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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

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