ORIGINAL ARTICLE

The Mauli Banana Stem's Function in Preventing Collagen Degradation During The Dentin Carious Process: Study *In Silico*

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ABSTRACT

Introduction: Mauli banana is a common plant in South Kalimantan, Indonesia. Mauli banana stem extract (MBS) contains cinnamic acid, caffeic acid, and citral, which can increase the minerals lost in the tooth demineralisation process. However, the specific mechanism by which the MBS prevents the breakdown of type I collagen and inhibits tooth demineralisation during the carious process in dentine remains unknown. Cathepsin B, MMP-2, MMP-8, and TIMP-1 are biomarkers for the breakdown of type I collagen. This study aimed to determine the molecular docking of MBS with cathepsin B, MMP-2, -8, and TIMP-1 to prevent collagen degradation in silico. **Methods:** This study was conducted in silico, utilising the molecular docking method. The docking process was performed using the PyRx application and visualised using Biovia Discovery Studio software. Chlorhexidine was used as the comparison ligand. **Results:** These molecular docking results show that the MBS best compound is caffeic acid. Binding affinity value of caffeic acid with cathepsin B is -6.1 kcal/mol, with MMP-2 is (-7.5 kcal/mol), with MMP-8 is (-7.7 kcal/mol) and with TIMP-1 is (-5.9 kcal/mol). The molecular docking results show that the most hydrogen bonds are generated by caffeic acid compound. Caffeic acid compound bonds with MMP-8 have amino acid residue similarities with chlorhexidine on residues HIS197, TYR219, and VAL194, while bonds with Cathepsin B, MMP-2, and TIMP-1 do not have amino acid residue similarities with chlorhexidine. **Conclusion:** The MBS is predicted to prevent collagen degradation in silico because it can bind to cathepsin B, MMP-2, MMP-8, and TIMP-1.

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Keywords: Cathepsin-B, Mauli banana stem extract, Molecular docking, MMP, TIMP-1

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INTRODUCTION

Traumatic Dental caries is a pathological condition affecting dental tissue characterised by tissue destruction that begins on the surface of the tooth enamel and dentine and extends to the pulp (1). The World Health Organization (WHO) states that over one-third of the global population suffers from untreated dental caries (2). According to Basic Health Research data from 2018, the prevalence of oral health issues in the Indonesian population was 45.3%, while in South Kalimantan Province, it was 46.90% (3,4). The caries process is initiated by oral microbes that produce lactic acid. This acid accumulates on the surface of the tooth enamel, causing a decrease in pH and leading to demineralisation (5). The continued demineralisation process will involve matrix metalloproteinase (MMPs) and cathepsin activity (6).

MMPs are one of the proteolytic enzymes that have collagen-specific degradative activity (7,8). The MMPs found in dentine are matrix metalloproteinase-2 (MMP-

2) and matrix metalloproteinase-8 (MMP-8). MMP-2 can disrupt the C-terminal of the collagen molecule, while MMP-8 can denatures type I collagen (9). The tissue inhibitor of metalloproteinase-1 (TIMP-1) is an endogenous inhibitor that controls the activity of MMP-8 in collagen denaturation (10). Cathepsin is a proteolytic enzyme that plays a role in collagen degradation and the cathepsins which found in dentine is cathepsin B (6). Cathepsin B, MMP-2, MMP-8, and TIMP-1 work together to degrade type I collagen in dentine (9,11,12). Therefore, it is necessary to analyse cathepsin B, MMP-2, MMP-8, and TIMP-1 to prevent collagen degradation in dentine during demineralisation.

Chlorhexidine (CHX) is considered a highly effective mouthwash due to its significant antibacterial properties and ability to prevent the formation of dental plaque, a leading cause of caries (13). CHX prevents dentine collagen degradation by inhibiting the activation of MMPs and cathepsin enzymes (14–16). However, the use of CHX is time-limited, as its efficacy diminishes over an extended period (17). Consequently, it is necessary to develop a substitute inhibitor of cathepsin and MMPs that may be employed for an extended duration, utilising natural ingredients such as Mauli banana plants.

