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In Silico Study of Quercetin and Its Derivatives as Potential Antituberculosis

Greachylia Chelzy[1)], Angelina Stevany Regina Masengi[2)*], Jimmy Posangi[2)] Trina Ekawati Tallei[3)], Fatimawali[4)], Christi Diana Mambo[2)], Dian Augina Rintibulawan Rambulangi[3)]

[1)] Medical Education Study Program, Faculty of Medicine, Sam Ratulangi University, Manado 95115, North Sulawesi, Indonesia

[2)] Department of Pharmacology and Therapeutics, Faculty of Medicine, Sam Ratulangi University, Manado 95115, North Sulawesi, Indonesia

[3)] Department of Biology, Faculty of Mathematics and Natural Sciences, Sam Ratulangi University, Manado 95115, North Sulawesi, Indonesia

[4)] Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Sam Ratulangi University, Manado 95115, North Sulawesi, Indonesia

**Coresponding email: asrmasengi@unsrat.ac.id*

ABSTRACT

Tuberculosis (TB) remains the second leading cause of death in the world, with the resistance of Mycobacterium tuberculosis to first-line drugs, such as isoniazid (INH), contributing to the emergence of multi-drug resistant TB (MDR-TB). This study aims to evaluate the potential of quercetin and its derivatives as InhA enzyme inhibitors through an in silico approach to offer innovative therapeutic alternatives to improve the effectiveness of TB treatment. The analysis includes physicochemical properties, ADMET profiles, molecular interactions, and affinity of compounds to the InhA enzyme as an antituberculosis target. The study workflow included ligand and receptor preparation, prediction of biological activity, physicochemical and ADMET analysis, docking validation, molecular docking, and visualization of molecular interactions. Molecular docking was performed using Gnina software, showing that rutin has the lowest binding energy (ΔG) of -12.22 kcal/mol, indicating strong interaction affinity. In addition, ADMET and toxicity analysis showed good pharmacokinetic potential for the test compounds Docking validation confirmed the reliability of the employed methodology, further supporting the potential of quercetin and its derivatives as antituberculosis candidates. However, although quercetin and its derivatives showed promising biological activity, the ADMET profile results were variable, requiring further optimization to develop effective and safe TB therapies.

Keywords: *antituberculosis; quercetin and its derivates; InhA; ADMET; molecular docking*

INTRODUCTION

Tuberculosis (TB) is an infectious disease that poses a global health challenge. According to the World Health Organization (WHO) report in 2022, TB ranked as the second highest cause of death after COVID-19, with an estimated 1.3 million deaths. Indonesia is one of the countries with the second largest TB burden in the world, recording 969,000 cases in the same year (World Health Organization, 2022). This high TB burden is accompanied by a significant challenge in the form of Mycobacterium tuberculosis (MTB) resistance to first-line drugs, such as isoniazid and rifampicin, leading to the emergence of multi-drug resistant tuberculosis (MDR-TB) (Farjallah et al., 2021). This situation is further exacerbated by inappropriate treatment management, direct transmission, or early treatment discontinuation, especially in high-density environments (World Health Organization, 2024).

In recent decades, studies to find new therapeutic targets have significantly focused on improving TB treatment's effectiveness. One of the main targets is the enzyme enoyl acyl carrier protein reductase (InhA), which plays an important role in mycolic acid biosynthesis, an essential component of the MTB cell wall (Kamsri et al., 2020). Isoniazid, as a first-line drug that explicitly targets InhA, has shown decreased effectiveness due to resistance. This resistance poses a

significant challenge to the successful treatment and control of the spread of MDR-TB (Stagg et al., 2017).

To address this challenge, natural compounds from plants are gaining attention as potential candidates for new anti-TB drugs. Quercetin, a flavonoid compound in various plants, exhibits broad antibacterial activity. Its mechanism of action includes inhibition of nucleic acid synthesis, changes in bacterial cell permeability, and cell wall destruction. Quercetin is also effective against pathogens such as Staphylococcus aureus and Pseudomonas aeruginosa (Nguyen & Bhattacharya, 2022).

