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**Research Article**

# *In Silico* Screening of *Syzygium myrtifolium* Flavonoid Compounds as Anti-Bacterial Activity

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**ABSTRACT**

Bacterial infection and antibiotic resistance are popular issues nowadays. Several previous reports performed antibacterial screening activities involving natural herbs and synthetic drugs. Alanine racemase and transglycosylase are essential proteins for peptidoglycan membrane synthesis in bacteria and an alternative target for antibacterial performance. This study identified six flavonoid compounds in *Syzygium myrtifolium* to perform the antibacterial activity. *In silico* study was conducted for modelling flavonoids – protein complexes. Five flavonoids from *S. myrtifolium* were taken out of the canonical smiles from the PubChem database and modelled three-dimensional structure using ChemDraw and molView. Targeted protein, alanine racemase and transglycosylase were downloaded from Protein Data Bank with ID 4WR3 and 1SLY. Ligands and proteins were interacted by Molegro virtual Docker 5.0 and visualized by Discovery studio version 21.1.1. Five flavonoids showed inhibition with alanine racemase and transglycosylase in the same active sites of control and sodium benzoate. According to the binding energy, calopiptin performed the lowest binding energy value in alanine racemase complexes, while 2-Propanone, 1,3-bis(5-nitro-2-furanyl) showed the lowest value of four other flavonoids at transglycosylase complexes. The type of interactions were electrostatic, hydrogen bonds, hydrophobic interactions and unfavorable ones. Low binding energy and varied interaction types indicated tight of ligand-protein interaction. In summary, five flavonoids inhibited alanine racemase and transglycosylase, and the peptidoglycane membrane synthesis in bacteria might be inferred.

*Keywords: Alanine racemase, Flavonoids, In silico, Transglycosylase*

## Introduction

Bacterial infection and antibiotic resistance have been the biggest issue nowadays. It threatens the health of societies because it causes millions of deaths every year [1]. The occurrence of antibiotic resistance in bacteria has reduced the efficacy of existing antibacterial drugs. It leads to the discovery of antibacterial therapeutic agents. The potential molecule could be non-antibiotic drugs which have antibacterial properties [2, 3]. The most desirable antibacterial agents were from bioactive compounds of natural products.

*Syzygium myrtifolium* is known for its potency as a therapeutic agent. This species is popular in Indonesia as an ornamental plant and for health treatment. *S. myrtifolium* is a possibility to be a therapeutic agent because it contains anthraquinones, phenolics, saponins, flavonoids, and betu

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linic acid [4, 5]. *S. myrtifolium* also performed antioxidant activity and antibacterial activity. Previously, the extracts of *S. myrtifolium* exhibited inhibitory activity against gram-positive and gram-negative bacteria [5]. The antibacterial properties of *S. myrtifolium* could be mainly attributed to two mechanisms. It could be through interfering chemically and/or mimicking the mechanism of antibacterial resistance. The target of antibacterial includes (a) bacterial protein biosynthesis; (b) bacterial cell wall biosynthesis; (c) bacterial cell membrane destruction; (iv) inhibition of the metabolic pathway, and (v) bacterial DNA replication and repair [3]. The proteins that are specifically ubiquitous and involved in the biosynthesis of prokaryotes are alanine racemase and transglycosylase [6–8].

Alanine racemase is a ubiquitous prokaryotic enzyme that is involved in bacterial cell wall synthesis by utilizing pyridoxal 5'-phosphate (PLP) to convert L-alanine into D-alanine [9]. This enzyme is often a target for studying the antibacterial properties of antibacterial candidates because it is found absent in higher eukaryotes [10]. Similarly, as alanine racemase, transglycosylase also participates in peptidoglycan cell wall biosynthesis [11]. It synthesized the peptidoglycan layer by acting as mono functionally or as an N-terminal domain of the class A multimodular penicillin-binding proteins. Considering the function, transglycosylase is now an attractive target for antibacterial drugs [7, 12].

This study focused on studying the antibacterial activity of bioactive compounds in *S.myrtifolium* by inhibiting alanine racemase and transglycosylase. The antibacterial properties of bioactive compounds in *S. myrtifolium* were validated with positive control and sodium benzoate, known for its antibacterial potency. The selection of sodium benzoate as an antibacterial control in this study was related to further application, especially for food products. Commonly, sodium benzoate is used as a food preservative in food products with concentrations up to 1,000 ppm and has the potential as an antibacterial agent [13, 14]. Previous studies have reported that the application of sodium benzoate has been shown to have antibacterial properties by reducing and or killing pathogenic bacteria such as *E. coli*, *S. enterica*, *L. monocytogenes*, and *S. typhimurium* in fresh foods such as vegetables and fruit, as well as in processed food products [13, 15].

