International Journal of Zoology and Applied Biosciences **ISSN: 2455-9571**
Volume 2, Issue 5, pp: 258-265, 2017 **http://www.ijzab.com**
https://doi.org/10.5281/zenodo.1312119
Research Article

IN SILICO MOLECULAR DOCKING STUDIES ON PHYTOCOMPOUNDS FROM THE PLANT *KALANCHOE PINNATA* TARGETING THE PI-CLASS GLUTATHIONE-S-TRANSFERASE OF *WUCHERERIA BANCROFTI*

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Article History: Received 3rd August 2017; Accepted 17th October 2017; Published 28th October 2017

ABSTRACT

Mosquitoes are serious threat to public health through which several dangerous diseases are transmitted in both animals and human beings. The mosquito *Culex quinquefasciatus* is a significant vector of the filarial nematode, Wuchereria bancrofti, and cause Lymphatic filariasis. The residual spray of insecticides in the control of vector borne diseases is limited. Majority of the chemical pesticides are harmful to man and animals, some of which not easily degradable and spreading toxic effects. In recent years interest in plant based products has been revived because of the development resistance, cross-resistance and possible toxicity hazardous associated with synthetic insecticides and the rise of their cost. In the present study molecular docking analysis were performed using secondary metabolites selected from the plant *Kalanchoe pinnata* against the glutathione-s-transferase protein of *Wuchereria bancrofti*. Result suggested that among the four bioactive compounds viz., vitamin D, beta-amyrin, alpha-amyrin and stigmasterolbonded with the Pi-class glutathione –S-transferase protein (PDB ID:5D73) producing a good glide score. Whereas the four compounds, the partition coefficient (QPlogPo/w) and water solubility (QPlogS), critical for estimation of absorption and distribution of drugs within the body ranged between 6.941 to 8.968 and -7.261 to -10.376. Cell permeability (QPPCaco2), a key factor governing drug metabolism and its access to biological membranes, ranged from 3413 to 4557, QPPMDCK ranges from 1864 to 2548M. Overall, the percentage human oral absorption for the compounds ranged 100%. All these pharmacokinetic parameters are within the acceptable range defined for human use, thereby indicating their potential as drug-like molecules.

Keywords: *Culex quinquefasciatus*, *Kalanchoe pinnata*, Lymphatic filariasis, Molecular docking, Pi-Class Glutathione-S-transferase, *Wuchereria bancrofti*.

INTRODUCTION

Mosquitoes are the most important vectors of human disease, responsible for thetransmission of pathogens that cause malaria (*Anopheles stephensi*), yellow fever and dengue (*Aedes aegypti*), lymphatic filariasis and West Nile encephalitis (*Culex quinquefasciatus*). The southern house mosquito, *Cx. quinquefasciatus* is an important mosquito vector of viruses such as West Nile virus and St. Louis encephalitis virus as well of nematodes that cause lymphaticfilariasis (Arensburger *et al.*, 2010). *Wuchereria bancrofti* is one of the most common human parasitic filarial nematode that is found mainly in tropical regions. *W. bancrofti* is endemic in more than 78 nations and affects 128 million persons worldwide. It is mainly found in Central Africa, South and Central America, Nile delta and the tropical regions of Asia including Southern China and the Pacific. There are three parasites which cause filariasis and it is one of them. It spreads by a mosquito vector and generally there aresix genera and 70 species of mosquitoes responsiblefor spreading. Analysing the structures and functions of different proteins of *W. bancrofti* is very important because till date no effective drug or vaccine has been discovered to treat lymphatic filariasis (LF) (Islam *et al.*, 2014).

Lymphatic filariasis is caused by tissue nematodes (roundworms) that inhabit the lymphatic vessels and lymph

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nodes of a human host (Rocha *et al*., 2009). There are three types of these thread-like filarial worms: *W. bancrofti*, which is responsible for 90% of the cases, *Brugia malayi* and *B. timori* are among other species responsible for LF (Rocha *et al*., 2009; Michael and Bundy, 1997) Adult worms lodge in the lymphatic system and disrupt the immune system. The live for 6-8 years and, during their life time, produce millions of microfilariae (small larvae) that circulate in the blood in the night (WHO, 2011). Lymphatic filariasis is transmitted by different types of mosquitoes; for example by the *Culex* mosquito, widespread across urban and semi-urban areas; *Anopheles* mainly in rural areas, and *Aedes*, mainly in endemic islands in the Pacific (Sasa, 1976; Indian Council of Medical Research, 2002).

