Nigerian Journal of Pharmaceutical and Applied Science Research, 11 (2): 19-26; June 2022 (ISSN 1485-8059). Available at www.nijophasr.net

Molecular Docking and Antimalarial Evaluation of Natural Phenolics and Their Derivatives on Plasmodium falciparum Lactate Dehydrogenase as Schizonticidal Drug Candidates

[1*]Andong Bassey Asuquo, [1]Onyechi Samuel Onyeka, [1]Etukakpan Ekemini Victor, [1]Umoh Mfonobong Effiong, [1]Pascal Anthony Chidera, [1]Ekarika Johnson, [1]Olorunfemi Eseyin Abraham.

1.Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmacy, University of Uyo, Uyo, Nigeria.

ABSTRACT

Background: Antimalarial drug resistance is increasing in Sub-Saharan Africa. Natural phenolic compounds are known to have antimalarial activity and should be harnessed to reduce the malaria burden. A potential mechanism of schizonticidal action is the inhibition of *Plasmodium falciparum* lactate dehydrogenase. This study aimed to evaluate the binding affinity of natural phenolics and their derivatives on *Plasmodium falciparum* lactate dehydrogenase.

***Methods*:** 35 compounds were downloaded from the Protein Data Bank and their binding energy on *Plasmodium falciparum* lactate dehydrogenase was evaluated using Autodock tools. Derivatives of compounds with the best binding energy and pharmacokinetic parameters were designed using ChemSketch and their binding energy was obtained. The protein-ligand interaction was analyzed using Discovery Studio.

***Results*:** Curcumin had binding energy of -6.95kcal/mol, vitexin had binding energy of -7.44kcal/mol and daidzein had binding energy of -7kcal/mol. Two derivatives of curcumin had binding energy of -7.61kcal/mol, and -7.24kcal/mol. Two derivatives of vitexin had binding energy of -8.02kcal/mol and -7.48kcal/mol. These compounds had favorable biological and pharmacokinetic properties and possessed binding energy better than reference compounds; dihydroartemisinin(-6.8kcal/mol), quinine(-7.2kcal/mol), and chloroquine(-5.76kcal/mol).

***Conclusion*:** Derivatized compounds had antiplasmodial potential and *in vitro, in vivo* work should be done to ascertain their schizonticidal activity.

Keywords: Molecular docking, *Plasmodium falciparum* lactate dehydrogenase, Antimalarial drug resistance, Phenolics.

1. INTRODUCTION

Malaria is a disease that is transmitted through the bite of an infected female *Anopheles* mosquito [1]. There are 6 known species of the malaria-causing parasite but the most prevalent in Africa is *Plasmodium falciparum* [2]. About 97% of Nigeria's population is at risk of getting malaria [3]. The current drugs used in treating malaria are chloroquine, mefloquine, quinine, and artemisinin derivatives. Drugs such as chloroquine, quinine, mefloquine are thought to act by disrupting the digestion of hemoglobin in the blood stage of the malaria parasite life cycle [4] while artemisinin and its derivatives (artemether, dihydroartemisinin, artesunate, arteether) act by producing free radicals which alkylate susceptible proteins and increase oxidative stress in the parasitic cells thus leading to the death of the malaria parasite [5]. However, there has been an increase in reports of antimalarial drug resistance in Africa due to the emergence of resistant strains of *Plasmodium falciparum* to current drugs [6]. This has necessitated the search for novel compounds with different mechanisms of action to kill the malaria parasite. It has been proven that intraerythrocytic *Plasmodium falciparum* parasites which are responsible for the clinical manifestation of malaria symptoms obtain energy through an anaerobic conversion of pyruvate to lactic acid [7–10]. Thus, it can be inferred that inhibition of pyruvate conversion will reduce the cellular energy of parasites which can reduce the rate of cell replication and lead to the death of parasitic cells. The enzyme *Plasmodium falciparum* lactate dehydrogenase (*Pf*LDH) has been discovered to catalyze the anaerobic conversion of pyruvate to lactic acid during the intraerythrocytic stage of malaria and has been recognized as a virulence factor of malaria

