ORIGINAL ARTICLE

Molecular docking studies and ADME-Tox prediction of phytocompounds from *Merremia peltata* as a potential anti-alopecia treatment

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ABSTRACT

Alopecia is a condition in which some or all of the hair from the scalp is lost. One recent preventative measure is the inhibition of the enzyme 5-α-reductase. Inhibition of the enzyme 5-α-reductase converts circulating testosterone to its more potent metabolite, dihydrotestosterone. Ethnobotically, *Merremia peltata* is used as a baldness medicine by utilising compounds contained within the leaves. This research aimed to test activity of 18 known compounds contained within *M. peltata*) as anti-alopecia. Activity was based on their interaction with the androgen receptor (PDB code 4K7a) using molecular docking and ADME-Tox prediction. The stages of research performed were: preparation of androgen protein structure databases; preparation and optimization of three-dimensional structures of compounds using ChemDraw 8.0; molecular docking to the androgen receptor protein using Autodock 1.5.6.; and ADME-Tox prediction using the pkCSM tool. The following test compounds had strong bond energies (ΔG): compound 16 (olean-12-en-3beta-ol, cinnamate)-7.71 kcal/mol, compound 17 (alpha-amyrine)-6.34 kcal/mol, and Finasteride-6.03 kcal/mol. Interestingly, the ΔG of compound 16 (olean-12-en-3beta-ol, cinnamate) is better than of minoxidil (-4.8 kcal/mol) and also to gold-standard treatment compound, finasteride. ADME-Tox prediction for compound 16 showed favorable results in several metrics such as skin permeability, absorption, and distribution. Compound 16 (olean-12-en-3beta-ol, cinnamate) is therefore a potential androgen receptor antagonist and may be beneficial in the treatment of alopecia.

Key words: ADME-Tox, alopecia, enzyme 5-α-reductase, *Merremia peltata,* molecular docking

INTRODUCTION

Alopecia is a medical condition that results in hair loss. In patients, who suffer from alopecia, the underlying abnormalities that cause hair loss are found predominately on the scalp but can extend to all areas of the body.[1,2] In 2014, alopecia was endured by 35 million men and 21 million women worldwide. Alopecia is caused by various factors, including genetics, environmental causes,

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and nutritional factors.[3] One effort to prevent baldness is via inhibition of the enzyme 5-α-reductase using the synthetic drug finasteride; however, continuous finasteride treatment can cause serious side effects such as a reduction in libido.[4] In addition to using synthetic drugs, various other methods can be used to treat alopecia, one of which is the utilization of the compounds contained within the *Merremia peltata* plant, which originates from Indonesia. In ethnobotany, this plant has been used by the people of Konawe, Southeast Sulawesi to treat dandruff and hair growth.[5]

According to Mustarichie *et al.*,[6] an *Erythrina variegate* ethanol extract that contains polyphenol compounds, terpenoids, tannins, saponins, and steroids increases hair growth in male rabbits. Furthermore, an in silico study used chemical modeling to identify compounds extracted from *E. variegate*; they bound Janus kinase 2 (JAK2) and therefore might be effective therapeutic treatments of alopecia.[7] A study that fractionated the extracts of Katuk (*Sauropus androgynus* (L.) Merr.) leaves showed that the ethanol, n-hexane, ethyl acetate, and water fractions stimulated hair growth.[8] In addition, research conducted by[9] showed that ethanol and n-hexane extracts of cocoa peel, also stimulated hair growth in rabbits. The non-polar n-hexane fraction in this study confirmed that the terpenoid and steroid compounds in the waste cocoa peel (*Theobroma cacao* L.). According to Perez *et al.*, Honesty *et al.*, Kondengis *et al.*,[10,11,12] the contents of secondary metabolites found in *M. peltata* leaves are terpenoids, steroids, alkaloids and flavonoids with 18 terpenoid derivatives already identified. Based on research of[6] compounds that have activity as antialopecia were compounds of the terpenoids, flavonoids, and alkaloids. Hence, we hypothesized 18 compounds of terpenoid derivatives identified in *M. peltata* will have an antialopecia activity too. Identification by using GC-MS on research of Kondengis *et al.*[12] for *M. peltata* revealed 18 compounds that we used on this docking study.

