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Curcumin Versus Curcumin-Iron Complex Docking in Tuberculosis Targets: A Insights on Synthesis & Molecular Docking Study

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Abstract

In this contemporary state Natural products play a significant role in drug discovery. This research investigates a Curcumin-Iron complex (CuFe) as a potential new weapon against tuberculosis (TB). The study highlights the global burden of TB and the need for alternatives due to rising drug resistance. Curcumin, a promising compound from turmeric, suffers from poor absorption in the body. The researchers created CuFe and confirmed its structure using XRD analysis to address this. Using computer simulations, they then tested CuFe's binding to key targets in the TB bacteria. Excitingly, CuFe showed superior binding compared to curcumin and existing drugs. The discussion emphasizes the potential of plant-based medicines like curcumin, along with metal complexes, mentioning garlic and piperine as further avenues. The authors conclude that CuFe is a promising candidate, but further testing in animals and humans, along with studies on absorption and regulatory approval, is needed before it can be considered a viable TB treatment.

Keywords: *Curcumin, Docking, Iron, Synthesis, Tuberculosis.*

Introduction

As per World Health Organization, *Tuberculosis* (TB) is an infectious disease caused by the *Mycobacterium tuberculosis*; so far, the mortality rate of tuberculosis is 1.6Million till 2021 from TB in 2021. 87% of new TB cases in 2021 were found in the 30 countries with the highest TB burden rate. Due to the possibility of drug resistance, there is still a significant gap between the rate of diagnosed and recovered patients, even if this treatment is effective and millions of individuals are treated absolutely [1]. From the ancient days in India, people have practiced some forms of herbal medicines as a first-line treatment for their primary healthcare needs. Several plants have historically been utilized to treat *Mycobacterium* infections due to the existence of chemically active bio components that have the potential to inhibit the multidrug efflux system of microbes. Plant-based medicines utilized in Tb control. Traditional medicines have several health benefits, from Anti-Oxidant to Liver protection [2]. Treating diseases with natural medicine therapy is an effective ancient practice. In the scenario of robust use of drugs, development of multidrug-resistant bacterial species, and rising ineffectiveness of available medications, natural remedies are growing as

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promising alternatives. Natural medicines bear the characteristics of no side effects and ease of availability over synthetic drugs. Moreover, bioactive moieties from natural cures also provide a base formulation for novel drug design by chemical modification which aids in minimizing the efforts and time required for the novel drug discovery [3]. Curcumin from turmeric is reported for numerous medicinal activities, such as hypoglycemic, neuroprotective, cardioprotective, hepatoprotective, and many more [4]. This property is attributed to the presence of a yellow-orange-colored active component, curcumin. Curcumin structure contains two phenolic rings attached to a carbon chain with a hydroxyl group and soluble solvents that are slightly nonpolar than water. This solubility factor restricts the bioavailability of the curcumin leading to low hydrophilicity and dissolution rate, common physicochemical instability, rapid metabolization, low bioactive adsorption, poor pharmacokinetics and bioavailability, and low penetration and target efficacy. The chemical modification and formulation preparation of curcumin structure helps to overcome several design-related issues. The Nano-formulations of curcumin, such as nanoparticles, curcumin stabilized metal nanoparticles, Nano-gels, micelles, polymers, liposomes, and conjugates were found to be efficient for bioavailability and targeted therapeutic application [5-7]. The effect of a methyl group on the solubility of curcumin was revealed upon the demethylation of methoxy groups. Various attempts have been made to modify the curcumin structure by prenylation for HDAC and mPGES-1 inhibitors, tetrahydroxylation, and, pyrimidinone functionalization for antiproliferative activity, methylation, and Hydroxy group substitution on aryl group for enhanced antioxidant activity, thiomethyl group for COX-1 selectiveness. The enhanced biological activities of chemical curcumin have been extensively reviewed. Moreover, bioconjugation of curcumin structure with biomolecules, specifically with amino acid and sugar conjugation, has been shown to enhance the antibacterial activity against several pathogenic bacteria due to improved solubility, increased cellular uptake, and slow metabolism [8-11]. Curcumin modification by forming metal-ligand complexes also has diverse biological applications. The first curcumin metal complex with gold was reported for antiarthritic studies. The transition metal complexes with curcumins are active against pathogenic bacteria such as *Staphylococcus aureus, Escherichia coli, Salmonella typhi, Hay bacillus, Pseudomonas aeruginosa* and a few fungi from Aspergillus family and *Penicillium verruculosum*. Lanthanide series curcumin complexes were explored for chemotherapeutic applications along with antibacterial activity against *Escherichia coli and Hay bacillus*. The metal-curcumin were proposed to act by higher penetrating bacterial cell walls than the curcumin structure alone [12, 13]. There is strong evidence of metals from the ancient period Since the Egyptians employed copper to sanitize their water and metal compounds in medicines. Tremendous works have been performed toward the biological coordination of metal-augmented agents [14]. In the present study, we are exploring the antibacterial potential of naturally isolated Curcumin along with iron as Curcumin iron complex.

