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In silico antiparasitic investigation of compounds derived from *Andrographis paniculata* on some parasites validated drug targets

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Abstract

Resistance to parasitic medicines is a recurring problem, hence the need to discover and develop new effective drugs. Phytochemicals derived from plants play an essential role in drug discovery. *Andrographis paniculata* is used widely as a medicinal herb for the treatment of various ailments. In this study, Gas Chromatography-Mass Spectrophotometry (GCMS) analysis was carried out on *A. paniculata*. The compounds obtained from the GCMS analysis were docked against validated drug targets from *Schistosoma mansoni* (Dihydrofolate reductase and cathepsin B1), *Leishmania major* (N-myristoyltransferase (NMT) and UDP Glucose pyrophosphorylase), *Plasmodium falciparum* (dihydroorotate dehydrogenase and plasmepsin II) and *Trypanosoma brucei brucei* (trypanothione reductase and ornithine decarboxylase), using SwissDock and Ligplot to determine the inhibitory potential and protein-ligand interactions. Out of the 16 compounds obtained from GCMS, 3,7,11,15-tetramethyl-2-hexadecen- 1-ol, phytol and 9,12-octadecadienoic acid (Z,Z)- presented a higher binding affinity and inhibitory potential than the standard drugs for *S. mansoni, P. falciparum* and *T. brucei* brucei respectively. Thus, 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol, Phytol and 9,12-Octadecadienoic acid (Z,Z) are predicted to be potent inhibitors to the survival of *S. mansoni*, *P. falciparum* and *T. brucei brucei* respectively. Therefore, *in vitro* and *in vivo* bioassays studies should be carried out on these compounds to establish the predictions.

Keywords: *Andrographis paniculata, Phytocompounds, Drug targets, Parasites, Molecular docking*

1. Introduction

Schistosomiasis is a neglected parasitic disease and it is common to developing countries. It is caused mainly by three medically important species of dioecious blood flukes, *Schistosoma mansoni, Schistosoma haematobium,*

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Schistosoma japonicum (Calixto *et al*., 2018). Transmission of this disease was recorded in 78 countries in 2016 with about 206 million people requiring preventive chemotherapy (World Health Organization, 2017). In terms of human morbidity, after malaria, schistosomiasis is the most important tropical disease (Singh *et al*., 2016). Cathepsin B1 is the major protease of the parasites, most abundant and important for the survival of the parasites (Tavares *et al*., 2016). It performs an important role in the proteolysis of the blood proteins of the host and has been identified as a target for chemotherapy of schistososmiasis (Jikova *et al*., 2018). Dihydrofolate Reductase (DHFR) is important for nucleotide metabolism to obtain energy and structural nucleic acids, therefore it has been suggested as the therapeutic targets for treating infectious diseases (Serrao *et al*., 2017). The World Health Organization (WHO) recommends the use of praziquantel (PZQ) drug for the treatment and chemoprophylaxis of schistosomiasis because of its low cost, effectiveness with a single dose and mild side effects (Doenhoff *et al*., 2008; Chai 2013; andWorld Health Organization, 2016). Although this drug is effective, its effectiveness is compromised because of the risk of resistance and its low efficiency against immature flukes, it is, therefore, important to develop new antischistosomal drugs (Calixto *et al*., 2018). Oxamniquine is another drug used in the treatment of schistosomiasis but it is only effective against *S. mansoni*. So the presence of limited drugs for the disease draws attention toward the search for new molecular drug targets and compounds that will inhibit the prospective threat from the schistosome resistant strain that has been reported and characterized in areas where it is prevalent (Singh *et al*., 2016; Doenhoff *et al*., 2008; and Melwam *et al*., 2009).

Leishmaniasis is a fatal Neglected Tropical Disease (NTD) caused by more than 20 species of *Leishmania* protozoan parasites. Approximately 20,000 people are killed each year by this disease and more than 1 billion are susceptible to the infection (Ferreira and Andricopulo, 2018). Leishmaniasis occurs in 98 tropical and subtropical countries including Mediterranean Basin, South-East Asia, Afro-Eurasia, East Africa and the Americas. N-Myristoyltransferase (NMT) remains one of the few genetically validated drug targets essential for the survival of this parasite (Corpas-Lopez *et al*., 2019). UDP-glucose pyrophosphorylase has been validated genetically as a valid antileishmanial drug target and essential for the survival of this parasite (Prakash *et al*., 2019). Due to drug resistance, high toxicity, serious side effects, high treatment cost and accessibility problem of the drugs, it is essential to develop novel drugs in the treatment of leishmaniasis (Ferreira and Andricopulo, 2018).

African trypanosomiasis also is known as sleeping sickness is a disease caused by a single-celled parasite known as *Trypanosoma brucei* and it widely distributed in sub-Saharan Africa (Hermann *et al*., 2015). Trypanosomiasis is a disease of both human and animal, endemic in 37 sub-Saharan African countries. *Trypanosoma b. gambiense* and *T. b. rhodesiense* causes Human African Trypanosomiasis (HAT) (Macedo *et al*., 2017). About 70 million people are endangered by this disease and an estimate of the occurrence of 20,000 acute cases per year have been recorded (Tissot, 2015). If left untreated, it ultimately results in death. *Trypanosoma brucei brucei*, *T. congolense and T. vivax* which are the related species cause wasting-cattle disease that causes serious economic loss, especially in the rural areas (World Health Organization, 2015). Ornithine decarboxylase is the target of eflornithine, the WHO recommended medicine for trypanosomiasis. However, eflornithine antagonizes effectiveness of suramin, another anti-HAT drug (Macedo *et al*., 2017). Also, trypanothione reductase is an important molecular drug target in *Trypanosoma* and has been investigated for the design of drugs against sleeping sickness (Ferreira and Andricopulo, 2013). Although there are some available drugs used in treating this disease, however, these drugs suffer from limited efficiency, availability, applicability, toxicity, side effects and emerging resistance (Hermann *et al*., 2015). Hence, the urgent need for the development of new antitrypanocidal agents to combat the disease.

