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ETHYL ACETATE FRACTION IN ETHANOL EXTRACT OF NONI FRUIT MODIFIED BY ZEOLITE AS ANTI-SEBORRHEIC DERMATITIS: *In-vitro* AND *In-silico* STUDIES

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ABSTRACT

Seborrheic dermatitis caused by *Malassezia globosa* is a relapsing disease that allows for multi-drug resistance. The discovery of new antifungal agents and zeolites as a carrier is needed for further antifungal treatment. This research aims to determine the antifungal activity from extracts and fractions of Noni fruits with or without activated zeolite and predict its inhibitory activity against LIP1(SMG1) enzyme by *in silico* test. According to statistical results, the extract 20%-zeolite and ethyl acetate fraction 5%-zeolite of Noni fruits provided a higher inhibition zone than those without zeolite. Ethyl acetate fractions as active compounds identified by GC-MS followed by molecular docking. The prediction of the molecular docking depicts that bromocriptine (alkaloid quinoline group) showed a lower binding affinity (ΔG) compared to ketoconazole as a standard with similar amino acid residues Asn253, Phe278, Gly291, and Gln282. The SEM-EDX description of ethyl acetate fraction modified by zeolite shows that the active compounds from Noni fruits adsorbed the zeolite framework well. ADMET-Tox properties of bromocriptine were neither mutagenic nor carcinogenic. Alkaloid group is effective as a new antifungal agent for Seborrheic dermatitis, and zeolite as a carrier matrix provides a better inhibitory activity.

Keywords: Noni Fruit, Anti-Seborrheic Dermatitis, Zeolite, *Mallasezia globosa*, Alkaloid.

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INTRODUCTION

Seborrheic Dermatitis (SD) is a skin disorder that usually occurs on the scalp characterized by scaly and peeling skin accompanied by itching, dandruff, and inflammation. *Malassezia* sp has been widely reported as the cause of this disease.[1,2] SD is associated with hair loss where the uncontrolled *Malassezia* sp disrupts the hair follicle cycle resulting in hair loss, and the telogen phase (the resting phase of the hair follicle) takes longer until baldness occurs.[3,4] Most of the antifungal drugs available are from the azole group found to have side effects of skin thinning and contact dermatitis.[5] In more severe cases, fungal infection often leads to the expansion of multi-drug resistances.[6,7] Clinical treatment of antifungal drugs was considered a failure with repeated recurrences of disease and the presence of high long-term cytotoxic effects.[8,9] From this context, discovering new antifungal agents for SD is essential, especially those from plants because they generally have low cytotoxic and side effects for long-term use. The public uses Noni fruit (*Morinda citrifolia* L.) as a hair mask to treat hair loss, dandruff, a hair blackener, and remove hair larvas and head lice. Several studies have reported that many Noni fruits are antifungal.[10,11] The 15% concentration of Noni fruit extracts can reduce fungal growth by 58.21% in the milk storage room.[12] In addition, the Noni plant is straightforward to grow in Indonesia, and scientific research has specifically not been done much as an antifungal of *Malassezia* sp for SD treatment. The bioactive compound of Noni fruit that potentially works as a fungal inhibitor is alkaloids. The same basic

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framework of the alkaloid group between herbal plants and the azole group of drugs is a nitrogenous base group that inhibits cytochrome P-450 in the lanosterol 14α-demethylase enzyme, which inhibits the conversion of lanosterol to fecosterol and then blocks the ergosterol biosynthesis.[13] An oily scalp characterizes symptoms of SD. SD is also caused by other factors such as temperature, pH, and uncertain environmental light, causing a decrease in antifungal compounds' ability to produce new derivative products that are not always safe for the human body.[14,15] Therefore, a drug carrier matrix is needed. This carrier matrix is expected to keep the active ingredient of the drug via a sustained-release system to produce the desired therapeutic effect by continuously releasing some other drugs over an extended time (8 to 12 hours).[16]

