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Research Article

In Silico Analysis of Phytochemicals from Herbs and Fruits against Mycobacterium Tuberculosis Potential Targets

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ABSTRACT

Tuberculosis (TB) due to Mycobacterium tuberculosis is still a worldwide health emergency. Resistance to first-line anti-tubercular drugs requires therapeutic modalities. This research utilized in-silico molecular docking to assess the anti-tubercular activity of phytochemicals from tulsi (Ocimum sanctum), orange (Citrus sinensis), black pepper (Piper nigrum), mango (Mangifera indica), and garlic (Allium sativum). To evaluate their drug-likeness, Lipinski's Rule of Five was applied to all selected phytochemicals. Based on this screening, 20 phytochemicals were identified as having favorable drug-like properties and were subsequently selected for molecular docking studies. The compounds, obtained from the Taiwan Indigenous Plant Database (TIPdb), were tested against twenty key M. tuberculosis protein targets. In the present study, a total of 750 docking experiments were conducted using SeamDock, considering interactions between 20 potential drug target proteins and the 50 selected ligands. Mangiferonic acid had the highest promising binding affinities, especially with proteins 1SR9 and 3G5F. These observations indicate the promise of phytochemicals as new anti-TB leads.

Keywords: anti-tubercular, phytochemicals, binding affinities, molecular docking, Mycobacterium tuberculosis, SeamDock, TIPdb, ligands

1. Introduction

Tuberculosis is a very infectious disease and one of the top 10 leading causes of death globally, with approximately 10.6 million new cases and 1.3 million deaths documented in 2022 alone (World Health Organization, 2023) [1]. Even though anti-tubercular drugs are available, the development of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB strains is a major global health threat (Lange et al., 2019) [2]. Phytochemicals from ancient medicinal plants have been found to possess potential in fighting infectious diseases. Natural compounds remain invaluable reservoirs of antimicrobial scaffolds, with a majority being of plant origin (Newman & Cragg, 2020) [3]. Their potential to disrupt bacterial targets with low toxicity has stimulated increased interest in drug hunting (Cowan, 1999) [4].

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Plants like garlic, tulsi, orange, black pepper, and mango are known to possess bioactive molecules with documented antimicrobial and immunomodulatory activities (Agarwal et al., 2021; Muneer et al., 2018) [5,6]. Molecules like allicin (garlic), eugenol (tulsi), hesperidin (orange), piperine (black pepper), and mangiferonic acid (mango) have earlier demonstrated encouraging biological activities (Saxena et al., 2013; Joseph & Raj, 2011) [7,8].

The World Health Organization (WHO) has again and again highlighted the urgent necessity of novel tools and interventions to combat TB, particularly within the framework of the End TB Strategy, aimed at decreasing deaths from TB by 95% and new cases by 90% by the year 2035. Nonetheless, the fulfillment of these objectives is uncertain given intricate socio-economic dynamics, prolonged delay in diagnosis, and growing cases of drug resistance. MDR-TB, characterized by resistance to isoniazid and rifampicin—the two most effective first-line drugs—affects close to half a million individuals every year. XDR-TB, which is resistant to even larger numbers of antibiotics, represents an even more formidable challenge, frequently necessitating toxic and long-term treatment with poor rates of success.

Another major shortcoming of existing anti-TB therapy is the extended treatment duration, which ranges at least six months for drug-susceptible TB and as long as two years for drug-resistant TB. This long regimen often leads to poor compliance on the part of patients, further fueling resistance and failure of treatment. Furthermore, most of the current TB medications have been linked to severe side effects, including hepatotoxicity and neuropathy, thus creating a demand for safer substitutes. These problems raise the imperative need for new paradigms that will seek novel therapeutic compounds with the capacity to reduce the length of treatment, enhance effectiveness, and reduce toxicity.

Owing to the intricate nature of TB pathology, the solution has to be multipronged. One of the most promising approaches is to target M. tuberculosis's diverse biochemical pathways and protein activities, including enzymes of cell wall biosynthesis, energy metabolism, or DNA replication. Natural products, because they possess such structural diversity and evolutionary optimization as defense molecules, are excellent candidates to disrupt these bacterial processes. They also tend to act synergistically with traditional drugs, perhaps increasing their potency or renewing their activity against resistant strains.

