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ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal

www.orientjchem.org

ISSN: 0970-020 X
CODEN: OJCHEG
2023, Vol. 39, No.(3):
Pg. 581-591

Investigating the Binding Efficacy of Snake Venom Proteins as GLP-1 Analogs for *Diabetes mellitus* Management: An *In silico* Study

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http://dx.doi.org/10.13005/ojc/390306

(Received: April 03, 2023; Accepted: May 23, 2023)

ABSTRACT

Objective: *Diabetes mellitus* (DM) is a metabolic condition defined by hyperglycemia driven by insulin deficiency or decreased insulin activity. GLP-1, a gut enzyme, stimulates insulin production and reduces hepatic glucose synthesis to regulate diabetes. GLP-1 agonists enhance insulin sensitivity and decrease blood glucose to relieve symptoms of DM. These medications represent a novel paradigm to manage diabetes as they improve glycaemic control in type 2 diabetic patients. Snake venom proteins have been investigated as a potential medicinal strategy for diabetes treatment. These proteins contain a multitude of bioactive constituents, such as insulinotropic cytotoxins, which have been found to influence insulin secretion and glucose homeostasis.Methods: In the present study, the snake venom proteins long neurotoxin 1 Cytotoxin 7, Cytotoxin 2a, and Cytotoxin 10 were modeled and their therapeutic efficacy as GLP-1 analogs was determined by employing molecular docking techniques. The binding of snake venom protein towards GLP-1 receptors was compared against the positive controls (Exenatide, Liraglutide, Semaglutide, and Lixisenatide). Results: The results demonstrated that the cytotoxins (Cytotoxin 2a, Cytotoxin 7, and Cytotoxin 10) exhibited comparable binding with the positive controls and majorly interacted with the hydrophobic amino acids in the binding pocket of the GLP-1 receptor. The modeled snake venom toxins demonstrated beneficial physicochemical properties and advocated them to be a novel contender for the development of GLP-1 analogs. Conclusion: Despite its beneficial outcomes, the utilization of snake venom proteins as a therapeutic agent for diabetes is still in its initial stages, and additional research is required to assess their effectiveness and safety in patients.

Keywords: Snake venom proteins, Cytotoxins, Neurotoxins, *Diabetes mellitus*, GLP-1.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic illness characterized by increased blood glucose levels and a wide range of comorbidities[1]. It primarily manifests in two forms: type 1 and type

2 diabetes. In both cases, there are abnormalities in insulin signaling and glucose regulation. Type 1 diabetes arises from the pancreas's inability to synthesize adequate insulin to control glucose levels, whereas type 2 diabetes occurs when cells become resistant to the actions of insulin. Glucagon-like peptide-1 (GLP-1) is a hormone secreted by intestinal L-cells in response to food consumption. It plays a vital role in glucose management and exhibits various physiological functions, including the regulation of insulin and glucagon secretion, as well as the slowing of gastric emptying[2,3]. These actions contribute to the maintenance of glucose levels and the enhancement of insulin sensitivity. GLP-1 exerts its effects on glucose regulation by stimulating insulin production from the pancreas[4-5]. It achieves this by binding to GLP-1 receptors on beta cells, which results in an increase in intracellular cyclic adenosine monophosphate (cAMP) levels. The elevation in camp activates the insulin secretion pathway, leading to the release of insulin into the bloodstream[6]. Increased insulin secretion helps lower blood glucose levels and improves the uptake of glucose by cells. Consequently, this controlled and sustained response to glucose following meals facilitates the regulation of blood sugar levels. Beyond its insulinotropic effects, GLP-1 also inhibits the production of glucagon from pancreatic alpha cells. Glucagon is a hormone that stimulates the liver to produce glucose. By suppressing glucagon secretion, GLP-1 further contributes to the reduction of blood sugar levels. This dual action of GLP-1, stimulating insulin release and inhibiting glucagon secretion, helps maintain glucose homeostasis in the body. Glp-1 plays a role in delaying gastric emptying. By slowing down the rate at which the stomach empties its contents, GLP-1 ensures a more gradual increase in blood glucose levels after a meal[7-8]. This delayed gastric emptying allows for better control of postprandial glucose levels and helps prevent sudden spikes in blood sugar. By modulating the rate of nutrient absorption, GLP-1 aids in achieving more stable and controlled blood glucose responses[9]. The involvement of GLP-1 in glucose management is crucial. Its stimulation of insulin secretion, inhibition of glucagon production, and delay in gastric emptying collectively contribute to the regulation of blood glucose levels. Medications known as GLP-1 receptor agonists, which mimic or enhance the effects of GLP-1, have been developed as an effective treatment option for diabetes. These medications improve blood glucose control, increase insulin sensitivity, and reduce the risk of complications associated with diabetes.[10-13].

