



**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**

**Supervisor**  
**Dr. Nima Razzaghi-Asl**

**By:**  
**Seyyedeh Niloufar Hashemi**

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## اهداء پایان نامه

سپاس و ستایش خدای را جل و جلاله که درهای علم را بر من گشوده و از روی کرم پدر و مادری شایسته

نصبیم ساخته تا در سایه درخت پر بار وجودشان بیاسایم.

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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 ( $\Delta G_b$ ). 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 ( $\Delta G_b$  -10.24 kcal/mol) and tithonine exerted multitarget binding potential. Hydrogen bond, vdw contacts and  $\pi$ - $\pi$  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

Chapter 1: Introduction.....	1
1-1-Infectious disease .....	2
1-2-Infectious agents.....	4
1-3-Leishmaniasis .....	7
1-3-1-Epidemiology of leishmaniasis.....	8
1-3-2-Cutaneous Leishmaniasis .....	10
1-3-2-1-Diagnosis .....	12
1-3-2-2-Treatment .....	13
1-3-2-3-Prevention .....	14
1-3-3-Visceral Leishmaniasis.....	15
1-3-3-1-Diagnosis .....	17
1-3-3-2-Treatment .....	18
1-3-3-3-Prevention .....	19
1-3-4-New drugs.....	20
1-4-Natural products .....	21
1-5-Molecular modeling .....	23
1-5-1-Computer aided drug design (CADD).....	23
1-5-1-1-Ligand-based drug design.....	24
1-5-1-2-Structure-based drug design.....	24
1-5-2-Docking .....	24
1-6-Importance of the subject .....	28
1-7-Thesis purposes .....	29
1-8-study assumptions and questions .....	29
1-9-Current Workflow .....	29
Chapter 2: Materials and Methods.....	31
2-1-Overall Methodology .....	32
2-2-Target data set .....	32
2-3-Ligand data set .....	32

2-4-Molecular docking .....	33
2-4-1-Structure preparation .....	33
2-4-1-1-Preparation of Ligand file .....	33
2-4-1-2-Preparation of Target file .....	33
2-4-2-Target validation.....	34
2-4-3-Doking process .....	34
2-5-SBR optimization .....	34
Chapter 3: Results and Discussions .....	35
3-1-Molecule selection .....	36
3-1-1-Target data set.....	36
3-1-1-1 Arginase .....	36
3-1-1-2-Dihydroorotate dehydrogenase (DHODH) .....	37
3-1-1-3-dUTPase.....	37
3-1-1-4-Farensyl diphosphate synthase (FPPS) .....	37
3-1-1-5-Froctose-1,6-bisphosphate adolase (aldolase) .....	38
3-1-1-6-Triosephosphate isomerase (TIM) .....	38
3-1-1-7- <i>N</i> -Myristoyl transferase (NMT).....	38
3-1-1-8-peroxidase .....	39
3-1-1-9-Ribokinase (RK) .....	39
3-1-1-10-Uracil DNA glycolase (UDG) .....	40
3-1-2-Ligand data set.....	40
3-2-Molecular docking .....	45
3-1-2-Docking Validation .....	46
3-2-2-Analysis of doking results .....	46
3-2-2-1-Top-ranked ligands .....	47
3-2-2-2-Top-ranked targets .....	51
3-2-2-3- Dominant ligand-protein complexes.....	52
3-3-Structure Binding Relationship (SBR).....	53
3-3-1-Arginase.....	53
3-3-2-DHODH.....	56



3-3-3-dUTPase .....	58
3-3-4-Farensyl diphosphate synthase (FPPS).....	61
3-3-5- Fructose-1,6-bisphosphate adolase (aldolase).....	64
3-3-6-Trioephosphate isomerase (TIM) .....	67
3-3-7- <i>N</i> -Myristoyl transferase (NMT) .....	69
3-3-8-Peroxidase.....	72
3-3-9-Ribokinase .....	74
3-3-10-UDG .....	76
3-3-10-1-Selectivity assesment (Homo sapiens UDG).....	81
3-3-11-Tithonine.....	82
3-4-SBR improvement.....	86
3-4-1-Arginase.....	87
3-4-2-DHODH.....	88
3-4-3-dUTPase .....	90
3-4-4-Farensyl diphosphate synthase (FPPS).....	92
3-4-5-Fructose-1,6-bisphosphate aldolase (aldolase).....	92
3-4-6-Triosphosphate isomerase (TIM) .....	94
3-4-7- <i>N</i> -myristoyl transferase (NMT).....	96
3-4-8-Peroxidase.....	98
3-4-9-Ribokinase .....	100
3-4-10-UDG .....	101
Chapter 4: Conclusion and Suggestions .....	104
4-1-Conclusion.....	104
4-2-Study limitations .....	107
4-3-Further suggestions .....	108
References:.....	109
Appendix.....	116
a-1-Docking results.....	117
a-2-PLIP studies.....	130
a-2-1-Arginase-Psilocybine interaction .....	130

