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Potential Inhibiting activities of Phytochemicals from *Enantia chlorantia* Bark Against Lactate Dehydrogenase: *in Silico* Approach

Malaria is a serious ailment, and it remains a serious challenge for global health organisations. The establishment of unconventional drugs to fight this ailment has drawn the attention of several researchers. In this work, selected phytochemicals from *Enantia chlorantia* bark as potential anti-lactate dehydrogenase were investigated using *in silico* approach. A number of softwares were used in this study namely: Spartan 14 for optimization, Pymol for treating the downloaded receptor, Autodock tool for identifying the active site of the target, Autodock Vina for docking calculation and Discovery Studio visualizer for observing the non-bonding interaction of the studied complex. The calculated descriptors from the optimized *Enantia chlorantia* bark phytochemicals described their anti-lactate dehydrogenase activities. Compounds **2, 4, 9, 15, 16** and **17** demonstrated higher binding affinity (in terms of negativity) than other studied compounds and the reference drug (Quinine). This predicts that they have a higher ability to inhibit lactate dehydrogenase downregulate malaria. Also, (1*R*,4*aS*,8*aS*)-7-methyl-4-methylidene-1-propan-2-yl-2,3,4*a*,5,6,8*a*-hexahydro-1*H*-naphthalene (compound **15**) showed higher values inhibition of lactate dehydrogenase than other studied compounds and reference drug Quinine. The developed quantitative structure-activity relationship model using binding affinity as a dependent variable proved to be predictive and this can help in the subsequent study.

Keywords: Lactate Dehydrogenase, Phytochemicals, *Enantia chlorantia*, *In Silico*, Malaria, Docking, Bark, Drug.

Introduction

Malaria, one of the most difficult to dare parasitic sicknesses, remains the disease with devastating effects in many countries globally [1]. A few years ago, above 210 million malaria cases and hundreds of thousands of malaria death cases were observed and reported by scientists [2, 3]. According to Schlitzer, 2008 [4], malaria in human beings could be attributed to *P. falciparum*, *P. knowlesi*, *P. ovale*, *P. vivax*, and *P. malariae*. Several synthesized drugs to cure malaria have significantly reduced malaria mortality [5]. According to Mutabingwa, 2005 [6], Artemisinin Combination therapy was recommended by World Health

Organization for proper combat against malaria, and in recent time, the call to overcome drug resistivity has attracted the attention of researchers, leading to the development of several potent antimalaria drugs such as artemether, lumefantrine [7]. Despite the efficiency of the synthesized drugs to fight the existence of malaria among humans, the case of anti-malaria drug resistivity in many part of Africa is still on the high side and this has necessitated the development of more potent antimalaria agents than the commercial drugs [8]. Moreover, the production of hundreds of drugs from over eighty-five medicinal plants has been carried out, which may be due to its easy accessibility, efficiency, as well as their mode of action in the human body system [9–11].

Two *Plasmodium* genus (*P. falciparum* and *P. vivax*) were the root cause of many malaria among humans [12–14]. Meanwhile, the mode of action of *P. falciparum* has led to the highest mortality compared to others [15]. Several malaria cases with the greatest number of mortality due to malaria have been observed and reported in Africa. The use of chemical compounds to combat this life-threatening disease (Malaria) has been employed by many scientists; however, resistance to antimalarial drugs remains a serious challenge, and this has called for more potent drug-like compounds as a lasting solution to this menace in the medical world [16–20].

Lactate dehydrogenase is a crucial proteinous compound that plays a significant role in all living cells [21]. It has been observed to be a usual target in malaria and it played a crucial role in the anaerobic existence of Plasmodium falciparum [22]. Any molecular drug-like compound with enough potency to hinder Plasmodium falciparum lactate dehydrogenase will destroy the Plasmodium falciparum in human body system [23]. It helps in transporting hydride among molecular compounds, and a series of health conditions such as liver disease, anemia, heart attack, muscle trauma, cancers, and HIV have been reported to increase lactate dehydrogenase in any living cell [24]. According to Garcia *et al*., 2014 [25], lactate in living beings can be increased by raising the level of glucose absorption, and this has attracted the attention of researchers globally.