Mauli banana (Musa acuminata) is one of the typical plants from South Kalimantan that can be used as a wound-healing treatment. Mauli banana stem extract (MBS) contain several active substances, such as tannin, saponin, alkaloids, flavonoids, and lycopene (18). Puspitasari (2023) discovered that the main components found in Mauli banana stems with Liquid Chromatography High Resolution Mass Spectrometry (LC-HRMS) tests are cinnamic acid, caffeic acid, and citral compounds (19). Carabelly (2024) found that MBS compounds can increase minerals such as carbon, oxygen, phosphorus, and calcium in dentine to prevent demineralisation (20). However, the prevention of the demineralisation process through inhibition of type I collagen degradation in dentine using MBS compounds is not yet known. This study aimed to determine the molecular docking of MBS with cathepsin B, MMP-2, MMP-8, and TIMP-1 to prevent collagen degradation in silico.

MATERIALS AND METHODS

Receptor Retrieval

The receptor was downloaded from Protein Data Bank (https://www.rcsb.org) in three-dimensional (3D) structure using .pdb format. The receptor was derived from the homo sapiens genome with a resolution of >2.0 E, which is considered as high resolution. The receptors used in this study were cathepsin B (PDB ID: 3AI8) has a resolution of 2.11 E (21), MMP-2 (PDB ID: 1CK7) has a resolution of 2.8 E (22), MMP-8 (PDB ID: 1MMB) has a resolution of 2.10 E (23), and TIMP-1 (PDB ID: 2J0T) has a resolution of 2.54 E (24).

Ligand Retrieval

The ligands used in this study were compounds derived from the extract of MBS. These compounds were cinnamic acid (CID 444539), caffeic acid (CID 689043), citral (CID 638011), and CHX as a comparison ligand (CID 9552079). The ligands were obtained from the PubChem website (https://PubChem.ncbi.nlm.nih.gov) in the .sdf format.

Receptor Preparation

The receptors retrieved from the Protein Data Bank (PDB) were processed using Biovia Discovery Studio software (https://discover.3ds.com/discovery-studio-visualizer-download). This involved eliminating the default ligands and water molecules. After that, the per-prepared receptor structure was saved in the Protein Data Bank Files format and stored in the previously created folder.

Ligand Minimization

The necessary steps for ligand reduction involved optimising the ligand's geometric shape using the PyRx 0.8 programme (https://pyrx.sourceforge.io/downloads/). Subsequently, the optimisation results were transformed into PDB files using Open Babel.

Molecular Docking Validation

The docking procedure was verified by re-docking the default ligand with the pre-prepared receptor. The purpose of this validation was to determine the deviations that occurred. The parameter was the value of RMSD (Root Mean Square Deviation) < 2.0 E. RMSD was a parameter used to quantify the extent of change in the interaction between a receptor and a ligand before and after docking, providing a measure of the deviation.

Molecular Docking

The study conducted blind docking between ligand and receptor because the right grid box parameters were unknown. Docking was performed using the PyRx version 0.8 application with the Autodock Vina program. The result of molecular docking was the conformation of the ligand in binding to the target receptor with the lowest binding energy.

Visualisation of Docking Results

Biovia Discovery Studio V21 software was used to analyse and visualise interactions in 2D. Interaction analysis was carried out on the types of amino acid residues between the MBS ligand and the reference ligand CHX against the cathepsin B, MMP-2, MMP-8, and TIMP-1 receptors.

ETHICAL CLEARANCE

This research has been ethically cleared with No. 050/KEPKG-FKGULM/EC/XII/2024 declared exempted by the Research Ethics Committee, Faculty of Dentistry, Lambung Mangkurat University.

