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Research Article

In Silico Discovery of Low-Toxicity Natural Ligands for Mycobacterial InhA: A Strategy Against Viral and Bacterial Co-Infections

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A B S T R A C T

Background: Tuberculosis (TB) remains a global challenge, intensified by drug resistance and HIV co-infection. Targeting enoyl-ACP reductase (InhA), vital for mycolic acid synthesis in *Mycobacterium tuberculosis*, is a promising approach. Natural products like flavonoids and alkaloids offer potential due to their bioactivity and structural diversity.

Methods: Molecular docking and *in silico* ADMET/toxicity predictions were used to evaluate kaempferol (flavonoid) and berberine (alkaloid). InhA's crystal structure (PDB ID: 4TZK) was the target. Ligands were prepared and minimized using MMFF94s in Avogadro, and docking was done via AutoDock Vina. pkCSM, SwissADME, and ProTox-II assessed pharmacokinetics and toxicity.

Results: Kaempferol showed stronger binding affinity (–7.1 kcal/mol) than berberine (–6.8 kcal/mol), interacting with residues like Glu219 and Trp230. Both formed stable hydrogen bonds and π–π interactions. ADMET predictions favored kaempferol, indicating good oral bioavailability and low toxicity, while berberine showed immunotoxic and genotoxic potential.

Conclusion: Kaempferol is the more promising candidate for InhA inhibition due to its higher binding affinity and favorable safety profile, warranting further optimization and experimental validation for TB treatment.

Keywords: Tuberculosis; Communicable diseases; InhA enzyme; *Mycobacterium tuberculosis*; Flavonoids; Alkaloids

Introduction

Tuberculosis (TB), a communicable disease of significant global concern, is caused by the bacterium *Mycobacterium tuberculosis*. While primarily impacting the respiratory system, TB can spread throughout the body. Declared a global health emergency almost twenty years ago, TB remains the leading cause of death attributable to a single bacterial species. World Health Organization (WHO) statistics.[1] indicate that in 2021, approximately 1.6 million deaths were due to TB, including 187,000 individuals also infected with the human immunodeficiency virus (HIV). The WHO emphasizes the substantial burden of TB-related morbidity and mortality, further exacerbated by the rising incidence of drug-resistant TB strains.[2] Consequently, research efforts have increasingly investigated phytochemicals, including alkaloids, flavonoids, and terpenoids, known for their antimicrobial activity. In numerous studies, these compounds have demonstrated inhibitory effects against *Mycobacterium tuberculosis*. Exploring these plant-derived medicinal compounds offers a promising avenue for developing innovative antitubercular drugs that could potentially provide improved efficacy and reduced side effects compared to existing treatments.[3,4] This approach leverages the vast potential of natural products and supports the global pursuit of alternative and sustainable strategies for combating infectious diseases.

The frontline TB drugs—isoniazid, rifampicin, ethambutol, and pyrazinamide—while effective, are associated with significant toxicity, particularly hepatotoxicity, and require prolonged treatment durations. Therefore, the identification of novel, safe, and orally bioavailable antitubercular agents is a pressing need in global health. One of the most validated targets for TB drug development is enoyl-acyl carrier protein reductase (InhA), a key enzyme involved in the fatty acid biosynthesis (FAS-II) pathway responsible for mycolic acid production, an essential component of the mycobacterial cell wall.[5-8] InhA has been targeted indirectly by isoniazid, which requires activation by the *katG* enzyme. However, mutations in *katG* or the InhA promoter region can lead to drug resistance, highlighting the importance of direct InhA inhibitors that bypass activation requirements.[9]

Natural products, particularly flavonoids, have gained attention as potential antimicrobial agents due to their structural diversity, broad-spectrum activity, and relatively low toxicity. Kaempferol, a dietary flavonoid found in various fruits and vegetables, has demonstrated antioxidant, anti-inflammatory, and antimicrobial properties. Recent studies suggest that kaempferol may interfere with bacterial enzymes and pathways, making it a suitable candidate for repurposing in antitubercular drug discovery. Also, another type of natural product is a type of alkaloid. Berberine is a low-toxicity natural isoquinoline alkaloid. In the Novel Coronavirus Infection Pneumonia Treatment Program (*Trial Eighth Edition*),[10] many traditional Chinese medicine compounds, such as *Huanglian Jiedu Decoction* (HLJDD), contain Coptis chinensis *rizhome*, of which the main active ingredient is berberine.[11] Berberine shows a great biochemical and pharmacological activity in the clinic, having a hypolipidemic effect.[12] anti-inflammatory, anti-cancer, anti-bacterial and antiviral, and other characteristics.[13] Berberine is able to penetrate most of the cells.[14] At the same time, berberine has strong antiviral activity against different viruses. The antiviral impact of berberine to herpes virus, influenza virus and respiratory syncytial virus has been proven scientifically.[15] In the context of infectious disease pharmacology, computational approaches such as molecular docking, ADMET profiling, and toxicity prediction offer rapid, cost-effective strategies to prioritize bioactive molecules for further in vitro and in vivo evaluation.[16, 17] These *in silico* tools enable screening for molecular interactions, pharmacokinetics, and safety early in the drug development process, especially critical in diseases where prolonged therapy increases the burden of adverse effects.

