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Anticipate of Three Dimensional Model of, Exendin-4 Protein of *Heloderma suspectum* Venom

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Abstract: The present study undertaken to envisage the three dimensional structure of exendin-4 protein of Gila Monster (Heloderma suspectum) venom was recognized from structural database using homology modeling or comparative modeling approach. Based on the knowledge of the template, a three-dimensional model was predicted and processed in to energy minimization, Ramachandran plot analysis, quality assessment and finally deposited into Protein Model Database. Exendin-4 is a novel peptide from Gila Monster (Heloderma suspectum) venom which is 53% homologous with GLP-1. Only GLP-1 causes insulin secretion in the diabetic state.
Key words: Heloderma suspectum, Glucagon-like peptide-1, Exenatide, Exendin-4.

Introduction:

The Gila Monster venom contains the drug that may be able to use to regulate blood glucose. It might seem strange that a useful drug could come from Gila Monster venom[4]. Exendin-4 is a novel peptide from Gila Monster (*Heloderma suspectum)* venom which is 53% homologous with Glucagon-like peptide-1 (GLP-1). Only GLP-1 causes insulin secretion in the diabetic state; however; GLP-1 itself is ineffective as a clinical treatment for diabetes as it has a very short half-life in vivo. Exenatide (a synthetic version of exendin-4) bears a 50% amino acid homology to GLP-1 and it has a longer half-life in vivo. Thus, it was tested for its ability to stimulate insulin secretion and lower blood glucose in mammals and was found to be effective in the diabetic state. In studies on rodents it has also been shown to increase the number of beta cells in the pancreas. Glucagon-like peptide-1 (GLP-1) is derived from the transcription product of the proglucagon gene. The major source of GLP-1 in the body is the intestinal L cell that secretes GLP-1 as a gut hormone. It is a potent antihyperglycemic hormone, inducing glucose-dependent stimulation of insulin secretion while suppressing glucagon secretion[3].

In this study, our intent was to derive a model of the tertiary structure of exendin-4 by using multiple templates and a model evaluation through a comparative modelling approach.

Materials and Methods:

Retrieval of Exendin-4 Sequence:

The protein sequence of exendin-4 was retrieved from the NCBI (http://www.ncbi.nlm.nih.gov/) and taken as target sequence. It was predetermined that the three-dimensional structure of this protein was not available in any three-dimensional structural databases. Hence,

the current study of developing the three-dimensional structure of this protein was undertaken.

Selection of Structural Templates:
An attempt was made to find a appropriate structural homolog or template for the modelling of this protein by blast[1] search and it used Protein Data Bank[2]as reference data base for identify the closely related sequences. But there were no suitable template founded through the blast search. So the multiple templates (2 templates) were selected to model exendin-4 protein. These two templates were 1JRJ and 2DBI.

Alignment of structural Templates:
Sequence alignment was performed for these three selected sequences by using salign module in MODELLER 9V2. With the support of this module these three templates were aligned.

Target – Templates Alignment:
The protein sequence of Exendin-4 was aligned with its analogous templates by using align-2D _mult module in MODELLER 9V2[5] ,which required some files such as a file containing target sequence in PIR format and an another files containing the aligned structural template which was created by salign module[10] . This stride is important to recognize the common conserved residues or active residues present in both the sequences.

Model Building:
MODELLER 9V2 was used to envisage the three-dimensional arrangement of exendin-4 protein using model_mult.py based on satisfaction of spatial restraints[6]. It is a python script, used to envisage the three dimensional model from multiple templates. The restraints include distance and dihedral angles for the backbone and side chains[11]. The values of DOPE score for five models are -4069.4868,-4058.3085,-4253.93066,-4351.4229 and -4269.2345. The fourth model was chosen due to lowest DOPE score value (Figure1).

Model Evaluation:
Superior model was subjected to a sequence of tests for testing its internal constancy along with trustworthiness. Backbone conformation of the refined model was assessed by the assessment of the Psi/Phi Ramachandran plot obtained from VADAR server and ProSA web server which are the protein structure validation web server.