Malaria, mosquito-borne disease is caused by the protozoan parasite of the genus *Plasmodium*. Dihydroorotate dehydrogenase in *Plasmodium falciparum* has been recognized as an essential target in drug discovery (Hoelz *et al*., 2018). This enzyme plays a role in *de novo* pyrimidine biosynthesis in the parasite, therefore, interfering with the activity of the enzyme inhibit to *de novo* pyrimidine biosynthesis and consequently prevents malarial infection (Philips and Rathod, 2010). Plasmepsin II is essential for the survival of malaria parasite (Gulati *et al*., 2015) and its inhibition disrupts the feeding of intraerythrocytic malaria parasite because it will not be able to digest hemoglobin protein, hence the propagation of the parasite will be unsuccessful. Over the years, there has been an increase in drug resistance among the available antimalarial drugs. Although a lot of researches have been carried out on this disease, there is a still an urgent need to develop new antimalarial drugs to treat resistant malaria strains and also reduce the burden worldwide (Singh *et al*., 2019).

In African as a whole, traditional medicine and the cure made from plants play an essential role in the health of millions of people (Monier, 2016). *Andrographis paniculata* (King of bitters) is an herbaceous plant belonging to the family Acanthaceae, it originated from India and Sri Lanka. It is an erect herb that grows annually. All the part of the plant is very bitter. It is an intensive bitter plant grown in Nigeria from seeds obtained in India but widely grown in southern and southeastern Asia where it is used for treating infections and some diseases (Ameh *et al*., 2010). Phytochemicals are compounds occurring naturally in plants and help in fighting pathogens, competitors and predators. Example of phytochemicals found in *A. paniculata* are alkaloids, terpenoid, cardiac glycosides, saponins and flavonoids (Ayodele *et al*., 2019). Diterpenoid compounds, the major component of *A. paniculata* named andrographolide has been proven to be an inhibitor of one of the important protease of malaria parasites (Megantra *et al*., 2015). Antiprotozoal activities was shown by xanthones isolated from the root of *A. paniculata* against *T. brucei, T. cruzi* and *Leishmania infantum* (Joselin and Jeeva, 2014).

In recent time, computational screening method has been a very useful technique deploy in the drug development process because it is quick and economical. The understanding of the ligand-protein interaction is one of the fastest ways to identify the candidate drug and target. Molecular docking, one of the computational modeling approaches in the drug discovery process, predicts the possible interactions between two molecules thereby producing binding energy. It does not only predict the binding mode of small molecules and a macromolecule (protein-ligand docking) but also between two macromolecules (protein-protein docking) (Prieto-Martinez and Medina-Franco, 2018). Using this technique, drugs are design based on the binding affinity and selectivity of the target molecules.

Through computational biology, the capacity for biological screening and chemical synthesis has increased dramatically so also the demand for early information on absorption, distribution, metabolism, excretion (ADME) and toxicity data (altogether called ADMET data). The Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) screening aid in choosing the most promising compound (Waterbeemd and Gifford, 2003). ADMET describes the reaction and fate of pharmaceutical compounds within an organism, especially in the human body. Poor ADMET makes drug development projects fail during clinical trials therefore it is advisable to obtain ADMET properties at the early stage of drug discovery (Shin *et al*., 2016).

This study was, therefore, conducted to predict valuable inhibitory compounds from *A. paniculata* against the validated drug targets of *S. mansoni*, *Leishmania major*, *T. brucei brucei*, *P. falciparum* which could aid the development of novel and effective drugs for the treatment, control and prevention of these parasitic diseases *in silico*.

2. Materials and methods

2.1. Collection and processing of plant

The aerial part of *A. paniculata* plants was collected fresh from Basorun, Ibadan. The plant was identified and authenticated at the herbarium of Department of Botany, the University of Ibadan where the voucher number was given as UIH- 22949. The plant materials were air-dried for two weeks at room temperature. The dried plants were ground to powder and stored in an airtight bottle. The bottle was labeled appropriately and put in a cupboard until it was used.

2.2. Extraction of plant material

Extraction of 115 g of the plant material was done by soaking it in 250 ml of a mixture of dichloromethane (DCM) and methanol in a ratio of 1:1 at room temperature for 48 h with constant agitation. It was then filtered using Whatman filter paper. The filtrate was further concentrated using a rotary evaporator until the solvents were completely exhausted and stored in an appropriately labeled bottle.

2.3. Gas Chromatography-Mass Spectrophotometry analysis

Gas Chromatography separates volatile and semi-volatile compounds with great resolution but cannot identify them. Identifications and quantification of these compounds were done by Mass Spectrophotometry which gives detailed structural information on most compounds. The Gas Chromatography-Mass Spectrophotometry (GCMS) analysis was carried out on the dichloromethane-methanol extract of *A. paniculata* and the relative percentage amount of each compound present were calculated. It was performed using an Agilent 7890A Gas Chromatograph interfaced to a Mass Spectrophotometer model 5975C with triple-axis detector and it was

equipped with an auto-injector (10 ul syringe). The carrier gas used was Helium gas. All chromatography separation was performed on a capillary column with specifications: length of 30 m, the internal diameter of 0.2 um and it was treated with 5% phenyl methyl silox. The temperature of the column started at 35 °C for 5 min and changed to 150 °C at the rate of 4 °C per minute, it was then raised to 250 °C at the rate of 20 °C per min and held for 5 min. The total elution time was 47.5 min.

2.4. Identification of compound

The mass spectrum obtained from the GC-MS was interpreted using the database of the National Institute of Standard and Technology (NIST). This has more than 82,000 patterns. The data spectrum of known compounds stored in the GCMS library was compared with the integrated peak of the chromatogram. The precise compounds present were identified by comparing the spectrum of the known NIST component with unknown compounds. The names of the compounds, molecular formulae and weight were recorded.

2.5. Preparation of target proteins

The three-dimension (3D) structures of the selected target proteins or drug targets were retrieved from Protein Data Bank (PDB). In preparation for docking, the drug targets were processed to ensure it is in the right format to be uploaded on SwissDock. This was done by exporting the drug target to UCSF Chimera to visualize and analyze H-bonds and also delete all the ligands attached to the protein.

2.6. Ligand preparation for docking

The ligands three-dimensional structures were downloaded from PubChem (http://pubchem.ncbi.nim.nih.gov), a public repository for information on chemical substances and their biological activities, launched in 2004 as a component of the molecular libraries for the US National Institutes of Health (NIH). Structures of the compounds retrieved from PubChem were converted using OpenBabel software (www.openbabel.org/) from SDF format to MOL2 format which is accepted by SwissDock. OpenBabel was also used to convert the ligand to SMILES format accepted by admetSAR server which gives the ADMET properties prediction (O'Boyle *et al.*, 2011).