[*]Corresponding author: Email: andongbassey@gmail.com; Phone: +2347031051508

parasite which has led to the design of several small molecules to inhibit *Pf*LDH enzyme [11]. Both quinine and artemisinin, the pioneer antimalarials are natural products that have played a huge role in the battle against malaria but due to the rising drug resistance, searching for new natural products with a distinct mechanism of action for schizonticidal activity on *Plasmodium falciparum* is a rational approach. Phenols are compounds that possess at least one hydroxyl group attached to a benzene ring. Natural phenolic compounds have been found to possess antimalarial activity [12][13]. This study aimed to use molecular docking tools to determine the drug-likeness, binding energy of some natural products, phenolics, and their derivatives on *Pf*LDH which could serve as potential antimalarials amidst increased resistance to reference compounds (quinine, dihydroartemisinin, chloroquine).

2. METHODS

35 natural compounds (ligands) with suspected antimalarial activity were obtained from literature search and authors' intuition. 3D structures of ligands were downloaded in SDF format from PubChem (https://pubchem.ncbi.nlm.nih.gov/). Downloaded ligands were converted to PDB format using Discovery Studio (Dassault Systèmes).

The target protein – *Plasmodium falciparum* lactate dehydrogenase in complex with chloroquine (1CET) was downloaded in PDB format from the Protein Data Bank (https://www.rcsb.org/).

Chloroquine was separated from the complex to obtain *Plasmodium falciparum* lactate dehydrogenase using Discovery Studio (Dassault Systèmes).

The ligands and optimized target protein were converted to pdbqt format and molecular docking of each ligand with target protein was done using Autodock 4.2 (http://mgltools.scripps.edu/) to obtain their binding energy. The grid box parameters were determined manually to cover the amino acid residues in the active site of *Plasmodium falciparum* lactate dehydrogenase. The values used were; x-center (34.792Å), y-center (15.612Å), and z-center (18.721Å).

Using Lipinski's rule of five and binding energy as criteria for selection, 31 derivatives of vitexin, 29 derivatives of curcumin, and 3 derivatives of daidzein were designed and saved in mol format with Chemsketch Freeware 2021.20 (http://www.acdlabs.com). All derivatives were converted to 3D PDB format using Discovery Studio (Dassault Systèmes). Molecular docking of each derivative with the target protein was done using Autodock 4.2 (http://mgltools.scripps.edu/).

Discovery Studio (Dassault Systèmes) was used to analyze ligand-protein binding interactions.

Molecular properties of ligands were obtained from the molinspiration website (https://www.molinspiration.com/cgi-bin/properties), while pharmacokinetic parameters were obtained from the pkcsm website (http://biosig.unimelb.edu.au/pkcsm/prediction).

RESULTS

The binding energy and pharmacokinetic parameters of the reference compounds and other natural products are provided in Table 1. The 3 phenolics; vitexin, daidzein, and curcumin were modified to get derivatives satisfying Lipinski's rule and subjected to molecular docking with *Pf*LDH.

Table 1: Binding Energy and Pharmacokinetic Parameters of Natural and Reference Compounds

Rank	Compounds	B.E (kcal /mol)	I.A (%)	LD_{50} (mol/ kg)	MW (g/ mol)	HBA	HBD	LogP	Lipinski Violation
1	Naringin	-8.49	25.5	2.6	580.5	14	8	-1.2	3
2	Quercitrin	-7.57	50.4	3.0	448.4	11	7	0.5	2
3	Vitexin	-7.44	38.3	2.7	432.4	10	7	0.1	1
4	Quinine	-7.20	96.0	3.2	324.4	4	1	3.2	0
'5	Daidzein	-7.00	92.8	1.9	254.2	4	2	2.9	0
6	Curcumin	-6.95	86.4	1.9	368.2	6	2	3.4	0
7	Dihydroartemisinin	-6.80	94.9	2.7	284.4	5	1	2.2	0
8	Genistein	-6.48	91.1	2.3	270.2	5	3	2.6	0
9	Luteolin	-6.42	79.0	2.7	286.2	6	4	2.3	0

