International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Special Issue 5, 2022

Original Article

THE POTENTIAL OF LANGIR (*ALBIZIA SAPONARIA* LOUR.) STEM BARK AS ANTI-DANDRUFF: *IN SILICO* AND *IN VITRO* STUDIES

HIMANIARWATI[1,2], MUHAMMAD ARBA[4], YASMIWAR SUSILAWATI[3*], RESMI MUSTARICHIE[1]

[1]Department of Pharmaceutical Analysis and Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran, Indonesia, [2]Departement of Pharmacy, Universitas Mandala Waluya, South-East Sulawesi, Indonesia, [3]Department of Pharmacy Biology, Faculty of Pharmacy, Universitas Padjadjaran Indonesia, [4]Faculty of Pharmacy, Halu Oleo University, Kendari, Indonesia
[*]Email: yasmiwar@unpad.ac.id

Received: 05 Oct 2022, Revised and Accepted: 13 Nov 2022

ABSTRACT

Objective: Dandruff is a scalp problem that occurs in almost all people in the world. The main cause of dandruff is the growth of fungus on the scalp. This study aims to evaluate the antifungal activity of the Langir bark against *Malassezia furfur, in vitro* and *in silico.*

Methods: *In vitro* testing was carried out using the agar diffusion method with paper disks to calculate the inhibition zones of the Langir stem bark extract and fractions, while the *in silico* test was carried out using the molecular docking method using Lanosterol 14-alpha demethylase receptors with a homology model using 5 compounds from the genus Albizia as ligands.

Results: Antifungal activity of Langir bark extract showed significant activity in all concentrations (5-20%), and also for all fractions ($p<0.05$). However, the water fraction had better activity than others, with an inhibition zone of 17.33 mm at a concentration of 15% and 18.67 mm at a concentration of 20%, while the positive control (ketoconazole 1%) had an inhibition zone of 16.67 mm. Furthermore, the *in silico* test revealed that the 5 metabolites in Langir plant provide better binding energy than ketoconazole (-10.1 kcal/mol), namely, Tamarixetin 3-rutinoside (-10.7 kcal/mol), Quercetin 3-rhamnosyl-galactoside (-10.4 kcal/mol), Albiziasaponin A (-11.6 kcal/mol), Albiziasaponin C (-11.9 kcal/mol) and Albiziasaponin D (-11.9 kcal/mol).

Conclusion: The water fraction of Langir bark has activity in inhibiting the growth of *M. furfur* so that it can be developed as a therapeutic alternative for anti-dandruff.

Keywords: Langir, *Albizia saponaria*, *Malassezia furfur*, *Dandruff,* Antifungal

DOI: https://dx.doi.org/10.22159/ijap.2022.v14s5.33 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Dandruff is formed from excessive exfoliation of dead skin cells on the scalp with effects that can cause itching and even inflammation of the scalp [1, 2]. Dandruff is one of the scalp that can happen to everyone in the world for all genders, socio-cultural, and geographical locations [3]. There are about 60% of the total population of America and Europe who have dandruff problems [4]. Dandruff is not life-threatening, but it can cause sufferers to feel insecure because they experience itching of the skin that accompanies it [5, 6]. There are several medical terms for dandruff, such as pityriasis capitis, seborrhea sicca, pityriasis sicca, sicca capitis, or mild sereboic dermatitis of the scalp [7, 8].

One of the causes of dandruff is the growth of the *Malassezia furfur* fungus on the scalp, which is dirty with sweat, excess oil (sebum) production and dust [9, 10]. Malassezia fungus is a lipophilic fungus with its existence as a normal flora on human skin [11].

One type of dandruff treatment is by using an anti-dandruff shampoo which contains many chemical compounds, such as sulfur, salicylic acid, selenium sulfide, and zinc pyrithione, which have side effects in the form of eczema (inflammation of the skin), hair loss, discoloration of the hair, and damage to the scalp hair when used continuously for a long time [12, 13]. So this study aims to find anti-dandruff alternatives from natural ingredients, which tend to be safer and more effective to use in the long term [14, 15].

Based on research conducted [16] one of the plants that has the potential as an anti-dandruff is the Langir plant (*Albizia saponaria* Lour.) The part of the plant that is used is the bark. Empirically this plant has been used by the Tolaki tribe in South Konawe Regency, Indonesia, by washing or extracting the bark with water until it foams and then applying it to the head as a shampoo to treat dandruff.

Therefore, a study was conducted to determine the activity of the Langir bark fraction as an antifungal against *Malassezia furfur,* which was tested *in vitro* and *in silico*. This research is expected to provide benefits in the form of information about the potential of langir bark as an anti-dandruff drug caused by the fungus *Malassezia furfur*.

MATERIALS AND METHODS

Materials

Etanol 96% technical grade, *n*-hexane technical grade, ethyl acetate technical grade, aquadest, DMSO ethyl acetate technical grade, ketoconazole, Potato Dextrose Agar Merck. All chemicals were purchased from a standard local source.

The *M. furfur* used *in vivo* study is a collection from the Microbiology Laboratory of the Pharmacy Departement, Faculty of Science and Technology, University of Mandala Waluya and *in silico* metode using Autodock tools 1.5.6 and visualisation using discovery studio BIOVIA.