2.7. Absorption, Distribution, Metabolism, Elimination and Toxicity (ADMET) Studies

The SMILES format of the ligands were submitted to admetSAR sever (http://Immd.ecust.edu.cn/admetsar2/) to examine their drug-likeness and different pharmacokinetics and pharmacodynamics parameters. The target compounds ADMET properties were obtained using admetSAR. Other properties calculated are the Blood-Brain Barrier (BBB) penetration, Human Intestinal Absorption (HIA), P-glycoprotein, AMES test carcinogenicity, Human Oral Bioavailability (HOB) and $CaCO_3$.

2.8. Molecular docking using swiss dock

The ligand with good ADMET properties were docked with the selected target proteins on SwissDock (www.swissdock.ch), a web server based on EADock DSS engine (Grosdidier *et al.*, 2011). Both the ligand (MOL2 format) and the protein (PDB format) were submitted on SwissDock and the results in terms of the full fitness and binding energies were sent some minutes later via email.

2.9. Protein-ligand complex visualization using ligplot

The best compounds with the lowest binding energies interaction with each of the drug targets were exported to Ligplot, (a program for automatically plotting protein-ligand interactions) for further docking. Before the docking was run on ligplot, the ligand and the protein were first uploaded on PyRx, a virtual screening tool to convert the ligands to PDB format which is required by Pymol, a software used to make the protein-ligand complex. The protein-ligand complex from Pymol was uploaded on Ligplot which reveals the number of hydrogen bonds and the ligand formed with the protein and the number of amino acid residues involved in the hydrophobic interaction.

3. Results

3.1. Gas Chromatography-Mass Spectrophotometry

Several compounds were identified from the result obtained from the GC-MS analyses from DCM-Methanol (1:1) extracts of *A. paniculata.* The extract shows several peaks which represent different compounds as shown in the total ion chromatogram by GC-MS analysis. 16 compounds with known structures were revealed by the active principles of their retention time shown in the mass spectra with respective library match with the

DCM-methanol extract of *A. paniculata* as shown in Table 1. The retention time, peak name and peak areas were also provided and NIST/NBS spectral database was used to match the phytoconstituents.

Table 1: List of compounds identified by GC-MS at various retention times from DCM-Methanol extract of leaves of *Andrographis paniculata*

Peak	Retention time	Area (%)	Compound name	Molecular formula	Pubchem CID
1	36.257	11.66	2-Dodecyne	$C_{12}H_{22}$	136452
2	36.257	11.66	7-Methyl-1,6-octadiene	C_9H_{16}	557579
3	36.564	1.70	E-11(12-Cyclopropyl)dodecen-1-ol	$C_{15}H_{28}O$	5365759
4	36.564	1.70	5-Eicosyne	$C_{20}H_{38}$	557014
5	36.564	1.70	1-Hexadecyne	$C_{16}H_{30}$	12396
6	36.764	7.94	3,7,11,15-Tetramethyl-2-hexadecen- 1-ol	$C_{20}H_{40}O$	5366244
7	36.764	7.94	9-Octadecyne	$C18H_{34}$	141998
8	36.764	7.94	2H-Pyran-2-one, 6-pentyl-	$C_{10}H_{14}O_2$	33960
9	37.746	17.06	n-Hexadecanoic acid	$C_{16}H_{32}O_2$	985
10	37.746	17.06	Tetradecanoic acid	$C_{14}H_{28}O_2$	11005
11	38.578	5.28	Phytol	$C_{20}H_{40}O$	5280435
12	38.859	18.16	9,12-Octadecadienoic acid (Z,Z)-	$C_{18}H_{32}O_2$	5280450
13	38.859	18.16	9,12,15-Octadecatrien-1-ol, (Z,Z,Z)-	$C_{18}H_{32}O$	6436081
14	44.189	38.2	1-Cycloheptenecarboxamide, N-phenyl-	$C_{14}H_{17}NO$	579370
15	44.189	38.2	1-(2-Pyridyl)piperazine	$C_9H_{13}N_3$	94459
16	44.189	38.2	(4-Fluorophenyl)(5-methyl-2-thioxo-2H-[1,2,4]triazolo[1,5-a]pyridin-3-yl)methanone	$C_{14}H_{10}FN_3OS$	707207

3.2. Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) prediction

Table 2 shows that all the compounds are positive for the BBB and Human Intestinal Absorption (HIA) and are also a nonsubstrate and non-inhibitor of P-glycoprotein. Five of the compounds (7-Methyl-1,6-octadiene, 2H-Pyran-2-one, 6-pentyl-, 1-Cycloheptenecarboxamide, N-phenyl-, 1-(2-Pyridyl) piperazine and

Table 2: Assessments of absorption of the compounds

Compound name	BBB	HIA	HOB	P-gp	$CaCO_3$
2-Dodecyne	+	+	–	Noninhibitor/Nonsubstrate	+
7-Methyl-1,6-octadiene	+	+	+	Noninhibitor/Nonsubstrate	+
E-11(12-Cyclopropyl)dodecen-1-Ol	+	+	–	Noninhibitor/Nonsubstrate	+
5-Eicosyne	+	+	–	Noninhibitor/Nonsubstrate	+
1-Hexadecyne	+	+	–	Noninhibitor/Nonsubstrate	+
3,7,11,15-Tetramethyl-2-hexadecen- 1-Ol	+	+	–	Noninhibitor/Nonsubstrate	+

Table 2 (Cont.)

Compound name	BBB	HIA	HOB	P-gp	$CaCO_3$
9-Octadecyne	+	+	–	Noninhibitor/Nonsubstrate	+
2h-Pyran-2-One, 6-pentyl-	+	+	+	Noninhibitor/Nonsubstrate	+
N-Hexadecanoic acid	+	+	–	Noninhibitor/Nonsubstrate	+
Tetradecanoic acid	+	+	–	Noninhibitor/Nonsubstrate	+
Phytol	+	+	–	Noninhibitor/Nonsubstrate	+
9,12-Octadecadienoic acid (Z,Z)-	+	+	–	Noninhibitor/Nonsubstrate	+
9,12,15-Octadecatrien-1-ol, (Z,Z,Z)-	+	+	–	Noninhibitor/Nonsubstrate	+
1-Cycloheptenecarboxamide, N-phenyl-	+	+	+	Noninhibitor/Nonsubstrate	+
1-(2-Pyridyl)piperazine	+	+	+	Noninhibitor/Nonsubstrate	+
(4-Fluorophenyl)(5-methyl-2-thioxo-2h-[1,2,4]triazolo[1,5-A]pyridin-3-Yl)methanone	+	+	+	Noninhibitor/Nonsubstrate	+