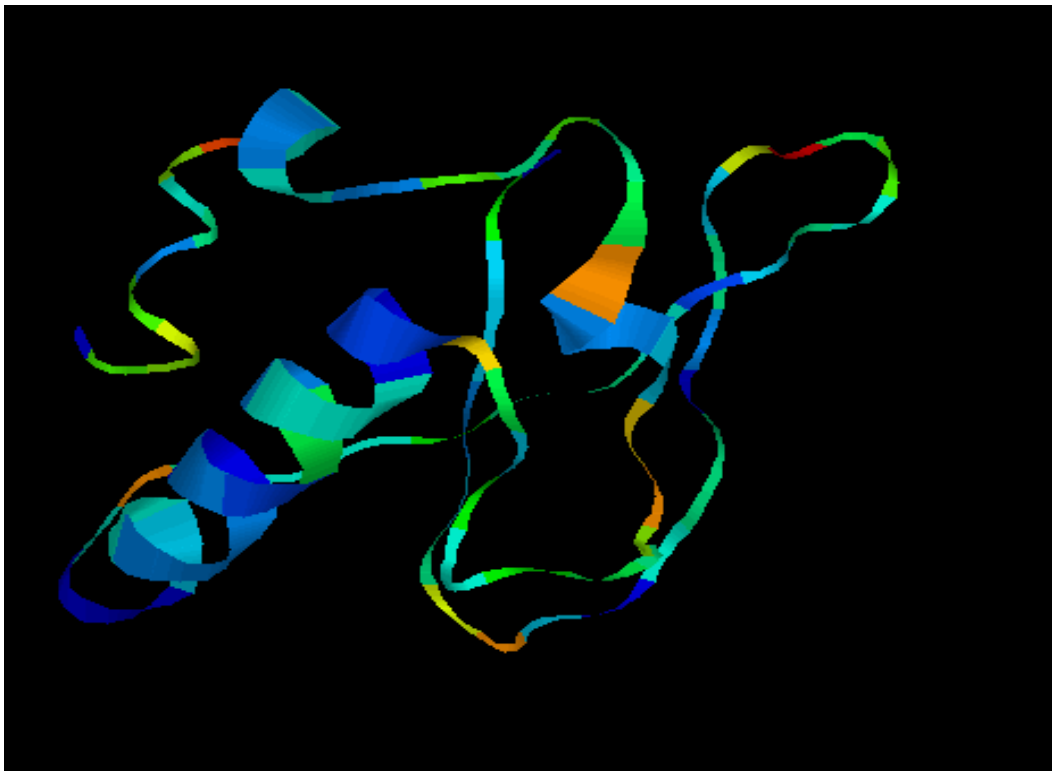

Figure: 1- Anticipate model of exendin-4 protein.