Preparation of plant materials

Langir stem bark (*Albizia saponaria*) obtained in the tropical forest of Duduria Village, Ranometo District, South Konawe Regency, Southeast Sulawesi Province, Indonesia. Langir was determined by observe the morphological characteristics of the plant, including shape, size, number, parts of leaves, flowers, fruit, seeds, and others [17]. The results of the analysis of the characteristics of the plants studied were compared with the plants whose identity had been identified. Sample determination was carried out at the Faculty of Biology, University of Haluoleo, Indonesia.

Extraction and fractionation of *Albizia saponaria* stem bark

9450 g of processed dried bark was extracted using the maceration method with 96% ethanol solvent. The maserate obtained was then concentrated with a rotary vacuum evaporator (Buchi) to obtain a thick extract. The fraction processing of the ethanol extract was carried out using the liquid-liquid extraction method with *n*-hexane,

ethyl acetate and distilled water as solvents. The resulting fraction was then concentrated with a rotary vacuum evaporator to obtain *n*-hexane, ethyl acetate and distilled water fractions.

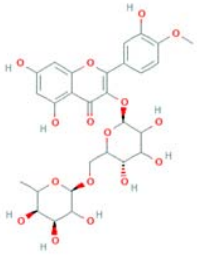
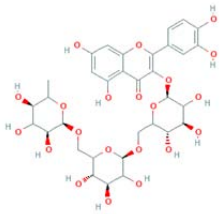
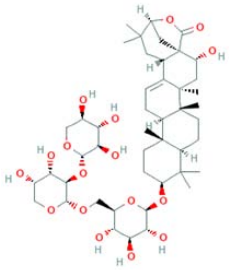
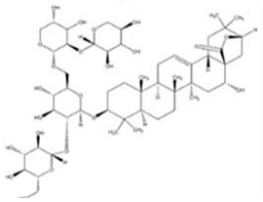
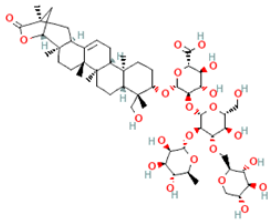
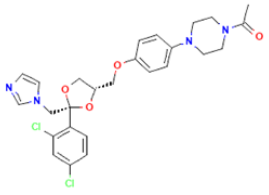
In vitro antifungal assay

The assay for the activity of *n*-hexane, ethyl acetate, and water fractions from *langir* (*A. saponaria* Lour.) stem bark as an anti-dandruff agent against fungi *M. furfur* was conducted by the agar diffusion method using a paper disk [18]. A total of 9 petri dishes were used in the test. Each of them used 15 ml of liquid PDA (Potato Dextrose Agar) to which 1 inoculation needle of *M. furfur* was added, and then were incubated at 37 °C for 1x24 h. Then, the petri dishes were divided into 3 parts, which were for each fraction. The *n*-hexane fractions with concentrations of 5, 10, 15, and 20% were added to one part, and the ethyl acetate and water fractions, respectively, were added to the other parts with the same concentration. As a comparison, DMSO was used as a negative control, and ketoconazole was used as a positive control. Then all cultures were incubated in an incubator with a temperature of 37 °C for 1x24 h, then the inhibition zone was observed.

Preparation of 3D metabolite structure

The compounds simulated *in silico* by molecular docking were compounds from the genus Albizia selected based on the KNapSAcK database, accessed via http://www.knapsackfamily.com/KNApSAcK/17 [19]. 5 compounds were selected (table 1).

Table 1: Two-dimensional structure of ketoconazole and test ligands from the genus of *Albizia saponaria*

No.	IUPAC name	Structure
1.	Compound 1: Tamarixetin 3-rutinoside	
2.	Compound 2: Quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside	
3.	Compound 3: Albiziasaponin A	
4.	Compound 4: Albiziasaponin C	
5.	Compound 5: Albiziasaponin D	
6.	Standard ligand: Ketokonazole	

Preparation of 3D receptor structure

The receptor used is lanosterol 14-alpha demethylase, which is a receptor that plays a role in the synthesis of the fungal cell wall. The FASTA format of the protein lanosterol 14-alpha demethylase Malassezia was obtained from UniProt with the ID A0A3Q9XYP8 [20]. Receptor preparation was carried out through a homology modeling approach with the help of the Swiss-Model® web server [21]. The process of creating a protein model using the homology modeling method begins with a template search using the NCBI® BLAST web server with the aim of obtaining a template that is similar to the protein [22]. Next is adjusting the target sequence with a template and creating a model using Swiss-Model®. The protein model obtained was then evaluated with Procheck® and identified using the Ramacandran plot [23]. Furthermore, the search for active sites based on the cavity area uses the BIOVIA Discovery Studio 2017 application which aims to obtain X, Y, and Z coordinates. This is done because the receptor does not have natural crystallized ligands.