Enantia chlorantha has been classified to the annonaceae family. Different names have been given to this tree based on different cultures, such as Dokitaigbo, Kakerim and Erenba-vbogo Yoruba, Boki, and Benin, respectively [26, 27]. It is a tree with yellow wood, 28 m high, and many researchers report that in Africa it can be found in tropical forests [28]. Every part (leaves, root and bark) of the tree has been observed and reported to be medicinal in treating diseases like malaria, typhoid fever, etc. [29]. Also, several biologically active compounds were found in *Enantia chlorantha*, which has reportedly given it exceptional medicinal value for humans [30]. Thus, the purpose of this work is to study the inhibiting capacity of phytochemicals from *Enantia chlorantia* bark against lactate dehydrogenase [31], as well as to identify their descriptors responsible for anti-lactate dehydrogenase activity.

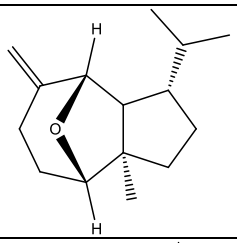
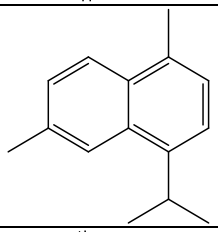
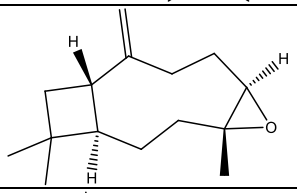
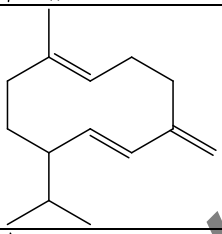
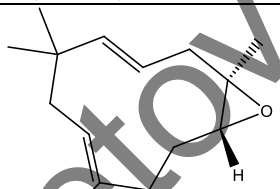
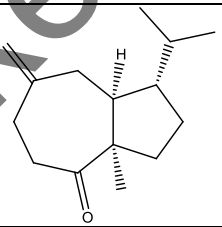
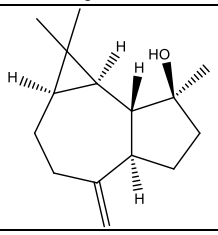
Experimental

Ligand Preparation via Quantum chemical method

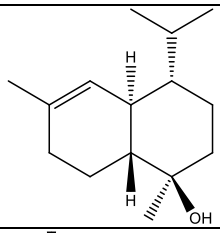
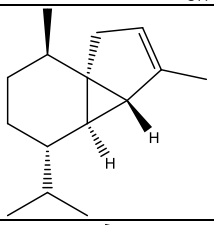
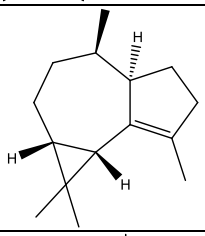
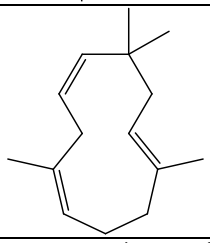
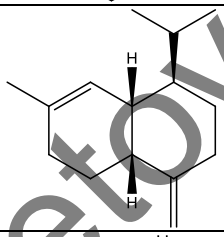
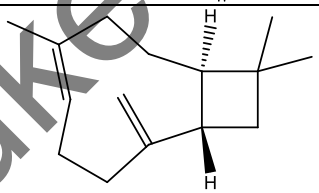
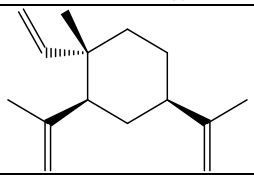
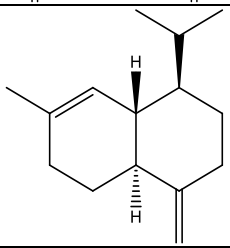
Eighteen phytochemicals (Table 1) from *Enantia chlorantia* bark were subjected to Spartan 14 software for geometry optimization [32]. The appropriate elements were bonded together according to the chemical formula for each compound using 6-31G* as basis set. The time required to complete processing of each compound is a function of the composition of each compound coupled with the basis set used. A series of activity descriptors for the studied compounds were obtained using Spartan 14 software and included: highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), bandgap (BG), dipole moment (DM), molecular weight (MW), lipophilicity (LogP), ovality, polar surface area (PSA), polarizability, hydrogen bond donor (HBD), and hydrogen bond acceptor (HBA). The studied compounds are presented in Table 1.