Natural zeolite is a composite mineral with a unique three-dimensional framework composed of a series of tetrahedral alumina silicate, which has higher porosity, thermal and chemical stability, low toxicity, and the possibility of controlling their physicochemical properties. Thus, zeolite minerals were suggested as excipients in pharmaceutical formulations.[17] Several studies reported that zeolite was applied as a carrier matrix of active ingredients of isoniazid for the treatment of tuberculosis[18], antitumor of ribonuclease binase[19], antibacterial of salicylate compounds[20], and anticancer of solasodine.[21] In this study, the zeolite's abilities and properties are expected to act as a carrier matrix for the active compound of Noni fruit. Natural zeolite characteristics used in this study are necessary to reveal the physical and chemical properties of zeolite particles so that zeolite utilization will be optimal and improve physical and chemical activation performance to remove impurities in the zeolite pores. Improving performance is one of the natural zeolite mineral resource conservation efforts that enhance the value-added minerals.[22]

Completeness of data on the *in vitro* mechanism of Noni fruit needs to be done through the *in silico* approach. This method is used to predict the ability of the medicinal compounds in the Noni fruit that act as inhibitors of *Malassezia globosa*, which causes SD through the small binding affinity value of the active compound of the ligand against the target protein. Other *in silico* approaches in predicting absorption, distribution, metabolism, excretion, and toxicity (ADME-Tox) are necessary for developing new drugs. They are the primary cause of a candidate molecule failure in a drug design.[23]

EXPERIMENTAL

Material and Instrumentations

Noni fruit, from the *Morinda citrifolia* L. plant, was harvested from local farmers in South Lampung, Lampung-Indonesia. The determination was carried out at the Botanical Laboratory, Biology Department, Universitas Lampung, Indonesia. The solvents used for extraction and fractionation were ethanol 96%, NaCMC 1%, ethyl acetate (EtOAc), *n*-hexane, and distilled water purchased from Merck Co. Ltd. The tested organism was *Malassezia globosa* purchased from the Parasitology Department, Universitas Indonesia. Potato Dextrose Agar (PDA) M096 was purchased from HiMedia Laboratories and 0.9% sterile physiological NaCl and ketoconazole as standard controls from Kimia Farma Co. Ltd.

Zeolite was purchased from CV. Minatama, Lampung-Indonesia is known as natural zeolite Lampung (NZL) with a particle size of approximately 5 µm. NZL was characterized using XRF (Omnian ED- XRF PANalytical Epsilon 3^{XLE}), chemically activated with HCl 1 M solution while heated at 70 °C for 1 hour and left overnight. NZL was filtered and washed with aquadest until it was neutral (pH = 7), then physically activated in an oven at 100–120 °C for 3 hours, resulting in an active zeolite.[24] SEM (ZEISS EBO MA 10, EHT 15.00 kV) equipped with EDX detector to investigate the difference in the surface morphology between the active fraction of Noni fruit, pure NZL, and active fraction-NZL with a magnification of 5000x. The compounds of the best fraction in the antifungal activity test were identified by GC-MS (CP-3800 Variant, MS Saturn 2200, Column HP-5ms 30 M x 0,25 MMID x 0.25µm) with a flow rate of 1 mL/min for further as a database for ligand compounds in the *in silico* test. Operating system Windows 10 Home Single Language 64-bit (10.0, Build 19041), AMD Ryzen 5 3500U (8 CPUs), hard disc drive 500 GB, and RAM 4 GB were used to run *in silico* process.

Preparation and Standardization of Extract (Specific and non-Specific Parameters)

The selected Noni fruits were extracted using the maceration method with 96% ethanol. The obtained viscous extract was standardized for specific parameters and non-specific parameters.[25] Phytochemical

screening of alkaloids, flavonoids, phytosterol, anthraquinones, saponins and tannins were accomplished using standard methods.[26-28] For further purification, the ethanol extract was then partitioned between *n*-hexane–H_2O and EtOAc–H_2O, respectively.

Preparation of the Extract and Fractions Modified by NZL (Extract-NZL and Fraction-NZL)
A total of 0.5 grams of Noni fruit extract was added with 0.1 gram of active NZL in 10 mL of 1% NaCMC (5%–NZL) solution. It was stirred and left for 24 hours, then filtered. The remaining sediment was heated in an oven at 105 °C for 1 hour.[20-21] The same treatment was also done for other concentrations of modified extracts and fractions with a constant NZL (0.1 gram).

