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Original Article

Metal Complexes of Curcumin: A Comprehensive Approach to Design, Synthesis, Characterization and Assessment of Anti-tubercular Activity

Paramita Das[1,*], Yamuna HM[1], Harshashree M[1], Raman Dang[2]

[1]Department of Pharmaceutical Chemistry, Krupanidhi College of Pharmacy, Chikkabellanduru, Carmelaram Post, Varthur, Bangalore, Karnataka, INDIA.
[2]Principal, Krupanidhi College of Pharmacy, Bangalore, Karnataka, INDIA.

ABSTRACT

Background: The primary challenge facing Tuberculosis (TB) is the growing prevalence of drug resistance and the hepatotoxicity secondary effects of first and second-line anti-TB treatments have reignited interest in exploring new metal drug complexes as possible sources of anti-TB medications. **Aim:** To perform *in silico* studies for Curcumin-metal complexes, synthesis and evaluate their antitubercular activity and cytotoxicity. **Materials and Methods:** Designed metal complexes were docked against 2NSD and performed ADMET studies. Based on binding affinity, a series of Curcumin-metal complexes were synthesized, characterized by IR, NMR, MASS, P-XRD and the antitubercular activity was evaluated by MABA and MTT assay for cytotoxicity investigations. **Results and Discussion:** The binding energies ranged from -8.0 to -10.1 'kcal/mol'. At -10.1 'kcal/mol', the Curcumin-Cu complex (C1) exhibited the best binding. The synthesized compounds was evaluated against *Mycobacterium tuberculosis* (H37Rv) using the MABA assay. Curcumin-Cu complex (C1) showed the highest activity and was the most sensitive at 0.8 µg/mL and showed less toxicity with an IC_{50} of 10.0 and a selectivity index of 4.0. Cytotoxicity was evaluated by the ATCC CCL-81 cell line. **Conclusion:** Therefore, we can conclude that the molecular hit will be a good lead to develop novel therapies for tuberculosis treatment.

Keywords: Tuberculosis, Curcumin metal complex, Docking, ADMET studies, MABA assay.

Correspondence:
Dr. Paramita Das
Department of Pharmaceutical Chemistry, Krupanidhi College of Pharmacy, #12/1 Chikkabellanduru, Carmelaram Post, Varthur, Bangalore-560035, Karnataka, INDIA.
Email: paramitadas04@gmail.com

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INTRODUCTION

The greatest barrier to tuberculosis chemotherapy is the rise in drug resistance to approved therapeutic treatments. The causative agent of tuberculosis is *Mycobacterium tuberculosis*, which is a major worldwide health emergency with millions of deaths recorded in a year.[1] The primary categories of antitubercular drugs mainly target processes such as cell wall production, mycolic acids, Arabinogalactan and DNA replication within bacterial cells. Unfortunately, each of these mechanisms is vulnerable to the development of bacterial resistance.[2] Multidrug-Resistant Tuberculosis (MDR-TB) is characterized by resistance to at least isoniazid and rifampicin, while Extensively Drug-Resistant Tuberculosis (XDR-TB) goes a step further by exhibiting resistance to second-line injectable drugs and fluoroquinolones. This necessitates long-term therapies, exposing patients to a higher risk of adverse effects.[3] One of the most common side effects of anti-TB treatment is drug-induced liver damage (hepatotoxicity).[4] Similarly, the growing demand for novel treatments is exacerbated by the dwindling effectiveness of already available anti-TB medications and the emergence of resistant strains. This called for more research into discovering novel chemical entities with distinctive modes of action, especially in light of a rise in drug resistance. Curcumin-based transition metal complexes are gaining interest lately as potential antitubercular medications. In order to overcome resistance and increase activity, metal coordination to physiologically active molecules is helpful.[5,6] Numerous studies have shown that Curcumin and metal ions coordinate to enhance the anticancer,[7] antioxidant,[8] and antibacterial effects.[9] A review of the literature reveals that while metals act as cytotoxic stimulators for the ligands, the ligand molecules are less active than their transition metal complexes.[10]

Curcumin possesses antitubercular effect and a wide spectrum of pharmacological characteristics research into its potential use as a chemotherapeutic is still going on.[11] In recent decades, curcumin complexes with different metal salts have been synthesised to overcome curcumin's limitations and increase its physiological activity. The overall structure of curcumin is altered

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