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Antibacterial Potency of Bioactive Compounds from *Areca catechu* Nuts: A Molecular Docking Study Targeting 8H1B

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ABSTRACT.

Areca catechu, a plant in the Arecaceae family, is rich in bioactive secondary metabolite compounds. *Areca catechu* has many benefits and potentials, including its antibacterial properties. This study aims to describe the potential of secondary metabolite compounds as antibacterials targeted at 8H1B and their toxicity profile through in silico analysis. The ligands used in this study were catechin, acatechu B, jacareubin, clindamycin as a comparison compound, and S-adenosylmethionine as a native ligand. The results showed that acatechu B had the lowest binding energy (-12.66 kcal/mol) compared to catechin (-9.44 kcal/mol), jacareubin (-8.99 kcal/mol), clindamycin (-10.93 kcal/mol), and S-adenosylmethionine (-11.76 kcal/mol). According to Biovia Discovery simulations, the *Areca catechu* bioactive compound interacts with 8H1B through van der Waals, conventional hydrogen bonds, and different variants of pi interaction. The toxicity profiles of the *Areca catechu* bioactive compound showed that they were not hepatotoxic, not mutagenic, not carcinogenic, and had safe LD50 values. These results suggest that the *Areca catechu* bioactive compound possesses antibacterial potential by targeting 8H1B.

Keywords: 8H1B, *Areca catechu*, in silico, molecular docking, toxicity.

1. INTRODUCTION

Areca catechu, known as areca nut, is a plant from the Arecaceae family that is widely found in South and Southeast Asia, such as Indonesia, India, Malaysia, China, Myanmar, and Bangladesh [1]. The seeds of this plant are used in traditional medicine due to their health benefits, including treating beri-beri, tenesmus, malaria, abdominal pain, dyspepsia, and diarrhoea. Additionally, areca nuts have the potential to treat conditions such as periodontitis, premature ejaculation, glaucoma, and urinary retention [2]. This is because areca seeds contain various active compounds, including gallic acid, tannins (Catechin, Epichatecin, Arecatannin A-C, Procyanidin A-B), alkaloids (Aracaidin, Arecolin, Acatechu A-B, Guvacine, Guvacoline), flavonoids (Jacereubin, Calquiquelignan N-M, Isorhamnetin, Chrysoeriol, Luteolin, Liquiritigenin), triterpenes, and steroids (Arborinol, Cycloartenol, Fernenol, and Arundoin). These compounds exhibit various pharmacological activities such as antioxidant, anti-parasitic, anti-inflammatory, analgesic, antibacterial, and anti-fungal [3]. One of the significant pharmacological activities of areca nut is antibacterial activity against gram-positive and gram-negative bacteria [4].

Acne vulgaris, commonly known as acne, is a prevalent skin disease resulting from chronic inflammation of the pilosebaceous unit on the face, chest, and back [5]. Acne is frequently associated with increased sebum production due to excess oil production, hyperkeratinization due to skin pore blockage, excess release of skin inflammatory mediators, and bacterial colonization of skin follicles [6]. Gram-positive bacteria that commonly cause acne are *Propionibacterium acnes*, *Staphylococcus epidermidis*, and *Staphylococcus aureus* [7]. Various therapeutic agents, such as retinoid acid, benzoyl peroxide,

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salicylic acid, azelaic acid, vitamins B and C, and various antibiotics (macrolides, clindamycin, and tetracycline), are commonly used to treat acne [8]. However, prolonged use of these chemicals can cause side effects including skin irritation, dizziness, and tinnitus. Additionally, light and laser therapy for acne treatment are also considered to have shortcomings because they cause pain and are expensive [9]. Therefore, the development and understanding of the molecular mechanisms of action of new anti-acne agents, especially natural ingredients, are urgently needed [10].

