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Repositioning the Bioactive Compounds Isolated from *Bauhinia Galpinii* Leaves as Potential Inhibitors Against Human Immunodeficiency Virus (HIV) II Protease Through Application of *In Silico* Studies

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Abstract *The global health implication of human immunodeficiency virus (HIV) II protease has posed an unmatched health challenge provoking increasing interest in search, design and development of new. Therapeutic agents with the capacity to curb the spread of the disease. The bioactive compound in the leaf extract of Bauhinia galpiniiand were investigated for inhibitory activity against human immunodeficiency virus (HIV) II protease using molecular docking technique. Result obtained from the docking analysis revealed that 24-isopropylcholest-5-en-3, 8-diol-1hsh interacted with binding energies of -5.6 Kcal/mol and was selected as the lead molecule. This molecule was observed to interact with PRO81, ILE84, ALA28, ASP29, ASP30, ILE32, MET76, VAL47, GLY48, GLY49 and ILE50 within the active site of the 1hsh. ADME prediction revealed that the lead molecule obeys the Lipinski rule without any violation and had a 0.55 bioavailability score. The blood-brain barrier (BBB) permeant and gastrointestinal absorption (GI) were hindered and low, respectively. The study concluded that 24-isopropylcholest-5-en-3, 8-diol is a promising candidate for the development of HIV drug.*
Key Words: *Morus alba, molecular docking, ADMET, bioactive compound*

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1.0 Introduction

Bauhinia galpinii (Fabaceae), commonly known as "Pride of De Kaap" or Pride of the Cape due to its attractive nature. It is commonly found in some parts of Eastern and Southern Africa. However, the plant originated from South Africa (Aderogba *et al*., 2007; Erhabor *et al*., 2020). *Bauhinia galpinii* is a shrub (creeper) and belongs to the Fabaceae family. Besides its usage as a garden plant, different part of *Bauhinia galpinii* are extensively used in folk medicine to treat a variety of ailments. Available literature reveals that the leaf of the plant is often used by alternative medical practitioner to manage epilepsy and convulsions (Risa *et al.*, 2004), diarrhoea and infertility are commonly treated using the bark and leaves of *Bauhinia galpinii.* The seeds are also used to treat amenorrhoea (Van Wyk & Gericke, 2000) while the root are useful for the treatment of stomach spasms and infertility challenge (Arnold & Gulumian, 1984). The tuber is used to treat pneumonia, venereal disease and diarrhoea (Van Wyk & Gericke, 2000). The treatment of diabetes, inflammation, gastrointestinal tract (GIT) disorders and infectious diseases are commonly achieved using *Bauhinia* species (Ahmed *et al*., 2012; Filho, 2009) (Ahmed *et al*., 2012; Filho, 2009). In a bid to define the pharmacological characteristics of *Bauhinia galpinii,* by several researchers, findings indicate that its leaves contain antiepileptic, antimutagenicity antioxidant, antimicrobial, and cytotoxicity properties (Aderogba *et al*., 2007; Reid *et al*., 2006; Risa *et al*., 2004).

In 1981 acquired immunodeficiency syndrome (AIDS) was recognized and was reported to be caused by human immunodeficiency virus (HIV-1). The high degree of human immunodeficiency virus replication results in high viral load and immune-mediated destruction of the key immune effector cell (CD4 lymphocyte). Different strain of HIV tend to vary and dominate with geographical location. Consequently, subtype B is most prevalent in the Americas and Europe, subtype C accounts for half of all strains identified globally. However, the exact mechanism underlying the CD4 decline in HIV patient is not fully understood (Lewthwaite & Wilkins, 2009). Owing to its global spread and health implication, HIV/AIDS was declared a pandemic on the 5th of June 1981. Currently, researches on discovery of new active antiretroviral therapy (HAART) with better activity and possibility of complete cure is ongoing and is receiving global research attention. Record from WHO (2007) reveals that globally, 33.2 million people are living with HIV/AIDS while 2.5 million new cases and 2.1 million deaths have also been estimated. Generally, the major routes of transmission of this virus are through sexual (heterosexual) intercourse, parenterally (from mother to child), blood or blood product recipients, illicit drug-use and occupational injury. According to Lewthwaite & Wilkins (2009), there is currently no vaccine/drug has been reported to have the capacity to truncate the viral replication of this virus (Lewthwaite & Wilkins, 2009) indicating that there is still a research vacuum on the discovery and trial of new drugs with the hope of finding better options. Therefore, the aim of this study is to repurpose the bioactive compounds in *Bauhinia galpinii* leaves as potential inhibitors against human immunodeficiency virus (HIV) II protease using the molecular docking technique.

