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RESEARCH ARTICLE

Molecular Modeling of Anti-Alopecia Compounds Found in *Sauropus Androgynus*

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Abstract

People in the village of Mak Kemas, Malaysia use the katuk leaves (*Sauropus androgynus*) to prevent anti-alopecia. It was thought that katuk leaves have secondary metabolites which could accelerate the growth of new hair. The objective of this study was to determine the molecular modeling of compounds contained in katuk leaves (*Sauropus androgynous*) providing docking and ADMET information in silico as anti-alopecia drugs. In this study, receptors were used (PDB code: 4K7A) derived from protein data banks (http://www.rscb.org/pdb) and visualized with Discovery Studio and tested 10 compounds that had the potential as ligands to prevent baldness. Molecular modeling of bioactive compounds was carried out by molecular docking computation using AutodockTools 1.5.6 and Pre-Admet to determine absorption, distribution, and toxicity. The results were an amino acid residue that showed the place-bound to the receptor, inhibitory constant (Ki), and free energy bonds (Δ G**).** Of the 11 compounds studied, 3 were 5-Alpha-Dihydrotestosterone; Finasteride; and Pyrene interacts well so that it could prevent baldness. From the results of docking and pre-admet that had been done, it concluded that the compounds contained in katuk leaves could be used as candidates for anti-alopecia drugs.

Keywords: *Anti-alopecia, ADMET, In-silico, Katuk Leaf, Sauropus androgynus.*

Introduction

Katuk leaf *(Sauropus androgynus*) is a plant that has been traditionally believed by the people of the village of Mak Kemas, Malaysia to overcome the problem of hair loss/baldness and hair nourishment. Topical use of katuk leaves obtained from the process of katuk leaves which are pounded with milk [1]. Hair loss that can affect 50% of men aged 18-40 years is called androgenetic alopecia (AGA).

Stressful events for patients cause considerable hair loss. Androgens and genetic factors play an important role in the pathogenesis of this disease. In the literature, it is confirmed that androgens are predominantly involved primarily in dihydrotestosterone (DHT). The enzyme 5 alpha-reductase works to convert testosterone to DHT. Some compounds used for alopecia treatments are finasteride, minoxidil, and dihydrotestosterone (DHT) [2]. The androgen hormone that binds to androgen receptors and has a greater potential for signal receptor induction than testosterone is Dihydrotestosterone (DHT). This steroid hormone is in the testes, hair follicles, and adrenal glands. This hormone plays a role in hair growth but the excess production of DHT can cause the risk of androgenic alopecia, acne, benign prostatic hyperplasia, prostate cancer, and hirsutism [3]. Finasteride and Minoxidil are 2 drugs that are pharmacologically chosen for baldness treatment.

Minoxidil is usually used topically. The increase in the duration of hair follicles in the anagen phase is caused by minoxidil. In dermal papilla, minoxidil stimulates prostaglandin production. Finasteride is usually given orally which has the activity of regrowing hair and reducing hair loss. But finasteride can reduce ejaculation and libido and cause erectile dysfunction in men. This drug is also not indicated for women and is contraindicated in pregnant women [4]. The use of these two synthetic drugs causes side effects such as erythema, skin irritation,

allergies, itching, and dermatitis. That's why herbal medicine is preferred for treating hair loss and stimulating hair growth. This study reports the molecular modeling of anti-alopecia compounds found in S. androgynus as a continuation of our previous studies [5, 6].

Material and Methods

Material

Hardware

Laptops-KHHGFQSN with specifications processor INTEL(R) Core (TM) i7-9750H CPU 2.60 GHz, 2.59 GHz, and memory 8GB RAM.

Software

Operating system Windows 10 Home Single Language with Bing 64-bit operating system, x64 based processor, Chem3D Pro 12.0, ChemDraw Ultra 12.0, Discovery Studio 2016 Client®, AutoDock Tools 1.5.6, Pre-ADMET.

Methods

Preparation of Receptors and Ligands

Receptor preparation for anti-alopecia was done by downloading the GDP code: 4K7A receptors derived from protein data banks [7] and visualized with Discovery Studio. In this program, water and natural ligands were removed from the receptors. Pure receptors were then stored in PDB (.pdb) format [8].

