Original Article

Homology Modeling and Molecular Docking of the *Leishmania* Protein Kinase, E9BJT5, A New Target for Leishmaniasis Therapeutics

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Abstract

Background & Objective: Leishmaniasis is taken into account as a parasitic disease caused by the *Leishmania* genus. A major challenge of the leishmaniasis is associated with the occurrence of treatment failure after drug treatment. Target identification is a significant factor to reach a drug development. Hence, protein kinases play an important role in drug designing (e.g, *Lmx*MPK and CRK3). This study is developed to predict and assess the three-dimensional structure for E9BJT5 protein in *Leishmania* and its binding affinity for different calcium channel blockers.

Materials & Methods: The three-dimensional structure was predicted and assessed for the protein by the I-TASSER and Procheck servers, respectively. In the molecular docking method, interactions between different calcium channel blockers and the predicted model of E9BJT5 were investigated using the Autodock vina in PyRx 0.8 software. Thereafter, the interaction results were analyzed by Chimera software, and thus the stronger potential interactions were identified.

Results: Docking results showed that the lidoflazine and lercanidipine (the values were -8.3 and -7.6 kcal/mol, respectively) were obtained as the top-ranked drugs in the binding to the active site of the protein.

Conclusion: In this study, using *in silico* approach, the E9BJT5 protein could be a viable target for designing the novel drugs against the *Leishmania* parasite. The docking results demonstrated that two drugs (i.e., lidoplasin and lercantipine) may be considered as anti-leishmanial drugs. Further studies are recommended to evaluate the interactions between these drugs and the target.

Keywords: *Leishmania*, Calcium channel blockers, Homology modeling, Molecular docking

Introduction

The World Health Organization stated that the annual number of leishmaniasis cases is increasing around the world (1). Leishmaniasis is caused by the *Leishmania* parasite, which is transmitted by phlebotomine-infected sand flies to a susceptible vertebrate host. Drug therapy is suggested while effective vaccines are not available for these patients (2). Pentavalent antimonials are the first-line treatment in most parts of the world. The pentavalent antimonials are reduced to the trivalent form and induce the host immune system anti-leishmanial activity (3). The oral drug of miltefosine acts as an anti-parasitic against *Leishmania*. It leads to several effects, including inhibiting the phosphatidylcholine (PC), increasing the phosphatidylethanolamines (4), inhibiting the

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mitochondrial cytochrome *c* oxidase (5), as well as inducing the cell-programmed death (6), and disturbing the intracellular calcium homeostasis (7). There is a lot of evidence for unsuccessful treatment in patients treated with miltefosine (8-10). The drug cost, its toxicity, and *Leishmania* species drug resistance are taken into consideration as the determinant factors for treatment failure in the leishmaniasis patients (11). It is essential to find a novel drug target for the treatment of the leishmaniases.

Phosphorylation plays a vital role in biological functions. As an example, it is necessary to employ the protein kinases for phosphorylation of voltage-dependent calcium channels in the nervous system, skeletal muscle, and normal cardiac function (12-14). In the cell membrane, calcium channels were inhibited by calcium blockers, which are used for heart patient therapy. These blockers are chemically placed in the phenyl-alkyl groups of amines (e.g., verapamil), dihydropyridines (e.g., amlodipine), and benzodiazepines (e.g., diltiazem) (15). Dihydropyridines have been considered promising drugs, mainly against *Leishmania* parasites (16-18). Antiprotozoal activities of non-dihydropyridines have been studied, too (19).

The *Leishmania* protein kinases are important factors for cell growth, differentiation, and response. About ninety kinases with no homology to the host (human) proteome were predicted, which could be potential targets for future drug screening in this parasite (20). The CMGC family of protein kinases includes cyclin-dependent kinases, mitogen-activated protein kinases, glycogen synthase kinase, and CDC-like kinase are relatively abundant in trypanosomatids. The *Leishmania* MAP kinase (*Lmx*MPK) and CRK3 (cdc-2 related kinase) showed potential as drug targets (21, 22). In trypanosomatid parasites, calcium ion plays an important role in host cell invasion, differentiation and bioenergetics (23). The activity of protein kinase is Ca^{2+}/phophatidylserine-dependent (24) and it has been associated with biological properties such as interacting with host macrophages and maintenance of ion homeostasis (25, 26). Therefore, these proteins are considered as the potential targets for designing the novel anti-parasitic drugs (21, 27).

