RJC

RASĀYAN *J. Chem.*
Vol. 15 | No. 2 |925-932| April - June | 2022
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

THE IDENTIFICATION OF MOLECULAR MECHANISMS FROM BIOACTIVE COMPOUNDS IN *Sansevieria trifasciata* PLANT AS ANTI-ALOPECIA: *In-Silico* APPROACH

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ABSTRACT

Alopecia is a condition characterized by excessive hair loss. This condition can be caused by various factors, such as heredity, aging, drugs, or lifestyle. This study aims to determine the affinity, stability, and pharmacokinetic profiles of several bioactive compounds from the *Sansevieria trifasciata* plant as anti-alopecia by applying the *In-Silico* method. Molecular simulation of forty-nine bioactive compounds was successfully docked to the active site of the androgen receptor (AR). The best compounds 1,2-(dipalmitoyl)-3-O-β-D-galactopyranosylglycerol, Sansevierigenin, and Spirosta-5,25(27)dien-1b,3b-diol-1-O-a-L-rhamnopyranosyl-(1,2)-a-L-arabinopyranoside showed stable results after 100 ns molecular dynamics simulation based on the root mean square deviation (RMSD) and the root mean squared fluctuation (RMSF). The binding free energy calculation using the MM-PBSA method and pharmacokinetic profiles of these three compounds showed satisfactory results compared to the minoxidil.

Keywords: Androgen Receptor, Anti-Alopecia, *In-Silico*, *Sansevieria trifasciata*

RASĀYAN *J.Chem*., Vol.15, No.2, 2022

INTRODUCTION

Alopecia is a dermatological disorder characterized by hair loss of more than 120 strands/day.[1] This disorder occurs mainly in men (58%) and about 21% in women.[2] In all cases of alopecia, 90% of them are caused by androgenetic alopecia (AGA). AGA is alopecia that leads to the progressive thinning of hair follicles, causing the hair to become weak (easy to fall out).[3,4] Treatments for AGA currently approved by the FDA are minoxidil and finasteride. This drug works by opening potassium channels resulting in inhibition of 5α-reductase and androgen receptors.[5] However, both drugs have side effects such as scalp irritation or hair damage and are less effective, only about 35-48%.[6] Therefore, it is necessary to find new drug candidates to treat AGA. *Sansevieria trifasciata* is a plant that has traditionally been used to treat alopecia.[7] This plant contains several secondary metabolites such as terpenoids, steroids, flavonoids, saponins, glycosides, tannins, polyphenols, and alkaloids.[8,9] Previous studies have shown that several compounds in *Sansevieria trifasciata* have an anti-alopecia activity, such as linoleic acid, which acts to the expression of the Vascular Endothelial Growth Factor (VEGF) to prolong the anagen phase of hair and interacts with 5α-reductase receptors to prevent alopecia[10,11]. In addition, it has been reported that trifasciatine, steroidal saponins, pyranoisoflavones, palmitic acid, quinolones, campesterol, pyridine, phytol, cyclocarya, and tocopherols can interact with androgen receptors.[12,13] The androgen receptor (AR) is a member of the thyroid-steroid receptor superfamily that regulates transcription factors.[14] Testosterone (T) and Dihydrotestosterone (DHT) activate AR, which governs and reduces androgen sensitivity in dermal papillae cells, causing hair loss. Therefore, to minimize the effect, DHT must be inhibited from binding to its receptor (AR) or inhibiting the translocation process of AR to nuclear induced by DHT.[15,16] Androgen inhibitors are classified into non-steroidal and steroid inhibitors based on their structure. Benzene groups in non-steroidal compounds in *Sansevieria trifasciata*, such as trifasciatine A, trifasciatine B, and trifasciatine C, are indispensable for

http://doi.org/10.31788/RJC.2022.1526731

binding AR.[11] Currently, there are no studies on the structural activity of steroid compounds against AR. Based on this description, This study aims to identify the content of other compounds in *Sansevieria trifasciata*, especially steroid compounds that inhibit androgen receptors, using the *In-Silico* method.