## Material and Methods

### *Protein retrieval and binding cavities prediction*

The protein alanine racemase (4WR3) [9] and transglycosylase (1SLY) [12] as receptors were downloaded from the PDB database. Alanine racemase and transglycosylase predicted their binding cavities using Molegro virtual docker version 5 with the molecular surface by van der Waals as a parameter [16–19].

### *Ligands acquiring and modelling*

The 3D structure of ligands 2-Propanone, 1,3-bis(5-nitro-2-furanyl) (CID152537), Quercetin-3-O-alpha-L-arabinopyranoside (CID 5481224), Calopiptin (CID 12302265), and Auraptenol (CID 13343540) were downloaded from PubChem database. The Quercetin-3-O-beta-D-glucuronide was computationally modeled by the Cheminfo web server (http://www.cheminfo.org/) and MolView (https://molview.org/).

### *Molecular docking simulation*

The receptors were docked to ligands by using Molegro Virtual Docker 5 with a specific area for alanine racemase as follows, X=43.87; Y=2.45; Z=2.99; Radius 9 and transglycosylase X=10.52 Y=47.19; Z=57.06 Radius 13. The parameters for docking were MolGrid 0.3A, 10x docking repetitions, and RMSD < 2 [17–20]. To validate the docking result of *S. myrtifolium* leaf, receptors were docked with antibacterial control Sodium Benzoate (CID243) from PubChem, Pyridoxal-5'-Phosphate (PDB ID 4WR3) for alanine racemase, and 4-O-(4-O-Sulfonyl-N Acetylglucosamininyl)-5-Methylhydroxy-L-Proline-Taurine (PDB ID 1SLY) for transglycosylase. The docking results were analyzed with PyMol 2.2 and Discovery Studio 21.1.0

## Results and Discussion

### *Interaction of bioactive compounds in S. myrtifolium with Alanine Racemase*

The data on alanine racemase interaction with ligands were compiled in Table 1. The control compound was posed binding with alanine racemase in LYS34, ARG129, TYR38, ARG280, SER341, TYR343, TYR255, and PHE274 amino acid residues. Antibacterial control, sodium benzoate, showed binding to alanine racemase in HIS159, PHE160, ALA193, GLY196, ILE191, TYR255, ALA161, ALA163, and ALA193 amino acid residues. Interestingly, bioactive compounds

Table 1. Binding energy and interaction sites of flavonoids in *S. myrtifolium* with alanine racemase and transglycosylase proteins