Until now, based on literature search, no research already conducted on anti-alopecia and ADMET of *M. peltata*. Hence, we investigate the anti-alopecia activity of *M. peltata* by studying molecular interactions between both terpenoid compounds and steroids isolated from this plant and their target proteins 4K7A. The 4K7A PDB receptor is an androgen receptor that acts as a transcription factor in the regulation of gene expression, especially the development of male sexual phenotypes with natural ligands of dihydrotestosterone (DHT) and minoxidil. Androgens have a profound effect on the growth of human scalp and body hair, such as promoting beard growth but leading to hair loss in androgenetic alopecia (AGA) in males.[13,14] Steroid hormone or DHT cause the baldness process by which has an affinity for the receptor androgens.[15,16]

SUBJECTS AND METHODS

Hardware and software

The hardware included a PC running Windows 7 Home 64-bit operating system, Intel® Core (TM) i5-3337U CPU @ 1.80GHz, NVIDIA Ge Force GTS 710M Graphic Card and 4 GB CPU memory (RAM). Analysis was performed with the following software: Discovery Studio Visualizer, AutoDock Tools 1.5.6 and ADME-Tox pkCSM tools.

Materials

The androgen receptor crystal structure (PDB code 4K7A), obtained from http://www. rcsb. org/pdb, is shown in Figure 1. Data and structures of minoxidil and finasteride were obtained from https://www.pubchem.org. A total of 18 test ligands were obtained from research journals.[12] The structures are shown in Table 1.

Preparation of ligand structure

Test ligand structures of the 18 compounds derived from *M. peltata* leaves,[17] the minoxidil and reference ligand finasteride are shown in Table 1.

Preparation of protein receptor

The crystal structure of the androgen receptor (PDB code 4K7A) was obtained from http/www/pdbbeta. rscb. org/pdb with a resolution of 2.44 Å. Furthermore, the AutoDock Tools 1.5.6 program were used to use to provide a grid box to determine spatial shape and spatial coordinates as docking materials.[18] Androgen receptor crystal structure used were exist with DHT and minoxidil. As DHT is natural ligand that caused baldness process, and minoxidil is a drug that already known protect against baldness, we used minoxidil position in the crystal structure of androgen receptor as position for all docking analysis.

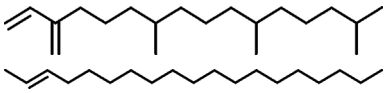
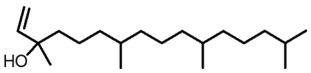
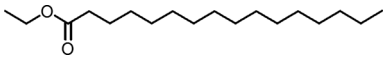
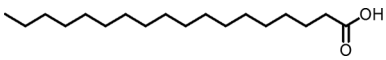
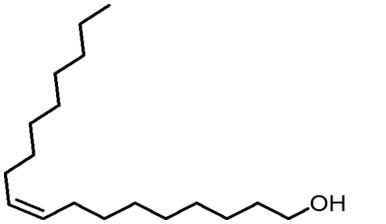
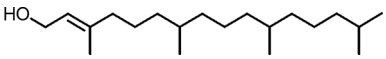
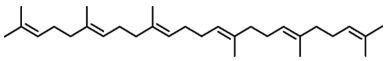
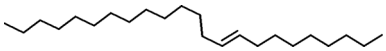
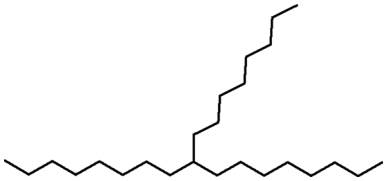
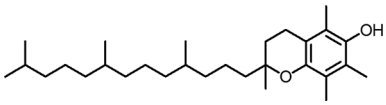
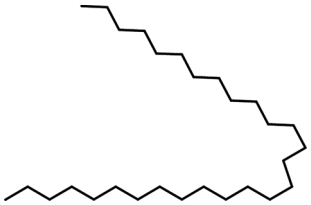
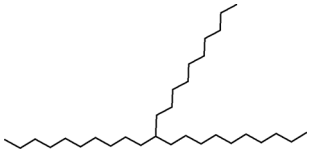
Validation of the molecular docking method

