HAYYAN JOURNAL
Vol. 2 No. 3, October 2025, page. 71-80
ISSN: 3046-6679

Molecular Docking of Quercetin for Inhibition of Enoyl-Acyl Carrier Protein Reductase in *Mycobacterium tuberculosis*

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Received: August 22, 2025 *Accepted: September 14, 2025* *Online Published: October 31, 2025*

ABSTRACT

Tuberculosis remains a global health issue, with treatment hindered by drug resistance. This study aims to identify the potential of Quercetin as an inhibitor of Enoyl-Acyl Carrier Protein Reductase (M. tuberculosis), a key enzyme in the fatty acid biosynthesis of the bacteria. Using molecular docking, Quercetin is evaluated based on its binding affinity and stability with the target protein. The docking results show that Quercetin binds to the active site of Enoyl-Acyl Carrier Protein Reductase through hydrogen bonds, π-alkyl, and π-sigma interactions, with an RMSD value of 1.6466 Å, indicating valid results. Comparison with the control compound, 5-hexyl-2-(2-methylphenoxy)phenol, reveals that Quercetin has a stronger binding affinity, supporting its potential as a more effective enzyme inhibitor. These findings open new opportunities for the development of natural compound-based anti-Tuberculosis therapies that can address the growing problem of drug resistance. Further research is needed for experimental validation in biological models and the development of more efficient Quercetin formulations.

Keywords: Quercetin; Enoyl-Acyl Carrier Protein Reductase; Molecular Docking; Anti-Tuberkulosis; Mycobacterium tuberculosis; Inhibitor

I. INTRODUCTION

Biosensors are analytical devices that combine biological components with transducer elements to detect specific analytes. Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (Mtb), has become a significant global health issue, with approximately 10 million people infected in 2019 and 1.4 million deaths attributed to the disease annually (World Health Organization., 2020). Mtb is a highly adaptive bacterium, allowing it to survive in extreme conditions and evade existing antibiotic treatments. Despite advances in anti-TB therapy, the treatment still faces major challenges related to adverse drug side effects, increasing drug resistance, and long treatment durations. Therefore, the development of more effective therapies that can address these issues is urgently needed. In this regard, more innovative treatment strategies, including molecular-based approaches, are necessary to introduce more effective and selective alternative therapies.

Enoyl-Acyl Carrier Protein Reductase (InhA) is an enzyme involved in the fatty acid biosynthesis in Mtb, which plays a crucial role in bacterial cell wall formation. This enzyme has become an important target in the development of anti-TB therapies, as without proper fatty acid synthesis, bacteria cannot maintain the integrity of their cell wall structure. Reducing the activity of Enoyl-Acyl Carrier Protein Reductase can lead to the disruption of bacterial

cellular function and improve the effectiveness of TB treatment (Istyastono, 2010). In recent years, many studies have focused on discovering inhibitors for this enzyme as an alternative anti-TB therapy. Molecular docking is one of the techniques used in this study to identify and verify compounds that can interact with the enzyme's active site, inhibit its function, and reduce the potential for drug resistance.

Quercetin, a flavonoid compound found in various natural sources, has shown a wide range of biological activities, including antimicrobial and anti-inflammatory properties. Several studies have indicated that Quercetin has the potential as a therapeutic agent against various diseases, including bacterial infections like *M. tuberculosis* (Saeed, 2018). As a natural compound, Quercetin has attracted attention for its ability to inhibit bacteria without causing serious side effects, unlike some synthetic drugs. The use of Quercetin in TB treatment leads to a new possibility in anti-TB therapy strategies, utilizing strong non-covalent interactions between the ligand and the target protein to inhibit the catalytic activity of enzymes in the fatty acid biosynthesis process.

