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In Silico Homology Modeling and Epitope Prediction of Outer Membrane Protein OMP W, A Potential Vaccine Candidate against *Edwardsiella tarda*

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A B S T R A C T

Edwardsiella tarda is a Gram negative bacterium with a wide host range, mainly affecting fishes. It is a dreaded pathogen of cat fish culture. The presence of large number of serotypes of the pathogen makes the vaccine production against the pathogen a difficult task. Here in this study the suitability of outer membrane protein W (OMP W) as a vaccine candidate against *E. tarda* was investigated. OMPs has the characteristics of localization in the outer membranes of Gram negative bacteria, which make them easily accessible to the host antibody there by triggering an antigen antibody reaction in the host body. The 3D structure of the protein was constructed using homology modeling, the quality of the model was evaluated and finally the factors for a biological molecule to be considered as a vaccine candidate were being checked for the OMP. The solvent accessible regions, the antigenic regions, epitope positions were found out. Further the domains, patterns, motifs detected together with the fact that OMP W is an adhesin strongly suggest OMP W of *E. tarda* as a potential vaccine candidate.

Introduction

Edwardsiella tarda (*E. tarda*) is a Gram negative, motile, short, rod-shaped bacterium (1 µm in diameter and 2–3 µm long) belonging to the family Enterobacteriaceae. The host range of the pathogen includes human beings, fresh water and salt water fishes, snakes (Czirják *et al.*, 2008), tortoises (Sechter *et al.*, 1983), crocodiles (Revol, 1995), seals (Thornton *et al.*, 1998) and frogs (Sharma *et al.*, 1974). *Edwardsiella* has been implicated in gastroenteritis in humans (Spencer *et al.*, 2008) and in bacteremic infections that include liver abscesses (Manchanda *et al.*, 2006) and peritonitis with sepsis (Clarridge *et al.*, 1980). The bacterium causes edwardsiellosis / emphysematous putrefactive disease leading to mass mortality in various populations and age groups of fish. It has become one of the most serious threats to flounder farming (Kusuda and Kawai, 1998) and cat fish farming (Ye *et al.*, 2009). Studies have shown that *E. tarda* is resistant to colicins (Stock and Wiedemann, 2001) and possess beta lactamase (Welch *et al.*, 2009)

activity that renders it resistant to most of the beta lactam antibiotics. Hence current research is focusing in the development of vaccine against this pathogen. In this scenario a protein which elicits antibody response in the host against the bacterium can be considered as a potential vaccine candidate. Large number of serotypes of *E. tarda* has been reported and hence developing a vaccine against *E. tarda* is very difficult. The outer membrane proteins are always a potent vaccine candidate against gram negative bacteria as they generate immunogenic response in the host by inducing the production of bactericidal antibodies that prevents the bacteria from establishing in the host body. In this study, using bioinformatic tools we look upon an outer membrane protein namely OMP W that could be used effectively against this pathogen. The immunogenic properties of OMP W in other gram negative bacteria like *Aeromonas hydrophila* (Maiti *et al.,* 2009) and *Vibrio cholerae* (Nandi *et al.,* 2005) is reported. Recent studies have also highlighted the action of OMP W as an oral vaccine (Dubey *et al.,* 2016) as well as its role in transport of hydrophobic molecules (Hong *et al.,* 2006) and also in osmoregulation (Xu *et al.,* 2004). Hence in this study we analyze OMP W of the enterobacterial pathogen *E. tarda* using bioinformatics tools to establish a structure function relationship and to predict the antigenic determinants of the protein which makes it a potential vaccine candidate.

Materials and Methods

Retrieval of target sequence

The amino acid sequence of OMP W of *E. tarda* was obtained from the Swissprot sequence database UniProtKB/Swiss-prot (http://www.expasy.org/uniprot) Accession D0ZH93. This is a 214aminoacid protein. Since the structure of *E. tarda* OMP W was not available in the protein data bank (PDB), we looked upon constructing a 3D model of the protein.

Homology modeling

The approach of homology modeling was used in constructing a 3D model of *E. tarda* OMP W. Here the protein is modeled based on the alignment between the target and template. The sequential diagram for homology modeling is illustrated in Figure 1. NCBI Protein BLAST of *E. tarda* OMP W (target) was done against PDB data base to obtain a structurally similar protein namely 'template'. The target - template sequence alignment was done using CLUSTAL W (www.ebi.ac.uk/clustalw/). The resulting alignment file is provided to SWISS MODEL server (http://swissmodel.expasy.org/workspace/index.php?func=modelling_align1) (Arnold *et al.,* 2006) with the alignment input format as CLUSAL W to obtain a 3D model for the protein. This model was viewed using the visualization software UCSF chimera (http://www.cgl.ucsf.edu/chimera) (Pettersen *et al.,* 2004).