***In Vitro* Activity Test**
According to previous methods, the antifungal activities of extract and fractions were evaluated using the agar well diffusion method on potato dextrose agar (PDA) against *M. globosa*.[29-30] The minimum inhibition concentration (MIC) was determined by measuring the inhibition zone diameter using digital slide calipers. The test was carried out in two repetitions and was statistically analyzed using SPSS 24.

***In Silico* Activity Test**
This stage was preceded by identifying the active fraction compounds from the results of the antifungal activity test using GC-MS. The structures of these compounds were retrieved from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov/) and downloaded in SDF format, then compound ligands were prepared using the AutoDock Tools program and stored in PDB format [31,32]. The selected target receptor was the LIP1 (SMG1) group (PDB ID: 3UUF), whose protein crystal structure was obtained from http://www.rscb.org/pdb/. This receptor was used to predict the lipase activity of *M. globosa.*[33,34] The docking process uses standard docking protocols, AutodockTools-1.5.6.[31,35] The docking conformation as the best pose was chosen from which it had low binding energy of less than 0.1 nm in positional root mean square deviation (RMSD).[36] Receptor and ligand interactions and amino acids bond with ligands were visualized using Biovia Discovery Studio Visualizer 2019.[37,38] The pharmacokinetic properties and the prediction of the toxicity of the test compound ligand as new drug candidates need to be known by using the Pre-ADMET on the https://preadmet.bmdrc.kr/site.

Surface Morphological Analysis
The results of the antifungal activity of the NZL-fraction group showing the minimum inhibitory concentration (MIC) were characterized by SEM to see differences in surface morphology between pure NZL, active fraction, and active fraction-NZL. Energy-dispersive X-ray (EDX) to detect the presence and quantity of elements on the surface of the zeolite sample, which has been loaded with the active fraction.

RESULTS AND DISCUSSION

Extract Standardization
According to The Cronquist Clarification System (1981) and APG II, the determination results of Noni plants refer to *Morinda citrifoli*a L. The viscous extract's yield, water content, and total ash content were 17.28%, 7.21%, and 4.41%, respectively. Phytochemical screening of extract on alkaloids, flavonoids, phytosterol, anthraquinones, saponins, and tannins showed positive results. The organoleptic of the extract showed a dark brown color, distinctive odor, and slight bitterness. The standardization parameter of Noni fruit extracts shows results by the Indonesian Herbal Pharmacopoeia Standards.[25] The crude extract (20.15 gram) was carried out with a liquid to liquid partitioning with *n*-hexane-H_2O, and EtOAc-H_2O, resulting in the yield of the fractions *n*-hexane (1.70%), EtOAc (42.11%), and H_2O (55.25%), successively.

XRF Characterization
XRF characterized NZL in addition to showing the level of safety against heavy metals. It also indicates the content of Si-9.494% and Al-63.167% as the main composition of zeolite. There were contents of other metals and oxides but in low amounts.

***In Vitro* Activity Test**

The antifungal activity for the extract and extract-NZL was carried out, and the inhibition zone diameters were measured and crude ethanol extract after partitioning liquid to liquid with *n*-hexane, EtOAc, and H_2O was also done against *M. globosa*, resulting in an average inhibition zone of 0; 20.19 and 16.27 mm, respectively. The results showed that the EtOAc was the most active fraction, followed by antifungal activity against *M. globosa* and modified with NZL. Data for the inhibition zone of EtOAc fraction and EtOAc fraction-NZL against *M. globosa* with a 5–50% concentration are presented in Table-1.

Table-1: Inhibition Zone of the Extract and Extract-NZL; EtOAc Fraction and EtOAc Fraction-NZL

Concentration (%)	Diameter of Inhibition Zone (mm)			
	Extract	Extract-NZL	EtOAc Fraction	EtOAc Fraction-NZL
5	4.63±0.69^{b}	6.25±0.07^{b}	0.00±0.00^{a}	5.7±0.15^{b}
10	5.78±0.56^{b}	7.31±0.72^{b}	8.29±0.61^{b}	11.13±0.36^{c}
20	10.25±1.0^{c}	13.52±0.14^{d}	9.83±0.40^{bc}	12.26±0.22^{c}
30	13.63±0.24^{d}	15.20±0.16^{de}	11.97±1.13^{c}	13.44±0.32^{d}
40	14.58±0.48^{d}	16.68±0.69^{e}	13.84±0.76^{d}	15.26±0.16^{e}
50	15.32±0.07^{d}	22.32±0.28^{f}	14.28±0.04^{d}	15.36±0.03^{e}
Ketoconazole	24.39±0.63^{f}	-	24.39±0.63^{f}	-
NaCMC 1%	0±0.00^{a}	-	0±0.00^{a}	-
NZL	0±0.00^{a}	-	0±0.00^{a}	-