To reduce the laboratory costs and the possibility of errors, the use of bioinformatics tools (e.g., homology modeling and molecular docking) have increasingly attracted attention in designing and discovering new drugs. This study focuses on the E9BJT5 protein kinase as a target in *Leishmania*, which is involved in *Leishmania* miltefosine- resistant (28). In this *in silico* study, before investigating the binding affinity for the target protein, the three- dimensional structure of the target was predicted and validated. In this study, a total of 14 calcium channel blockers were analyzed in terms of interaction energies between ligands and residues of the target site.

Materials & Methods

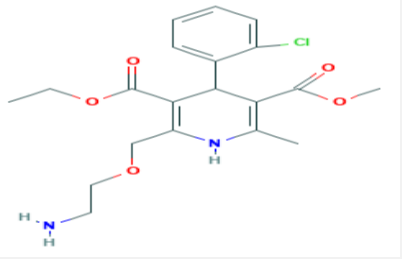
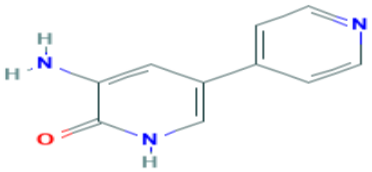
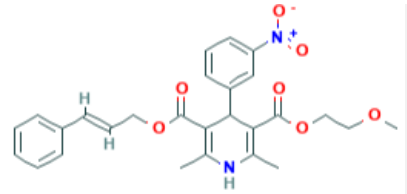
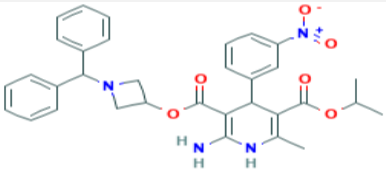
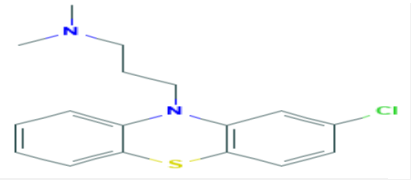
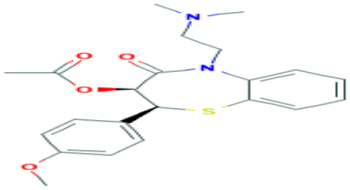
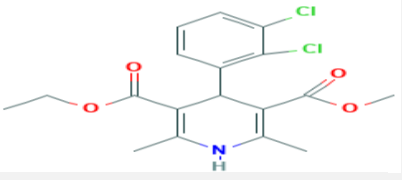
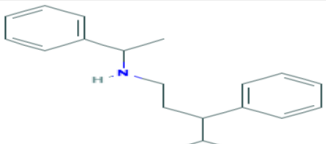
The E9BJT5 protein is a serine/ threonine protein kinase that has been reported as one of the *Leishmania donovani* proteins involved in the resistance of miltefosine (28). The E9BJT5 is a non-host homologous protein using Blast*p* and OrthoMCL (29). This will probably result in the least interaction with the host proteomes (20, 30). This issue reveals the importance of this protein as a target. Amino acid sequence of the target (XP_003862313.1) was prepared from the National Center for Biotechnology Information (NCBI, https://www.ncbi.nlm.nih.gov/) database in fasta format. The Blast*p* search showed high sequence identity between the E9BJT5 protein and the two strains of *Leishmania*, *L. infantum* (99.2 %) and *L. major* (90.4 %). Because proteins with similar sequences, i.e. more than 30% identity, have the same structures (31), these *Leishmania* strains can be structurally similar that needs further investigation.