Materials and Methods

The curcumin was isolated from *Curcuma longa* as per our previous report[15]. The Synthesis of curcumin-iron complex was synthesized by following the reported method with few modifications. In a typical synthesis process, methanolic solutions of curcumin and FeCl 3 were mixed dropwise with stirring in a 2:1 molar ratio. The system was stirred at 60 ºC for 15-20 min. The obtained red-brown colored precipitate was isolated by centrifugation, washed thoroughly with methanol, and dried at 60 ºC under vacuum [16-18].

Molecular Docking Procedure

The molecular docking method was employed to estimate the drug binding ability at atomic-level. For this investigation tuberculosis inhibition potential of Curcumin Iron Complex, a total of eight targets were identified and selected. The Molegro Molecular Viewer was used to prepare these compounds for computational research followed by MMFF4 force field algorithm has been used to reduce the ligand geometry. CB-Dock2 online tool[https://cadd.labshare.cn/cb-dock2/php/index.php] was used in this study for the estimation of binding affinity of the investigation product and targets [19-21]. The 3D crystal structures of the selected targets were downloaded from RCSB Protein Data Bank (RCSB PDB) [https://www.rcsb.org/] such as PDB: 4DRE is the crystal structure of *Mycobacterium tuberculosis* InhA in complex with NADH [22] PDB: 1BVR is the crystal structure of Crystal structure of the *Mycobacterium tuberculosis* enoyl-ACP reductase, InhA, in complex with NAD+ and a C16 fatty acyl substrate [23]. PDB: 3FNG is crystal structure of InhA bound to triclosan derivative [24]. PDB: 4P8C is crystal structure of M. tuberculosis DprE1 in complex with the non-covalent inhibitor QN127[25] PDB: 5V3Y is crystal structure of Mtb Pks13 Thioesterase domain in complex with inhibitor TAM16 [26] PDB: is crystal structure of ranscriptional Regulatory Repressor Protein - EthR from *Mycobacterium tuberculosis* in complex with compound 5 at 1.57A resolution [27] PDB: 3G1M is crystal structure of EthR from *Mycobacterium tuberculosis* in complex with compound BDM31381[28] PDB: 2QKX is crystal structure of N-acetyl glucosamine 1-phosphate uridyltransferase from Mycobacterium tuberculosis complex with N-acetyl glucosamine 1-phosphate [29]. For the better understanding the docking was performed for both Curcumin and Curcumin iron complex structures again 08 different targets using Isoniazid and Pyrazinamide as standard reference.

Results

The molecular docking results reveal that CUFE has a strong binding affinity when compared with Curcumin and reference standards. CUFE shows higher binding affinity towards the targets 3FNG, 4P8C, and 5V3Y with a binding energy of -11.01 kcal/mol, -10.8kcal/mol, and -11.0 kcal/mol respectively. The Binding energy is notably high CUFE complex when compared with curcumin -9.6 kcal/mol, -9.5 kcal/mol, and -9.2 kcal/mol for 3FNG, 4P8C, and 5V3Y targets respectively. There was a significant difference in the binding energy levels of curcumin and CUFE complex with reference standard Isoniazid and Pyrazinamide. The binding scores represent the strength of interaction between the mentioned compounds and their target proteins or structures. A more negative value typically indicates a stronger binding affinity, implying a lower energy state of the complex. In this context, the Curcumin-iron complex (CUFE) generally has more favorable binding scores than Curcumin alone, Isoniazid, and Pyrazinamide for the given PDB IDs. This suggests that the Curcumin-iron complex may have a stronger binding affinity with the target proteins associated with tuberculosis and could be a promising candidate for further investigation in tuberculosis treatment. The molecular docking image is illustrated in Figure 1 & the molecular docking binding scores are given in Table 1.

