Original Article

Molecular Modeling and Docking Studies on the First Chlorotoxin-Like Peptide from Iranian Scorpion *Mesobuthuseupeus* (Meict) and SNP Variants of Matrix Methaloproteinase-2 (MMP-2)

*Farzaneh Mohammadi Farsani [1], Hoda Ayat[*1], Ali Mohammad Ahadi [1]*

Received: 29.04.2015 *Accepted: 22.06.2015*

ABSTRACT

Background: MeICT is the first chlorotoxin-like peptide isolated from the Iranian Scorpion *Mesobuthus eupeus.* Chlorotoxin (CTX) is a neurotoxin that specially binds to (MMP-2) on malignant cells and now is used in treatment of glioma. In the present study, we have used homology modeling to propose the 3D structure of MeICTand analyze its interaction with MMP-2 and its SNP types.

Methods: The structure of MeICT was modeled by using homology modeling through the Swiss-Model workspace. Structural evaluation and stereo-chemical analysis of modeled structure of MeICT was performed using ProSA-web Z-scores and Mol Probity Ramachandran plots. Hex Server was used to investigate the interactions between MeICT and catalytic domain of MMP-2 and SNP types. Binding energies calculation and complementarity scores were used for evaluation of protein docking.

Results: The comparable Z-scores, Ramachandran plot characteristics and RMSD values confirmed the quality of the homology model of MeICT. About 17 SNP variants in catalytic domain of MMP2 were detected. According to the total and electrostatic energies and the number of interactive residues by hydrogen bond, the structure of MeICT-rs200271857, MeICT-rs144334568, MeICT-rs111590299 and MeICT-rs201083413complexes are more stable.

Conclusion: The structure of MeICT is similar to CTX, somight be used as therapeutic agent in glioma. We could find some variants of MMP-2 that can bind to MeICT with more or less affinity and can affect treatment pathway.

Keywords: Docking Simulation, Matrix Methaloproteinase-2, Meict, Molecular Modeling.

IJT 2015; 1368-1376

INTRODUCTION

Chlorotoxin (Cltx) is a 36-amino acid peptide isolated from the venom of scorpion *Leiurusquinquestriatus* [1]. This peptide binds specifically to the surface of glioma cells and inhibits its metastasis and growth of these cells [2-4]. Because of highly specific binding ability of Cltx and its high stability, it is a good substance for treatment of glioma [5,6]. The receptor of Cltx on the surface of glioma cells is matrix metalloproteinase-2 (MMP-2) [7]. MMP-2 degrades collagen type IV, the major component of basement membranes and denatures collagen [8]. This type of MMPs is not normally expressed in brain and is specifically up regulated in gliomas and cancers. Anti-invasive effect of Cltx on glioma cells is due to its interactions with MMP-2 that reduces the expression of it on the surface of cells [7]. The expression of MMP-2 are reduced Chlorotoxin has been achieved clearance from US FDA and presently is used in cancer therapy [9]. Although pharmacological and clinical studies have been performed on chlorotoxin, there are few studies on the structure and function of this peptide, which needs more investigations [10].

In this study, we modeled the structure of a chlorotoxin-like peptide named MeICT and analyzed its interactions with MMP-2 by docking procedures. MeICT is the first chlorotoxin-like peptide isolated from the Iranian scorpion *Mesobuthu seupeus*. There are some differences in the sequences of MeICT compared with Cltx that can be specific for Iranian subspecies [11]. Furthermore, because of much similarity with chlo-

1. Department of Genetics, University of Shahrekord, Shahrekord, IR Iran.
*Corresponding Author: E-mail: ayat-h@sci.sku.ac.ir

rotoxin, MeICT may be used as therapeutic agent in glioma.

We also analyzed interactions between MeICT and single nucleotide polymorphism (SNP) variants of MMP-2 in the current study.Common genetic variations such as SNPs present in patient's genes often affect their response to a drug [12]. Depending on where SNPs occur, they can result in no change or a change in the protein amino acid sequence (synonymous SNPand non-synonymous SNP, respectively) that can have no functional consequence or can result in altered protein function. The latter can have significant clinical and/or therapeutic implications [13]. SNP in drug target genes may reduce the respond to the medication [14].