RESULT

Validation of Molecular Docking

Molecular docking validation is crucial in determining whether the approach employed meets the requirement. Validation in this study involved re-docking the default ligand of the target receptor and its target receptor. The parameter obtained from the validation results was the RMSD value. The test was declared valid when the RMSD result was ≤ 2.0 E. MMP-2 receptor was redocked with the native ligand Sulfate ion. MMP-8 receptor redocking with native ligand in the form of complex of batimastat. Cathepsin B receptor was redocked with the native ligand nitroxoline. Also, the TIMP-1 receptor was redocked with the catalytic domain of MMP-1. The docking validation process in this study yielded an RMSD value of 0.0 E, indicating that the docking parameters are valid and can be utilised for the compound's docking process.

Molecular Docking Simulation

Table I presents the results of the molecular docking simulation, including the binding affinity and type of binding interaction between MBS compounds against cathepsin B, MMP-2, MMP-8, and TIMP-1.

The molecular docking simulation results in Table I demonstrate that all MBS compounds exhibit different binding affinity values against cathepsin B, MMP-2, MMP-8, and TIMP-1 receptors. The chemical with the highest binding affinity in extract was caffeic acid. It exhibited binding affinity values of -6.1 kcal/mol, -7.5 kcal/mol, -7.7 kcal/mol, and -5.9 kcal/mol against cathepsin B, MMP-2, MMP-8, and TIMP-1 receptors, respectively. The binding affinity values of cinammic acid compounds with cathepsin B, MMP-2, MMP-8, and TIMP-1 were -5.6 kcal/mol, -6.4 kcal/mol, -7.0 kcal/mol, and -5.6 kcal/mol, respectively. The binding affinity values of citral compounds for cathepsin B, MMP-2, MMP-8, and TIMP-1 with -4.7 kcal/mol, -6.2 kcal/mol, -4.7 kcal/mol, and -5.2 kcal/mol, respectively.

The binding affinity value of CHX as a comparison ligand against cathepsin B, MMP-2, MMP-8, and TIMP-1 receptors was higher than than those of caffeic acid, cinnamic acid and citral. The binding affinity values of CHX for cathepsin B, MMP-2, MMP-8, and TIMP-1 were -7.9 kcal/mol, -7.5 kcal/mol, -9.0 kcal/mol, and -7.4 kcal/mol, respectively.

Table I: Forward and reverse primer sequences of ECM markers and housekeeping genes.

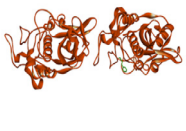
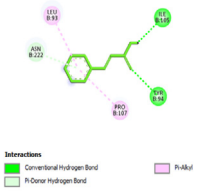
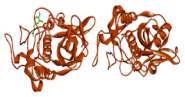
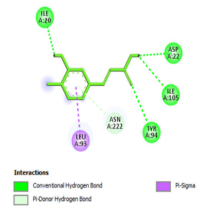
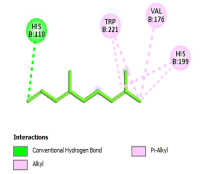
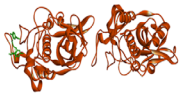
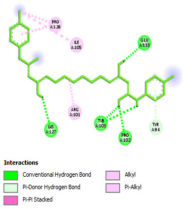
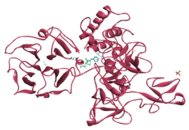
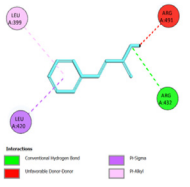
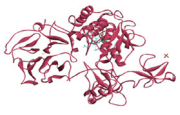
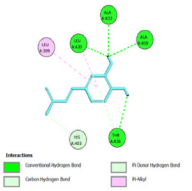
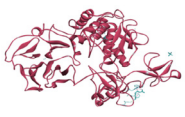
Receptor	Compound	Binding Affinity (kcal/mol)	Hydrogen Bond	Hydrophobic Interaction
Cathepsin B	Cinnamic acid	-5,6	TYR94, ILE105	LEU93, PRO107, ASN222,
	Caffeic acid	-6,1	ILE20, ASP22, ILE105, TYR94, ASN222	LEU943
	Citral	-4,7	HIS110	VAL176, TRP221, HIS199, HIS199
	Chlorhexidine (Comparison Ligand)	-7,9	LYS127, TYR103, TYR103, PRO102, GLU133, TYR94	TYR94, PRO126, PRO126, ILE105, ARG101
MMP-2	Cinnamic acid	-6,4	ARG343	LUE420, LEU399
	Caffeic acid	-7,5	ALA429, LEU420, ALA422, THR426, HIS403, THR426	LEU399, LEU420
	Citral	-6,2	ARG252	PHE280, PHE256, TYR223, TYR225, PHE256, PHE280
	Chlorhexidine (Comparison Ligand)	-7,5	ASP106, ASP106, HIS413, GLU412, ASP430, ASP436, ASN109	LEU444, TYR110, LEU411, LEU444
MMP-8	Cinnamic acid	-7,0	LEU160, ALA161, ALA161, GLU198,	*HIS197, *VAL194
	Caffeic acid	-7,7	LEU160, ALA161, ARG222, ALA161, TYR216, ASN218, LEU193	*HIS197, *TYR219, ASN218, *VAL194
	Citral	-4,7	-	ALA112, ARG111, PHE192
	Chlorhexidine (Comparison Ligand)	-9,0	SER151, PRO217	HIS197, PHE164, TYR219, ASN218, ILE170, LEU214, HIS197, HIS201, VAL194
TIMP-1	Cinnamic acid	-5,6	ASN30, GLU28, TYR35	TYR35
	Caffeic acid	-5,9	GLU28, TYR35	TYR62, ARG37
	Citral	-5,2	-	ARG37, ARG37
	Chlorhexidine (Comparison Ligand)	-7,4	PHE73, GLU67, THR98, THR98	PHE101, TYR72, ALA103, PHE101, ARG75, ALA103