Using in-silico molecular docking methods, it is now feasible to effectively screen a large number of phytochemicals for their binding affinities to these important targets. Computational screening has the potential to give useful insights into the drug-likeness, binding modes, and inhibitory activity of plant-derived molecules. The merging of traditional knowledge with contemporary computational biology can potentially hasten the discovery of new therapeutics against tuberculosis and assist in the battle against one of the most intractable global infectious diseases.

The aim of this research is to assess the promise of such phytochemicals by employing in-silico molecular docking techniques. In this research, in-silico molecular docking is used to assess certain phytochemicals from the Taiwan Indigenous Plant Database (TIPdb) for their interaction with critical proteins of *Mycobacterium tuberculosis*. This computational method estimates the interaction of ligands and proteins, approximating binding affinity and stability (Trott & Olson, 2010) [9]. By targeting critical M. tuberculosis proteins, this approach can screen potential inhibitory candidates with high efficiency and low cost (Sliwoski et al., 2014) [10].

2. Materials and Methods

2.1. Ligand Preparation

Allium sativum (garlic), *Ocimum sanctum* (tulsi), *Citrus sinensis* (orange), *Piper nigrum* (black pepper), and *Mangifera indica* (mango) phytochemicals were chosen. Phytochemicals obtained from the Taiwan Indigenous Plant Database (TIPdb) from selected traditional medicine plants were selected on the basis of their reported bioactivity and presence in the Taiwan Indigenous Plant Database. All the ligands were downloaded in 3D SDF format and were converted to PDBQT format using Open

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Babel with MMFF94 force field optimization (O'Boyle et al., 2011) [11]. Table 1 shows a list of phytochemicals which showed the most effective interactions with the potential *Mycobacterium tuberculosis* targets.

Table 1: List of phytochemicals that demonstrated the best interactions with the potential Mycobacterium tuberculosis targets.

Scientific Name	Common Name	Chemical Constituents	ID
Mangifera indica	Mango	Mangiferonic acid	TIP002579
Piper nigrum	Black pepper	Blestriarene B	TIP009452
Ocimum sanctum	Tulsi	Betulinic acid	TIP002270
Citrus sinesis	Orange	Luteolin-5-O-beta-D-glucopyranoside	TIP006642
Allium sativum	Garlic	Gibberellin A19	TIP002554
Citrus sinesis	Orange	Honyucitrin	TIP010934

2.2. Protein Selection

Twenty *M. tuberculosis* proteins were selected because of their critical roles in bacterial survival and drug susceptibility. Target protein structures related to TB were retrieved from the RCSB Protein Data Bank. These proteins are established drug targets in TB drug discovery pipelines. These proteins are involved in playing important roles in cell wall biosynthesis, energy metabolism, and transcription regulation (Raman et al., 2020; Liu et al., 2018) [12,13]. Table 2 presents a comprehensive list of potential targets in *Mycobacterium tuberculosis*.

Table 2: List of potential targets in *Mycobacterium tuberculosis*

S.No.	Targets	**Remarks**	**Target ID**
1.	FabH	Possible target of thiolactomycin	1HZP
2.	InhA	Known target for isoniazid , ethionamide	3OEY
3.	PcaA	Suggested as possible target of thiacetazone	1LIE
4.	DesA3	Suggested as a possible target	1ZAO
5.	TrpD	Lysine auxotroph has vaccine potential	1ZVW
6.	LeuA	Suggested as potential target	1SR9
7.	DapB	Suggested as potential target	1YL5
8.	AroB	Shikimate pathway suggested as an attractive target	3QBE
9.	DfrA	Important drug target in many pathogents	4KNE
10.	PanB	Critical for pantothenic acid synthesis	1OYO
11.	PanC	Critical for pantothenic acid synthesis	3COY
12.	Pan K	Prokaryotic enzymes involved in the synthesis of CoA are good targets	2GES
13.	CysH	Suggested as an attractive drug target	1SUR
14.	Cyp121	Putative essential gene. Possible role in virulence through studies with AraC/ XyIS gene regulator mutant	3G5F
15.	PknG	Crucial virulence factor	2PZI
16.	IdeR	Suggested as target	1BIB. 1FX7
17.	GyrA	Known target of uoroquinolones	3ILW
18.	MtrA	Essential for growth of Mtb	2GWR
19.	GlnE	Essential for growth of Mtb	2WGS
20.	PknB	Possibly essential for mycobacterial growth	1O6Y

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2.3. Docking Protocol

The molecular docking simulations were carried out with SeamDock , an easy-to-use online tool for interactive and structure-based virtual screening as shown in Figure 1. SeamDock embeds AutoDock Vina in a web browser interface and provides real-time visualization of docking results (Biot et al., 2021) [9].