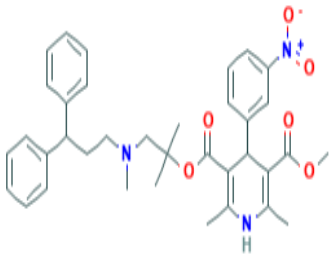
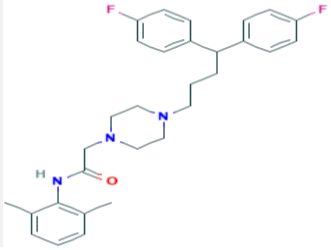
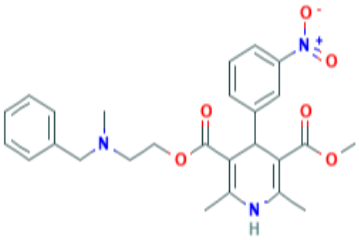
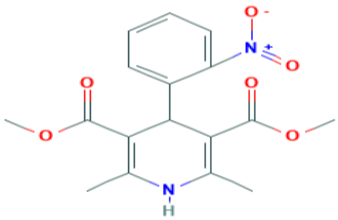
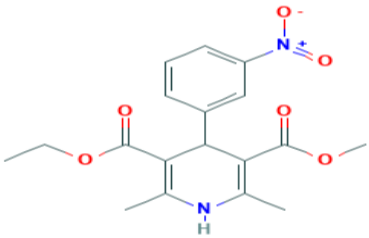
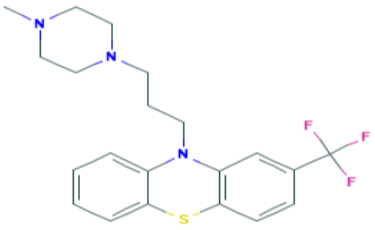
Protein sequences fold into a particular three-dimensional structure, which is determined by the order of atoms in an amino acid-chain. The structure of the E9BJT5 protein is not presented in the database of Protein Data Bank (PDB). Therefore, the three-dimensional structure of this target was modeled and observed by I-TASSER server (Iterative Threading Assembly Refinement) (32) and UCSF Chimera (33), respectively. Validation and qualification were evaluated for the model using the PROCHECK (34) and ProSA-web (35) servers. According to the PROCHECK server, the Ramachandran plot was developed to determine the favorable and allowed regions for amino acid residues in the model. The target active site was predicted by DoGSiteScorer server (36).

In this study, PubCHEM database (37) was used to obtain the chemical structure for the

number of 14 calcium channel blockers (Table 1). The target preparation was performed for docking by removing water molecules, cofactors, and other non-standard molecules, as well as

Table 1. Chemical structures of the 14 calcium channel blockers studied in this work

Compound	Compound Structure	Molecular weight (g mol-1)	Hydrogen acceptor	Hydrogen donor
Amlodipine		408.9	5	2
Amrinone		187.2	1	3
Cilnidipine		492.5	8	1
Azelnidipine		582.6	8	2
Chlorpromazine		318.9	2	0
Diltiazem		414.5	6	0
Felodipine		384.2	4	1
Fendiline		315.5	0	1

Lercanidipine		611.7	8	1
Lidoflazine		491.6	3	1
Nicardipine		479.5	8	1
Nifedipine		346.3	7	1
Nitrendipine		360.4	6	1
Trifluoroperazine		407.5	3	0

adding hydrogen atoms to the protein structure. PyRx 0.8 (38) was employed to investigate the protein-ligand interactions in the binding site of the target protein. In docking, conformations were calculated for each docked complex, and the lowest binding energy conformation (kcal/mol) was chosen as the result.

Results

In homology modeling of the E9BJT5 protein, the I-TASSER server was used to select the best model (39) with a higher *C*-score (-1.96), as shown in Fig 1. The 3D-structure of protein showed that it had a sequence similarity of 25.53% with the CDPK kinase domain from