10	Epicatechin	-6.38	62.7	2.3	290.3	6	5	1.5	0
11	Ellagic Acid	-6.34	80.1	2.5	302.2	8	4	1.3	0
12	Cinnamic Aldehyde	-6.25	87.3	2.6	93.1	2	1	0.3	0
13	Hesperetin	-6.21	84.5	2.2	302.3	6	3	2.5	0
14	Apigenin	-6.21	91.4	2.4	270.2	5	3	2.6	0
15	Butein	-6.21	73.9	1.8	272.3	5	4	2.4	0
16	Naringenin	-6.12	90.9	2.2	272.3	5	3	2.5	0
17	Catechin	-6.11	62.7	2.3	290.3	6	5	1.5	0
18	Chrysin	-6.08	93.8	2.0	254.2	4	2	2.9	0
19	Kaempferol	-5.83	85.0	2.7	286.2	6	4	2.3	0
20	Chloroquine	-5.76	90.0	2.9	319.9	3	1	4.8	0
21	Phloretin	-5.76	71.2	2.1	274.3	5	4	2.3	0
22	Hesperidin	-5.64	27.6	2.5	610.6	15	8	-1.2	3
23	Gallic Acid	-5.58	40.2	2.0	170.1	4	4	0.5	0
24	Myricetin	-5.54	62.7	2.8	318.2	8	6	1.7	1
25	Caffeic Acid	-5.11	55.5	2.0	180.2	3	3	1.2	0
26	Silymarin	-5.02	76.4	2.6	482.4	10	5	2.4	0
27	Cinnamic Acid	-5.01	94.0	2.2	148.2	1	1	1.8	0
28	p-Coumaric Acid	-5.01	93.1	2.1	164.2	2	2	1.5	0
29	Vanillic Acid	-4.94	75.0	2.0	168.1	3	2	1.1	0
30	Ferulic Acid	-4.76	94.7	2.1	194.2	3	2	1.5	0
31	Rutin	-4.60	20.5	2.5	610.5	16	10	-1.7	2
32	Sinapic Acid	-4.57	94.8	2.2	224.2	2	1	0.3	0
33	Salicylic Acid	-4.42	70.9	1.8	138.1	2	2	1.1	0
34	Phlorizin	-2.50	30.3	2.1	436.4	10	7	-0.2	1
35	Lycopene	8.05	89.2	2.2	536.8	0	0	12.9	2

I.A= Intestinal Absorption, MW= Molecular weight, B.E= Binding energy, HBA=Hydrogen bond acceptors, HBD= Hydrogen bond donors.

Derivatives of curcumin were designed by adding acetate and methoxy groups to position R_1 and R_2 with variations in double bonds of the parent curcumin chain (Figure 1). Table 2 shows the binding energy and pharmacokinetic parameters of 29 curcumin derivatives.