Lymphatic Filariasis (LF) is a disabling, disfiguring, and poverty promoting disease that affects an estimated 120 million individuals in developing countries (Michael and Bundy, 1997, Durrheim *et al*., 2004). The nematode parasite *Wuchereria bancrofti* is responsible for 90% of this global disease burden. This mosquito-borne disease threatens more than 1.2 billion individuals living in endemic countries (Ottesen *et al*., 2008). For this reason, the Global Program to Eliminate Lymphatic Filariasis (GPELF) was established with the goal of eliminating LF as a public health problem by 2020 (Ottesen, 2000; Molyneux *et al*., 2002). The strategy for the interruption of disease transmission is largely based on mass drug administration (MDA) of antifilarial medications to endemic populations to treat those who are currently infected and to reduce the reservoir of parasites available to mosquitoes that transmit the infection.

Natural products from medicinal plants, either as pure compounds or as standardized extracts, provide unlimited opportunities for new drug leads because of the unmatched availability of chemical diversity. Due to an increasing demand for chemical diversity in screening programs, seeking therapeutic drugs from natural products, interest particularly in edible plants has grown throughout the world. Botanicals and herbal preparations for medicinal usage contain various types of bioactive compounds (Sasidharan *et al.*, 2011).

Plants constitute major source of drugs for prevention and spread of wide range of pathogenic carriers and also treating various diseases of human beings. Modern people increasingly prefer drugs of natural origin mostly from plant origin due to abundant accessibility and fewer side effects. Whereas synthetic drugs and antibiotics often cause wide spread toxicity and harmful side effects to the end user other than targeted health condition / pathogen carrier. Novel active compounds with thereupatic properties from plant origin were efficient with minimum side effects (Gaddaguti *et al*., 2012).

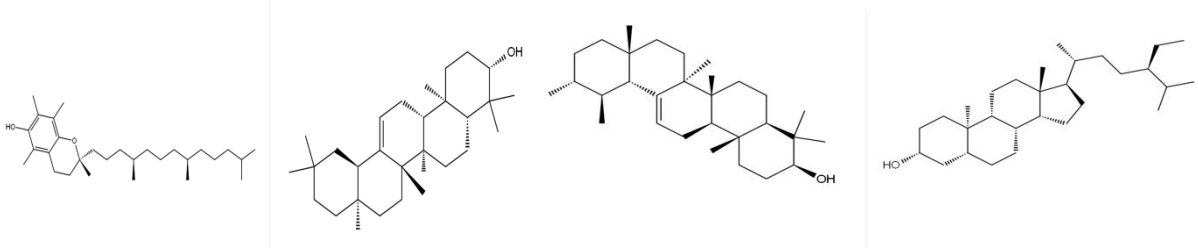
Molecular docking approaches are generally used in modern drug design process to understand the protein ligand interactions. The three-dimensional structure of the protein-ligand composite could be served as a considerable source of understanding the way of proteins interact with one another and perform biological functions. Thus, knowing the detailed structure of protein-ligand and its complexes in atomic level is one of the significant issues in biological sciences (Gaddaguti *et al*., 2012).

Docking the molecules frequently used to predict the binding orientation of small molecule drugcandidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs (Kitchen *et al*., 2004). The present study has been based on platform to understand the molecular docking interaction mechanism of pi-class Glutathione-S-transferase (detoxification enzyme) of *W. bancrofti* (nematode parasite) with the selected significant ligands from the plant *K. pinnata.*

MATERIALS AND METHODS

Selection of ligands from *Kalanchoe pinnata*

The computational prediction of potential drugs by the process of molecular docking, the important bioactive phytochemical of the plant *Kalanchoe pinnata* such as Vitamin D, Beta-amyrin, Alpha-amyrin and Stigmasterol were selected from two different solvent(acetone and benzene) extracts of plant leaf by GC-MS analysis and their structure were represented in figure 1.