Ligand preparation for 6-Piperidin-1-Ylpyrimidine-2, 4-Diamine 3-Oxide Minoxidil and 5-Alpha-Dihydrotestosterone as natural ligands obtained from PDB and draw structures that were found using ChemDraw Ultra 12.0. Then the structure was minimized energy using Chem3D Pro 12.0 and visualized with Discovery Studio and saved in PDB (.pdb) format [8].

Validation Method

The ligand was reattached to the receptor for the validation method shown by looking at the value of the Root Mean Square Deviation (RMSD), the standard value of the overlapping molecules was ≤ 2.00 Å.

Docking Test Compound With Receptor

AutodockTools 1.5.6 was used for docking ligands and tethered receptors. The standard docking parameter used was the 40x40x40 grid box. Docking simulations were carried out with GA run 100 [3] then the results were obtained using Autodock4, (run-autodock). Then edit cmd by deleting the directory so that it only existed in the cmd column (D: / Autodock / Autodock4 -p dock.dpf -l dock.dlg &) [8]

Molecular Tethering Analysis and Visualization

Notepad saved the output of the docking that had been done. To see the determination of the results indicated by the lowest bond energy (best pose). The orientation and position of the amino acids bound to the ligand were visualized with Discovery Studio.

Predicting the Absorption, Distribution and Toxicity Properties

The Pre-Admet program is accessed at https://preadmet.bmdrc.kr (pre-ADMET, 2020) Anti-alopecia compounds commonly found in some compound and plant synthesis were generally drawn in this program and automatically predicted Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET).

Results and Discussions

Receptor and Ligand

In this research, molecular docking computation was done with an in silico approach. The use code 4K7A receptor (Fig. 1), while the previous study used the PDB of computational chemistry, was useful for providing initial ADMET information on new drug research before further in vivo and in vitro testing was carried out. In this study the PDB cod4C61 to test anti-alopecia activity [9].

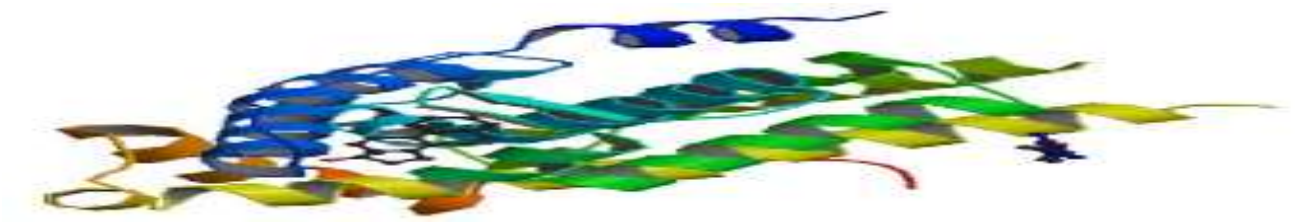


Fig.1: Receptor and ligand of 4K7A

The Auto docks Tools 1.5.6 program was used to determine the position of the ligand in the area of the box located on the receptor called the active site of the receptor (Fig. 2).Setting parameters to determine the size of the box using distance (angstrom). In the 4K7A receptor, the center of the box is x = -2,592; y = 0.864; and z = -6,729 with grid point spacing of 0.375 Angstroms.

