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Evaluation of 6-Gingerol and its modified analogues as therapeutic candidates against *Schistosoma mansoni* phosphofructokinase

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The African most prevalent tropical disease after malaria is schistosomiasis and this disease in the developing countries is a massive socio-economic and public health burden. The disease also caused over 200,000 deaths. The development and design of new and novel antischistosomal drugs is now very important, as there are no vaccines currently and there is only one drug at the moment for the treatment of schistosomiasis. In this article, 6-gingerol was docked against the *Schistosoma mansoni* phosphofructokinase and the docking result was compared to those obtained from the docking of its modified analogues against the same enzyme. The chemical structure of 6-gingerol was obtained from the PubChem database while the modified analogues were designed using the ChemAxon software. The molecular docking procedure was carried out with the aid of the AutoDock Vina software while polar interactions which were eventually used in predicting the amino acid residues at the *Schistosoma mansoni* phosphofructokinase active site were visualized using the Pymol software. The *Schistosoma mansoni* phosphofructokinase 3D crystallized structure was modeled using the Swiss Model server. The molecular docking result showed that the modifications made on 6-gingerol had a positive effect on the binding energy of the compound to the enzyme active site as an appreciable increase was observed. 6-Gingerol and its modified analogues also violated none of the Lipinski's rule with suggests that the experimental compounds are drug-like. The C_2H_5 analogue of 6 gingerol was selected as the ideal therapeutic agent based on the pharmacokinetics study and the exhibited binding energy.

Keywords: *Schistosoma mansoni*, Schistosomiasis, Molecular docking, Phosphofructokinase, Pharmacokinetics.

Introduction

Schistosomiasis and many other worm related diseases likewise infections caused by protozoa, viruses and bacteria have not been given enough attention unlike the HIV/AIDS, tuberculosis and malaria. Indeed, most neglected tropical diseases especially schistosomiasis lacks any form of global funding whereas the positive impact as a result of the funds pumped into the HIV/AIDS, tuberculosis and malaria research is clear for all to see as it raised their profile and served as the eventual game changer for them. The reason for the neglect faced by schistosomiasis and other neglected tropical diseases can be linked to poverty, isolation geographically, global burden that has been underappreciated, stigmatization, inadequate political voice to speak for infected people and the fact that there is no established global funding mechanism.[1]

Schistosomiasis is mostly experienced by the inhabitants of the world's tropical belt which constitute a third of the world's population and over a billion individuals stand the risk of infection. Over 200 million are infected and close to 800 million re on a daily risk of becoming infected. The varying estimation in the disease prevalence is dependent on the focal character of the epidemiology and these generally includes a wide range of relatively safe land but these are dotted with many, but limited, areas where the transmission is high.

Generally, the distribution of schistosomiasis cuts across a wide range of areas especially in Africa and also the South America, Middle East and South East Asia (Fig. 1). Eradicating schistosomiasis has proven very difficult but it can be controlled where there is an existence of financial resources.[2]

The importance of the role played by anaerobic glycolysis for the adult *Schistosoma mansoni* survival cannot be over-emphasized as it aids the metabolism of both exogenous glucose and endogenous glycogen through the Embden–Meyerhof pathway. The phosphofructokinase has been known to be a glycolytic regulatory enzyme in both the mammalian and parasitic cells and this makes

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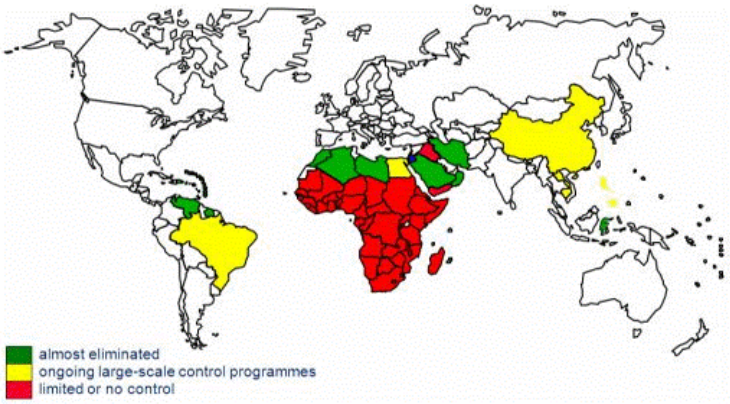

Fig. 1. Current situation of schistosomiasis around the world.

the *Schistosoma mansoni* phosphofructokinase a target for antimonial agents. Being a regulatory enzyme also makes it a good target for prospective anti-parasitic agents.[3]

Praziquantel is drug used in the treatment of a good number of infections as a result of parasitic worms. It is specifically used for the treatment of schistosomiasis, hydatid disease, opisthorchiasis, tapeworm infections, cysticercosis, clonorchiasis, and other fluke infections.