This research investigates the potential of kaempferol and berberine to inhibit the InhA enzyme through structure-based molecular docking, complemented by *in silico* toxicity and ADMET profiling. Integrating pharmacodynamic and pharmacokinetic assessments, the study highlights kaempferol as a prospective therapeutic agent for tuberculosis, a communicable disease of significant global concern as prioritized by the World Health Organization.

Ethical Approval

This study did not involve human participants, animal subjects, or the use of biological materials. All analyses were conducted using publicly available structural data (PDB ID: 4TZK) and computational tools (AutoDock 4.5 and Discovery Studio). Therefore, ethical approval was not required.

Experimental Methodology (Computational Approach)

Ligand Selection and Preparation

Two natural compounds, kaempferol and berberine, were selected based on their reported antimicrobial and antiviral potential. The 2D structures were downloaded from the PubChem database, then imported into Avogadro 1.2.0 for 3D optimization using the MMFF94 force field. Energy minimization was applied to obtain the most stable conformers for docking.

Protein Preparation

The crystal structure of enoyl-acyl carrier protein reductase (InhA) from *Mycobacterium tuberculosis* (PDB ID: 4TZK)

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was retrieved from the Protein Data Bank (PDB). Water molecules and co-crystallized ligands were removed using PyMOL 2.5, and hydrogen atoms were added. The protein was then saved in PDBQT format using AutoDockTools 1.5.6.

Molecular Docking

Docking simulations were conducted using AutoDock Vina, integrated through the PyRx 0.9.8 platform. The grid box was centered on the NADH-binding site of InhA. For each ligand, nine docking poses were generated, and the best pose (lowest binding affinity) was selected for further analysis.

Visualization and Interaction Analysis

Post-docking interaction analysis was performed using:

1. PyMOL for 3D visualization of ligand–protein complexes.
2. Discovery Studio Visualizer 2021 for hydrogen bond, π-π stacking, and hydrophobic interaction mapping.
3. BIOVIA LigPlot+ and Protein-Ligand Interaction Profiler (PLIP) to confirm and annotate binding residues.
4. ADMET and Toxicity Predictions

In silico pharmacokinetic and toxicity assessments were performed using:

1. SwissADME for drug-likeness, solubility, Lipinski rules, and GI absorption.
2. pkCSM for ADME profiling, including Caco-2 permeability, VDss, CYP450 inhibition, clearance, and renal excretion.
3. ProTox-II and ProTox-3.0 for organ toxicity, immunotoxicity, hepatotoxicity, and mutagenicity predictions.
4. Tox21 Pathway Predictors for receptor binding and nuclear signaling interference analysis.

Results and Discussion

Molecular docking of Kaempferol and Berberine with 4TZK

Subsequent molecular docking of Kaempferol and Berberine with 4TZK was performed to provide more intuitive details of the binding conformation and molecular interactions. Fig. 1A and Fig. 2A show the 3D docked conformation with the lowest binding energy (most stable). Fig. 1B and Fig. 2B showed detailed molecular docking information of ligand with amino acids associated with the active site of 4TZK, and the relevant amino acid residues and the interactions were displayed in a 2D plot (Fig. 1C and fig. 2C). After the binding of Kaempferol and Berberine with 4TZK, the microenvironment of the amino acid at binding site exhibited irregular hydrophobicity, hydrogen bonding, and interpolated charge varied distribution (Figs. 1 D and fig. 2D) shows for Hydrogen bonding, which were complementary to the binding interactions. The summary of interactions of Kaempferol–InhA Interactions (4TZK) Docking Score: –7.1 kcal/mol; Hydrogen Bonds: Ala211, Glu219; Pi-Alkyl & π-π Interactions: Val203, Trp230; Hydrophobic Contacts: Ile202, Leu218; Pose stability: RMSD 0.000 (best conformation), also for interactions of Berberine–InhA Interactions (4TZK): Docking Score: –6.8 kcal/mol; Hydrogen Bonds: Asn159; π–π Stacking: Phe108, Phe109; Alkyl Interactions: Val163, Ala154. As shown in Figure 3 and Table 1:

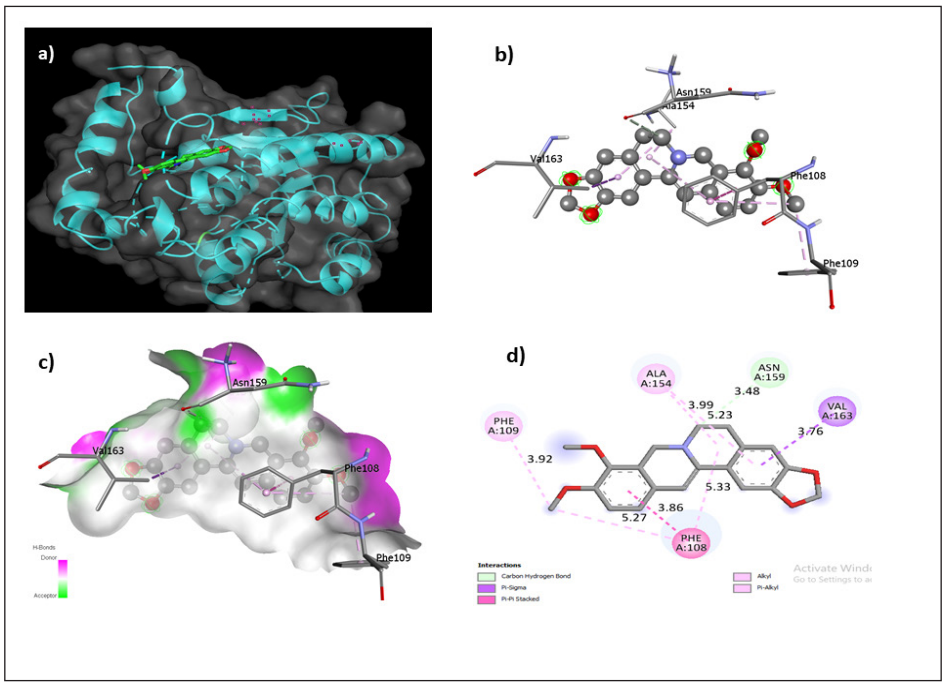

Figure 1.Molecular docking of Kaempferol with 4TZK. (A) Lowest energy conformation of Kaempferol with 4TZK docking; (B) Detailed 3D image of the binding mode of Kaempferol with 4TZK; (C) Detailed 2D image of the interaction of Kaempferol with surrounding amino acid residues; (D) H-bonds distribution after docking of Kaempferol with 4TZK

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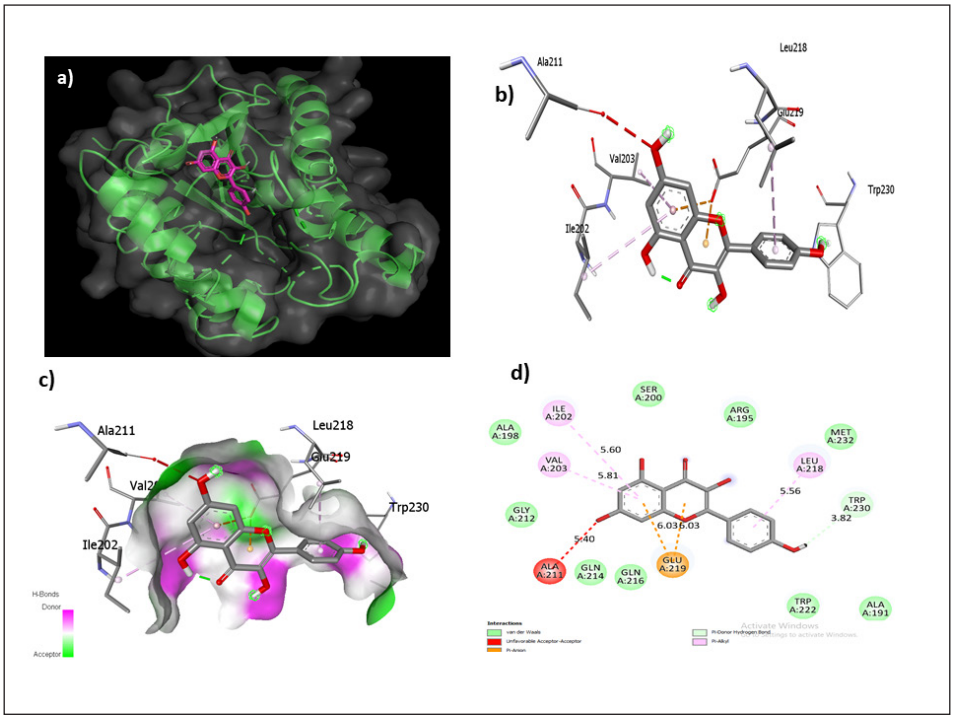