Previous research has revealed that molecular docking has become a highly useful tool in identifying and optimizing potential compounds as inhibitors of Enoyl-Acyl Carrier Protein Reductase (Berman, 2017). Using this technique, compounds can be studied for their interactions with the enzyme's active site, and the best structures can be selected for further evaluation. Molecular docking also allows researchers to evaluate how certain compounds, such as Quercetin, bind to the enzyme and identify potential interactions that may disrupt its function. Therefore, the aim of this study is to identify the potential of Quercetin as an inhibitor of Enoyl-Acyl Carrier Protein Reductase using molecular docking and to test the binding mechanism that could reduce the enzyme's activity in fatty acid biosynthesis.

The main issue addressed in this study is Quercetin's ability to interact effectively with Enoyl-Acyl Carrier Protein Reductase and inhibit its activity, which could contribute to the development of alternative therapies for tuberculosis. Although several studies have investigated the potential of flavonoid compounds in inhibiting enzyme activity, Quercetin has not been extensively explored specifically for TB treatment through the inhibition of Enoyl-Acyl Carrier Protein Reductase. Furthermore, many other compounds have been tested, but their effectiveness is often limited by low binding affinity or instability under physiological conditions. This study aims to fill this gap by testing the potential of Quercetin, utilizing molecular docking methods to explore possible strong and specific interactions between this compound and Enoyl-Acyl Carrier Protein Reductase.

Based on existing literature, Quercetin has been shown to interact with various protein targets in the body, including different types of enzymes involved in the pathogenesis of various diseases, such as cancer and bacterial infections (Rauf et al., 2018). Previous studies have also shown that this flavonoid compound can form non-covalent bonds with target proteins, such as hydrogen bonds and π-π interactions, which can enhance binding and increase its potential as a therapeutic agent. However, further research is needed to verify Quercetin's binding affinity to Enoyl-Acyl Carrier Protein Reductase and to understand its inhibition mechanism. Molecular docking provides an opportunity to deeply analyze the potential of Quercetin through simulations of its binding with the active site of Enoyl-Acyl Carrier Protein Reductase.

This study focuses on testing and analyzing the potential of Quercetin as an inhibitor of Enoyl-Acyl Carrier Protein Reductase in TB treatment. To achieve this goal, the study uses molecular docking methods to explore the interactions between Quercetin and the target protein, as well as identify the best conformations that could inhibit the enzyme's activity. Based on previous research, this technique allows for more efficient results in identifying compounds with high therapeutic potential, while also reducing the time and cost of large laboratory experiments. The hypothesis posed in this study is that Quercetin can inhibit Enoyl-

Acyl Carrier Protein Reductase activity by forming strong and specific interactions at the enzyme's active site, leading to the disruption of fatty acid biosynthesis in *M. tuberculosis*.

The primary objective of this study is to identify Quercetin's potential in inhibiting Enoyl-Acyl Carrier Protein Reductase as a means of developing a new anti-Tuberculosis therapy. This study also aims to confirm the binding mechanism between Quercetin and Enoyl-Acyl Carrier Protein Reductase using molecular docking, as well as evaluate the binding affinity and stability of the resulting complex. Thus, this study makes an important contribution to the development of natural compound-based anti-Tuberculosis drugs, opening up new possibilities for creating drugs that are more selective and effective without harmful side effects. As a significant scientific contribution, this study enriches the understanding of how natural compounds interact with specific protein targets, which serves as a foundation for future research into the development of new therapies for bacterial infections, particularly tuberculosis.