EXPERIMENTAL

Protein Structure Preparation

The target used in this study was the 3D androgen receptor complex obtained from the Protein Data Bank (http://www.rcsb.org/pdb/) with code 4K7A. Crystallography of the androgen receptors is first prepared by eliminating water molecules and adding a Kollman charge and hydrogen polar.[17,18]

Ligand Structure Preparation

The compound contained in *Sansevieria trifasciata* was used as a test compound and minoxidil as a comparison. Forty-nine compounds were selected from several references. Their geometries were optimized using Hyperchem by applying the semi-empirical Austin-Model 1 method.[19]

Molecular Docking Simulation

The docking procedure was validated by redocking the natural ligand (minoxidil) to the receptors using AutoDock Vina software. The active site of the receptor was set to coordinates x = 6.529, center y = 4.864, center z = -4.729. Box size of 27 x 27 x 27 Å with point spacing 0.375 Å. Reasonable procedures were used to dock all test compounds. The docking results are then analyzed, and their orientation was visualized using the Discovery Studio Visualizer software.

Molecular Dynamics Simulation

The molecular dynamics (MD) simulation process on the androgen receptor-ligand complex was employed by the GROMACS 2016.3 software.[20] ACPYPE was used to generate topological parameters of the ligands. The receptor and ligands were applied with the AMBER99SB-ILDN force field.[21] The Ewald Particle Mesh method was applied to calculate the electrostatic force of the system.[22] The addition of Na^+ and Cl^- achieves the neutralization processions and the TIP3P water model for the solvation stage. The production process was carried out for 100 ns simulation, and the results were analyzed the RMSD, RMSF, and hydrogen bonding occupancy of each complex.

Binding Free Energy Calculation and Pharmacokinetic Properties Analysis

The energy calculation utilizes by the MM-PBSA calculation running on the g_mmpbsa packages.[23] The Poisson-Boltzmann equation to calculate the polar desolvation energy. The Dielectric constant of water is set to 80.[24] The surface area of the protein accessed by the solvent is used to calculate the non-polar energy.[25] The free energy calculations were carried out on the stable trajectories of each complex. The best compounds in each stage were followed by determining their pharmacokinetic profiles using the pkCSM web server (http://biosig.unimelb.edu.au/pkcsm/).[26]

RESULTS AND DISCUSSION

The docking procedure was validated using the natural ligand redocking method based on the RMSD value criteria. The RMSD values were obtained after overlapping the x-ray conformation of the minoxidil with the conformation after the redocking process.[27] The validation process with an RMSD value <2 Å indicates that the docking method has met the recommended criteria. The best confirmation of minoxidil showed an RMSD value of 1.64 Å. The lower RMSD value suggests that the confirmation after the redocking process is very similar to the x-ray conformation of the natural ligand (Fig-1). Minoxidil has a binding affinity value of -4.79 kcal/mol, and electrostatic interactions are formed with the amino acids Glu793, Trp796, and His789. In addition, hydrophobic interactions with the amino acid Lys861 were also observed.

Binding affinity indicates the degree of stability of the chemical bond between the ligand and the receptor. Ligand-receptor complex with lower binding energy, showing that the complex is stable and the ligand and receptor form strong bonds. Negative affinity values indicate that the compound can interact spontaneously with androgen receptors. There are forty-four bioactive compounds from this plant that have a better binding affinity when compared to minoxidil while demonstrating their potential to inhibit androgen receptors. Two hydrogen bonds were observed in compound 1,2-(Dipalmitoyl)-3-O-β-D-

galactopyranosylglycerol (**Comp.1**), where the hydroxyl and ether groups formed hydrogen bonds to the residues Gln798 and Arg855.