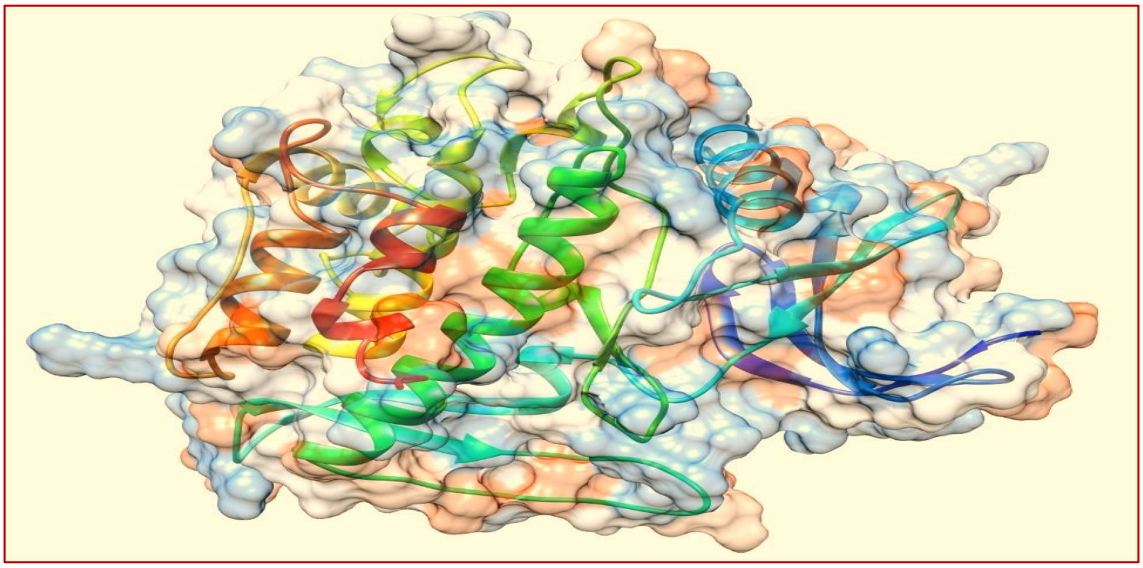


Figure 1. The three-dimensional structure of the *Leishmania* E9BJT5 protein using I-TASSER server