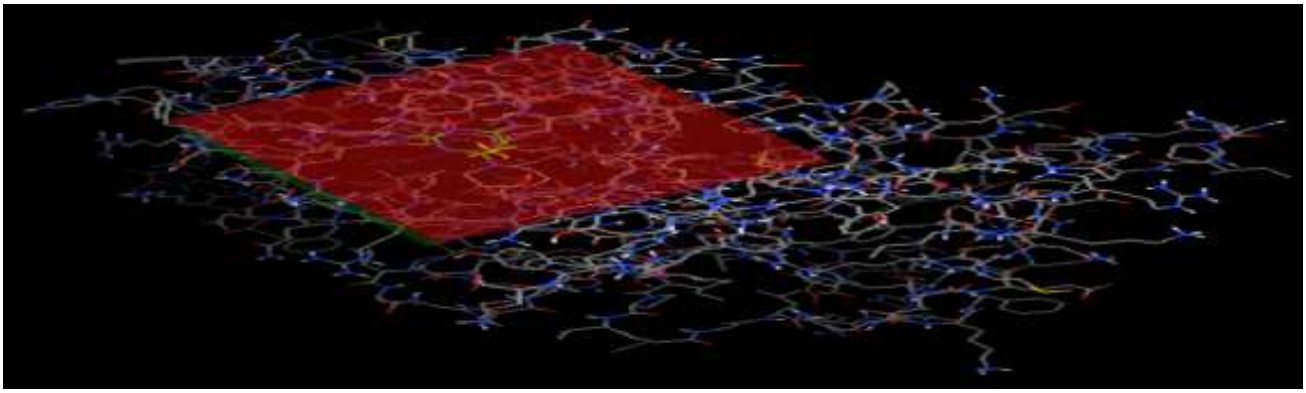
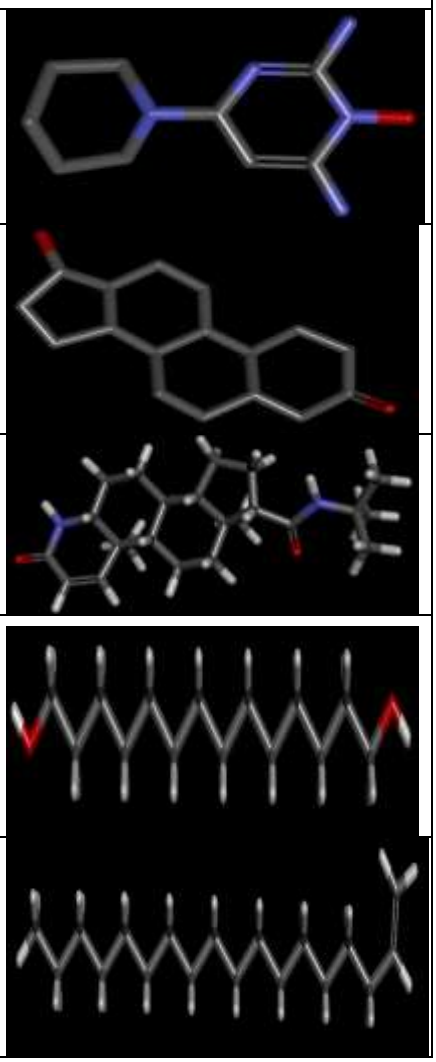
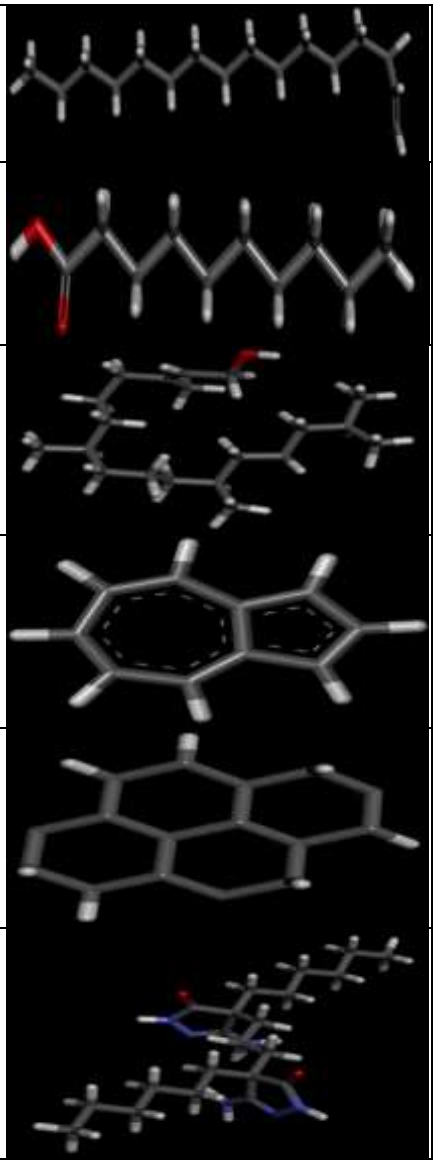


Fig. 2: Receptor and Ligand on Grid Box with AutodockTools 1.5.6

Ligand preparation, katuk leaf compound (Sauropus androgynus) has 7 compounds to be tested. This compound consists of 1, 14-tetradecanediol; Octadec-1-ene; 1-Hexadecene; Decanoic acid; Phytol; Azulene; and Pyrene. 6-Piperidin-1-Ylpyrimidine-2, 4-Diamine 3-Oxide Minoxidil as a comparison drug [9-11].Molecular formula and their structures are given in Table 1.