The mechanism of action at present is not exactly known, but evidences according to several experiments have shown that praziquantel increases the calcium ion permeability of the schistosome cell membranes. The drug thereby induces contraction which results into the paralysis of the contracted parasite. The dying parasites are channeled away from their action site and passed into the host's systemic circulation or destroyed by phagocytosis.[4]

Ginger (*Zingiber officinale L., Zingiberaceae*) is commonly utilized in various foods and drinks as a spice. It is also used in traditional Chinese medicine. The treatment can be considered effective for the common cold, asthma, nervous disease, stroke, gastrointestinal constipation, inflammation, oxidant stress, hypercholesterolaemia, schistosomiasis and helminthiasis.

According to several literature reviews, ginger is made up of paradol, zingerone, gingerols and shogaols as constituents. Derived phenolic compounds from ginger such as [6]-gingerol, [10]-shogaol, [10]-gingerol and [6]-shogaol have many common activities and therapeutic applications involving its parasitidal, physiological and pharmacological propriety.[5]

This study is aimed at modifying 6-gingerol through the addition of various functional groups and testing their antischistosomal activity against the *Schistosoma mansoni* phosphofructokinase. The polar interactions were also used in the prediction of the *Schistosoma mansoni* binding pocket.

Materials and Methods

Sequence Retrieval

The *Schistosoma mansoni* and human phosphofructokinase amino acid sequences were retrieved from the National Center for Biotechnology Information (NCBI) Database. The NCBI houses database series with relevance to biotechnology and biomedicine and is also a useful resource for bioinformatics services, analysis and tools.

Major databases comprise the GenBank which is for sequences of DNA and PubMed which is a bibliographic repository for literatures regarding biomedicine. Other databases include the NCBI and the Epigenomics database.[6]

Schistosoma mansoni and human phosphofructokinase were assigned the accession number of CCD81856.1 and NP_001350474.1 respectively.

Sequence Alignment

The *Schistosoma mansoni* and human phosphofructokinase sequences were aligned using the clustalW software. Just like other Clustal tools, ClustalW is used for multiple nucleotide and protein sequence alignment in a manner that is efficient. ClustalW make use of progressive alignment methods, where the first set of aligned sequences are the most similar down to the least similar up to the point of creation of a global alignment.[7]

Protein 3D Structure

The crystallized 3D structure of the *Schistosoma mansoni* phosphofructokinase was not available for downloads from the Protein Data Bank (PDB) repository there for a homology model of the 3D structure was generated using the SWISS-MODEL structural bioinformatics server.[8]

Ligand Preparation

The 2D structure of 6-gingerol and its modified analogues were designed using the MarvinSketch software.[9] All designed structures were downloaded and saved as mrv files in preparation for docking.

File Conversion

Saved mrv files from the ligand preparation process were converted into SMILES strings (Simplified Molecular Input-Line-Entry System) using the Open Babel Open Source Chemistry Toolbox. Open Babel, a chemical toolbox is designed to speak many of the languages of chemical data. It's an open and collaborative project allowing anyone to make searches, conversions, analysis, or storage data from molecular modeling, chemistry, solid-state materials, biochemistry, or related areas.[10]

Ligand Minimization

6-Gingerol and its modified analogues were minimized using the UCSF Chimera software. UCSF Chimera is an extensible program for analyzing and interactively visualizing molecular structures and related data which include supramolecular assemblies, density maps, alignment of sequences, results from molecular docking, trajectories and conformational ensembles.[11]

Polar Interaction Visualization

Weak interactions between 6-gingerol, its modified analogues and the *Schistosoma mansoni* phosphofructokinase were visualized using the Pymol molecular visualize. PyMOL is an open-source tool for model visualization and it is made available for utilization in structural biology. The Py aspect of the name of the software is a reference pointer that it is extensible and extends by the python programming language.[12]

Molecular Docking

The binding energy scores between the experimental ligands and the *Schistosoma mansoni* phosphofructokinase was predicted using the AutoDock Vina software. AutoDock Vina is a molecular modeling and simulation software. It is especially designed and effective for protein-ligand docking.[13] The size of the grid box for x, y and z was set at 47, 42 and 62Å respectively while the center of the grid for x, y and z was set at 57, 70 and 55 Å respectively.