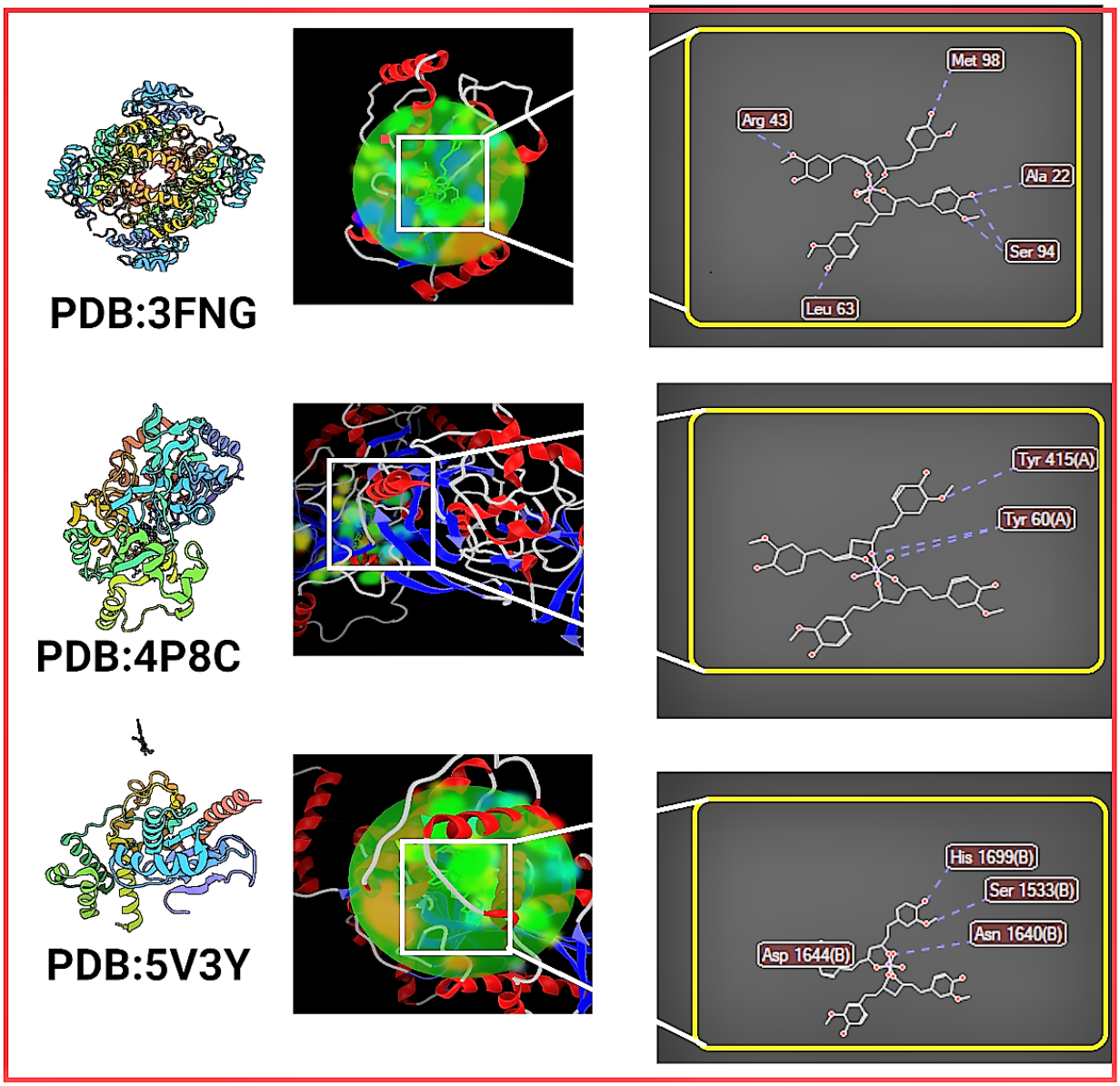

Figure 1. Molecular Docking Image of CUFE Towards PDB:3FNG, 4P8C, and 5V3Y

Table 1. Molecular Docking Score of CuFe Complex

S.No	PDB ID	CuFe Binding score (Kcal/mol)	Curcumin alone Binding score (Kcal/mol)	Isoniazid Binding score (Kcal/mol)	Pyrazinamide Binding score (Kcal/mol)
1.	4DRE	-10.0	-7.6	-5.7	-4.7
2.	1BVR	-10.0	-8.4	-5.7	-4.8
3.	3FNG	-11.1	-9.6	-6.0	-5.0
4.	4P8C	-10.8	-9.5	-6.1	-5.3
5.	5V3Y	-11.0	-9.2	-6.2	-5.1
6.	5EYR	-9.0	-9.9	-6.6	-5.3
7.	3G1M	-8.1	-9.2	-6.4	-5.1
8.	2QKX	-9.7	-7.2	-5.2	-4.8

Discussion

TB is a continual, progressive life-threatening infection with high mortality rates worldwide. The drug-resistance is the major obstacle to the eradication of *Mycobacterium* tuberculosis. It is much more imperative in this condition to find out the alternative treatment pattern from plant-based medicines since plant-based medicines exist with secondary uses like anti-oxidant properties. Plant-based medicines are the essential origins of producing bioactive compounds, which play a fundamental role in discovering novel drugs for various chronic and infectious diseases. Plant-based bioactive compounds were the best mycobacteria-inhibitory agents, with fewer (or no) adverse effects that guaranteed the patients' quick recovery[30]. Metal-based compounds acquired much interest 50 years ago due to their peculiar characteristic like antibacterial and many more. Certain Metals are crucial components for maintaining human equilibrium. A variety of biologically active metals, including bismuth (Bi), samarium (Sm), technetium (Tc), iron (Fe), gold (Au), silver (Ag), platinum (Pt), and gadolinium (Gd). These metallic atoms modulate the pharmacodynamic properties, pharmacokinetic characteristics, and biological activity of the compounds [31]. Iron dextran (Proferdex, Dexferrum, InFeD) or iron sucrose (Venofer) are administered