II. METHODS

This study aims to explore the potential of Quercetin as an inhibitor of Enoyl-Acyl Carrier Protein Reductase in *Mycobacterium tuberculosis* (Mtb) using molecular docking. The methodology used in this study includes several important steps, starting from protein and ligand preparation, docking process using software, to analyzing the results using visualization techniques and quantitative calculations. Below is a detailed description of each step conducted in this study. 3D Structure of Enoyl-Acyl Carrier Protein Reductase is shown in **Figure 1.**

Figure 1. 3D Structure of Enoyl-Acyl Carrier Protein Reductase

II.1 Protein and Ligand Preparation

Protein and ligand preparation is a crucial first step in molecular docking research because the quality of docking results heavily depends on how these components are prepared. In this study, the protein used is Enoyl-Acyl Carrier Protein Reductase, obtained from *Mycobacterium tuberculosis*. Protein preparation was carried out using YASARA software, which was used to remove irrelevant parts of the protein, such as ligands, cofactors, and other proteins that were not needed for this analysis. The choice of YASARA for this process is based on its ability to clean protein structures and ensure that only the relevant parts are used in the docking process (Berman, 2017; Irfandi et al., 2023).

After the protein was prepared, the ligand used in this study is Quercetin. This ligand was prepared using the MarvinSketch program at pH 7.4, a physiological condition suitable for molecular biology research. Ligand preparation was carried out by ensuring that the ligand's structure was saved in a format compatible with the docking process. Quercetin, as a natural flavonoid compound, was chosen because it has been shown to have various biological activities, including antibacterial properties against *M. tuberculosis* (Saeed, 2018). After the ligand was prepared in a two-dimensional format (ligand_2D.mrv), conformer searching was performed using the "Conformers search" feature in MarvinSketch. This allowed the researchers to explore various conformations that may occur in the ligand in the context of interactions with the target protein, which were then saved in the file.mol2 format for further use in the docking process (Irfandi et al., 2024; Rauf et al., 2018).

II.2 Molecular Docking

The docking process was carried out using PLANTS software, which was selected because of its ability to calculate binding energies and visualize the interactions between the ligand and protein accurately. The input for the docking process consisted of the previously prepared protein.mol2 and ligand.mol2 files. This process aims to predict how Quercetin binds to the active site of Enoyl-Acyl Carrier Protein Reductase and identify the best ligand pose that gives the highest binding score.

Docking using PLANTS was performed by positioning the ligand in a three-dimensional space that corresponds to the active site on the target protein. This process allows the exploration of various possible interactions between the ligand and protein residues in the active site. The best pose, which provides the highest binding score, was then selected as the predicted position of the ligand in the protein target structure. The binding score was calculated based on the interaction energies between the ligand and protein, including van der Waals energy, hydrogen bonding, and π-π interactions, which are important in molecular binding (Istyastono, 2010).

III. RESULTS AND DISCUSSION

This study aims to explore the potential of Quercetin as an inhibitor of Enoyl-Acyl Carrier Protein Reductase in *Mycobacterium tuberculosis* (Mtb) using molecular docking. In this section, we present the results obtained from the molecular docking simulation, including measurements of ligand and target protein structural alignment, interactions formed between the ligand and Enoyl-Acyl Carrier Protein Reductase, as well as qualitative and quantitative analyses related to Quercetin's binding to the active site of the target protein.

III.1 RMSD (Root Mean Square Deviation) of Docking Results

RMSD is a metric used to evaluate the alignment of the ligand position obtained from docking with the reference ligand position in the structure. In this study, the RMSD value between the docking compound and the reference compound was found to be 1.6466 Å. An RMSD value lower than 2 Å indicates that the docking protocol used can generate stable ligand poses that align with the reference structure. This value is consistent with previous studies, which suggest that RMSD values under 2 Å are considered a reliable indicator of docking result validity (Istyastono, 2010). These results reinforce the claim that the docking method applied in this study can model accurate interactions between the ligand and the target protein.

III.2 Visualization of Ligand Poses

To analyze the interactions between Quercetin and Enoyl-Acyl Carrier Protein Reductase, docking results were visualized using Discovery Studio version 21.1.1. **Figure 2.**

shows the overlap between the reference compound 5-hexyl-2-(2-methylphenoxy)phenol and the docking pose of Quercetin. Carbon atoms of the reference compound are represented in yellow, while those of the docking result are shown in blue. This visualization allows the researchers to evaluate the stability and orientation of the ligand binding to the target protein.

