Ardabil University of Medical Sciences

School of Pharmacy

Title of Dissertation

Structural Optimization of Flavonoids, Carotenoids, Alkaloids and Saponins as Antileishmanial Agents by molecular modeling methods

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بسم الله الرحمن الرحيم

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سپاس و ستایش خدای را جل و جلاله که درهای علم را بر من گشوده و از روی کرم پدر و مادری شایسته نصیبم ساخته تا در سایه درخت پربار وجودشان بیاسایم.

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به پدر و مادر عزیزتر از جانم، پناه خستگیهایم و امید زندگانیم که مهر آسمانیشان آرامبخش آلام زمینیم است،

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پروردگارا حسن عاقبت، سلامت و سعادت را برای آنان مقدر فرما...

تقدیر و تشکر

شکر و سپاس خدای را که بزرگترین امید و یاور در لحظه لحظه ی زندگیست.

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Abstract

Introduction: Leishmaniasis is a parasitic disease caused by Leishmania parasites which transmission to humans is facilitated by the bite of a sandfly. The disease can cause different symptoms, from self-healing cutaneous Leishmaniasis to potentially fatal kala-azar or visceral Leishmaniasis. Approximately one billion people live in areas endemic for Leishmaniasis and an estimated 30000 new cases of Visceral Leishmaniasis and more than 1 million new cases of Cutaneous Leishmaniasis occur annually. The important issue in the chemotherapy of Leishmaniasis include availability of very few drugs, the emergence of resistance to the existing drugs, their toxicity and also lack of cost-effectiveness. Therefore, it is of utmost importance to search for and develop new effective drugs and drug targets for the treatment of Leishmaniasis. Natural products are already used in the men's daily diet; thus, they could be considered as suitable source for exploration of safe therapeutic goals.

Materials and methods: Present study aimed at proposing effective and safe antileishmanial compounds among natural products, using molecular docking methods. For this purpose, 67 flavonoids and 45 alkaloids were subjected to molecular docking process in order to obtain potential Leishmanial target-binding agents. AutoDock 4.2 was used for molecular docking simulations and PLIP webserver was also applied to analyze the complex interaction results. Top-ranked molecules were subjected to intermolecular binding interaction analysis via density functional method by Gaussian 03 software.

Results and Discussions: Candidate ligands were docked into active sites of 10 validated Leishmanial targets and then ranked with regard to obtained binding affinities (ΔG_b). Subsequently, on the basis of structure binding relationship studies, top-ranked ligands were evaluated and probable antileishmanial pharmacophores were proposed. It was found that mostly alkaloids and flavonoids exhibited high binding affinities to the validated leishmanial targets in comparison to crystallographic ligands. The tightest binding belonged to acerosin-uracil DNA glycolase (UDG) complex (ΔG_b -10.24 kcal/mol) and tithonine exerted multitarget binding potential. Hydrogen bond, vdw contacts and π-π stacking were found to be determinant binding interactions within flavonoids structures while alkaloids were associated with vdw contacts and salt bridge.

Conclusion and Suggestions: In general flavonoids exhibited better binding affinity into active site of validated leishmanial targets in comparison to alkaloids. On the basis of obtained results, UDG can be considered as a potential target for upcoming antileishmanial purposes due to the association with superior binding affinities toward flavonoids which are appropriate chemical scaffolds to be developed as antileishmanial agents.

Keywords:

Leishmaniasis, Natural products, Flavonoids, Alkaloids, Molecular docking, Density functional theory

Contents List

Signs and Abbreviations

WHO: World health Organization

L: Leishmania

CL: Cutaneous leishmaniasis

LCL: localized cutaneous leishmaniasis

DCL: Diffuse cutaneous leishmaniasis

MCL: Mucocutaneous leishmaniasis

VL: Visceral leishmaniasis

PKDL: Post-kala-azar dermal leishmaniasis

LST: Leishmania intradermal skin test

MST: Montenegro skin test

PCR: Polymerase chain reaction

ELISA: Enzyme-linked immunosorbent assay

NCE: New chemical entities

QSAR: Quantitative structure activity relationship

QSBR: Quantitative structure binding relationship

HTS: High-throughput screening

DHODH: Dihydroorotate dehydrogenase

dUTPase: Deoxyuridine triosephosphase

FPPS: Farensyl diphosphate synthase

TIM: Triosephosphate isomerase

NMT: N-Myristoyl transferase

RK: Ribokinase

UDG: Uracil DNA glycolase

PLIP: Protein-ligand interaction profiler

ADME: Absorption, distribution, metabolism, elimination

CADD: Computer-aided drug design

SAR: Structure activity relationship

SBR: Structure binding relationship

PDB: Protein data bank

RMSD: Root mean squared deviation

ΔG_b: Binding free energy

K_i: Inhibition constant

HBA: Hydrogen bond donor

HBA: Hydrogen bond acceptor

VdW: Vam der Walss

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