Molecular docking simulation

Molecular docking simulations were carried out to predict the description of the metabolite molecule that has the strongest inhibitory effect on the previously modeled lanosterol 14-alpha demethylase. The docking process was carried out using the Autodock4 software using 100 GA run [24]. The drid box coordinates used were x =-75.83, y = 162.36, and z = 8.7541 with npts values of 50 × 50 × 50, respectively. The docking results were analyzed and visualized on the ligand-receptor interactions using BIOVIA Discovery Studio 2017 [25]. In addition, analysis of ketoconazole as a control was carried out to compare the binding strength and interaction of lanosterol 14-alpha demethylase from Malassezia with the test ligand in the form of a compound found in the genus albizia. ADME-Tox SAR is carried out via the website http://biosig.unimelb.edu.au/pkcsm/prediction by changing the molecular structure to SMILES format in the PubChem program.

RESULTS

Extraction and fractionation

As much as 1300 g (14.28% yield) ethanol extract of Langir stem bark was fractionated using the liquid-liquid extraction method and obtained 20.36 g of *n*-hexane fraction (13.57% yield), 40.66 g of ethyl acetate fraction (yield 27.10%) and water fraction as much as 60.23 g (40.15% yield). %).

***In vitro* antifungal activity of extract and fraction**

The results of the *in vitro* antifungal activity of Langir bark extract are shown in table 2 and fig. 1 and the result of Langir bark fraction are shown in table 3 and fig. 2.

Table 2: Inhibition zone of ethanol extract of Langir bark as antifungal against *M. furfur*

Samples	Average±Standard deviation (n=3)
Langir extract 5%	14±0.5
Langir extract 10%	15.56±0.53
Langir extract 15%	16.78±0.44
Langir extract 20%	17.44±0.53
Ketoconazole 1%	16.89±0.78
DMSO	0±0

(The average value is the mean of three replicate (N=3))

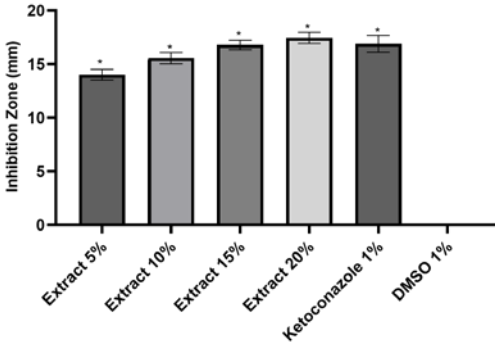


Fig. 1: Inhibition zone of ethanol extract of langir bark as antifungal against *M. furfur* (*: significantly different with the negative control (DMSO))

The test results showed that the Langir bark ethanol extract at concentrations of 5%, 10%, 15% and 20% showed a significant difference with the negative control DMSO, this indicated that the extract showed inhibitory activity against the *M. furfur*. Extracts at concentrations of 15% and 20% did not show the difference in the inhibition zone with the positive control (Ketoconazole 1%).

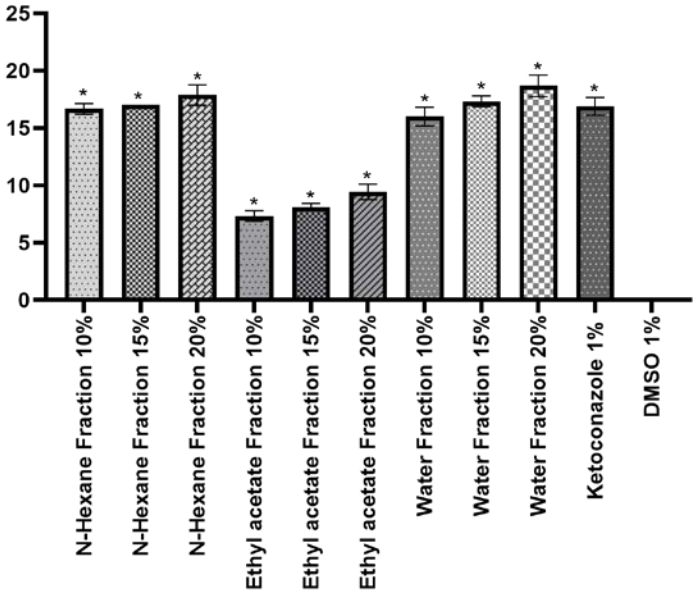


Fig. 2: Inhibition zone of fraction of langir bark extract as antifungal against *M. furfur* (*: significantly different with the negative control (DMSO))

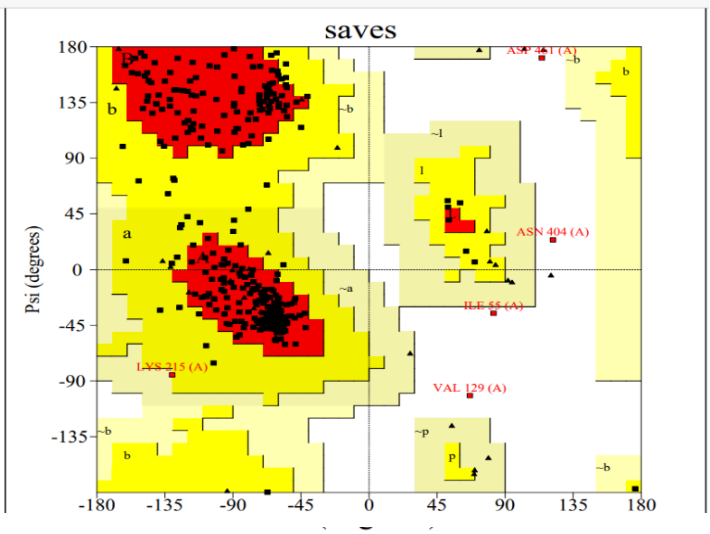
Table 3: Inhibition zone of langir bark fraction as an antifungal against *M. furfur*