Glp-1 also has a multitude of other significant benefits in dm management. Glp-1, for instance, has been demonstrated to reduce blood pressure, decrease body mass, and improve insulin sensitivity[14]. The propensity of GLP-1 to regulate glucagon release, its insulinotropic actions, and its corresponding impact on the hypothalamus, where it stimulates pathways that govern energy balance and food intake, are all perceived to contribute to these ramifications[15]. Several GLP-1-based medicines for type 2 diabetes mellitus (T2DM) have been developed including, GLP-1 receptor agonists and dipeptidyl-peptidase 4 (DPP-4) inhibitors, which augments endogenous GLP-1 bioavailability by blocking its disintegration in individuals with T2DM which subsequently lower HBA1C levels, and minimizes the risk of cardiovascular events[16-20]. They work by prolonging the activity of endogenous GLP-1, resulting in better glucose control and insulin sensitivity. DPP-4 inhibitors enhance the quantities of active GLP-1 in circulation by preventing GLP-1 breakdown, resulting in better insulin production and glucose management[2]. Traditionally, GLP-1 receptor agonists, such as exenatide[21-23], lixisenatide[24], semaglutide[25,26], liraglutide[27], etc. Are administered to emulate the properties of GLP-1 by binding to and activating GLP-1 receptors. They function by promoting insulin production, blocking glucagon release, and delaying gastric emptying, which leads to improved glucose regulation and insulin responsiveness[28].

Among the prevalent therapies, administration of exogenous insulin is associated with several limitations including, risk of hypoglycemia, dose optimization, insulin resistance, scar development, and requirement of multiple doses which havdirectly influences efficacy and safety. These limitations emphasize the necessity of complementary therapies that can enhance glycaemic control and the quality of life for individuals with DM. To effectiv there is significant interest in researching alternative medicines such as oral drugs, non-insulin injectables, and glucose-responsive insulin to effectively treat dmernative therapies intend to grant more practical and efficient therapeutic interventions whilst reducing the probability of long-term consequences related to insulin therapy[29].

Currently, the pharmaceutical efficacy of venom-derived therapeutics is apparent as there are notable fda-approved while a multitude of venom-derived products is under clinical trials

to establish their therapeutic efficacy. Proteins and peptides constitute the majority of the dry weight of snake venom and are of particular importance for biomedical studies. Snake venom Contains enzymatic and non-enzymatic proteins and peptides that are classified into various groups depending on their structural architecture and function[30]. Representatives of a single-family possess considerable resemblance in their primary, secondary, and tertiary architectures, despite having diverse pharmacological functionalities and bioactivities. The application of snake venom in numerous pathophysiological circumstances has been referenced in ayurveda, homeopathy, and traditional medicine. Snake venom comprises a variety of neurotoxins, cardiotoxins, cytotoxins, nerve growth factors, lectins, disintegrins, hemorrhages, and enzymes[31,32]. These proteins can be commonly used to address thrombosis, rheumatism, carcinoma, diabetes, and other ailments in addition to inflicting death. When compared to synthetically synthetic molecules, the effectiveness of venom-derived substances can be attributed to their higher bioactivity, selectivity, and stability[33].

Glp-1 is a propitious target for the management of dm because it portrays an important function in the glucose metabolism in the body. Peptide-based medications offer an optimistic strategy for increasing GLP-1 secretion in diabetics and represent a novel therapeutic and management option. Snake venom proteins have been investigated for their putative relevance in the management of diabetes and its comorbidities and the promising role of exendin-4 in mimicking naturally occurring GLP-1 has motivated the present research to model comparable peptides that could help alleviate DM.