Table 1

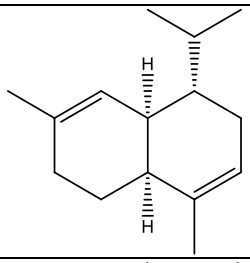
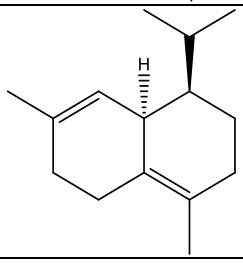
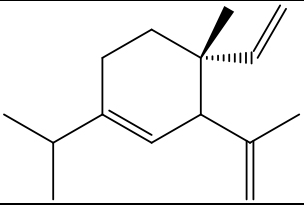
Studied phytochemicals obtained from *Enantia chlorantia* bark

No.	Structures	IUPAC Names
1		(1*S*,2*R*,5*S*,7*S*)-2-methyl-8-methylidene-5-propan-2-yl-11-oxatricyclo[5.3.1.$0^{2,6}$]undecane
2		1,6-dimethyl-4-propan-2-ylnaphthalene
3		(1*R*,4*R*,6*R*,10*S*)-4,12,12-trimethyl-9-methylidene-5-oxatricyclo[8.2.0.$0^{4,6}$]dodecane
4		(1*E*,6*E*)-1-methyl-5-methylidene-8-propan-2-ylcyclodeca-1,6-diene
5		(1*R*,3*E*,7*E*,11*R*)-1,5,5,8-tetramethyl-12-oxabicyclo[9.1.0]dodeca-3,7-diene
6		(1*S*,3*aR*,8*aS*)-3*a*-methyl-7-methylidene-1-propan-2-yl-2,3,5,6,8,8*a*-hexahydro-1*H*-azulen-4-one
7		(1*aR*,4*aR*,7*S*,7*aR*,7*bR*)-1,1,7-trimethyl-4-methylidene-1*a*,2,3,4*a*,5,6,7*a*,7*b*-octahydrocyclopropa[h]azulen-7-ol

Continuation of Table 1

No.	Structures	IUPAC Names
8		(1*R*,4*S*,4*aR*,8*aR*)-1,6-dimethyl-4-propan-2-yl-3,4,4*a*,7,8,8*a*-hexahydro-2*H*-naphthalen-1-ol
9		(1*R*,5*S*,6*R*,7*S*,10*R*)-4,10-dimethyl-7-propan-2-yltricyclo[4.4.0.0^{1,5}]dec-3-ene
10		(1*aR*,4*R*,4*aR*,7*bS*)-1,1,4,7-tetramethyl-1*a*,2,3,4,4*a*,5,6,7*b*-octahydrocyclopropa[e]azulene
11		(1*Z*,4*Z*,8*E*)-2,6,6,9-tetramethylcycloundeca-1,4,8-triene
12		(1*R*,4*aR*,8*aS*)-7-methyl-4-methylidene-1-propan-2-yl-2,3,4*a*,5,6,8*a*-hexahydro-1*H*-naphthalene
13		(1*R*,4*E*,9*S*)-4,11,11-trimethyl-8-methylidenebicyclo[7.2.0]undec-4-ene
14		(1*S*,2*S*,4*R*)-1-ethenyl-1-methyl-2,4-bis(prop-1-en-2-yl)cyclohexane
15		(1*R*,4*aS*,8*aS*)-7-methyl-4-methylidene-1-propan-2-yl-2,3,4*a*,5,6,8*a*-hexahydro-1*H*-naphthalene