Bioinformatics and computational technology developments provide opportunities to predict compounds' structure and biological activity more quickly and accurately through in silico methods. This approach uses computer simulations to identify compounds with high potency and selectivity without complex laboratory experiments, thus accelerating the drug discovery process (Wang et al., 2015).

Although quercetin has various benefits, its potential in inhibiting the InhA enzyme still requires in-depth study, so this study aims to analyze the antituberculosis potential of quercetin and its derivatives, such as quercetin dihydrate, quercitrin, rutin, rhamnetin, and tamarixetin, and compare them with isoniazid through an in-silico approach. In addition, this study also evaluated the physicochemical properties, pharmacokinetic and toxicity prediction (ADMET), and ligand interaction with molecular targets. This study is expected to contribute to developing new, more effective therapies against TB.

METHODS

This study is an in silico experimental research study that uses a molecular docking approach and involves analyzing physicochemical properties and ADMET to evaluate the potential molecular interactions of the tested compounds. This research was conducted at the Pharmacology and Therapeutics Department of Sam Ratulangi University from August to November 2024.

This study begins with preparing the InhA protein by searching for the complete sequence of the InhA protein on NCBI. Then, the modeling process was carried out using SwissMODEL. The modeled receptor structure was then entered into AutoDock Tools to be separated from the native ligand and determined the ligand binding region (gridbox) based on active sites that have been identified in previous studies such as Ile15, Ile16, Ser20, Ile21, Phe41, Leu63, Asp64, Val65, Ser94, Gly96, Ile95, Ile122, Met147, Asp148, Phe149, Lys165, Ala191, Ile194, Pro193, and Thr196 (Dasoondi, Blundell, & Pandurangan, 2023). After that, the test and comparison ligands preparation began by downloading the three-dimensional form through the PubChem site. Then, all ligands were examined for biological activity using two main parameters, Pa (Probable Activity) and Pi (Probable Inactivity), as antimicrobials, antituberculosis, and inhibitors of Inha through the PASS Online site. After that, the physicochemical properties, pharmacokinetics, and toxicity prediction were carried out on all ligands using the SMILES code from PubChem, which was copied on the pkCSM site. Prediction of physicochemical properties was done based on Lipinski's Rule 5 and violation of Lipinski's Rule 5 for predicting pharmacokinetics and toxicity using parameters tailored to the study.

Before performing molecular docking, the docking method was validated to measure the docking simulation's accuracy level. Suppose the redocking result shows a Root Mean Square Deviation (RMSD) value of less than 2 Å. In that case, the method is considered valid because the shift of the ligand position to its original position in the protein is minimal (Fadhil Pratama, Poerwono, & Siswodihardjo, 2021). Docking validation was performed by re-docking the native ligand to the protein prepared using Gnina. After that, the receptor and all the ligands that had been prepared were molecularly tethered using Gnina. The tethering process follows the text format Gnina determined and uses a predetermined grid box size. The molecular tethering results will be displayed as a table containing the free binding energy (ΔG) value. From these results, the most negative binding energy value is selected to indicate the best result of the tethering process (Agu et al., 2023). Then, visualization of the tethering results between the InhA protein and quercetin compounds and their derivatives was carried out using Discovery Studio Visualizer 2024 to display the bond interactions formed between the receptor and the ligand on the active side of the amino acid residues on the protein in the form of 2D diagrams.

RESULTS AND DISCUSSION

The increasing resistance to isoniazid and other first-line TB drugs demands innovative drug discovery approaches, such as identifying compounds that target novel essential pathways in MTB to circumvent existing resistance mechanisms (O'Donnell, 2018). Quercetin emerged as a potential candidate with significant anti-TB activity, supported by quantitative structure-activity relationship (QSAR) analysis showing the important role of free hydroxyl groups and lipophilic properties in enhancing its antimycobacterial activity (Sasikumar, Ghosh, & Dusthackeer, 2018). These findings became the basis for this study to determine the potential of quercetin and its derivatives as antituberculosis agents, especially in dealing with isoniazid resistance.