2.0 Materials and Methods

2.0 Receptor and ligand preparation

The chemical structure of the bioactive compounds was built using ACD/ChemSketch 2018.2.5 Freeware version. The 2D conformation of the bioactive compounds was converted into their 3D forms. Thereafter, the molecules were optimized using the MMF94 force field on Avogadro interface (Hanwell *et al.*, 2012). The dock-prep tools on the UCSF Chimera interface were used to prepare the optimized chemical structures before the molecular docking step. The crystallized structure of human immunodeficiency virus (HIV) II protease complexing with a L-735,524, an orally bioavailable inhibitor (ID: 1hsh) with 1.9 Å resolution was retrieved from the Protein Data Bank (https://www.rcsb.org). The structure of the human immunodeficiency virus (HIV) II protease consist of four distinct chains bounded to small chemical residues (MK1). The preparation of the biological target (1hsh) was performed on the UCSF Chimera interface (Pettersen *et al*., 2004).

2.2 Molecular docking

Molecular docking simulation was performed using AutoDockVina software (Morris *et al*., 1998). Specific docking of the ligands to the active site of the human immunodeficiency virus (HIV) II protease (ID: 1hsh) was achieved by generating grid box coordinate of the ligand to be substituted on the receptor. The grid box that defines the pocket of 1hsh receptor was designed by making use of AutoDock Vina functionality on UCSF Chimera interface (Pettersen *et al*., 2004). The grid box size and centre coordinates for the 1hsh were x(11.1811, 14.871)Å, y (0.52812, 12.0096)Å and z (9.07564, 16.4572)Å respectively. The bioactive compound with the highest binding affinity for the human immunodeficiency virus (HIV) II protease (ID: 1hsh) was selected for further *in silico* ADME analysis.

Fig 1: The crystalized structure of human immunodeficiency virus (HIV) II protease (ID:1hsh).

2.3 Validation and ADME analysis of lead molecule

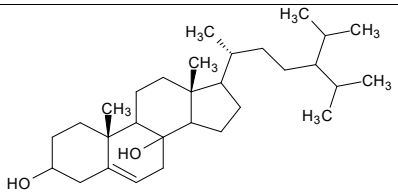
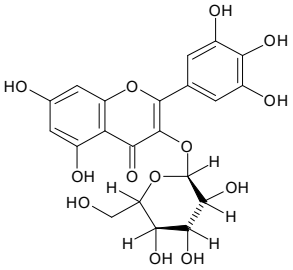
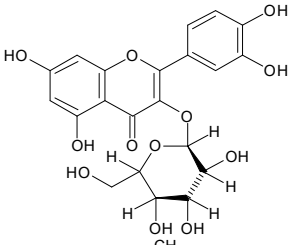
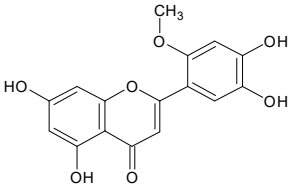
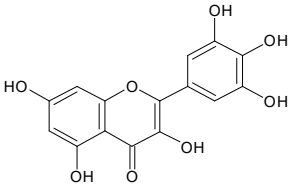
It is imperative to evaluate phenotypical side effects or potential cross-reactivity caused by the action of small biomolecules in molecular simulation of ligand-receptor interaction *(Gfeller et al*., 2014; Keiser *et al*., 2007). The online web server, SWISS-ADME (Adsorption, distribution, metabolism and excretion) was used to predict the drug-likeness, solubility uniqueness and pharmacokinetics characteristics of the lead molecule (https://www.swissadme.ch).