Results and Discussion

Sequence Alignment

Figure 2 shows the sequence alignment between the *Schistosoma mansoni* and human phosphofructokinase. The occurrence of the (*) mark indicates regions of sequence conservation while the blank spaces reveals regions with no sequence identity. The calculated percentage identity from the alignment was 53.41%. The distinctive difference between the *Schistosoma mansoni* and human phosphofructokinase can be observed through the coloration of the displayed picture

Fig. 2. Sequence alignment result between the *Schistosoma mansoni* and human phosphofructokinase.

in Figure 2 as identical amino acid residues between the primary structure of the phosphofructokinase of both organisms are shown in red color while the green color show strongly similar amino acids and the blue color indicates amino acids that are weakly similar.

The usefulness of sequence alignment is for the discovery structural and functional information in biological sequences. The importance also gives important information about the evolutionary relationship between sequences of different species of organisms. In discovering the said information, it is important to get the best possible and optimal form of sequence alignment. Similar sequences may probably have similar functions and their roles may be regulatory if the sequences are amino acid sequences. In addition, sequences from varying organisms can be said to be homologous if they exhibit high similarity and this implies that they might have originated from common ancestors.[14]

The 53.41% identity observed from the alignment result between the *Schistosoma mansoni* and human phosphofructokinase primary structures is an indication that the *Schistosoma mansoni* phosphofructokinase might be an ideal target for drug-like compounds based on the average percentage similarity that exists between the two amino acid sequences. The average percentage similarity also consequently serves as an indicator to the close relationship between the two sequences with regards to evolution.

2D Structure of 6-Gingerol

Figure 3 shows the 2D structure of 6-gingerol as designed by the MarvinSketch software. Modifications that resulted into the derivatives of this compound were made through the substitution of the OCH_3 group attachment to the carbon-1 (C_1) of the compound with other functional groups such as the C=O, C_2H_5, CH_3, $CONH_2$, COOH, NH_2 and OH groups.

The 3D Structure of 6-Gingerol

The 3D structure of 6-gingerol was generated though the input of the canonical SMILES obtained from the OpenBabel conversion of the 2D structure of the compound into the Chimera visualizer. The "Build Structure" function of the Chimera visualizer was enacted to generate a 3D structure which was saved as a Mol2 file. The saved Mol2 file was viewed using the Pymol visualize and this same software was used in labeling and viewing each atom making up the compound.

The 6-gingerol modifications as reported in Figure 3 were made by substituting the OCH_3 functional group attachment of the compound with other functional groups. This OCH_3 group is clearly depicted in the 6-gingerol 3D structure in Figure 4. The oxygen component of the functional group is labeled O_4 while the CH_3 component is labeled C_{17}, H_{24}, H_{25}, H_{26}.

Schistosoma mansoni Phosphofructokinase Secondary Structure Prediction

Modeling the 3D secondary structure of the *Schistosoma mansoni* phosphofructokinase was a step directed towards viewing the predicted secondary structure components of the enzyme. Each secondary structure components were colored distinctively for the ease of

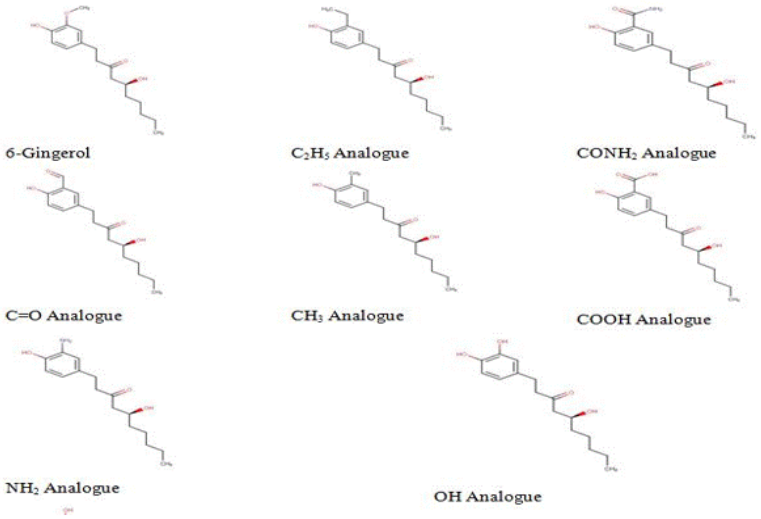

Fig. 3. The two dimensional (2D) structure of 6-gingerol and its modified derivatives as designed using the MarvinSketch software.

visualization (Fig. 5). The alpha helices were colored in red while the beta sheets and loops were colored in yellow and green respectively.