Validation of the molecular docking method is performed by redocking a minoxidil to a target protein that has been removed from androgen receptor using the AutoDock Tools 1.5.6. Docking validation was carried out by redocking the natural minoxidil ligand at the 4K7A androgen receptor by removing the natural DHT and minoxidil ligands contained in the protein receptor which was then adjusted to the grid box position on the natural minoxidil ligand. The redocking process was then carried out to determine the root-mean-square deviation (RMSD) value by overlaying the natural ligand which was separated before docking and the minoxidil natural ligand that had been redocked. The method is deemed successful if the RMSD value returned is ≤3Å.[19]

Docking simulation of the minoxidil, finasteride, and test ligands (phytocompounds extracted from *Merremia peltata* leaves)

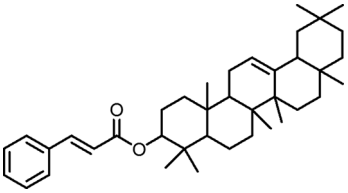
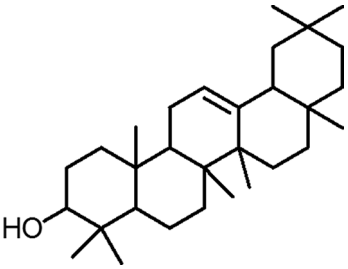
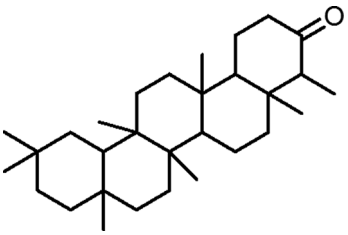
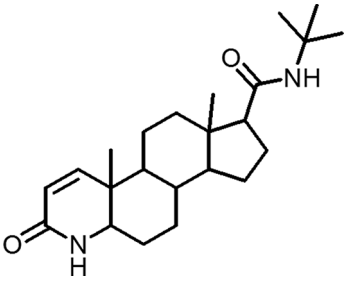
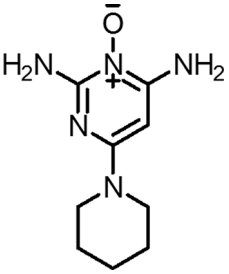
The three-dimensional (3D) structure of ligands was created and optimized using Chem 3D Ultra 8.0 with MM2

Table 1: Two-dimensional structures of minoxidil, finasteride and test ligands derived from the leaves of *Merremia peltata*

Structure	IUPAC name
	Compound 1 neophytadiene
	Compound 2 icosone
	Compound 3 isophytol
	Compound 4 hexadecaneoic acid-ethyl ester
	Compound 5 hexadecaneoic acid
	Compound 6 oleyl alcohol
	Compound 7 L-heptadecene
	Compound 8 (E)-3,7,11,15-tetramethylhexadec-2-en-1-ol
	Compound 9 (Z)-9-tricosene
	Compound 10 squalene
	Compound 11 heneicosane
	Compound 12 octyl heptadecane
	Compound 13 vitamin E
	Compound 14 octacosane
	Compound 15 11-eecyldocosane

Contd...

Table 1: Contd...

Structure	IUPAC name
	Compound 16 olean-12-en-3beta-ol, cinnamate
	Compound 17 alpha-amyrine
	Compound 18 friedeline
	Reference ligand Finasteride
	Natural ligand minoxidil

IUPAC: International union of pure and applied chemistry

semi-empirical method.[17] The structure of the ligands in the pdb format was converted into. pdbqt format using the AutoDock Tools 1.5.6. The docking method was performed by tethering each ligand to androgen receptors using the tether coordinates (Grid Center) x = 40, y = 40, z = 40 Å and the Grid Box size coordinates x = −2.592 y = 0.864 z = −6.729Å. Docking results were assessed for binding energy and chemical interactions.

Discovery studio visualizer

Discovery Studio is a comprehensive software includes functionality for viewing and editing data along with tools for performing basic data analysis suite for analyzing and modeling molecular structures, and sequences. Visualization of docking result was done using Discovery Studio to determine hydrogen bond distance (Å) and nearest amino acid residue.[20]

Prediction of ADME-Tox

The ADME-Tox SAR program is accessed at http://biosig.unimelb.edu.au/pkcsm/prediction.[21] The structure of the generated compound was changed to a smile format using the PubChem program.

RESULTS

Preparation of protein receptor

The androgen receptor binds to natural ligands with chemical bonds. The structure of the androgen receptor and minoxidil is depicted in Figures 2 and 3.