Continuation of Table 1

No.	Structures	IUPAC Names
16		(1*S*,4*aS*,8*aR*)-4,7-dimethyl-1-propan-2-yl-1,2,4*a*,5,6,8*a*-hexahydronaphthalene
17		(1*R*,8*aR*)-4,7-dimethyl-1-propan-2-yl-1,2,3,5,6,8*a*-hexahydronaphthalene
18		(4*R*)-4-ethenyl-4-methyl-1-propan-2-yl-3-prop-1-en-2-ylcyclohexene

Preparation of Studied Ligands and Receptor for Molecular Docking

Preparation of the Studied Phytochemicals

The optimized structures were converted from .spartan to .pdb format using Spartan software. Before Autodock Vina docking calculation the .pdb format of the studied phytochemicals was converted to the .pdbqt format using Autodock Tool software.

Preparation of the Lactate Dehydrogenase for Docking Study

The downloaded lactate dehydrogenase structure (PDB ID: 1LDG) (Fig. 1) [31] from the Protein Data Bank was processed using Pymol software to identify any extraneous molecules (small molecules and water molecules) downloaded with the desired protein. Other molecules downloaded with lactate dehydrogenase were removed and subjected to Autodock Tool software to locate the appropriate binding site for the studied compounds. The calculated value for the centre and binding site in X, Y and Z directions that show the located binding site were 27.729 Å, 16.305 Å, and 36.464 Å for the centre and 66Å, 56 Å and 66 Å for site (Fig. 2). The binding affinity for the studied complex was determined using Autodock Vina software.

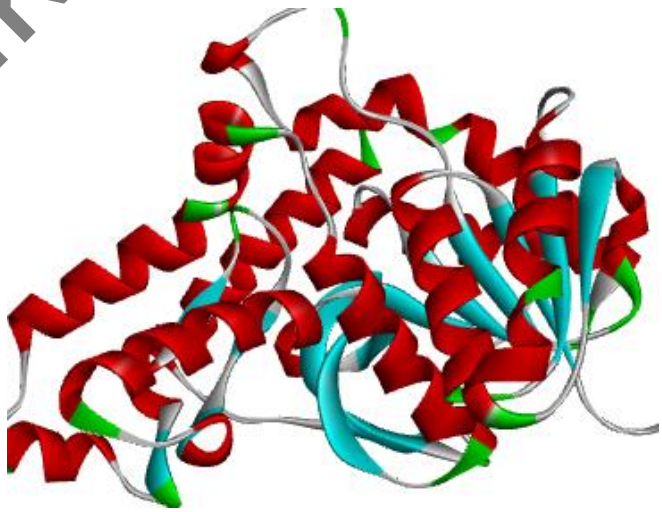


Figure 1. 3D structure of lactate dehydrogenase (PDB ID: 1LDG)

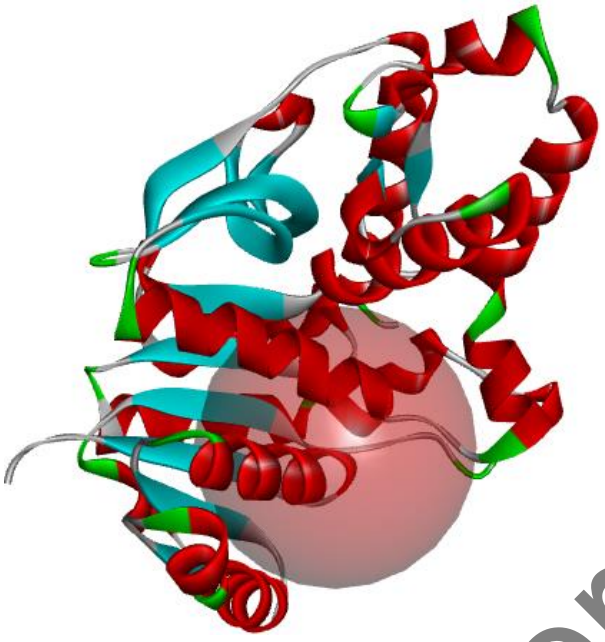


Figure 2. 3D structure of lactate dehydrogenase (PDB ID: 1LDG) with binding site located

Molecular Dynamic Simulation Study

In this work, compound **15** with the lowest binding affinity and reference drug (quinine) were subjected to molecular dynamics simulation using AMBER14 molecular dynamics package [33]. Hydrogen atoms were added to the complexes under study via a leap sector of AMBER14. AMBER force field 99SB was used for the protein while general AMBER force field was used for ligand [34, 35]. Appropriate number of counterions were added so as to neutralize the investigated complexes before solvation which was executed in a condensed octahedral cell of TIP3P [36] water molecules, and 12˚A was overextended beyond the protein.

