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Evaluating Natural Metabolites as Potential Therapeutics Against Drug-Resistant Mycobacterium Tuberculosis Using Computational Approaches

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Abstract: *Mycobacterium tuberculosis (MTB) causing Tuberculosis infection is a leading source of illness and death in developing nations, and the emergence of drug-resistant tuberculosis is a global threat. The spread of drug-resistant TB is one crucial concern to world health. Mutations in the proteins encoded by the inhA, katG and rpoB genes are connected to the principal molecular mechanism of Isoniazid and Rifampicin resistance. Structure-based drug discovery approaches on Traditional natural compounds are the contemporary source to identify significant lead molecules. This work focuses on discovering effective small compounds from Natural Compound Libraries by applying pharmacophore-based virtual screening to filter out the molecules. A three-dimensional e-pharmacophore hypothesis and screening generated 63 & 91 hits based on phase fitness scores from the pharmacophore models of INH & RIF. Based on virtual screening and molecular docking experiments in Maestro's GLIDE module indicate that ZINC000002383126, asn22022 and asn:98397 may be potential inhibitors of inhA, katG & rpoB receptors respectively (native and mutants). The docking results revealed that new compounds more effectively inhibited the wild & mutant receptors, on the contrary, INH & RIF had lesser interaction with the receptors signifying less inhibition thus showing resistance. Molecular dynamics simulations were performed on leading hit complex structures to investigate their rigidity, interconnections, and longevity; and indicates that the docked complex has good stability and remains compact in the binding pocket of the targets. In vitro studies can further validate these compounds to act as competitive inhibitors.*

Keywords*:* Resistance, receptors, Natural compounds, pharmacophore, dynamics

I. INTRODUCTION

Tuberculosis is a deadly airborne sickness caused by bacterial infection. Despite its propensity to injure any area of the body, tuberculosis most commonly affects the lungs. Depending on the kind of illness, it is usually treated with a treatment regimen that is followed for six months to 2 years. TB is a grave communicable ailment that is instigated by the bacterium *Mycobacterium tuberculosis*. Although it is preventable and treatable, it continues to pose a significant public health challenge globally, affecting approximately 10 million individuals and claiming the lives of 1.5 million people annually (Global Tuberculosis Reports, 2024 a). When the TB bacteria cannot be treated with either Isoniazid (INH) or Rifampin (RIF), which are widely used to treat tuberculosis, it results in MDR tuberculosis, a kind of drug-resistant tuberculosis. XDR tuberculosis (Extensive drug-resistant) is an uncommon MDR TB that appears to be resistant to a minimum of one of the three intravenous second-line medicines and any three first-line treatments. Treatment for Drug-resistant TB is a complicated and time-consuming process (Al-Humadi, Al-Saigh and Al-Humadi, 2017). Tuberculosis therapy necessitates a wide range of antibiotics over an extended period. Therapy for TB is having serious problems because of antibiotic resistance.

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Drug-resistant tuberculosis (DR-TB) is a grave issue stemming from fortuitous genetic alterations that confer resistance upon the bacteria against the majority of commonly employed anti-TB medications. It is imperative to bear in mind that DR-TB is a predicament of human origin (Palomino and Martin, 2014; Prasad and Srivastava, 2013). Antibiotic resistance is the root cause of all drug-resistant tuberculosis subtypes, including multidrug-resistant (MDR-TB), extensively drug-resistant (XDR-TB), and completely drug-resistant (TDR-TB) (Figure 1) (Zignol et al., 2013; Seung, Keshavjee and Rich, 2015).