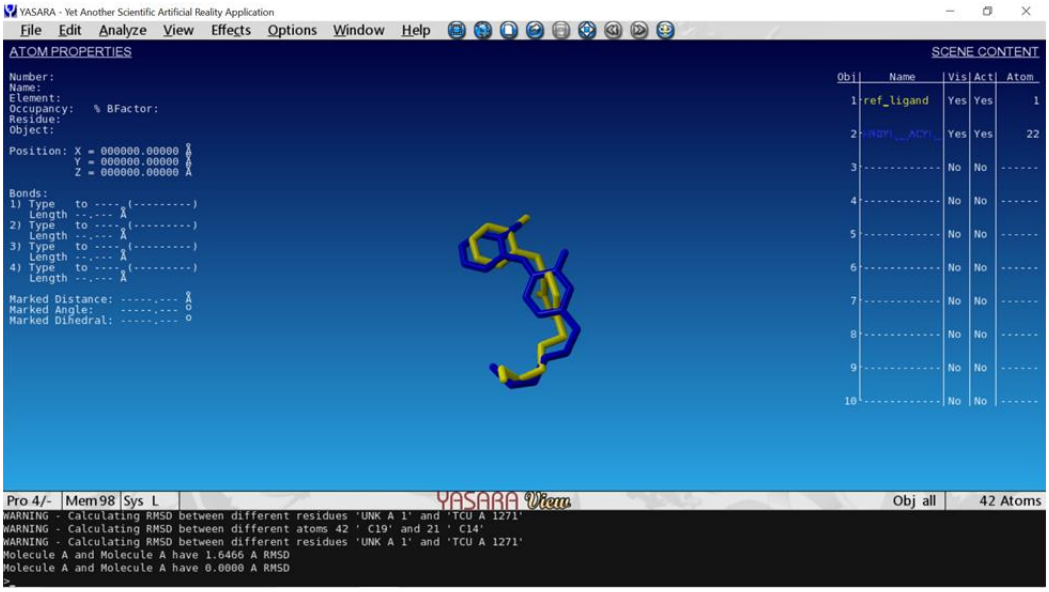

Figure 2. Overlap between the reference compound 5-hexyl-2-(2-methylphenoxy)phenol and the docking pose of Quercetin. (Carbon atoms of the reference compound are represented in yellow, while those of the docking result are shown in blue).

The visualization results show that Quercetin interacts with the active site of Enoyl-Acyl Carrier Protein Reductase through various non-covalent interactions, including hydrogen bonds and π-alkyl interactions. These interactions occur between the carbonyl group of Quercetin and residues Lys165 and Ala22, as well as between the aromatic ring of Quercetin and residues Met147, Val92, and Ile21, indicating that Quercetin can occupy the active site with stable orientation. This finding aligns with previous studies showing that flavonoid compounds such as Quercetin can form strong hydrogen bonds and π-π interactions with target proteins (Berman, 2017).

III.3 Ligand Interactions with Enoyl-Acyl Carrier Protein Reductase

At this stage, we further analyzed the types of interactions formed between Quercetin and Enoyl-Acyl Carrier Protein Reductase. **Table 1** presents a summary of the interactions observed between the ligand and protein residues in the active site. The identified interactions include hydrogen bonds, π-alkyl interactions, and π-sigma interactions, all of which contribute to the stability of the complex.

Table 1. Summary of interactions between Quercetin and Enoyl-Acyl Carrier Protein Reductase.