Samples	Dose	Average±standard deviation (n=3)
n-hexane fraction	10%	16.67±0.47
	15%	17.00±0.00
	20%	17.89±0.87
Ethyl acetate fraction	10%	7.33±0.47
	15%	8.11±0.31
	20%	9.44±0.68
Water fraction	10%	16.00±0.82
	15%	17.33±0.47
	20%	18.67±0.94
Ketoconazole	1%	16.89±0.78
DMSO	1 %	0±0

The test results of Langir bark fraction showed that the *n*-hexane, ethyl acetate, and water fractions showed inhibitory activity against *M. furfur* and showed significant differences with the negative control (DMSO). The water fractions showed the best inhibition activity and did not show any difference with the positive control (Ketoconazole 1%).

Modelling of lanosterol 14-alpha demethylase receptor

The modeling results obtained 50 templates that are similar to the lanosterol 14-alpha demethylase receptor and the receptor coded 6cr2.1. A was chosen because it has a similarity of 56.29%. According to [26] templates with more than 50% identity can be used because they have small errors in predicting the three-dimensional structure of the target sequence. Furthermore, protein lanosterol 14-alpha demethylase was modeled and validated using the Ramachandran plot for the yield on areas that are not permitted is 1.0%. Based on these data, it shows that the quality of the model made is good because the distribution of amino acids in the most favored areas is higher than in the prohibited areas, and a Ramachandran value of 90% is obtained (fig. 3), indicating that the model has similarities with structures that have a resolution of 2.0 Angstroms. According to [27], the greater the value in the most favored region, the better and more stable the quality of the protein model.



Plot statistics

Residues in most favoured regions [A,B,L]	371	90.3%
Residues in additional allowed regions [a,b,l,p]	35	8.5%
Residues in generously allowed regions [~a,~b,~l,~p]	1	0.2%
Residues in disallowed regions	4	1.0%
	----	------
Number of non-glycine and non-proline residues	411	100.0%
Number of end-residues (excl. Gly and Pro)	0	
Number of glycine residues (shown as triangles)	37	
Number of proline residues	29	

Total number of residues	477	

Based on an analysis of 118 structures of resolution of at least 2.0 Angstroms and R-factor no greater than 20%, a good quality model would be expected to have over 90% in the most favoured regions.

Fig. 3: Ramachandran plot of lanosterol 14-alpha demethylase receptor

Molecular docking simulation

Molecular docking simulation results obtained 5 compounds that have the lowest bond energy values with standard compounds (Ketoconazole-10.1 kcal/mol). The compound consists of 2 flavonoid compounds namely, Tamarixetin 3-rutinoside (-10.7 kcal/mol) and Quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside (-10.4 kcal/mol) and 3 saponin group compounds, namely Albiziasaponin A (-11.6 kcal/mol), Albiziasaponin C (-11.9 kcal/mol) and Albiziasaponin D (-11.9 kcal/mol).