(4-Fluorophenyl)(5-methyl-2-thioxo-2H-[1,2,4]triazolo[1,5-a]pyridin-3-yl)methanone) are positive for Human Intestinal Absorption (HOB) while the remaining compounds are negative. Compound 1-Hexadecyne, 9,12-Octadecadienoic acid and 1-Cycloheptenecarboxamide, N-phenyl- (Z,Z)- are inhibitors of CYP1A2 while 2H-Pyran-2-one, 6-pentyl- acid is an inhibitor of CYP2C19 and CYP1A2. Tetradecanoic acid and n-Hexadecanoic acid is a substrate of CYP2C9 and an inhibitor of CYP1A2; 1-(2-Pyridyl) piperazine is CYP2D6 substrate and CYP1A2 inhibitor and (4-Fluorophenyl)(5-methyl-2-thioxo-2H-[1,2,4]triazolo[1,5-a]pyridin-3-yl) methanone is a CYP2C9, CYP2C19 and CYP1A2 inhibitor. The other compounds are non-inhibitor and nonsubstrate. Only five compounds (2-Dodecyne, 7-Methyl-1, 6-octadiene, 5-Eicosyne, 1-Hexadecyne and 9-Octadecyne) are carcinogenic, others are non-carcinogenic and non-mutagenic (Table 3).

Table 3: Assessment of toxicity and carcinogenicity of the compounds

Compound name	Ames Mutagenesis	Acute oral toxicity	Carcinogenicity
2-Dodecyne	Nonmutagenic	2.174	Carcinogenic
7-Methyl-1,6-octadiene	Nonmutagenic	1.662	Carcinogenic
E-11(12-cyclopropyl)dodecen-1-ol	Nonmutagenic	1.791	Noncarcinogenic
5-Eicosyne	Nonmutagenic	1.182	Carcinogenic
1-Hexadecyne	Nonmutagenic	1.899	Carcinogenic
3,7,11,15-Tetramethyl-2-hexadecen- 1-ol	Nonmutagenic	2.421	Noncarcinogenic
9-Octadecyne	Nonmutagenic	1.169	Carcinogenic
2h-Pyran-2-one, 6-pentyl-	Nonmutagenic	2.967	Noncarcinogenic
n-Hexadecanoic acid	Nonmutagenic	1.376	Noncarcinogenic
Tetradecanoic acid	Nonmutagenic	1.43	Noncarcinogenic
Phytol	Nonmutagenic	2.421	Noncarcinogenic

Table 3 (Cont.)

Compound name	AmesMutagenesis	Acute oral toxicity	Carcinogenicity
9,12-Octadecadienoic acid (z,z)-	Nonmutagenic	1.605	Noncarcinogenic
9,12,15-Octadecatrien-1-ol, (z,z,z)-	Nonmutagenic	2.027	Noncarcinogenic
1-Cycloheptenecarboxamide, n-phenyl-	Nonmutagenic	2.1	Noncarcinogenic
1-(2-Pyridyl)piperazine	Nonmutagenic	2.715	Noncarcinogenic
(4-Fluorophenyl)(5-methyl-2-thioxo-2h-[1,2,4]triazolo[1,5-a]pyridin-3-yl)methanone	Nonmutagenic	3.384	Noncarcinogenic

3.3. Docking outcomes of the ligands against drug targets in S. mansoni

The docking analysis of the 16 compounds against target Cathepsin B1 (3qsd) showed that 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol, Phytol, n-Hexadecanoic acid and 9,12,15-Octadecatrien-1-ol, (Z,Z,Z)- displays the lowest binding energy of –8.44 kcal/mol, –8.13 kcal/mol, –8.03 kcal/mol and –8.01 kcal/mol respectively against the target (Table 4).

Dihydrofolate reductase (3vco), the docking showed that 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol, phytol, 9,12,15-Octadecatrien-1-ol, (Z,Z,Z)-, 9,12-Octadecadienoic acid (Z,Z)- and n-Hexadecanoic acid display the lowest binding energy of –7.85 kcal/mol, –7.84 kcal/mol, –7.74 kcal/mol, –7.51 kcal/mol and –7.43 kcal/mol respectively (Table 4).

Table 4: Docking results of *S. mansoni* molecular drug targets

Ligands	*S. mansoni* molecular targets			
	Cathepsin B1(3qsd)		Dihydrofolate Reductase (3vco)	
	Full fitness (Kcal/mol)	ΔG (Kcal/mol)	Full fitness (Kcal/mol)	ΔG (Kcal/mol)
3,7,11,15 Tetramethyl-2-hexadecen- 1-ol	–1587.62	–8.44	–1270.68	–7.87
Phytol	–1597.50	–8.13	–1263.93	–7.84
n-Hexadecanoic acid	–1622.82	–8.03	–1293.90	–7.43
9,12,15-Octadecatrien-1-ol, (Z,Z,Z)-	–1586.95	–8.01	–1250.87	–7.74
9,12-Octadecadienoic acid (Z,Z)-	–1612.75	–7.96	–1283.74	–7.51
Control			Control	
Divinyl Sulfone	–1550.37/ –6.25		Pyrimethamine –1315.40/ –7.32	

3.4. Protein-ligand interaction between S. mansoni drug targets and the phytocompounds

Complex Cathepsin B1_3,7,11,15-Tetramethyl-2-hexadecen- 1-ol displayed the lowest binding energy. The results from Ligplot shows that the complex between the oxygen of ligand forms one hydrogen bond of length 2.98 with Lys164 (Figure 1).

Complex Dihydrofolate Reductase_3,7,11,15-Tetramethyl-2-hexadecen- 1-ol that has the lowest binding energy forms 2 hydrogen bonds of length 3.01 and 3.06 with Phe82 and Asm69 respectively (Figure 2).

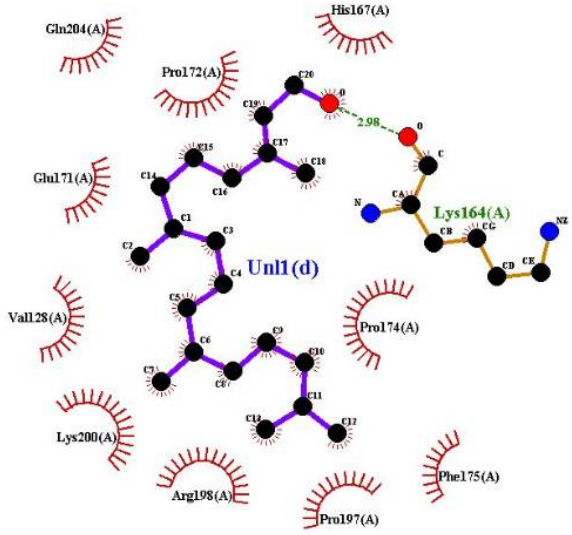


Figure 1: Protein-ligand interaction of complex Cathepsin B1_3,7,11,15-Tetramethyl-2-hexadecen- 1-ol

Note: In the interaction between Cathepsin B1 (protein) and 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol (ligand), the ligand form single hydrogen bond (represented as broken lines with bond length) with amino acid Lys164 of protein.