Table 1: Component of compounds on the native ligand, comparative drug, and test compounds

Compounds	Molecular Formula	Structure
6-Piperidin-1-Ylpyrimidine-2,4-Diamine 3-Oxide Minoxidil	$C_9H_{15}N_5O$	
5-Alpha-Dihydrotestosterone	$C_{19}H_{30}O_2$	
Finasteride	$C_{23}H_{36}N_2O_2$	
1,14-tetradecanediol	$C_{14}H_{30}O_2$	
Octadec-1-ene	$C_{18}H_{36}$	

1-Hexadecene	$C_{16}H_{32}$	
Decanoic acid	$C_{10}H_{20}O_2$	
Phytol	$C_{20}H_{40}O$	
Azulene	$C_{10}H_8$	
Pyrene	$C_{16}H_{10}$	
(4S,4'S)-4,4'-(propane-1,3-diyl)bis(3-amino-4-hexyl-1H-pyrazol-5(4H)-one)	$C_{21}H_{38}N_6O_2$	

Validation Method

Evaluate validation by looking at RSMD results and binding locations. This test parameter was considered valid if RSMD ≤ 2.00 Å [12, 13] which indicated the overlapping position was very close between the copy ligand and the original ligand (see Fig. 3).The validation results obtained in this study were 1.730 Å, this meant that the parameters for docking simulation of test compounds and comparative drugs had fulfilled the specified requirements.