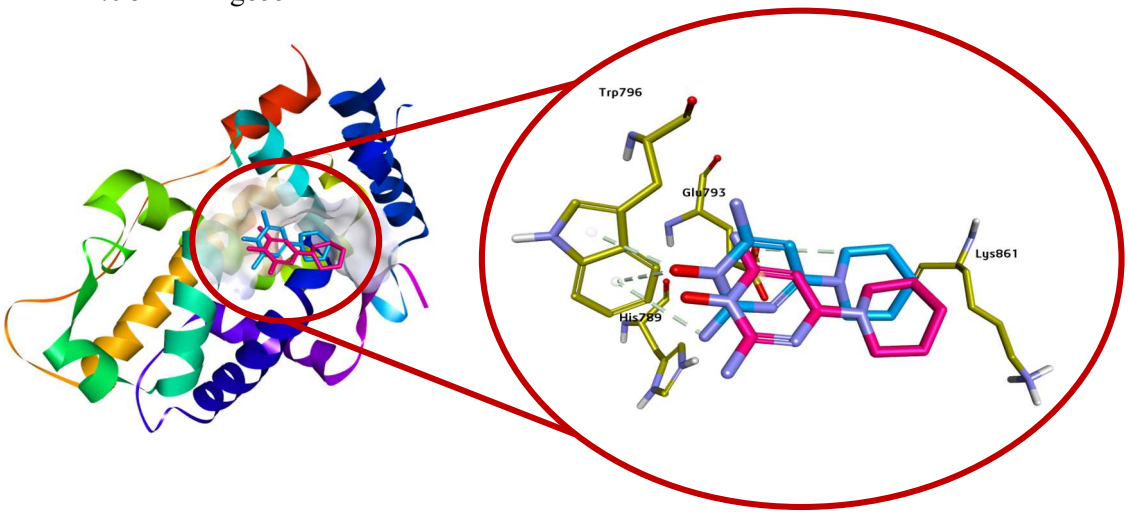

Fig.-1: Overlay 3D conformation of co-crystallized (pink) and docked minoxidil (blue) against AR

Table-1: The Binding Affinity of Bioactive Compounds in *Sansevieria trifasciata* and minoxidil

Compounds	Binding Affinity (Kcal/mol)	Compounds	Binding Affinity (Kcal/mol)
1,2-(dipalmitoyl)-3-O-β-D-galactopyranosylglycerol	-8.0	(20S,22S,25R)-Spirost-5-en-1β,3β-diol-23-nitrimine diacetate	-6.0
Sansevierigenin	-7.1	lβ,3β-dihydroxypregna-5,16-dien-20-one 1-O-{O-α-L-rhamnopyranosyl-(1,2)-0-[β-D-xylopyranosyl-(1,3)]-β-D-glucopyranoside}	-6.0
Spirosta-5,25(27)dien-1 b,3b-diol-L-rhamnopyranosyl-(1,2)-L-arabinopyranoside	-7.0	(20S,22S,25S)-Spirost-5-en-1β,3β-diol-23-nitrimine diacetate	-5.9
Ruscogenin	-6.9	(20S,22S,23,25R)-Spirost-5-en-1β,3β,23-triol 1,3 diacetate	-5.9
Luvigenin	-6.8	lβ,3β-dihydroxypregna-5,16-dien-20-one 1-O-{O-α-L-rhamnopyranosyl-(1→2)-0-[β-D-xylopyranosyl-(1→3)]-6-O-acetyl-β-D-glucopyranoside}	-5.9
(20S,22S,23S,25S)-Spirosost-5-en-1β,3β,23-triol,dihidroksi	-6.8	lβ,3β-dihydroxypregna-5,16-dien-20-one 1-O-{O-α-L-rhamnopyranosyl-(1,2)-0-[β-D-xylopyranosyl-(1,3)]- α-L-arabinopyranoside)	-5.9
(20S,22S,25R)-Spirost-5-en-1β,3β-diol-23-one dihidroksi	-6.8	Saosevierigenin acetate	-5.8
Neoruscogenin	-6.7	lβ,3β-dihydroxypregna-5,16-dien-20-one 1-O-{O-α-L-rhamnopyranosyl-(1,2)- α-L-arabinopyranoside)	-5.8
Ruscogenin Acetate	-6.7	(23S, 24S)-spirosta-5,25(27)-diene-β,3β,23,24-tetrol- 1-O-{O-α-L-rhamnopyranosyl- (1,2)- O- [β-D-xylopyranosyl -(l,3)]-α-L-arabinopyranoside}	-5.8
(20S,22S,23,25R)-Spirost-5-en-1β,3β-diol 1,3,23 trihidroksi	-6.6	Trifasciatine A	-5.7
Neoruscogenin Acetate	-6.5	(23S,24S)-spirosta-5,25(27)-	-5.6