a-2-2- DHODH-Serpyllin interaction.....	131
a-2-3-dUTPase-Acetylcorynoline interaction .....	132
a-2-4-FPPS-Sinensetin interaction .....	133
a-2-5-Aldolase-Pedalitin interaction .....	134
a-2-6-TIM-Pinocemberin interaction .....	135
a-2-7-NMT-Zapotinin interaction .....	136
a-2-8-Ribokinase-Canadine interaction.....	137
a-3-SAR/SBR optimization .....	138
a-3-1-Arginase .....	138
a-3-2-DHODH.....	138
a-3-3-dUTPase.....	139
a-3-4-Aldolase .....	140
a-3-5-TIM.....	140
a-3-6-NMT .....	141
a-3-7-Peroxidase.....	142
a-3-8-Ribokinase .....	142
a-3-9-UDG.....	143

## 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 triosephosphate  
FPPS: Farnesyl diphosphate synthase  
TIM: Triosephosphate isomerase  
NMT: N-Myristoyl transferase  
RK: Ribokinase  
UDG: Uracil DNA glycosylase  
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

$\Delta G_b$ : Binding free energy

$K_i$ : Inhibition constant

HBA: Hydrogen bond donor

HBA: Hydrogen bond acceptor

VdW: Van der Waals

## Tables list

<b>Table 3-1.</b> Physicochemical characteristics of candidated molecules .....	41
<b>Table 3-2.</b> AutoDock-4.2 validation results for different holo PDB structures of potential leishmanial targets .....	46
<b>Table 3-3.</b> Docking results of top-ranked compounds for studied targets of leishmania ...	47
<b>Table 3-4.</b> Ligands which have high affinity toward more than one target of leishmania .	50
<b>Table 3-5.</b> Top-ranked Thitonone-target complexes in AutoDock4.2 based simulation against leishmanial targets .....	51
<b>Table 3-6.</b> AutoDock4.2 based Binding affinity ranges for docked complexes of the assessed flavonoids and alkaloids within leishmanial targets .....	51
<b>Table 3-7.</b> Top-ranked flavonoids within docked leishmanial targets .....	52
<b>Table 3-8.</b> Leishmanial ligand-target complexes with $\Delta G_b \leq -10$ Kcal/mol in AutoDock4.2 based simulation .....	52
<b>Table 3-9.</b> Binding characteristics of Cuscohygrine-Arginase H-bond interactions .....	54
<b>Table 3-10.</b> Binding characteristics of Cuscohygrine-Arginase interactions.....	54
<b>Table 3-11.</b> Binding characteristics of DHODH-Gardenin D H-bond interactions.....	57
<b>Table 3-12.</b> Binding characteristics of dUTPase-Dehydrocorybulbine interactions .....	59
<b>Table 3-13.</b> Binding characteristics of dUTPase-Dehydrocorybulbine interactions .....	60
<b>Table 3-14.</b> Binding characteristics of Psilocybin-FPPS H-bond interactions .....	62
Table 3-15. Binding characteristics of Psilocybin-FPPS interactions .....	62
<b>Table 3-16.</b> Binding characteristics of Aldolase-Cirsiliol interactions.....	65
Table 3-17 Binding characteristics of 3,7-dihydroxyflavone-TIM interactions.....	68
<b>Table 3-18.</b> Binding characteristics of NMT-Acetylcorynoline H-bond interactions .....	70
<b>Table 3-19.</b> Binding characteristics of NMT-Acetylcorynoline interactions.....	70
<b>Table 3-20.</b> binding characteristics of Peroxidase-Fagaronine H-bond interactions .....	73
<b>Table 3-21.</b> Binding characteristics of Peroxidase-Fagaronine interactions.....	73
<b>Table 3-22.</b> Binding characteristics of Ribokinase-3.6-dihydroxyflavone interaction .....	75
<b>Table 3-23.</b> Binding characteristics of UDG H-bond interactions with top-ranked ligands (a).....	78
<b>Table 3-24.</b> Binding characteristics of UDG interaction with top-ranked ligands (b).....	79
<b>Table 3-25.</b> Validation and binding characteristics of Homo sapiens UDG interactions ...	81
<b>Table 3-26.</b> Binding characteristics of Tithonine with leishmanial targets (a).....	84
<b>Table 3-27.</b> Binding characteristics of Tithonine with leishmanial targets .....	85
<b>Table 3-28.</b> Binding comparison of Arginase-compound A vs Arginase-Cuscohygrine interactions.....	88
<b>Table 3-29.</b> Binding comparison of DHODH-molecule B vs DHODH-Gardenin D interactions.....	89