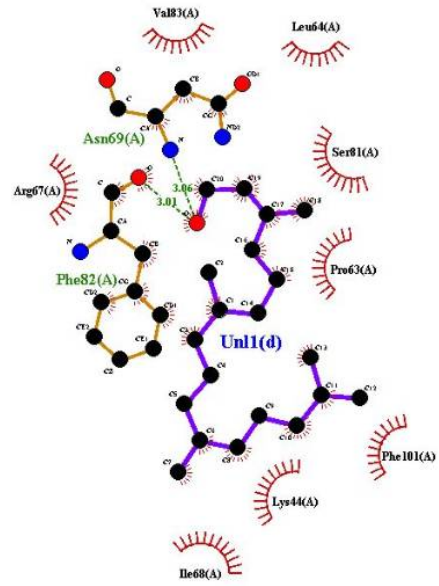
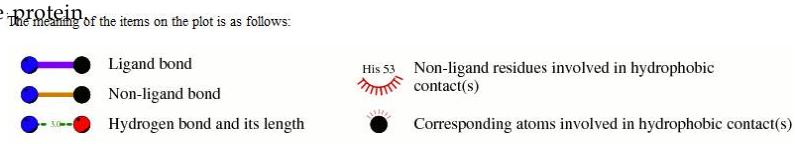


Figure 2: Protein-ligand interaction of complex Dihydrofolate Reductase_3,7,11,15-Tetramethyl-2-hexadecen- 1-ol

Note: In the interaction between Dihydrofolate Reductase (protein) and 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol (ligand), the ligand form two hydrogen bonds (represented as broken lines with bond length) with amino acid Asn69 and Phe82 of the protein.



3.5. Docking outcome of ligand against drug targets L. major

The docking analysis showed that Phytol, 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol, n-Hexadecanoic acid and 9,12,15-Octadecatrien-1-ol, (Z,Z,Z)- have the lowest binding energy of –7.96 kcal/mol, –7.93 kcal/mol, –7.79 kcal/mol and –7.76 kcal/mol respectively against the target UDP-glucose pyrophosphate (Table 5).

The docking analysis of N-myristolytransferase showed that compounds 9,12-Octadecadienoic acid (Z,Z)- , 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol, 9,12,15-Octadecatrien-1-ol, (Z,Z,Z)- and phytol have the lowest binding energy of –9.25 kcal/mol, –8.74 kcal/mol, –8.70 kcal/mol and –8.60 kcal/mol respectively for target N-myristolytransferase (Table 5).

Table 5: Docking result of *L. major* molecular drug targets

Ligands	*L. major* molecular targets			
	UDP-glucose pyrophosphate (4m28)		N-myristolytransferase (6gnt)	
	Full fitness (Kcal/mol)	ΔG (Kcal/mol)	Full fitness (Kcal/mol)	ΔG (Kcal/mol)
Phytol	–2602.60	–7.96	–2260.88	–8.60
3,7,11,15-Tetramethyl-2-hexadecen- 1-ol	–2610.70	–7.93	–2269.32	–8.74
9,12-Octadecadienoic acid (Z,Z)-	–2627.38	–7.74	–2292.07	–9.25
9,12,15-Octadecatrien-1-ol, (Z,Z,Z)-	–2602.28	–7.76	–2262.64	–8.70
n-Hexadecanoic acid	–2635.26	–7.79	–2291.56	–8.59
Control			**Control**	
3-Fluoro-4-methoxyphenyl)methyl-methyl-[2-oxo-2-(2-phenoxyanilino) ethyl]azanm	–2517.22/–9.01		2,6-Dichloro-N -difluoromethyl) -4-[3-(1-methyl piperidin-4-Yl) propyl]-N-(1,3,5-trimethylpyrazol-4Yl) benzenesulfonamide	–2345.18/–10.05

3.6. Protein-Ligand Interaction between L. major *Drug Targets and the Phytocompounds*

Complex UDP-glucose pyrophosphate_phytol displayed the lowest binding energy out of other complexes in *L. major*. From Ligplot, it was seen that the complex between the oxygen of ligand forms hydrogen bond of length 2.84 with Asn163 (Figure 3). Complex N-myristolytransferase and 9,12-Octadecadienoic acid (Z,Z)- is the complex with the lowest binding energy of –9.25 in the docking of *L. major* N-myristolytransferase. According to Ligplot, the complex between the oxygen of ligand of this complex forms double hydrogen bond of length 3.63 and 2.96 with Leu169 and single hydrogen bond of the length of 3.02 with Try80 (Figure 4).

3.7. Docking outcome of ligands against drug targets in P. falciparum

The docking result revealed that phytol, (4-Fluorophenyl)(5-methyl-2-thioxo-2H-[1,2,4]triazolo[1,5-a]pyridin-3-yl)methanone, 9,12-Octadecadienoic acid (Z,Z)-, E-11(12-Cyclopropyl)dodecen-1-ol, 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol displayed the lowest binding energy of –8.07 kcal/mol, –7.94 kcal/mol, –7.81 kcal/mol, –7.80 kcal/mol and –7.75 kcal/mol respectively against target dihydroorotate dehydrogenase (Table 6).

The docking analysis of Plasmepsin II revealed that Phytol, 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol, 9,12-Octadecadienoic acid (Z,Z)- and n-Hexadecanoic acid displayed the lowest binding energy of –8.45 kcal/mol, –8.41 kcal/mol, –8.14 kcal/mol and –8.13 kcal/mol respectively (Table 6).