		diene- lβ,3β,23,24-tetrol-1-O-{O-(2,3-O-diacetyl-α-L-rhamnopyranosyl)-(1,2)-O-[β-D-xylopyranosyl - (1,3)] –α-L - arabinopyranoside} 24-O- β-D-Fucopyranoside	
(20s,22S, 25S)-Spirost-5-en-1β,3β-diol-23-one diacetate	-6.5	Trifasciatosides M	-5.5
(20S,22S,23S,25S)-Spirosost-5-en-1β,3β,23-triol 1,3-diacetate	-6.5	Trifasciatoside F	-5.5
25-S-ruscogenin	-6.4	Trifasciatoside H	-5.5
(20S,22S,25R)-Spirost-5-en-1β,3β-diol-23-one diacetate	-6.4	Trifasciatoside G	-5.5
Trifasciatoside E	-6.3	Trifasciatoside A	-5.5
25S-Ruscogenin acetate	-6.3	(23S)-spirosta-5,25(27)-diene-1β,3β,23-triol- 1-O-{O-(4-O-acetyl-α-L-rhamnopyranosyl- (1, 2)- O- [β-D-xylopyranosyl -(l,3)]-α-L-arabinopyranoside}	-5.4
Trifasciatoside B	-6.3	(23S,24S)-spirosta-5,25(27)-diene- lβ,3β,23,24-tetrol-1-O-{O-(4-O-acetyl-α-L-rhamnopyranosyl)-(1,2)-O-[β-D-xylopyranosyl - (1,3)] –α-L - arabinopyranoside} 24-O- β-D-Fucopyranoside	-5.3
Trifasciatosides N	-6.2	(23S,24S)-spirosta-5,25(27)-diene- lβ,3β,23,24-tetrol-1-O-{O-(2,3,4-O-triacetyl-α-L-rhamnopyranosyl)-(1,2)-O-[β-D-xylopyranosyl - (1,3)] –α-L - arabinopyranoside}	-5.2
(20S,22S,23,25R)-Spirost-5-en-1β,3β,23-triol 1,3 diacetate	-6.2	Minoxidil	-4.2
(23S)-spirosta-5,25(27)-diene-β,3β,23-triol- 1-O-{O-α-L-rhamnopyranosyl-(1,2)- O- [β-D- xylopyranosyl -(l,3)]-α-L-arabinopyranoside}	-6.2	1-(stearoyl)-glycerol	-4.0
(23S,24S)-spirosta-5,25(27)-diene- lβ,3β,23,24-tetrol-1-O-{O-(4-O-acetyl-α-L-rhamnopyranosyl)-(1,2)-O-[β-D-xylopyranosyl - (1,3)] –α-L - arabinopyranoside}	-6.2	1-methyl aconitic acid	-3.8
(23S,24S)-spirosta-5,25(27)-diene- lβ,3β,23,24-tetrol-1-O-{O-(2,3,4-O-triacetyl-α-L-rhamnopyranosyl)-(1,2)-O-[β-D-xylopyranosyl-(1,3)]–α-L - arabinopyranoside} 24-O- β-D-Fucopyranoside	-6.1	Linoleic Acid	-3.8
Trifasciatine B	-6.1	Aconitic Acid	-3.7
(20S,22S,23S,25S)-Spirosost-5-en-1β,3β-diol 1,3,23-tiacetate	-6.0		

In **Comp.1**, no hydrophobic interactions were observed. However, Van der Waals interactions with several residues on the active site of the androgen receptor were kept. The compounds Sansevierigenin (**Comp.2**) and Spirosta-5,25(27)dien-1b,3b-diol-L-rhamnopyranosyl-(1,2)-L-arabinopyranoside (**Comp.3**) was dominated by hydrophobic interactions with Arg855, Leu797, Cys852, and Ile842. Additionally, hydrogen