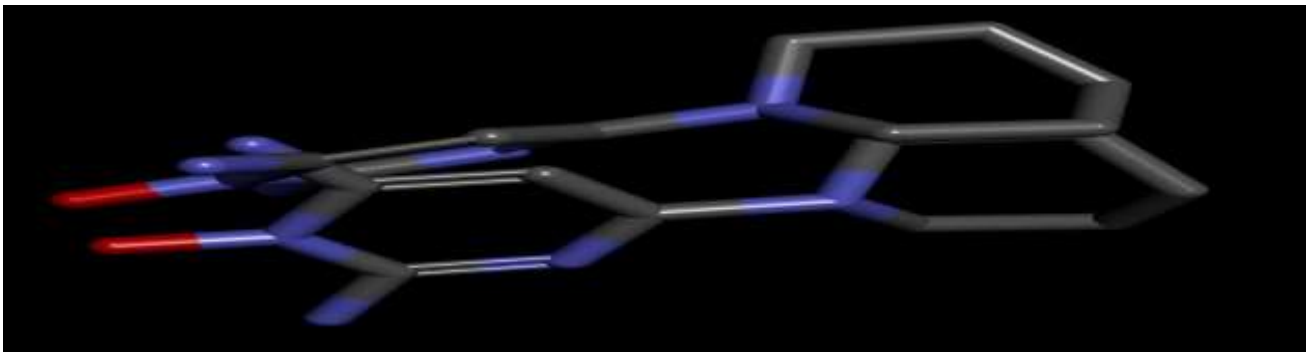


Fig.3: Overlapping position of original and copy ligands using Discovery Studio

Docking Interaction of Test Compounds and Visualization

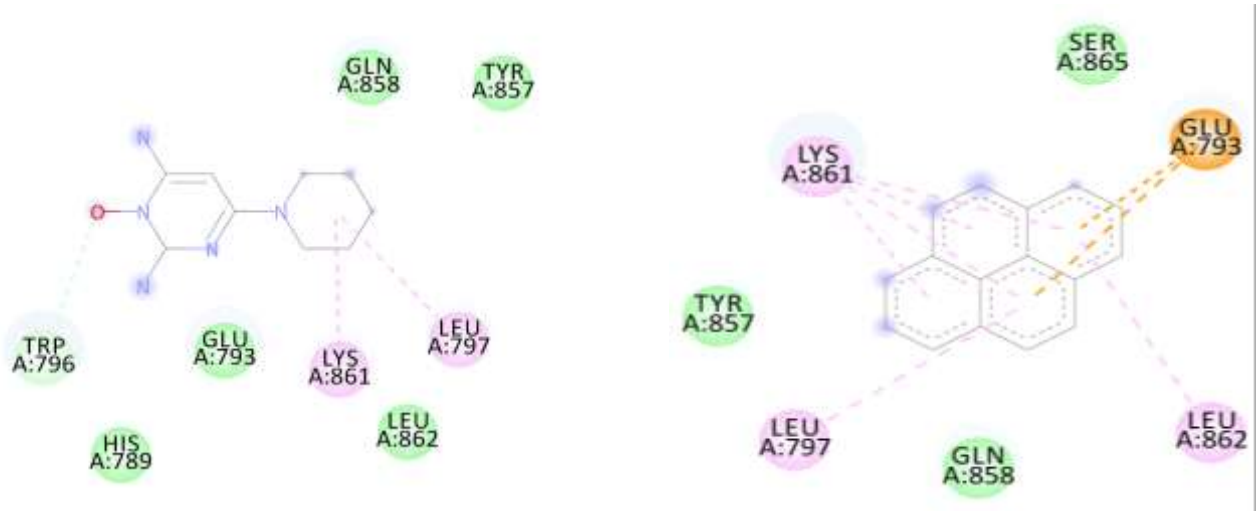
In this study, comparison drugs, natural ligands, and katuk leaf test compounds were performed molecular docking using AutoDockTools 1.5.6 with 40x40x40 box dimensions. The results obtained were an amino acid residue that showed the place-bound to the receptor, inhibitory constant (Ki), and free energy bonds (Δ G) (Table 2).

Table 2: Docking interaction on the comparative drug, native ligands and test compounds

Compounds	Interactions with Amino Acid Residues		Ki	(ΔG)
	Hydrogen Bonds	Van der Waals (hydrophobic)	(μM)	(Kcal/mol)
6-Piperidin-1-Ylpyrimidine-2,4-Diamine 3-Oxide Minoxidil	Hydrogen Bonds: TRP 796; Carbon Hydrogen Bonds: LYS 861; LEU 797	HIS 789; GLU 793; GLN 858; TYR 857; LEU 862	286.72	-4.83
5-Alpha-Dihydrotestosterone	Hydrogen Bonds: No; Carbon Hydrogen Bonds: TYR 857; LYS 861	GLN 858; LEU 797; LEU 862; SER 865; GLU 793; LEU 790	30.92	-6.15
Finasteride	Hydrogen Bonds: SER 865; Carbon Hydrogen Bonds: LEU 862; HIS 789; LYS 861; LEU 797; TYR 857	LEU 790; GLU 793; GLN 858	8.31	-6.93
1,14-tetradecanediol	Hydrogen Bonds: GLU 793; Carbon Hydrogen Bonds: No	TRP 796; LEU 797; HIS 789; GLN 858; SER 865; LEU 790; LEU 862; LYS 861	9790	-2.74
Octadec-1-ene	Hydrogen Bonds: No; Carbon Hydrogen Bonds: TRP 796; HIS 789; LEU 790; LEU 862	LEU 797; GLN 858; LYS 861; SER 865; GLU 793	10140	-2.72
1-Hexadecene	Hydrogen Bonds: No; Carbon Hydrogen Bonds: LYS 861; ARG 854; TYR 857	SER 865; ASP 864; GLU 793; LEU 862; LEU 797;GLN 858	5410	-3.09
Decanoic acid	Hydrogen Bonds: ARG 854; Carbon Hydrogen Bonds: LEU 862; LYS 861	SER 865;GLU 793; LEU 797; GLN 858; TYR 857	762.76	-4.25
Phytol	Hydrogen Bonds: HIS 789; GLU 793; Carbon Hydrogen Bonds: LYS 861; TRP 796; PRO 868	TYR 857; LEU 862; LEU 797; GLN 858; HIS 917; ASP 864; SER 865	1310	-3.93
Azulene	Hydrogen Bonds: No; Carbon Hydrogen Bonds: LYS 861; LEU 862; GLU 793	GLN 858; LEU 797; SER 865	835.04	-4.2
Pyrene	Hydrogen Bonds: No; Carbon Hydrogen Bonds: LYS 861; LEU 797; LEU 862; GLU	TYR 857; GLN 858; SER 865	107.97	-5.41