Thus, it seems that study of the interactions between SNP forms of MMP-2 and MeICT as a potential therapeutic agent may be helpful to treatment of glioma. In the present study; we have used homology modeling to propose the 3D structure of MeICT and analyze its interaction with MMP-2 and its SNP types.

MATERIAL AND METHODS

Tools Used for the Study

In the present study, we used biological databases like NCBI (http://ncbi.nlm.nih.gov/) and Protein Data Bank ((http://www.ebi.ac.uk/pdbe/) to obtain amino acid sequences and structure of proteins, respectively. Prediction of three-dimensional structures of proteins was performed by Swiss-Model workspace (http://swissmodel.expasy.org/). For validation of modeled structures, we used Mol Probity (http://molprobity.biochem.duke.edu/), Dali (http://ekhidna.biocenter.helsinki.fi/dali_server/) and ProSA-web (https://prosa.services.came.sbg.ac.at/prosa.php) servers. Swiss-PdbViewer software (http://www.expasy.org/spdbv/) was used for optimization of models. Docking studies were performed with Hex Server (http://hexserver.loria.fr/) and generated binding models were optimized by MD simulation through MDWeb server (http://mmb.irbbarcelona.org/MDWeb/) and analyzed with Swiss-PdbViewer software [15].

Preparation of the Structures of Meict and Snp Variants of Mmp-2

Protein amino acid sequence of MeICT (GeneBank: ADY02962.1) and SNP variants of human catalytic domain of MMP-2 or gelatinase A (Accession: NP_004521) were obtained from NCBI. The structure of MeICT was modeled using homology modeling through the Swiss-Model workspace. The atomic coordinates of catalytic domain of MMP-2 (PDB code: 1QIB) was obtained from the Protein Data Bank and the structures of SNP variants of this protein were also modeled with Swiss-Model server.

Protein Structure Validation and Optimization

Structural evaluation and stereochemical analysis of modeled structure of MeICT was performed using ProSA-web Z-scores and MolProbity Ramachandran plots [16, 17]. Furthermore, Root Mean Squared Deviation (RMSD) of this structure was calculated using Dali server [18]. This structure and models predicted for SNP types of MMP-2 catalytic domain were subjected to refinement by energy minimization through Swiss-Pdb Viewer software and then were used for docking analysis.

Docking Analysis and Molecular Dynamics Simulations (Md) Of Complexes

The docking analysis of MeICT with MMP-2 catalytic domain and its SNPs were carried by Hex Server. Hex is an FFT-based protein-docking server. Two protein structures in PDB format are essential for uploading by this server and it produces a ranked list of up to 1000 docking predictions [19]. In our study, MMP-2 and its SNP variants were treated as receptors and MeICT was treated as ligand. The parameters used for the docking process via Hex Server were Correlation type Shape + Electrostatics, Receptor Range 180, Ligand Range 180, Step Sizes 7.5 and Solutions 100. Docking was conducted between receptors and ligand and the modeled three-dimensional structures were subjected to MD simulation with MD Web server [20]. The modeled three-dimensional structures were subjected to refinement by optimization, 300 steps of conjugate gradient minimization. MD simulation was performed via 150 ps with

the step size of 1fs at 300K. Total energy and electrostatic energy of each complex model was computed and H-bond interactions and lengths were visualized by Swiss-Pdb Viewer software.

RESULTS

Molecular Model of Meict and Snp Variants of Mmp-2

Swiss-model generated three models for MeICT that were ranked based on their QMEAN4 score (Table1). The model-1 structure based on the solution structures of insect toxin 15A (PDB code: 1SIS) from *Buthuserpeus* was selected as template for further studies. Secondary structure alignment of modeled structure for MeICT (Model-2) with insect toxin 15A (1sis) and its 3D structure in comparison with Cltx and insect toxin 15A, are shown in Figure 1 (a, b). Reliability of the selected 3D model was analyzed with structure assessment methods including Z-scores, Ramachandran plots and RMSD (Root Mean Square Deviation). As it is shown in Figure1c, the template (insect toxin 15A) Z-score was -7.02 and it was -7.04 for the homology model (MeICT). The Ramachandran plots were obtained for both the template and the homology model from MolProbity server. Ramachandran plots analysis of the models displayed that 96.9% (31/32) of all residues of modeled structure and 97.1% (33/34) of all residues of template were in allowed regions (Table 2). The RMSD value obtained from superimposition of modeled structure for MeICT in Dali server. It was also 0.1 Å. Peptide structure then was subjected to refinement by energy minimization that is shown in Figure 1d.