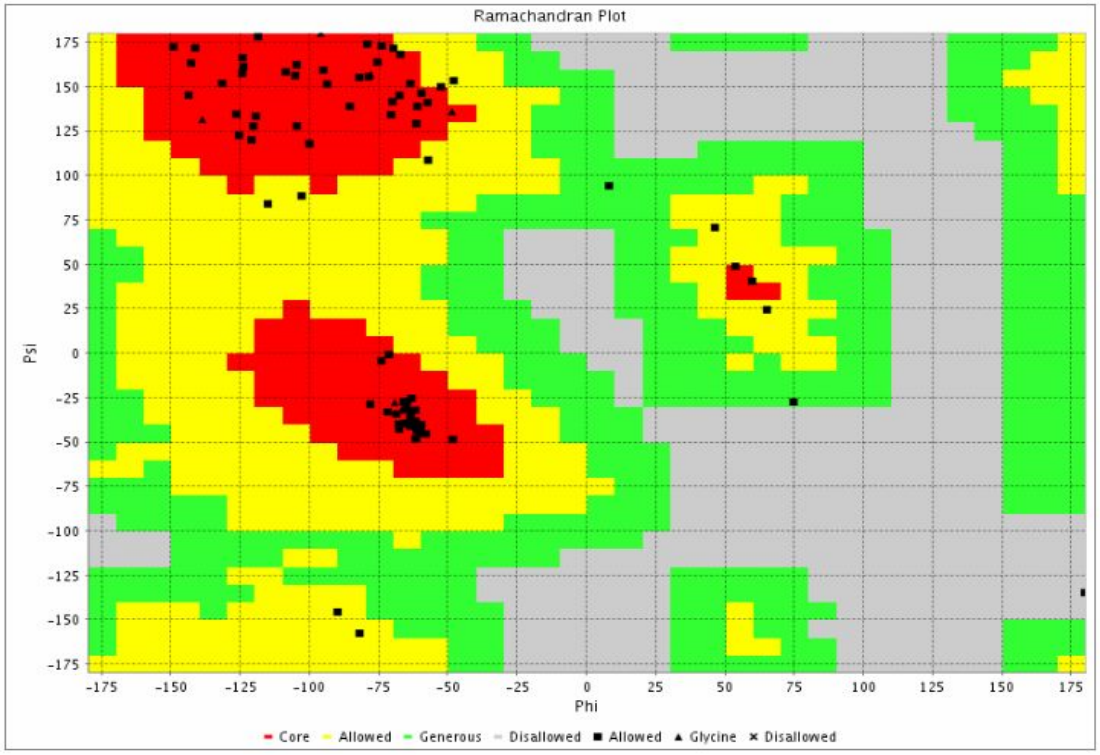

Figure: 2- Protien Structure Quality By Using Vadar Server.

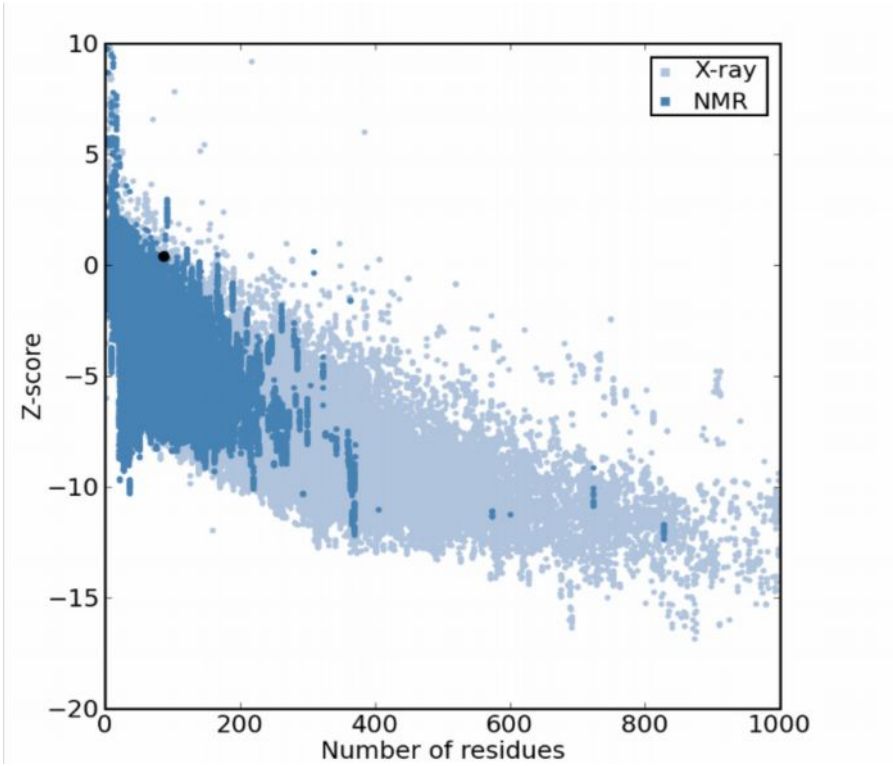

Figure: 3- Protein Structure Quality By Using Prosa Server.

Result and discussion:

A valuation of the developed model concerned two self-determining tests. The first test was to compare the residue backbone conformations in our developed model with the favoured values obtained from Protein Data Bank of known structures[7]. The results of VADAR web serve explored that 97% residues of developed model of exendin-4 were found to be in the most favoured region of the Ramachandran Plot (Figure 2) which is more than the cut-off value of 96.1% in most of the reliable models[8, 9]. The stereo chemical quality of the predicted model was found to be acceptable and low percentage of residues having phi/psi angles in the outlier region.

The second test was conceded by using ProSA web server. ProSA-web provides an easy-to-use interface to the program ProSA [12] which is frequently employed in protein structure validation. ProSA calculates an overall quality score for a specific input structure. If this score is outside a range characteristic for native proteins the structure probably contains errors. A plot of local quality scores points to problematic parts of the model which are also highlighted in a 3D molecule viewer to facilitate their detection.

The *z*-score indicates overall model quality. Its value is displayed in a plot that contains the *z*-scores of all experimentally determined protein chains in current PDB[13]. In this plot, groups of structures from different sources (X-ray, NMR) are distinguished by different colours. It can be used to check whether the *z*-score of the input structure is within the range of scores typically found for native proteins of similar size and the intended z-score illustrate that the developed model is fine (Figure 3).

At last the predicted model was submitted to PMDB (protein model database) server and its PMDB id is pm0077421.

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