Note: each value shows the mean±SD. Values with different symbols are significantly different from ketoconazole control $p<0.05$

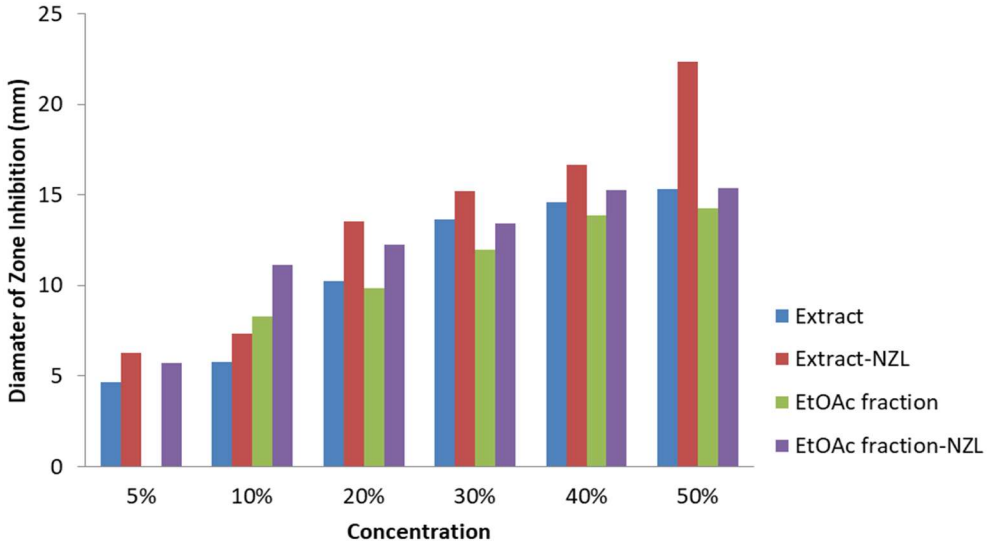


Fig.-1: The Graph of Inhibition Zone Extract and Extract-NZL; EtOAc Fraction and EtOAc Fraction-NZL against *M. globosa*

The statistical results showed that the data variants were homogeneous and followed by the ANOVA test. A significance value of $p<0.05$ was obtained, which means an effect of the addition of NZL treatment. Thus, it continued with Tukey's further test and showed significant differences between groups, as seen from the top letter. The diameter of the inhibition zone in the extract was consistently lower than that of the extract-NZL. Starting at a concentration of 20% extract and 20% extract-NZL, it looks significantly different determined from statistical tests. The 50% extract-NZL showed the same inhibition zone diameter as ketoconazole. The same phenomenon also occurred in the antifungal activity test of the

EtOAc partition. The EtOAc fraction inhibition zone diameter was consistently lower than EtOAc fraction-NZL. After testing the statistics, it showed that the concentrations of 5% EtOAc fraction and 5% EtOAc fraction-NZL were significantly different. Overall, the results of statistical tests explained that there was an effect of the addition of NZL in each concentration group which caused the performance of Noni fruit extracts and the results of its EtOAc partition were better in inhibiting the *M. globosa* fungus than those without NZL.

The role of NZL was thought to be the main factor that causes this phenomenon; NZL acts as a carrier matrix with an adsorption mechanism because NZL has many surface pores so that the molecules of compound ions contained in the Noni fruit can be adsorbed into the NZL framework. NZL pores have been reported to be 1.63 m^2/g and 3.628 nm.[39] The molecules of compound ions of the Noni fruit can move so freely that ion exchanges occur reversibly without damaging the main framework of the NZL and will undergo a slow-release process during its antifungal activity. Another exciting thing was that the results of the inhibition zone activity in the NZL control did not show any antifungal activity, the same as the results of NaCMC 1% as a negative control (Table-3). There were no active compounds in NZL control adsorbed into the zeolite framework. Therefore no active compounds were released during the activity. This NZL carrier matrix was also confirmed to contain unhazardous heavy metals after XRF analysis.