Figure 2.Molecular docking of Berberine with 4TZK. (A) Lowest energy conformation of Berberine with 4TZK docking; (B) Detailed 3D image of the binding mode of Berberine with 4TZK; (C) Detailed 2D image of the interaction of Berberine with surrounding amino acid residues; (D) H-bonds distribution after docking of Berberine with 4TZK

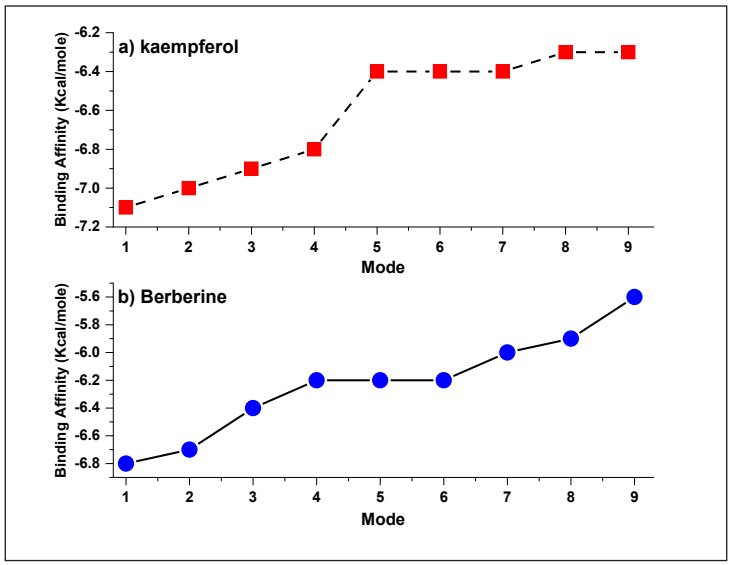

Figure 3.Best energies of molecular docking of interaction of a) Kaempferol and b) Berberine with 4TZK

Table 1.Molecular Docking Summary of Kaempferol and Berberine interactions with 4TZK

Ligand	Best Binding Affinity (kcal/mol)	Key Interacting Residues	Pose RMSD	Docking Site
Kaempferol	–7.1	Glu219, Ala211, Trp230, Ile202, Val203	0.000 Å	NADH cofactor site
Berberine	–6.8	Phe108, Phe109, Ala154, Asn159, Val163	0.000 Å	NADH cofactor site

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Kaempferol demonstrated a more favorable binding profile with InhA, showing a stronger docking affinity than berberine (–7.1 vs. –6.8 kcal/mol) results are shown in Figure 3, and forming multiple stabilizing interactions in the enzyme's active site. Hydrogen bonding with Glu219 and Ala211, π-π stacking with Trp230, and van der Waals contacts contribute to a highly stable complex. These findings align with known reports of kaempferol's antimicrobial and enzymatic inhibitory properties.[18, 19]

Berberine, although slightly weaker in docking score, also showed meaningful binding via π-stacking with Phe108 and Phe109, consistent with previous studies identifying these residues as key anchoring points for InhA inhibitors.[6, 20] Its isoquinoline core provides rigidity and planarity beneficial for aromatic interactions.

When integrated with toxicity profiles, kaempferol again proves superior, being non-hepatotoxic, non-mutagenic, and non-carcinogenic. In contrast, berberine exhibits predicted immunotoxicity, mutagenicity, and potential drug–drug interaction risk due to CYP enzyme inhibition. This presents a critical concern in co-infected TB patients, especially those with HIV or on multidrug regimens.[21,22] Both molecules target the NADH-binding region of InhA, a validated mechanism shared with clinical drugs like isoniazid. Therefore, kaempferol's strong binding and clean ADMET profile support its candidacy for development into a safe, plant-derived antitubercular agent, with potential application in broader communicable disease therapy due to its anti-inflammatory and antiviral effects

