Drug repurposing approach to target DNA gyrase from *Mycobacterium tuberculosis*

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Owing to the rise in drug resistance in tuberculosis combined with the global spread of its causative pathogen, *Mycobacterium tuberculosis (Mtb)*, innovative anti-mycobacterial agents are urgently needed. To address this problem, we have employed drug repurposing approach to discover novel FDA-approved drugs to inhibit *Mtb* growth. Here, we have used essential *Mtb* enzyme, DNA gyrase, a promising and potential target for novel anti-tuberculosis chemotherapeutics. High-throughput screening of compounds (using FDA-compounds library) was done against the active site of *Mtb* DNA gyrase, the region of ATP binding (N-terminal domain) pocket on gyrase B subunit. Here, we identified total of 4 compounds (Doxorubicin, Epirubicin, Idarubicin, Terlipressin) tightly binds to ATPase binding pocket of N-terminal domain of gyrase B (*Mtb*GyrB47). We investigated both inhibition of *Mtb* DNA gyrase and the inhibitory activity against *in vitro* growth of *Mtb* and *M. smegmatis (Msm)* by FDA-drugs. Among which, doxorubicin, an anthracycline antibiotic (used as an anticancer drug), was found to be a potent inhibitor of *Mtb* DNA gyrase. Low-µM inhibition of *Mtb* DNA gyrase was correlated with their low-µM minimum inhibitory concentrations for all screened FDA-drugs. Doxorubicin exhibited IC_{50} value of 0.6±0.14 µM against *Mtb*GyrB47, kD values of 0.06±0.21 µM and MIC_{90} values of 0.12 µg/ml. Our results strongly suggests that the screened compounds (anthracyclines) target mycobacterial DNA gyarse, inhibits gyrase catalytic cycle and retard *Mtb* growth. Hence, anthracyclines inhibitors of Gyrase B exhibit many of the characteristics required for their consideration as a potential front-line antimycobacterial therapeutic.

References

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