Vitamin D Beta amyrin Alpha amyrin Stigmasterol

Figure 1. Structure of compounds.

Molecular docking

The molecular docking approach has been used to model the interaction between the drug molecules and the receptor protein as well as the phytochemicals and the receptor; at the atomic level, which helps in characterizing the behaviour of small molecules in the binding site of target protein. The docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within these sites and assessment of the binding affinity. Molecular docking studies were performed using the Schrodinger 9.5 software. To analyze the docking results and execute the protocol, the maestro users inter face was employed and the validating of the protocol was evaluated by re-docking. Glide grid generation wizard has been used to define the docking space. Docking was performed using XP docking protocol.

Preparation Ligands

Chemdraw freeware is one of the chemical compounds drawing package that allows us to draw chemical structures including organics, organometallics, polymers, and Markush structures. It also includes features such as calculation of molecular properties e.g., molecular weight, density, molar refractivity etc., 2D and 3D structure cleaning and viewing, functionality for naming structures, and prediction of logP. We have drawn alpha-amyrin, beta-amyrin, vitamin D, stigmasterol compounds and saved in mol file format and eventually input file for molecular docking studies.

Retrieval of Epidermal growth factor receptor Protein

Protein Data Bank

Three dimensional NMR structure of *W. bancrofti* Pi-class glutathione S-transferase (PDB ID:5D73) is obtained and selected only one chain from the resulting structure. Search was made against resolution of the structure, experimental designing solution and methods followed from the wet-lab. Maestro is Schrodinger's powerful, united, multi-platform graphical user interface (GUI). It is designed to simplify modelling tasks, such as molecule building and data analysis, and also to facilitate the set up and submission of Schrodinger's computational programs. The main Maestro features include a project-based data management facility, a scripting language for automating large or repetitive tasks, a wide range of useful display options, a comprehensive molecular builder, and surfacing and entry plotting facilities (Schrodinger, 2013).

Maestro is the graphical user interface for nearly all of the products that Schrödinger distributes: CombiGlide, ConfGen, Desmond, Epik, Glide, Impact, Jaguar, Liaison, LigPrep, Macro-Model, MCPRO+, Phase, Prime, PrimeX, QikProp, QSite, SiteMap, Strike, and WaterMap. It contains tools for building, displaying, and manipulating chemical structures; for organizing, loading, and storing these structures and associated data; and for setting up, monitoring, and visualizing the results of calculations on these structures. The preparation of a protein involves a number of steps, which are outlined below. The procedure assumes that the initial protein structure is in PDB-format file, includes a co-crystallized ligand, and does not include explicit hydrogen. The result is refined, hydrogenated structures of the ligand and the ligand-receptor complex, suitable to use with other Schrödinger product.

Grid generation

Grid files represent physical properties of a volume of the receptor (specifically the active site) that are searched when attempting to dock a ligand. The complex for this exercise is actually in two files, one containing the receptor and one containing the ligand. The prepared protein is displayed in ribbon representation. The receptor structures used for grid generation were taken from the Workspace, so we excluded the ligand atoms from consideration as part of the receptor. The Receptor Grid Generation panel opened with the Receptor tab displayed. Dark green markers appear on the ligand. In the Van der Waals radii scaling section choose Scaling factor default value of 1.00 (no scaling). Now that the ligand was excluded, the volume for which grids would be calculated. The entire complex was shown with several types of markers. The enclosing box is shown in purple. The centred of the enclosing box is marked by green coordinate axes. The purple colour enclosing box represents the volume of the protein for which grids was calculated. We made the enclosing box as small as is consistent with the shape and character of the protein's active site and with the Ligands to expect to dock.

The receptor grid can be set up and generated from the Receptor Grid Generation panel. The options in each tab of this panel allow us to define the receptor structure by excluding any co-crystallized ligand that may be present, determine the position and size of the active site as it will be represented by receptor grids, set up Glide constraints and set up flexible hydroxyl groups. Ligand docking jobs cannot be performed until the receptor grids have been generated. Receptor grid generation requires a "prepared" structure: an all-atom structure with appropriate bond orders and formal charges.