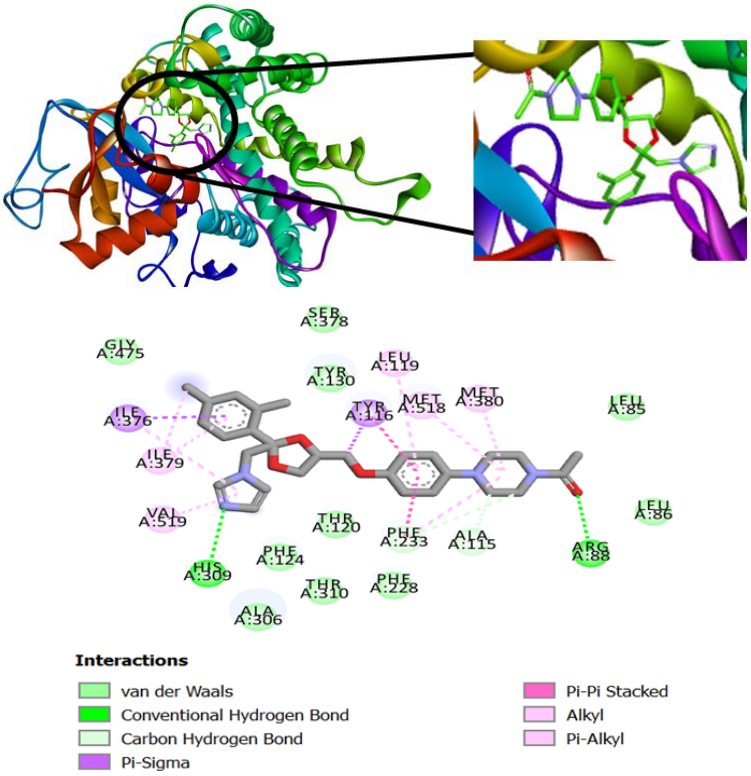


Fig. 4: Ketoconazole interaction on Lanosterol 14-alpha demethylase

Table 4: Absorption and distribution prediction values

Compound	Absorption			Distribution				
	1	2	3	4	5	6	7	8
Ketoconazole	-3.668	1.492	93.184	-2.735	0.179	0.187	-1.443	-2.514
Tamarixetin 3-rutinoside	-2.884	-0.853	0	-2.735	0.816	0.197	-2.359	-5.833
Quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside	-2.892	-1.149	0	-2.735	0.553	0.231	-2.619	-6.172
Albiziasaponin A	-3.06	-0.889	29.838	-2.735	-0.23	0.442	-1.69	-4.639
Albiziasaponin C	-2.901	-0.668	18.146	-2.735	-0.689	0.4	-1.671	-4.409
Albiziasaponin D	-2.892	-0.997	0	-2.735	-0.334	0.401	-2.441	-5.312

Model name and unit; 1: Water solubility (Numeric log mol/l), 2: Caco2 permeability (Numeric (log Papp in 10^{-6} cm/s), 3: Intestinal absorption (human) (Numeric [% Absorbed]), 4: Skin Permeability (Numeric [log Kp]), 5: Vdss (human) (Numeric [log L/kg]), 6: Fraction unbound (human) (Numeric [Fu]), 7: BBB permeability (Numeric [log BB]), 8: CNS permeability (Numeric [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
Ketoconazole	Yes	Yes	0.601	No	0.957	No	Yes	2.84	Yes	No	-0.434
Tamarixetin 3-rutinoside	No	No	-0.365	No	0.448	No	Yes	2.478	No	No	9.484
Quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside	No	No	-0.4	No	0.438	No	Yes	2.481	No	No	11.548
Albiziasaponin A	No	No	-0.128	No	-2.183	No	Yes	2.818	No	No	9.211
Albiziasaponin C	No	No	-0.113	No	0.116	No	Yes	2.576	No	No	8.308
Albiziasaponin D	No	No	-0.197	No	0.203	No	No	2.482	No	No	14.403

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) ([mol/kg]), 17: Hepatotoxicity ([Yes/No]), 18: Skin sensitization ([Yes/No]), 19: Minnow toxicity ([log mmol])