	793			
(4S,4'S)-4,4'-(propane-1,3-diyl)bis(3-amino-4-hexyl-1H-pyrazole-5(4H)-one)	Hydrogen Bonds: GLN A 858; Carbon Hydrogen Bonds: LYS A 861	SER A 861; GLU A 793; LEU A 797; LEU A 867; TYR A 857	974.31	-4.11

The results of the docking interactions obtained in Table 2 showed that the inhibition constants and free energy bonds that could potentially be anti-alopecia drugs on katuk leaves were pyrene compounds, where the value of ΔG (-5.41 Kcal/mol) and Ki 107.97 μM. then compared with the values obtained in the drug comparison compounds of 6-Piperidin-1-Ylpyrimidine-2, 4-Diamine 3-Oxide Minoxidil, where the values of ΔG (-4.83 Kcal/mol) and Ki (286.72 μM). This implied that the pyrene compound contained in katuk leaves had potential as a drug candidate for anti-alopecia because the ΔG and Ki it had was smaller than 6-Piperidin-1-Ylpyrimidine-2,4-Diamine 3-Oxide Minoxidil significantly had an interaction that was significantly more spontaneous. Smaller free energy bonds (ΔG) indicated that ligands could easily bind to receptors and were able to inhibit constants. Whereas Ki shows the affinity of ligands in binding to receptors. Other results were shown on 5-Alpha-Dihydrotestosterone and Finasteride which had a greater G and Ki than others [14]



(a) (b)

Fig. 4: Residue of amino acids from (a) minoxidil and (b) Pyrene

Also, Table 2 showed the interaction of amino acid residues in 6-Piperidin-1-Ylpyrimidine-2, 4-Diamine 3-Oxide Minoxidil and pyrene with hydrogen bonds and van der Waals bonds they have. Then visualized with 2D images in Fig. 4.

Table 3: Result of compounds screening based on Lipinski Rule of Five

Compounds	BM	Log P	Hydrogen Donors	Hydrogen Acceptors	Molar Refractivity	Description
6-Piperidin-1-Ylpyrimidine-2,4-Diamine 3-Oxide Minoxidil	312	-0.053101	5	6	77.145782	meet the requirement
5-Alpha Dihydrotestosterone	260	0.110620	0	2	70.199997	meet the requirement
Finasteride	372	3.814499	2	4	106.842346	meet the requirement
1,14-tetradecanediol	230	3.652199	2	2	69.575569	meet the requirement
Octadec-1-ene	252	7.043802	0	0	85.125969	did not meet the requirements
1-Hexadecene	224	6.263601	0	0	75.891975	did not meet the requirements
Decanoic acid	172	3.211699	1	2	50.245785	meet the requirement
Phytol	296	6.364101	1	1	95.561760	did not meet the requirements
Azulene	128	2.455750	0	0	43.412994	meet the requirement
Pyrene	202	4.476799	0	0	70.381981	meet the requirement
(4S,4'S)-4,4'-(propane-1,3-diyl)bis(3-amino-4-hexyl-1H-pyrazole-5(4H)-one)	406	2.874299	6	8	115.765167	meet the requirement

Lipinski rule of five is a rule that gives a difference between drug and non-drug molecular compounds. This rule can provide a high probability of failure or success due to molecular similarities according to 2 or more of the following rules: Molecular mass less than 500 Daltons, High lipophilicity (expressed as LogP less than 5, Less than 5 hydrogen bond donors, Less than 10 squares hydrogen bonds, and molar refractivity must be between 40-130 [15].