The biological activity prediction results showed that although isoniazid showed the highest activity as an antituberculosis and antimycobacterial agent, quercetin and its derivatives, especially quercetin dihydrate, showed promising potential, especially as an InhA enzyme inhibitor with the highest Pa>Pi value (**Table 1**). This makes the compound worthy to be developed as an alternative therapy for tuberculosis, especially in the face of resistance to isoniazid.

Table 1. Values of biological activity based on the PASS Online

Compund	Parameter					
	Anti-mycobacterial		Anti-tuberculosic		Enoyl-[acyl-carrier-protein] reductase (NADH) inhibitor	
	Pa	Pi	Pa	Pi	Pa	Pi
Quercetin	0,421	0,034	0,420	0,026	0,345	0,002
Quercetin dihydrate	0,421	0,034	0,420	0,026	0,345	0,002
Quercitrin	0,608	0,009	0,394	0,033	0,072	0,006
Rhamnetin	0,432	0,031	0,402	0,031	0,236	0,003
Rutin	0,605	0,010	0,366	0,043	0,061	0,010
Tamarixetin	0,431	0,032	0,403	0,030	0,187	0,003
Isoniazid	0,798	0,004	0,810	0,003	-	-

Quercetin and its derivatives were assessed for physicochemical properties using pkCSM based on Lipinski's rule (**Table 2**), which includes the parameters molecular weight (≤500 g/mol), log P (≤5), number of hydrogen bond donors (≤5), and number of hydrogen bond acceptors (≤10) (Tsantili-Kakoulidou & Demopoulos, 2021). The prediction results showed that two compounds did not fully fulfill this rule. However, natural compounds can violate Lipinski's rule due to the complexity of their structure and biological roles, such as an increased number of hydrogen bond donors and acceptors (Seidel et al., 2020).

Table 2. Lipinski's Rule of Five Predictive Value of Physicochemical Properties

Compound	MW (g/mol)	Log P	H-Bond donor	H-Bond acceptor	Lipinski's Violations	Drug Likeness
Quercetin	302,238	1.988	5	7	0	Yes
Quercetin dihydrate	338,268	0.3386	5	7	0	Yes
Quercitrin	448,38	0.4887	7	11	2	No
Rutin	610,521	-1.6871	16	10	2	No
Rhamnetin	316,265	2.291	4	7	0	Yes
Tamarixetin	316,625	2.291	4	7	0	Yes
Isoniazid	137,142	-0.3149	2	3	0	Yes

The absorption parameters used in this analysis include water solubility, Caco-2 permeability, intestinal absorption, and skin permeability (**Table 3**). Based on these parameters, rhamnetin has a higher bioavailability potential than the other test compounds.

Table 3. Test and comparison ligand absorption prediction results

Compound	Water Solubility (log mol/L)	Caco2 permeability (log µcm/s)	Intestinal absorption (human) (%)	Skin permeability (Log Kp)
Quercetin	-2,925	-0,229	77,207	-2,735
Quercetin dihydrate	-2,92	0,248	67,387	-2,735
Quercitrin	-2,903	0,048	52,709	-2,735
Rutin	-2,892	-0,949	23,446	-2,735
Rhamnetin	-3,212	-0,361	80,214	-2,735
Tamarixetin	-3,007	0,002	73,005	-2,735
Isoniazid	-1,6	0,52	92,601	-3,351

Distribution parameters are expressed in several indicators, namely the volume of distribution at steady state (VDss), the fraction unbound (human), BBB permeability, and CNS permeability (**Table 4**). Quercetin and other flavonoid compounds have good tissue distribution (high VDss values) but difficulty penetrating the blood-brain barrier (negative BBB permeability) and low penetration rates into the central nervous system.