Note:
* : Amino acid residue of Mauli banana stem extract compound is the same as the amino acid residue of the comparison ligand.

Molecular docking simulations also produced interactions in hydrogen and hydrophobic bonds on certain amino acid residues. The caffeic acid compound that bind to MMP-8 had amino acid residues similar to CHX. These were found at residues HIS197, TYR219, and VAL194. The cinnamic acid compound that binds to MMP-8 also has amino acid residues similar to CHX, namely residues HIS 197 and VAL194. When the citral compound binds to MMP-8, there are no amino acid residues similar to CHX. The interactions of cinnamic acid, caffeic acid, and citral compounds with cathepsin B, MMP-2, and TIMP-1 don't have any amino acid residues that are the same as CHX.

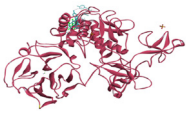
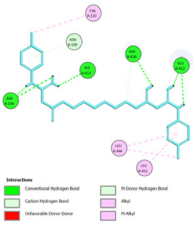
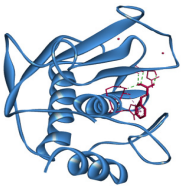
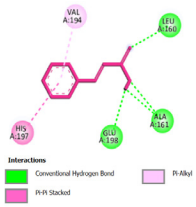
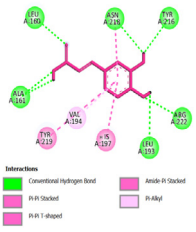
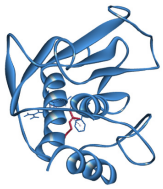
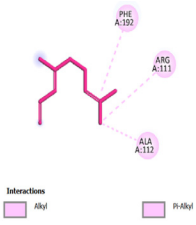
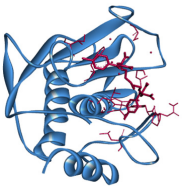
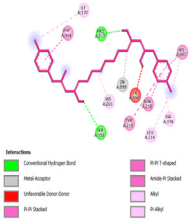
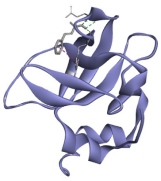
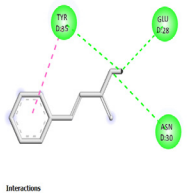
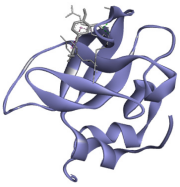
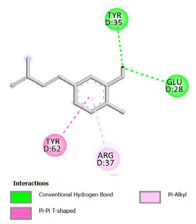
The 3D and 2D visualisations of docking results from Discovery Studio Visualizer software showed the types of bonds and amino acid residues. The bonds that occur between MBS compounds and cathepsin B, MMP-2, MMP-8, and TIMP-1 are presented in Table II.