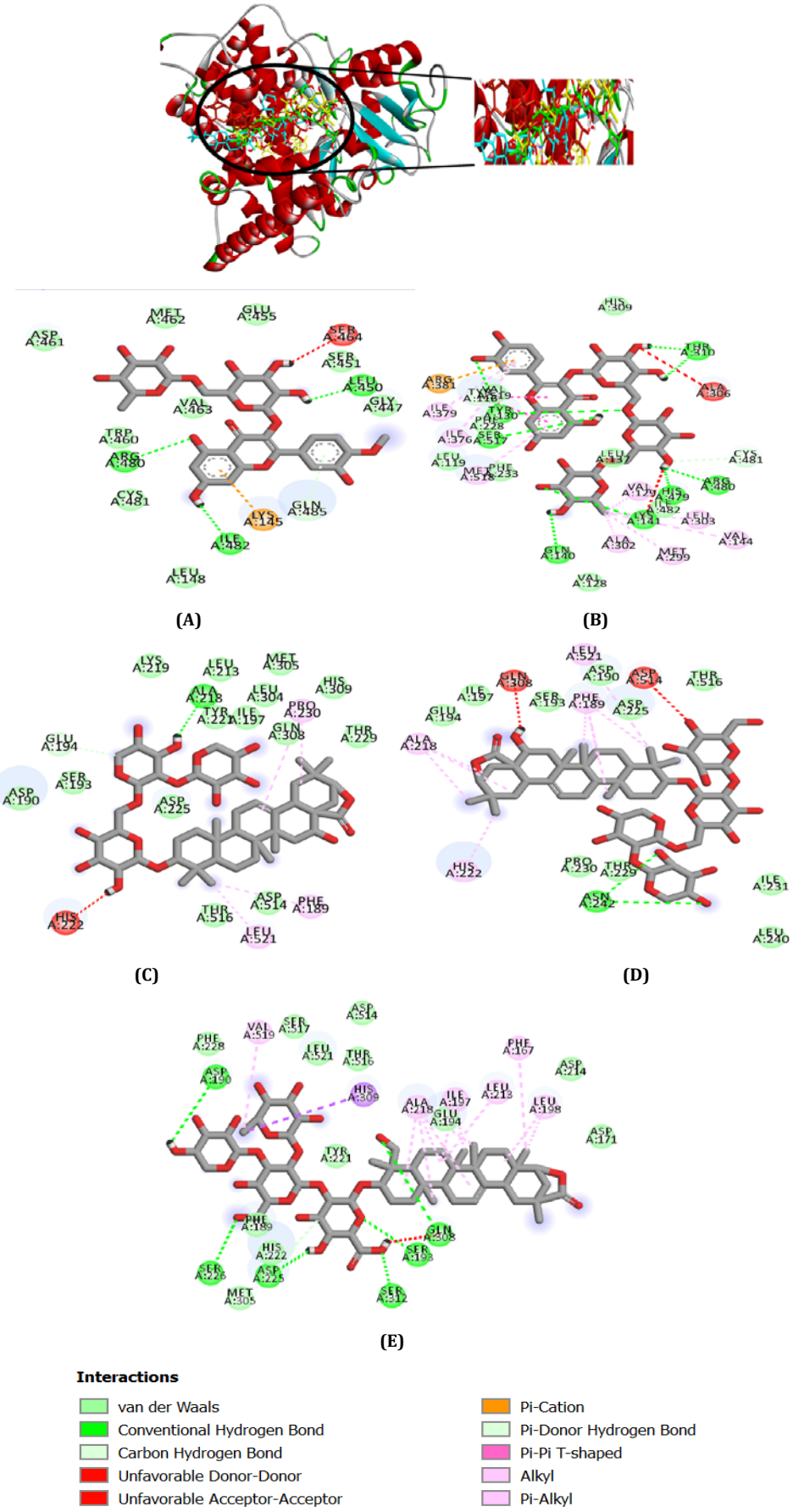


Fig. 5: Interaction on Lanosterol 14-alpha demethylase, A) Tamarixetin 3-rutinoside, B) Quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside, C) Albiziasaponin A, D) Albiziasaponin C and E) Albiziasaponin D

ADMET prediction

Predictive analysis of absorption, distribution of metabolism, excretion and toxicity of the compounds Tamarixetin 3-rutinoside, Quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside, Albiziasaponin A, Albiziasaponin C and Albiziasaponin D can be seen in table 4.

In general, only unbound drug molecules are available for diffusion or transport across cell membranes and for interaction with pharmacological targets. Consequently, the degree of plasma protein binding (%PB) of a drug influences its action, properties and efficacy. The ketoconazole compound has a protein binding value of 99%, Vd = 0.179 and the Albiziasaponin C compound has a protein binding value of 90%, Vd =-0.689. Based on these results, the ketoconazole compound and the Albiziasaponin C compound have good plasma protein binding.

Distribution prediction using the pkCSM tool predicted Vdss, BBB, and CNS. Volume of Distribution at Steady State (VDSS) is the theoretical volume that the total dose of drug needs to be distributed evenly to provide the same concentration as in blood plasma. The higher the VDSS value, the more drug content is distributed to the tissues rather than the plasma. A compound is said to have a low volume of distribution if the Log VDSS value is<-0.15, and high if it is>0.45. Based on the results of the analysis, the standard compound Ketoconazole had a log VDSS value of 0.179 while the compound Tamarixetin 3-rutinoside had a log VDSS value of 0.816. Based on the standard VDSS value data, the Tamarixetin 3-rutinoside compound is better than the standard Ketoconazole compound.

The blood-brain barrier (BBB) is a highly selective, semi-permeable border of endothelial cells that prevents circulating blood solutes from non-selectively crossing into the extracellular fluid of the central nervous system where neurons reside. A compound is said to be able to penetrate the brain barrier if it has logBB>0.3 and is not well distributed if logBB<-1. Based on the results of the analysis of the standard ketoconazole compounds, the value of logBB was-1.443 and that of Albiziasaponin A (-1.69 log BB). These data show that ketoconazole is better at penetrating the brain barrier.

Permeability of the Central Nervous System (CNS) is the ability of a drug to penetrate the central nervous system. Compounds said to be LogPS>-2 are considered to be able to penetrate the CNS, while logPS<-3 are considered to be unable to penetrate the CNS. The results of the analysis for the standard ketoconazole compound were LogPS-2.514 while for Quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside LogPS-6.172. based on the data obtained that the test compound Quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside can penetrate the CNS.

DISCUSSION

The antifungal activity of the Langir bark fraction was tested on *Malassezia furfur* with *in vitro* and *in silico* approaches. *Malassezia furfur* is one of the fungi that causes dandruff in the hair so that the test results can later be used with the development of the Langir bark fraction formula as an anti-dandruff.

In vitro testing of *Malassezia furfur* was carried out on extracts and fractions. The test results showed that extracts and fractions showed inhibition against the growth of *Malassezia furfur*. The *n*-hexane and water fractions showed the best inhibitory activity and their activity did not show any difference with 1% ketoconazole positive control. Based on the Clinical and Laboratory Standards Institute (CSLI), which categorizes antimicrobial inhibition as susceptible (>20 mm), intermediate (15-19 mm), and resistant (<14 mm) [28]. The *n*-hexane and water fractions are in the intermediate category.

Molecular docking uses the Lanosterol 14-alpha demethylase receptor, which plays a role in the process of synthesizing the fungal cell wall with the test ligand which is then visualized to see the interaction between the ligand and the receptor. The interactions that are formed between the ligand and the receptor are in the form of hydrogen bonds, electrostatic interactions, hydrophobic interactions and bonds that give the value of the bond energy (ΔG) of the ligand-receptor [29]. Based on fig. 4 and 5, there is an interaction produced between the ligand and the receptor in the form of Van der Waals bonds, hydrogen bonds, unfavorable donors, pi-cation, pi-pi T-shape, alkyl, and pi-alkyl.