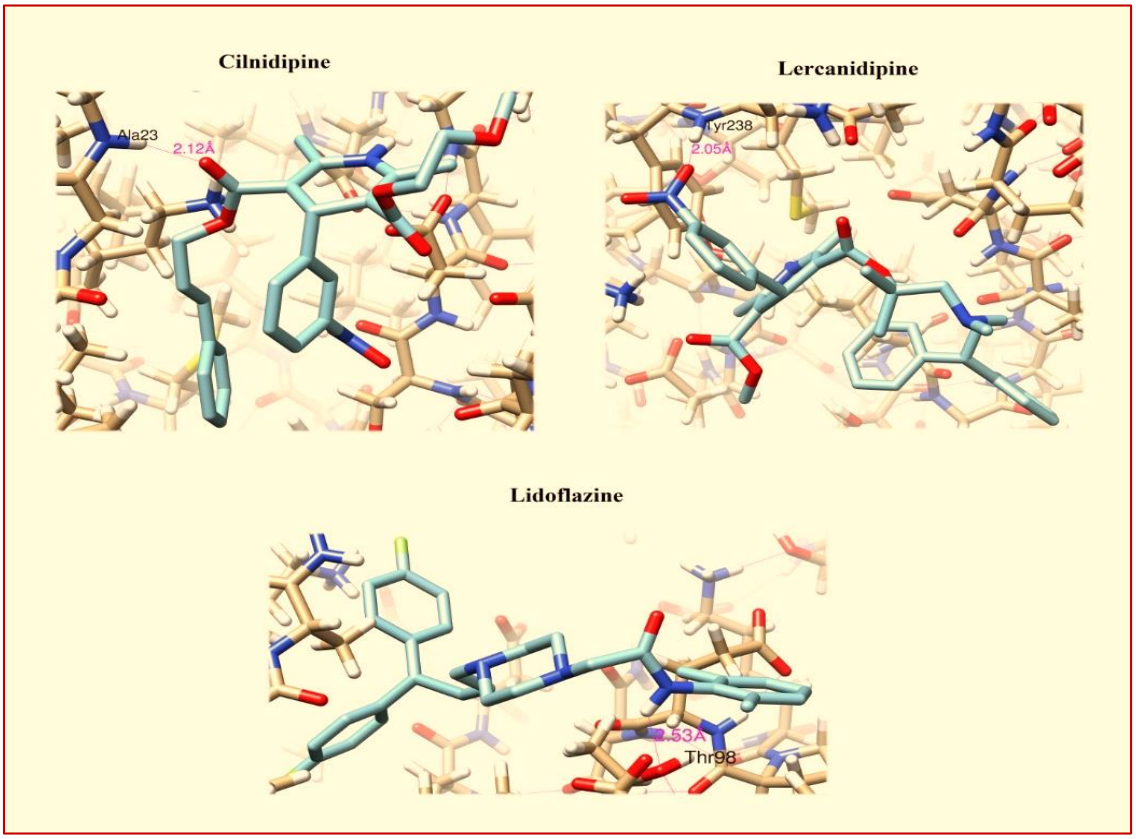


Figure2. Ligands binding mode on the 3D-model of the *Leishmania* E9BJT5 protein

cryptosporidium Parvum (PDB: 3hko) and the *E*-value of 9E $^{-26}$. The quality of the three dimensional model was assessed using PROCHECK server, and the Ramachandran plot indicated that were more than 85% of the amino acids within proteins, which were located in the favorable and allowed regions. ProSA web showed that the predicted model by Z-score -6.28 is commonly found in native structures.

Docking analysis was performed for the target-ligand complexes using PyRx software. This procedure was accomplished to rank them based on their binding energy and hydrogen bonds. The results revealed that about half of the calcium

channel blockers cannot form the hydrogen bonds within the active site of the target protein. Among the remaining seven inhibitors, five drugs are dihydropyridine-type calcium channel blockers (dihydropyridine CCB), including lercanidipine, cilnidipine, nicardipine, nitrendipine, and amlodipine. Also, two drugs are non-dihydropyridines, consisting of amrinone and lidoflazine. UCSF Chimera software was employed to investigate the docked complexes for these seven inhibitors interactions within the target site. Docking analysis results demonstrated that these seven inhibitors could successfully be docked into the active site of the target with favorable binding energies. According to the docking results, the best docked compounds were obtained by two inhibitors, including lidoflazine and lercanidipine. The binding energies were -8.3 and -7.6 kcal/mol for the lidoflazine and lercanidipine, respectively. In the ligand- target docked complexes as shown in Fig 2, the 2,6-dimethylphenyl acetamide of lidoflazine formed one hydrogen bond with the Thr98 residue; the 3-nitrophenyl of lercanidipine formed one hydrogen bond with Tyr238 residue; the carboxylate group of the cilnidipine formed one hydrogen bond with the Ala23 residue. As shown in Fig 3, the 1,4-dihydropyridine-3,5-dicarboxylate of the nicardipine formed two hydrogen bonds with Lys42 and Glu167 residues, the 2-aminoethoxy of amlodipine formed two hydrogen bonds with Thr75 and Asp92, and two hydrogen bonds were formed with Lys42 and Asp182 residues in the amrinone- target docked complexes. Furthermore, the nitrophenyl and carboxylate groups of the nitrendipine formed three hydrogen bonds with Arg107 and Tyr238 residues, in Fig