Ribonucleic acids (RNAs) play a crucial role in the process of protein synthesis. The translation machinery primarily consists of ribosomal RNA, transfer RNAs, and messenger RNAs. Transfer RNAs (tRNAs) play a crucial role as intermediary molecules in the process of protein synthesis. They transport amino acids to the ribosome in a certain sequence determined by the genetic code. The ability of tRNAs to interpret messenger RNA (mRNA) blueprints during translation is critical for ensuring accurate amino acid sequencing and functional protein production [11]. The enzymatic addition of an extensive range of post-transcriptional modifications to tRNAs' structures sets them apart from other RNA molecules. Chemically modified nucleosides are present throughout the tRNA structure, but modifications specifically found in the anticodon stem loop (ASL) region near the site where mRNA and tRNA interact are particularly important [12]. These modifications are often necessary to ensure that the translation process accurately and efficiently decodes mRNA sequences [13]. The crystal structure 8H1B represents the MnmM complex of *S. aureus* with SAM (S-adenosyl-L-methionine) and the tRNA anti-codon stem-loop, this complex playing a crucial role in protein sequencing [14]. This study aims to determine the potential interactions between the active compounds of areca nut (Jacareubin, Acatechu B, and Catechin) and the target protein 8H1B to predict their molecular interactions with 8H1B to assess their potential as anti-acne agents.

2. MATERIALS AND METHODS

2.1 Ligand and Target Protein Preparation

The PDB database [15] was used to obtain the crystal structures of the target protein, 8H1B. Several parameters were considered in the selection of crystal structures. Firstly, it must be a binding structure of the target protein with a native ligand or a small-molecule inhibitor. Secondly, the binding site or catalytic site should not have mutations. The 3D configurations of areca nut active compounds (Jacareubin, Acatechu B, and Catechin) were constructed with Avogadro software [16]. The structures were further optimized using Gaussview 5.0.8 software.

2.2 Molecular Docking and Interaction Visualization

The method of docking was validated using Autodock 1.5.6 [17]. This validation was performed by redocking of the ligand or inhibitor into the binding site of the target protein using a grid box with dimensions of 44 x 18 x 24. The validation process generated an RMSD with value less than 2 Å, indicates that the docking method is suitable for the docking process using the crystal structure. The sizes and positions of the grid box generated from the validation step were used for molecular docking with areca nut active compounds (Jacareubin, Acatechu B, and Catechin), S-adenosyl-L-methionine, and clindamycin as the tested ligands. The interactions between ligands and target proteins were simulated using Biovia Discovery Studio software.

2.3 Toxicity Prediction

Toxicity prediction was performed using the ProTox website, including parameters of hepatotoxicity, carcinogenicity, mutagenicity, and LD50 values.

3. RESULTS AND DISCUSSION

In this study, jacareubin (flavonoid), catechin (tannin), and acatechu B (alkaloid) compounds were used to study their potential as anti-bacterial targeted for the 8H1B protein through an in-silico approach using molecular docking. In addition to these secondary metabolite compounds, clindamycin as a comparative drug and S-adenosylmethionine as a native ligand were used for comparison. The structure of each metabolite and comparator compound can be seen in Figure 1.

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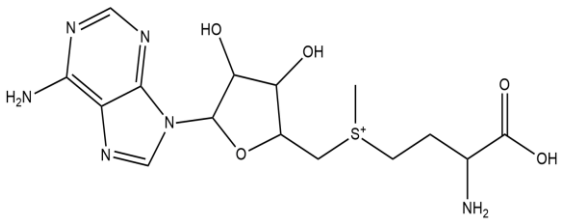

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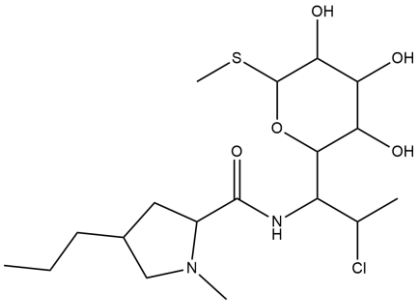

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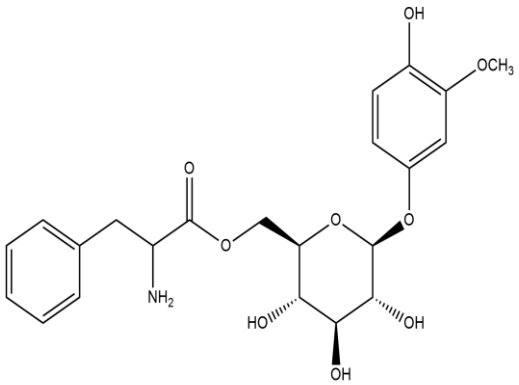

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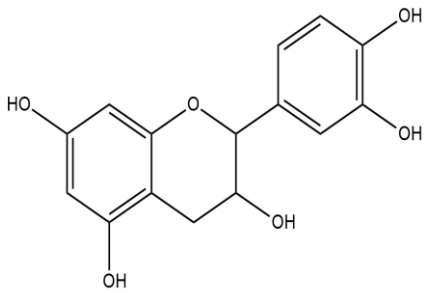

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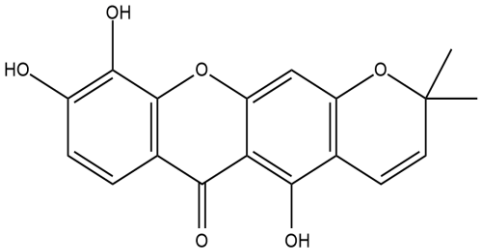

Figure 1.Molecular structure: (a) S-adenosylmethionine, (b) clindamycin, (c) acatechu B, (d) catechin, (e) jacareubin.