3.0 Results and Discussion

3.1 *Docking scores*

Chemical identity (structure and IUPAC name) as well as docking score obtained for the isolated compounds are presented in Table 1.

Table 1: 2D chemical structure of bioactive compound isolated from the leaf extract of *Bauhinia galpiniiand* their corresponding Glide score (G-Score) value calculated for the related query

Code	Names	Score *ΔG (Kcal/mol)	Stucture
CPD1	24-Isopropylcholest-5-en-3, 8-diol	-7.3	
CPD2	Myricetin-3-O-beta galactopyranose	-7.2	
CPD3	Quercetin-3-O-beta galactopyranose	-6.9	
CPD4	5, 7, 4', 5' tetrahydroxy-2-methoxyflavone (Isoetin 2'-methyl ether)	-6.9	
CPD5	3, 5, 7, 3' 4', 5' Hexahydroxyflavone (Myricetin)	-6.8	

In this study, six compounds reported to have been isolated from the leaf extract of *Bauhinia galpiniiand* were studied to evaluate their binding potential against human immunodeficiency virus (HIV) II protease. The docking study revealed that CPD1 (24-Isopropylcholest-5-en-3, 8-diol),

CPD2 (Myricetin-3-O-beta galactopyranose), CPD3 (Quercetin-3-O-beta galactopyranose), CPD4 (5, 7, 4', 5' tetrahydroxy-2-methoxyflavone), CPD5 (3, 5, 7, 3' 4', 5' Hexahydroxyflavone) and CPD6 (3, 5, 7, 3' 4' Pentahydroxyflavone) had a favourable predicted docking score of -7.3 kcal/mol, -7.2 kcal/mol, -6.9 kcal/mol, -6.9 kcal/mol, -6.8 kcal/mol and -6.6 kcal/mol respectively. Owing to the highest minimum energy of 24-isopropylcholest-5-en-3, 8-diol, CPD1 was selected as the lead molecule. Fig 2 showed that the lead molecule had intermolecular ligand-receptor interactions with PRO81, ILE84, ALA28, ASP29, ASP30, ILE32, MET76, VAL47, GLY48, GLY49 and ILE50 at the active site of the target. On the other hand, the second-best compound (24-Isopropylcholest-5-en-3, 8-diol) was noticed to interact with 21 amino acid residues and they including PRO81, ILE84, ALA28, ASP29, ASP30, ILE32, MET76, VAL47, GLY48, GLY49, ILE50, ASP25, SER31, ASP79, THR80, ILE82, LEU 23, GLY51, GLY 52, PHE and ILE 54. Hydrogen bonds formation was observed for ASP 30 and THR80 residues (see Fig 3). Quercetin-3-O-beta galactopyranose was also observed to interact with ASP30, ILE32, ASP25, VAL47, PRO81, ILE84, ILE82, GLY27, ALA28, ASP29, GLY48, GLY49, ILE54 and THR80 residues which led to the formation of hydrogen bonds with ASP30 and ASP25 (Fig 4). Fig 5 displayed the 5, 7, 4', 5' tetrahydroxy-2-methoxyflavone-1hsh interaction with PHE53, ILE54, GLY52, PRO81, ILE84, ILE50, GLY27, ALA28, ASP29, ASP30, ILE32, ASP79, VAL47, GLY48, GLY49 and THR80 residues with three hydrogen bonds formation. However, 3, 5, 7, 3' 4', 5' hexahydroxyflavone formed interacted with 13 amino acids (ILE54, PRO81, ILE84, GLY27, ALA28, ASP29, ASP30, ILE32, ASP79, VAL47, GLY48, GLY49, ILE50 and THR80) with a single H-bond (see Fig 6). Finally, 3, 5, 7, 3' 4' Pentahydroxyflavone was noticed to interact with 12 amino acids (ASP25, VAL28, ILE54, PRO81, ILE84, ASP29, ASP30, VAL47, GLY48, GLY49, ILE32 and THR80) (see Fig 7).