Protein preparation: Protein structures were retrieved from the RCSB Protein Data Bank. Water molecules, ligands, and unnecessary chains were removed with PyMOL. The prepared structures were imported into SeamDock, where automatic addition of hydrogens and partial charge assignment were performed.

Ligand preparation: TIPdb phytochemicals were converted into MOL2 format using Open Babel. The structures were then imported into SeamDock's ligand editor, optimized, and saved.

Docking setup: Pockets were picked manually from regions of known active sites or recognized automatically by SeamDock. Default Vina values were used as docking parameters except for exhaustiveness = 8.

Visualization: Binding poses and interactions were analyzed in SeamDock's real-time 3D viewer. Each ligand-target pair's best-scoring pose was inspected with regard to binding energy and residues of interaction. This protocol provided efficient and reproducible docking simulations with the least software installation and was thus suitable for academic and educational research environments.

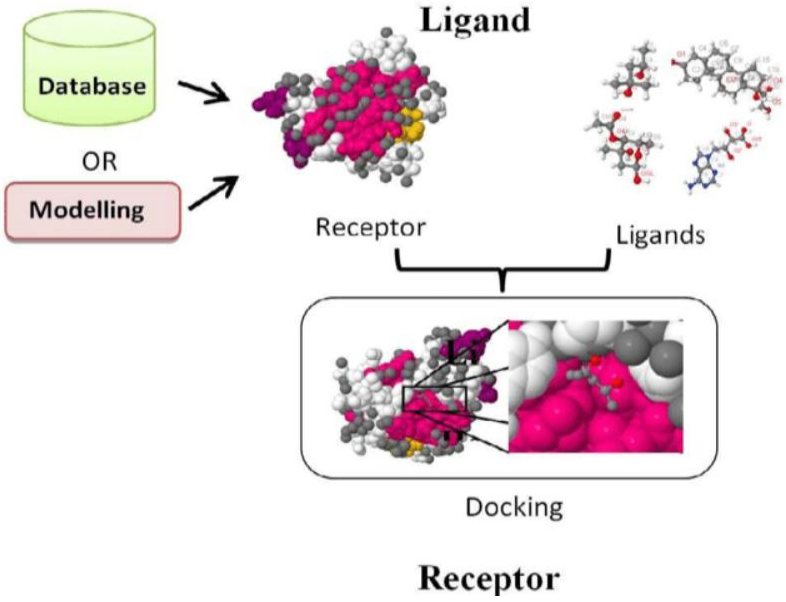

Figure 1: Molecular Docking

3. Results and Discussion

Docking scores (kcal/mol) of each compound with the best protein interaction are shown below. Table 3 presents the docking scores for each ligand with their respective target proteins. Figure 2 presents the molecular docking interactions among chosen phytochemicals from the Taiwan Indigenous Plant Database (TIPdb) and the target proteins of *Mycobacterium tuberculosis*

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Table 3: Docking Scores of Phytochemicals against *M. tuberculosis* Proteins

Compound	TIP ID	Docking Score (kcal/mol)	Target Protein
Mangiferonic acid	TIP002579	-10.4	1SR9
Mangiferonic acid	TIP002579	-10.4	3G5F
Blestriarene B	TIP009452	-10.3	3QBE
Betulinic acid	TIP002270	-10.0	3OEY
Luteolin-5-O-beta-D-glucopyranoside	TIP006642	-9.7	1LIE
Gibberellin A19	TIP002554	-9.4	2GES
Honyucitrin	TIP010934	-9.3	2XWN