Validation of molecular docking method

The analysis results of the bonds formed are shown in Table 2.

A hydrogen bond between minoxidil and the androgen receptor formed with amino acid SER^{865} and GLU ^{793} of the androgen receptor [Figures 4 and 5].

Docking simulation of minoxidil, finasteride, and test ligands (phytocompounds extracted from *Merremia peltata* leaves)

The analysis of docking simulation was performed for binding energy and hydrogen bond. Docking simulation results are shown in Table 3.

Visualization of the docking interactions that occur between finasteride and compound 16 to the androgen receptor (4K7A) is shown in Figure 6.

ADME-Tox prediction

The pharmacokinetic parameters of absorption and distribution were investigated to select compounds for drug candidates. ADME-Tox prediction values of reference ligand and test ligands (compound 16) are shown in Table 4 meanwhile data from other ligands are not shown.

The ADME-Tox analysis that predicts metabolism, secretion, and toxicity is shown in Table 5.

DISCUSSION

Preparation of the androgen receptor protein

The androgen receptor is a nuclear hormone receptor whose activity can be stimulated through the formation of bonding interactions with androgen hormones.[22] The androgen receptor is a transcription factor that regulates gene expression in developing males.[23] Besides the androgen receptor, exploration of the docking process requires a ligand. Ligand selection used in the process of tethering the target protein is based on initial screening results according to Lipinski's Rule of Five.[24] The androgen receptor (4K7A) forms a hydrogen bond of 2.28 and 2.90 Å with minoxidil. The-NH_2 and-NO group in minoxidil forms a hydrogen bond with SER^{865} and GLU^{793} of the androgen receptor with a binding energy of-4.8 kcal/mol. A smaller ΔG

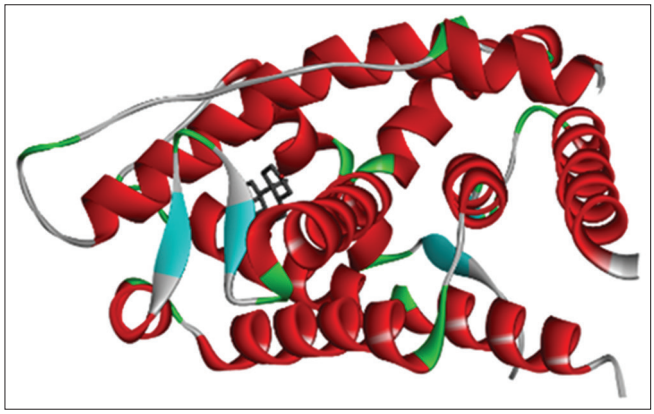


Figure 1: Androgen receptor (46Ka)

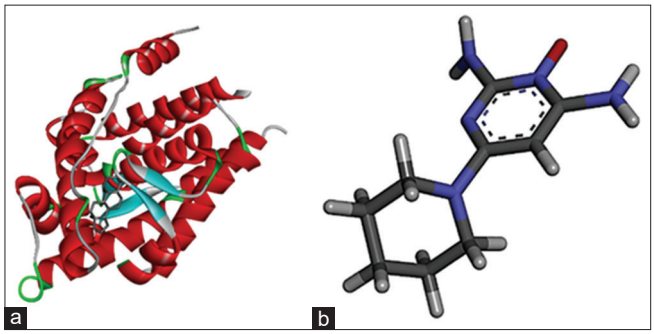


Figure 2: Structure of (a) the androgen receptor (4K7a) and (b) minoxidil which has been separated from its receptor

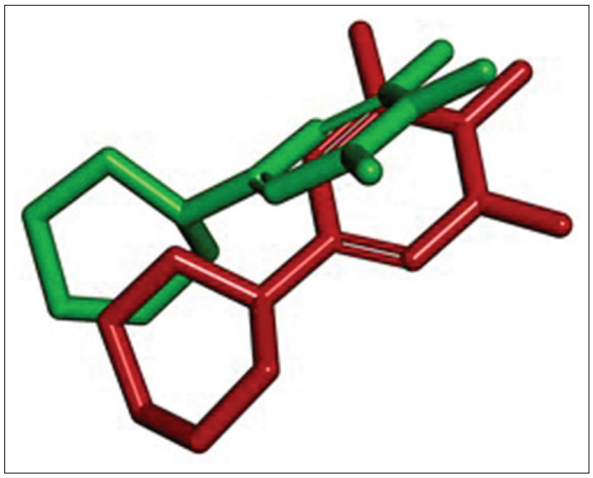


Figure 3: Overlay of docked pose of minoxidil with that of the co-crystallized ligand of 4K7A