Molecular Docking

Selected docking results obtained from the use of the AutoDock Vina docking software were displayed in Figure 6 and 7. The displayed pictures show the differential poses and binding orientation of 6-gingerol and its C_2H_5 analogue to the *Schistosoma mansoni* phosphofructokinase.

At the left portion of the displayed picture is the table depicting the series of possible binding scores that can be obtained based on the differential binding poses of the experimental compounds. The best binding score for each docking processes were selected for the purpose of this study.

Binding Energy Prediction and In Silico Pharmacokinetics

Table 1 illustrates the specific pharmacokinetics and druglikeness parameters of each experimental compound. The binding energy scores which are pointers to the binding affinity of compounds to enzymes were also illustrated in the Table.

Lipinski's rule of five which can also be referred to as the Pfizer's rule of five is a rule described for the evaluation of druglikeness or for the determination of biological and pharmacological activities in specific compounds for the purpose of evaluating physical and chemical properties in determining likely orally active drugs for administration. The rule states that, orally active drugs in general must not violate more than one of the following criteria: The hydrogen bond donors must not be more than 5 (the summation of nitrogen–hydrogen and oxygen–hydrogen bonds), hydrogen bond acceptors must not exceed 10 (all nitrogen or oxygen atoms), the molecular mass of the compound must be less than 500 Da, an octanol-water partition coefficient (log P) must not exceed 5. The results obtained from Table 1 as regarding the Lipinski's rule shows that all the experimental ligands might be orally active compounds and as such can be considered drug-like. Also, none of the experimental compounds violated any of the Lipinski's rule.

The polar surface area (PSA), also known as the topological polar surface area (TPSA) of a molecule is defined as the sum of all polar atoms (oxygen and nitrogen), with the inclusion of the hydrogen atom attachments. The polar surface area is a metric that is often used in medicinal chemistry to optimize the cell permeation ability of drugs. Molecules with a PSA value higher than 140 angstroms squared are known to be poor in cell membrane penetration. For molecules to penetrate the blood–brain barrier (BBB) (in order to act on the central nervous system receptors), the value assigned to the polar surface area must be less than 90 angstroms squared.[15] 6-Gingerol and five of its modified analogues (C=O, C_2H_5, CH_3, NH_2 and OH) might possess the blood-brain barrier permeation attributes as their TPSA values appeared lower than 90 angstroms.

The partition coefficient between n-octanol and water (log Po/w) serves as the classical method for the description of lipophilicity. The diversity of the models backing the predictors will increase the accuracy in the prediction using the consensus log Po/w. The Lipinski's rule was used as the druglikeness descriptor for the purpose of this study and the optimal lipophilicity range (Log Po/w) allowed should not exceed 5.[15] The observation from the consensus lipophilicity column of Table 1 shows that 6-gingerol and all the analogues derived from it are within the optimal lipophilicity range and as such can be regarded as druglike compounds.

Activities regarding drug development can be facilitated and made easier in cases where molecules are soluble.

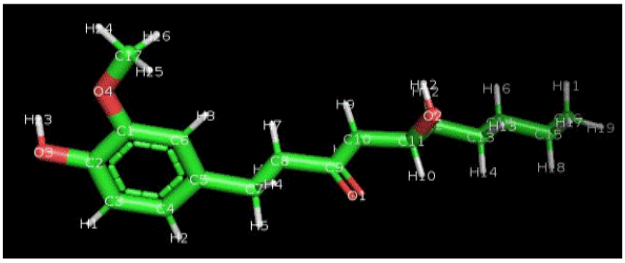

Fig. 4. 3D structure of 6-Gingerol showing all labeled atoms.