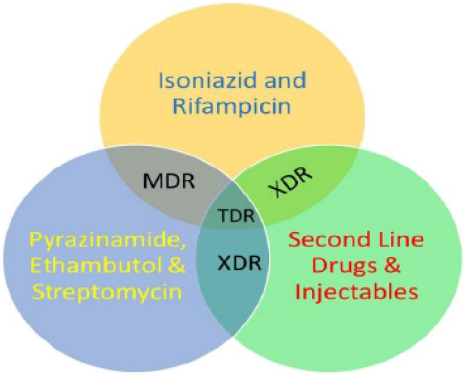

Figure 1: Types of Resistance Patterns seen in *Mycobacterium tuberculosis*

Bacteria have the ability to acquire antibiotic resistance through diverse mechanisms, including active efflux mechanisms and porins. Active efflux mechanisms entail the utilization of proteins to expel antibiotics from the cell, thereby reducing the susceptibility of the bacteria to the drug. Active efflux mechanisms can contribute to the development of high-level antibiotic resistance.

The mechanisms of tuberculosis propagation, as well as the discovery and creation of novel anti-TB drugs, may be significantly impacted (Nachega and Chaisson, 2003). MDR-TB has emerged as a severe concern not just in India but also globally. This type of illness is more resistant to treatment than regular TB and can take up to two years of antibiotic therapy. Only a few investigations of pathogenic variations responsible for the illness have been conducted using bioinformatics tools (Singh et al., 2021).

II. LITERATURE REVIEW

Despite the existence of numerous medications for tuberculosis, the pathogen responsible for the disease, M. tuberculosis, is progressively developing resistance to conventional treatments. This has led to the emergence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). The worldwide health community has been horrified by this predicament, which has increased the need for new anti-tuberculosis medications. Because of the range of chemical components that may have some vital restorative characteristics, medicinal plants have already been employed by ancient civilisations to heal several common and deadly ailments (Debnath et al., 2012).

India is also one of the world's largest producers of herbal medicines. Researchers are always looking for new medication compounds to tackle MDR/XDR-TB. More than 250 Indian medicinal herbs have been documented to have anti-mycobacterial action (Chevtchouk Jurno et al., 2019). Before these plants may be used efficiently as therapeutic and/or preventative drugs against tuberculosis, they must undergo extensive safety, toxicology, and clinical trials (Pandit, Singh and Kumar, 2015).

The Patipukur TB Hospital in Kolkata established the first Ayurvedic tuberculosis treatment centre in 1933. Later, an extensive research unit with its funding was established. It was the first time of its kind in pre-independence India that therapeutic recommendations based on Ayurveda ideas for therapy had been created. This regimen was phased out with the release of synthetic ATDs on November 1, 1947. Drugs, including mercury, gold, and calcium, were made in-house and supplied to patients with fresh juice from plants grown in the medical garden. Vasantamalati, Kanchanabhra rasa, Rajamriganka rasa, Bhallataka (Semicarpus anacardium) rasayan, Mallasindura, Vasa (Adatoda vasica), and other

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formulations were used. The information regarding the utilization of Ayurvedic medicine for the treatment of PTB over a span of 13 years holds significant importance (Debnath et al., 2012).

Few investigations have demonstrated that certain herbs have anti-TB activities in vitro, which can possibly be tested in human subjects in a clinical study. The majority of the Ayurvedic medicinal formulations evaluated in various clinical settings essentially represented their adjuvant characteristics for treating tuberculosis. Ayurvedic therapies have demonstrated significant efficacy in alleviating associated symptoms and mitigating the adverse pharmacological effects of anti-TB drugs (ATDs). Additionally, various Ayurvedic preparations have exhibited promising hepatoprotective properties, making them suitable for concurrent administration with ATDs (Samal, 2016).

Anti-TB medications have been linked to liver impairment, prompting many patients all over the world to abandon therapy. Medicinal plants offer a variety of medicinal properties. The efficacy of treating hepatic rehabilitation through the assessment of plants' biological activity against Mycobacterium has been proven. Medicinal plants, due to their abundance of secondary metabolites and phytochemicals, provide ample protection to hepatic cells against the hepatotoxicity caused by anti-TB drugs. These substances effectively restore normal function, enzymatic activity, and structure of the liver (Mangwani, Singh and Kumar, 2020).