Ligand Docking

Glide (Rackham *et al.,* 2012; Reddy and Erion, 1998; Taylor *et al.,* 2002; Schrodinger, 2014) ligand docking jobs require a set of previously calculated receptor grids and one or more ligand structures. Preparation of the ligands before docking is strongly recommended. If a correct Lewis structure cannot be generated for a ligand, it is skipped by the docking job. Glide also automatically skips ligands containing un-parameterized elements, such as arsenic, or atom types not supported by the OPLS force fields, such as explicit lone pair "atoms".

The Ligand Docking Panel

To open the Ligand Docking panel, choose Ligand Docking from the Glide submenu of the Applications

menu. The Ligand Docking panel has six tabs: Settings, Ligands, Core, Constraints, Similarity and Output.

Examining Glide Data

Glide results are examined with an emphasis on visual rather than numerical appraisal. The first set of exercises use the Project Table to display the results of the SP Glide docking job, examine individual ligand poses and their contacts with the input receptor structure. The second set of exercises uses the Glide XP Visualizer panel to display information on the terms in the Glide XP scoring function that contribute to the ligand binding. Importing and Selecting Pose Data to entry group *Wuchereria bancrofti* Pi-class glutathione S-transferase protein.

QikProp

QikProp is a quick, accurate, easy-to-use absorption, distribution, metabolism, and excretion (ADME) prediction program designed by Professor William L. Jorgensen (Prueksaritanont and Tang, 2012; Qikprop 2013; Lipinski *et al.*, 1997). QikProp predicts physically significant descriptors and pharmaceutically relevant properties of organic molecules, either individually or in batches. In addition to predicting molecular properties, QikProp provides ranges for comparing a particular molecule's properties with those of 95% of known drugs. QikProp also flags 30 types of reactive functional groups that may cause false positives in high-throughput screening (HTS) assays. QikProp properties and descriptors can be used as input to Strike, which is a collection of chemically-aware statistical tools for examining correlations within data. It can develop and employ QSAR/QSPR models using partial least squares, principal component analysis, and multiple linear regression; generate univariate and bivariate statistics; and perform similarity/diversity analysis in descriptor and 2D-structure space.

RESULTS

In silico molecular Docking

The present computational tools as molecular docking and *insilico* pharmacokinetics prediction are employed to know the significance of synthesized phytocoponents. The 2D, 3D structures of important phytocompouds explore the binding mechanism of target enzyme protein, pi-class glutathione S-transferase of *W. bancrofti* molecular docking studies have been performed (Figure 2). Among the four as best ligands from the fifty-six phytocoponents were docked against the enzyme of nematode worm. The bonding interaction between the receptor and ligand can be visualized and in order to control the lymphatic filariasis through the phytochemical of *K. pinnata.*

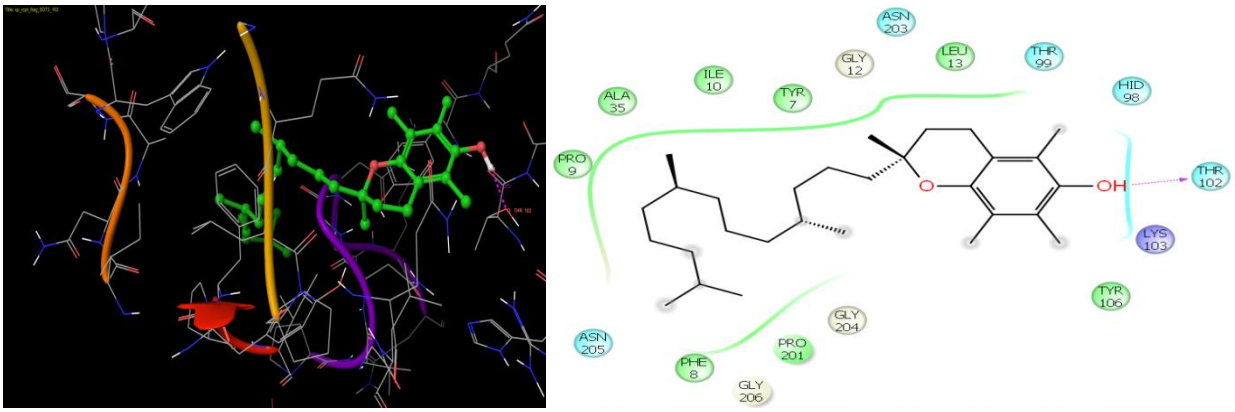


Figure 2. 3D,2D structures of target protein Pi-class glutathione S-transferase docked with drug molecule vitamin D.