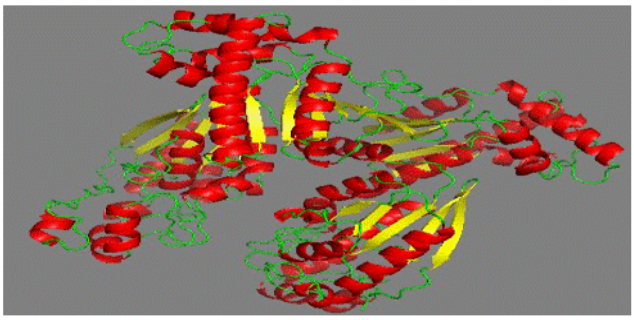

Fig. 5. Homology model of the *Schistosoma mansoni* 3D structure colored by secondary structures; Helix in red, Sheet in yellow and Loop in green.

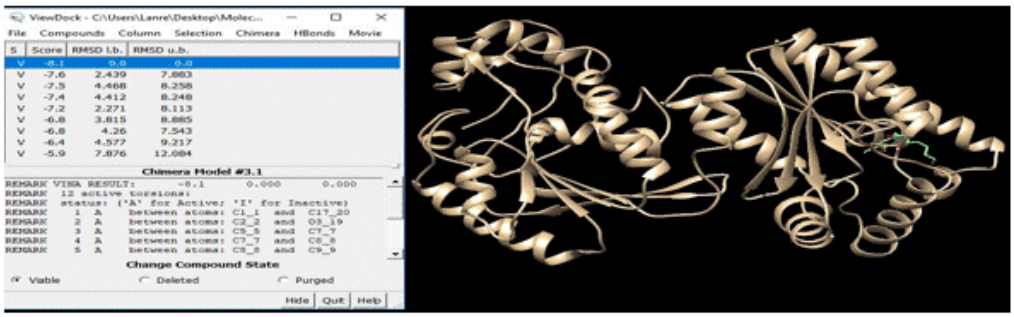

Fig. 6. Predicted molecular docking score and binding pose between *Schistosoma mansoni* phosphofructokinase and the C_2H_5 analogue of 6-gingerol.

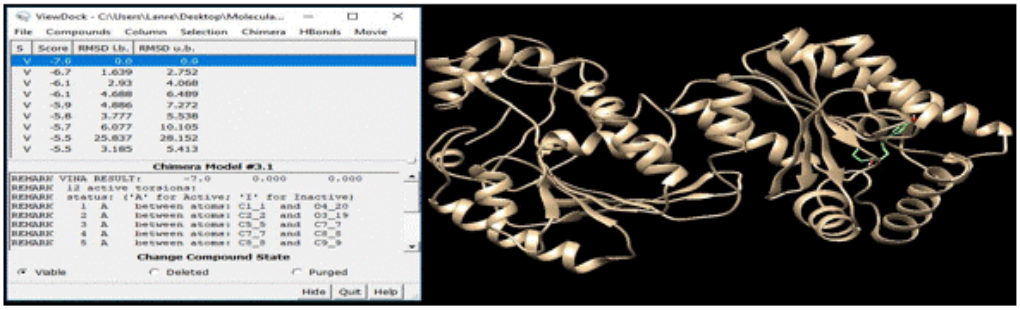

Fig. 7. Predicted molecular docking score and binding pose between *Schistosoma mansoni* phosphofructokinase and 6-gingerol.

Table 1. Physicochemical properties, lipophilicity, solubility, pharmacokinetics and Lipinski druglikeness of antifolate drugs, gedunin and its modified derivatives.

Parameters	**6-Gingerol**	**C=O analogue**	**C_2H_5 analogue**	**CH_3 analogue**	**$CONH_2$ analogue**	**COOH analogue**	**NH_2 analogue**	**OH analogue**
Formula	$C_{17}H_26O_4$	$C_{17}H_24O_4$	$C_{18}H_28O_3$	$C_{17}H_26O_3$	$C_{17}H_25NO_4$	$C_{17}H_24O_5$	$C_{16}H_25NO_3$	$C_{16}H_24O_4$
Molecular weight g/mol	294.39	292.37	292.41	278.39	307.38	308.37	279.37	280.36
Docking score Kcal/mol	-7.0	-7.7	-8.1	-7.7	-7.5	-8.0	-7.7	-6.8
Num. H-Bond acceptors	4	4	3	3	4	5	3	4
Num. H-Bond donors	2	2	2	2	3	3	3	3
TPSA Å²	66.76	74.60	57.53	57.53	100.62	94.83	83.55	77.76
Lipophilicity Consensus Log $P_{o/w}$	3.13	2.96	3.81	3.49	2.47	2.80	2.55	2.75
Water Solubility Log S	Soluble	Moderately Soluble	Moderately Soluble	Moderately Soluble	Moderately Soluble	Soluble	Soluble	Soluble
GI absorption	High	High	High	High	High	High	High	High
BBB permeant	Yes	Yes	Yes	Yes	No	No	No	Yes
P-gp substrate	No	No	Yes	No	No	No	Yes	No
CYP3A4 inhibitor	No	Yes	Yes	No	No	No	No	No
Lipinski Druglikeness	Yes; 0 Violation	Yes; 0 Violation	Yes; 0 Violation	Yes; 0 Violation	Yes; 0 Violation	Yes; 0 Violation	Yes; 0 Violation	Yes; 0 Violation
Synthetic accessibility	2.81	2.67	2.77	2.58	2.71	2.84	2.57	2.61