A survey was conducted in the Capricorn, Sekhukhune, and Waterberg regions of Limpopo Province, questioning 52 traditional healers from 17 towns. The majority of the healers (61.9%) were native, while the remaining were exotics found as weeds or planted in private gardens. The Hyacinthaceae, Moraceae, and Rutaceae families had the highest representation (9.5% each) in terms of species counts. Herbs and trees (38% each) were the most commonly utilised therapeutic plant growth types. Leaves (34%) were the primary ingredient in tuberculosis cures, followed by roots (21%). The therapeutic claims made by Bapedi traditional healers on medicinal plants used to cure tuberculosis are highly supported by literature, with 71.4% of the species possessing antibacterial qualities or having comparable Ethno medicinal applications in other countries (Semenya and Maroyi, 2013).

An effective and comprehensive approach for mitigating technological flaws and improving therapeutic medication efficacy remains a key problem for pharmaceutical technology. The idea of nanoparticles has demonstrated persuasive therapy and optimistic solutions for chronic infectious illnesses. Various nanocarriers have been assessed as effective drug delivery methods for various routes of administration. One benefit of nanoparticle-based anti-tuberculosis medications over free pharmaceuticals is controlled and prolonged drug release. It also decreases the dosing frequency and overcomes the problem of low compliance. The development of nanoparticle-based delivery systems is a highly promising, practical, and financially viable alternative to potential TB chemotherapy. Even at moderate therapeutic doses of the composition, more medication accessibility and therapeutic value may be attained, and chemotherapy time can be cut down. The essential aspects encompass the eradication of these interactions with anti-HIV medications, the decrease in expenses associated with treatment, and the enhancement of MDR-TB and latent TB care (Nasiruddin, Neyaz and Das, 2017).

Nanotechnology has significantly improved pharmacology by allowing medication delivery devices to attack phagocytic cells infected with intracellular pathogens such as mycobacteria. In experimental infections, antimycobacterial medications' therapeutic index was enhanced, dosage frequency was reduced, and the solubility of hydrophobic compounds was improved, allowing bigger doses to be administered. Nanotechnology presents a new potential for the advancement of anti-TB medications (Kia et al., 2023). Nanotechnology encompasses numerous nanoparticles (NPs) that have the potential to facilitate diverse approaches for delivering anti-TB medication. These advanced techniques could significantly impact the development of innovative and improved treatment and care regimens for tuberculosis (Wani and Ahmad, 2020).

Due to poor adherence to treatment, delayed-acting medications, and drug resistance, tuberculosis has existing therapies that still demand drug development. This discovery of a pretty efficient new antibiotic targets unique tuberculosis proteins as part of a growing approach to combat the worldwide TB epidemic. To enhance the speed of identifying new anti-TB medications, computational methods play a crucial role across multiple stages of the drug development process. The present study has integrated conventional biochemical approaches with these methods in order to enhance the treatment of TB. This amalgamation is intended to combat drug resistance and maximize the effectiveness of computational tools throughout the various stages of tuberculosis drug discovery (Canales et al., 2024).

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Structure-based tools provide a comprehensive framework for comprehending structural properties and examining them at a molecular level. The tools are Comparative Modeling, Binding Site Prediction and Druggability, Pharmacophore Modeling and Molecular Docking, Molecular Dynamics CHARMM, Amber, GROMOS, OPLS-AA, PCA, FES & MMPBSA (Srivastava, Tiwari and Sharma, 2018). Similarly, Ligand-Based Tools are also available, which provide Similarity-Based and Quantitative Structure-Activity/Property Relationship Methods, Ligand-Based Pharmacophore Modeling Density, and Functional Theory (Ejalonibu et al., 2021).

The emergence of drug-resistant strains of Mycobacterium tuberculosis (Mtb) poses a substantial hurdle to the World Health Organization's (WHO) End TB Strategy. This strategy endeavors to eliminate tuberculosis-related diseases, fatalities, and suffering across the globe. The development of drug resistance in Mtb is primarily attributed to mutations occurring within the pharmaceutical targets used to combat tuberculosis. Computational techniques and technologies are utilised to understand the mechanisms underlying drug resistance.