Table 2: Validation results for the molecular docking method

Protein	Compound	Binding energy (kcal/mol)	RMSD	Hydrogen bond distance (Å)	Amino acids that bind	Nearest residues
4K7A	Minoxidil	-4.8	2.31	2.28 and 2.90	SER^{865} and GLU^{793}	LEU^{862}, LYS^{861}, TYR^{857}

RMSD: Root-mean-square deviation

Table 3: Docking simulation results

Compound	Binding energy (kcal/mol)	Hydrogen bond distance (Å)	Hydrogen bonds	Nearest amino acid residue(s)
Minoxidil	−4.8	2.28 and 2.90	SER^{865} and GLU^{793}	LEU^{862}, LYS^{861}, TYR^{857}
Finasteride	−6.03	2.86, 1.88 and 2.13	ARG^{854}, GLU^{793} and SER^{865}	LYS^{861}, LUE^{797}
Compound 1	−3,97	-	-	LEU^{797}, LYS^{861}, LEU^{862} ILE^{869}, HIS^{789}
Compound 2	−2.89	-	-	PRO^{868}, TYR^{857}, ARG^{854}
Compound 3	−3.08	2.05 and 1.96	GLU^{793} and HIS^{789}	PRO^{868}, LYS^{861}, TRP^{796}, LUE^{797}, LUE^{862}
Compound 4	−2.36	1.86	VAL^{854}	LYS^{861}
Compound 5	−3.4	1.74	ARG^{854}	-
Compound 6	−2.25	1.76	LYS^{861}	-
Compound 7	−2.67	-	-	TYR^{857}, ARG^{854}
Compound 8	−3.01	1.87	GLU^{793}	LYS^{861}, TRP^{796}, LUE^{797}, HIS^{789}
Compound 9	−1.74	-	-	TRP^{796}
Compound 10	−3.3	-	-	LUE^{797}, LUE^{862}, LYS^{861}, TYR^{857}
Compound 11	−2.05	-	-	LYS^{861}, HIS^{789}
Compound 12	−2.21	-	-	TYR^{857}, ARG^{854}, LYS^{861}, TRP^{796}
Compound 13	−4.72	2.09	SER^{865}	LUE^{862}, LYS^{861}, TRP^{796}, LUE^{797}, HIS^{789}
Compound 14	−0.24	-	-	ARG^{854}, TRP^{796}
Compound 15	−0.96	-	-	LUE^{797}
Compound 16	−7.71	2.43	SER^{865}	LYS^{861}, TRP^{796}, LUE^{797}
Compound 17	−6.34	-	-	LYS^{861}, TRP^{796}, LUE^{797}
Compound 18	−6.17	-	-	TYR^{857}, TRP^{796}, LUE^{797}

Table 4: Absorption and distribution prediction values

Compound	Absorption				Distribution			
	1	2	3	4	5	6	7	8
Minoxidil	−2.871	0.653	94.641	−2.798	0.142	0.773	−0.951	−3.471
Finasteride	−5.148	1.269	93.742	−3.463	−0.185	0.01	−0.18	−1.821
Compound 16	− 5.772	1.475	95.733	− 2.692	0.09	0	0.334	−1.267

Model name and unit: 1: Water solubility (log mol/L), 2: Caco2 permeability (log Papp in 10^{-6} cm/s), 3: Intestinal absorption (human) ([% Absorbed]), 4: Skin permeability ([log Kp]), 5: Vdss (human) ([log L/kg]), 6: Fraction unbound (human) ([Fu]), 7: BBB permeability ([log BB]), 8: CNS permeability ([log PS])

Table 5: Metabolism, excretion and toxicity prediction results

Compound	Metabolism		Excretion	Toxicity						
	9	10	11	12	13	14	15	16	17	18	19
Minoxidil	No	No	0.275	No	−0.359	No	No	2.286	Yes	No	3.516
Finasteride	Yes	Yes	0.38	No	−1.355	No	No	2.424	Yes	No	0.638
Compound 16	Yes	No	−0.294	No	0.672	No	Yes	2.718	No	No	−3.596

