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NATURAL PRODUCTS AS POTENTIAL ANTI-TUBERCULAR AGENTS: IN-SILICO STUDY

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ABSTRACT

Tuberculosis (TB), a severe infectious disease instigated by Mycobacterium tuberculosis, continues to pose a major public health concern worldwide. The situation is increasingly dire due to the rise of multidrug-resistant and extensively drug-resistant strains, which significantly limit the effectiveness of standard therapeutic regimens. In light of these challenges, there is a growing interest in identifying alternative treatment strategies that are both effective and sustainable. This study investigates the potential of naturally occurring compounds as promising candidates for antitubercular drug development. By employing molecular docking methods, we assess the binding affinities and interactions of selected natural products with key TB-related protein targets. The results underscore the potential of these bioactive compounds to serve as leads for the development of novel antitubercular therapies, offering a complementary approach to traditional treatment protocols and contributing to the global effort to control TB.

No. of Pages: 4 **No. of Table: 1** **Nos. of Fig.: 2** **References: 16**

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INTRODUCTION

Tuberculosis (TB), a contagious disease caused primarily by *Mycobacterium tuberculosis*, continues to pose a critical threat to global health, particularly in developing countries where healthcare infrastructure is often limited (Verma, 2017). Despite the existence of standardized treatment protocols, TB remains among the top 10 causes of death worldwide, claiming over a million lives each year (World Health Organization [WHO], 2023). A major challenge in TB control is the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains, which undermine the efficacy of first- and second-line antibiotics (Dheda et al., 2017). These growing resistance patterns, combined with the long duration and adverse side effects of existing treatments, underscore the urgent need for novel, safer, and more effective therapeutic agents.

Natural products have historically served as a rich source of medicinal compounds, with nearly half of all current pharmaceuticals derived from or inspired by natural sources (Newman & Cragg, 2020). Among these, phytochemicalsbioactive compounds found in plantshave gained significant attention for their antimicrobial, anti-inflammatory, and immunomodulatory properties. This study focuses on the potential of selected natural compounds, particularly curcumin from *Curcuma longa* (turmeric) and phloretin from *Malus domestica* (apple tree), both

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of which exhibit documented antimicrobial activities (Jiao et al., 2019; Rai et al., 2021).Curcumin, a polyphenolic compound found in turmeric, has been widely studied for its broad pharmacological properties, including its ability to inhibit the growth of *M. tuberculosis* by targeting its cell wall synthesis and interfering with bacterial enzymes (Rai et al., 2021). Similarly, phloretin, a dihydrochalcone flavonoid primarily found in apples, has demonstrated potential in modulating immune responses and inhibiting microbial proliferation through various biochemical pathways (Maiolini et al., 2020).This research employs molecular docking simulations to evaluate how these compounds interact with key proteins involved in the survival and virulence of *M. tuberculosis*. Molecular docking is a computational method used to predict the orientation and binding affinity of small molecules with target proteins, thus aiding in the identification of promising lead compounds for drug development (Ferreira et al., 2015). By simulating the interactions of curcumin and phloretin with critical mycobacterial targets, the study aims to provide insight into their potential as scaffolds for novel antitubercular drug development.

MATERIALS AND METHODS

The natural compounds selected for this study were obtained from the PubChem database (National Centre for Biotechnology Information [NCBI], n.d.), which offers comprehensive chemical information on a wide array of biologically relevant molecules. To study the interaction between these compounds and a potential mycobacterial drug target, the three-dimensional crystal structure of the *Mycobacterium tuberculosis* - *oxidation trifunctional enzyme was retrieved from the RCSB Protein Data Bank (PDB), using the entry with the PDB ID: 4B3I (RCSB PDB, n.d.). The chemical structures of the selected natural compounds as well as the target protein are depicted in Figure X* for visual reference.Before conducting molecular docking simulations, the protein structure was prepared by removing all non-essential molecules, including water molecules, extraneous heteroatoms, and bound cofactors. To enhance docking accuracy, polar hydrogen atoms were added, and Kollman partial charges were assigned to the protein structure using standard protocols. This preparation step is essential to ensure accurate modeling of molecular interactions during docking (Morris et al., 2009).

For the docking simulations, a grid box was defined around the active site of the target protein with the following coordinates and dimensions: center at x = -26.283, y = 12.599, z = 58.966, and size set to 80 Å in each direction (x, y, z), with a grid spacing of 0.475 Å. These parameters were carefully chosen to encompass the entire binding pocket and ensure that the docking software could explore all relevant binding conformations.Molecular docking was performed using AutoDock, a widely used software tool for predicting the binding affinity and orientation of ligands within a protein's active site (Morris et al., 2009). The resulting docking complexes were further visualized and analyzed using PyMOL, a molecular visualization tool that provides detailed three-dimensional representations of protein-ligand interactions (Schrödinger, LLC, 2015). This combination of computational tools allowed for a comprehensive analysis of potential binding interactions and the identification of promising ligand candidates for further study.