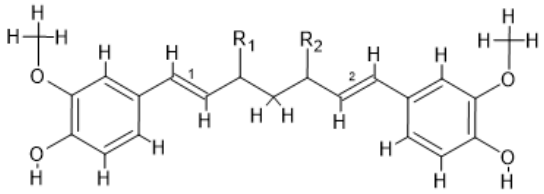

Figure 1. Curcumin Parent Chain

Table 2: Binding Energy and Pharmacokinetic Parameters of Curcumin Derivatives

Compounds	R_1	R_2	Double Bond	B.E (kcal/ mol)	I.A (%)	LD_{50} (mol/ kg)	MW (g/ mol)	HBA	HBD	LogP	Lipinski Violation
Curcumin	=O	=O	1,2	-6.95	86.4	1.9	368.4	6	2	3.4	0
Compound 1	OH	OH	1,2	-7.61	76.0	2.0	372.4	6	4	3.0	0
Compound 2	OCH_3	OH	1,2	-7.24	98.1	1.9	386.4	6	3	3.6	0
Compound 3	CH_3COO	CH_3COO	1	-7.12	83.6	2.9	458.5	8	2	4.0	0
Compound 4	OH	OH	1	-6.82	75.4	2.0	374.4	6	4	2.9	0
Compound 5	CH_3COO	=O	1,2	-6.56	83.6	2.1	412.4	7	2	3.7	0
Compound 6	OCH_3	=O	1,2	-6.50	94.6	1.9	384.4	6	2	3.8	0
Compound 7	OCH_3	=O	1	-6.01	94.8	1.9	386.4	6	2	3.7	0
Compound 8	OCH_3	OH	1	-5.95	92.6	1.9	388.5	6	3	3.5	0
Compound 9	OH	=O	1,2	-5.91	80.5	1.8	372.4	6	3	3.8	0
Compound 10	OH	CH_3COO	1,2	-5.79	80.7	3.0	414.5	7	3	3.5	0
Compound 11	CH_3COO	CH_3COO	1,2	-5.78	84.2	2.9	456.5	8	2	4.1	0

Compound 12	CH_3COO	OH	1	-5.72	77.8	2.0	416.5	7	3	3.4	0
Compound 13	=O	=O	1	-5.71	85.8	1.9	370.4	6	2	3.3	0
Compound 14	CH_3COO	=O	1	-5.69	83.1	2.1	414.5	7	2	3.7	0
Compound 15	OCH_3	CH_3COO	1,2	-5.68	87.0	2.5	428.5	7	2	4.2	0
Compound 16	OH	=O	1	-5.60	81.1	1.8	370.4	6	3	3.2	0
Compound 17	CH_3COO	OCH_3	1	-5.45	86.6	2.6	430.5	7	2	4.1	0
Compound 18	=O	=O		-5.43	85.2	1.8	372.4	6	2	3.2	0
Compound 19	OCH_3	OCH_3	1	-5.35	94.9	2.3	402.5	6	2	4.2	0
Compound 20	OCH_3	OCH_3	1,2	-5.30	94.8	2.3	400.5	6	2	4.3	0
Compound 21	OH	OH		-5.16	74.8	2.0	376.4	6	4	2.8	0
Compound 22	OH	=O		-5.16	79.9	1.8	374.4	6	3	3.0	0
Compound 23	OCH_3	OH		-4.43	92.4	1.8	390.5	6	3	3.4	0
Compound 24	CH_3COO	OH		-4.19	77.2	2.1	418.5	7	3	3.4	0
Compound 25	CH_3COO	OCH_3		-4.06	86.0	2.6	432.5	7	2	4.0	0
Compound 26	CH_3COO	=O		-3.95	82.5	2.1	416.5	7	2	3.6	0
Compound 27	OCH_3	=O		-3.77	95.0	1.9	388.5	6	2	3.7	0
Compound 28	CH_3COO	CH_3COO		-3.42	83.0	2.8	460.5	8	2	3.9	0
Compound 29	OCH_3	OCH_3		-3.39	95.1	2.2	404.5	6	2	4.1	0

I.A= Intestinal Absorption, MW= Molecular weight, B.E= Binding energy, HBA=Hydrogen bond acceptors, HBD= Hydrogen bond donors

Derivatives of vitexin were designed by adding methyl and acetyl groups to position R_1, R_2, R_3, and R_4 on the vitexin parent chain (Figure 2). Table 3 shows the binding energy and pharmacokinetic parameters of 31 vitexin derivatives.