Moreover, 5000 frames of steepest descent minimization were used for minimization, and 10000 frames of conjugated gradient minimization were also employed in order to eradicate unwanted atom interactions. The temperature used for the entire system was 300K at 100ns and the study was executed at 1 atm via the particle mesh Ewald method [37]. Also, molecular dynamics trajectories analysis was executed via CPPTRAJ module [34].

Quantitative Structure-activity Relationship (QSAR) Study

The optimized compounds were converted to .sdf format before subjecting to PaDEL (Pharmaceutical Data Exploration Laboratory) version 2.21 to generate 2D descriptors [38, 39]. For reliability, the studied compounds were divided into two different sets ((training set (80%) and test set (20%)), and the training set compounds were subjected to Material Studio software to develop a valid QSAR model via genetic function algorithm (Equation 1):

$$Y = 0.117614842(ALogp2) + 0.006900712\ (ATS1m) + 0.002645580\ (ATS7m) - 0.007905861\ (ATS0v) + 29.444475533. \quad (1)$$

The studied QSAR model was validated by considering CVR^2, adjusted R^2, and F-value.

R-squared = 0.80602900, Adjusted R-squared = 0.72844100,

Cross validated R-squared = 0.61235600, Significance-of-regression F-value = 10.38855500

Result and Discussion

Calculated Descriptors for Obtained Phytochemicals from Enantia chlorantia Bark

In this work, a series of descriptors were obtained, and four descriptors were selected using Lipinski rule of five, i.e. Molecular Weight ≤ 500 amu, Log P ≤ 5, Hydrogen Bond Donor (HBD) ≤ 5 and Hydrogen Bond Acceptor (HBA) ≤ 10 [40] (Table 2).

Table 2

Calculated descriptors for studied compounds

	MW	LogP	HBD	HBA
1	220.35	3.47	0	1
2	198.30	2.87	0	0
3	220.35	3.29	0	1
4	204.35	4.69	0	0
5	220.35	3.6	0	1
6	220.356	4.35	0	1
7	220.356	3.01	1	1
8	222.372	3.49	1	1
9	204.357	4.23	0	0
10	204.357	4.08	0	0
11	204.357	4.78	0	0
12	204.357	4.34	0	0
13	204.357	4.48	0	0
14	204.357	4.76	0	0
15	204.357	4.34	0	0
16	204.357	4.29	0	0
17	204.357	4.14	0	0
18	204.357	4.71	0	0

According to Lien, 1982 [41], the calculated molecular weight from optimized molecular structures using computational tools remains an important characteristic that reveals the state (solubility, Van der Waals forces, molar refraction, steric factors, molecular connectivity, thermodynamic activity, partition coefficient, etc.) of such compound. The oral bioavailability of any compounds is a function of molecular weight in the range of 150–500 amu [42]; thus, all the calculated compounds proved to be orally bioavailable.

Moreover, the solubility of molecular compounds in lipophilic phase reveals the role of Log P in drug design [43]. Also, the report by Meanwell 2011 [44] showed that there may be possible complications which human body system may experience if the calculated Log P value is higher than 5 for oral absorption of drug-like molecule; therefore, all the calculated Log *P* value were within the accepted range for Log *P* (Log $P \leq 5$). This implies that the studied compounds have the ability to be taken orally without any complication.

It was observed that all the studied compounds obeyed the Lipinski rule of five, and this shows that all they have the potential ability to act as a drug.