<b>Table 3-30.</b> Binding comparison of dUTPase-molecule C vs dUTPase-Dehydrocorybulbine interactions.....	91
<b>Table 3-31.</b> Binding comparison of Aldolase-molecule D vs Aldolase-Cirsiliol interaction .....	93
<b>Table 3-32.</b> Binding comparison of TIM-molecule E vs 3,7-dihydroxyflavone-TIM interaction .....	95
<b>Table 3-33.</b> Binding comparison of NMT-molecule F vs Acetylcorynoline-NMT interaction .....	97
<b>Table 3-34.</b> Binding comparison of Peroxidase-compound G VS Peroxidase-Fagaronine interaction .....	99
<b>Table 3-35.</b> Binding comparison of Ribokinase-molecule H vs 3,6-dihydroxyflavone-Ribokinaseinteraction .....	100
<b>Table 3-36.</b> Binding comparison of UDG-molecule I vs Acerosin-UDG interaction .....	102
<b>Table a-1.</b> docking results for ligands-Arginase and ligands-DHODH interactions .....	117
<b>Table a-2.</b> docking results for ligands-dUTPase and ligands-FPPS interactions.....	119
<b>Table a-3.</b> docking results for ligands-Aldolase and ligands-TIM interactions.....	122
<b>Table a-4.</b> docking results for ligands-NMT and ligands-Peroxidase interactions.....	124
<b>Table a-5.</b> docking results for ligands-Ribokinase and ligands-UDG interactions .....	127
<b>Table a-6.</b> Binding characteristics of Arginase-Psilocybin interaction .....	130
<b>Table a-7.</b> Binding characteristics of DHODH-Serpyllin interaction.....	131
<b>Table a-8.</b> Binding characteristics of dUTPase-Acetylcorynoline interaction .....	132
<b>Table a-9.</b> Binding characteristics of FPPS-Sinensetin interaction .....	133
<b>Table a-10.</b> Binding characteristics of Aldolase-Pedalitin interaction .....	134
<b>Table a-11.</b> Binding characteristics of TIM-Pinocemberin interaction .....	135
<b>Table a-12.</b> Binding characteristics of NMT-Zapotinin interaction .....	136
<b>Table a-13.</b> Binding characteristics of Ribokinase-Canadine interaction.....	137
<b>Table a-14.</b> Docking results of proposed compounds-Arginase interaction.....	138
<b>Table a-15.</b> Docking results of proposed compounds-DHODH interaction.....	139
<b>Table a-16.</b> Docking results of proposed compounds-dUTPase interaction.....	139
<b>Table a-17.</b> Docking results of proposed compounds-Aldolase interaction .....	140
<b>Table a-18.</b> Docking results of proposed compounds-TIM interaction .....	141
<b>Table a-19.</b> Docking results of proposed compounds-NMT interaction .....	141
<b>Table a-20.</b> Docking results of proposed compounds-Peroxidase interaction.....	142
<b>Table a-21.</b> Docking results of proposed compounds-Ribokinase interaction .....	143
<b>Table a-22.</b> Docking results of proposed compounds-UDG interaction .....	143

