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Research Article

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Homology Modeling and Docking Study of Defense Related Protein (*DRD-1*) in Potato

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ABSTRACT

DRD-1 (Defense-related Alcohol Dehydrogenase) protein plays an important part in detoxification of a pathogen-derived compound against Erwinia carotovora. The present study aims to predict the structure of the protein through homology modeling for better understanding of the mechanism of protein ligand interaction. 3D structure model of protein DRD-1 was constructed based on the structure of the template 1YQD. All the structural models were verified by a series of tests like Procheck, What_check, Errata, Verify 3D and Prove. Also, Gnuplot between the profiles of the predicted model and the template also shows that generated model is the best based on selected templates. After the model was designed, it underwent docking with 6 different ligands and their analogs and it was found out that an analog of o-vanillin was the best fit ligand for our model among other ligands. This Study will be useful will be useful in designing better lead compound to overcome toxicity aspects.

Keywords: *DRD-1*; 3D; Homology modeling; Procheck; Ramachandra plot; Docking

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INTRODUCTION

Erwinia carotovora is very dangerous bacterial species causing Blackleg, aerial stem rot, and tuber soft rot. Though this is very common and has an extensive host range, including most fleshy vegetables but mostly associated with potatoes. It survives readily in soil and surface waters such as rivers, lakes, and even oceans. These bacteria are capable of multiplying and persisting in the root zones of many host and non-host crop and weed species. The production and secretion of PCWDEs (plant cell wall-degrading enzymes) is central to the virulence of *E. carotovora*, and these PCWDEs were used as elicitors of potato and tobacco defense responses [1-6]. Identification of potato genes responsive to PCWDEs from *E. carotovora* led to the isolation of various defense related genes including *DRD-1* (defense related dehydrogenase), *DRD-1* is a gene encoding a novel alcohol known as NADP+ oxidoreductase. The prediction process consists of fold assignment, target-template alignment, model building, and model evaluation. The quality of the model generated by the programs has to be evaluated by Ramachandran plot followed by validation through Gnuplot, Procheck, What check, Errata, Verify 3D and Prove. The structure of the designed model was refined by molprobity, a web based tool for structure refinement. Further molecular docking was used to show the interaction of ligand molecules with *DRD-1* protein.

MATERIALS AND METHODS

Search and Retrieval of Target Protein Sequence
Information about protein sequence of *DRD-1* was retrieved from NCBI.

Selection of Template
Template was selected by homology search of query protein (*DRD-1*) sequence against the databases available on PDB (http://ww.rcsb.org). Homologous structure of sequence having the lowest E-value, 50% and above identity, lower resolution was selected as template (Table 1).

Table 1: List of templates and related information

S No	PDB ID	Resolution	E-Value	Identity
1	1YQD	1.65	6.30E-140	64%
2	1YQX	2.5	6.30E-140	64%
3	2CF5	2	1.70E-78	45%
4	2CF6	2.6	1.70E-78	45%
5	1UUF	1.76	6.81E-71	43%
6	1PIW	3	6.49E-38	32%

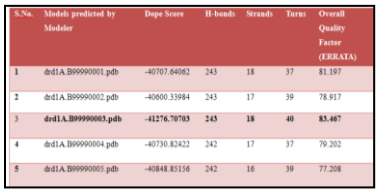
Homology Modeling
Homology modeling was done using Modeler 9v3.

Evaluation and Refinement of Predicted Models
All predicted 5 models were evaluated by Procheck , What_check, Errata, Verify_3D and Prove (PROtein Volume Evaluation). Ramachandran plot statistics was used to evaluate the stability of the model. Gnuplot was finally used to plot the profiles generated by Modeler (http://www.gnuplot.info) to validate substantially the structure. Refinement of the structure was done by molprobity (http://molprobity.biochem.duke.edu/) server. CASTp [6-9] program was used to find the accessible surface of predicted protein.

Docking Analysis
In our study, we have used the tool iGEMDOCK for docking the protein [10-14].

RESULTS AND DISCUSSION

Search for template on Protein Data Bank through blastP has generated 55 homologous structures. Most probable homologous proteins are listed in Figure 1. Among them 1YQD was selected on the basis of low resolution (1.65), high identity (64%) and lowest E-Value (6.29625E-140). By using 1YQD as a template Modeler 9v3 has predicted five 3D models of our query protein '*DRD-1'*. The best model (Figure 1) was selected according to its lowest Dope score (Figure 2). The parameters like hydrogen bonds, strands and turns were calculated by RasMol [15,16]. The presence of maximum numbers of turns and H-bonds in the model 3 confirms that this structure is more compact than others. Thus, the model-3 (drd1A.B99990003FH.pdb) would truly represent the *DRD-1* protein and could be utilized for the protein-protein and ligand-protein interactions studies leading to designing of effective drug against Erwinia.