SNP variants of human catalytic domain of MMP-2 were obtained from NCBI. We found 17 SNP variants in this domain (Table 3). The structure of these SNP types was predicted by Swiss-Model server. Three models for every protein were generated. In each case, the model that was built based on 1QIB structure as template was used. Selected models then were refined by energy minimization and used for docking analysis.

Analysis of Meict-Mmp-2 Catalytic Domain Complexes by Hexserver and Md Simulation

To investigate the interactions between MeICT and catalytic domain of MMP-2 (and SNP types), we used Hex Server. Total binding and electrostatic energy results of each complex were calculated after MD simulation with MD Web server that are shown in Figure 2 and Table 4. Binding and electrostatic energy values of MeICT-MMP-2 catalytic domain complex are -994 and -1555.999KJ/mol, respectively. The amino acid residues that contact by hydrogen bond between MeICT and MMP-2 catalytic domain (orSNP variants) are also indicated in Figure 3 and Table 4.

Table1. Comparative study of QMEAN4 score of three models predicted for MeICT through Swiss-model.

Model predicted through Swiss-model	Template	QMEAN4 score
Model-3	1sis	0.78
Model-1	1sis	0.30
Model-2	1chl	-0.86

Table2. Ramachandran plot calculations for 3D model of MeICT and template (insect toxin 15A).

Ramachandran plot statistics	Modeled protein	Template
% Amino acid in most favored regions	87.5	85.3
% Amino acid in allowed regions	9.4	11.8
% Amino acid in disallowed regions	3.1	2.9

Table3.SNP variants in the catalytic domain of MMP-2.

SNP ID	Amino acid position	Allele change	Residue change
rs112710941	1	CGC ⇒ CAC	R ⇒ H
rs200271857	28	GAT ⇒ TAT	D ⇒ Y
rs368499410	31	GCT ⇒ ACT	A ⇒ T
rs144334568	39	GAT ⇒ AAT	D ⇒ N
rs148810689	40	GTG ⇒ ATG	V ⇒ M
rs368486758	44	CGG ⇒ CAG	R ⇒ Q
rs375159741	44	CGG ⇒ TGG	R ⇒ W
rs147947052	52	GAG ⇒ AAG	E ⇒ K
rs141565911	53	GCA ⇒ ACA	A ⇒ T
rs145337551	61	CGC ⇒ CAC	R ⇒ H
rs111590299	69	CCC ⇒ TCC	P ⇒ S
rs200772153	108	AGC ⇒ AGA	S ⇒ R
rs121912955	116	GAG ⇒ AAG	E ⇒ K
rs121908741	118	GGC ⇒ GAC	G ⇒ D
rs59727333	121	ATG ⇒ ATA	M ⇒ I
rs201083413	141	AAG ⇒ AAT	K ⇒ N
rs17859943	159	GCC ⇒ GTC	A ⇒ V