Van der Waals bonds are hydrophobic, which contributes to the formation of protein stability and are included in the category of weak bonds that are easily separated and these bonds occur when the atoms are close enough. This bond is generated between the receptor and Tamarixetin 3-rutinoside with amino acid residues Asp461, Met462, Glu455, Ser451, Gly447, Trp460, Cys481, and Val463, Quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside with amino acids Leu119, Phe233, Leu137, Val128, and His309, Albiziasaponin A with amino acids Lys219, Leu213, Met305, Leu304, His304, Tyr221, Ile197, Gln308, Thr229, Ser193, Asp225, Thr516, and Asp516, Albiziasaponin C compounds with amino acids Ile197, Glu194, Ser193, Asp190, Asp225, Thr516, Pro230, Thr229, Ile231, and Leu240, Albiziasaponin D compounds with amino acids Ser226, Thr229, Asn242, Asp187, Ala218, Gln308, Ile197, and Ser193.

One of the factors that can affect the stability of proteins is hydrogen bonding. This type of bond is very strong because it can produce bonds with long distances between the ligand and the receptor [30]. This bond is formed between the receptor and the compound Tamarixetin 3-rutinoside with the amino acids Ile482, Leu450, and Arg480, the compound Quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside with the amino acid Thr310, Val119, Ser517, Gln140, Lys141, His479, and Arg480, Albiziasaponin A with amino acid Ala218, compound Albiziasaponin C with amino acid Asn242, Albiziasaponin D compound with amino acids Glu194, and Asp190.

The pi-alkyl bond is a weak bond that results from the interaction of the aromatic group and the electron-withdrawing group of the alkyl group. Based on the analysis results, this bond is formed between the receptor and the Tamarixetin 3-rutinoside compound with the amino acid Lys 145, the quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside compound with the amino acid Tyr119, the Albiziasaponin A compound with amino acid Pro 230, Albiziasaponin C with amino acid Ala 218, and Albiziasaponin D with amino acids Leu213, and Ala218. This bond is quite weak and easily released [30].

The ADME-Tox prediction for Tamarixetin 3-rutinoside, Quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside, Albiziasaponin A, Albiziasaponin C and Albiziasaponin D showed that the tested compounds had absorption profiles, good metabolism and excretion compared to the standard compound ketoconazole.

CONCLUSION

The Langir bark fraction has the potential to inhibit the growth of *M. furfur*, and the water fraction has the best inhibitory activity with an inhibition zone of 17.33 mm at 15% and 18.67 mm at 20% (moderate category). Molecular docking results on the Lanosterol 14-alpha demethylase receptor with the test compound having a very low binding energy derived from the compound Tamarixetin 3-rutinoside, Quercetin-3-glucosyl-(1,3)-rhamnosyl-(1,6)-galactoside, Albiziasaponin A, Albiziasaponin C and Albiziasaponin D.

ACKNOWLEDGEMENT

The authors would like to thank the Department of Pharmacy of Mandala Waluya University, Kendari, and all related parties for their support and assistance during the study.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare that there is no conflict of interest.

REFERENCES

1. Borda LJ, Wikramanayake TC. Seborrheic dermatitis and dandruff: A comprehensive review. J Clin Investig Dermatol. 2015 Dec;3(2). doi: 10.13188/2373-1044.1000019, PMID 27148560.
2. Manuel F. Is dandruff a disease? Int J Trichology. 2010 Jan;2(1):68. doi: 10.4103/0974-7753.66922, PMID 21188033.