Molecular Docking Studies on Phytochemicals from Enantia chlorantia Bark and Lactate dehydrogenase

The studied compounds obtained from *Enantia chlorantia* bark were screened for inhibitory activities against Lactate dehydrogenase using the molecular docking method. As reported in several literature sources, the higher binding affinity (in terms of negativity) corresponds to the better ability of the compound to inhibit the receptor [45]. The inhibitory activity of the individual studied ligand was compared with the inhibitory activity of the reference drug (quinine) and presented in Table 3.

Table 3

Calculated binding affinity for Phytochemicals from *Enantia chlorantia* Bark–Lactate dehydrogenase complex

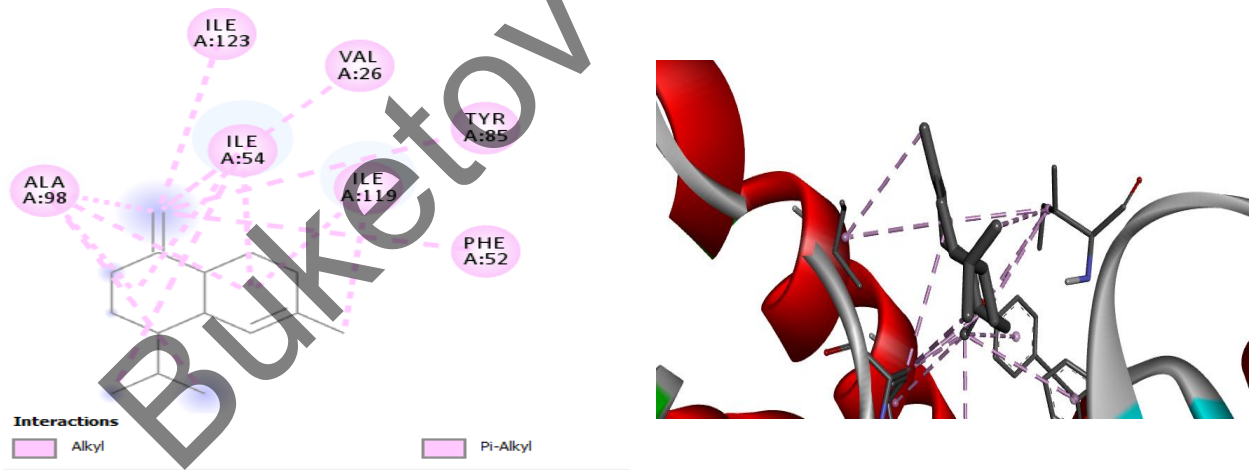
No	Binding Affinity (kcal/mol)	Residues involved in the interactions	Types of Non-bonding interaction involved
1	–6.4	PHE52, ILE54, ALA98, ILE119	Pi-Alkyl, Alkyl
2	–7.4	PHE100, ILE119, VAL26, ILE54, PHE52, ALA98	Pi-Alkyl, Alkyl, Pi-Sigma
3	–5.9	LEU201, VAL200, LYS314, PHE229, LEU202, LYS203	Pi-Alkyl, Alkyl
4	–7.0	ILE119, VAL55, ALA98, VAL26, TYR85, PHE52, ILE123, ILE54	Pi-Alkyl, Alkyl
5	–6.0	LYS203, LEU201, PHE229, LEU202, VAL200, LYS314	Pi-Alkyl, Alkyl
6	–6.2	LYS314, LYS198, VAL200, VAL233	Alkyl