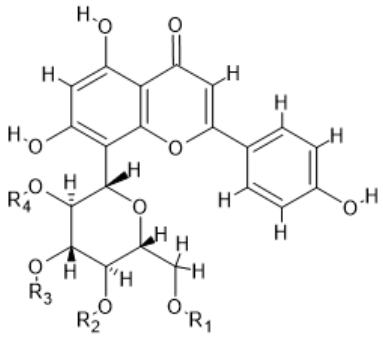

Figure 2. Vitexin parent chain

Table 3. Binding Energy and Pharmacokinetic Parameters of Vitexin Derivatives

Compounds	R_1	R_2	R_3	R_4	B.E (kcal/ mol)	I.A (%)	LD_{50} (mol/ kg)	MW (g/ mol)	HBA	HBD	LogP	Lipinski Violation
Vitexin	H	H	H	H	-7.44	38.3	2.7	432.4	10	7	0.1	1
Compound 1	CH_3	$COCH_3$	H	H	-8.02	42.4	2.8	488.4	11	5	1.3	1
Compound 2	$COCH_3$	CH_3	H	H	-7.48	52.7	2.8	488.4	11	5	1.3	1
Compound 3	CH_3	CH_3	H	H	-7.46	50.0	2.8	460.4	10	5	1.4	0
Compound 4	CH_3	H	$COCH_3$	H	-7.37	45.2	2.8	488.4	11	6	0.7	1
Compound 5	H	$COCH_3$	CH_3	H	-7.33	42.3	2.8	488.4	11	5	1.3	1
Compound 6	H	$COCH_3$	H	CH_3	-7.29	42.2	2.8	488.4	11	5	1.3	1
Compound 7	H	CH_3	$COCH_3$	H	-7.29	52.2	2.9	488.4	10	5	1.3	0
Compound 8	H	$COCH_3$	H	H	-7.24	39.4	2.8	474.4	11	6	0.7	2
Compound 9	$COCH_3$	H	H	H	-7.22	46.8	2.8	474.4	11	6	0.7	2
Compound 10	CH_3	CH_3	H	CH_3	-7.20	55.6	2.7	474.5	10	4	2.1	0
Compound 11	CH_3	H	CH_3	CH_3	-7.19	55.5	2.7	474.5	10	4	2.1	0
Compound 12	CH_3	CH_3	CH_3	H	-7.12	55.7	2.7	474.5	10	4	2.1	0
Compound 13	H	H	CH_3	$COCH_3$	-7.12	45.0	2.8	488.4	11	5	1.3	1
Compound 14	$COCH_3$	H	H	CH_3	-7.09	52.4	2.8	488.4	11	5	1.3	1
Compound 15	$COCH_3$	H	CH_3	H	-7.04	52.5	2.8	488.4	11	5	1.3	1
Compound 16	CH_3	H	CH_3	H	-7.03	49.9	2.8	460.4	10	5	1.4	0
Compound 17	H	CH_3	CH_3	H	-7.02	49.9	2.8	460.4	10	5	1.4	0
Compound 18	CH_3	CH_3	CH_3	CH_3	-7.01	61.3	2.5	488.5	10	3	2.7	0

Compound 19	H	H	CH_3	CH_3	-7.01	49.6	2.8	460.4	10	5	1.4	0
Compound 20	H	CH_3	H	$COCH_3$	-6.96	45.1	2.8	488.4	11	5	1.3	1
Compound 21	CH_3	H	H	H	-6.96	44.1	2.8	446.4	10	6	0.7	1
Compound 22	H	H	H	$COCH_3$	-6.94	39.3	2.8	474.4	11	6	0.6	2
Compound 23	H	H	$COCH_3$	H	-6.86	39.4	2.8	474.4	11	6	0.7	2
Compound 24	H	H	$COCH_3$	CH_3	-6.86	45.0	2.8	488.4	11	5	1.3	1
Compound 25	H	CH_3	CH_3	CH_3	-6.78	55.5	2.7	474.5	10	4	2.1	0
Compound 26	H	CH_3	H	H	-6.74	44.1	2.8	446.4	10	6	0.7	1
Compound 27	CH_3	H	H	CH_3	-6.72	49.8	2.8	460.4	10	5	1.4	0
Compound 28	H	CH_3	H	CH_3	-6.62	49.8	2.8	460.4	10	5	1.4	0
Compound 29	CH_3	H	H	$COCH_3$	-6.59	45.1	2.8	488.4	11	5	1.3	1
Compound 30	H	H	H	CH_3	-6.42	44.0	2.8	446.4	10	6	0.7	1
Compound 31	H	H	CH_3	H	-6.23	44.0	2.8	446.4	10	6	0.7	1

I.A= Intestinal Absorption, MW= Molecular weight, B.E= Binding energy, HBA=Hydrogen bond acceptors, HBD= Hydrogen bond donors

Derivatives of daidzein were designed by adding methoxy, acetate, hydroxy, and oxo groups to R on the parent daidzein chain (Figure 3). Table 4 shows the binding energy and pharmacokinetic parameters of 3 daidzein derivatives.