The SEM image reveals the differences between EtOAc 5%, pure NZL, and EtOAc 5%-NZL (Fig.-2). The EtOAc 5% looks like a cloud bubble with a dense surface without gaps (Fig.-2a), pure NZL looks like a crystal in the form of needle fragments and porous (Fig.-2b). Natural Zeolite Lampung (NZL) was a type of clinoptilolite with a needle crystal surface and confirmed with the prominent characteristic peaks of clinoptilolite by XRD analysis based on the previous literature.[39] There was agglomeration between the EtOAc 5% compound molecules with NZL crystals, with the appearance of porous aggregates such as cavities and canals more clearly visible (Fig.-2c). It identified that the EtOAc 5% compounds molecules were bound into the zeolite crystal framework with the appearance of more cavities and canals. However, the bound was weak, released, or exchanged after receiving a particular treatment (ion exchange). A similar result, adsorption of ZnO into zeolite, also gave a micrograph that looked denser and coarser than before the addition of ZnO.[40]

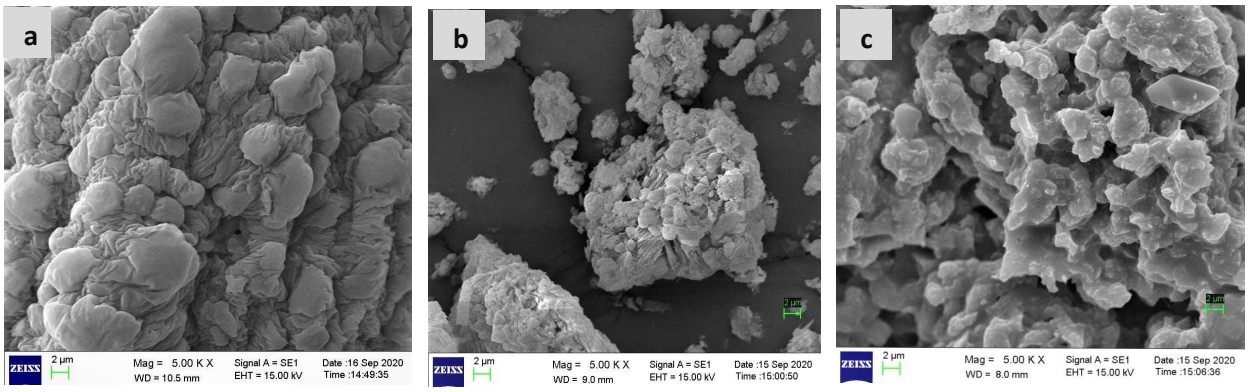


Fig.-2: Morphology of EtOAc 5% (a), pure NZL (b), EtOAc 5%-NZL (c)

The EDX-ray results showed an increase in the amount of carbon in the EtOAc 5%-NZL compared to pure NZL, and this result confirmed that the amount of carbon from the EtOAc 5% compound molecule was well adsorbed to the surface of the NZL structure, increasing the number of carbon elements as much as 89.86% (Table-2). In addition, the number of structural elements of NZL Si and Al did not change significantly, which confirmed that the NZL framework structure was stable before and after loading by EtOAc 5% molecules. Similar results were obtained in previous work on zeolite 5A showing the ratio of Si and Al, which did not change significantly before and after loading by curcumin.[41]

In Silico Activity Test

The compounds in the EtOAc fraction need to be known, referring to the database in silico testing to information on new candidate compounds in the treatment of SD. The results of GC-MS showed twelve

peaks of the compound, and their respective chemical structures were identified in Table-3. Based on the antifungal activity test, a molecular mechanism was carried out to predict the EtOAc fraction compounds as an inhibitor of the SMG1 group of the lipase enzyme (LIP1) from *M. globosa*, which causes SD through the *in-silico* test. The molecular docking analysis of EtOAc fraction and ketoconazole as a standard was presented as the binding affinity (Kcal/mol) value (Table-4).