Table II. Visualisation of docking results of MBS compounds with cathepsin B, MMP 2, MMP-8, and TIMP-1.

Receptor	Compound	Visualisation	
		3D	2D
Cathepsin B	Cinnamic acid		
	Caffeic acid		
	Citral		
	Chlorhexidine (Comparison Ligand)		
MMP-2	Cinnamic acid		
	Caffeic acid		
	Citral		

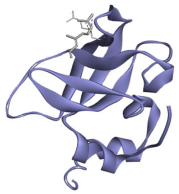
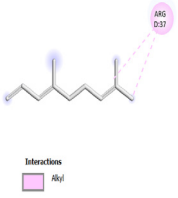
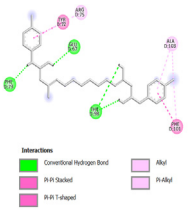
CONTINUE

Table II. Visualisation of docking results of MBS compounds with cathepsin B, MMP 2, MMP-8, and TIMP-1 (CONT.)

Receptor	Compound	Visualisation	
		3D	2D
MMP-2	Chlorhexidine (Comparison Ligand)		
MMP-8	Cinnamic acid		
	Caffeic acid		
	Citral		
	Chlorhexidine (Comparison Ligand)		
TIMP-1	Cinnamic acid		
	Caffeic acid		

CONTINUE

Table II. Visualisation of docking results of MBS compounds with cathepsin B, MMP 2, MMP-8, and TIMP-1 (CONT.)

Receptor	Compound	Visualisation	
		3D	2D
TIMP-1	Citral		
	Chlorhexidine (Comparison Ligand)		

DISCUSSION

The molecular docking analysis revealed that the cinnamic acid, caffeic acid, and citral compounds on MBS exhibit varied binding affinities to cathepsin B, MMP-2, MMP-8, and TIMP-1. The activity of cathepsin B, MMP-2, MMP-8, and TIMP-1 will induce collagen degradation in dentine. Cathepsin B, which has been active in the caries process when acidic conditions occur, will cleave the non-helical telopeptide of type I collagen. When pH conditions return to neutral, MMP-8 will work to cut type I collagen into 1/4 and 3/4 peptide fragments. Excessive collagenase activity of MMP-8 will result in the hydrolysis of collagen fibrils, which should be inhibited by TIMP-1. However, TIMP-1 is unable to inhibit the activity of MMP-8 in hydrolysing collagen fibrils. As a result, the peptide fragments with triple helix structures will continue to be detected, and MMP-2 gelatinase will degrade the collagen (9,11,12).

The result of molecular docking in this study is the binding affinity value. The binding affinity value is the ability of cinnamic acid, caffeic acid, and citral ligands from MBS to bind to cathepsin B, MMP-2, MMP-8, and TIMP-1 receptors. The most negative binding affinity value indicates the smallest energy used by the ligand to bind to the receptor. (25). The smaller the binding affinity value, the more stable the bond formed (26,27). The results of this study show that the most negative binding affinity value is the binding of cathepsin B, MMP-2, MMP-8, and TIMP-1 receptors with caffeic acid ligands. This shows that caffeic acid ligands are predicted to have more potential to inhibit the work of cathepsin B, MMP-2, and MMP-8 in degrading collagen in the caries process compared to cinnamic acid and citral ligands. Caffeic acid ligands are also more potential than cinnamic acid and citral in stimulating TIMP-1 which plays a role in preventing collagen degradation. Ulakar's (2021) research supports this, demonstrating that caffeic acid can inhibit cathepsin B (28). Afrin et al. (2019) state that caffeic acid can inhibit the activity and expression of MMP-2 in vitro (29). Taherkhani (2022) predicted that caffeic acid compounds have MMP-8 inhibitory activity (30). Pavlнkovб (2023) also discovered that caffeic acid compounds can increase TIMP-1 levels (31).

