth of *Plasmodium falciparum*.

Table 2: ADME Prediction Properties Results of the Promising Phytocompounds of *Alstonia boonei* and the Standard Drug against *Plasmodium falciparum* Dihydroorotate Dehydrogenase Protein

S/n	Phytocompound	Molecular weight	HB donor	HB acceptor	Water partition coefficient	Rule of five
1	Sweroside	358.344	4	9	-1.581	0
2	7-Deoxyloganic acid	360.360	5	9	-0.982	0
3	Swertiamarin	374.344	5	10	-1.948	0
4	Secologanoside methyl ester	404.370	5	11	-1.283	1
5	Caffeic acid	180.160	3	4	0.545	0
6	Artemether	298.378	0	5	2.505	0

HB: Hydrogen-Bond

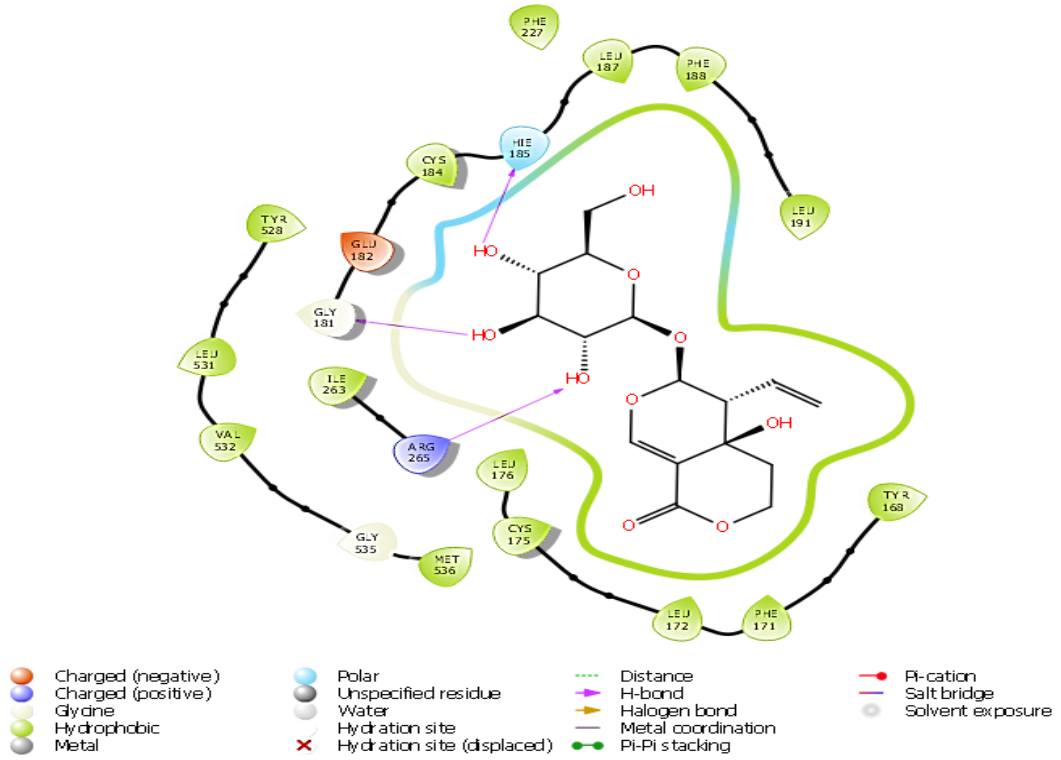


Figure 3: 2D Interaction of Swertiamarin with amino acid residue within the binding site of *Plasmodium falciparum* dihydroorotate dehydrogenase protein