Pre-ADMET

ADME and Toxicity prediction was done as a material for selecting drug candidates based on their pharmacokinetic parameters. Predicted traits included absorption of skin cells (Caco-2) as a potential identification of drugs for transdermal or oral delivery, absorption of the human intestine (% HIA) and distribution, namely BBB Penetration (Barrier brain blood) and PPB (Protein-Plasma binding). Prediction of toxicity in silico was very important in drug discovery and development because many drugs fail because of this. This was very important because it guarantees safety during drug use [16]. AdmetSAR programs were accessible in http://www.admetexp.org. The structure of all compounds converted into molfile (*.Mol).

The program automatically calculated predictive absorption to Caco-2 cells, HIA (human intestinal absorption), and plasma protein binding [17, 18]. Predicting toxicity properties performed using the free software and uses the Toxtree Benigni/Bossa rule-based method, for mutagenicity and carcinogenicity [19-21]. Tabel 3 showed PreAdmet results of tested compounds.

Tabel 3: Pre-ADMET

Compounds	Absorption		Distribution		Mutagenic	Carcinogenic
	HIA (%)	Caco-2 (nm sec^{-1})	PPB (%)	BBB		
6-Piperidin-1-Ylpyrimidine-2,4-Diamine 3-Oxide Minoxidil	82.1139	0.1701	70.6662	0.2672	+	-
5-Alpha-Dihydrotestosterone	95.4445	20.9615	100	3.7245	-	+
Finasteride	93.0715	22.3272	90.9829	1.5732	-	+
1,14-tetradecanediol	89.5998	23.0814	100	7.9572	-	-
Octadec-1-ene	100	23.0054	100	24.9129	-	-
1-Hexadecene	100	23.0054	100	24.6372	-	-
Decanoic acid	95.6759	19.7466	100	0.72028	+	+
Phytol	100	37.6292	100	19.0797	-	+
Azulene	100	23.4418	100	2.4997	+	+
Pyrene	100	23.4427	100	2.9437	+	+
(4S,4'S)-4,4'-(propane-1,3-diyl)bis(3-amino-4-hexyl-1H-pyrazole-5(4H)-one)	70.383194	21.0948	93.264598	0.451659	+	-

Based on the literature absorption of% HIA, the value of 0-20% was not good in returning absorbed compounds, 20 - 70% (enough), and 70-100% (good). In Caco-2 (nm second-1) cell permeability with values <4 nm second-1 (low permeability), 40 - 70 nm second-1 (medium permeability) and> 70 nm second-1 (higher permeability) [22].

In Table 3 the Pre-Admet results show that% HIA of all test compounds is in the range of 70-100%, this indicated a good intestinal absorption of all compounds tested. Then in Caco-2, only 6-Piperidin-1-Ylpyrimidine-2,4-Diamine 3-Oxide Minoxidil had the lowest Caco-2 cell permeability among others while pyrene has sufficient permeability for the drug to be absorbed in the human intestine. Based on the protein-plasma binding distribution parameters in Table 3 showed that all compounds interact with pharmacological targets and diffuse well through the plasma membrane even though 6-Piperidin-1-Ylpyrimidine-2,4-Diamine 3-Oxide Minoxidil has the lowest PPB value that was 70%. Human plasma had albumin (Human Serum Albumin HAS) with 70% protein, lipoprotein and α 1-glycoprotein (AGP) as the main component [23]. Toxicity test results showed that 6-Piperidin-1-Ylpyrimidine-2, 4-Diamine 3-Oxide Minoxidil and pyrene were mutagenic which were harmful to health because they have a direct impact on mutating or damaging DNA. This mutagenic effect might be less if it would be

used as a topical medicine. However in oral use, present of acute lung toxicity of Juice and Soup of Katuk (*S.androgynus*) leaves as breastmilk booster related to bronchiolitis obliterans had been studied by others [24].

Conclusion

The results of 11 compounds that had been screened for computational molecular docking and pre-admet with the in-silico method were from 7 *S.adrogynus* leaf compounds which had the best affinity for anti-alopecia drug candidates was pyrene based on comparison with 6-Piperidin- 1-Ylpyrimidine-2,4-Diamine 3-Oxide Minoxidil.

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