3. Misery L, Rahhali N, Duhamel A, Taieb C. Epidemiology of dandruff, scalp pruritus and associated symptoms. Acta Derm Venereol. 2013;93(1):80-1. doi: 10.2340/00015555-1315, PMID 22277979.
4. Lopez Ponce D, Zuazo F, Cartes C, Salinas Toro D, Perez Valenzuela C, Valenzuela F. High prevalence of demodex spp. infestation among patients with posterior blepharitis: correlation with age and cylindrical dandruff. Arch Soc Esp Oftalmol. 2017 Sep;92(9):412-8. doi: 10.1016/j.oftal.2017.01.001, PMID 28552438.
5. Paulino LC. New perspectives on dandruff and seborrheic dermatitis: lessons we learned from bacterial and fungal skin microbiota. Eur J Dermatol. 2017 Jun;27Suppl 1:4-7. doi: 10.1684/ejd.2017.3038, PMID 28690211.
6. Ranganathan S, Mukhopadhyay T. Dandruff: the most commercially exploited skin disease. Indian J Dermatol. 2010;55(2):130-4. doi: 10.4103/0019-5154.62734, PMID 20606879.
7. Manuel F, Ranganathan S. A new postulate on two stages of dandruff: a clinical perspective. Int J Trichology. 2011 Jan;3(1):3-6. doi: 10.4103/0974-7753.82117, PMID 21769228.
8. Turner GA, Hoptroff M, Harding CR. Stratum corneum dysfunction in dandruff. Int J Cosmet Sci. 2012 Aug;34(4):298-306. doi: 10.1111/j.1468-2494.2012.00723.x, PMID 22515370.
9. Lin Q, Panchamukhi A, Li P, Shan W, Zhou H, Hou L. Malassezia and staphylococcus dominate scalp microbiome for seborrheic dermatitis. Bioprocess Biosyst Eng. 2021 May;44(5):965-75. doi: 10.1007/s00449-020-02333-5, PMID 32219537.
10. Rudramurthy SM, Honnavar P, Dogra S, Yegneswaran PP, Handa S, Chakrabarti A. Association of malassezia species with dandruff. Indian J Med Res. 2014 Mar;139(3):431-7. PMID 24820838.
11. Cabanes FJ. Malassezia yeasts: how many species infect humans and animals? PLOS Pathog. 2014 Feb;10(2):e1003892. doi: 10.1371/journal.ppat.1003892, PMID 24586146.
12. Punyoyai C, Sirilun S, Chantawannakul P, Chaiyana W. Development of antidandruff shampoo from the fermented product of Ocimum sanctum Linn. Cosmetics. 2018;5(3):1-12. doi: 10.3390/cosmetics5030043.
13. Bulmer AC, Bulmer GS. The antifungal action of dandruff shampoos. Mycopathologia. 1999;147(2):63-5. doi: 10.1023/a:1007132830164, PMID 10967964.
14. Loing E, Lamarque E, Borel M. New targets in the battle against dandruff. J Cosmet Sci. 2017;68(1):107-13. PMID 29465391.
15. Angiolella L, Carradori S, Maccallini C, Giusiano G, Supuran CT. Targeting Malassezia species for novel synthetic and natural antidandruff agents. Curr Med Chem. 2017;24(22):2392-412. doi: 10.2174/0929867324666170404110631, PMID 28393697.
16. Hamundu M, Sahidin R. Identifikasi dan determinasi tanaman obat tradisional masyarakat sulawesi tenggara pada arboretum prof. Mahmud Hamundu Universitas Haluoleo. Maj Farm Indones. 2008;19(2):101-7.
17. Hassoon IM, Kassir SA, Altaie SM. A review of plant species identification techniques. International Journal of Science and Research 2018;7(8):2016-9.
18. Balouiri M, Sadiki M, Ibnsouda SK. Methods for *in vitro* evaluating antimicrobial activity: a review. J Pharm Anal. 2016 Apr;6(2):71-9. doi: 10.1016/j.jpha.2015.11.005, PMID 29403965.
19. Afendi FM, Okada T, Yamazaki M, Hirai Morita A, Nakamura Y, Nakamura K. KNApSAcK family databases: integrated metabolite-plant species databases for multifaceted plant research. Plant Cell Physiol. 2012 Feb;53(2):e1. doi: 10.1093/pcp/pcr165, PMID 22123792.
20. Apweiler R, Bairoch A, Wu CH, Barker WC, Boeckmann B, Ferro S. UniProt: the universal protein knowledge base. Nucleic Acids Res. 2004 Jan;32:D115-9. doi: 10.1093/nar/gkh131, PMID 14681372.
21. Schwede T, Kopp J, Guex N, Peitsch MC. SWISS-MODEL: An automated protein homology-modeling server. Nucleic Acids Res. 2003 Jul;31(13):3381-5. doi: 10.1093/nar/gkg520, PMID 12824332.
22. McGinnis S, Madden TL. BLAST: at the core of a powerful and diverse set of sequence analysis tools. Nucleic Acids Res. 2004 Jul;32:W20-5. doi: 10.1093/nar/gkh435, PMID 15215342.
23. Hollingsworth SA, Karplus PA. A fresh look at the Ramachandran plot and the occurrence of standard structures in proteins. Biomol Concepts. 2010 Oct;1(3-4):271-83. doi: 10.1515/BMC.2010.022, PMID 21436958.
24. Huey R, Morris GM, Forli S. Using AutoDock 4 and AutoDock vina with AutoDockTools: A tutorial. Mol: Scripps Research Institute; 2012.
25. Abdurrahman S, Ruslin R, Hasanah AN, Mustarichie R, Ifaya M. Active antialopecia chemical identification of merremia peltata leaves and computational study toward androgen receptor using molecular docking and molecular dynamic simulation. Scientific World Journal. 2022;2022:1123047. doi: 10.1155/2022/1123047. PMID 35978863.
26. Fiser A. Template-based protein structure modeling. Methods Mol Biol. 2010;673:73-94. doi: 10.1007/978-1-60761-842-3_6, PMID 20835794.
27. Ho BK, Brasseur R. The Ramachandran plots of glycine and pre-proline. BMC Struct Biol. 2005;5:14. doi: 10.1186/1472-6807-5-14. PMID 16105172.
28. Iatta R, Figueredo LA, Montagna MT, Otranto D, Cafarchia C. *In vitro* antifungal susceptibility of Malassezia furfur from bloodstream infections. J Med Microbiol. 2014 Nov;63(11):1467-73. doi: 10.1099/jmm.0.078709-0, PMID 25168965.
29. Fang Y. Ligand–receptor interaction platforms and their applications for drug discovery. Expert Opin Drug Discov. 2012;7(10):969-88. doi: 10.1517/17460441.2012.715631, PMID 22860803.
30. Chen D, Oezguen N, Urvil P, Ferguson C, Dann SM, Savidge TC. Regulation of protein-ligand binding affinity by hydrogen bond pairing. Sci Adv. 2016 Mar;2(3):e1501240. doi: 10.1126/sciadv.1501240, PMID 27051863.