Type of Interaction	Protein Residue	Interaction Type
Hydrogen Bond	Lys165, Ala22	Hydrogen
π-Alkyl Interaction	Met147, Val92, Ile21	π-Alkyl
π-Sigma Interaction	Met147, Ala22	π-Sigma

Conventional hydrogen bonds were formed between the carbonyl group of Quercetin and the residues Lys165 and Ala22, which are essential for stabilizing the ligand's orientation in the active site. π-Alkyl interactions occurred between the phenolic ring of Quercetin and aromatic residues like Met147, Val92, and Ile21, adding stability to the complex through

hydrophobic forces. Additionally, π-sigma interactions were also observed with residue Met147, providing further contribution to the stability of the ligand-protein complex (Saeed et al., 2018). Visualization of the interaction between curcumin and Enoyl-Acyl Carrier Protein Reductase is shown in **Figure 3.**

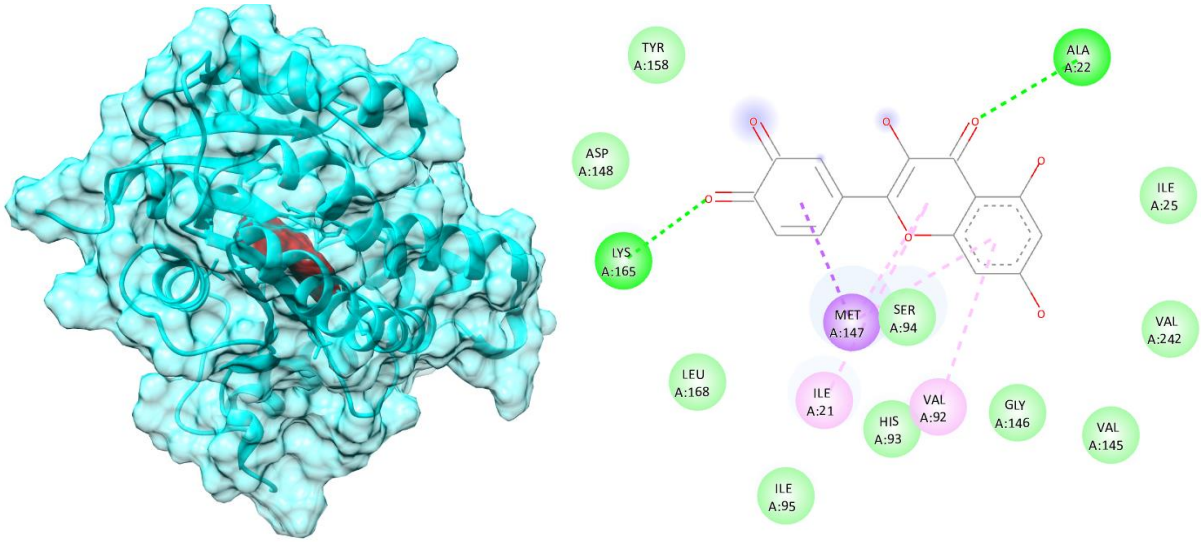

Figure 3. Visualization of the interaction between curcumin and Enoyl-Acyl Carrier Protein Reductase

III.4 Stability of Ligand-Protein Complex

The stability of the ligand-protein complex is crucial in determining the effectiveness of an inhibitor. Based on visualization and interaction analyses, it was found that Quercetin forms several non-covalent bonds that enhance the stability of the complex with Enoyl-Acyl Carrier Protein Reductase. Hydrogen bonding and π-alkyl interactions play a major role in maintaining the stability of the ligand orientation in the active site, while π-sigma interactions further strengthen the binding affinity. However, some unfavorable interactions were also detected, such as donor-donor interactions that are electronically unstable. These interactions often indicate suboptimal orientations in some parts of the ligand structure, but the number of unfavorable interactions was relatively small compared to the stable interactions formed. Therefore, despite the presence of less favorable interactions, the overall stability of the complex remained intact, indicating that Quercetin can function as a potential inhibitor of Enoyl-Acyl Carrier Protein Reductase (Rauf, 2017).