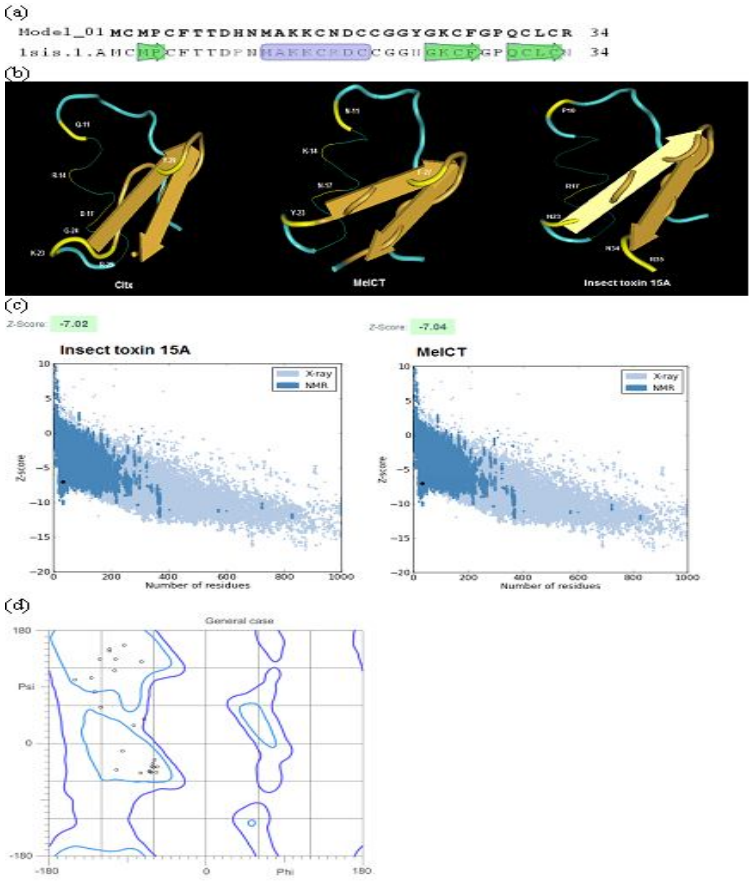


Figure1. Sequence and structure analysis of MeICT.(a) Secondary structure alignment of modeled structure for MeICT (Model-2) with insect toxin 15A (1sis).β-sheets and α-helix are shown with green objects and violet box, respectively (b) Backbone ribbon representation of the model of MeICT compared with the structure of Cltx and insect toxin 15A. Amino acids difference between MeICTandchlorotoxin are represented (c) Z-score of template (insect toxin 15A) and modeled structure for MeICT (d) Ramachandran map of modeled MeICTafter energy minimization with Swiss-PdbViewer software.

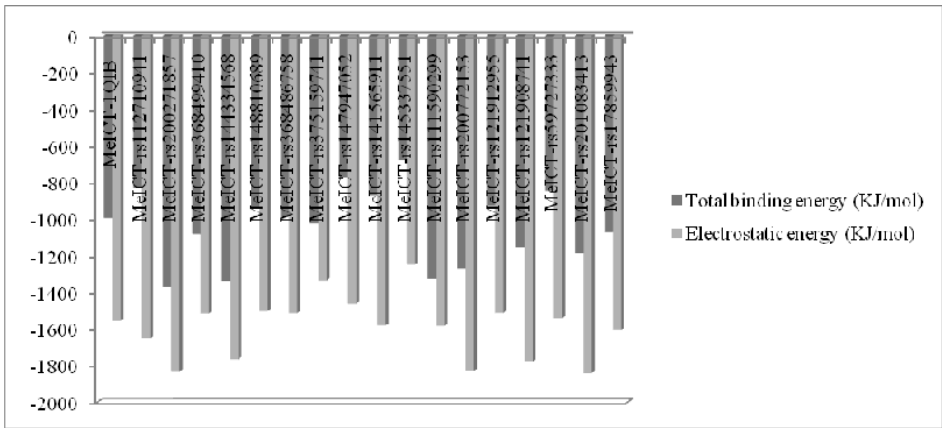
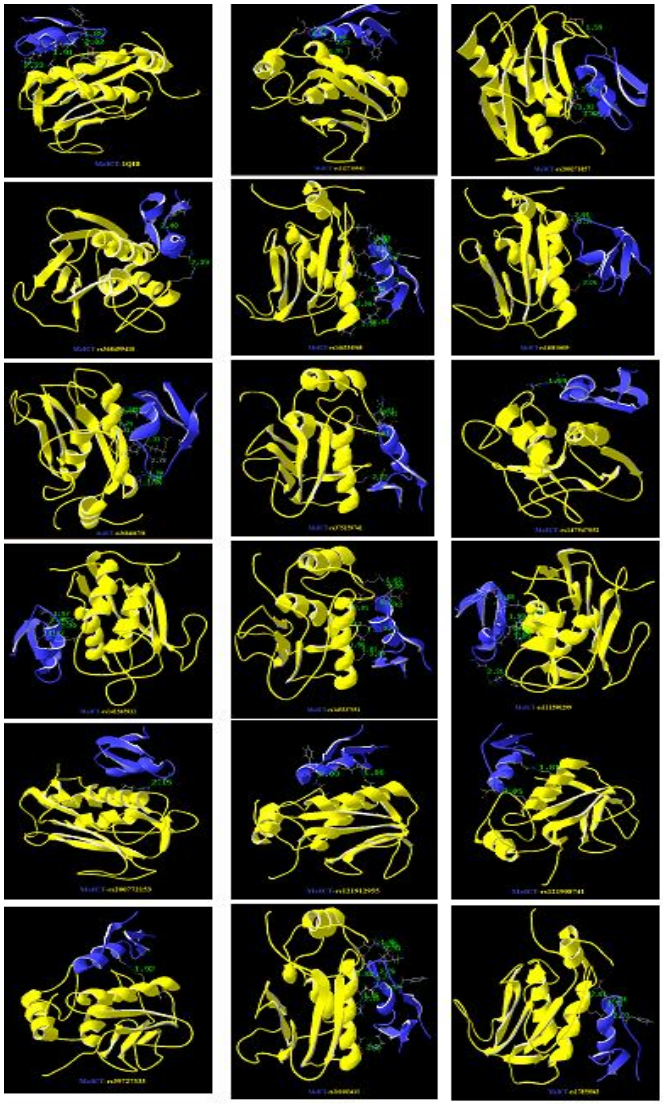