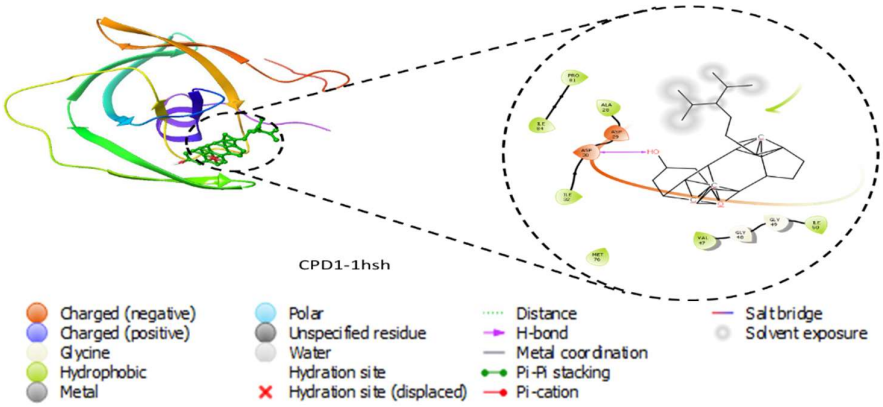


Fig. 2. The 3D X-ray crystal structure of 1hsh complex with CPD1 showing also the binding site region and the residues that constitute this binding site region.

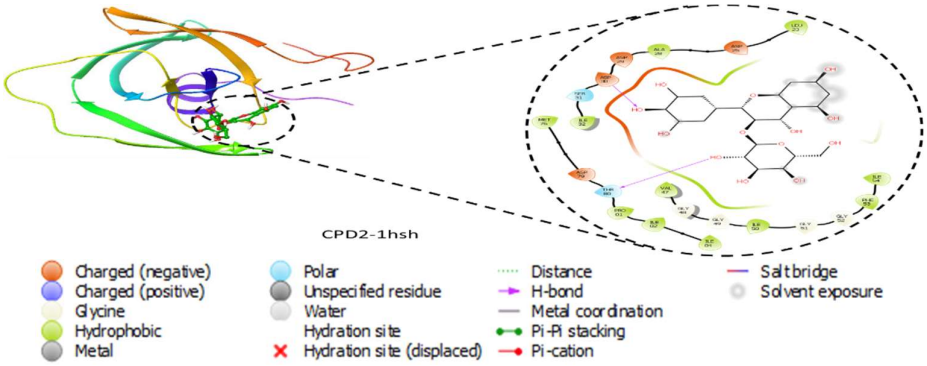


Fig. 3 The 3D X-ray crystal structure of 1hsh complex with CPD2 showing also the binding site region and the residues that constitute this binding site region.

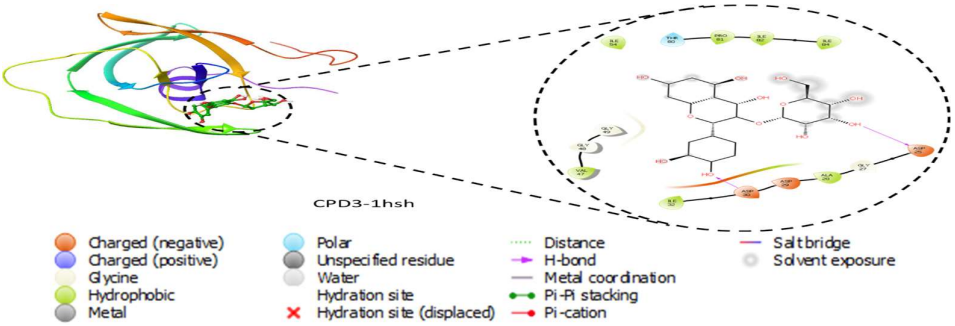


Fig. 4. The 3D X-ray crystal structure of 1hsh complex with CPD3 showing also the binding site region and the residues that constitute this binding site region.