Methodology

Ligand preparation

The hypoglycaemic GLP-1 analogs belonging to the insulin secretagogues drug class were appraised as positive control in the present study. The drugs including exenatide (PubChem CID: 45588096), liraglutide (pubchem CID: 16134956), semaglutide (PubChem CID: 56843331), and lixisenatide (PubChem CID: 90472060) were downloaded from the pubchem (https://pubchem.ncbi.nlm.nih.gov/) database as the 2D SDF files[34]. The structure of the positive control was preliminarily analyzed and prepared through protonation in marvin's sketch. The mikowski matrix was implemented to MMFF94 energy minimization of the ligand using divide and conquer algorithm[35].

Retrieval of protein structures

Comprehending the structural architecture of the proteins is crucial in determining the enzymes' biochemical properties and cellular functions. In the present study, the Cytotoxins and neurotoxins with less than 100 amino acids were selected to build the GLP-1 analogs. The fasta sequence of the venom toxins from *Naja naja* (indian cobra) including long neurotoxin 1 (UniProt ID:P25668), cytotoxin 7 (UniProt ID:P86382), cytotoxin 2a (UniProt ID: P86538), and cytotoxin 10 (UniProt ID: P86541) was retrieved from the UniProt[36] (https://www.UniProt.Org/) for homology modeling as the 3D structures were unavailable in PDB. The 3D structure of the GLP-1 protein (PDB ID: 5vew) was retrieved from the PDB databank (https://www.rcsb.org/). The structure was resolved at 2.70 Å using the X-ray diffraction technique[37].

Homology modeling

Homology modeling enables the construction of stable 3D architecture for the protein by identifying suitable templates to model the structure. In the present study, swiss model (https://swissmodel.expasy.org/interactive)[38] was used to construct the 3D structures of the venom protein wherein, 6zfm.1.A (alpha-cobra toxin), 4om4.1.A (cytotoxin 2), 1h0j.2.A (cardiotoxin 3), and 2bhi.2.A (cardiotoxin A3) were taken as a template to construct the 3D structures of long neurotoxin 1, cytotoxin 2a, cytotoxin 7 and cytotoxin 10 respectively. All the structures demonstrated more than 80% structural similarity with that of the template. The modeled structures were downloaded in PDB format and the quality of the structures was analyzed based on GMQE, qmeandisco, and z score parameters.

Structural analysis of the modeled peptides

The physicochemical properties of the modeled long neurotoxin 1, cytotoxin 2a, cytotoxin 7, and cytotoxin 10 were examined in the ProtParam webserver (https://web.expasy.org/protparam/)[39]. The physicochemical variables like hydropathicity (GRAVY), molecular weight, amino acids, and aliphatic index which determine the protein structure and stability were computed using the webserver. The GRAVY score is computed by adding up the hydropathy values of all of the amino acids, dividing that total by the number of residues in the sequence, and then rounding up to the nearest whole number.

Molecular docking and visualization

The modeled proteins long neurotoxin 1, cytotoxin 2a, cytotoxin 7, and cytotoxin 10 and the

GLP-1 protein (PDB id: 5vew) were prepared before docking in ds biovia discovery studio[40]. The non-structural water molecules and unwanted hetero atoms were eliminated from the protein structure this was followed by the addition of polar hydrogen atoms. The prepared structures were saved in PDB format for further investigations. Molecular docking is a computational method used to predict the binding mode of a small molecule ligand to a target protein. HDOCK (http://hdock.phys.hust.edu.cn/) is a powerful tool for the molecular docking of proteins, allowing researchers to predict the binding modes of ligands to proteins, and providing crucial information for drug discovery and design. HDOCK is a high-performance molecular docking program that utilizes a hybrid molecular dynamics and genetic algorithm approach to predict the binding of a ligand to its target protein. The program starts by generating a pool of initial ligand conformations and using molecular dynamics simulations to explore their binding energies and stabilities. The genetic algorithm then takes over, using this information to evolve the best-performing ligand conformations and refine their positions. Finally, the final docking results are ranked based on their binding energies and other relevant parameters[41]. The best models were downloaded based on the docking score and the structures were visualized for various molecular interactions at the binding site of the receptor protein using ds biovia discovery studio[42].