Table 4. Test and comparison ligand distribution prediction results

Compound	VDss (human) (log L/kg)	Fraction unbound (human)	BBB permeability (log BB)	CNS permeability (log PS)
Quercetin	1.559	0.206	-1.098	-3.065
Quercetin dihydrate	1.577	0.199	-1.11	-3.375
Quercitrin	1.517	0.13	-1.495	-4.156
Rutin	1.663	0.187	-1.899	-5.178
Rhamnetin	0.419	0.073	-1.345	-3.235
Tamarixetin	1.089	0.089	-1.161	-3.172
Isoniazid	-0.352	0.728	0.002	-3.351

Metabolic analysis of the compounds was also done by observing the interaction of the compounds with cytochrome P450 enzymes (**Table 5**). Most of the test compounds in this study did not interact significantly with CYP450 enzymes, thus having a low risk of interfering with the metabolism of other drugs. Quercetin and its derivatives, such as rhamnetin and tamarixetin, could support inhibiting CYP1A2 enzymes, which may help regulate specific metabolisms. These compounds show a safe metabolic profile and potential for further development.

Table 5. Test ligand and comparator metabolism prediction results

Compound	CYP2D6 substrate	CYP3A4 substrate	CYP1A2 inhibitior	CYP2C19 inhibitior	CYP2C9 inhibitior	CYP2D6 inhibitior	CYP3A4 inhibitior
Quercetin	No	No	Yes	No	No	No	No
Quercetin dihydrate	No	No	No	No	No	No	No
Quercitrin	No	No	No	No	No	No	No
Rutin	No	No	No	No	No	No	No
Rhamnetin	No	No	Yes	No	No	No	No
Tamarixetin	No	No	Yes	No	No	No	No
Isoniazid	No	No	No	No	No	No	No

The excretion parameters of the six test compounds showed that most of the compounds could be excreted by the body with varying degrees of excretion and not through the OCT2 renal excretion mechanism (**Table 6**).

Table 6. Test ligand and comparator excretion prediction results

Compound	Total Clearance (log ml/min/kg)	Renal OCT2 substrate
Quercetin	0.407	No
Quercetin dihydrate	0.49	No
Quercitrin	0.364	No
Rutin	-0.369	No
Rhamnetin	0.473	No
Tamarixetin	0.508	No
Isoniazid	0.722	No

Toxicity parameters showed that quercetin and its derivatives have a good toxicity profile without genetic toxicity, hepatotoxicity, and skin sensitization (**Table 7**). However, some parameters, such as the inhibitory potential of hERG II in rutin, need to be considered in depth.

Table 7. Test ligand and comparator toxicity prediction results

	Quercetin	Quercetin dihydrate	Quercitrin	Rutin	Rhamnetin	Tamarixetin	Isoniazid
AMES toxicity	No	No	No	No	No	No	No
Max. tolerated dose (human)	0.499	0.491	0.495	0.452	0.56	0.577	1.166
hERG I inhibitor	No	No	No	No	No	No	No
hERG II inhibitor	No	No	No	Yes	No	No	No
Oral Rat Acute Toxicity (LD50)	2.471	2.46	2.586	2.491	2.453	2.407	2.304
Oral Rat Chronic Toxicity (LOAEL)	2.612	2.609	3.022	3.673	2.679	2.476	1.395
Hepatoto-xicity	No	No	No	No	No	No	No
Skin Sensiti-sation	No	No	No	No	No	No	No
T.Pyrifor-mis toxi-city	0.2888	0.287	0.285	0.285	0.331	0.299	-0.134
Minnow toxicity	3.721	4.154	4.954	7.677	1.885	2.289	3.12