This brings about ease in drug handling and its formulation. Moreover, for discovery projects that target the oral form of administration, one of the major absorption property influencers the solubility of the compound. Also, drugs that are designed for parenteral administration requires a high solubility attribute to aid the delivery of an appreciable amount of the active ingredient in smaller volumes of pharmaceutical dosage. A compound can be considered as soluble if the Log S value is less than 6.[16] 6-Gingerol and its modified analogues used for the purpose of this study, according to the column projecting the solubility result in Table 1 are all water soluble, implying that they might be easily absorbed.

The nature of the gastrointestinal mucosal membrane surface area plays an important role in the process of drug absorption and it has a varying and differential effect from the stomach to the rectum. The physiochemical properties of the luminal content are also implicated to have an influence in drug absorption process. The absorption process itself is continually described in terms of hypothesis of simple partition of pH, where absorption is controlled by the equilibrium position between the ionized and non-ionized forms of the drug at varying physiological pH values encountered in the gastrointestinal tract.[17] All the experimental possess a high gastrointestinal absorption rate, indicating their ability to aid drug bioavailability.

Overcoming the ability of a non neuroactive drug to cross the blood brain barrier is a major challenge to be solved in the processes of designing drugs. Only neuroactive drugs are required to possess the blood brain permeation attribute for functionality On the contrary, non neuroactive drugs should not cross the blood brain barrier for the avoidance of psychotropic side effects.[15]

Blood-brain barrier permeation results from Table 1 showed that three of the modified analogues of 6-gingerol ($CONH_2$, COOH and NH_2) cannot penetrate the blood brain barrier. It was also interesting to note that the NH_2 analogue of 6-gingerol did not possess the blood-brain barrier permeation attribute even though the TPSA value is below 90 angstroms.

The P-glycoprotein (P-gp) is involved physiologically in the reduction of the harmful effects of toxic compounds, xenobiotics and drugs which the body is exposed to by constantly pumping them out of cells. The need for the role played by the P-glycoprotein has led to the recognition of the modulation it confers on many important and clinical therapeutic agents and this pharmacokinetic importance has led to the incorporation of its screening in any process involving drug discovery. Drug pharmacokinetic parameters can also be affected through various drug induced induction or inhibition directed at modulating drug transporters and this can lead to a significant drug-drug interaction.[18] Excluding the C_2H_5 and NH_2 analogues of 6-gingerol, other experimental ligands were no substrates to the P-glycoprotein hence their oral bioavailability remains intact.

The bioavailability of drugs designed for oral administration can be determined by the biotransformation process mediated by the intestinal CYP3A4 and the constant pumping of absorbed drugs out of the cell which is a process mediated by the P-glycoprotein. It has been hypothesized that the action of the CYP3A4 and P-glycoprotein may be in concert to reduce oral drug bioavailability and viewing this hypothesis from a theoretical point of view makes it more attractive. The recent test on the hypothesis of the possibility of the enhancement of substrate disappearance mediated by the CYP3A4 being stimulated by drugs interacting with the apical efflux pump suggests that the P-gp/CYP3A4 are cosubstrates and that P-glycoprotein increases the potentials of CYP3A4-mediated disappearance of drugs during secretary detoxification in the intestine. It is also possible for the P-glycoprotein to have an influence on first-pass metabolism in a manner describing cooperativity.[18]

Table 1 showed that the C=O analogue of 6-gingerol unlike other experimental ligands might exhibit a higher bioavailability, being an inhibitor of the CYP3A4. Other experimental ligands might undergo CYP3A4-mediated intestinal biotransformation which in turn lowers their bioavailability. The results from this column of Table 1 also showed that the C_2H_5 analogue of 6-gingerol can inhibit the CYP3A4 and this suggests the drug might be orally bioavailable even though it appeared to be a P-glycoprotein substrate.