Continuation of Table 3

No	Binding Affinity (kcal/mol)	Residues involved in the interactions	Types of Non-bonding interaction involved
7	–6.6	VAL233, LYS314, VAL200, LEU201	Unfavorable Donor-Donor, Alkyl
8	–6.3	VAL55, ALA98, PHE52, ILE119, ILE54, VAL26	Pi-Alkyl, Alkyl
9	–7.3	ILE54, PHE100, ILE119, VAL26, ALA98, PHE52, TYR85, ILE123	Pi-Alkyl, Alkyl
10	–6.4	ALA98, ILE54, ILE119, PHE100	Pi-Alkyl, Alkyl
11	–5.8	LYS314, VAL200, LEU202, PHE229, ARG204, LY203	Pi-Alkyl, Alkyl
12	–5.8	TYR174, TYR175, ILE239, ARG171, ALA249	Pi-Alkyl, Alkyl
13	–5.9	ILE54, ILE119, ALA98	Alkyl
14	–6.1	ILE119, ALA98, PHE52, ILE54, PHE100, LYS118	Pi-Alkyl, Alkyl
15	–7.8	ALA98, ILE123, VAL26, ILE54, ILE119, TYR85, PHE52	Pi-Alkyl, Alkyl
16	–7.0	ILE54, ILE119, PHE100, VAL26, ILE123, TYR85, PHE52, ALA98	Pi-Alkyl, Alkyl
17	–7.0	PHE52, ALA98, ILE54, ILE119, PHE100	Pi-Alkyl, Alkyl
18	–6.4	PHE52, VAL26, ALA98, ILE54, ILE123, TYR85, ILE119, PHE100	Pi-Alkyl, Alkyl
Quinine	–6.7	-	-

According to the data in Table 3, compound **15,** with the highest binding affinity value in terms of negative, has the highest tendency to inhibit Lactate dehydrogenase compared with other studied compounds and the reference drug (Fig. 3).

It can also be seen from Table 3 that six compounds (**2**, **4**, **9**, **15**, **16** and **17**) have better binding affinities than the other studied compounds and the reference drug. This showed that these phytochemicals enhanced the biological activities of *Enantia chlorantia* bark as a potential antimalaria agent. The reference drug with -6.7 kcal/mol binding affinity showed a greater tendency to inhibit Lactate dehydrogenase than compounds **1**, **3**, **5**, **6**, **7**, **8**, **10**, **11**, **12**, **13**, **14** and **18**.



a) 2D structure *b*) 3D structure

Figure 3. Binding site of Lactate dehydrogenase amino acid residues with compound **15**

Molecular Dynamic Simulation Analysis

Root of Mean Square Deviation (RMSD)

Root of mean square deviation of Lactate dehydrogenase backbone atoms in connection to the initial structure of the studied enzyme in forming complexes with compounds **15** and quinine during the 100 ns MD simulation is presented in Figure 4.

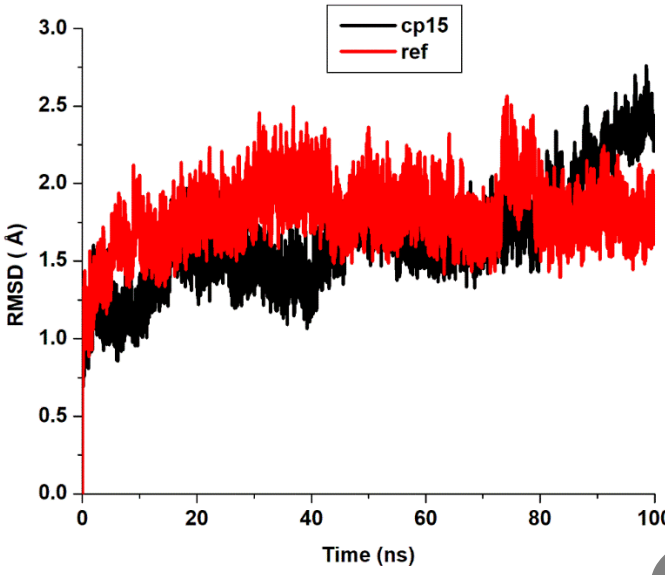


Figure 4. RMSD of **Compound 15-**1LDG (black) and **Quinine-ILDG** (red) complexes during the 100 ns MD simulations

This study was carried out to investigate the rate of deviation of the initial studied compounds upon binding, as well as the stability of the simulated complexes. Therefore, as shown in Figure 4, compound **15-**Lactate dehydrogenase complex proved to be more stable after sixty nanoseconds (60 ns) of the simulation time than quinine- Lactate dehydrogenase complex.

Binding Energy Calculation

Table 4 presents the calculated binding energy components (total binding energy; van der Waals energy; electrostatic energy; gas-phase energy; solvation energy).

