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In Silico Modeling and Validation of L-Arginase, an Anti-Cancer Enzyme using Computational Tools

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Abstract **- The microbial L-Arginase is a potent drug which can be used for the treatment of various forms of cancer and other severe complications. In the present work L-Arginase sequence of a bacterium was obtained from UniProt server and it is analyzed in SWISS MODEL to develop its 3-D model. The L-Arginase enzyme model was verified and validated in ProSA web server. Further the efficiency of L-Arginase can be enhanced by using sophisticated computational tools and such L-Arginase with enhanced activity can be produced by microbes in the laboratory.**

Key words – L-Arginase; drug; cancer; UniProt; SWISS MODEL; ProSA

I. INTRODUCTION

The L-Arginase enzyme produced by microbes can be used as a multiple drug. It is used as a potent drug to treat different cancers. It is also used to cure rheumatoid arthritis, allergy associated asthma and neurological complications. In humans L-Arginase occurs in two forms *viz.*, L-Arginase-I and L-Arginase-II. *In vitro* studies had proved L-Arginase as a genuine therapeutic agent to cure different forms of cancer. The L-Arginine is an important amino acid required for living cells. It is necessary for the synthesis of nucleic acids and proteins. Healthy cells are capable of synthesizing L-Arginine whereas cancer cells lack the ability to synthesize L-Arginine. The cancer cells depend upon dietary L-Arginine which circulates in blood after digestion and absorption of food. If L-Arginase is administered into a cancer patient it degrades L-Arginine present in blood into L-ornithine and urea. Thus, L-Arginine is not available to cancer cells and eventually they die. The normal cells are unaffected as they can synthesize L-Arginine. Many microbes have been reported to produce L-Arginase by researchers. The microbial L-Arginase can be easily produced by microbes and is a stable compound [1, 2].

The researchers from different areas of sciences have integrated their ideas to develop the bioinformatics tools. The bioinformatics tools are extensively used to design and improve the biomolecules. The tools are available online and can be freely used. Various online servers can be employed for *In Silico* modeling and improvement of protein models [3].

In the present paper the sequence of L-Arginase enzyme was downloaded from UniProt server and used in SWISS MODEL to build three-dimensional model of L-Arginase. Then the model quality of L-Arginase structure was validated in ProSA server.

II. MATERIALS AND METHODS

A. Retrieving the sequence of L-Arginase enzyme

The sequence of L-Arginase enzyme was obtained from UniProt server. The UniProt server is a source of protein data collected from different protein databases [4].

B. Construction of three-dimensional model of L-Arginase enzyme

The L-Arginase enzyme sequence was used to build the corresponding 3-D model of L-Arginase in SWISS MODEL. The SWISS MODEL is an online web server in which protein models can be developed based on their amino acid sequences [5].

C. Determination of validity of L-Arginase enzyme model structure

The quality of model of L-Arginase was checked in ProSA web sever. The PDB file of L-Arginase was submitted to ProSA in which protein models are verified based on structural details generated by X-ray and NMR spectroscopy [6].

III. RESULTS AND DISCUSSION

A. Sequence of L-Arginase enzyme obtained from Uniprot server

The sequence of L-Arginase (L-Arginase-I) enzyme of Flammeovirgaceae bacterium 311 in FASTA format was derived from UniProt server. The following is the sequence of L-Arginase.

MERIKFIEVASELGAGTRGASLGIGALKAASLAKGSDF
FKKYPCLAVPTLNEQLFEDILHPYAKRIPQVRQILEHT
AGAVKNTLAEGCFPVVLAGDHSTAAGTIAGIKMQMP
HKRIGVIWIDAHADLHTPYTTPSGNVHGMPLSVVTGI
DNKECQVNYPQTETVEEWNKCKNIGVEGAKIDPSDIV
FIGMRSFEEPEKAIINRHGIRNFSVEEVRTKGVAAVVG
EIMEVLNNCDAIYISFDVDSLDPEISTGTGTPVPQGLTA
EEGRALNHSLIMQPKVVCWEMVEINPTLDNLNKMAV
TAFEIMEHAINARASNGKLVDVAL

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The UniProt server allows the users to obtain the desired protein sequences freely [7].

B. Generation of three-dimensional model of L-Arginase in SWISS MODEL

The FASTA format sequence of L-Arginase was entered in SWISS MODEL to develop its structure by automated mode. The sequence of L-Arginase (query sequence) was matched with similar protein sequences available in SWISS MODEL. The protein sequence which was exhibiting maximum similarity to the L-Arginase sequence was regarded as template protein [8]. The protein, 4ie1.1.A showed highest similarity to L-Arginase. The alignment of sequence of protein, 4ie1.1.A and L-Arginase sequence is shown in figure-1. The protein 4ie1.1.A was used as template model (Figure-2) to develop L-Arginase model (Figure-3).

The L-Arginase enzyme exists as trimer made up of three identical monomer units [9]. The three monomer units of L-Arginase were matched with one of the three identical units of template, 4ie1.1.A.