Figure2. Total binding and electrostatic energies for docking models after MD simulation.



Firgure3. Ribbon models of MeICT-MMP-2 catalytic domain (a) and MeICT-SNP variants of MMP-2 complexes. Whole backbones of complexes are shown. The amino acid residues of contacts by hydrogen bond (indicated by green line) between MeICT and MMP-2 catalytic domain (or SNP variants) are indicated.

Table4. Total binding energy, electrostatic energy and interactive residues by hydrogen bond of MeICT and SNP variants of MMP-2 complexes after MD simulation.

Complexes	Total binding energy (KJ/mol)	Electrostatic energy (KJ/mol)	Contacts between residue pairwise	H-bonds distances (Å)
MeICT-1QIB	-994.9	-1555.99	Phe6-Gln35	1.85
			Lys14-Phe143	2.02
			Lys25-Thr25	2.33
			Cys26-Asp28	1.91
MeICT-rs112710941	-832.660	-1651.68	Thr7-Ser160	1.76
			Thr8-Asp39	2.54
			Ala13-Asp39	2.46
			Cys26-Gln35	2.07
MeICT-rs200271857	-1369.679	-1833.44	Cys2-Ala82	2.25
			Asn11-Glu124	1.78
			Asn11-His125	1.96
			Tyr23-Asp71	1.61
MeICT-rs368499410	-1079.555	-1513.66	Phe6-Gln35	2.4
			Asn11-Arg144	2.39
MeICT-rs144334568	-1336.956	-1766.41	Phe6-Gln35	2.06
			Thr7-Arg44	1.83 & 2.56
			Asp9-Gln35	2.00
			Asp18-Lys141	1.83
			Lys25-Asp22	1.91
			Lys25-Glu24	1.83
			Cys26-Asp28	1.80
MeICT-rs148810689	-934.01	-1502.37	Asp9-Arg144	2.04, 2.14 & 2.59
			Asn17-Asp28	2.26
MeICT-rs368486758	-989.428	-1512.92	Asp9-Arg144	1.90, 1.97 & 2.39
			Met12-Gln35	2.33
			Ala13-Arg32	1.85 & 2.35
			Asn17-Asp28	2.12 & 2.19
MeICT-rs375159741	-1023.07	1335.31	Thr8-Asp39	1.97
			Asp9-Arg144	1.91 & 2.41
			Cys26-Asp28	2.22
MeICT-rs147947052	-771.947	-1461.65	Asn11-Arg144	1.99
MeICT-rs141565911	-871.601	-1580.10	Asp9-Gln35	1.97
			Asn11-Arg144	1.87
			Met12-Gln35	2.72
			Ala13-Gln35	2.30
(*Continued)*				
MeICT-rs145337551	-677.035	-1247.89	Thr8-Asp39	1.95
			Asp9-Arg144	1.82, 2.02 & 2.43
			Met12-Gln35	2.46
			Ala13-Arg32	1.86
			Cys26-Asp28	2.00
MeICT-rs111590299	-1326.78	-1582.49	Phe6-Gln35	1.88
			Ala13-Arg32	1.89 & 2.27
			Asn17-Asp28	2.12
			Gly21-Lys103	2.31
			Cys26-Asp28	1.98
MeICT-rs200772153	-1272.465	-1831.05	Gly22-Arg32	2.15
MeICT-rs121912955	-927.526	1511.89	Phe6-Gln35	2.03
			Cys26-Asp28	1.86
MeICT-rs121908741	-1153.857	-1778.94	Thr8-Gln35	2.05
			Asn17-Asp28	1.81
MeICT-rs59727333	-846.183	-1541.19	Asn17-Asp28	1.92
MeICT-rs201083413	-1183.996	-1841.50	Phe6-Gln35	1.90
			Thr8-Asp39	2.26
			Asp9-Arg144	1.93, 1.95 & 2.16
			Ala13-Arg32	1.96 & 2.16
			Lys25-Thr25	2.05
MeICT-rs17859943	-1070.931	-1606.29	Phe6-Gln35	2.03
			Asp9-Asp39	2.04