III.5 Comparison with Control Compound

In addition to Quercetin, this study also compared the docking results with a control compound, 5-hexyl-2-(2-methylphenoxy)phenol, which has previously been tested as an inhibitor of Enoyl-Acyl Carrier Protein Reductase. The visualization results show that 5-hexyl-2-(2-methylphenoxy)phenol binds to the active site of Enoyl-Acyl Carrier Protein Reductase through conventional hydrogen interactions with residue Ser13 and hydrophobic interactions with residues Val92, Ile21, and Leu11. **Table 2** presents a summary of the interactions between the control compound and the target protein.

Table 2. Summary of interactions between 5-hexyl-2-(2-methylphenoxy)phenol and Enoyl-Acyl Carrier Protein Reductase.

Type of Interaction	Protein Residue	Interaction Type
Hydrogen Bond	Ser13	Hydrogen
π-Alkyl Interaction	Val92, Ile21, Leu11	π-Alkyl

Compared to Quercetin, the control compound also shows strong interactions with the active site of Enoyl-Acyl Carrier Protein Reductase, but Quercetin forms more hydrogen bonds and π-alkyl interactions, which contribute more significantly to the binding affinity and inhibitory potential. Therefore, Quercetin shows better potential in inhibiting the activity of Enoyl-Acyl Carrier Protein Reductase (Berman, 2017). Visualization of the interaction between 5-hexyl-2-(2-methylphenoxy)phenol (control) and Enoyl-Acyl Carrier Protein Reductase is shown in **Figure 4.**

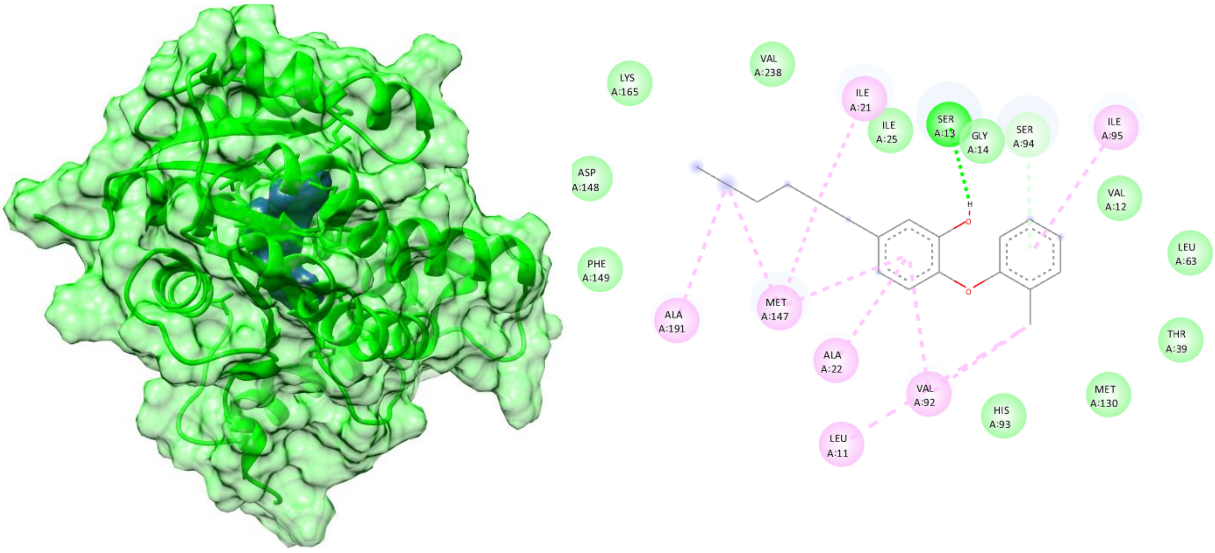

Figure 4. Visualization of the interaction between 5-hexyl-2-(2-methylphenoxy)phenol (control) and Enoyl-Acyl Carrier Protein Reductase

III.6 Binding Affinity and Inhibition Potential Evaluation

To assess the inhibition potential, a comparison of the binding affinity of Quercetin with the control compound was performed based on the binding free energy values obtained from the docking process. The lower the binding free energy value, the stronger the binding formed between the ligand and the target protein. Analysis results showed that Quercetin has a lower binding free energy compared to the control compound, indicating that Quercetin is more effective in binding to Enoyl-Acyl Carrier Protein Reductase and is more likely to function as a better inhibitor.