| Compounds | Alanine Racemase | | Transglycosylase | |
|---|---|---|---|---|
| | Binding Energy (kJ/mol) | Interaction | Binding Energy (kJ/mol) | Interaction |
| Control* | -285.6 | Electrostatic: LYS34 (3.2; 3.1), ARG129 (5.2)<br>Hydrogen Bond: TYR38 (2.8), ARG280 (3.1), SER341 (2.1)<br>Hydrophobic: TYR343 (3.1; 5.0; 4.1), TYR255 (4.1), PHE274 (4.0) | -279.2 | Electrostatic: ARG476 (2.4)<br>Hydrogen Bond: ARG476 (2.4), GLN477 (2.8), LYS486 (3.2), TYR594 (3.1; 2.8; 5.7), GLN477 (2.5; 2.8; 2.2; 1.3), GLU478 (2.9; 2.1; 1.9; 1.6), GLN496 (1.7)<br>Pi-Sulfur: TYR594 (5.7); Unfavorable Acceptor-Acceptor: GLU478 (2.9) |
| Sodium Benzoate | -183 | Hydrogen Bond: HIS159 (3.1), PHE160 (3.1), ALA193 (2.8), GLY196 (2.8), ILE191 (2.4)<br>Hydrophobic: TYR255 (5.4), ALA163 (4.2), ALA193 (4.6) | -144.5 | Hydrogen Bond: GLN434 (2.8)<br>Hydrophobic: VAL433 (5.2), ALA480 (4.2); Unfavorable: ASN482 (2.0) |
| 2-Propanone, 1,3-bis(5-nitro-2-furanyl) | -385 | Hydrogen Bond: ASP164 (3.2), SER194 (2.9; 2.8; 2.7), GLY195 (3.1, 3.5), GLY211 (2.9), ILE212 (3.1), TYR343 (2.7; 3.6)<br>Hydrophobic: TYR255 (3.9), ALA193 (3.2) | -238.4 | Hydrogen Bond: ASN482 (3.0), GLN434 (3.6),<br>Hydrophobic: ALA480 (3.9; 4.1), VAL433 (4.2), VAL433 (4.8), ILE437 (5.1), VAL485 (4.8) |
| Quercetin-3-O-alpha-L-arabinopyranoside | -393.8 | Hydrogen Bond: GLY196 (2.9), ILE212 (2.5), TYR343 (2.5; 2.5; 3.1), ARG209 (2.1; 3.0), TYR38 (1.8), PHE160 (1.9), SER194 (2.3)<br>Hydrophobic: ALA193 (3.7), TYR343 (4.1; 3.9), TYR255 (3.7; 4.2), ALA163 (4.5) | -226.2 | Hydrogen Bond: ASN553 (2.6; 2.3); GLU583 (2.1, 1.9); GLN496 (1.8; 2.6); GLU478 (1.9; 2.4); LYS486 (2.6); PRO488 (3.2)<br>Hydrophobic: PRO488(5.4, 5.4); VAL485 (4.9); Unfavorable: GLU478 (2.5); Electrostatic: GLU583(3.8) |
| Calopiptin | -421.2 | Hydrogen Bond: GLY196 (2.6), TYR343 (2.8), VAL301 (3.1)<br>Hydrophobic: TYR343 (3.7), TYR255 (3.6; 5.2; 4.1; 4.5; 5.0), ALA163 (3.8; 4.0), ALA193(3.3; 4.2), ALA302 (3.9), ARG300 (4.1), MET303 (4.1), HIS159 (4.9), PHE160 (5.0), PHE274 (4.7) | -155 | Hydrogen Bond: GLN477 (3.1; 3.1; 3.5), ASP430 (2.7; 2.3), ALA480 (2.9)<br>Hydrophobic: ALA480 (3.8; 3.9; 4.3), VAL485 (3.5; 5.2), TYR594 (4.3), GLU478 (1.7); Unfavorable: TYR594 (2.0), TYR594 (0.9) |
| Auraptenol | -308 | Hydrogen Bond: TYR343 (3.3; 1.6; 5.4), HIS159 (3.4), SER194 (3.7), TYR255 (3.8; 4.6)<br>Hydrophobic: TYR255 (4.6), ALA163 (3.7; 4.8), ALA193 (3.1; 4.3; 3.4), ILE212 (4.7), HIS159 (4.9), PHE160 (5.3), TYR343 (4.9) | -195.6 | Hydrogen Bond: GLN434 (3.3; 3.8), ASN482 (2.7)<br>Hydrophobic: GLN434 (3.2), ARG401 (4.7; 5.0), ILE437 (3.6; 5.4), ALA480 (5.2; 4.8) |
| Quercetin-3-O-beta-D-glucoronide - Alanin Racemase | -373.4 | Hydrogen Bond: LYS34 (3.1), HIS159 (2.9; 2.7; 2.8), ILE212 (3.2), TYR343 (2.7; 2.4; 2.6), SER194 (1.5), PRO219 (2.4), ILE191 (2.6), TYR255 (2.3; 2.2; 1.8), TYR38 (1.7)<br>Electrostatic: ASP164 (3.1)<br>Hydrophobic: PHE160 (3.6), ALA163 (3.9), TYR255 (4.9), ALA193 (4.0) | -218 | Hydrogen Bond: ARG476 (2.6); GLU478 (1.9); GLN496 (2.0); TYR594 (2.6); GLN477 (1.8); GLU583 (1.6; 2.9; 2.7); PRO488 (3.7)<br>Hydrophobic: VAL485 (5.4), ALA480 (4.4);<br>Unfavorable: GLN477 (1.9), ASN553 (2.5), GLU478 (2.8) |

Note: *Pyridoxal-5'-Phosphate (PDB ID 4WR3) and 4-O-(4-O-Sulfonyl-N-Acetylglucosamininyl)-5-Methylhydroxy-L-Proline-Taurine (PDB ID 1SLY) were used as control for alanine racemase and transglycosylase, respectively.