bonds of Gln858 with the hydroxy group in the octahedron-naphthalene ring of the **Comp.2** were also observed. In **Comp.3**, three hydrogen bonds were observed to the two amino acids of the androgen receptor active site. At positions five and three, the hydroxy groups on the tetrahydro-pyrene ring make hydrogen bonds with Ile842 and Arg855. Furthermore, the oxygen atom in the ether group of **Comp.3** was also observed to have hydrogen bonds with Arg855. Visualization of their interaction with AR can be seen in Fig-2. The three compounds with the best docking score passed to the MD simulation stage to see their stability with the receptor during the 100 ns simulation. The system's stability can be observed through the RMSD value achieved at the 10 ns simulation (Fig-3a). **Comp.2** and **Comp.3** tend to be stable until the end of the simulation. In contrast, **Comp.1** and minoxidil increased from 42 ns to 2.6 Å and persisted until the end of the simulation. Slightly different in minoxidil which increased to 2.4 Å at a simulation time of 71 ns until the simulation ended. Meanwhile, fluctuations and flexibility of the amino acid of the androgen receptor during the simulation can be observed in the RMSF value plot (Fig.-3b). The RMSF plots showed that all complexes with androgen receptors fluctuated similarly. This condition can illustrate the similarity of the binding modes of the molecule.