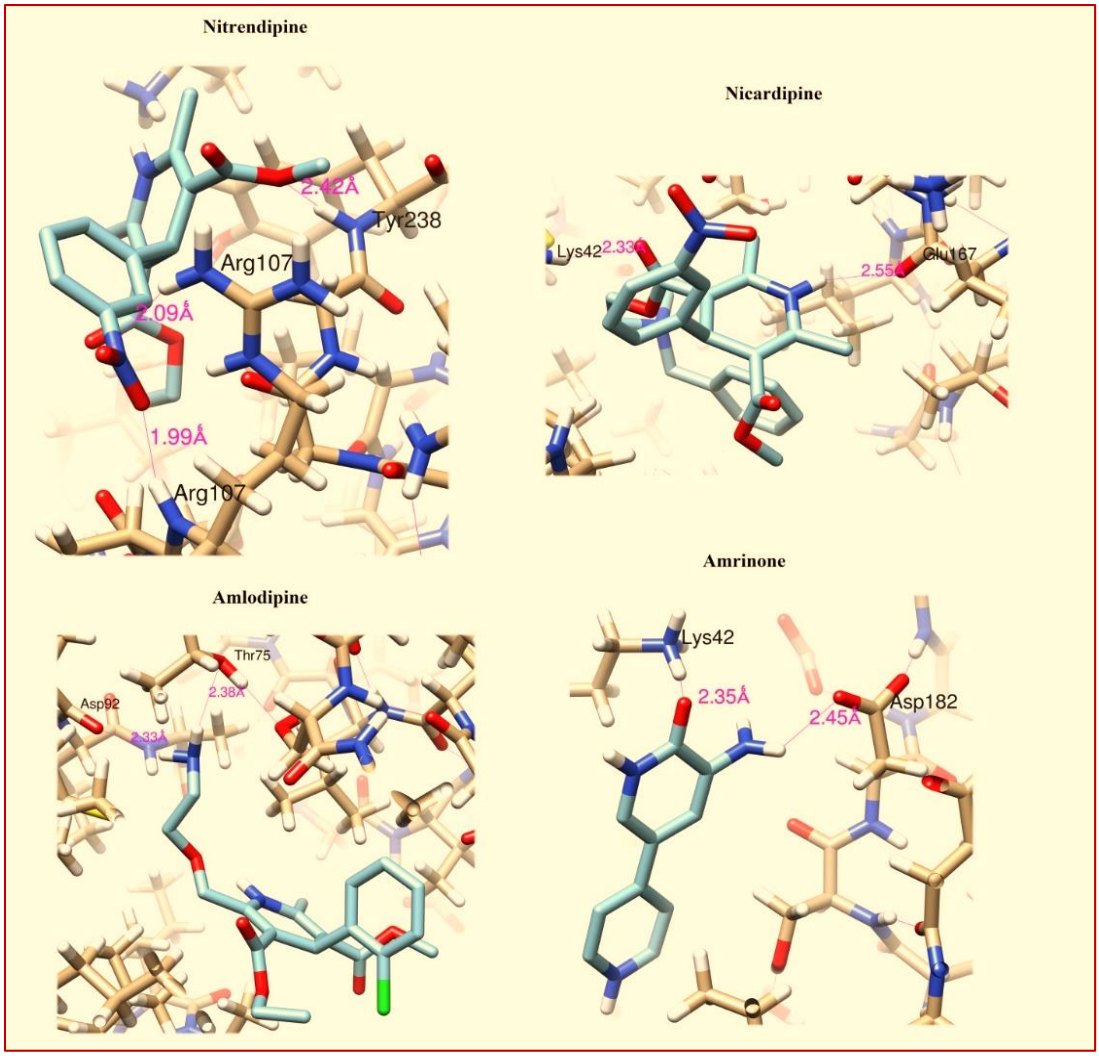


Figure 3. Molecular docking analysis between the active site residues of E9BJT5 protein and the four ligands include Nitrendipine, Nicardipine, Amlodipine, and Amrinone

3. Table 2 lists the binding energies obtained from these seven ligands that are related to the target with hydrogen bonding and hydrophobic interactions.

structure for the E9BJT5 protein. The best model was generated for the target using I-TASSER server. In this context, the molecular docking was made between the E9BJT5 protein and 14

Table 2. Calculated binding energies, the hydrogen bond and hydrophobic interactions of the *Leishmania* E9BJT5 protein with seven calcium channel blockers

Compound	Binding energy, ΔG (kcal/mol)	Hydrogen bond	Hydrophobic interaction
Lidoflazine	-8.3	Thr98	Lys42, Asp101, Glu167
Lercanidipine	-7.6	Tyr238	Arg104, Glu105, Arg106, Lys203, Gly237
Nicardipine	-6.8	Lys42 and Glu167	Lys42, Glu167, Asn168, Asp182,
Cilnidipine	-6.4	Ala23	Lys42, Lys165, Glu167, Asn168, Asp182
Nitrendipine	-6	2 Arg107, Tyr238	Glu105, Arg106, Arg107, Lys203, Arg241
Amrinone	-5.9	Lys42 and Asp182	Lys42, Glu61, Asp92, Asp182
Amlodipine	-5.7	Thr75 and Asp92	Lys42, Asp92, Glu167, Asn168, Asp182

Discussion

Calcium ions are involved in different physiological, biochemical, and signaling pathways of cells. The moderation of calcium signaling causes *Leishmania* survival within the macrophages. The crucial role of Ca^{2+} in the modulation of cytokine balance during pathogenesis was studied (40). Also, impairment of Ca^{2+}-dependent protein kinase C signaling is a key factor for the *Leishmania* infected macrophages (41). Hence, the effect of binding has also been studied on some of the calcium channel blockers (16, 19, 42). For example, calcium channel blockers (e.g., nifedipine and verapamil) inhibit *Leishmania*-macrophage attachment (43).