The binding affinity value of cinnamic ligand and citral ligand is not as good as the binding affinity value of caffeic acid ligand, but cinnamic acid ligand and citral ligand are also predicted to inhibit the work of cathepsin B, MMP-2, and MMP-8 receptors. Cinnamic ligands and citral ligands are also predicted to stimulate TIMP-1 receptors that play a role in degrading collagen in the caries process. This is supported by research by Verma (2019), which shows that cinnamic acid is predicted to inhibit the activity expression of MMP-2 (32). Taherkhani's research (2022) shows that cinnamic acid compounds are predicted to have MMP-8 inhibitory activity (30). Salsabila et al (2022) shows that citral can reduce the activity expression of MMP-2 (33).

The caffeic acid compound has the best binding affinity value of all MBS compounds to ligands, but this value is not better than the CHX comparison ligand. The CHX ligand has a more negative binding affinity value than the caffeic acid ligand, so that the CHX ligand bond with the cathepsin B, MMP-2, MMP-8, and TIMP-1 receptors is more stable than the bond with the caffeic acid ligand. This shows that CHX is predicted to have a greater influence on receptor work than the caffeic acid compound.

Besides the binding affinity value, the type of amino acid residue interaction also affects the strength and stability of the bond between compound ligands from MBS and cathepsin B, MMP-2, MMP-8, and TIMP-1 receptors. The observation of the type of amino acid residue interaction aims to determine the interaction that occurs between the ligand and the receptor. Interactions can be in the form of hydrogen bonds, hydrophobic interactions, and electrostatic interactions (25). Hydrogen bonding is the strongest and most stable bond in the interaction between molecules. The more hydrogen bonds, the stronger the bond of a ligand to the receptor (26,34). Hydrophobic and electrostatic interactions play a role in increasing the stability of ligands with receptors (25,35).

The results of this research show that the ligand that has the most types of hydrogen bond interactions with cathepsin B, MMP-2, and MMP-8 receptors is a caffeic acid ligand. The bond of caffeic acid ligand with cathepsin B has 5 hydrogen bonds and 1 hydrophobic bond. The bond of caffeic acid ligand with MMP-2 has 6 hydrogen bonds and 2 hydrophobic bonds. Caffeic acid ligands bond with MMP-8, forming 7 hydrogen bonds and 4 hydrophobic bonds. On the other hand,

the ligand that has the most types of hydrogen bond interactions with the TIMP-1 receptor is the cinnamic acid compound, which consists of 3 hydrogen bonds and 2 hydrophobic bonds.

The molecular docking results in this study also compared the similarity of amino acid residues of MBS ligands with CHX comparator ligands. If the test ligand has many amino acid residue similarities, the more similar the test ligand is to the comparator ligand (36). The results of this study showed that MBS ligand bonds that have amino acid residue similarities with CHX comparator ligands are only caffeic acid ligand bonds with MMP-8 receptors. The bonds of the three MBS ligands with captesin B, MMP-2, and TIMP-1 receptors do not have amino acid residue similarities with CHX comparator ligands. The same caffeic acid amino acid residues as CHX in the MMP-8 receptor are residues ASN218, HIS197, TYR219, and VAL194. Amino acid residues are the active side of the receptor that binds to the ligand (37). The amino acid residues ASN218, HIS197, TYR219, and VAL194 are the active side of the MMP-8 receptor where the caffeic acid and CHX ligands bind.

The limitation of this study is that it only uses molecular docking methods, which predict receptor-ligand interactions in a virtual context. We will continue this research with in vivo research to formulate anti-caries gel. In the future clinical use of MBS, we will develop anti-caries drug in gel form. The application method involves applying the MBS gel directly onto the teeth.

CONCLUSION

The MBS is predicted to prevent collagen degradation in silico because it can bind to cathepsin B, MMP-2, MMP-8, and TIMP-1. The next research study can focus on MBS remineralisation ability, so that MBS will be able to become one of the alternative caries prevention drug.

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