Model name and unit: 9: CYP3A4 substrate ([Yes/No]), 10: CYP2C9 inhibitor ([Yes/No]), 11: Total clearance ([log ml/min/kg]), 12: AMES toxicity ([Yes/No]), 13: Maximum tolerated dose (human) ([log mg/kg/day]), 14: hERG I inhibitor ([Yes/No]), 15: hERG II inhibitor ([Yes/No]), 16: Oral rat acute toxicity (LD_{50}) ([mol/kg]), 17: Hepatotoxicity ([Yes/No]), 18: Skin sensitisation ([Yes/No]), 19: Minnow toxicity ([log mM])

value indicates that the bonds are more balanced. Based on Lipinski's criteria, compounds from *M. peltata* are predicted to have good bioavailability in the body.[25]

Validation of the molecular docking method

The molecular docking method is validated by redocking minoxidil to the target protein. The redocking results had an RMSD value of 2.31 Å and a bond energy of −4.8 kcal/mol. According to,[19] an RMSD ≤3Å and a bond energy similar to what we obtained with the redocking results indicates that the interaction between the ligand and the receptor is at a low energy condition; thus, the molecule will be more stable. Visualisation of interactions between minoxidil and androgen receptors (4K7A), also its overlay can be seen in Figures 4 and 5.

Docking simulation of minoxidil, reference ligand, and test ligands (phytocompounds identified from *Merremia peltata* leaves)

Docking is a process of tethering interactions between ligands and proteins; it will produces ΔG, which is the stability parameter of the conformation between the ligand and the androgen receptor.[26] Based on the androgen receptor docking results, the ΔG values for the compound 16 (olean-12-en-3beta-ol, cinnamate)-7.71 kcal/mol is close to the value for minoxidil [−4.8 kcal/mol; Table 2].

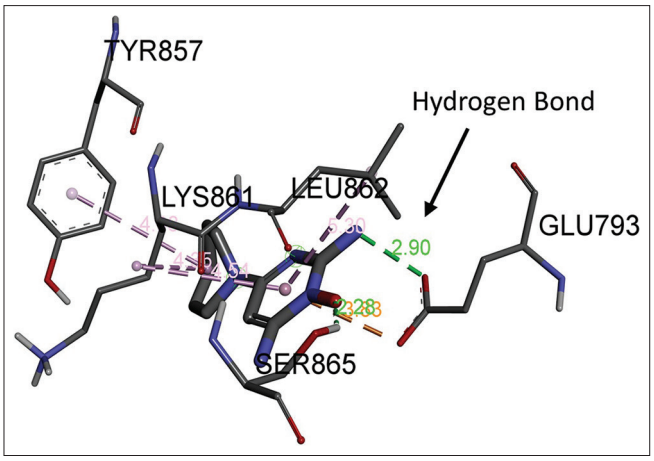


Figure 4: Visualisation of interactions between minoxidil and androgen receptors (4K7A). Hydrogen bonds are represented by green bonds, minoxidil is represented by grey structures