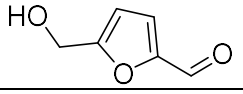
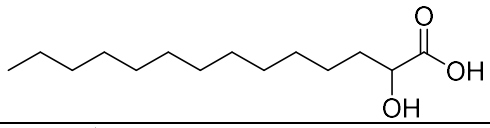
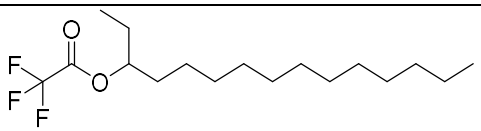
Table-2: EDX-Ray of EtOAc 5%, Pure NZL and EtOAc 5%-NZL

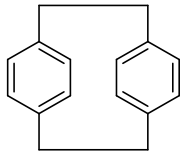
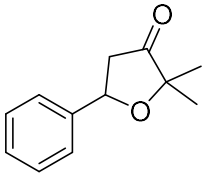
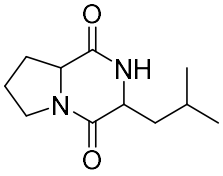
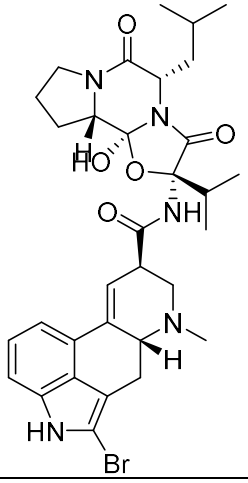
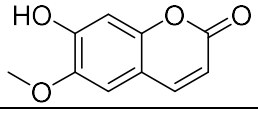
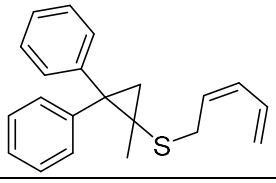
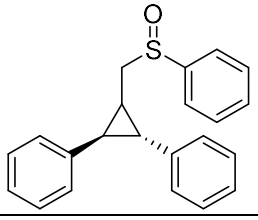
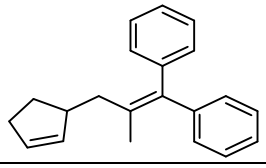
Elements	EtOAc 5% (wt%)	Pure NZL (wt%)	EtOAc 5%-NZL (wt%)
O	17.74	50.36	35.06
Si	-	37.82	30.71
Al	-	3.71	3.28
C	41.23	2.32	20.56

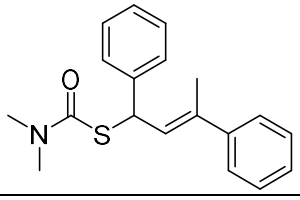
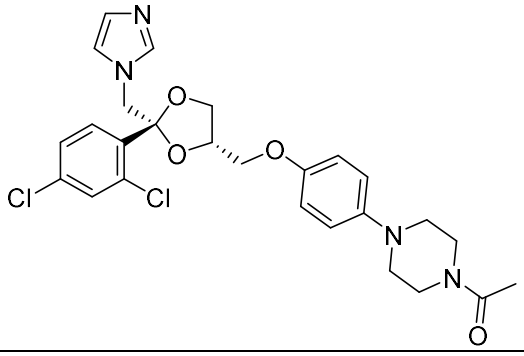
In silico test results confirmed the superiority of the alkaloid group as an antifungal, namely the bromocriptine (Ligand **7**), a derivative of quinoline with the IUPAC name: (6a*R*,9*R*)-5-bromo-*N*-((1*S*,2S,4*R*,7*S*)-2-hydroxy-7-(2-methylpropyl)-5,8-dioxo-4-propan-2-yl-3-oxa-6,9-diazatricyclo[7.3.0.02,6]dodecan-4-yl]-7-methyl-6,6a,8,9-tetrahydro-4H-indolo[4,3-fg]quinoline-9-carboxamide which was the smallest binding affinity value (ΔG = -7.17 kcal/ mol). It indicates the ease of the compound in binding and inhibiting the receptors (Table-4), these results were relevant to the ketoconazole as a standard compound, a piperazine derivative from the alkaloid group. Although the chemical structure of ligand **7** and ketoconazole was different, they have the same interaction of amino acid targets by forming hydrogen interaction with the amino acid Asn253 and by forming hydrophobic interaction with the same amino acid residues Phe278, Gly291, and Gln282 (Table 5). These results were relevant to the previous studies, which stated that hydrophobic interactions in the inhibitory activity of the LIP1 enzyme resulted in the amino acid residue Phe278[33]. Studies of Noni fruit in treating SD have not been widely carried out, but it was suspected that the alkaloid compounds from Noni fruit have an important role in antifungal activity. The alkaloid group was characterized by a free and single pair of *N*-atoms in the amine group. Primary, secondary, and tertiary amines could penetrate and inhibit the biosynthesis of chitin in fungi. The group of alkaloids from the leaf extract of *Stachytarpheta jamaicensis* (L.) has also been proven as an anti-microbial human pathogenic bacteria.[42]