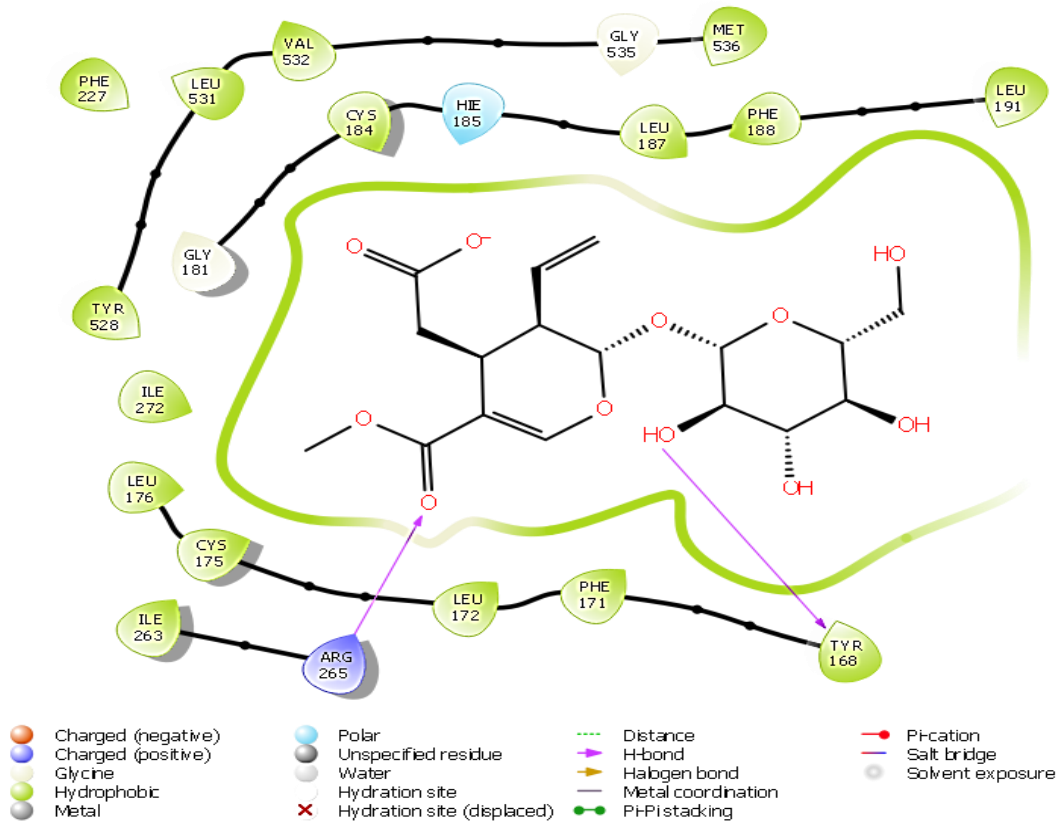


Figure 4: 2D Interaction of Secologanoside methyl ester with amino acid residue within the binding site of *Plasmodium falciparum* dihydroorotate dehydrogenase protein