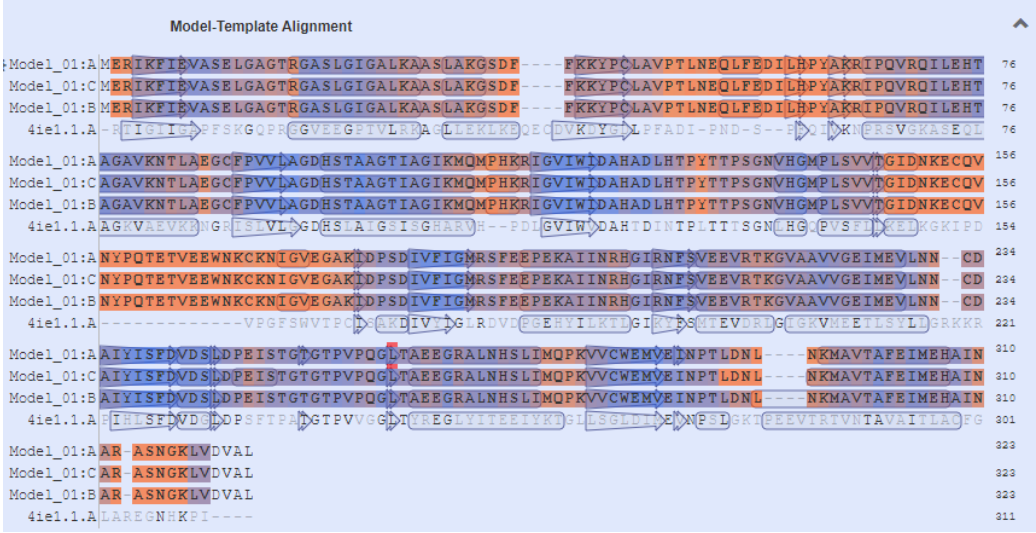

Figure-1: Alignment of template, 4ie1.1.A sequence with the sequences of L-Arginase enzyme (trimer)

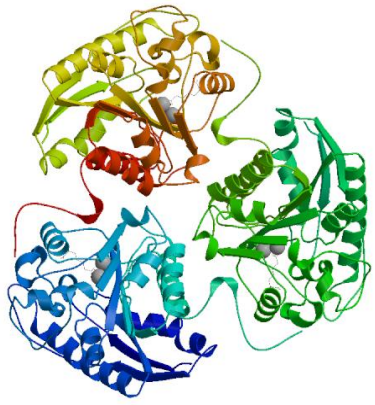

Figure-2: Template (4ie1.1.A) model

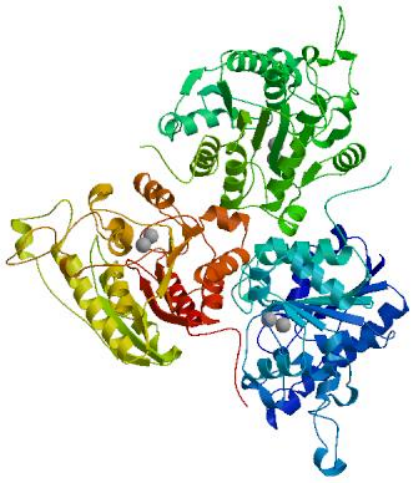

Figure-3: L-Arginase enzyme model (trimer)

C. Validation of L-Arginase enzyme model in ProSA

The 3-D model of L-Arginase was verified and validated in ProSA. The PDB format of L-Arginase was submitted to ProSA server. The ProSA server generates an overall quality score denoted as Z-score for a submitted protein model. The Z-score (black dot) of the polypeptide chains of L-Arginase enzyme calculated based on X-ray (light blue) and NMR spectrum (dark blue) analysis are depicted in Figure-4. The Z-score (-8.31) calculated in ProSA web for L-Arginase enzyme model was not deviating significantly from similar pre-determined native protein models which inferred the reliability of L-Arginase model [10-12].

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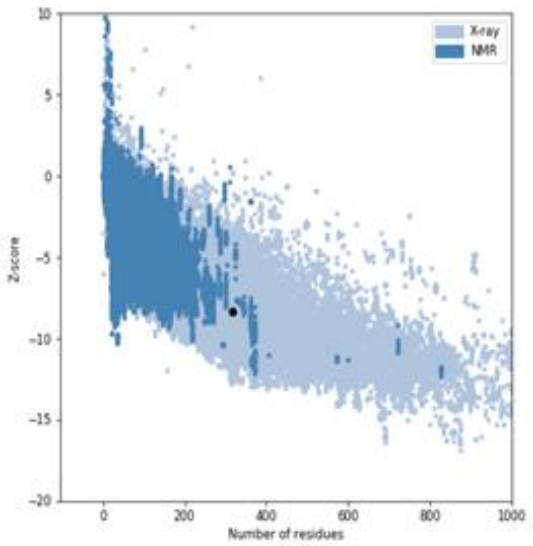

Figure-4: Z-score of L-Arginase model generated in ProSA web

IV. CONCLUSION

The bioinformatics tools were extensively used to construct and validate the 3-D model of bacterial L-Arginase enzyme which is an important multi therapeutic drug. The activity of L-Arginase model can be improved by modifying amino acids at certain sites using advanced tools of computational biology. Such improved L-Arginase can be produced commercially on large scale by making required modifications in L-Arginase gene of microbes.

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