Polar Contacts

As presented in Table 2, a total of 4 amino acid residues were involved in the formation of polar contacts with the experimental ligands. The experimental ligands include 6-gingerol and 7 of its modified analogues.

Figure 8 shows the positioning of the amino acid residues making up the binding pocket of the *Schistosoma mansoni* phosphofructokinase as predicted through the polar interactions between the enzyme and each of the

Table 2. Polar interactions between the experimental ligands and the amino acid residues of the *Schistosoma mansoni phosphofructokinase.*

Ligands	Amino Acid Residues				
	Gly	ARG	THR	ASN	SER
Gingerol			42, 66, 100, 157		
C=O Analogue		42	94, 96	95	
C_2H_5 Analogue		42	94, 96	95	
CH_3 Analogue		43, 157			
$CONH_2$ Analogue		66, 157			
COOH Analogue		42	94, 96		
NH_2 Analogue		42	94, 96	95	
OH Analogue	39	43			139

experimental ligands while it also selectively reveals the polar contact exhibited by 6-gingerol with the enzyme amino acid residues.

Amino Acid Composition of the Predicted Binding Pockets

Table 2 shows the list of amino acid residues which make up the predicted binding pockets of the *Schistosoma mansoni* phosphofructokinase.

Such weak molecular interaction as the hydrogen bonds and the hydrophobic interactions are considered generally as good protein-ligand binding facilitators.

They specifically contribute to the ligand stability and efficacy at the active site of a protein structure. [19] Retrieved information from the polar interactions between the *Schistosoma mansoni* phosphofructokinase were used in the prediction of the ligand binding pocket of the enzyme as shown in Figure 8.

The experimental ligands with the strongest binding energies were also observed to have consistently interacted with the ARG-42, THR-94, ASN-95 and THR-96 amino acid residues at the *Schistosoma mansoni* phosphofructokinase binding pocket. This suggests there is a link between the polar interactions formed with these residues and the eventual binding energy score.

The alpha helices and the beta sheets are the commonest elements of the secondary structure, although there is an occurrence of the omega loops as well as the beta turns. The spontaneous formation of the secondary structure elements serves as an intermediate before the folding of the protein into its 3D tertiary structure. The α-helices have been shown to be more stable, easily designable and more robust to mutation when compared to the β-strands in naturally existing proteins.[20] The protein secondary structure displayed in figure was colored according the secondary structural elements and it showed the abundance of the α-helices over other secondary structural elements. This implies that the *Schistosoma mansoni* phosphofructokinase is a very stable protein.

The application of molecular docking methods both in the world of academics and the pharmaceutical industries has been on the increase due to the increasing reliability of simulation theories and software used for

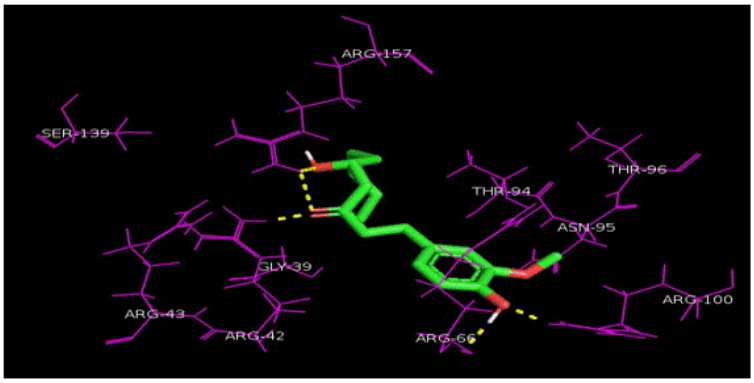

Fig. 8. Predicted binding pocket with bound 6-Gingerol.

the molecular docking processes.[19] The result of the molecular docking study has shown that the OH analogue might be the least potent of all the ligands when docked against the *Schistosoma mansoni* phosphofructokinase haven shown the highest binding score of -6.8Kcal/mol. This implies that it might be the ligand with the least binding energy as. The C_2H_5 and COOH analogues of 6-gingerol exhibited the highest binding energies with binding scores of -8.1 and -8.0 Kcal/mol. This imply that the two ligands might be the most potent against the *Schistosoma mansoni* phosphofructokinase.