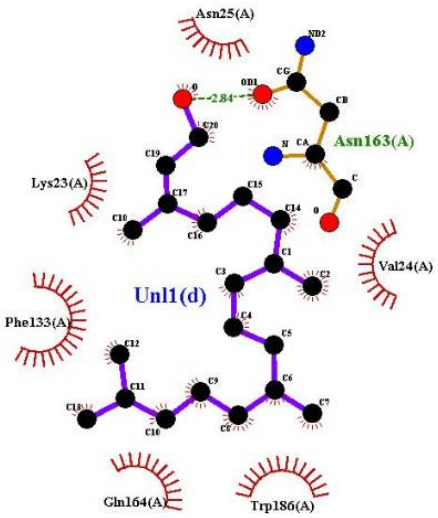
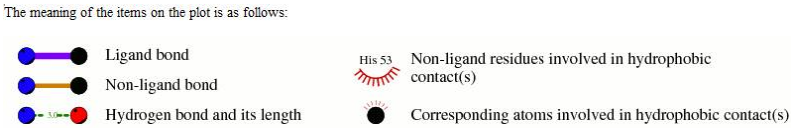


Figure 3: In UDP-glucose pyrophosphate (protein) and phytol (ligand) complex, the ligand form a single hydrogen bond (represented as green broken lines with bond length) with amino acid Asn163 of the protein

Note: In N-myristolytransferase (protein) and 9,12-Octadecadienoic acid (Z,Z) (ligand) complex, the ligand form double and single hydrogen bonds (represented as green broken lines with bond length) with amino acid Leu169 and Try80 of the protein respectively.



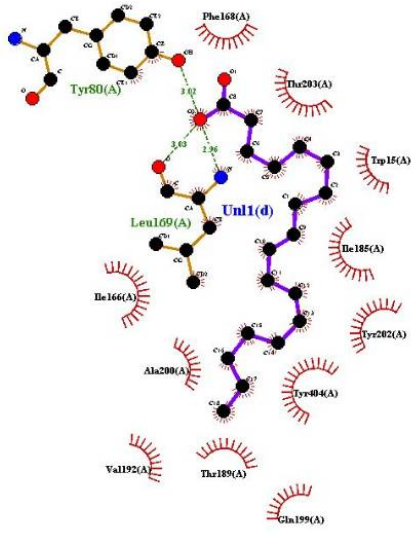


Figure 4: Protein-ligand interaction of Complex N-myristolytransferase_9,12-Octadecadienoic acid (Z,Z)

Note: In N-myristolytransferase (protein) and 9,12-Octadecadienoic acid (Z,Z) (ligand) complex, the ligand form double and single hydrogen bonds (represented as green broken lines with bond length) with amino acid Leu169 and Try80 of the protein respectively.

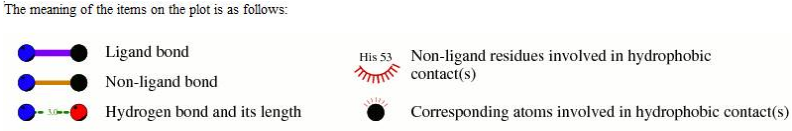


Table 6: Docking result of *P. falciparum* molecular drug targets

Ligands	*P. falciparum* molecular targets			
	Dihydroorotate dehydrogenase (1tv5)		Plasmepsin II (4z22)	
	Full fitness (Kcal/mol)	ΔG (Kcal/mol)	Full fitness (Kcal/mol)	ΔG (Kcal/mol)
Phytol	–2021.11	–8.07	–2990.53	–8.45
3,7,11,15-Tetramethyl-2-hexadecen- 1-ol	–2022.28	–7.75	–2995.66	–8.41
9,12-Octadecadienoic acid (Z,Z)-	–2030.06	–7.81	–3006.53	–8.14
E-11(12-Cyclopropyl)dodecen-1-ol	–1797.52	–7.80	–2770.01	–7.63
(4-Fluorophenyl)(5-methyl-2-thioxo-2H-[1,2,4]triazolo[1,5-a]pyridin-3-yl) methanone	–1948.39	–7.94	–2921.30	–7.42
n-Hexadecanoic acid	–2045.41	–7.45	–3017.94	–8.13
Control			**Control**	
Atovaquone	–1956.99/–7.55		Halofantrine	–2955.84/–9.74

3.8. Protein-ligand interaction between P. falciparum drug targets and the phytocompounds

Complex dihydroorotate dehydrogenase_phytol has the lowest binding energy of –8.07 in the docking of *P. falciparum* dihydroorotate dehydrogenase with the plant compounds. The result from Ligplot shows that the complex between the oxygen of the ligand forms 1 hydrogen bond of length 3.11 with Gln 552 (Figure 5).

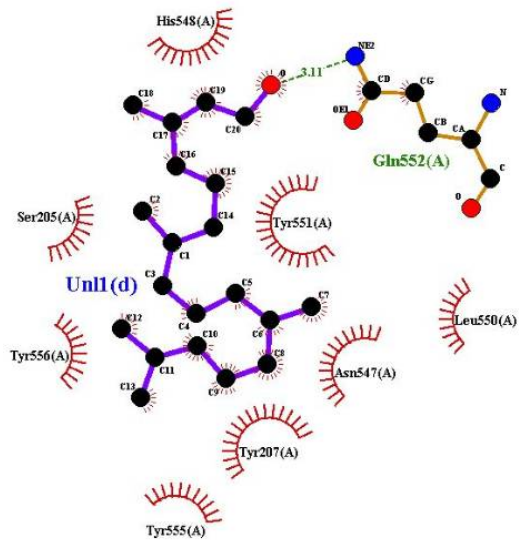
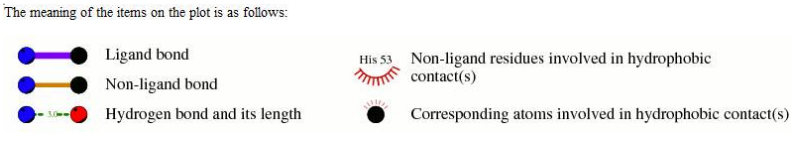
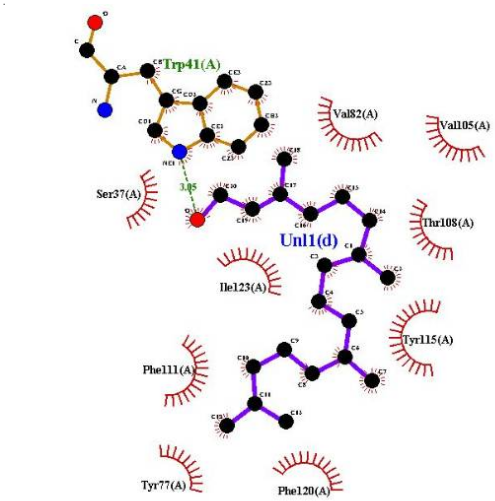


Figure 5: Protein-ligand interaction of Complex Dihydroorotate Dehydrogenase_Phytol

Note: Phytol (ligand) form one hydrogen bond (represented as green broken lines with bond length) with amino acid Gln552 of dihydroorotate dehydrogenase (protein).