Molecular docking simulations were conducted to determine the potential of areca nut active compounds interaction with 8H1B on the active side. Molecular docking is done by tethering the ligand to the active side of the receptor to determine the binding affinity value of each test compound. The results of the molecular docking analysis are presented in Table 1. The simulations yielded binding energy values, also known as docking scores, which indicate the strength of the interaction between the ligands and the target receptors [18]. The binding energy values of S-adenosylmethionine, clindamycin, acatechu B catechin, and jacareubin are -11,76, -10.93, -12,66, -9,44, and -8,99 kcal/mol, respectively. This shows that acatechu B has a stronger binding interaction compared to the native ligand and the commercial drug clindamycin, indicating its potency as an antibacterial agent.

Table 1. Molecular Docking Analysis Results

Compound	Binding Energy (kcal/mol)
S-adenosylmethionine	-11,76
Clindamycin	-10.93
Acatechu B	-12,66
Catechin	-9,44
Jacareubin	-8,99

The docking results were visualized using Biovia Discovery Studio to obtain position and interaction type data. The visualization results of the ligand compound and 8H1B receptor are presented in Figure 2, showing various types of interactions, such as hydrogen bonds, van der Waals, etc. The stability of the complex increases with the number of interactions formed [19]. The visualization results in Figure 2 show that the potential compound, acatechu B, has more diverse types of interactions than other compounds.

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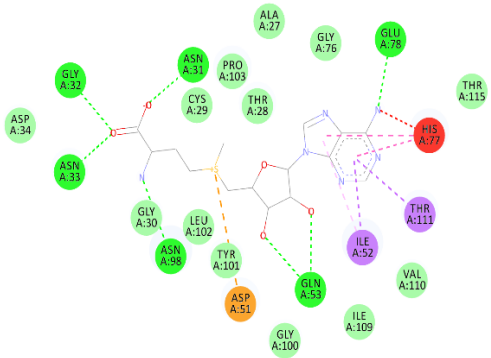

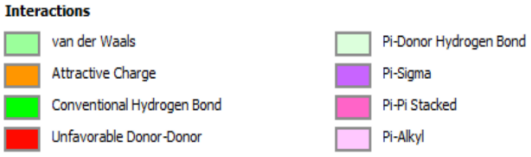

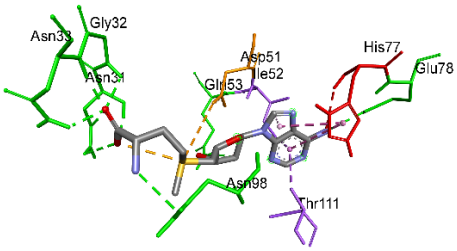

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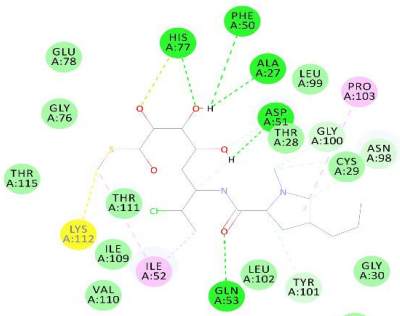

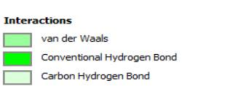

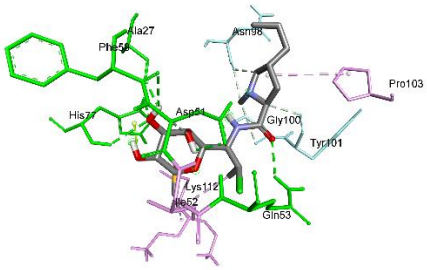

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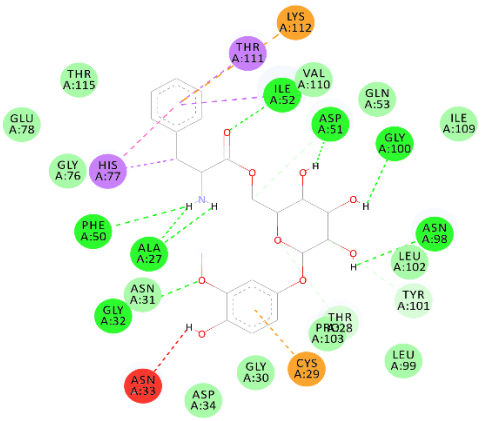