## Charts and Figures List

Figure 1-1. Geographical distribution of Leishmaniasis in the world .....	8
Figure 1-2. Geographical distribution of cutaneous Leishmaniasis in Iran .....	9
Figure 1-3. Geographical distribution of visceral Leishmaniasis in Iran .....	10
Figure 1-4. Hierarchical workflow of the current project.....	30
Figure 3-1 a) Chemical structure of Cuscohygrine, b) 2D scheme of[...]. .....	54
Figure 3-2. Proposed pharmacophore of alkaloid structures as leishmanial Arginase binders .....	56
Figure 3-3. a) Chemical structure of Gardenin D, b) 2D scheme of[...]. .....	57
Figure 3-4. Proposed pharmacophore of flavonoid structures as leishmanial DHODH binders.....	58
Figure 3-5 a) Chemical structure of Dehydrocorybulbine b) 2D scheme of f[...]. .....	59
Figure 3-6. Proposed pharmacophore of alkaloid structures as leishmanial dUTPase binders .....	61
Figure 3-7 a) Chemical structure of Psilocybin b) 2D scheme of f[...]. .....	62
Figure 3-8. Proposed pharmacophore of alkaloid structures as leishmanial FPPS binders .	64
Figure 3-9 a) Chemical structure of Cirsiolol b) 2D scheme of f[...]. .....	65
Figure 3-10. Proposed pharmacophore of flavonoid structures as leishmanial Aldolase binders.....	67
Figure 3-11 a) Chemical structure of 3,7-dihydroxyflavone b) 2D scheme of f[...]. .....	67
Figure 3-12. Proposed pharmacophore of flavonoid structures as leishmanial TIM binders .....	69
Figure 3-13 a) Chemical structure of Acetylcholine b) 2D scheme of f[...]. .....	70
Figure 3-14. Proposed pharmacophore of alkaloid structures as leishmanial NMT binders	72
Figure 3-15 a) Chemical structure of Fagaronine b) 2D scheme of f[...]. .....	72
Figure 3-16. Proposed pharmacophore of alkaloid structures as leishmanial peroxidase inhibitor.....	74
Figure 3-17 a) Chemical structure of 3,6-dihydroxyflavone b) 2D scheme of f[...]. .....	75
Figure 3-18. Proposed pharmacophore of flavonoid structures as leishmanial Ribokinase binders.....	76
Figure 3-19. a) Chemical structures of Acerosin (left) and 2D scheme of f[...]. .....	78
Figure 3-20. Proposed pharmacophore of flavonoid structures as leishmanial UDG inhibitor.....	81
Figure 3-21 a) Chemical structure of Tithonine b) 2D scheme of f[...]. .....	83
Figure 3-22 a) Chemical structure of compound A b) 2D scheme of f[...]. .....	87
Figure 3-23 a) Chemical structure of molecule B b) 2D scheme of f[...]. .....	89
Figure 3-24 a) Chemical structure of molecule C b) 2D scheme of f[...]. .....	91

Figure 3-25 a) Chemical structure of compound D b) 2D scheme of f[...]	93
Figure 3-26. a) Chemical structure of molecule E b) 2D scheme of f[...]	95
Figure 3-27 a) Chemical structure of molecule F b) 2D scheme of f[...]	97
Figure 3-28 a) Chemical structure of molecule G b) 2D scheme of f[...]	99
Figure 3-29 a) Chemical structure of compound H b) 2D scheme of f[...]	100
Figure 3-30 a) Chemical structure of compound I b) 2D scheme of f[...]	102

Figure 4-1. Chemical structures of proposed antileishmanial flavonoid/alkaloid based structures derived from structure binding relationship studies	107
-----------------------------------------------------------------------------------------------------------------------------------------------------	-----

Figure a-1 PLIP 2D scheme of Arginase-Psilocybin interactions	1305
Figure a-2 PLIP 2D scheme of DHODH-Serpyllin interactions.	1316
Figure a-3 PLIP 2D scheme of dUTPase-Acetylcorynoline interactions	1327
Figure a-4 PLIP 2D scheme of FPPS-Sinensetin interactions.	1338
Figure a-5 PLIP 2D scheme of Aldolase-Pedalitin interactions.	1349
Figure a-6. PLIP 2D scheme of TIM-Pinocemberin interactions	13530
Figure a-7 PLIP 2D scheme of NMT-Zapotinin interactions.	1361
Figure a-8 PL IP 2D scheme of Ribokinase-Canadine interactions.	1372
Figure a-9. Template structure for proposing Arginase inhibitor compounds	1383
Figure a-10. Template structure for proposing DHODH inhibitor compounds	1383
Figure a-11. Template structure for proposing dUTPase inhibitor compounds	1394
Figure a-12. Template structure for proposing Aldolase inhibitor compounds	1405
Figure a-13. Template structure for proposing TIM inhibitor compounds	1405
Figure a-14. Template structure for proposing NMT inhibitor compounds	1416
Figure a-15. Template structure for proposing Peroxidase inhibitor compounds	1427
Figure a-16. Template structure for proposing Ribokinase inhibitor compounds	1427
Figure a- 17. Template structure for proposing UDG inhibitor compounds	1438