in *S. myrtifolium* leaf mostly bind to alanine racemase with similar amino acids in alanine racemase (Table 1, Figure 1). The 2-Propanone, 1,3-bis(5-nitro-2-furanyl) was attached to alanine racemase through ASP164, SER194, SER195, GLY211, ILE212, TYR343, GLY195, ALA193, and TYR255 with hydrogen bond and hydrophobic interaction. The ligand and protein were bound to each other by spending -385 kJ/mol. Quercetin-3-O-alpha-L-arabinopyranoside and alanine race-

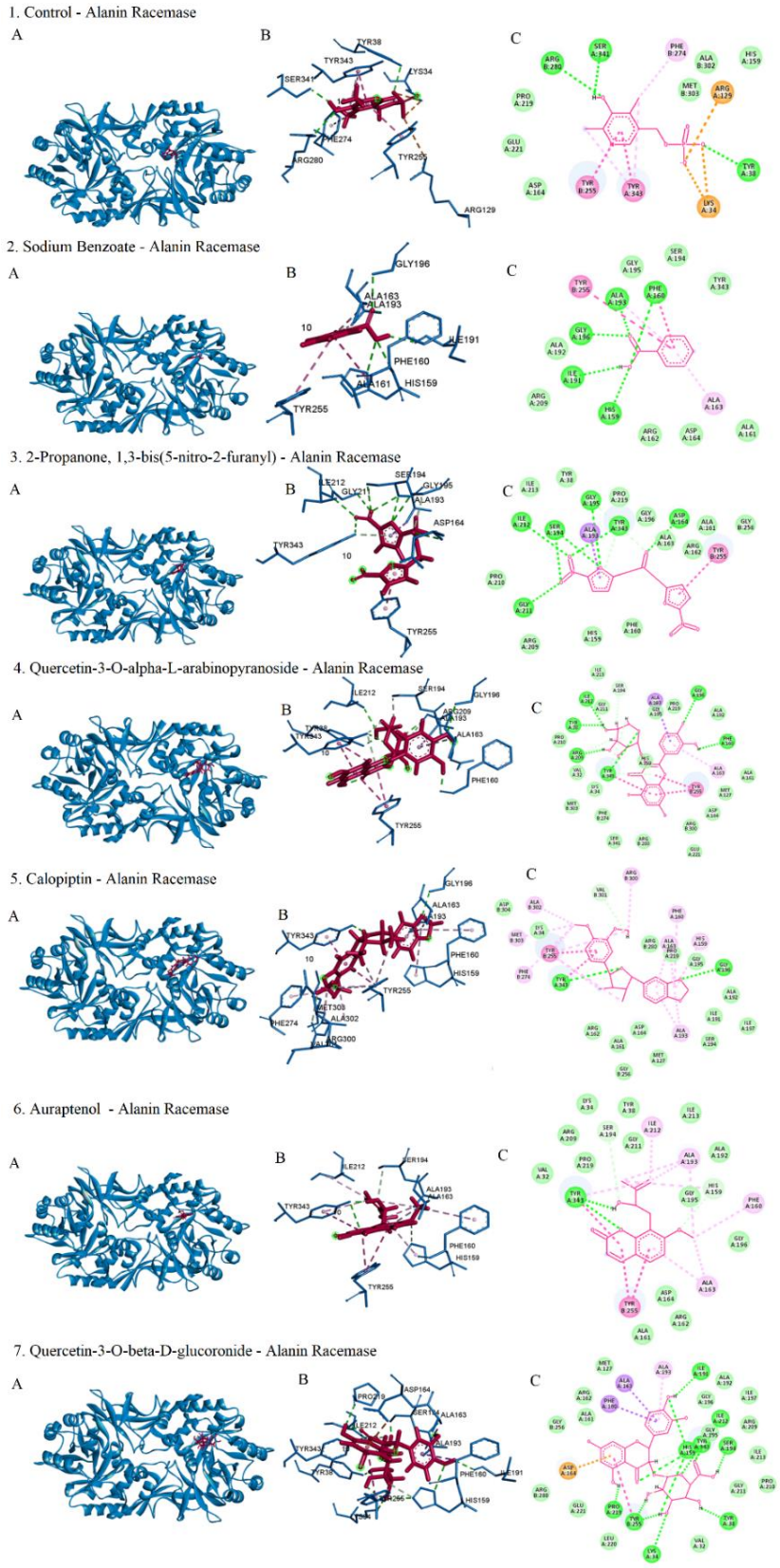


Figure 1. Interaction of flavonoids in *S. myrtifolium* with alanine racemase: A-B) The 3D structure of ligands-protein, C) The 2D of ligand-proteins, alanine racemase was illustrated in blue ribbon structure, while pink stick structure was ligands.