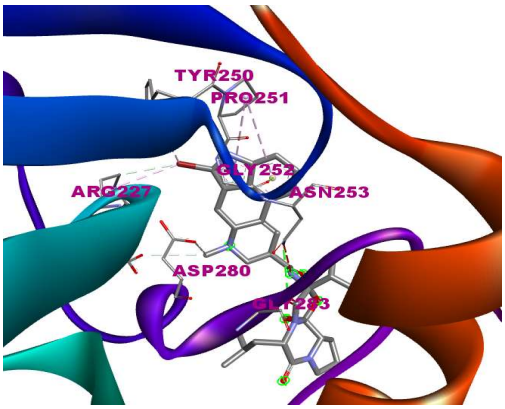
Another study also reported that the quinoline-derived alkaloids from the extract of *Waltheria Indica* L. roots had been shown to have the antifungal activity of *Candida albicans.*[43] Another quinoline derivative, synthesized azitidinone, showed good antifungal activity against *A. niger*.[44] Furthermore, to complement the *in silico* data, the prediction of ADME-Tox properties of ligand 7 was carried out as a reference in the development of new drug candidates in the treatment of SD, and compared with ketoconazole as a standard (Table-6).

Table-3: Major Chemical Compounds of the EtOAc Fraction from Noni Fruit

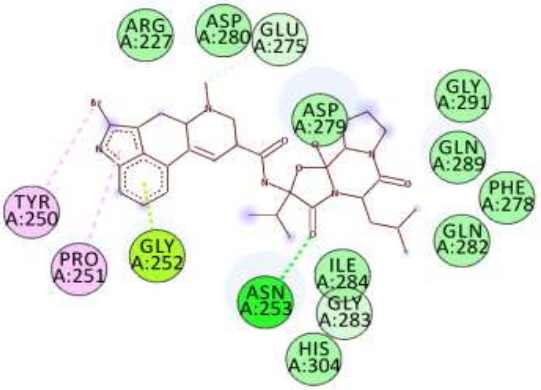
Peak	RT (Min)	Compound	MW (g/mol)	Structure	% Area
1	14.155	2-Furancarboxaldehyde,5-(hydroxymethyl)	126		17.42
2	16.083	Tetradecanoic acid, 2-hydroxy-	244		1.25
3	20.721	3-Trifluoroacetoxypentadecane	324		1.79

4	25.951	[2.2]Paracyclophane	208		4.55
5	27.801	3(2H)-Furanone,dihydro-2,2-dimethyl-5-phenyl-	190		10.92
6	28.743	Pyrrolo[1,2-a]pyrazine-1,4-dione,hexahydro-3-(2-methylpropyl)-	210		10.11
7	31.042	Bromocriptine	653		6.14
8	31.542	7-Hydroxy-6-methoxy-2H-1-benzopyran-2-one	192		17.86
9	40.164	Benzene,1,1'-[2-methyl-2-(phenylthio)cyclopropylidene]bis-	316		1.94
10	42.253	(2,3-Diphenylcyclopropyl)methyl phenyl sulfoxide,trans-	332		8.75
11	42.654	1-Propene,3-(2-cyclopentenyl)-2-methyl-1,1-diphenyl-	274		13.98