According to, Tetrahydropyrimidinethiones as Potential Thymidylate Kinase Inhibitors with Anti-Mycobacterium tuberculosis Activity. Preliminary docking experiments have shown that tetrahydro pyrimidinone derivatives have favorable interactions with the thymidylate kinase receptor. The production and microbiological action of pyrimidinethiones and pyrimidinones as powerful thymidylate kinase inhibitors were obvious and described in this paper. The molecular modelling was carried out using Accelry's Discovery Studio 4.0 client application to examine and understand the bioactivity of the compounds. The pharmacokinetic features of the synthesised compounds were also investigated and anticipated (Venugopala et al., 2020).

According to Kumar et al., Anti-TB medications, including first-line fluoroquinolones and second-line injectable treatments, are ineffective against XDR-MTB strains. This study concentrated on the signalling cascades, connected gene networks, and differentially expressed genes (DEGs) that contribute to this pathogen's resistance to a variety of drugs, such as isoniazid, rifampicin, and capreomycin (Udhaya Kumar et al., 2021)

Unissa et al. 2017 mentioned that Isoniazid (INH) impedes the success of Mycobacterium TB multi-drug resistance. This occurs because of a mutation in the 315th codon of the *katG* gene, which refers to catalase-peroxidase. S315T, S315I, S315R, S315N, and S315G are the most prevalent substitutions in the katG receptor. These were then docked and simulated using 50INH derivatives and the wild type. By the conclusion of docking, it was clear that C45, C30, and C50 had superior scores with the wild type as well as with the mutants S315T, S315I, and S315R, with C50 showing the least variance between mutants and wild type when matched to the other C30 and C45. As a result, this C50 is utilised to identify organisms' mutations and isolate lead compounds (Unissa et al., 2017).

Isoniazid (INH) is a first-line defence for MDR-Mycobacterium TB, according to Unissa et al 2018. A change in the katG genes' 315th codon results in resistance. Apart from MT-S315R, the docking-based binding affinity was higher for MTs than wild-type (WT) isolates, indicating tight binding of INH with MT proteins as opposed to the flexible binding seen in the WT. A molecular dynamics analysis explains why the deviations for MTs are greater with more INH binding residues than for the WT. These mutants affect enzyme activity in multiple ways and cause structural changes in MT katG. This leads to INH resistance (Unissa et al., 2018).

III. RESEARCH METHODOLOGY

The block diagram illustrates a comprehensive computational workflow for identifying and analyzing potential inhibitors against protein targets using in-silico approaches. The process begins with the retrieval of protein information from the UniProt and Protein Data Bank (PDB) databases, ensuring accurate structural and sequence data. Next, a collection of mutations relevant to drug resistance or disease mechanisms is compiled to understand structural variations.

Following this, structure analysis is conducted to visualize and assess the 3D conformation of proteins. The protein preparation and energy minimization step, often performed using software such as Schrödinger, refines the protein structure by removing steric clashes and optimizing geometry for reliable docking studies. Subsequently, natural compound databases are screened, and ligand optimization is performed to enhance molecular interactions.