mase built a complex via GLY196, ILE212, TYR343, ARG209, TYR38, PHE160, ARG209, SER194, ALA193, TYR255, and ALA163 by using hydrogen bond and hydrophobic interaction. The TYR38 amino acid residue was identified in the Quercetin-3-O-alpha-L-arabinopyranoside - alanine racemase complex (-393.8 kJ/mol) Quercetin-3-O-beta-D-glucuronide – alanine racemase complex. Other than TYR38, Quercetin-3-O-beta-D-glucuronide posed binding to alanine racemase (-373.4 kJ/mol) via LYS34, HIS159, ILE212, TYR343, SER194, PRO219, ILE191, TYR255, HIS159, ASP164, PHE160, ALA163, and ALA193. The LYS34 amino acid residue is identified as an active site of control treatment. This amino acid residue was also found in Quercetin-3-O-beta-D-glucuronide – Alanine Racemase complex. The HIS159 were found in the binding of alanine racemase with Quercetin-3-O-beta-D-glucuronide, copeptin, and auraptenol. Calopiptin was bound to alanine racemase with the strongest binding (-421.2 kJ/mol), and the binding mostly consisted of hydrophobic interaction. Also, some of them were hydrogen bonds. Calopiptin - alanine racemase could bind to each other through GLY196, TYR343, VAL301, TYR255, ALA163, ALA193, ALA302, ARG300, MET303, HIS159, PHE160, and PHE274 (Figure 1). Auraptenol - alanine racemase (-308 kJ/mol) was building the binding through TYR343, HIS159, SER194, TYR255, ALA163, ALA193, ILE212, and PHE160.

Interestingly, all bioactive compounds of *S. myrtifolium* were bound to alanine racemase via ALA193, TYR343, and TYR255 amino acid residues. This study found that bioactive compounds in *S. myrtifolium* posed a specific binding to alanine racemase, similarly to sodium benzoate. It indicated that flavonoids of *S. myrtifolium* could be able to inhibit alanine racemase with a similar mechanism as sodium benzoate. Based on the result, this study found Quercetin-3-O-beta-D-glucuronide of *S. myrtifolium* as the most potent antibacterial. Quercetin-3-O-beta-D-glucuronide interacted with alanine racemase via amino acid residue that was also involved in control and sodium benzoate binding with alanine racemase.

### *Interaction of bioactive compounds in S. myrtifolium with transglycosylase*

Based on the result, the control was bound to transglycosylase via ARG476, GLN477, LYS486, TYR594, GLU478, and GLN496 (Table 1, Figure 2). The antibacterial control sodium benzoate was bound with transglycosylase through GLN434, VAL433, ALA480, and ASN482. The GLN434 amino acid residue of sodium benzoate - transglycosylase was also involved in 2-Propanone, 1,3-bis (5-nitro-2-furanyl) and auraptenol binding with transglycosylase. 2-Propanone, 1,3-bis(5-nitro-2-furanyl) was bound to transglycosylase (-238.4 kJ/mol) by hydrogen bond and hydrophobic interaction following amino acid residues, ASN482, GLN434, ALA480, VAL433, ILE437, and VAL485. Auraptenol - transglycosylase (-195.6 kJ/mol) formed interaction with hydrogen bond and hydrophobic interaction via GLN434, ASN482, ARG401, ILE437, ALA480, and ILE437. Calopiptin - transglycosylase (-155 kJ/mol) was formed through GLN477, ASP430, ALA480, VAL485, GLU478, and TYR594 amino acid residues. Calopiptin - transglycosylase complex shared similar amino acid residues, GLN477 and TYR594, with Quercetin-3-O-beta-D-glucuronide - transglycosylase complex. Quercetin-3-O-beta-D-glucuronide bound to transglycosylase (-218 kJ/mol) through ARG476, GLU478, GLN496, TYR594, GLN477, GLU583, PRO488, VAL485, ALA480, and ASN553 amino acid residues (Figure 2). Interestingly, Quercetin-3-O-beta-D-glucuronide was formed by binding with transglycosylase through the amino acid residues also found in control - transglycosylase and sodium benzoate - transglycosylase. The ARG476, GLU478, ALA480, and GLU496 found in Quercetin-3-O-beta-D-glucuronide were the amino acid residue of control transglycosylase interaction. Quercetin-3-O-alpha-L arabinopyranoside - transglycosylase (-226.2 kJ/mol) was built through the interaction of ASN553, GLU583, GLN496, GLU478, LYS486, PRO488, VAL485 amino acid residues (Figure 2). Quercetin-3-O-alpha-L-arabinopyranoside showed the binding with LYS486, which is also involved in control - transglycosylase binding. The GLU496 in control - transglycosylase complex was also found in Quercetin-3-O-alpha-L-arabinopyranoside - transglycosylase and Quercetin-3-O-beta-D-glucuronide - transglycosylase.