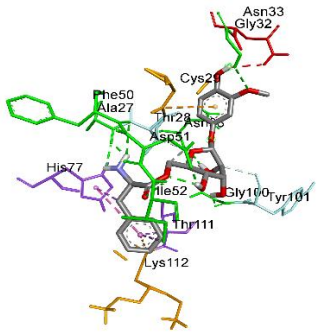

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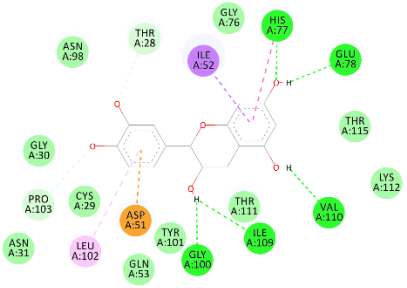

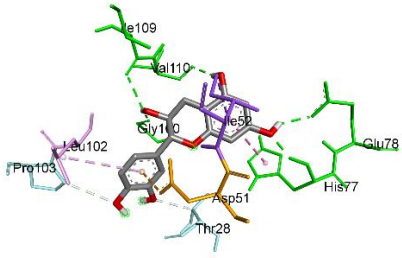

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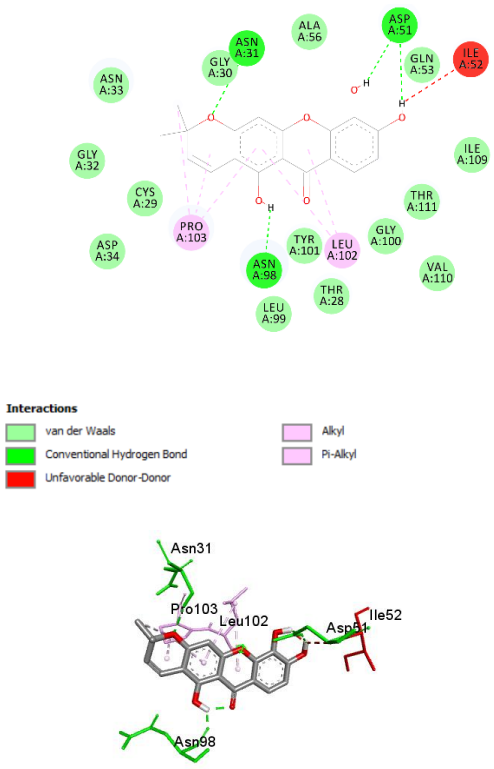

Figure 2. Visualization of Docking Results of Testing Compounds with 8H1B: (a) S-adenosylmethionine, (b) clindamycin, (c) acatechu B, (d) catechin, (e) jacareubin.

Toxicity prediction is performed to determine the toxicity profile of secondary metabolite compounds in-silico. Toxicity is the degree of damage a compound can cause when it enters an organism [20]. In this study, the toxicity parameters used are mutagenicity, hepatotoxicity, carcinogenicity, and LD50. The results of the analysis in Table 2 show that secondary metabolite compounds do not have the potential to be mutagenic, hepatotoxic, or carcinogenic substances and have an LD50 that is relatively harmless.

Table 2. Toxicity Prediction Result

Compound	Mutagenicity	Hepatotoxicity	Carsinogenicity	LD50 (mg/kg)
S-adenosyl methionine	No	No	No	3320
Clindamycin	No	No	No	1095
Acatechu B	No	No	No	3750
Catechin	No	No	No	10000
Jacareubin	No	No	No	4000

4. CONCLUSION

Areca catechu active compounds have good interactions with 8H1B that indicated by the acatechu B has more negative binding energy than the comparator. The active compounds are potent antibacterial agents with a favorable toxicity profile, being non-mutagenic, non-hepatotoxic, non-carcinogenic, and having a safe LD50. Further studies are needed to uncover its potential through in-vitro and in-vivo tests.

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