Binding mode of vitamin D with *Wuchereria bancrofti* Pi-class glutathione S-transferase

The binding conformation of compound vitamin Dwithin the active site of the Pi-class glutathione S-transferase has been analyzed. The glide score and glide energy values for compound vitamin D were -4.236Kca/mol and -42.171kcal/mol, respectively. Examination of docking features between the compound vitamin D and pi-class glutathione S-transferase and it was found only one hydrogen bond interaction. The hydrogen atom of the compound vitamin D was interacted with oxygen atom of the polar residue of THR 102 with bond length (2.072Å). Furthermore that the following residues are mainly involved in hydrophobic interactions PRO 21, PHE 8, TYR 106, ALA 35, TYR 7, and PRO 9.

Binding mode of stigmasterol with *Wuchereria bancrofti*Pi-class glutathione S-transferase

The binding conformation of compound stigmasterolwithin the active site of the Pi-class glutathione S-transferase has been analyzed (Figure 3). The glide score and glide energy values for compound stigmasterol were -4.210Kcal/mol and -32.281kcal/mol respectively. Examination of docking features between the compound stigmasteroland pi-class glutathione S-transferase and it was found only one hydrogen bond interaction. The hydrogen atom of the compound stigma sterolwas interacted with oxygen atom of the hydrophobic residue of LEU 50 of with bond length (2.125Å). Furthermore that the following residues are mainly involved in hydrophobic interactions PRO 21, PHE 8, TYR 106, ALA 35, TYR 7, PRO 9, and PRO 51.

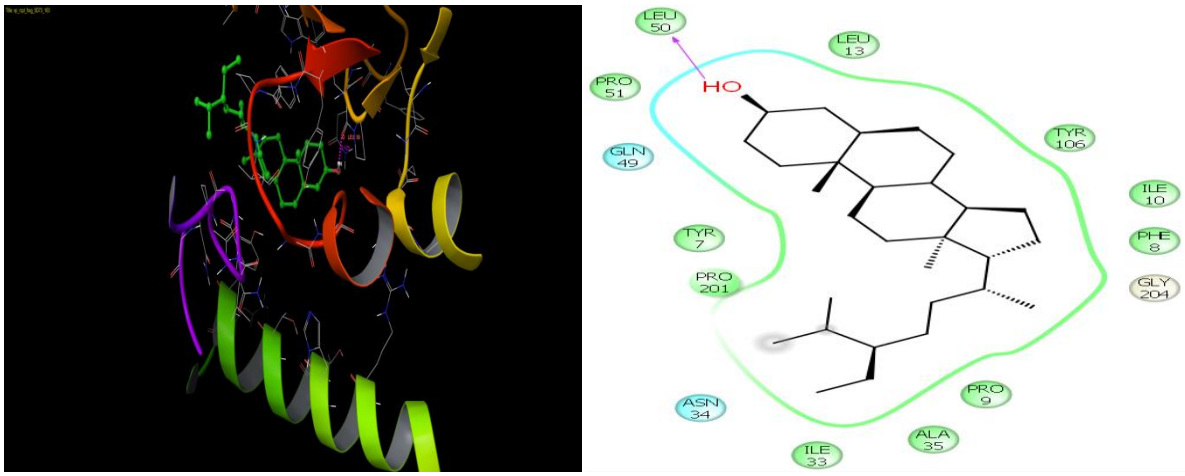


Figure 3. 3D,2D structures of target protein bancrofti Pi-class glutathione S-transferase docked with drug molecule Stigmasterol.