Complex Plasmepsin II_Phytol has the lowest binding energy of –8.45 in the docking of *P. falciparum* plasmepsin II with the plant compounds. It was seen from the Ligplot that the complex between the oxygen of the ligand forms hydrogen bond of length 3.05 with Trp41 (Figure 6).



Note: Phytol (ligand) form one hydrogen bond (represented as green broken lines with bond length) with amino acid Try41 of plasmepsin II (protein).

Figure 6: Protein-ligand interaction of Complex Plasmepsin II_Phytol

3.9. Docking outcome of ligands against drug targets in T. brucei brucei

The docking result showed that among the compounds, 9,12-Octadecadienoic acid (Z,Z)-, phytol, 9,12,15-Octadecatrien-1-ol, (Z,Z,Z)- has the lowest binding energies of –8.27 kcal/mol, –8.15 kcal/mol and –8.14 kcal/mol respectively against drug target trypanothione reductase (Table 7). The docking result showed that 9,12-Octadecadienoic acid (Z,Z), 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, Phytol, 9,12,15-Octadecatrien-1-ol, (Z,Z,Z)-

Table 7: Docking result of *T. brucei brucei* molecular drug targets

Ligands	*T. brucei brucei* molecular targets			
	Trypanothione reductase (2woi)		Ornithine decarboxylase (1f3t)	
	Full fitness (Kcal/mol)	ΔG (Kcal/mol)	Full fitness (Kcal/mol)	ΔG (Kcal/mol)
9,12-Octadecadienoic acid (Z,Z)-	–4306.19	–8.27	–3843.78	–8.32
Phytol	–4285.46	–8.15	–3821.41	–8.13
9,12,15-Octadecatrien-1-ol, (Z,Z,Z)-	–4271.88	–8.14	–3814.34	–8.08
5-Eicosyne	–2030.49	–7.48	–3011.12	–8.28
n-Hexadecanoic acid	–2045.41	–7.45	–3017.94	–8.13
Control			**Control**	
Quinacrine mustard	–4248.37/–9.24		Dl-alpha-Difluoro-methylornithine	–3777.96/ –7.39

and n-Hexadecanoic acid displayed the lowest binding energy of –8.32 kcal/mol, –8.17 kcal/mol, –8.13 kcal/mol, –8.08 kcal/mol and –7.97 kcal/mol respectively against target ornithine decarboxylase (Table 7).

3.10. Protein-ligand interaction between *T. brucei brucei* drug targets and the compounds

The oxygen of ligand in complex trypanothione reductase and 9,12-Octadecadienoic acid (Z,Z)- forms 1 hydrogen bond with the bond length 2.97 with Ser464 (Figure 7).

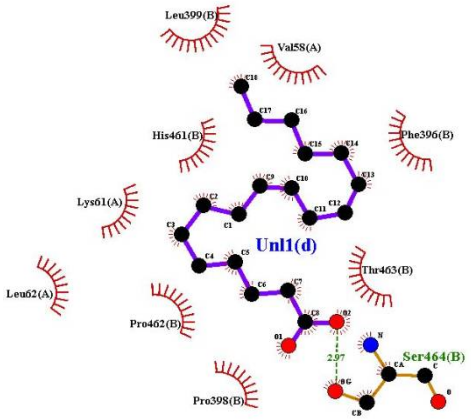
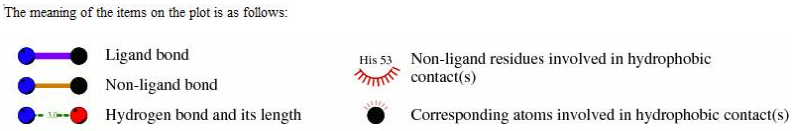


Figure 7: Protein-ligand interaction of Complex Trypanothione Reductase_9,12-Octadecadienoic acid (Z,Z)-

Note: 9,12-Octadecadienoic acid (Z,Z)- (ligand) form one hydrogen bond (represented as green broken lines with bond length) with amino acid Ser464 of trypanothione reductase (protein).



The complex between the oxygen of ligand in ornithine decarboxylase and 9,12-Octadecadienoic acid (Z,Z)- forms 2 hydrogen bond of length 3.04 and 3.14 with Gly237 and Gly276 respectively (Figure 8).

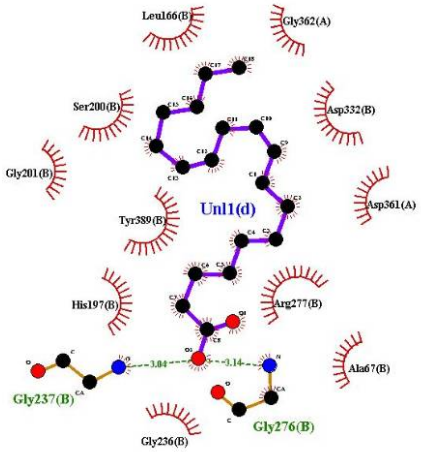
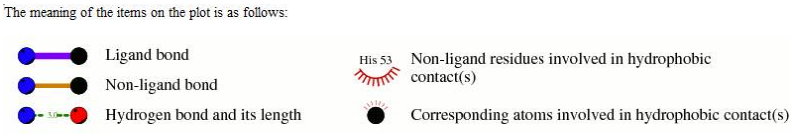


Figure 8: Protein-ligand interaction of Complex Ornithine Decarboxylase_9,12-Octadecadienoic acid (Z,Z)-

Note: 9,12-Octadecadienoic acid (Z,Z)- (ligand) form two hydrogen bonds (represented as green broken lines with bond length) with amino acid Gly237 and Gly276 of ornithine decarboxylase (protein).



3.11. Docking outcome of control

Vinyl sulfone, a known and potent antischistosomal inhibitor of *S. mansoni* cathepsinB1 (Jílková *et al*., 2011; and Abdulla *et al*., 2007) was selected as the control in this study. Pyrimethamine, a drug used to inhibit *S. mansoni* dihydrofolate reductase was also adopted as the control.

The control compound used to inhibit *L. major* N-myristolytransferase is 2,6-Dichloro-N-(difluoromethyl)-4-[3-(1-methylpiperidin-4-yl)propyl]-N-(1,3,5-trimethylpyrazol-4yl)benzenesulfonamide (DDD100097), a compound that has been used in the treatment of leishmaniasis (Corpas-Lopez *et al*., 2019). UDP-glucose pyrophosphorylase has been inhibited 3-Fluoro-4-methoxyphenyl)methyl-methyl-[2-oxo-2-(2-phenoxyanilino)ethyl]azanium, therefore it was adopted as the control (Prakash *et al*., 2019).