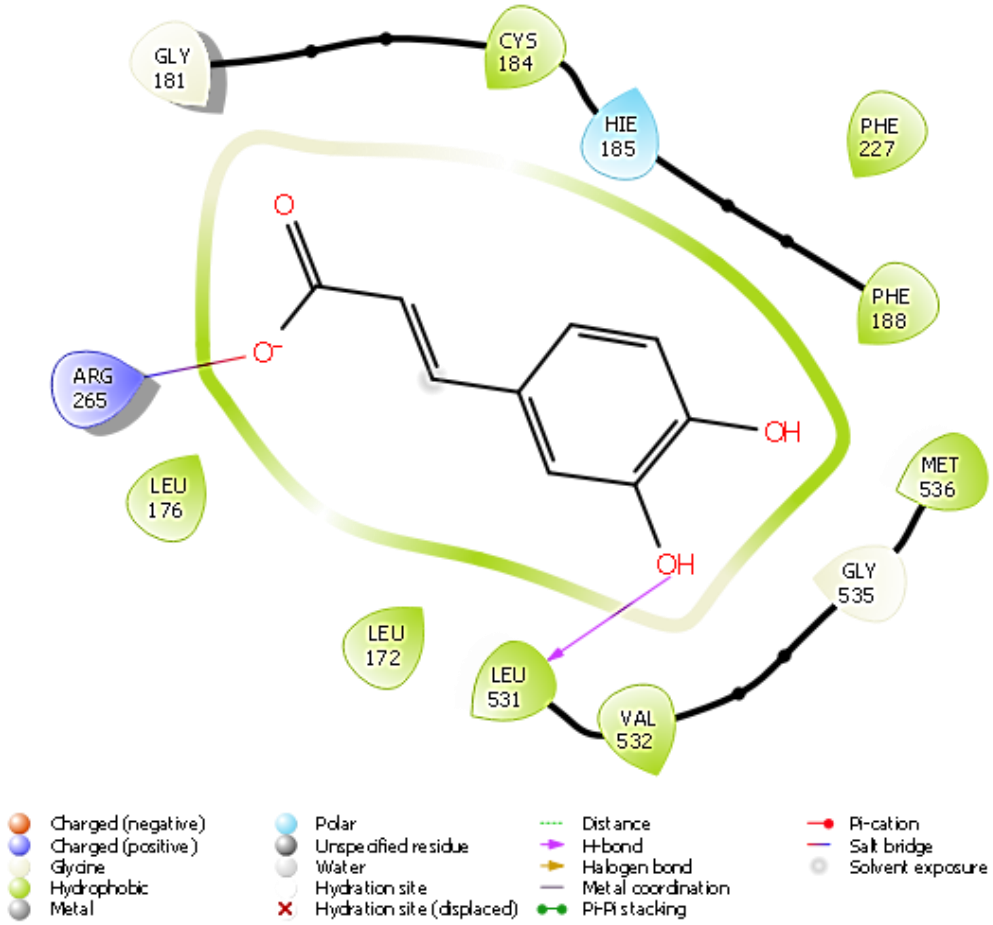


Figure 5: 2D Interaction of Caffeic acid with amino acid residue within the binding site of *Plasmodium falciparum* dihydroorotate dehydrogenase protein

Table 3: Binding free energy, induced fit docking and predictive pIC_{50}. Results of the promising phytocompounds of *Alstonia boonei* and the standard drug against *Plasmodium falciparum* dihydroorotate dehydrogenase protein

S/n	Phytocompound	MMGBSA ΔG bind (kcal/mol)	IFD score (kcal/mol)	Pred. pIC_{50}
1	Sweroside	-47.00	-850.41	6.57
2	7-Deoxyloganic acid	-41.49	-851.67	6.06
3	Swertiamarin	-44.58	-849.32	7.00
4	Secologanoside methyl ester	-19.58	-847.60	6.57
5	Caffeic acid	-33.20	-843.85	4.36
6	Artemether	-24.61	-841.64	6.30

MMGBSA: Molecular Mechanics with Generalized Born and Surface Area, IFD: Induced Fit Docking

Since *Plasmodium falciparum* cannot generate its own pyrimidine, they rely on the pyrimidine generated by the de novo biosynthesis pathway of its host. Dihydroorotate dehydrogenase is the enzyme responsible for the committed step in this pathway. If this enzyme can be inhibited, pyrimidine is not generated and therefore, *Plasmodium falciparum* is starved of growth. Phytocompounds of *Alstonia boonei* and a standard drug, Artemether, were screened against a *Plasmodium falciparum* dihydroorotate dehydrogenase protein using the Maestro Schrodinger Suite. This yielded five (5) compounds identified as potential antimalarial compounds. Sweroside (-10.152 kcal/mol), 7-Deoxyloganic acid (-10.066 kcal/mol), Swertiamarin (-9.611 kcal/mol), Secologanoside methyl ester (-9.013 kcal/mol) and Caffeic acid (-8.178 kcal/mol) all show a higher binding affinity to *Plasmodium falciparum* dihydroorotate dehydrogenase protein when compared to the standard drug artemether (-2.652 kcal/mol). This comparison helps to understand the binding strength and stability of the ligands in the protein's active site [12].