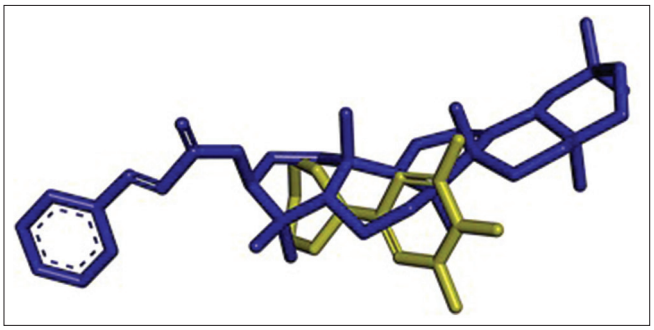


Figure 5: Overlay of the docked poses of the test compounds on that of minoxidil

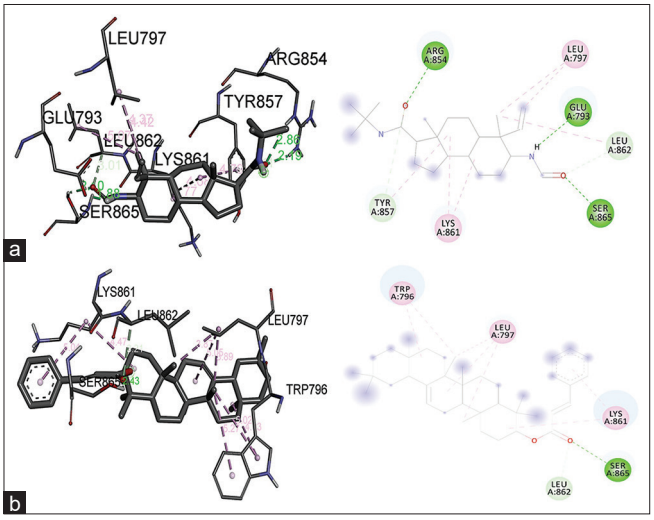


Figure 6: Visualisation of molecular docking between the androgen receptor and (a) finasteride and (b) compound 16 (olean-12-en-3beta-ol, cinnamate)

Therefore, compound 16 is potential as an inhibitors of androgen receptor and potential for antialopecia treatments.

Hydrogen bonding between minoxidil and the androgen receptor occurs at SER^{865} and GLU ^{793}, with the other closest amino acid residues being LEU^{862}, LYS,^{861} and TYR^{857}. Compound 16 has lower binding energy than minoxidil. This can be caused by the presence of proximal amino acids of compound 16 that also found in the finasteride. These include: LYS^{861} and LUE^{797} [Figure 3]. Factors that cause the binding energy for finasteride and test compounds to be higher than minoxidil are different amino acid residues forming a hydrogen bond with the androgen receptor. Minoxidil form hydrogen bonds with SER^{865} and GLU ^{793} of the androgen receptor, finasteride forms hydrogen bonds with ARG^{854}, GLU^{793} and SER^{865}, whereas compound 16 forms hydrogen bonds with SER^{865}. Additional hydrophobic interactions play a role in determining ligand stability with the androgen receptor. Hydrophobic interactions, which repel liquid, are more likely to group together in the globular structure of proteins.[27] Based on the simulation results of natural ligands, serine is predicted to play an important role in the androgen receptor ligand binding domain.[28]

ADME-Tox prediction

The level of binding of the plasma protein (% PB) to the drug candidate influences the action of the drug, its properties and its efficacy. Therefore, % PB is an important pharmacokinetic factor that determines the dose regimen (frequency) but not the daily dose.[26] Minoxidil has 99% PB value while compound 16 has a PB of 93%. Based on these results, minoxidil and compound 16 have good plasma protein bonding attributes.[29]

Distribution prediction using the pkCSM tool predicts Vdss, BBB permeability and CNS permeability. The higher the Vdss value, the more drug reserves are distributed to the tissue from the plasma.[22] agreed to accept a low distribution volume if the log Vdss value <-0.15 and >0.45. Analysis indicates that the log Vdss value of minoxidil is 0.142, whereas compound 16 has a log Vdss value of 0.09. Based on the definition of an acceptable Vdss value as defined by[30-32], compound 16 is less favourable than minoxidil.

Caco-2 single cell monolayer permeability is an *in vitro* model of the intestinal mucosa that is used to predict the absorption of drugs given orally. According to Lee and Chang,[28] a compound is considered to have high Caco-2 permeability if the P_{app} >8 × 10^6 cm/s. However, in this study, permeability predictions were made using the pkCSM permeability tool. pkCSM values >0.90 are deemed as high log Pap*P* values and indicate that a compound is permeable.[29-31]. Minoxidil and compound 16 have Pap*P* values of 0.653 and 1.475, respectively. This suggests that compound 16 has greater Caco-2 permeability than minoxidil.

CONCLUSIONS

Based on *in silico* analysis using the androgen receptor (4K7A), we found that compound 16 (olean-12-en-3beta-ol, cinnamate) had the best binding energy value; indeed, it is close to the value for minoxidil, a natural androgen receptor ligand. ADME-Tox analysis on minoxidil and compound 16 (olean-12-en-3beta-ol, cinnamate) showed a good profile. Hence, compound 16 (olean-12-en-3beta-ol, cinnamate) potentially as successful anti-alopecia drug. Further research is needed to isolate the biological compounds contained within *M. peltata* leaves and perform *in vitro* and *in vivo* tests.

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Conflicts of interest
There are no conflicts of interest.

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