The Physicochemical; ADME, and toxicity predictions of ligands

The Physicochemical and ligand-like Properties of Kaempferol exhibited a molecular weight of 286.24 g/mol, 6 H-bond acceptors, and 4 donors, with a polar surface area (TPSA) of 111.13 Å². It passed all major drug-likeness filters (Lipinski, Veber, Egan, Muegge). Furthermore of Berberine had a molecular weight of 336.36 g/mol, 4 H-bond acceptors, no donors, and a lower TPSA (40.80 Å²). It also passed drug-likeness filters, though with 1 Brenk alert due to its quaternary nitrogen. Besides Physicochemical and Drug-Likeness Properties, the Absorption, Distribution, Metabolism, and Excretion (ADME) have been studied, results shown in Table 2. Finally, the toxicity predictions were also determined, results shown in Table 3. The updated *in silico* toxicity profiling reveals notable contrasts between kaempferol and berberine in terms of organ toxicity and predicted safety for clinical applications in communicable disease management.

Kaempferol now demonstrates a significantly improved safety profile, showing no hepatotoxicity, neurotoxicity, cardiotoxicity, or mutagenicity, and is also non-carcinogenic and non-immunotoxic. This aligns with prior studies indicating kaempferol's anti-inflammatory and immunomodulatory roles in infectious disease models.[23,24] These features make it particularly attractive for chronic infections such as tuberculosis and viral diseases requiring long-term therapy. However, kaempferol was predicted to inhibit CYP1A2 and CYP2D6, which are major enzymes in drug metabolism. Inhibiting these enzymes may increase the plasma concentration of co-administered drugs and lead to adverse effects, particularly in TB patients undergoing polytherapy.[25, 26]

Berberine, while hepatologically safe, now raises concern due to newly predicted neurotoxicity, immunotoxicity (probability 0.99), mutagenicity, and carcinogenicity. These findings are consistent with some experimental reports suggesting berberine's dual pro-oxidant and genotoxic effects at higher concentrations.[27, 28] Its predicted immunotoxicity is especially limiting in the context of HIV co-infection or viral hepatitis, where immune suppression can be fatal. Furthermore, berberine's inhibition of CYP1A2 and CYP2D6 may lead to unfavorable interactions with antiretrovirals, antifungals, or antibiotics, all commonly co-administered in communicable disease care.[29, 30] Altogether, kaempferol appears to offer greater therapeutic safety and versatility than berberine for drug discovery in bacterial and viral communicable diseases.

Table 2.Absorption, Distribution, Metabolism, and Excretion (ADME) of Kaempferol and Berberine ligands

Property	Kaempferol	Berberine
GI Absorption	High (97.1%)	High
BBB Permeability	Moderate (0.198)	Yes
Caco-2 Permeability	1.73 log Papp	Low (0.032 log Papp previously)
P-gp Substrate	Yes	Yes
CYP Inhibition	CYP1A2, 2D6, 3A4 (inhibitors)	CYP1A2, 3A4 (inhibitors)
Total Clearance	1.27 log ml/min/kg	0.477 log ml/min/kg
Renal OCT2 Substrate	No	No
Bioavailability Score	0.55	0.55

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Table 3.Toxicity Predictions of Kaempferol and Berberine Ligands

Toxicity Predictions	Kaempferol	Berberine
Hepatotoxicity	Inactive (0.68)	Inactive (0.82)
Neurotoxicity	Inactive (0.89)	Active (0.55)
Cardiotoxicity	Inactive (0.91)	Inactive (0.72)
Carcinogenicity	Inactive (0.72)	Active (0.56)
Immunotoxicity	Inactive (0.96)	Active (0.99)
Mutagenicity	Inactive (0.52)	Active (0.62)
CYP1A2 Inhibitor	Active (0.93)	Active (0.69)
CYP2D6 Inhibitor	Active (0.62)	Active (0.93)

Conclusion

This study reveals that kaempferol binds more effectively and safely to the InhA active site than berberine, making it a more suitable candidate for antitubercular drug development. Its –7.1 kcal/mol binding affinity, supported by hydrogen bonding and hydrophobic interactions, aligns with a favorable toxicity profile and oral bioavailability. Berberine, while active, presents toxicity challenges that may limit its standalone use but still holds promise for synergistic or modified therapeutic approaches. These findings emphasize the role of natural products as valuable scaffolds in the fight against communicable diseases, especially when integrated with computational screening to accelerate safe drug development for resource-constrained settings. Ultimately, these findings support kaempferol's progression to experimental validation as a safe, orally available, and bioactive flavonoid suitable for use in multi-pathogen strategies targeting bacterial and viral communicable diseases.

Conflict of Interest: None

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Authors Contribution: AMJ, AFAH, HHA, ASA, HFH, SJT, ZHA, WDK: Conceived the study, conducted molecular docking and ADMET analyses, interpreted the results, and wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

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