Binding mode of Beta-amyrinwith *Wuchereria bancrofti*Pi-class glutathione S-transferase

The binding conformation of beta-amyrinwithin the active site of the Pi-class glutathione S-transferase has been analyzed (Figure 4). The glide score and glide energy values for compound beta-amyrin were -3.450Kcal/mol and –39.999kcal/mol, respectively. Examination of docking features between compound beta-amyrin and Pi-class glutathione S-transferase and it was found only one hydrogen bond interaction. The hydrogen atom of the compound beta-amyrin was interacted with oxygen atom of the polar residue of THR 102 with bond length (2.012Å). Furthermore that the following residues are mainly involved in hydrophobic interactions PRO 21, PHE 8, TYR 106, ALA 35, TYR 7, and PRO 9.

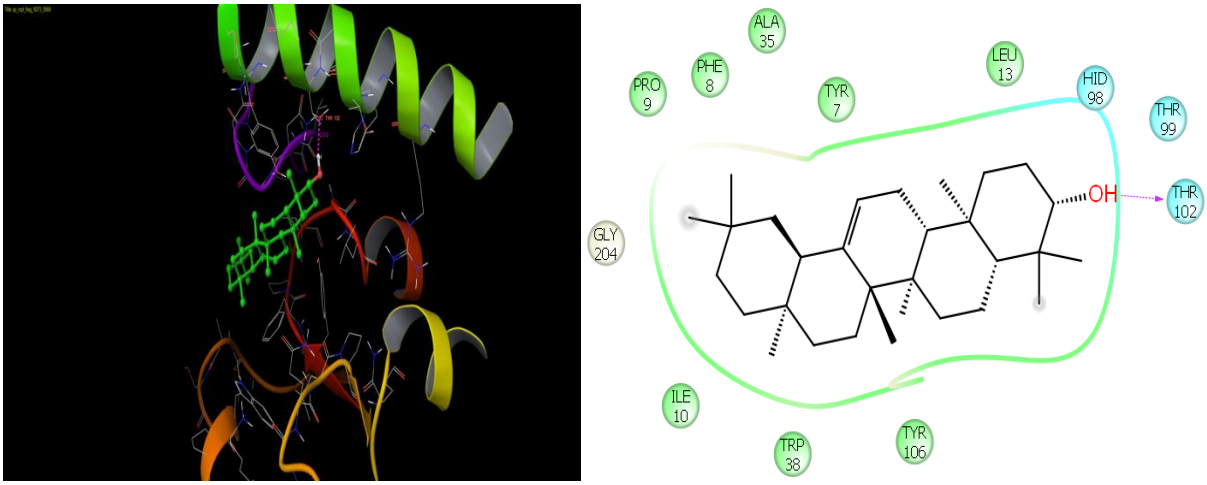


Figure 4. 3D, 2D structures of target protein Pi-class glutathione S-transferase docked with drug molecule beta-amyrin.

Binding mode of Alpha-amyrinwith *Wuchereria bancrofti*Pi-class glutathione S-transferase.

The binding conformation of alpha-amyrin within the active site of the Pi-class glutathione S-transferase has been analyzed (Figure 5). The glide score and glide energy values for compound alpha-amyrinwere -2.191Kcal/mol and –31.060kcal/mol, respectively. Examination of docking features between compound alpha-amyrinand Pi-class glutathione S-transferase and it was found only one hydrogen bond interaction. The oxygen atom of positive charged residue of ARG 95 was interacted with hydrogen atom of the alpha-amyrin with bond length (1.43Å). Furthermore that the following residues are mainly involved in hydrophobic interactions PRO 21, PHE 8, TYR 106, ALA 35, TYR 7, and PRO 9.