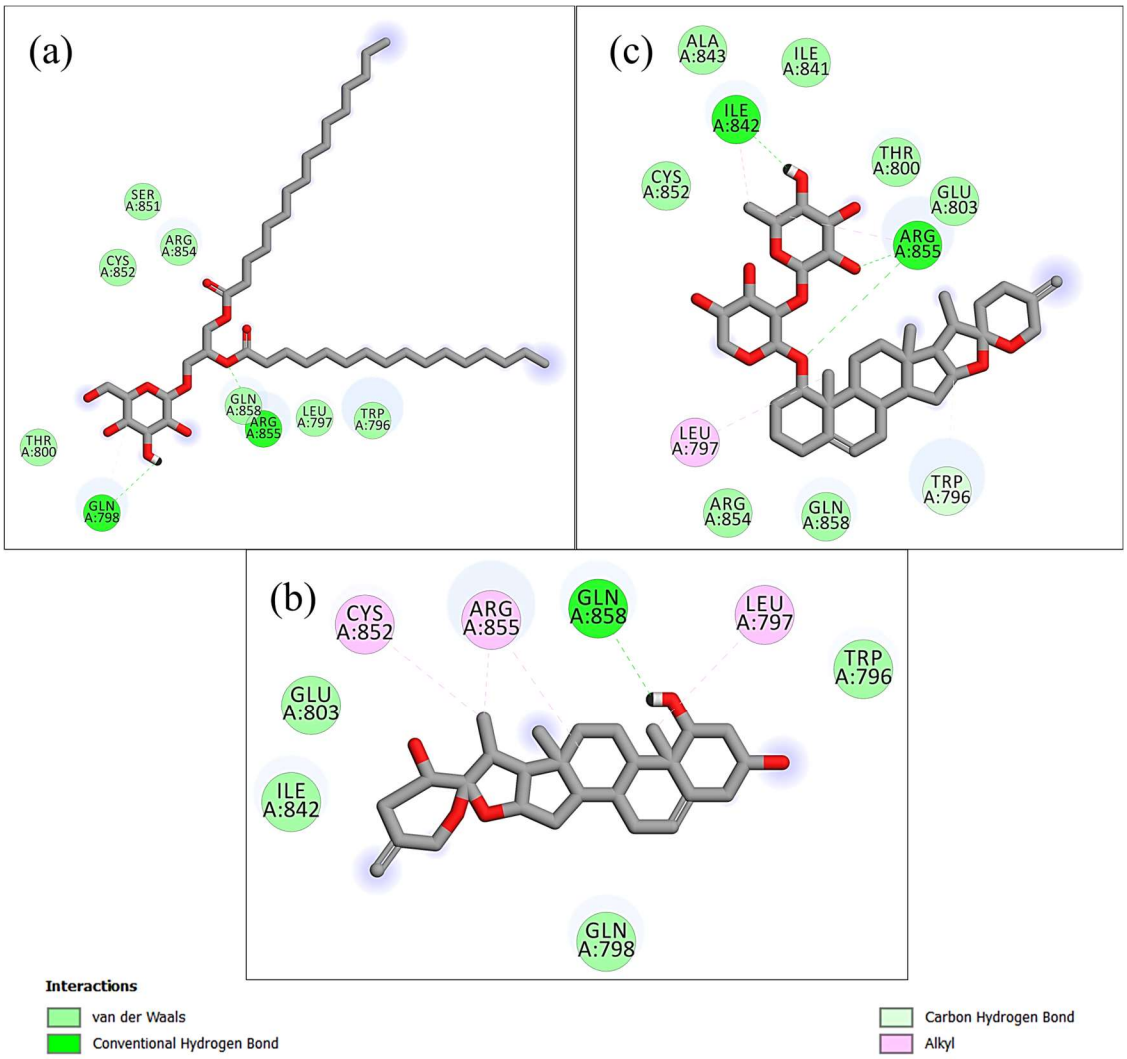

Fig.-2: Interaction of (a) Comp.1, (b) Comp.2, and (c) Comp.3

It was observed that there was a slight increase in the fluctuation with Asn823 and Asp890 on **Comp.1** complex. The amino acid peaks of Gln670 and Thr918 are higher than other regions because they are the end regions of the receptor. Other regions exhibit a rigid pattern, suggesting that ligand binding induces receptor stability during simulation. In addition, the occupancy of hydrogen bonds (H-bonds) was also

monitored during the molecular dynamics simulations. The H-bonds interaction showed varying occupancy where the H-bonds from **Comp.1** with Glu803 residue as acceptor was 24.14%. The H-bond donor with residue Gln858 was also observed at 16.47%. Differences were seen in H-bonds with very low occupancy with residues of Ile841 and Gln802, which were 3.13% and 2.54%, respectively. In the binding of **Comp.2**, 21.61% and 11.07% of H-bond acceptors with Glu803 and Gln858 were formed.
This situation is very different from the occupancy of Thr755 and Arg855, which are only 4.39% and 3.10%, respectively. The H-bond interaction in **Comp.3** had almost the same occupancy percentage as the other compounds, namely 27.84% for the Glu678 residue and the H-bond with low occupancy of 5.46% and 4.40% for the Trp751 and Asn758 residues, respectively.

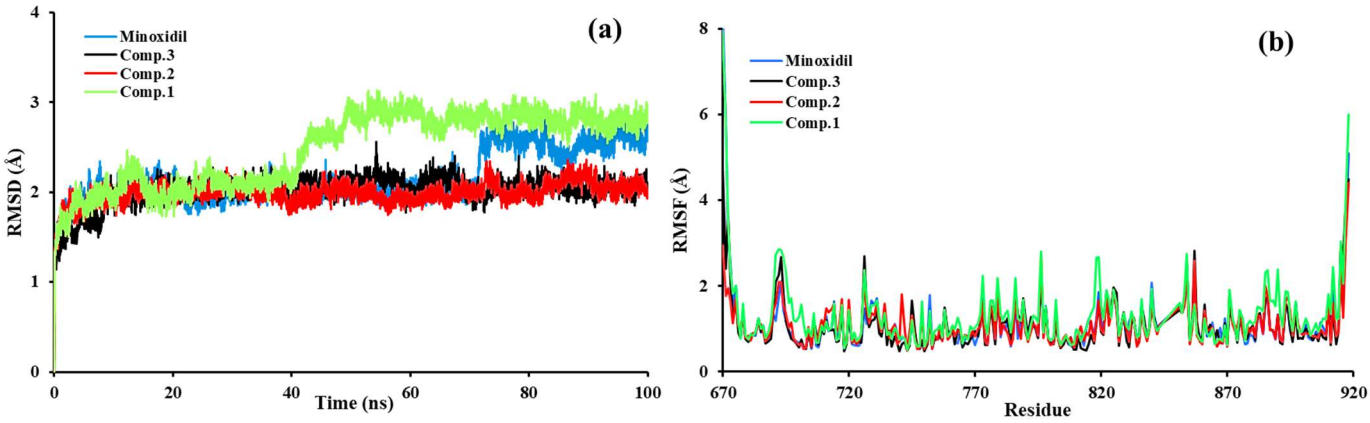

Fig-3: The Plots of (a) RMSD and (b) RMSF backbone atoms for the AR-ligand complex over 100ns of simulation.