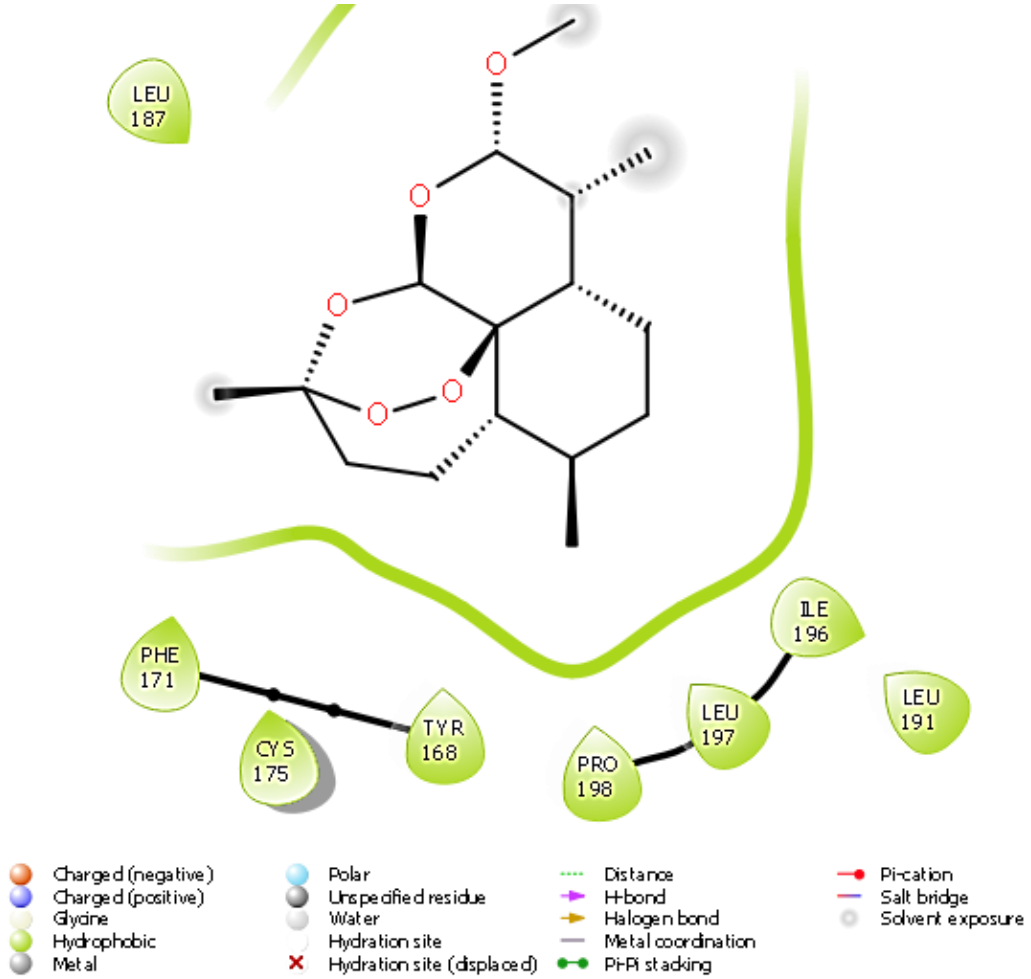


Figure 6: 2D Interaction of Artemether with amino acid residue within the binding site of *Plasmodium falciparum* dihydroorotate dehydrogenase protein

Molecular docking has been employed as a reliable and efficient tool in determining the forces that control the binding stability of ligands within the binding site of a protein [16]. The two-dimensional (2D) structural images show the interaction between the promising phytocompounds and the protein target. It also details the key amino acids that are responsible for stabilizing these phytocompounds within the binding site of the protein target. Hydrophobic interactions can increase the binding affinity between a ligand and its protein target [17]. The purple lines represent the hydrogen bond, and the amino acids with a green background represent the hydrophobic interactions. The 2D interaction diagram showed that the promising phytocompounds were inserted into the active sites of the target protein, where they interacted with many amino acids. Some active amino acids were common in all the interaction diagrams. These amino acids include PHE227, PHE188, CYS184, LEU531, VAL532, MET536, LEU172 and LEU176. This suggests that these amino acids are key to the interaction and stability of phytocompounds from *Alstonia boonei*. For the phytocompound, Sweroside, it formed a double hydrogen bond with ARG265 and HIE185, indicating a stronger stability of the phytocompound's orientation. The double bond from the hydrogen bond and the high number of hydrophobic interactions of Sweroside in its interaction with *Plasmodium falciparum* dihydroorotate dehydrogenase protein contribute to its better docking score when compared to other promising phytocompounds and the standard drug.

The pharmacokinetic characteristics of these five promising phytocompounds and the standard drug were assessed by predicting their ADME properties. ADME properties, when determined helps to understand the drug-likeness of a compound and this is usually done by following a set of rules known as Lipinski's rule of five (RO5). The Lipinski's RO5 gives four (4) conditions that can be used to determine the drug-likeness of a compound. The conditions are: molecular weight should not be more than

500 Da, hydrogen bond donor should be less than or equal to 5, hydrogen bond acceptor should be less than or equal to 10 and the water partition coefficient should be less than or equal to 5 [11]. A compound with good drug-likeness should not violate more than one of these conditions. The ADME properties prediction results from this study revealed that the 5 promising phytocompounds of *Alstonia boonei* adhered to Lipinski's RO5, with the exception of Secologanoside methyl ester with more hydrogen bond acceptors than 10. This result indicates a favourable drug-likeness prediction for the promising phytocompounds of *Alstonia boonei* and puts them as potential drug candidates since obeying the RO5 during clinical trial increases the chances of passing all phases of the clinical trial.