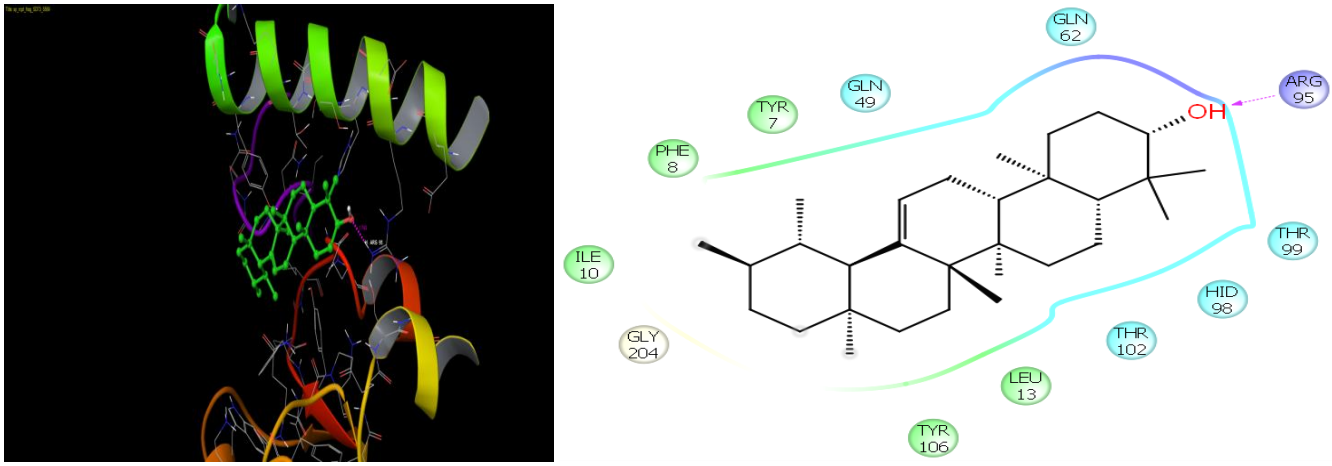


Figure 5. 3D, 2D structures of target protein pi- class glutathione S-transferase docked with drug molecule beta-amyrin.

Table 1. Glide extra-precision (XP) results for four molecules by use of Schrodinger 9.5.

S. No.	Compound Name	Glide Score(Kcal/mol)	Glide Energy(Kcal/mol)	Interacting Residues	Distance (Å)
1	vitamin D	-4.236	–42.171	THR 102	2.072
2	stigma residue	-4.210	–32.281	LEU 50	2.125
3	Beta amyrin	-3.450	–39.999	THR 102	2.012
4	Alpha amyrin	-2.191	–31.060	ARG 95	1.43

Distance between the protein and ligand (Å).

ADME Properties Prediction

We analyzed 56 physically significant descriptors and pharmaceutically relevant properties of four compounds, among which were molecular weight, H-bond donors, H-bond acceptors, log p, log p MDCK, log Kp, human oral absorption according to Lipinski's rule of 5 (Table 2). Lipinski's rule of 5 is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including its ADME. These compounds were further evaluated for their drug-like behaviour through analysis of pharmacokinetic parameters required for absorption, distribution, metabolism and excretion (ADME) by use of QikProp. For the four compounds, the partition coefficient (QPlogPo/w) and water solubility (QPlogS), critical for estimation of absorption and distribution of drugs within the body ranged between 6.941 to 8.968 and -7.261 to -10.376. Cell permeability (QPPCaco2), a key factor governing drug metabolism and its access to biological membranes, ranged from 3413 to 4557, QPPMDCK ranges from 1864 to 2548M. Overall, the percentage human oral absorption for the compounds ranged 100%. All these pharmacokinetic parameters are within the acceptable range defined for human use, thereby indicating their potential as drug-like molecules.

Table 2. ADME properties of the four molecules as verified by using QikProp (Schrodinger 9.5).

Ligand	HERG	QPlogS	Caco2	%Human oral absorption	QPlogKhsa	LogBB	MW	HBD	HBA	QPlog(o/w)	MDCK
Vitamin D	-5.814	-10.376	4557	100	2.377	-0.649	430.713	1.000	1.500	8.968	2548M
Beta-amyrin	-3.757	-8.100	4440	100	2.052	0.178	426.724	1.000	1.700	7.055	2478
Alpha-amyrin	-3.512	-7.261	4439	100	2.005	0.188	426.724	1.000	1.700	6.941	2477
Stigmasterol	-4.298	-8.150	3413	100	1.978	-0.332	416.729	1.000	1.700	7.365	1864

log HERG, HERG K+ channel blockage (concern below −5).