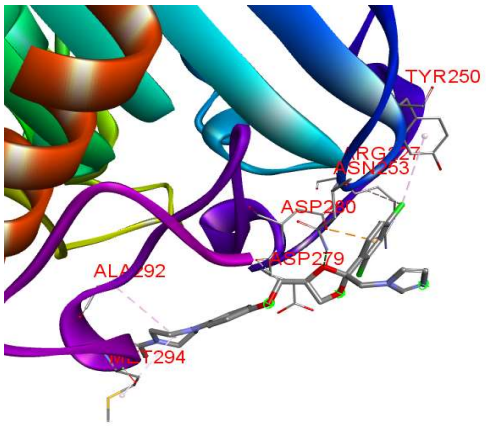
12	43.136	Thiocarbamic acid, N,N-dimethyl,S-1,3-diphenyl-2-butenyl ester	311		5.29
Standard		Ketoconazole			



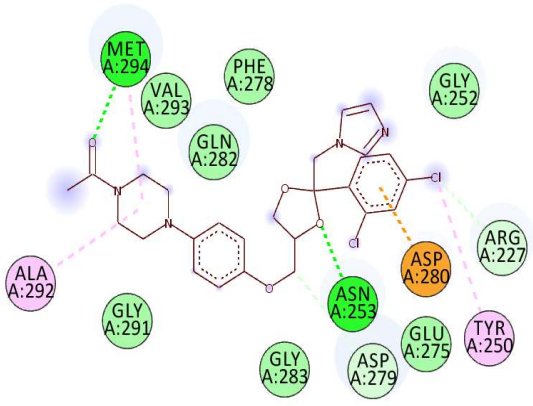
(a)



(b)



(c)



(d)

Fig.-3: Visualization of Molecular Docking Results of Ligand **7**-receptor in 3D (a) 2D (b) and Ketoconazole-receptor in 3D (c) dan 2D (d)

The results of the ADME-Tox properties of ligand **7** show that the HIA (human internal absorption) value was almost the same as that of ketoconazole. It indicates that the ligand **7** compound was well absorbed through the intestine but showed lower permeability than ketoconazole through the barrier between Caco2

intestinal epithelial cells. In contrast, ligand **7** could diffuse across the plasma membrane and interact with plasma proteins better than ketoconazole, as indicated by plasma protein binding (PPB). The toxicity test results for ligand **7** were neither mutagenic nor carcinogenic, which indicates that this compound was safe for long-term use.

Table-4: Antifungal Activity Prediction of EtOAc Fraction from Noni Fruit

Ligand (peak)	Binding Affinity (ΔG) (Kcal/mol)	Ligand (peak)	Binding Affinity (ΔG) (Kcal/mol)
1	-2.24	8	-4.19
2	-1.24	9	-5.20
3	-2.47	10	-5.37
4	-4.03	11	-5.07
5	-3.94	12	-5.30
6	-4.41	Ketoconazole	-6.02
7	-7.17		

Table-5: The Results of Ligand-receptor Amino Acid Residues

Ligand	Residue with Interaction Type	
	Hydrogen Interaction	Hydrophobic Interaction
Ligand 7	Asn253	Phe278,Gly291,Gln282,Gln289,Ile284,Asp279, His304, Arg227, Asp280
Ketoconazole	Asn253, Met294	Phe278,Gly291,Gln282, Val293,Gly252, Glu275,Gly283

Table-6: Results of Prediction of ADME-Tox Properties

Compounds	Absorption		Distribution	Mutagenic	Carcinogenic
	HIA (%)	Caco-2 (nm sec^{-1})	PPB (%)		
Ligand 7	93.38	22.80	72.38	-	-
Ketoconazole	95.35	51.74	18.26	+	-

CONCLUSION

Acquired from the *in vitro* study, it has been proven that Noni fruit extracts and the results of EtOAc partition of Noni fruit act as an antifungal for *Malassezia globosa*, which causes Seborrheic dermatitis. However, there was an important point: the addition of NZL provides the better inhibitory activity. Thus, it can be concluded that the role of NZL as a carrier matrix for active compounds can be accounted for, which was confirmed by changes in the micrograph morphology.

In the silico study approach, the compounds were predicted as an antifungal for *Malassezia globosa*, causing SD to be a quinoline-alkaloid, namely bromocriptine supported by ADME-Tox properties with good results. Thus, it can be concluded that the quinoline alkaloid groups can be used as new antifungal medicinal agents in treating Seborrheic dermatitis.

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