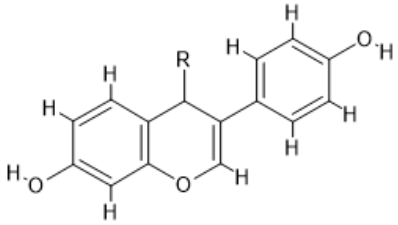

Figure 3. Daidzein parent chain

Table 4. Binding Energy and Pharmacokinetic Parameters of Daidzein Derivatives

Compounds	R	B.E (kcal/mol)	I.A (%)	LD_{50} (mol/kg)	MW (g/mol)	HBA	HBD	LogP	Lipinski Violation
Daidzein	=O	-7	92.8	1.9	254.2	4	2	2.9	0
Compound 1	CH_3COO	-6.35	93.1	2.4	298.3	5	2	3.1	0
Compound 2	OH	-6.35	89.5	1.9	256.3	4	3	2.6	0
Compound 3	OCH_3	-5.79	93.5	2.3	270.3	4	2	3.2	0

I.A= Intestinal Absorption, MW= Molecular weight, B.E= Binding energy, HBA=Hydrogen bond acceptors, HBD= Hydrogen bond donors

The binding interactions of curcumin and its derivative are shown in Figures 4a, 4b respectively.

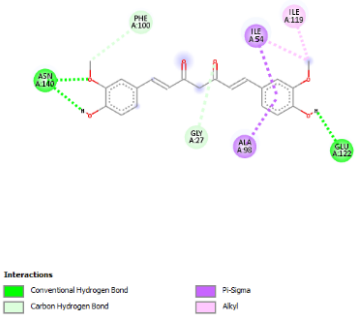

Figure 4a. Curcumin-protein interaction

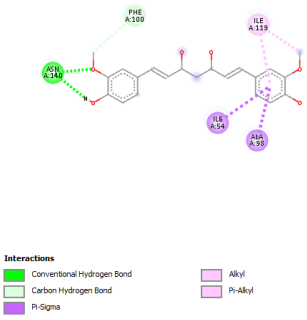

Figure 4b. Compound1-protein interaction

The binding interactions of vitexin and its derivative are shown in Figures 5a, 5b respectively

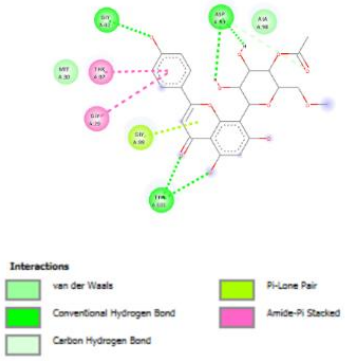

Figure 5a. Vitexin-protein interaction

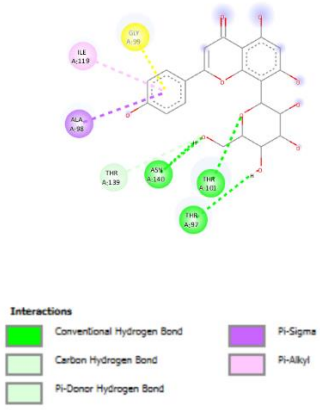

Figure 5b. Compound1-protein interaction

The binding interaction of daidzein is shown in Figure 6.