DISCUSSION

The structure of MeICT model-1 obtained from Swiss-model consisted of a small three-stranded anti-parallel β-sheet and one α-helix which was in agreement with those observed in the known three dimensional structures of Cltx (PDB code: 1CHL) and other short toxins (Figure1 a, b) [21, 22]. The Z-score is indicative of overall model quality and Z-score of MeICT indicates that the input structure is within the range of scores typically found for native proteins of similar size (insect toxin 15A). Ramachandran plots analysis of this model determined the residues were falling in the most favored region. The RMSD value of MeICT indicated the more similarity degree to 3D structure of template peptide [23]. The comparable Z-scores, Ramachandran plot characteristics and RMSD values confirmed the quality of the homology model of MeICT. The structure then was subjected to refinement by energy minimization through Swiss-Pdb Viewer software [15] and Ramachandran plot was obtained again for this structure using Mol Probity server (Figure1 d). As Ramachandran plot showed, 100.0% (32/32) of all residues were in allowed regions after energy minimization.

The MMP-2 catalytic domain contains three α-helices and five β-sheets arranged in a typical matrix in fold, and two zinc ions (PDB code: 1QIB) [24]. In this domain, about 17 SNP variants were detected. All of these SNPs caused mis-sense mutations (Table 3) and rs121912955variant that affects the active site of MMP-2 is associated with some clinical features (Torg Winchester syndrome) [25].

To performance docking, energy in rotational and translational degrees of freedom was minimized [26]. Binding energies calculation and complementarity scores are used for evaluation of docking [27]. The negative and low value of binding energy showed strong and most favorable binding between protein and ligand molecules [28-30]. Moreover, the complex strength is influenced by the number of H_2 bonds and electrostatic energy [31]. Value energies of MeICT-rs200271857, MeICT-rs144334568, MeICT-rs111590299, MeICT-rs200772153, MeICT-rs121908741, MeICT-rs201083413 and MeICT-rs17859943are more negative than those of other complexes. The highest total binding and electrostatic energies were seen in MeICT-rs145337551that were -677.035 and -1247.89KJ/mol. As shown, there are 4 hydrogen bonds between MeICT and MMP-2 catalytic domain and involved residues in this interaction are Phe6-Gln35, Lys14-Phe143, Lys25-Thr25 and Cys26-Asp28.