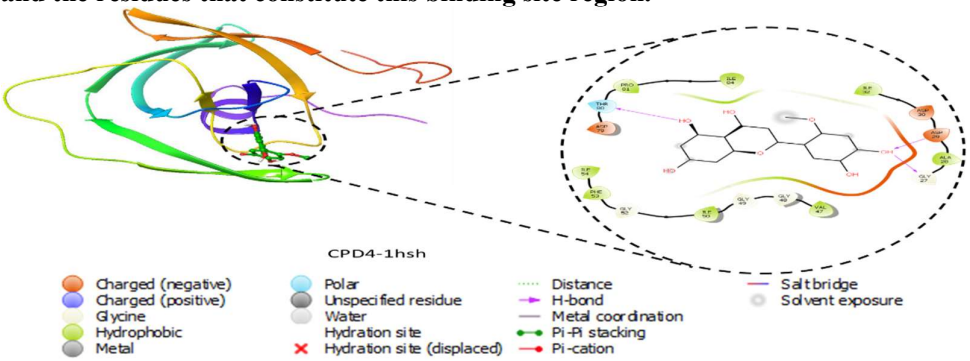


Fig. 5. The 3D X-ray crystal structure of 1hsh complex with CPD4 showing also the binding site region and the residues that constitute this binding site region.

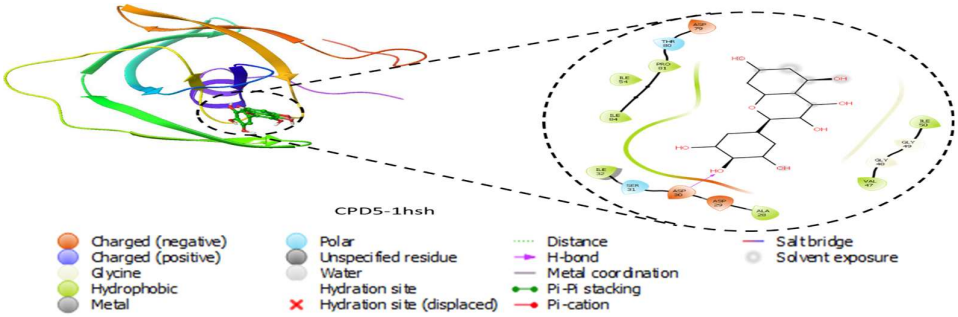


Fig. 6. The 3D X-ray crystal structure of 1hsh complex with CPD5 showing also the binding site region and the residues that constitute this binding site region.

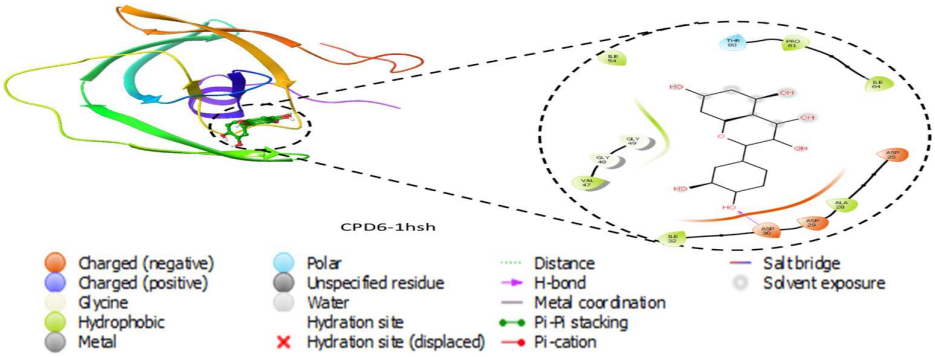


Fig. 7. The 3D X-ray crystal structure of 1hsh complex with CPD6 showing also the binding site region and the residues that constitute this binding site region

3.2 ADME assessment of potential human immunodeficiency virus (HIV) II protease inhibitors

The physicochemical space employed for the ADME prediction of 24-Isopropylcholest-5-en-3, 8-diol is displayed in the coloured zone of the bioavailability radar shown in Fig. 8.