Molecular dynamic simulation

From the results of molecular docking, it is evident the protein P86538 demonstrated better binding among the venom proteins and had comparable results with the positive control. Therefore the docked complex of P86538-GLP-1 was subjected to molecular dynamic simulation (MDS) to examine the stability of the complex. The mds was performed by employing the GROMOS96 54a7[43] force field with the GROMACS package[44] in the linux operating system with graphical interference with the default variables. The protein topology files were prepared and the simulation was carried out in a cubic box. The complex was subjected to energy minimization followed by equilibration by employing the steepest descent approach. In the initial phase of the heating period, the system was maintained at 300 K in the NVT ensemble. The complex was then constrained for 5 NS while gradually allowing the solvent to settle around it, followed by another 10 ND of NPT equilibration by gradually removing the restraints. A berendsen barostat was used to keep the pressure constant while maintaining an average temperature and pressure level[45,46]. The equilibrated systems were then treated to 100 NS of mmpbsa for the last 50 NS while maintaining a pressure of 1 bar and a temperature of 300 K. The md simulation was used to determine the standard fluctuations in the complex's RMSD, RMSF (root mean square fluctuation), gyration radius (RG), sasa (solvent accessible surface area), and hydrogen bond count.

RESULTS

Ligand retrieval

The drugs administered as GLP-1 agonists including, exenatide (PubChem CID: 45588096), liraglutide (PubChem CID: 16134956), semaglutide (PubChem CID: 56843331) and lixisenatide (PubChem CID: 90472060) were taken as positive controls in the present study. The sdf structures of the approved drugs were downloaded from the pdb database and prepared in the marvin sketch. These drugs belong to the drug class delineated as drugs known as glucagon-like peptide-1 (GLP-1) receptor agonists, which mimic the action of naturally occurring hormones called incretins in the body. In individuals with type 2 diabetes, the body does not produce enough insulin or is unable to use insulin effectively, leading to high blood sugar levels. These drugs work by increasing the release of insulin from the pancreas and reducing the production of glucose by the liver. It also suppresses appetite, leading to a reduction in food intake and weight loss, which can be beneficial in managing T2DM. These drugs are generally administered as a subcutaneous injection and are typically used in combination with other diabetes medications, such as metformin or sulfonylurea.

Homology modeling

The 3D structures of the venom protein, P25668, P86538, P86382 and P86541 were modeled using 6zfm.1.A (alpha-cobratoxin), 4om4.1.A (cytotoxin 2), 1h0j.2.A (cardiotoxin 3), and 2bhi.2.A (cardiotoxin A3) respectively as a template. The modeled structure of long neurotoxin 1 (uniprot ID: P25668) exhibited a molprobity score of 1.46, With 94.24% of amino acids in the ramachandran-favoured region (Fig. 1). The modeled structure of cytotoxin 2a (UniProt ID: p86538) exhibited a molprobity score of 1.99, With 98.28% of amino acids in the ramachandran-favoured region (Fig. 2). The modeled structure of cytotoxin 7 (UniProt ID: P86382) exhibited a molprobity score of 1.79, With 93.10% of amino acids in the ramachandran-favoured region (Fig. 3). The modeled structure of cytotoxin 10 (UniProt ID: P86541) exhibited a molprobity score of 2.41, With 96.55% of amino acids in the ramachandran-favoured region (Figure 4).

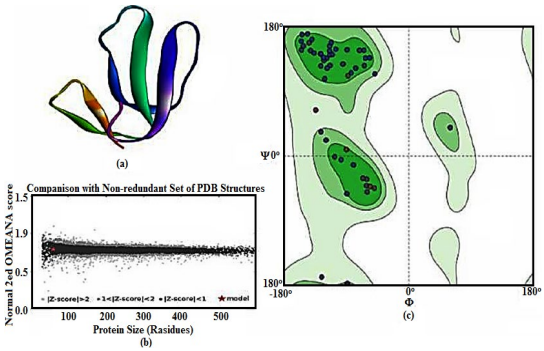

Fig. 1. 3D structure of long neurotoxin 1 (P25668), (a) The protein has 71 amino acids. The QMeanDisCo Global values for the protein were 0.69± 0.05, (b)The modeled protein exhibited 94.24% of amino acids in the Ramachandran-favoured region with 3.46% rotamer outliners, (c) The Z-score for the modeled protein was less than 1 indicating the modeled structure was close to the native structure