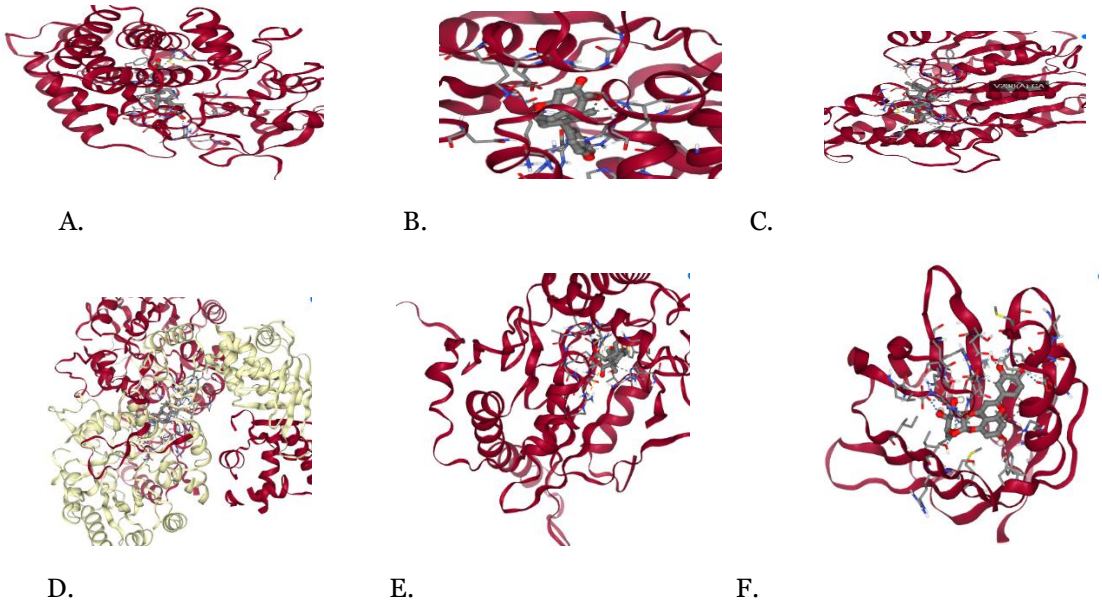

Figure 2: Molecular docking interactions of chosen phytochemicals of the Taiwan Indigenous Plant Database (TIPdb) with principal *Mycobacterium tuberculosis* proteins: (A) TIP002579 against protein 3G5F; (B) TIP009452 against 3QBE; (C) TIP002270 against 3OEY; (D) TIP002579 against 1SR9; (E) TIP002554 against 2GES; and (F) TIP006642 against 1LIE.

Mangiferonic acid showed stable hydrogen bonding with the catalytic domain of 1SR9 and hydrophobic interaction with the NADH-binding site of 3G5F. Betulinic acid showed interaction with residues

essential for DHFR activity in 3OEY. Luteolin-5-O-glucopyranoside indicated π-π stacking as well as polar interactions with ATP synthase (1LIE). Mangiferonic acid indicated the highest binding to both 1SR9 and 3G5F. The docking scores show that Mangiferonic acid possesses the highest binding affinity, particularly against 1SR9 and 3G5F, which are involved in fatty acid biosynthesis and mycolic acid synthesis – important for TB virulence and drug resistance (Takayama et al., 2005) [14]. These interactions point to its potential use as a lead compound for anti-TB therapy. Blestriarene B, a derivative of black pepper, demonstrated high affinity towards the 3QBE target, which is an isoniazid-NAD adduct mimic, a reported drug-binding conformation. This points towards the potential of designing alternative inhibitors with new scaffolds (Baulard et al., 2000) [15]. Betulinic acid from tulsi and Luteolin-5-O-glucopyranoside from orange also demonstrated good interactions.

Betulinic acid has reported anti-mycobacterial activity, as observed in our in-silico findings (Mukherjee et al., 2017) [16]. In general, the findings are in agreement with past research showing the therapeutic significance of natural products in TB therapy (Dey et al., 2020; Saini et al., 2015) [17,18].

4. Conclusion

This research proves that certain phytochemicals from the Taiwan Indigenous Plant Database (TIPdb) exhibit encouraging in-silico binding affinities against critical *M. tuberculosis* proteins. Mangiferonic acid, for instance, exhibited dual-target potential. Blestriarene B and Betulinic acid also exhibited encouraging docking scores, which suggest their potential for further assessment. Docking scores indicate the thermodynamic feasibility of ligand-receptor complex formation. Lower (more negative) scores suggest higher binding affinity, which is related to potential bioactivity. In-silico molecular docking provides a high-throughput screening method for the identification of likely anti-TB compounds. Subsequent confirmation by in vitro, in vivo, and ADMET studies is necessary to validate therapeutic activity, bioactivity, toxicity, and drug-likeness.

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