The results of molecular tethering between ligand and receptor were analyzed based on the free bond energy (ΔG) value obtained through Gnina (**Table 8**). A negative ΔG value indicates a stable and energetically favorable interaction, so the lower the ΔG value, the stronger the bond between the ligand and the receptor (Tallei et al., 2024). The results of the study on all quercetin compounds and their derivatives showed high-affinity energy to the receptor compared to the standard drug isoniazid with a range of -9.30 to -12.22 kcal/mol with the lowest ΔG value owned by rutin which is -12.22 kcal/mol. This is in line with a previous study that studied the antituberculosis profile of seven plant-based polyphenolic compounds with the results of molecular docking analysis; quercetin showed the highest affinity energy between -8 to -11 kcal/mol, compared to the standard drug isoniazid with a docking score of -5 to -7 kcal/mol (Swain, Rout, Sahoo, Oyedemi, & Hussain, 2022).

Table 8. Free bond energies with Gnina

Compound	Free bond energies (ΔG) (kcal/mol)
Quercetin	-9,61
Quercetin dihydrate	-9,61
Quercitrin	-10,15
Rutin	-12,22
Tamarixetin	-9,30
Rhamnetin	-9,53
Isoniazid	-5,90

The visualization results (**Table 9**) show that the test ligand can interact significantly on the active side, as identified through the involvement of specific amino acid residues with the primary interaction types, including hydrogen bonds and hydrophobic interactions. Hydrogen bonds help stabilize the molecular conformation, increase the binding specificity between the ligand and the receptor, and decrease the ΔG value, indicating a stronger and more stable interaction (Chen et al., 2016). Hydrogen bonds formed on the test ligands are dominated mainly by amino acid residues such as Ile194, Tyr158, and Lys165.

Hydrophobic interactions play a role in determining the stability of the ligand to the receptor. The stronger the hydrophobic interaction, the more stable the complex between ligand and receptor, and the higher the affinity of the ligand to the receptor (Arwansyah et al., 2015). Several compounds interact hydrophobically with receptors on identical residues, such as quercetin and quercetin dihydrate, which have hydrophobic interactions on active site residues, namely Ala22, Gly14, Thr196, Pro193, Ile215, Ile95, Met147, Ser94, and Ser20).

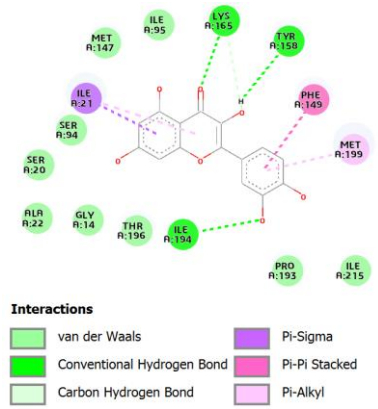
Table 9. Visualize ligand-receptor interactions in 2D

Ligan	Ikatan Hidrogen		Interaksi Hidrofobik
	AA	Jarak (Å)	
Quercetin	Ile194	2,89	Ala22, Gly14, Thr196, Pro193, Ile215, Ile95, Met147, Ser94, Ser20
	Tyr158	2,78	
	Lys165	3,03:3,55	
Quercetin dihydrate	Ile194	2,89	Ala22, Gly14, Thr196, Pro193, Ile215, Ile95, Met147, Ser94, Ser20
	Tyr158	2,78	
	Lys165	3,03:3,55	
Quercitrin	Gly14	2,77	Thr196, Ser20, Ile21, Ser94, Ala22, Phe97, Ser13, Thr39, Ile47, Gly40, Arg43
	Gly96	2,30;3,02	
	Ile15	1,89	
Rhamnetin	Ile194	3,18	Thr17, Thr196, Ile16, Ile15, Met147, Lys165, Tyr158, Ala191
	Asp148	2,57	
	Ile21	3,25;3,42;5,22	
	Ala22	3,17	
	Ser94	3,26	
	Gly14	1,91;2,14	
	Ser20	2,19	
Rutin	Asp148	2,66	Ala22, Ser94, Ile15, Ile47, Thr39, Gly40, Ser13, Leu63, Ala198, Met147, Phe149, Ala191, Met161, Ile21, Thr196, Ser20
	Gly14	1,86;3,93;4,63	
	Gly96	3,27;3,31	
	Lys165	3,22	
	Tyr158	2,31	
Tamarixetin	Lys165	3,02	Asp148, Ile215, Pro193, Thr196, Gly14, Ala22, Ser20, Ser94, Ile95, Met147,
	Tyr158	3,10;4,87	
	Ile194	2,88	
Isoniazid	Leu63	2,79;2,08	Asp64, Ser13, Gly40, Gly14
	Thr39	2,35	