In this study, we aimed to investigate homology modeling of the *Leishmania* protein kinase (E9BJT5) and its molecular docking with fourteen calcium channel blockers. As mentioned before, there is no three-dimensional calcium channel blockers to predict the ligand-target interactions. Ligands binding affinity and hydrogen bonding were characterized using UCSF Chimera. Among the 14 inhibitors, seven of them could form at least one hydrogen bond within the target site. According to the docking results, lercanidipine (dihydropyridine) and lidoflazine (non-dihydropyridines) formed hydrogen bonds with the most favorable binding energies in the ligand binding site (Table 2).

Taken together, the bioinformatics methods (e.g., molecular docking) have led to the identification of important interactions in the ligand-target binding mode. The findings of this study reveal that the E9BJT5 protein could be a new target for designing leishmanicidal agents. Based on the ligands docking scores against the active site domain of the target, two blockers, lidoflazine and lercanidipine, could be used as novel drug candidates as anti-leishmaniasis drugs, which needs further investigations.

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Conflict of Interests

The authors declare no conflicting interests in this manuscript.

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مقاله پژوهشی

هموlوژی مدلینگ و داکینگ مولکولی پروتئین کیناز *لیشمانیا*، E9BJT5، هدفی جدید برای درمان لیشمانیوز

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چکیده

زمینه و هدف: لیشمانیوز به‌عنوان یک بیماری انگلی ناشی از جنس *لیشمانیا* درنظر گرفته می‌شود. عدم درمان بعد از درمان دارویی یکی از مشکلات عمده بیماری لیشمانیوز است. شناسایی پروتئین هدف یک عامل مهم برای دستیابی به توسعه دارو است. از این‌رو، پروتئین‌کینازها نقش مهمی در طراحی دارو دارند (مانند، *Lmx*MPK و CRK3). این مطالعه به‌منظور پیش‌بینی و ارزیابی ساختار سه‌بعدی پروتئین E9BJT5 در *لیشمانیا* و تمایل اتصال آن برای مسدودکننده‌های مختلف کانال کلسیم انجام شده‌است.

مواد و روش‌ها: ساختار سه‌بعدی پروتئین E9BJT5 توسط سرورهای I-TASSER و Procheck، به‌ترتیب، پیش‌بینی و ارزیابی گردید. در روش داکینگ مولکولی، فعل‌وانفعالات مسدودکننده‌های مختلف کانال کلسیم در مدل پیش‌بینی‌شده E9BJT5 با کمک نرم‌افزار PyRx در Autodock vina بررسی گردید. پس از آن، نتایج تعامل با نرم افزار Chimera مورد تجزیه‌وتحلیل قرار گرفت، و بنابراین فعل‌وانفعالات قوی‌تر شناسایی شد.

نتایج: نتایج داکینگ نشان داد که لیدوفلازین و لرکانیدیپین (به‌ترتیب با مقادیر ۸/۳- و ۷/۶- کیلوکالری بر مول) به‌عنوان داروهای برتر در اتصال به جایگاه فعال پروتئین شناخته می‌شوند.

نتیجه‌گیری: در این مطالعه، به روش *in silico*، پروتئین E9BJT5 می‌تواند هدفی مناسب برای طراحی داروهای جدید دربرابر انگل *لیشمانیا* باشد. نتایج داکینگ نشان می‌دهد که دو داروی (لیدوفلازین و لرکانیدیپین) ممکن است به‌عنوان داروهای بالقوه ضد لیشمانیایی درنظر گرفته‌شوند. برای ارزیابی تعاملات بین لیگاندها و هدف مطالعات بیشتر توصیه می‌گردد.

کلمات کلیدی: لیشمانیا، مسدود کننده‌های کانال کلسیم، هموlوژی مدلینگ، داکینگ مولکولی

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