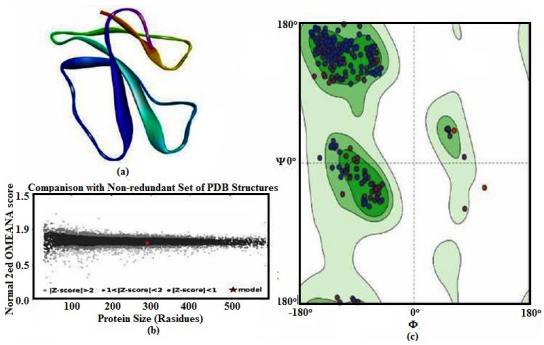

Fig. 2. 3D structure of Cytotoxin 2a (P86538), (a) The protein has 60 amino acids. The QMeanDisCo Global values for the protein were 0.79± 0.05(b)The modeled protein exhibited 98.28% of amino acids in the Ramachandran favored region with 14.39% rotamer outliners, (c) The Z-score for the modeled protein was less than 1 indicating the modeled structure was close to the native structure

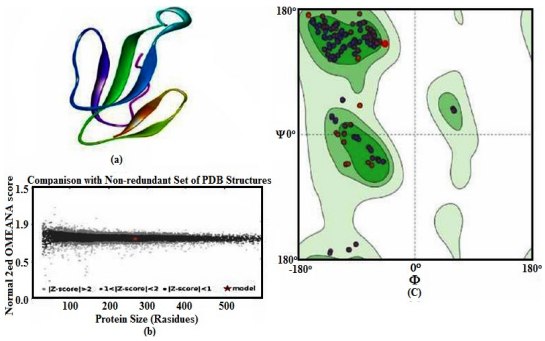

Fig. 3. 3D structure of Cytotoxin 7 (P86382), (a) The protein has 60 amino acids. The QMeanDisCo Global values for the protein were 0.78± 0.11, (b) The modeled protein exhibited 93.10% of amino acids in the Ramachandran-favoured region with 5.36% rotamer outliners, (c) The Z-score for the modeled protein was less than 1 indicating the modeled structure was close to the native structure

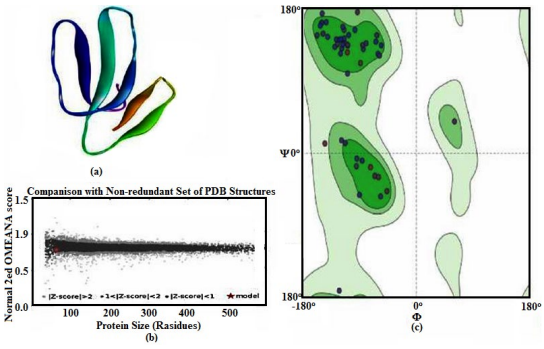

Fig. 4. 3D structure of Cytotoxin 10 (P86541), (a) The protein has 60 amino acids. The QMeanDisCo Global values for the protein were 0.77± 0.11, (b) The modeled protein exhibited 96.55% of amino acids in the Ramachandran favored region with 5.36% rotamer outliners, (c) The Z-score for the modeled protein was less than 1 indicating the modeled structure was close to the native structure

Structural analysis of modeled proteins

Assessing the physicochemical parameters is critical in determining the efficacy and bioavailability of the drugs. The hydropathicity (GRAVY) of a peptide-based drug can greatly affect its efficacy and bioavailability[47]. Hydrophobic peptides tend to be more effective when delivered through non-oral routes as they tend to aggregate and form insoluble structures, making it difficult for them to dissolve and be absorbed in the gut when taken orally. While hydrophilic peptides tend to be more easily absorbed when taken orally but are more susceptible to degradation and clearance. The optimal hydropathy of a peptide-based drug will depend on the desired route of administration and desired efficacy and bioavailability[48].

The aliphatic index of a peptide can affect its efficacy as a drug by influencing its hydrophobic character, stability, and bioavailability. Peptides with a high aliphatic index tend to be more hydrophobic and resistant to degradation but may have limited oral bioavailability, while peptides with a low aliphatic index tend to be more hydrophilic and have improved oral bioavailability but may be more susceptible to degradation and rapid clearance from the body. The optimal aliphatic index for a peptide-based drug will depend on the desired route of administration and desired efficacy and bioavailability[49].