MM-PBSA Calculations

The calculation of the binding energy was carried out to predict the contribution of each energy to the stability of the complex bonds during the simulation using the MM-PBSA method (Table-2). It can be seen that the three best compounds have stronger binding energy than minoxidil. The free energy of minoxidil is -34,645 ± 14,015 kJ/mol. **Comp.1** has the lowest binding free energy of -135.509 ± 40,868 kJ/mol. **Comp.2** and **Comp.3** have similar binding free energy values, namely -64,540 ± 15,901 kJ/mol and -64,743 ± 15,017 kJ/mol. In addition, polar solvation energy is less favorable than other energies in complex systems. It is known that the van der Waals, SASA, and electrostatic energies are very beneficial for the system because they contribute to the negative binding free energy during the MD simulations.

Table-2: MM-PBSA Summary Energy of Minoxidil and The Three Best Compounds

Compound	Van der Waal Energy (kJ/mol)	Electrostatic Energy (kJ/mol)	Polar Solvation Energy (kJ/mol)	SASA Energy (kJ/mol)	Binding Energy (kJ/mol)
Minoxidil	-60.986 ± 17.69	-12.995 ± 6.64	47.057 ± 22.82	-7.721 ± 1.58	-34.645 ± 14.01
Comp.1	-200.765 ± 39.70	-36.170 ± 22.19	125.004 ± 33.96	-23.577 ± 4.47	-135.509 ± 40.86
Comp.2	-100.569 ± 20.94	-21.985 ± 10.97	69.260 ± 13.57	-11.246 ± 1.53	-64.540 ± 15.90
Comp.3	-114.720 ± 22.89	-30.751 ± 25.79	93.498 ± 38.70	-12.769 ± 2.30	-64.743 ± 15.01

The best compounds were then predicted for their pharmacokinetic profiles, as shown in Table-3. All the best compounds had relatively low permeability to the skin. Compounds with good skin permeability (SP) are beneficial in pharmaceutical preparations and can increase the potential activity of compounds. No compounds can cross the blood-brain barrier (BBB). It was observed that **Comp.1** and **Comp.3** had CNS values <-3, indicating that these compounds could not penetrate the central nervous system (CNS), and **Comp.2** with CNS values <-2 could penetrate the CNS. All compounds identified did not inhibit the CYP2D6 enzyme. This enzyme plays a role in catalytic processes in drug metabolism, cholesterol, and steroid synthesis. Mutagenicity prediction (Ames) showed that all the best compounds were non-mutagenic. Hepatotoxicity (HPT) and skin sensitization (SS) properties showed good results except for **Comp.1**, which was predicted to be toxic to the liver.

Table-3: ADMET Prediction Results

Compound	ADME					Toxicity		
	SP (logKP)	BBB (logBB)	CNS (logPS)	CYP2D6	TC (ml/min/kg)	Ames	HPT	SS
Comp.1	-2.735	-1.995	-3.321	No	2.256	No	Yes	No
Comp.2	-3.879	-0.467	-1.937	No	0.433	No	No	No
Comp.3	-2.778	-1.303	-3.297	No	0.331	No	No	No

CONCLUSION

This study succeeded in identifying two steroid compounds (sansevierigenin and Spirosta-5,25(27) dien-1b,3b-diol-L-rhamnopyranosyl-(1,2)-L-arabinopyranoside) and 1,2-(dipalmitoyl)-3-O-β-D-galactopyranoylglycerol in *Sansevieria trifasciata*, which is thought to have anti-alopecia activity. These three compounds can inhibit androgen receptors based on the results of molecular docking and molecular dynamics simulations compared to minoxidil. All compounds were predicted to have good pharmacokinetic profiles. This research can be an impetus for further research to prove the anti-alopecia activity of these compounds through in vitro and in vivo tests.

ACKNOWLEDGMENT

We greatly thank to the "Universitas Padjajaran, Bandung, Indonesia and Universitas Halu Oleo, Kendari, Indonesia".

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[RJC-6826/2021]