This study also found two amino acid residues that were possibly declared as a specific binding site of *S. myrtifolium*'s bioactive compounds with transglycosylase. Those were GLU478 and ALA480 amino acid residues. Almost all the bio-

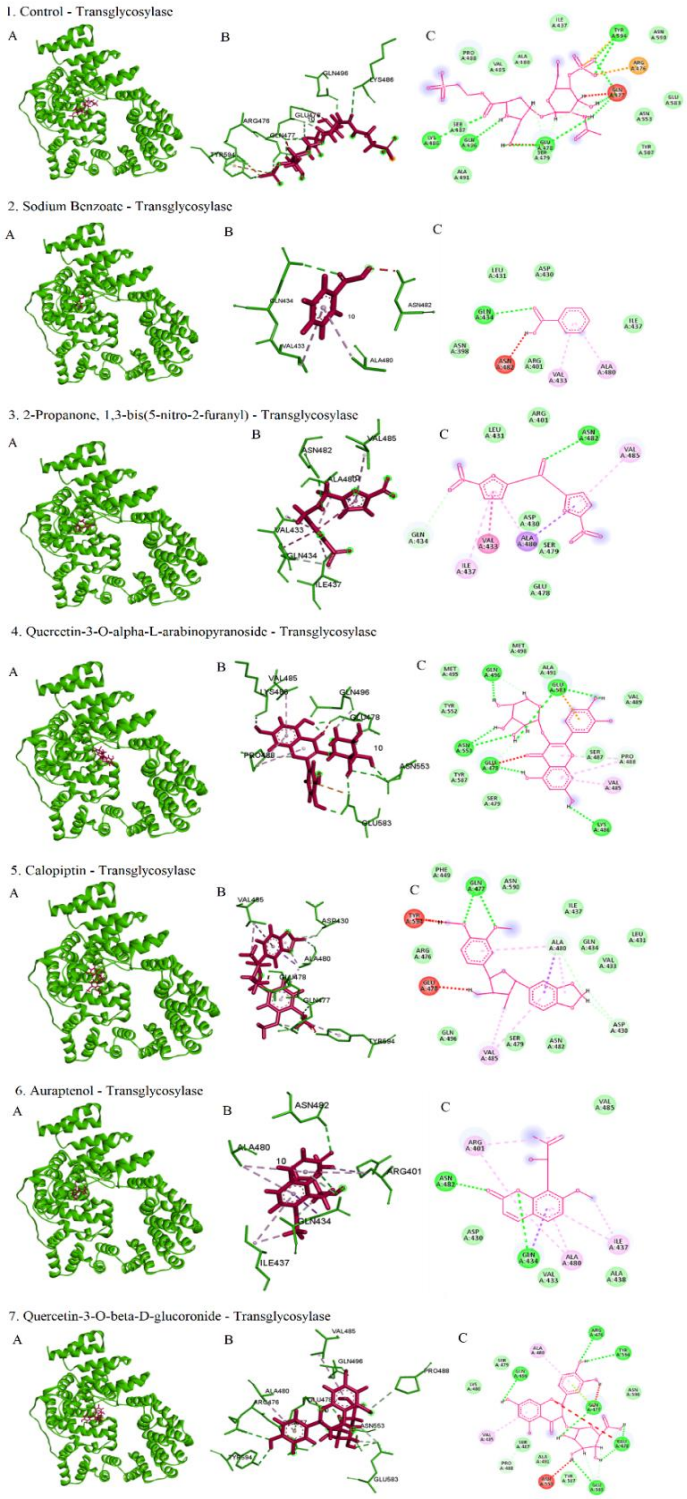


Figure 2. Interaction of flavonoids in *S. myrtifolium* with transglycosylase: A-B) The 3D structure of ligands-protein, C) The 2D of ligand-proteins green ribbon structure was transglycosylase, while pink color was ligands.