The half-life of a peptide-based drug can affect its efficacy by influencing the duration and stability of its effects in the body. Peptides with a long half-life tend to provide a sustained and stable effect, but may be more susceptible to accumulation and

adverse effects, while peptides with a short half-life tend to provide a more rapid and transient effect, but may have a higher risk of rapid clearance and limited efficacy. The optimal half-life for a peptide-based drug will depend on the desired duration and stability of its effects on the body and the risk of adverse effects. The physicochemical properties of the modeled proteins are documented in Table 1.

Table 1: Physicochemical properties of the modeled venom proteins

Protein no	Acids amino	Mol. Wt.	GRAVY score	Aliphatic index	Estimated half-life
P25668	71	7847.01	-0.327	52.11	20 h (*In vitro*) 30 min(*In vitro*, yeast)
P86538	60	6711.08	-0.025	84.33	5.5 h (*In vitro*) 3 min(*In vitro*, yeast)
P86382	60	6792.20	-0.192	79.50	5.5 h (*In vitro*) 3 min(*In vitro*, yeast)
P86541	60	6764.27	0.068	82.67	5.5 h (*In vitro*) 3 min(*In vitro*, yeast)

Molecular docking

The molecular docking analysis was performed to ascertain the binding of the modeled GLP-1 analog (venom proteins) in the binding pocket of GLP-1 proteins. From the results of molecular docking, it is evident that positive controls (exenatide, liraglutide, semaglutide, and lixisenatide) demonstrated significantly better binding than the modeled proteins (P25668, P86541, P86538, and P86382) (Table 2). Amongst the modeled proteins P86358, P86541, and P86382 displayed comparable binding with the positive controls.

Table 2: Molecular docking score of GLP-1 against positive control and venom proteins

Receptor	Ligand	Docking Score	Average RMSD
	P25668	-283.3	62.75
	P86541	-319.74	35.56
	P86538	-329	67.17
5VEW	P86382	-307.66	74.94
	Exenatide	-424.47	78.52
	Liraglutide	-432.1	39.84
	Semaglutide	-382.33	61.17
	Lixisenatide	-415.5	86.47

Visualization

From the docking analysis (Table 2) it is evident that the positive controls exenatide and liraglutide exhibited better docking scores and the venom proteins P86541 (cytotoxin 2a) and P86538 (cytotoxin 7) had comparable results with that of the positive controls. These associations were visualized at the molecular levels to identify the interactions at the binding pocket. It was noticed that the protein P86541 was predominantly interacting with hydrophobic amino acids like LEU, ALA, and PHE (Fig. 5) while the protein P86538 was interacting with ILE, VAL, LEU, ALA, and PHE (Figure 6).

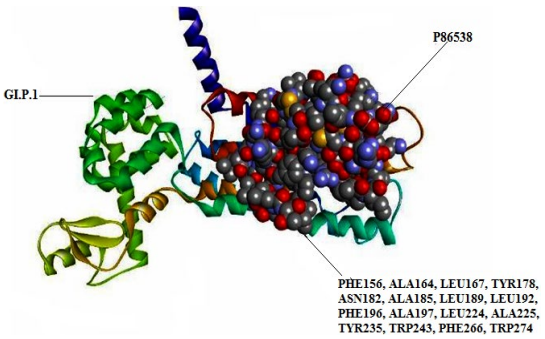

Fig. 5. Molecular interactions of P86541with GLP-1 P86541 majorly interacts with LEU and ALA amino acids in the binding pocket of GLP-1

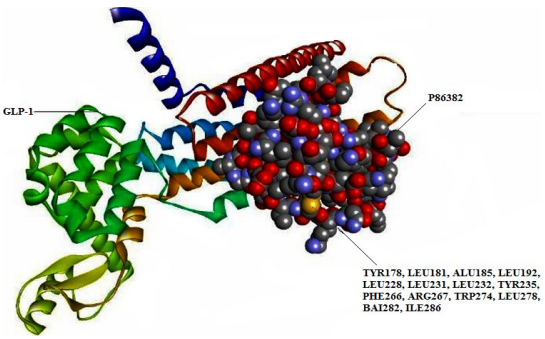

Fig. 6. Molecular interactions of P86538with GLP-1 P86538 majorly interacts with LEU and ALA amino acids in the binding pocket of GLP-1