intravenously to treat severe iron deficiency anemia [32]. Small molecule target-based screening is a trending technique in the drug discovery pipeline. In this regard, in silico studies helps in the detection of the therapeutic potential of investigation compound at the early-stages of drug discovery [33]. Ethnomedicinal plants plays a significant role in communicable, Non-communicable and immunomodulatory. As part of an Ethnomedicinal medicinal plant and adjuvant in day-to-day life food, garlic (*Allium sativum*), Allicin is the primary bioactive compound in garlic. Allicin has direct ability to kill the Mtb and also inhibit the Mtb Ag 85b which helps in TNF α. Piperine is an alkaloid which has immunomodulatory effect due to the presence of piperine as main active compound. Piperine helps in Tb eradication by inhibiting the efflux pump activity of Mtb and increases the bioavailability profile of antibiotics in pathogen cells [34]. Natural products plays a crucial role in drug discovery [35-37].

Conclusion

In this current state, structurally modified bio compounds and metallodrugs have grown remarkably in the past five decades, especially in the Molecular biology/Phytochemistry and Drug discovery sectors. Furthermore, several bioactive compounds and metal-based complexes have been investigated to treat many disorders, including infectious diseases. In this study, we established the therapeutic potential of metal (Fe) augmented curcumin against Mtb. However, to meet the regulatory standards, stringent multi-centric preclinical and clinical testing must be addressed before clinical trials, and extensive pharmacological tests must be performed to claim its bioavailability in different organs and serum.

Conflict of Interests

"The authors have no relevant financial or non-financial interests to disclose."

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