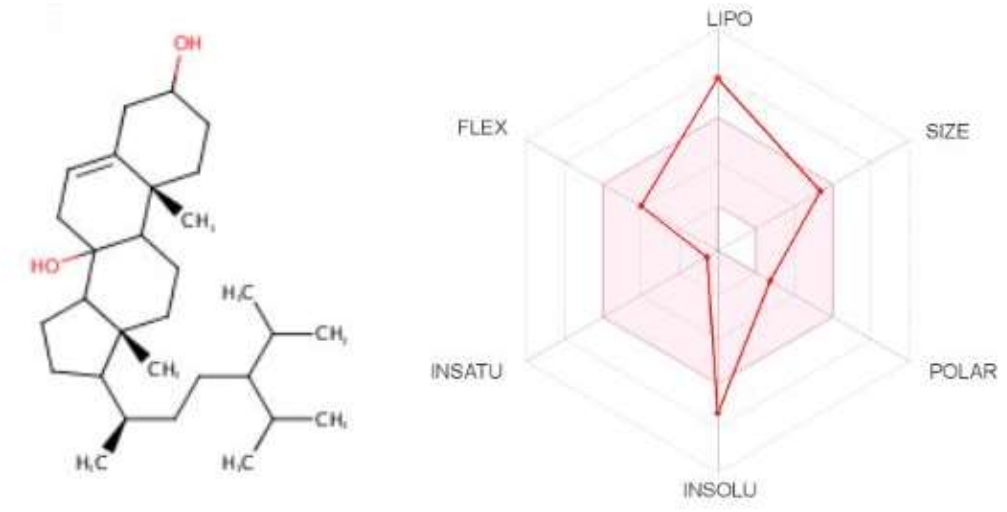


Fig. 8. The bioavailability radar of 24-Isopropylcholest-5-en-3, 8-diol using Swiss ADME predictor.

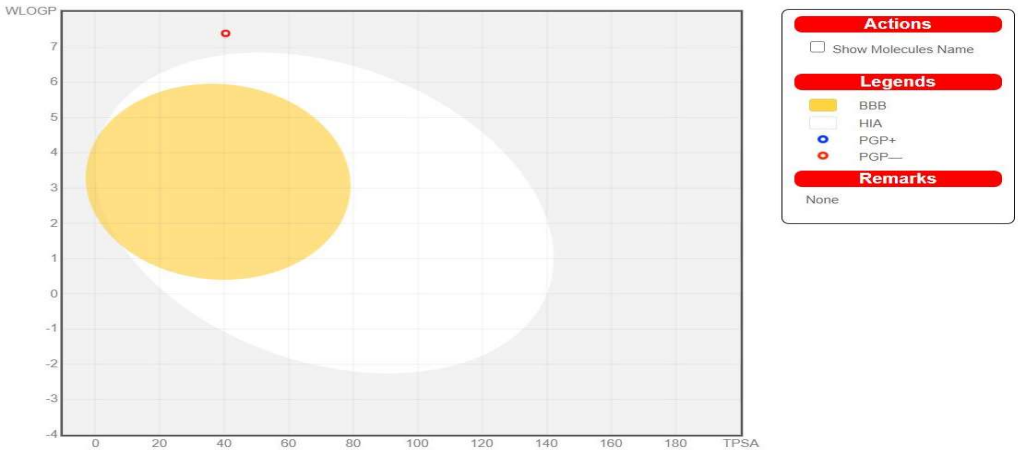


Fig. 9. Molecule falling in egg's yolk prediction 24-Isopropylcholest-5-en-3, 8-diol.

The prediction of absorption, distribution, metabolism and elimination (ADME) profile of drug candidates before their synthesis, is better, cheaper and provides accurate results quickly. This also eliminates wasting of financial resources. The ADME prediction of the lead molecule was (24-Isopropylcholest-5-en-3, 8-diol) was performed using SWISSADME online webserver. The physiochemical properties of the 24-Isopropylcholest-5-en-3, 8-diol included 32 heavy atoms, 2 hydrogen bond acceptors, 2 hydrogen bond donors, molar refractivity of 139.24 and topological polar surface area (TPSA) of 40.46 $Å^2$. The lipophilicity indices of 24-Isopropylcholest-5-en-3, 8-diol was also calculated and the results obtained were iLOGP = -5.12, XLOGP3 = ~~is~~ 8.16, WLOGP = ~~is~~ 7.39, MLOGP = ~~is~~ 6.00, SILICOS-IT = ~~is~~ 6.79 and Consensus P0/W = 6.69.