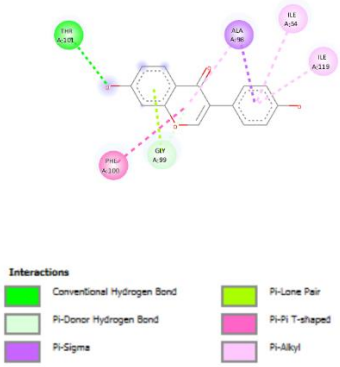

Figure 6. Daidzein-protein interaction

4. DISCUSSION

Naringin, a naturally occurring flavonoid found in grapefruits showed the best binding energy. However, it had a total of 3 Lipinski violations thus reducing its drug likeliness. Quercitrin, a derivative of quercetin had 2 violations. Vitexin showed the best binding energy with minimum violations. Curcumin and daidzein had binding energy better than dihydroartemisinin, and chloroquine but higher than quinine. Although quinine showed good binding energy, *Plasmodium falciparum* quinine-resistant phenotypes are to be treated with novel compounds[4]. Curcumin showed binding energy of -6.95 kcal/mol with *Pf*LDH. The binding affinity of curcumin to *Plasmodium falciparum* Ca(2+)-ATPase (*Pf*ATP6) was determined to be -5.25 kcal/mol [14]. The better binding energy might be due to the hydrogen bonding between curcumin and ASN 140, GLU 122 amino acid residues of *Pf*LDH (Figure 4a). This also suggests that curcumin can inhibit parasite replication and induce death through multiple mechanisms of action thus making it a potential antimalarial drug. Compound 1 showed the best binding affinity with *Pf*LDH. Replacing the two ketone groups at R1 and R2 of the parent curcumin chain while still maintaining the double bonds in compound 1 prevented the interaction of the ligand with GLU 112 (Figure 4b). However, interaction with ASN 140 was maintained. Two pi-sigma bonds formed between ALA 98 and ILE 54. The alkyl bond with ILE 119 was maintained. This suggests that compound 1 binds in a similar site with curcumin but with better binding energy. Although compound 1 showed better binding energy than curcumin, it had a lower intestinal absorption of 76% when compared to curcumin which had 86%. This will affect bioavailability slightly. Compound 2 showed the best intestinal absorption of 98% with a binding energy of -7.24kcal/mol. Although it

showed higher binding energy than compound 1, its increased intestinal absorption could improve drug therapy. Vitexin formed three hydrogen bonds with ASN 140, THR 101, and THR 97 (Figure 5a). Interactions between ILE 119, and ALA 98 were present in vitexin and curcumin. Intestinal absorption of vitexin was poor when compared to curcumin. Compound 1 showed the best binding energy of -8.02kcal/mol. It had three hydrogen bonds interaction with GLY 32, ASP 53, and THR 101 (Figure 5b). Van der Waals interaction occurred between compound 1 and ALA 98, MET 30. Daidzein possessed binding energy of -7kcal/mol, no Lipinski violation, and 92.8% intestinal absorption. Figure 6 shows interactions of daidzein with *Pf*LDH amino acid residues. All derivatives of daidzein showed higher binding energy than daidzein and the differences in intestinal absorption were negligible, thus, daidzein is the most druggable ligand in this category.

5. CONCLUSION

Antimalarial drug resistance plays a great role in the increasing death toll of malaria in Sub-Saharan Africa. Daidzein, curcumin, vitexin, and their derivatives have the potential of killing malaria parasites by inhibiting *Plasmodium falciparum* lactate dehydrogenase although this might not be the only mechanism of their schizonticidal action. The sources of these phenolic compounds are abundant in nature, thus, will reduce the cost of production which will have a positive influence on drug affordability. Further *in vitro* and *in vivo* studies should be carried out on these compounds to ascertain their potential to solve antimalarial drug resistance.

Conflict of Interest: The authors declare no conflict of interest.

Contribution of Authors: Olorunfemi Eseyin conceived, designed, and supervised the study. Ekarika Johnson designed, and supervised the study. Onyechi Samuel carried out molecular docking and retrieval of pharmacokinetic parameters of compounds. Etukakpan Ekemini carried out molecular docking of compounds. Chidera Pascal carried out molecular docking of compounds. Umoh Mfonobong carried out molecular docking and analysis of compounds. Andong Bassey carried out molecular docking of compounds, design of derivatives, analysis of compounds, coordination of all activities, and writing of the manuscript.