active compounds in *S. myrtifolium* interacted with transglycosylase via ALA480, except Quercetin-3-O- alpha- L-arabinopyranoside. In addition, Quercetin-3-O-alpha-L-arabinopyranoside, copeptin, and Quercetin-3-O-beta-D-glucuronide were bound to transglycosylase through GLU478. From the data mentioned in the result, Quercetin-3-O-beta-D-glucuronide could be assumed to have

the highest antibacterial activity because it mostly showed a similar binding site as the control and sodium benzoate.

Antibacterial properties are one parameter to testing therapeutic compounds. It is caused by the high case of microbial infections, antibiotic resistance, and biofilm production [3]. Hypothetically, *S. myrtifolium* has therapeutic activity such as antibacterial activity [5, 21, 22]. This study used alanine racemase and transglycosylase as the receptor to test the antibacterial activity of bioactive compounds from *S. myrtifolium*. Positive control and sodium benzoate were used to validate the antibacterial properties test of *S. myrtifolium*. The binding site of bioactive compounds from *S. myrtifolium* to alanine racemase and transglycosylase were compared with positive control and sodium benzoate binding to receptors. Bioactive compounds are assumed to have antibacterial activity if they can inhibit alanine racemase and transglycosylase.

Alanine racemase is a pyridoxal-5'-phosphate (PLP)-containing homodimeric enzyme that catalyzes the interconversion of L-alanine to D-alanine. The D-alanine synthesized by alanine racemase is an essential component of gram-positive and gram-negative bacteria [7, 9, 10, 23, 24]. It is ubiquitous in prokaryotes and absents in higher eukaryotes, making alanine racemase a potential target for antibacterial therapeutic drug development. There were many mechanisms of alanine racemase inhibition, such as D-Cycloserine (DCS), an antibiotic produced by *Streptomyces lavendulae* and *Streptomyces garyphalus* which targets Ala site of alanine racemase, attacks PLP, displaces the lysine side chain, and forms linkage to PLP [24, 25]. The following amino acid residues, TYR274, TYR343, ARG280, TYR255, LYS34, and ARG129, are important amino acid residues in cell wall synthesis. The inhibition of alanine racemase active sites will result in the inhibition of cell wall biosynthesis. The TYR255 has been identified as the catalytic base [9, 26]. Interestingly, all bioactive compounds in *S. myrtifolium* showed binding to TYR255, which has a high chance of disrupting the cell wall biosynthesis of bacteria.

Peptidoglycan, composed of the cell wall of bacteria, is often a target for antibiotic and antibacterial drug development. Bacterial transglycosylase is a critical component of cell wall biosynthesis. It is involved in the peptidoglycan layer synthesis. Blocking the peptidoglycan synthesis or peptidoglycan binding will possibly disrupt bacterial cell walls [6, 12]. Previously, there was a study of transglycosylase inhibitors. The inhibitor showed binding to transglycosylase through TYR552, MET498, THR501, TYR533, GLU478, SER487, and GLY583[26]. According to the previous study, flavonoids of *S. myrtifolium* could bind with transglycosylase via GLU478. The GLU478 is an amino acid residue comprising the active site of transglycosylase. The inhibition of protein through the active site assumedly could result in optimum inhibition. Thus, the peptidoglycan cell wall biosynthesis is also inhibited. Furthermore, all binding energy showed low binding energy and varied interactions. Previous reports stated that low binding energy indicated tight ligand-protein interaction, and various interactions, including hydrophobic and hydrogen bonds, contributed to the binding energy calculations [27–31].

## Conclusion

In conclusion, flavonoids compound from *S. myrtifolium* were inhibited peptidoglycan cell wall inhibition via blocking alanine racemase and transglycosylase activities. Further molecular dynamic and *in vitro* studies were required.

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