Table 2: Water solubility of 24-Isopropylcholest-5-en-3, 8-diol.

Log *S* (ESOL)		-7.34
	Solubility	$2.02e^{+05}$ mg ml^{-1}; $4.55e^{-08}$ mol ml^{-1}
	Class	Poorly soluble
Log *S* (Ali)		-8.87
	Solubility	$6.02e^{-07}$ mg ml^{-1}; $1.35e^{-9}$ mol ml^{-1}
	Class	Poorly soluble
Log *S* (SILICOS-IT)		-5.83
	Solubility	$6.52e^{-04}$ $mgml^{-1}$; $1.47e^{-06}$ mol ml^{-1}
	Class	Moderately soluble

24-Isopropylcholest-5-en-3, 8-diol was observed to obeys Lipinski's rule with a violation, it also obeyed Veber score rule. However, Ghose did ~~was~~ not obeyed with ~~3~~-violation. A similar trend was observed for Egan and Muegge score rules but with a violation. (Table 4). Meanwhile, 24-isopropylcholest-5-en-3, 8-diol was observed to have a 0.55 bioavailability score. The blood-brain barrier (BBB) permeant and gastrointestinal absorption (GI) were hindered and low, respectively. Hence, for clarity, the BBB and GI were better demonstrated using the molecule falling in egg's yolk model as shown in Fig. 9. As listed in Table 2, the solubility of 24-isopropylcholest-5-en-3, 8-diol was moderately soluble in the solvent employed for the assay. Isoenzymes such as CYP1A2, CYP2C19, CYP2D6, CYP3A4 and CYP2C9 were not inhibited by 24-isopropyicholest-5-en-3, 8-diol. This suggests that the elimination of drug-drug interaction may lead to cytotoxicity. Hence, 24-isopropylcholest-5-en-3, 8-diol have demonstrated moderate ADME characteristics and can be projected as a therapeutic agent for clinical trials on human immunodeficiency virus (HIV) II protease.

Table 3. Pharmacokinetics of 24-Isopropylcholest-5-en-3, 8-diol.

GI adsorption	Low
BBB permeant	No
P-gp substrate	No
CYP 1A2	No
CYP2C19	No
CYP2C9	No
CYP2D6	No
CYP3A4	No
Log Kp (skin permeation)	-3.22 cm s^{-1}

Table 4. Druglikeness of 24-Isopropylcholest-5-en-3, 8-diol.

Lipinski	Yes, 0 violation MLOGP>4.15
Ghose	No; 3 violation: WLOGP>5.6, MR>130, atoms>7o
Veber	Yes
Egan	No; 1 violation: WLOGP>5.8
Muegge	No; 1 violation: XLOGP3>5
Bioavailability score	0.55

4.0 Conclusion

In summary, molecular docking and SWISS-ADME tools were successfully used to determine the best bioactive compound isolated from the leaf extract of *Bauhinia galpiniiand* against human immunodeficiency virus (HIV) II protease. Among the studied 6 phytochemicals previously reported, 24-isopropylcholest-5-en-3, 8-diol show the highest binding affinity and strong interactions within the pocket of 1hsh *via* non-covalent interactions, such as hydrogen bonding, hydrophobic, and electrostatic interactions. Meanwhile, the ADME characteristics of 24-Isopropylcholest-5-en-3, 8-diol revealed favourable pharmacokinetics and druggable characteristics. Hence, it can be concluded that 24-Isopropylcholest-5-en-3, 8-diol have demonstrated druglike characteristics and can be used to design effective antiviral drugs against the human immunodeficiency virus (HIV).

5.0 Acknowledgement

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6.0 Reference

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