Table 4

Binding energy profiles of Compound 15-Lactate dehydrogenase complex and Quinine-Lactate dehydrogenase complex

Complexes	Binding Energy Components (kcal/mol)				
	ΔE_{vdw}	ΔE_{ele}	ΔG_{gas}	ΔG_{sol}	ΔG_{bind}
CP15-protein	–26.95 ± 0.08	–1.30 ± 0.01	–28.25 ± 0.08	3.08 ± 0.02	–25.17 ± 0.08
REF-protein	–13.34 ±0.17	10.69 ±0.18	–2.65 ±0.44	–7.51 ± 0.44	–10.17 ±0.13

Note: ΔG_{bind} = total binding energy; ΔE_{vdw} = van der Waals energy; ΔE_{ele} = electrostatic energy; ΔG_{gas} = gas-phase energy; ΔG_{sol} = solvation energy.

The calculated binding free energy for compound **15**–Lactate dehydrogenase complex (–25.17 kJ/mol) confirmed the outstanding activity of compound **15** as potential Lactate dehydrogenase inhibitor. The presented molecular dynamic simulation result revealed that van der Waal energy, electrostatic energy, and gas-phase energy were favourable while polar solvation energy was not favourable for the binding of compound **15** to lactate dehydrogenase.

Quantitative Structure Activities Relationship Study

The obtained descriptors were screened, and the selected descriptors were divided into two sets, i.e. training and test sets. Compounds **2**, **6** and **10** were used as test sets, while other compounds obtained from *Enantia chlorantia* bark were used as the training set. The descriptors from the training set were used as the independent variable, while calculated binding affinity was used as the dependent variable. The 2D-QSAR model shown in Equation 1 included four descriptors which align with ratio 1:4 of the descriptors to the entire studied compounds as described in several reports [46]. The developed model was used to predict the calculated binding affinity. It was observed that the predicted binding affinity of the training set was closer to the original binding affinity. This is proof that the developed QSAR model is predictive, and its reliability was confirmed via the test set, which also goes in line with the squared correlation coefficient (R^2). Also,

according to Adegoke *et al*., 2020 [47], the predictive ability of any developed QSAR model is not enough to justify its potency; thus, this calls for 2D-QSAR validation. Adjusted R-squared, Cross validated R-squared and Significance-of-regression F-value were considered for QSAR validation. According to Oyebamiji *et al*., 2022 [48], Adjusted R-squared must be less than or equal to 0.6 while Cross validated R-squared must be less than or equal to 0.5 for any developed QSAR model to be considered valid; thus, the developed 2D-QSAR model can be considered valid and efficient (Table 5).

Table 5

Observed and predicted binding affinity

	Original Binding Affinity	Predicted Binding Affinity
1	–6.4	–6.4
2*	–7.4	–0.6
3	–5.9	–5.9
4	–7.0	–7.0
5	–6.0	–6.0
6*	–6.2	2.9
7	–6.6	–6.6
8	–6.3	–6.3
9	–7.3	–7.3
10*	–6.4	2.2
11	–5.8	–5.8
12	–5.8	–5.8
13	–5.9	–5.9
14	–6.1	–6.1
15	–7.8	–7.8
16	–7.0	–7.0
17	–7.0	–7.0
18	–6.4	–6.4
Note: *Denote test set.		

Conclusions

Eighteen phytochemicals were selected from the entire compounds in *Enantia chlorantia* bark for *in silico* study. The structure of the selected compounds was subjected to optimization using Spartan 14 software, and a series of descriptors describing the antimalaria activities of the studied plant were obtained. Compound **15** (1*R*,4*aS*,8*aS*)-7-methyl-4-methylidene-1-propan-2-yl-2,3,4*a*,5,6,8*a*-hexahydro-1*H*-naphthalene) showed –7.8 kcal/mol binding affinity, that is higher than all other studied compounds, as well as the reference drug. This proves that Compound **15** has better ability to inhibit Lactate dehydrogenase, thereby downregulating malaria. Also, the QSAR model developed using binding affinity as the dependent variable showed good prediction, and was found to be reliable and valid.

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