Molecular dynamic simulation

The molecular dynamic stimulation was performed to the P86538-GLP-1 complex to demonstrate its stability. The rmsd graph is a plot of RMSD values over time, which provides insights into the stability and conformational changes of the simulated system. For the P86538- GLP-1 complex it was noticed that the system remained stable from ~35ns to ~65 NS, following a minimal transition the system remained stable from ~70 NS to 100 NS at 0.5 RMSD (Fig. 7). The rmsf graph is used to identify the flexible regions of the protein which are important

for function or interaction with other molecules. The peaks in the RMSF graphs are representative of the region that are highly flexible. In general, the secondary structure elements like loops and terminals are highly flexible and exhibit high RMSF, conversely, helices and beta sheets are more rigid (Fig. 8). The compactness of the macromolecule ID determined with radius of gyration (RG) plots, which represents the average distance of all the atoms in the molecule from its centre mass. It was observed that the system remained relatively constant over the period of simulation suggesting that the protein is maintaining its overall structure and Shape (Fig. 9). The sasa values remained relatively constant from ~30 NS to ~100 NS indicating that the molecule was stable during the simulation (Figure 10).

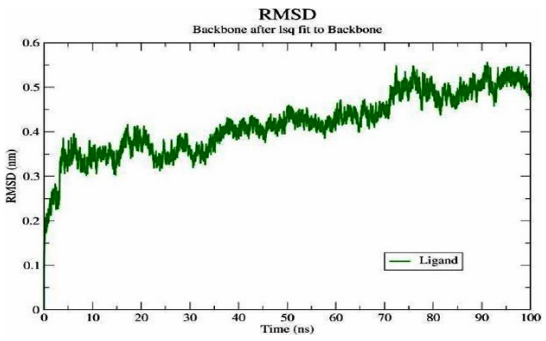

Fig. 7. Root Mean Square Deviation

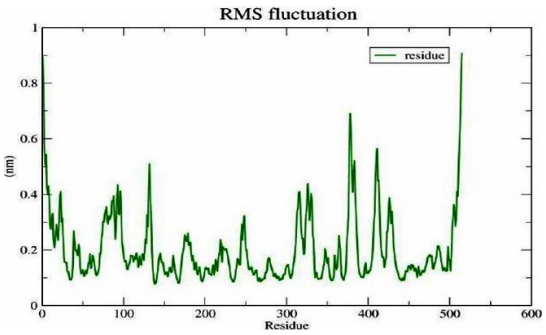

Fig. 8. Root Mean Square Fluctuation

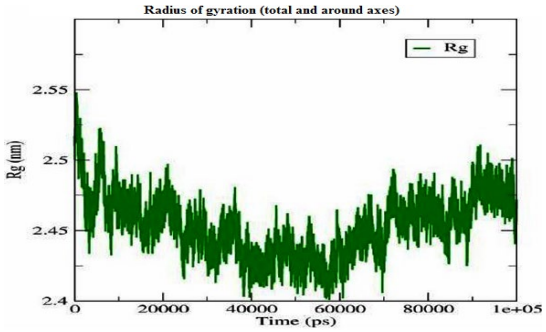

Fig. 9. Radius of Gyration

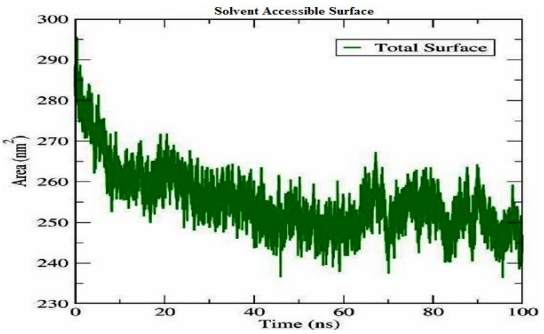

Fig. 10. Solvent Accessible Surface Area

DISCUSSION

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels and a wide range of associated complications. Glp-1 is an interesting target for the management of dm because it plays an important function in the control of blood sugar levels in the body. Glp-1 improves glucose management and lowers the risk of related problems by influencing insulin secretion, glucagon secretion, and stomach emptying. Peptide-based medications offer a promising strategy for increase GLP-1 secretion in diabetics and represent a novel therapeutic and management option for this complex and prevalent condition. The potential significance of snake venom proteins in the management of diabetes and related comorbidities, as well as the promising role of exendin-4 in replicating naturally occurring GLP-1 has inspired the current study to create comparable peptides that could aid in the treatment of diabetes. Insulin therapy is a standard treatment for diabetics that involves the administration of exogenous insulin to assist regulate blood glucose levels. While insulin therapy can be beneficial in regulating glucose levels, it has various limitations that can impair its efficacy and safety. Dose dependence, resistance development, and the risk of hypoglycemia have prompted researchers to look for alternate treatments.