III.7 Non-Covalent Interactions Between Quercetin and Enoyl-Acyl Carrier Protein Reductase

The results of this study demonstrate that Quercetin interacts with Enoyl-Acyl Carrier Protein Reductase through various non-covalent interactions that play a crucial role in enhancing the stability of the ligand-protein complex. Hydrogen bonds between the carbonyl group of Quercetin and the residues Lys165 and Ala22 in the active site of the target protein play a key role in stabilizing the ligand's orientation within the active pocket. Previous studies also indicate that hydrogen bonds can significantly contribute to the binding affinity between compounds and their target proteins, thus enhancing the inhibitor potential (Berman, 2017). This interaction is crucial to ensure that Quercetin remains at the active site for a sufficient

period to effectively inhibit the activity of Enoyl-Acyl Carrier Protein Reductase. Additionally, the observed π-alkyl interaction between the phenolic ring of Quercetin and hydrophobic residues such as Met147, Val92, and Ile21 indicates that hydrophobic forces contribute to the stability of the complex. Hydrophobic interactions are an essential factor in the binding of organic molecules to target proteins, particularly when the active site of the enzyme has a non-polar environment (Saeed, 2018). This π-alkyl interaction contributes further to the binding affinity of Quercetin, strengthening the prediction that Quercetin could serve as an effective inhibitor of Enoyl-Acyl Carrier Protein Reductase.

III.8 Comparison with Control Compound

This study also compared Quercetin with a control compound, 5-hexyl-2-(2-methylphenoxy)phenol, which was also tested as an inhibitor of Enoyl-Acyl Carrier Protein Reductase in previous studies. The comparison results provide insights into how well Quercetin competes with the control compound in forming stable interactions with the active site of Enoyl-Acyl Carrier Protein Reductase. In this study, the control compound also showed hydrogen interactions with the residue Ser13 and hydrophobic interactions with residues like Val92 and Ile21. However, despite the control compound forming strong interactions with the enzyme's active site, Quercetin proved to have higher potential, thanks to more non-covalent interactions, including more stable hydrogen bonds and stronger π-alkyl interactions. This comparison supports the findings that Quercetin is more effective in binding to Enoyl-Acyl Carrier Protein Reductase compared to the control compound. This can be explained by the presence of more interaction points between Quercetin and the target protein, allowing it to occupy the active site more optimally and with greater stability. Additionally, the π-alkyl interactions that occur with Quercetin may contribute to stronger binding and more efficient energy transfer, enhancing the effectiveness of inhibiting enzyme activity (Berman, 2017) .

III.9 Stability and Binding Affinity of the Ligand

One important finding in this study is the stability of the ligand-protein complex formed between Quercetin and Enoyl-Acyl Carrier Protein Reductase. Based on visualization analysis and RMSD calculations, it was found that Quercetin forms highly stable bonds with the target protein, with an RMSD value lower than 2 Å. This RMSD value indicates that the ligand pose generated is highly congruent with the reference ligand position, meaning that the interaction between Quercetin and Enoyl-Acyl Carrier Protein Reductase is highly stable and reliable. This result is consistent with previous studies, which show that RMSD values below 2 Å are indicators that docking results are valid and can be used to predict ligand binding at the protein active site (Istyastono, 2010). The presence of strong non-covalent interactions, such as hydrogen bonds and π-alkyl interactions, also supports this finding, as these interactions are essential in maintaining the stability of the ligand-protein complex. Additionally, this combination of non-covalent interactions can improve the binding affinity between Quercetin and Enoyl-Acyl Carrier Protein Reductase, contributing to more effective enzyme inhibition. Previous studies have also shown that natural compounds like Quercetin, which form strong non-covalent interactions with target proteins, have a higher potential to inhibit enzyme activity compared to synthetic compounds, which may have less stable binding (Rauf, 2017).