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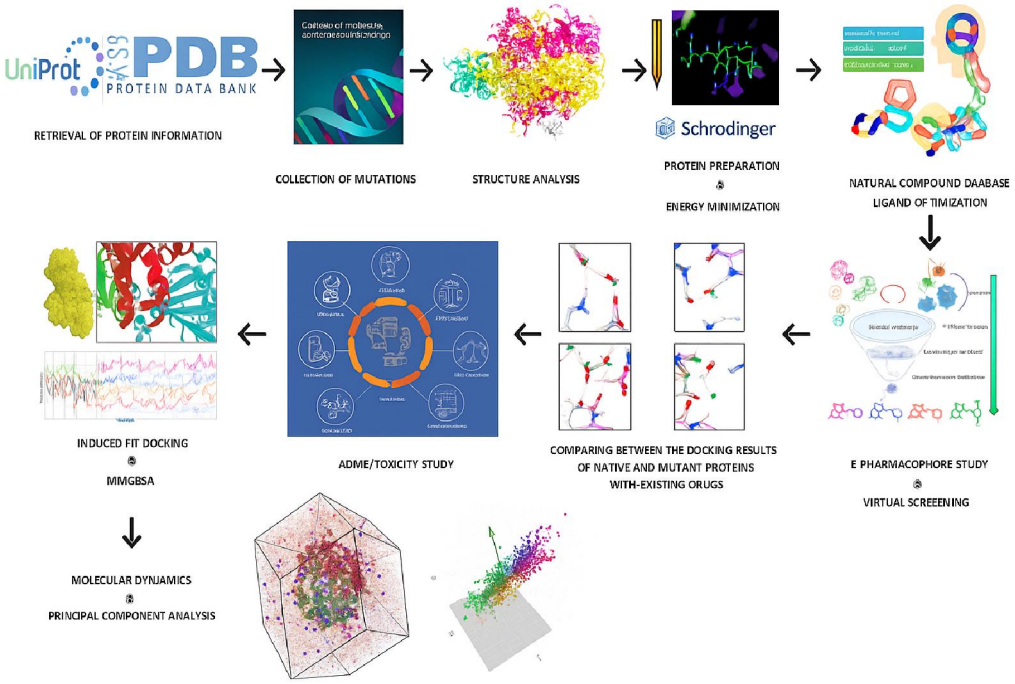

Fig 1 Computational Workflow for Structure-Based Virtual Screening and Molecular Analysis of Protein Targets

The optimized ligands undergo E-pharmacophore modeling and virtual screening, which identify essential chemical features required for biological activity and shortlist potential lead compounds. The docking results of native and mutant proteins with selected ligands are compared to assess binding affinity and stability. ADME/toxicity studies follow to evaluate the pharmacokinetic and safety profiles of candidate molecules, ensuring their drug-likeness.

Next, induced fit docking and MM-GBSA (Molecular Mechanics Generalized Born Surface Area) calculations are performed to refine binding interactions and estimate binding free energy. These results provide insights into ligand flexibility and receptor adaptation. Finally, molecular dynamics (MD) simulations and principal component analysis (PCA) are carried out to examine the dynamic behavior and conformational stability of protein-ligand complexes over time.

IV. RESULTS AND DISCUSSION

The primary goal of molecular dynamics simulation is to compute the biological fluctuations in molecular complexes on various timescales inside a liquid environment. This aids in the computation of the fluid characteristics and time-of-movements of each atom in the system. In order to comprehend the stability of the complex during 100 ns MD simulation and to comprehend the rotational and conformational changes, the chosen protein–ligand complexes of inhA-ZINC000002383126, katG-asn22022 complexes and rpoB-asn:98397 were examined (Figures 17-26). By the end of the simulation time, the docked ligand molecules also displayed structural rotation, according to the 3D structural assessment of the complexes, which also revealed that the target protein underwent slight structural changes.

The MDS on all the protein-ligand complexes, including natural and mutant, were carried out as per the IFD data. For the long-term stability of the protein-ligand complexes, molecular dynamics simulations ranging from 100 ns were performed using GROMACS. The RMSD was determined to test the stability of the complexes throughout simulations (Figure 17 & 18).