Nature has long been a fascinating source for pharmacological drug design. Insects and reptiles are significant repositories for discovering substances with promising therapeutic benefits[50]. Several bioactive proteins and peptides have been isolated from the venom of numerous serpents, beetles, millipedes, lizards, scorpions, mollusks, etc. Snake venom proteins are the subject of current research as several pharmaceutically valuable

proteins have already been identified and described from snake venoms[51,52].

Peptides are an intriguing element of snake venom. Although otherwise deadly, some venom proteins can be employed directly as medications or as drug candidates when administered in the appropriate dosage. These peptides are extremely valuable due to their diverse and unique therapeutic potential, as well as their binding ability and specificity toward their targets. Snake venom toxins, like alpha-neurotoxins, have proven to be incredibly valuable in evaluating the composition and function of receptor proteins. Snake venom proteins are mainly stable molecules that can withstand the proteolytic conditions of the venomous glands. Furthermore, the innate stability of these proteins enables them to reach their target receptors within their prey.

Snake venom cytotoxins are attracting attention as possible therapeutic agents because of their unique properties and mechanisms of action. Originally developed to immobilize prey and defend against predators, these cytotoxic proteins found in snake venom can also have therapeutic effects in certain circumstances. Promising results have been shown in the treatment of cardiovascular diseases, where snake venom cytotoxins have potent vasodilatory and anti-inflammatory effects, making them valuable for managing hypertension, heart failure, and angina. Additionally, some cytotoxins have anticoagulant properties, making them useful for preventing blood clots and treating thromboembolic disorders. Furthermore, snake venom cytotoxins have potent analgesic effects and could be promising candidates for managing conditions such as chronic pain, neuropathic pain, and diabetes. The snake venom neurotoxins are beneficial in managing neurological disorders such as parkinson's and alzheimer's diseases, epilepsy, stroke, and traumatic brain injury. Snake venom neurotoxins also have potent analgesic effects, and they are being investigated for their potential role in drug development. The modeled venom proteins have favorable physicochemical properties, making them promising contenders for the development of insulinotropic cytotoxin and neurotoxin-based drug candidates that could mimic GLP-1. This area of investigation is ongoing, and scientists are exploring the potential of snake venom proteins to improve glycemic control and offer new hope to patients living with diabetes.

CONCLUSION

One of the key hormones involved in glucose regulation is GLP-1 which is indispensable for insulin secretion, inhibition of glucagon secretion and slowing of gastric emptying, which help to regulate glucose levels and improve insulin sensitivity. These actions help to regulate glucose levels and improve insulin sensitivity, making GLP-1 an important target for the treatment of diabetes. GLP-1-based therapies have provided a new tool for the management of type 2 diabetes, but more research is needed to fully understand their mechanisms of action, safety, and efficacy, particularly in populations with comorbidities such as cardiovascular disease and obesity. Snake venom cytotoxins have garnered attention as potential therapeutic agents due to their unique properties and mechanisms of action. In the present study, the snake venom cytotoxins (cytotoxin 2a, cytotoxin 7, and cytotoxin 10) demonstrated comparable results with the positive controls. It is crucial to recognize that while the therapeutic potential of snake venom cytotoxins is intriguing, more research is necessary to fully understand their mechanism of action and safety profile. While some cytotoxins have demonstrated promise in preclinical studies, it is still a long way from being considered a viable therapy for any condition. Further research is needed to determine the safety and efficacy of snake venom cytotoxins and to develop appropriate dosing regimens and delivery methods.

ACKNOWLEDGEMENT

We thank bionome (www.Bionome.In) for providing the bioinformatics analysis.

Conflict of interest

The authors declare no conflict of interest.

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