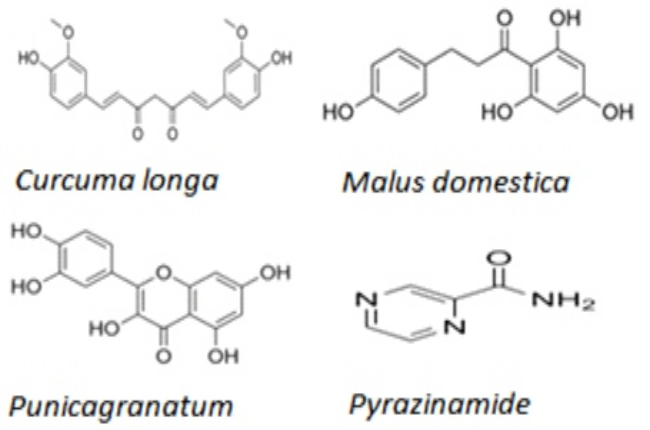


Fig. 1: Chemical structure of ligands (natural products)

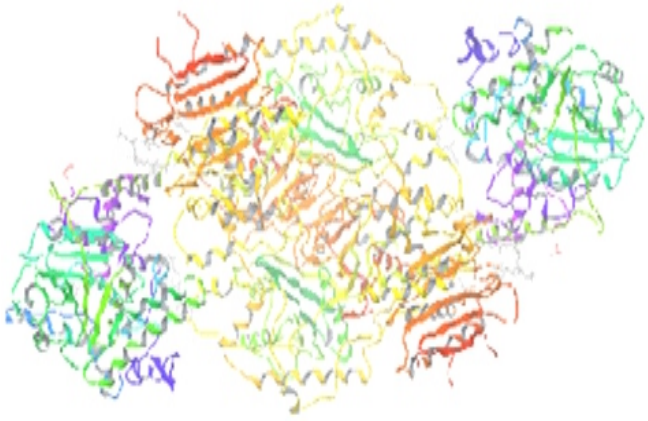


Fig. 2: Structure of target mtTFE protein (PDB ID : 4B3I)

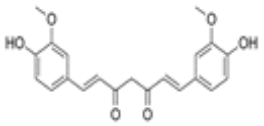
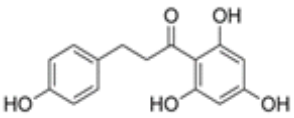
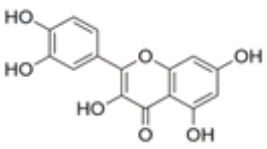
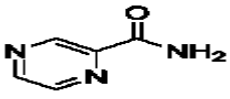
RESULTS AND DISCUSSION

The molecular docking results obtained through AutoDock revealed differential binding affinities of the selected natural compounds and reference drug toward the active site of the *Mycobacterium tuberculosis* β-*oxidation trifunctional enzyme (PDB ID: 4B3I). The docking scores, which represent the predicted binding energies, are summarized in Table 1. These values provide insight into the strength and stability of interactions between each ligand and the target* protein.

Among the tested ligands, Compound 3 (Quercetin, derived from *Punica granatum*) exhibited the most favorable binding energy at –8.397 kcal/mol, indicating a strong and stable interaction with the enzyme's active site. This suggests a higher potential for inhibitory activity and highlights quercetin as a promising lead compound for further antitubercular investigation. Compound 1 (Curcumin, from *Curcuma longa*) showed the second strongest binding affinity with a docking score of –6.462 kcal/mol, followed closely by Compound 2 (Phloretin, from *Malus domestica*), which scored –6.178 kcal/mol. These values suggest moderate binding and support previous findings on their antimicrobial and immunomodulatory activities. Notably, curcumin has been reported to aid in reducing post-treatment susceptibility to reinfection or reactivation of *M. tuberculosis* (Khan et al., 2020), while phloretin is known to suppress inflammatory pathways, including MAPK signaling, which plays a role in TB pathogenesis (Maiolini et al., 2020). Compound 4 (Pyrazinamide, the standard reference drug) showed the least favorable docking score of –5.834 kcal/mol, suggesting weaker binding affinity compared to the natural compounds. While this may reflect limitations in static docking simulations, it emphasizes the potential of the selected phytochemicals, particularly quercetin, as alternative or complementary therapeutic agents.

Overall, these results underscore Quercetin's superior binding affinity, indicating its potential as a novel antitubercular lead compound. The comparable performance of Curcumin and Phloretin also suggests their value in combination or scaffold-based drug development. Further validation through experimental and *in vivo* studies is recommended to confirm their inhibitory effects and pharmacological suitability.

Table 1: Results as obtained through Autodock.

S. No.	Name of Natural Product	Chemical constituent	Source	Chemical Structure	Docking Score (kcal/mol)
1	Curcuma longa	Curcumin	Turmeric		-6.462
2	Malus domestica	Phloretin	Apples (peels), apple leaves		-6.178
3	Punicagranatum	Quercetin	Pomegranate juice and peel		-8.397
4	Pyrazinamide	(Reference drug)			-5.834

CONCLUSION

The findings from this molecular docking study suggest that several natural compounds possess promising inhibitory potential against the *Mycobacterium tuberculosis* β-*oxidation trifunctional enzyme, a critical target in mycobacterial metabolism. Among the compounds analyzed, Quercetin from Punica granatum* demonstrated the strongest binding affinity, surpassing both the standard drug Pyrazinamide and other tested phytochemicals. Curcumin and Phloretin, derived from *Curcuma longa* and *Malus domestica* respectively, also exhibited moderate but notable binding energies, reinforcing their potential therapeutic value.These results support the hypothesis that plant-derived compounds can serve as effective alternatives or adjuncts to current TB treatments. Their ability to interact with key enzymatic targets highlights their potential role in future drug development efforts. Overall, this study contributes to the growing body of evidence supporting the exploration of natural products in the search for novel antitubercular agents

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