RMSD values were observed to be at an acceptable range for the inhA and katG complex backbone, where the RMSD of Isoniazid was seen to be greater than the lead compound complexes. The mean RMSD of ZINC000002383126

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bound inhA complexes were around 0.25nm, and the katG receptor complexed with asn:22022 remained constant between 0.4nm to 0.55nm. The plots initially had high RMSD values and then stabilized towards the end. The RMSD of inhA-Isoniazid and katG-Isoniazid complexes were significantly higher than the inhA-ZINC000002383126 and katG-asn22022 complexes. The ligand binding makes the structures stable during the simulation time (Figure 17)

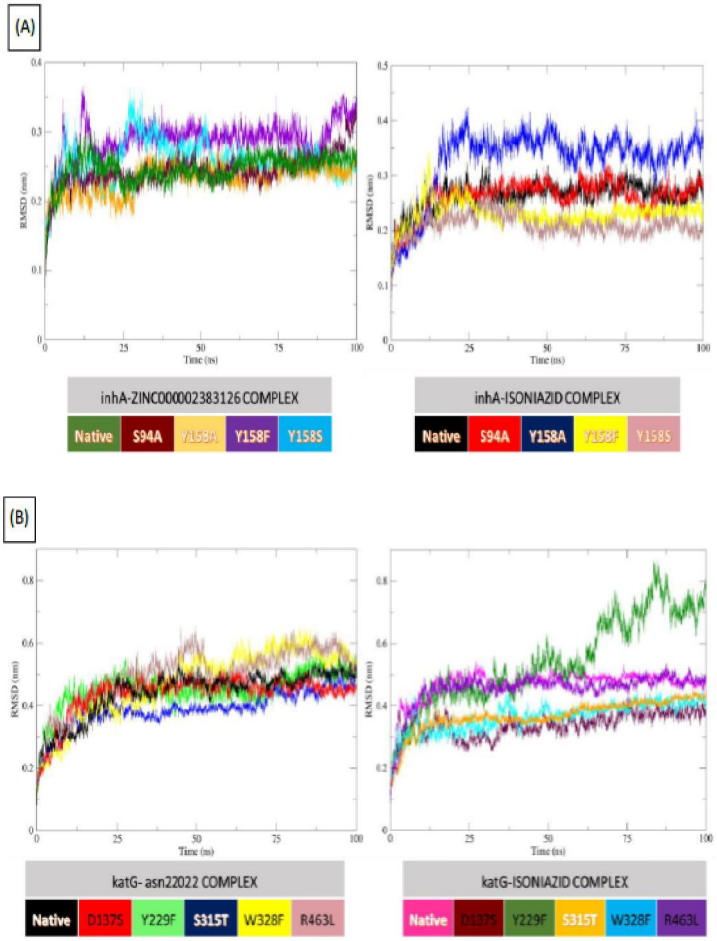

Fig 2 RMSD Analysis of inhA and katG Native and Mutant Complexes Over 100 ns Molecular Dynamics Simulation
RMSD of inhA and katG native and mutant complexes for 100ns simulation period. (A) represents the RMSD of inhA-ZINC000002383126 & inhA-Isoniazid (B) depicts RMSD of katG-asn22022 & katG-Isoniazid. The conformational and structural alterations of inhA-ZINC000002383126, inhA-Isoniazid, katG-asn22022 and katG-Isoniazid complexes were identified by analysing the RMSD plot using a 100 ns MD simulation. Each complex displayed similar volatility in the 0-45 ns simulation plot. After 50ns, inhA-ZINC000002383126 & katG-asn22022 displayed increasing instability than inhA-Isoniazid & katG-Isoniazid Complexes.

V. CONCLUSION

The proteins encoded by *inhA, katG & rpoB* genes cause resistance to INH & RIF. The occurring mutations at these proteins reduce the drug affinity. 2,53,468 natural compounds from databases such as Asinex Biodesign Library, Zinc Natural Library, NPASS Library, IMPPAT Plant Library & SelleckChem Natural Library were retrieved. Further Pharmacophore hypothesis was generated for INH & RIF to be AARDDD & AARRH respectively. The compounds ZINC000002383126, asn:22022 & asn:98397 had potential activity in virtual screening. The selected compounds were docked against the mutants utilising XP in order to assess the inhibitory property. Low binding energy indicates more

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stable and viable binding. The protein-ligand complexes were seen to be stable during the simulation period, according to molecular dynamics investigation. The nature of ZINC000002383126, asn:22022 & asn:98397 was characterised by electrostatic analysis

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