6. REFERENCES

[1] Meibalan E, Marti M. Biology of Malaria Transmission. Cold Spring Harbor Perspectives in Medicine 2017;7:a025452. https://doi.org/10.1101/CSHPERSPECT.A025452

[2] Garrido-Cardenas, J.A., González-Cerón, L., Manzano-Agugliaro, F. et al. Plasmodium genomics: an approach for learning about and ending human malaria. Parasitol Res 118, 1–27 (2019). https://doi.org/10.1007/s00436-018-6127-9

[3] Okorie PN, Popoola KO, Awobifa OM, Ibrahim KT, Ademowo GO. Species composition and temporal distribution of mosquito populations in Ibadan, Southwestern Nigeria. J Entomol Zool Stud. 2014 Aug;2(4):164-169. PMID: 25520960; PMCID: PMC4266488

[4] Foley M, Tilley L. Quinoline antimalarials: Mechanisms of action and resistance. International Journal for Parasitology 1997;27:231–40. https://doi.org/10.1016/S0020-7519(96)00152-X

[5] Yang J, He Y, Li Y, Zhang X, Wong YK, Shen S, et al. Advances in the research on the targets of anti-malaria actions of artemisinin. Pharmacology & Therapeutics 2020;216:107697. https://doi.org/10.1016/J.PHARMTHERA.2020.107697

[6] Hemming-Schroeder E, Umukoro E, Lo E, Fung B, Tomás-Domingo P, Zhou G, et al. Impacts of Antimalarial Drugs on Plasmodium falciparum Drug Resistance Markers, Western Kenya, 2003–2015. The American Journal of Tropical Medicine and Hygiene 2018;98:692–9. https://doi.org/10.4269/ajtmh.17-0763

[7] Marchetti R v., Lehane AM, Shafik SH, Winterberg M, Martin RE, Kirk K. A lactate and formate transporter in the intraerythrocytic malaria parasite, Plasmodium falciparum. Nat Commun 2015;6. https://doi.org/10.1038/NCOMMS7721

[8] Elliott JL, Saliba KJ, Kirk K. Transport of lactate and pyruvate in the intraerythrocytic malaria parasite, Plasmodium falciparum. Biochem J 2001;355:733–9. https://doi.org/10.1042/BJ3550733

[9] Possemiers H, Vandermosten L, van den Steen PE. Etiology of lactic acidosis in malaria. PLoS Pathog 2021;17. https://doi.org/10.1371/JOURNAL.PPAT.1009122

[10] Oyelade J, Isewon I, Rotimi S, Okunoren I. Modeling of the Glycolysis Pathway in Plasmodium falciparum using Petri Nets. Bioinform Biol Insights 2016;10:49–57. https://doi.org/10.4137/BBI.S37296

[11] Granchi C, Bertini S, Macchia M, Minutolo F. Inhibitors of Lactate Dehydrogenase Isoforms and their Therapeutic Potentials. Current Medicinal Chemistry 2010;17:672–97. https://doi.org/10.2174/092986710790416263

[12] Mamede L, Ledoux A, Jansen O, Frédérich M. Natural Phenolic Compounds and Derivatives as Potential Antimalarial Agents. Planta Medica 2020;86:585–618. https://doi.org/10.1055/A-1148-9000

[13] Martí Coma-Cros E, Biosca A, Lantero E, Letizia Manca M, Caddeo C, Gutiérrez L, et al. Antimalarial Activity of Orally Administered Curcumin Incorporated in Eudragit ®-Containing Liposomes. Int J Mol Sci. 2018 May 4;19(5):1361. doi: 10.3390/ijms19051361 https://doi.org/10.3390/ijms19051361

[14] Dohutia C, Chetia D, Gogoi K, Bhattacharyya DR, Sarma K. Molecular docking, synthesis and in vitro antimalarial evaluation of certain novel curcumin analogs. Brazilian Journal of Pharmaceutical Sciences 2018;53:84. https://doi.org/10.1590/S2175-97902017000400084