Recent studies by Bueding and Mansour, 1957 has shown that the *Schistosoma mansoni* phosphofructokinase might not be a major immunogen as regarding natural infections in mice and humans, but focusing on the glycolytic pathway of the schistosomes, inhibiting the phosphofructokinase which is a rate limiting enzyme in this pathway using selective inhibitors has been reported to be the basis for the chemotherapeutic effect of trivalent organic antimonials on the enzyme. Reports from the pharmacological studies on gingerol showed that it exhibits antischistosomal properties and this makes it an ideal candidate for the inhibition of the *Schistosoma mansoni* phosphfructokinase.[3]

Conclusions

Finding another alternative to praziquantel is now imperative as it remains the only antihelmitic drug for the treatment of schistosomiasis around the world. Basically, this study has shown that structural modifications of compounds generally affects their pharmacokinetics, druglikeness and potency.

The C_2H_5 analogue of 6-gingerol exhibited the highest binding energy against the *Schistosoma mansoni* phosphofructokinase but cannot be selected as the most ideal drug candidate against the schistosoma parasite because of its ability to cross the blood brain barrier. The COOH analogue of 6-gingerol showed all the characteristics of a pharmacokinetically drug-like compound and also exhibited a high binding energy with the parasitic enzyme. This means that the COOH analogue of 6-gingerol might be selected based on this study as the most ideal drug candidate against the parasitic enzyme. The fact that the *Schistosoma mansoni* phosphofructokinase was predicted to be a stable enzyme based on the alpha helix composition of the secondary structure is another pointer to the fact that a ligand that exhibits a high binding energy will be needed to play an inhibitory role against the functionality of the enzyme and the COOH analogue of 6-gingerol has been observed to exhibit such attributes.

The laboratory synthesis of the COOH analogue of 6-gingerol is therefore recommended as the synthetic accessibility score has revealed the ease of its synthesis. Furthermore, preclinical studies on this compound is also recommended in order to confirm its inhibitory role against the parasitic enzyme.

Conflicts of interest

The authors declare there are no conflicts of interest.

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Evaluación de 6-Gingerol y sus análogos modificados como candidatos terapéuticos contra la fosfofructoquinasa de *Schistosoma mansoni*

Resumen

La enfermedad tropical con más prevalencia en África después de la malaria es la esquistosomiasis; en los países en vías de desarrollo constituye una carga socio-económica y de salud pública enorme. La enfermedad ha ocasionado más de 200.000 muertes anuales. El desarrollo y diseño de nuevas y novedosas drogas antiesquistosomales es muy importante, ya que actualmente no existe vacuna disponible y solo hay una sola droga licenciada para su tratamiento. En esta investigación, el compuesto 6-gingerol se acopló a la enzima fosfofructoquinasa de *Schistosoma mansoni* y se comparó con los resultados obtenidos a partir de las interacciones de sus análogos modificados a la misma enzima. La estructura química del 6-gingerol se obtuvo de la base de datos PubChem, mientras que los análogos modificados se diseñaron utilizando el software ChemAxon. El procedimiento de acoplamiento molecular se llevó a cabo con la ayuda del software AutoDockVina, mientras las interacciones polares eventualmente utilizadas para predecir los residuos de aminoácidos en el sitio activo de la enzima fosfofructoquinasa de *Schistosoma mansoni* se visualizaron empleando el software Pymol. La estructura cristalizada tridimensional de la enzima fosfofructoquinasa de *Schistosoma mansoni* se modeló utilizando el programa Swiss Model. Se demostró que las modificaciones realizadas en el 6-gingerol tuvieron un efecto positivo en la energía de unión del compuesto al sitio activo de la enzima, tras observarse un aumento apreciable de dicha energía. El compuesto 6-Gingerol y sus análogos modificados tampoco violaron ninguna de las reglas de Lipinski, lo que sugiere que estos compuestos experimentales tienen propiedades similares a los medicamentos. El análogo C_2H_5 de 6-gingerol se seleccionó como el agente terapéutico ideal, basados en el estudio de farmacocinética y la energía de enlace demostrada.

Palabras clave: *Schistosoma mansoni*, Esquistosomiasis, Acoplamiento Molecular, Fosfofructoquinasa, Farmacocinética.

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