According to the total and electrostatic energies and the number of interactive residues by hydrogen bond, it was concluded that the structure of MeICT-rs200271857, MeICT-rs144334568, MeICT-rs111590299 and MeICT-rs201083413complexes are more stable. These SNPs may lead to the increase of MeICT effects on glioma cells and improve glioma treatment with MeICT. Instead, the structure of MeICT-rs147947052 is less stable than MeICT-MMP-2 catalytic domain and other complexes. This SNP can decrease the effect of MeICT on glioma cells. According to these results, diversity in effect of MeICT on glioma cells can be originated from different SNPs in thecatalytic domain of MMP-2 protein. Since MeICT have high similarity with Cltx, these SNPs may be responsible for alterations in action of Cltx and MMP-2 and cause variety in effect of this drug in treatment of the patients.

CONCLUSION

MeICT is the first chlorotoxin-like peptide isolated from an Iranian scorpion. Our study showed that the structure of this peptide is very similar with CTX and it mightbe a new agent for glioma therapy. Docking analysis demonstrated that there are 4 hydrogen bonds between MeICT and MMP-2 catalytic domain and involved residues are Phe6-Gln35, Lys14-Phe143, Lys25-Thr25 and Cys26-Asp28. In addition, we could find some SNP types that are more or less stable than MeICT-MMP-2 complex and may help predict the associated drug dosage and drug response.

ACKNOWLEDGMENTS

The authors would like to thanks Shahrekord University for their financial supports. The authors declare that there is no conflict of interests.

