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Computational repurposing of potential inhibitors targeting leishmanial DNA topoisomerase IB

Mariam Salem Alghamdi [*1], Saeed M. N. Alasmari [2], Maryam Abdulrahman Alahdal[3], Ahmed Saif [4]

[1,3] Department of Biology, Faculty of Sciences, Umm Al-Qura University, Makkah 24381, Saudi Arabia
[2] Department of Biology, Faculty of Science and Arts, Najran University, 1988 Najran, Saudi Arabia.
[4] Department of Clinical Laboratory Sciences, College of Applied Medical Science, King Khalid University, Abha 61321, Saudi Arabia

* Correspondence: msghamidy@uqu.edu.sa ORCID ID: https://orcid.org/0000-0002-7778-1875
SMNA: smalasmari@nu.edu.sa ORCID ID: https://orcid.org/0009-0006-4407-6172
Ma: Mayahdal@uqu.edu.sa
AS: amsaif8080@gmail.com ORCID ID: https://orcid.org/0000-0002-9614-3238

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1 ABSTRACT

Leishmanial DNA topoisomerase IB (LdTOP1) is an appealing drug target owing to its crucial roles during DNA replication and transcription. The increasing drug resistance towards anti-leishmanial chemotherapeutics necessitates the search of alternative drugs that overcome the current resistance mechanisms. This study employed the computational approach to repurpose currently approved drugs as well as those in the preclinical stage but well characterized biologically. Molecular dynamics (MD) simulation was performed to investigate LdTOP1 flexibility and to sample possible conformers for subsequent virtual screening of the selected chemical libraries. Top potential hits from the initial virtual screening were subjected to exhaustive molecular docking to find more accurate binding poses and binding affinities. To validate the docking results, unbiased MD simulations and free energy calculation via Molecular Mechanics with Generalized Born Surface Area were employed. Computational simulations and free energy calculations suggest Lifitegrast is a potential LdTOP1 inhibitor. The interactions of Lifitegrast suggest it would bind and affect LdTOP1 in a different way than currently known topoisomerase inhibitors to which mutation-based resistance is already known. The suggested modulators could provide an opportunity to rapidly develop antileishmanial drugs by eliminating the toxicity testing since these two molecules (Lifitegrast and AMG900) are well-characterized in terms of their pharmacokinetic profiles. Validation of these findings and further investigation to determined how the molecules affect the function of LdTOP1 are worth investigations.