Amino acid residues that play a role in the formation of receptor interactions with ligands are seen in the binding site area, which is the area where binding between proteins and ligands occurs. Through amino acid interactions, the structural differences of each test compound and their activity can be determined (Prasetiawati et al., 2021).

The visualization results (**Figure 1**) also show that isoniazid, as a comparison drug, binds to active site residues through hydrogen bonds such as Leu63 at a distance of 2.79 and 2.08 Å and Thr39 at a distance of 2.35 Å. The interaction of isoniazid with the target receptor also involves hydrophobic interactions in the form of van der Waals bonds that occur with active site residues, namely Asp64, Ser13, Gly40, and Gly14. The van der Waals bonds formed can optimize other stronger interactions, such as hydrogen bonds, by precisely aligning the position of the ligand and receptor.

A



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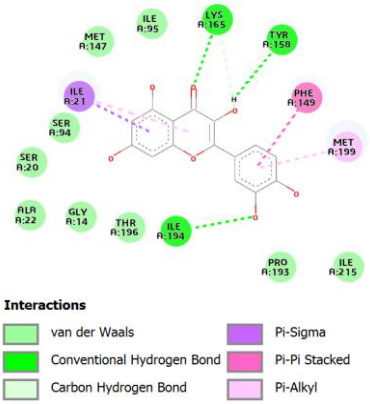

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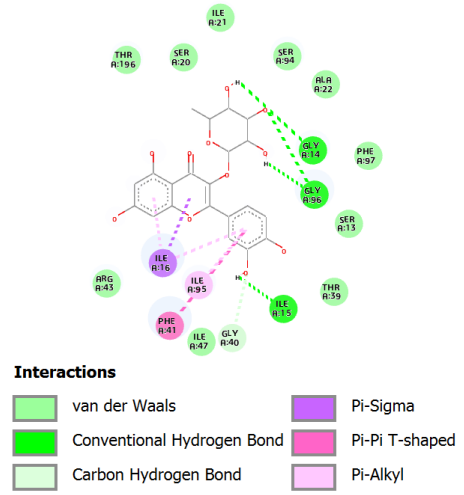

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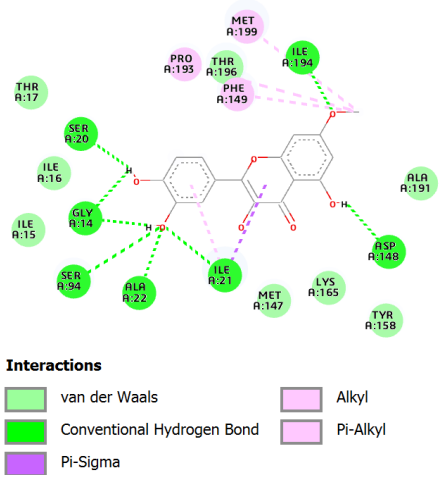