REFERENCES

1. DeBin J, Strichartz G. Chloride channel inhibition by the venom of the scorpion *Leiurusquinquestriatus*. Toxicon 1991;29(11):1403-8.
2. Soroceanu L, Manning TJ, Sontheimer H. Modulation of glioma cell migration and invasion using Cl− and K+ ion channel blockers. J Neurosci 1999;19(14):5942-54.
3. Ullrich N, Sontheimer H. Biophysical and pharmacological characterization of chloride currents in human astrocytoma cells. Am J Physiol Cell Physiol 1996; 270(5):C1511-C21.
4. Soroceanu L, Gillespie Y, Khazaeli M, Sontheimer H. Use of chlorotoxin for targeting of primary brain tumors. Cancer Res 1998; 58(21):4871-9.
5. Lyons SA, O'Neal J, Sontheimer H. Chlorotoxin, a scorpion-derived peptide, specifically binds to gliomas and tumors of neuroectodermal origin. Glia 2002; 39(2):162-73.
6. Wu X, Jian X, Yin B, He Z. Development of the research on the application of chlorotoxin in imaging diagnostics and targeted therapies for tumors. Membranes 2010; 1(9):10-1.
7. Deshane J, Garner CC, Sontheimer H. Chlorotoxin inhibits glioma cell invasion via matrix metalloproteinase-2. J Biol Chem 2003; 278(6):4135-44.
8. Birkedal-Hansen H. Proteolytic remodeling of extracellular matrix.Cur. Opinion Cell Bio 1995; 7(5):728-35.
9. Mamelak AN, Rosenfeld S, Bucholz R, Raubitschek A, Nabors LB, Fiveash JB, et al. Phase I single-dose study of intracavitary-administered iodine-131-TM-601 in adults with recurrent high-grade glioma. J Clin Onc 2006; 24(22):3644-50.
10. Rjeibi I, Mabrouk K, Mosrati H, Berenguer C, Mejdoub H, Villard C, et al. Purification, synthesis and characterization of AaCtx, the first chlorotoxin-like peptide from Androctonusaustralis scorpion venom. Peptides 2011; 32(4):656-63.
11. Ilkhanizade S, Ayat H, Ahadi A, Pirali K. Sequencing and comparative-bioinformatic analysis of chlorotoxin-like peptide from Iranian scorpion Mesobuthus eupeus. J SKU Med Sci2011, 13:27-36.[persian]
12. Meyer UA. Pharmacogenetics–five decades of therapeutic lessons from genetic diversity. Nat Rev Gene 2004; 5(9):669-76.
13. Drysdale CM, McGraw DW, Stack CB, Stephens JC, Judson RS, Nandabalan K, et al. Complex promoter and coding region β2-adrenergic receptor haplotypes alter receptor expression and predict in vivo responsiveness. Proc Nat Aca Sci 2000; 97(19):10483-8.
14. Ma Q, Lu AY.Pharmacogenetics, pharmacogenomics, and individualized medicine. Pharma Rev 2011; 63(2):437-59.
15. Guex N, Peitsch MC. SWISS-MODEL and the Swiss-Pdb Viewer: an environment for comparative protein modeling. Electrophoresis 1997; 18(15):2714-23.
16. Wiederstein M, Sippl MJ. ProSA-web: interactive web service for the recognition of errors in three-dimensional structures of proteins. Nuc Acids Res 2007; 35(2):W407-W10.
17. Chen VB, Arendall WB, Headd JJ, Keedy DA, Immormino RM, Kapral GJ, et al. MolProbity: all-atom structure validation for macromolecular crystallography. Acta Crystallographica Section D: Biological Crystallography 2009; 66(1):12-21.
18. Holm L, Rosenström P. Dali server: conservation mapping in 3D. Nucleic Acid Res 2010; 38(2):W545-W9.
19. Macindoe G, Mavridis L, Venkatraman V, Devignes M-D, Ritchie DW. HexServer: an FFT-based protein docking server powered by graphics processors. Nucleic Acid Res 2010: 38:445-9.
20. Andrio P, Fenollosa C, Cicin-Sain D, Orozco M, Gelpí JL. MDWeb and MDMoby: an integrated web-based platform for molecular dynamics simulations. Bioinfo 2012; 28(9):1278-9.
21. Lippens G, Najib J, Wodak S, Tartar A. NMR sequential assignments and solution structure of chlorotoxin, a small scorpion toxin that blocks chloride channels. Biochem 1995; 34(1):13-21.
22. Lomize A, Maĭorov V, Arsen'ev A. Determination of the spatial structure of insectotoxin 15A from Buthuserpeus by (1) H-NMR spectroscopy data. Bio Ska 1991; 17(12):1613-32.
23. Butt AM, Batool M, Tong Y. Homology modeling, comparative genomics and functional annotation of Mycoplasma genitalium hypothetical protein MG_237. Bioinfo 2011; 7(6):299-303.
24. Falconi M, Altobelli G, Iovino MC, Politi V, Desideri A. Molecular dynamics simulation of matrix metalloproteinase 2: fluctuations and time evolution of recognition pockets. J Computer-Aided Molec Design 2003; 17(12):837-48.
25. Zankl A, Bonafe L, Calcaterra V, Di Rocco M, Superti-Furga A. Winchester syndrome caused by a homozygous mutation affecting the active site of matrix metalloproteinase 2. Clinical Gene 2005; 67(3):261-6.
26. Zacharias M. Protein–protein docking with a reduced protein model accounting for side-chain flexibility. Protein Sci 2003; 12(6):1271-82.
27. Wei BQ, Weaver LH, Ferrari AM, Matthews BW, Shoichet BK. Testing a flexible-receptor

docking algorithm in a model binding site. J Mol Bio 2004; 337(5):1161-82.
28. Yadav BS, Tripathi V, Kumar A, Khan MF, Barate A, Kumar A, et al. Molecular modeling and docking characterization of Dectin-1 (PAMP) receptor of Bubalusbubalis. Exp Mol Pathol 2012;92(1):7-12.
29. Chandramohan D, Muthukrishnakumar K, Chinnapparaj C, Rajadurai M. Insilico screening of nnrti as potential targets for tumor control. Int J Engin Sci Tech2010; 2:4229-38.
30. Bikádi Z, Hazai E, Zsila F, Lockwood SF. Molecular modeling of non-covalent binding of homochiral (3S, 3′ S)-astaxanthin to matrix metalloproteinase-13 (MMP-13). Bioorganic Med Chem 2006; 14(16):5451-8.
31. Fu Y-J, An N, Chan K-G, Wu Y-B, Zheng S-H, Liang A-H. A model of BmK CT in inhibiting glioma cell migration via matrix metalloproteinase-2 from experimental and molecular dynamics simulation study. Biotech Let2011;33(7):1309-.