Apparent Caco-2 permeability (nm/s) (<25 poor, >500 great).

Apparent MDCK permeability (nm/s) (<25 poor, >500 great)

Predicted aqueous solubility; S in mol/L (acceptable range; -6.5 to 0.5)

Percentage of human oral absorption; (<25% is poor and >80% is high)

Prediction of binding to human serum albumin; (acceptable range; -1.0 to 1.5)

Prediction of brain/blood; (acceptable range; -3.0 to 1.2)

Molecular weight (< 500Da)

Hydrogen bond donor (< 5)

Hydrogen bond acceptor (< 10)

Predicted octanol /water partition co-efficient log p(acceptable range; -2.0 to 6.5).

DISCUSSION

The binding modes exhibited by four docked compounds illustrated the importance of specific residues within the active site region of the targets. Role of some important amino acids have also been revealed, that were found to be playing important role in the positioning of inhibitor within the active site and ADME properties are acceptable range. Thus based on docking results we confirm that these inhibitors as a lead to promising compounds against the target selected for our study. To discuss with other references the EGFR is one of the specific targets approached in bladder cancer. This study aimed to unlock the therapeutic potential of six azo derivatives 4,6-diacetylresorcinol. Computational tools such as molecular docking and *insilico* pharmacokinetics prediction is employed to know the significance of synthesized molecules. All the synthesized azo compounds of 4,6-diacetylresorcinl (I-VI) have minimum binding energy, good affinity towards the active pocket and furthermore values of ADME are highly promising which warrants the therapeutic use of six azo derivatives (Loganathan *et al.*, 2015).

Traditionally, drugs were synthesized first and then there pharmacokinetic properties, metabolism and toxicity were studied. With the use of combinatorial chemistry and high throughput screening a large no of new lead compounds are screened, many of these compounds fail because of inappropriate ADME properties. With advancement in technology, these studies are done much earlier before evaluating compounds in clinic through in-silico methods, saving both time and cost. In ADME studies, pharmacokinetics parameters are evaluated. A large no of these approaches have been developed to predict ADME properties (Waterbeemd Gifford, 2003; Nuez and Rodriguez, 2008). Phytochemical that are used are aspidin, cardinolide, curcumin, filixic acid, Iridoid, napthaquinone, ricinoleic acid, stearic, and Strebloside. Curcumin obtained from turmeric. Curcumin appears to possess a wide range of pharmacological properties, primarily resulted to its inhibitory effects on metabolic enzymes.

The present investigations adopt the computational tools as molecular docking and insilico pharmacokinetics prediction was employed to know the significance of synthesized molecules. The present docking result were confirmed that the target protein (ID: PDB 5D73) have best binding affinities of four compounds (Vitamin D, Beta-amyrin, Alpha-amyrin and Stigmasterol) among the 56 phytocomponents through the GC-MS analysis. These compounds exhibited its best glide score and also recorded the formation of one hydrogen bond interactions. When the ligand binds with the protein, conformation of the protein structure will change the functions of the protein automatically. Therefore, the compound may have an ability to inhibit the contact between human and pathogenic nematode worm which are transmitted through C. *quinquefasciatus*. The ADME properties of four compounds 100% acceptable range defined for human use, thereby indicating their potential drug-like molecules.

CONCLUSION

Lymphatic filariasis (LF) is a mosquito-borne tropical disease caused by the nematode parasites *W. bancrofti* live in human lymph system. The pi-class Glutathione-S-transferase is a detoxification enzyme in parasitic helminthes. Filarial nematodes depend on the detoxification enzymes for their survival in the host. Pi-class GST plays an important role in filariasis and other diseases. GST from *W. bancrofti* is very much different from human GST. In this study we have conclude the efficacy of some well-known antifilarial compounds against Pi-class GST. Molecular docking study reveals that the plant, *Kalanchoe pinnata* residues play important role to binds with the active site of pi-class GST filarial parasites. The Pi-class GST structural information and docking studies could aid in screening new antifilarials/ selective inhibitors astherapeutic agents for filariasis. Finally conclude all these pharmacokinetic parameters are 100% human acceptable range.

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