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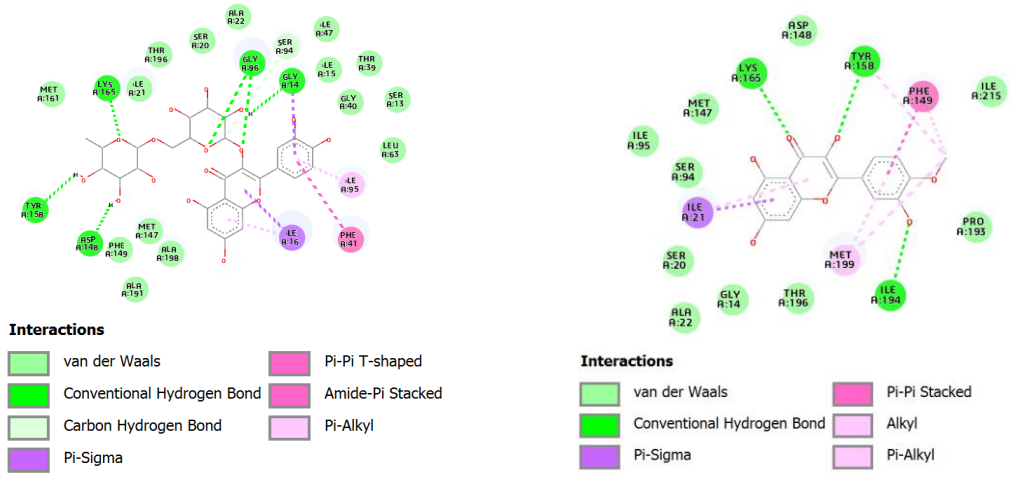

G

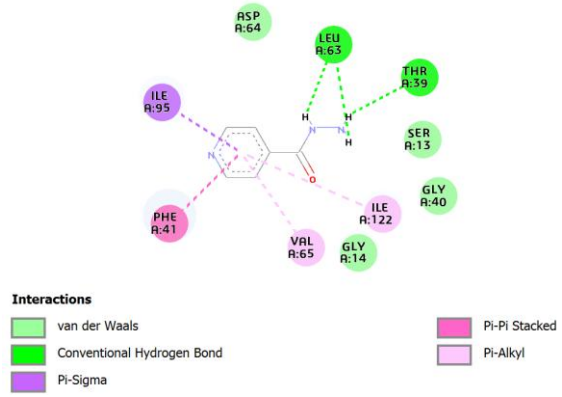

Figure 1. Visualization of InhA receptor binding results with each ligand. Description: (A) Quercetin; (B) Quercetin dihydrate; (C) Quercitrin; (D) Rhamnetin; (E) Rutin; (F) Tamarixetin; (G) Isoniazid.

Based on the results, further studies are needed to evaluate the potential of quercetin and its derivatives as antituberculosis, given the diverse physicochemical properties and ADMET profiles of these compounds. In addition, analysis of the active metabolite of isoniazid as a comparative drug must also be done. Isoniazid, a prodrug, is converted to isonicotinoyl radical through oxidation by the enzyme catalase peroxidase (KatG). This active metabolite binds to nicotinamide adenine dinucleotide (NAD+) to form the INH-NAD adduct complex, inhibiting InhA enzyme activity (Qin et al., 2019). Comparative analysis between quercetin and its derivatives with this active metabolite is important to provide a more comprehensive picture of the binding affinity to the InhA enzyme. However, this study could not do this analysis due to time constraints.

CONCLUSIONS

Based on their biological activity and binding energy, quercetin and its derivatives have potential as antituberculosis agents. In physicochemical terms, most of these compounds satisfy the Lipinski rule of 5, except rutin and quercitrin. ADMET analysis showed variable results, so further optimization is required for development as drug candidates. The interaction of these compounds with the

InhA enzyme involves hydrogen bonding and hydrophobic interactions with key residues such as Ile194, Gly14, and Tyr158, which supports their potential in therapeutic applications. Further study is needed to explore the biological activity in vitro and in vivo, as well as analyze the interaction of the compound with the active metabolite of isoniazid to gain a more comprehensive understanding of its effectiveness and mechanism of action as an antituberculosis drug candidate.

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