S.No.	Models predicted by Modeler	Dope Score	H-bonds	Strands	Turns	Overall Quality Factor (ERRATA)
1	drd1A.B99990001.pdb	-40707.64062	243	18	37	81.197
2	drd1A.B99990002.pdb	-40600.33984	243	17	39	78.917
3	**drd1A.B99990003.pdb**	**-41276.70703**	**243**	**18**	**40**	**83.467**
4	drd1A.B99990004.pdb	-40730.82422	242	17	37	79.202
5	drd1A.B99990005.pdb	-40848.85156	242	16	39	77.208

Figure 1: Dope score of models and comparative study of number of H-bonds, strands and turns in 5 models

Table 3: Comparative Ramachandran Statistics of five models**Predicted Structure**

	No. of Residues in				
	Most favored Region	Additional allowed Region	Generously allowed Region	Disallowed Region	Percentage of residues in most favored and additional allowed Region
drd1A.B99990001.pdb	283	18	1	0	99.7%
drd1A.B99990002.pdb	284	18	1	1	99.4%
drd1A.B99990003.pdb	**281**	**22**	**1**	**0**	**99.7%**
drd1A.B99990004.pdb	282	21	1	0	99.7%
drd1A.B99990005.pdb	282	21	1	0	99.7%

Figure 2: Comparative Ramachandran statistics and Whatif check result of five models

The total numbers of ligand molecules used in docking were 251. Out of which, 2-methoxybenzaldehyde,3-methoxybenzaldehyde, Cinnamaldehyde, hydrocinnamaldehyde, o-Vanillin and Salicylaldehyde analogues were present in numbers of 42, 40, 2, 39, 100 and 28 respectively [17-20]. It was found that 42 analogues were found to be repeated more than one time, therefore a total of 209 ligand molecules were subjected to docking analysis. It was found that the best fit ligand molecule for the protein was drd1A.B99990003-zinc_34770735-0 ligand, which is analogous with o-vanillin (Figures 3-7).

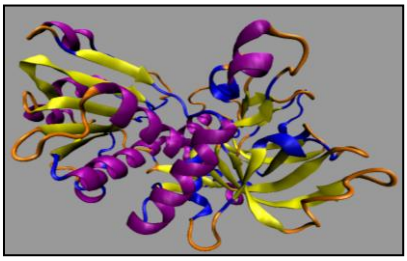


Figure 3: 3D structure of Model drd1A.B99990003FH.pdb

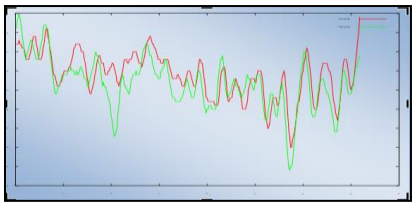


Figure 4: GNUPLOT for model (drd1A.profile) and template (3yqdA.profile)

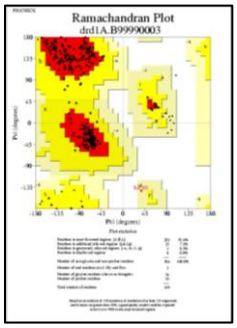


Figure 5: Ramachandran plot for the model neu1A.B99990005

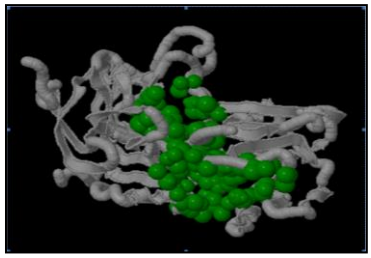


Figure 6: Active site prediction result with CASTp

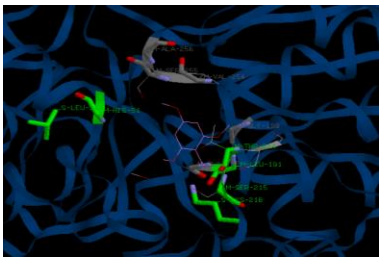


Figure 7: Interaction analysis of the bonds of drd1A.B99990003-zinc_34770735-0.pdb model of o-vanillin

CONCLUSION

The result of comparative structural analysis shows that model-3 (drd1A.B99990003FH.pdb) is the best structural model for *DRD-1*, a target of Erwinia based on its lowest Dope score, maximum residues (99.7%) in the favored and allowed region with the highest Z score value of 0.970. This model was also utilized for ligand binding study of the *DRD-1* protein and we found out that the analog (drd1A.B99990003-zinc_34770735-0.pdb) of o-vanillin is the best fit ligand to the protein *DRD-1*. These models could be utilized designing of effective compound to combat against the dreaded infection of potato.

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