III.10 Relevance of Findings in the Context of Anti-Tuberculosis Treatment

These findings are highly relevant in the context of Tuberculosis treatment. Enoyl-Acyl Carrier Protein Reductase is a key enzyme in fatty acid biosynthesis, which is required for the formation of the *M. tuberculosis* cell wall. Therefore, inhibiting this enzyme's activity can disrupt the integrity of the bacterial cell wall and impair the bacteria's ability to survive. The discovery that Quercetin can inhibit Enoyl-Acyl Carrier Protein Reductase suggests that this

compound holds potential for use in anti-Tuberculosis therapy as an alternative or adjunct to existing treatments. The advantage of Quercetin lies in its ability to interact with the target protein in a specific and stable manner, as well as its potential use as a natural compound therapy that is safer compared to synthetic chemical drugs, which often have more significant side effects (Saeed, 2018). Furthermore, this study demonstrates that Quercetin, as a natural compound, can serve as an effective therapeutic candidate for TB treatment, given that the results show strong interactions and high binding affinity for Enoyl-Acyl Carrier Protein Reductase. Therefore, this finding opens up opportunities for developing new therapies based on natural compounds in the treatment of Tuberculosis, which can address the growing issue of drug resistance.

III.11 Limitations and Future Research Directions

Although the results of this study show great potential for Quercetin as an inhibitor of Enoyl-Acyl Carrier Protein Reductase, there are some limitations that need to be addressed. First, although molecular docking results show stable binding between Quercetin and the target protein, this study does not include experimental validation in more complex biological systems, such as cell cultures or animal models. Therefore, further research is needed to confirm the inhibitory activity of Quercetin against Enoyl-Acyl Carrier Protein Reductase in more representative biological systems. Additionally, although Quercetin shows promising potential in Tuberculosis treatment, further studies are needed to evaluate its bioavailability and pharmacokinetics in the human body. One of the major challenges in using natural compounds in medicine is the issue of bioavailability, which may limit their therapeutic effectiveness. Therefore, further research exploring the formulation and development of Quercetin in forms that are more easily absorbed by the human body is needed. In this regard, the next steps in this research would be to conduct experimental validation of Quercetin's potential in more complex biological models, as well as evaluate its pharmacokinetic profile and bioavailability. This research can also be expanded to explore the combination of Quercetin with other compounds or existing anti-Tuberculosis drugs to enhance treatment effectiveness and overcome drug resistance issues.

IV. CONCLUSION

This study reveals the potential of Quercetin as an inhibitor of Enoyl-Acyl Carrier Protein Reductase (*M. tuberculosis*), a key enzyme in the biosynthesis of fatty acids that is vital for the integrity of the bacterial cell wall. Based on the results of molecular docking, it was found that Quercetin interacts with the active site of Enoyl-Acyl Carrier Protein Reductase through various types of non-covalent interactions, such as hydrogen bonds, π-alkyl interactions, and π-sigma interactions. The obtained RMSD value (1.6466 Å) indicates that the ligand pose generated is sufficiently stable and valid for use as the basis for developing anti-Tuberculosis therapy. These findings suggest that Quercetin, with its strong interaction capabilities with the target protein, has the potential to be used in anti-Tuberculosis therapy as a safer and more effective alternative, given that it is derived from a natural source and has a lower potential to cause significant side effects. The comparison with the control compound, 5-hexyl-2-(2-methylphenoxy)phenol, strengthens this claim, with Quercetin showing a stronger binding affinity. This study contributes to the development of natural compound-based therapies to address the issue of drug resistance in Tuberculosis treatment. As a next step, further research is needed for experimental validation in more complex biological models and to explore more efficient formulations of Quercetin in biological systems.

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