To accurately rank ligands based on their binding potential with the *Plasmodium falciparum* dihydroorotate dehydrogenase protein and determine the stability of the protein-ligand complex, the MMGBSA post-docking method that calculates ligand binding and strain energies is used. From this study, the MMGBSA result shows that the 5 promising phytocompounds of *Alstonia boonei*, Sweroside (-47.00 kcal/mol), 7-Deoxyloganic acid (-41.49 kcal/mol), Swertiamarin (-44.58 kcal/mol), Secologanoside methyl ester (-19.58 kcal/mol) and Caffeic acid (-33.20 kcal/mol) and the standard drug, artemether (-24.61 kcal/mol) has a negative binding free energy (ΔG bind) indicating a favourable binding. Only Secologanoside methyl ester with a binding free energy of -19.58 kcal/mol suggested a weaker binding affinity to the protein when compared with the standard drug (-24.61 kcal/mol). The remaining four (4) promising phytocompounds suggest a stronger binding energy when compared to the standard drug. The binding free energy result gives better credibility to the 5 promising compounds of *Alstonia boonei* by establishing their stability in the active site of the *Plasmodium falciparum* dihydroorotate dehydrogenase protein.

The induced fit docking (IFD) method gives a more precise prediction of the ligand-protein interaction because it allows the protein's binding pocket to change its conformation so as to better accommodate the ligand's flexibility [12]. According to the hypothesis from Koshland-developed induced fit theory, proteins and ligands should be viewed as flexible during molecular docking [11]. The induced fit docking score from this study suggested that these promising phytocompounds enhanced the binding potential of *Plasmodium falciparum* dihydroorotate dehydrogenase protein by inducing favourable structural changes in the protein. The result showed 7-Deoxyloganic acid with the highest IFD score of -851.67 kcal/mol, Sweroside with an IFD score of -850.41 kcal/mol, Swertiamarin with an IFD score of -849.32 kcal/mol, Secologanoside methyl ester with an IFD score of -847.60, Caffeic acid with an IFD score of -843.85 kcal/mol and the standard drug artemether with an IFD score of -841.64 kcal/mol. This result shows that the 5 promising phytocompounds have a more significant binding adaptability and stronger interaction with the protein when compared with the standard drug. This further enhances the potential of these phytocompounds as promising drugs against malaria when they target *Plasmodium falciparum* dihydroorotate dehydrogenase protein.

AutoQSAR uses a combination of machine learning tools and independent variables to build different models. Each model's quality is scored based on its predictive performance on both the training and test sets [18]. This performance is measured as the negative logarithm of inhibitor concentration (pIC_{50}). This result shows that Swertiamarin has the highest predicted pIC_{50} value (7.00), suggesting a higher potency when compared to other promising phytocompounds and the standard drug. This value is followed by that of Sweroside and Secologanoside methyl ester with pred. pIC_{50} value of 6.57 each, while the pred. pIC_{50} value of the standard drug, artemether, is 6.30. This result shows that three (3) of the five (5) promising phytocompounds have better predicted. pIC_{50} value than the standard drug, artemether, indicating a stronger inhibitory potential on *Plasmodium falciparum* dihydroorotate dehydrogenase protein.

CONCLUSION

Promising phytocompounds of *Alstonia boonei* are highlighted in this study as effective inhibitors of *Plasmodium falciparum* dihydroorotate dehydrogenase protein. Since resistance to commercially available drugs is on the rise and malaria continues to pose as a deadly disease in different parts of the world, it is now a necessity to begin to look for protein targets that could help to cure malaria and also look for phytocompounds with potential as a cure against malaria. Sweroside, 7-Deoxyloganic acid, Swertiamarin, Secologanoside methyl ester and Caffeic acid showed better docking score, binding affinity and inhibitory potential when compared to the standard drug, artemether. This indicates that these phytocompounds possess drug-like characteristics, making them promising therapeutic candidates that can be explored in the treatment of malaria. In vitro and in vivo

analysis should be done to further validate the findings from this study.

DECLARATIONS

Acknowledgement/Funding

None.

Ethical approval

None provided.

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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