Atovaquone, a known clinically approved drug used to inhibit *P. falciparum* dihydroorotate dehydrogenase was used as the control and standard drug. Halofantrine, an approved drug used to inhibit *P. falciparum* plasmepsin II, was used as the control and standard drug.

Drugs or compounds used commercially as antitrypanosomal were adopted as the control in this study. Clinically, quinacrine mustard is used to inhibit enzyme *Trypanonosoma brucei* trypanothione reductase as it irreversibly inactive the enzyme (Saravanamuthu *et al*., 2004) and DL-alpha-Difluoromethylornithine (DFMO) is a specific enzyme-activated irreversible inhibitor of ornithine decarboxylase (ODC) and also used clinically (Mccann *et al*., 1981).

All these controls were docked against the chosen drug targets and the result was obtained (Tables 4, 5, 6 and 7).

4. Discussion

The nature of the extracting solvent and the method used strongly influence the phytochemical extracted from a medicinal plant because of the presence of different chemical compounds of varied polarity and chemical characteristics which may be soluble or insoluble in a particular solvent (Sultana *et al*., 2009; Jakopic *et al*., 2009; and Afolayan *et al*., 2020). Dichloromethane and methanol were combined as the solvent of organic extraction because dichloromethane is a non-polar solvent while methanol is classified as a polar solvent according to the solvent polarity profile table. Consequently, dichloromethane will be able to extract the non-polar active compounds in the plant material while methanol will be able to extract polar active compounds in the plant material. Previous studies showed that the dichloromethane:methanol (1:1) extracts of *Lawsonia. inermis*, *Chromolaena odorata*, *Tithonia. diversifolia* singly and in combination were active against Plasmodium parasite than the aqueous extracts. Also, the dichloromethane:methanol (1:1) extracts of *L. inermis*, *T. diversifolia* and *Nauclea latifolia* were also active against *Plasmodium berghei* (Afolayan 2014; Afolayan *et al*., 2016; and Afolayan *et al*., 2020).

The ADMET is made of the pharmacokinetic profile of a drug molecule and it is very important in determining its pharmacodynamic activities (Nisha *et al*., 2016). The ADMET study revealed that most of the compounds which were predicted to have lower binding energies than their respective controls have good pharmacokinetic and pharmacodynamic properties.

Binding energy is a good parameter obtained from molecular docking. It gives the strength and affinity of the interaction between the ligand and receptors. Phytocompounds with the lowest binding energy are good inhibitors because the greater the binding energy, the weaker the interaction between the ligand and receptor.

In this study, it was observed that 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol compound had better binding affinity with dihydrofolate reductase and capthesin B1 than the standard drugs (pyrimethamine and divinyl sulfone). This corroborated the findings of some researches that 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol reduced the schistosoma worm burden and inhibited the activities of the parasites (Cheuka *et al*., 2017).

Furthermore, a higher binding affinity is a function of the number of hydrogen bonds formed as well as the ability of the ligands to form more hydrophobic interactions with the hydrophobic amino acids around the binding site of the ligand (Ejelonu and Adanlawo, 2016). This is because hydrogen bond aids the binding of protein-ligand by enhancing the binding affinity of the ligand through the displacement of protein-bound water molecules and also plays a role in the protein-ligand complex stability (Chen *et al*., 2016; and Dhorajiwala *et al*., 2019). It was observed that 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol forms 1 hydrogen bond and 10 hydrophobic interactions with *S. mansoni* Cathepsin B1 while it forms 2 hydrogen bonds and 8 hydrophobic

interactions with *S. mansoni* dihydrofolate reductase thereby making it a good inhibitor. This, therefore, indicate that 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol could be a potential drug candidate of schistosomiasis.

The binding energies of all the compounds docked against *L. major* targets were considerably low but it was observed to be higher than those of the controls. This could be as a result of the compounds having lower binding affinity to the receptor compared to the standard drugs.

Phytol was observed to have the lowest binding energy among the group of compounds docked against dehydroorotate dehydrogenase and plasmepsin II targets of *P. falciparum*. We further noticed that Phytol had lower binding energy than the control drug, Atovaquone. The 2D structure displayed 1 hydrogen bond and 8 hydrophobic interactions between phytol and dihydrorotate dehydrogenase, showing that it has a good binding affinity as revealed by the good number of the non-polar amino acid involved in the hydrophobic interactions and the hydrogen bond formed. This inhibitory effect of phytol is in line with previous studies which identified phytol as a compound with antiplasmodial activity (Grace *et al.*, 2012; and Novian, 2019). Other compounds that were docked with *P. falciparum* targets and showed better binding affinity than atovaquone, the standard drugs, are 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol, 9,12-Octadecadienoic acid (Z,Z)- , E-11(12-Cyclopropyl)dodecen-1-ol as well as (4-Fluorophenyl)(5-methyl-2-thioxo-2H-[1,2,4]triazolo[1,5-a]pyridin-3-yl)methanone.

Also, 9,12-Octadecadienoic acid (Z,Z)- has a lower binding energy than the standard drug (DL-alpha-Difluoromethylornithine, DFMO) against ornithine decarboxylase of *T. brucei brucei*. This could be due to the strong interaction it poses with the protein. From 2D structure, 9,12-Octadecadienoic acid (Z,Z)- formed 2 hydrogen bond and 11 hydrophobic interactions with *T. brucei brucei* ornithine decarboxylase, predicting that it is a good inhibitor. Meanwhile, it was observed that Quinacrine mustard had better binding affinity than all the compounds docked against Trypanothione Reductase.

This study, therefore, predicted 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, phytol and 9,12-Octadecadienoic acid (Z,Z)- to be strong antischistosomal, antimalarial and antitrypanocidal compounds, respectively. Therefore, considerable attention should be given to them by conducting preclinical studies on them.

5. Conclusion

Phytocompounds present in plants have been useful and plays important role in the synthesis of novel drugs. *A. paniculata* exhibits notable pharmacological activities. This *in silico* molecular study has given insight into and predicted 3,7,11,15-Tetramethyl-2-hexadecen- 1-ol, Phytol and 9,12-Octadecadienoic acid (Z,Z)- which could serve as leads for therapeutic novel drugs of schistosomiasis, malaria, trypanosomiasis, respectively, thereby enhancing the effective management and control of these diseases.

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