Validation of model

The protein model created need to be evaluated for quality. Hence the model was further checked with QMEAN, ANOLEA and GROMOS. QMEAN is a composite scoring function for both the estimation of the global quality of the entire model as well as for the local per-residue analysis of different regions within a model (Benkert, 2008). The reliability of the model ranges from 0-1. The atomic empirical mean force potential ANOLEA (Melo and Feytmans, 1998) is used to assess packing quality of the models. The program performs energy calculations on a protein chain, evaluating the "Non- Local Environment" (NLE) of each heavy atom in the molecule. GROMOS (Van Gunsteren *et al.,,* 1996) is a general-purpose molecular

dynamics computer simulation package for the study of biomolecular systems and can be applied to the analysis of conformations obtained by experiment or by computer simulation. The model was further checked by Ramachandran plot at VADAR (Willard *et al.,* 2003). WHAT IF server (http://swift.cmbi.ru.nl/servers/html/index.html) was used to check the nomenclature of torsion angles (Name check), the normality of the local environment of amino acids (Coarse Packing Quality Control), Anomalous bond lengths, Planarity, Fine Packing Quality Control, distribution of omega angles, Proline puckering and Anomalous bond angles.

Solvent accessible regions

The most biologically interesting residues are often exposed, as these are able to interact with the environment. So we looked in to the structure to predict the solvent accessible regions of the protein. The Solvent accessible prediction of OMP W of *E. tarda* was done using NetSurfP. (Petersen *et al.,* 2009)

Prediction of Antigenic Peptides

Prediction of antigenic peptides was done using the EMBOSS tool 'Antigenic'. Antigenic predicts potentially antigenic regions of a protein sequence, using the method of Kolaskar and Tongaonkar (Rice *et al.,* 2000). Analysis of data from experimentally determined antigenic sites on proteins has revealed that the hydrophobic residues Cys, Leu and Val, if they occur on the surface of a protein, are more likely to be a part of antigenic sites.

Cytotoxic T lymphocyte (CTL) epitopes in OMP W of *E. tarda* was identified by NetCTL 1.2 server. Computational tools involved in the prediction of subcellular localization illustrates where the protein resides in the cell. So if the protein is present in the outer membrane, there is more possibility that it can be highlighted as a potential drug target. The program PSORTb V.3.0 (http://www.psort.org/psortb/index.html) was used for sub cellular localization prediction (Gardy *et al.,* 2005). Conserved domains of OMPs, which could be defined as part of protein sequence and structure that can evolve, function, and exist independent of the rest of the protein chain were identified using NCBI web interface 'CD search' (http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi). Protein motifs, which are, short segments of protein three-dimensional structure or amino acid sequence that were found in a large number of different proteins were identified by 'motif search' of Genome Net Database Resources (http://www.genome.jp/tools/motif/).

Biologically significant protein patterns were determined using PROSCAN ((http://npsa-pbil.ibcp.fr/). PROSCAN help scan a sequence against the PROSITE database using its algorithm to find biologically relevant sites and signatures.

A protein if virulent has the property of adhesion. The software SEAPATH was used to determine the adhesive properties of OMP W of *E. tarda*. The programme works on Linux operating system and shows whether the protein is an adhesin, non adhesin or is in the twilight zone. Artificial neural networks (ANN) were used to develop SEAPATH, which predicts the probability of a protein being an adhesin (Pad) based on 105 compositional properties of a sequence. SEAPATH draws upon the base algorithm SPAAN (a software program for prediction of adhesins and adhesin-like proteins using neural networks), which had optimal sensitivity of 89% and specificity of 100% and could identify 97.4% of adhesins from a wide range of bacterial pathogens causing a broad range of diseases in humans and other hosts.

Results and Discussion

OMP W of *E. tarda* is a 214 amino acid protein. The sequential diagram for homology modeling is depicted in Figure 1. Amino acid sequence of *E. tarda* OMP W (D0ZH93) is shown in Figure 2. NCBI Protein BLAST of *E. tarda* OMP W against PDB data base revealed that 2F1T_A; the OMP W of *Escherichia Coli* exhibited 61% identity with the protein, and hence was selected as the template for homology modeling. It is well established that proteins sharing more than 50% sequence homology adopt the same fold (Chothia and Lesk, 1986).

Proteins homologous over a length of at least 80 residues with at least 30% identical residues are predicted to share more than 70% secondary structure identity (Sander and Schneider, 1991); two or more proteins with 30% sequence identity differ in their three-dimensional core structure by less than 1.5 A^{o}.

Taking all these facts into consideration homology modelling could be a suitable method to obtain the 3D structure. The target (D0ZH93) template (2F1T_A) sequence alignment was done using CLUSTAL W and the resultant alignment file is shown in Figure 3. The 3D structure of outer membrane protein of *E. tarda* obtained by homology modeling is shown in Figure 4A and 4B. Figure 4A reveals the central porous region enclosed by the transmembrane strands. In Figure 4B, the transmembrane strands, folding into antiparallel β-barrels could be seen.

Validation of the model

The QMEAN4 score is a composite score consisting of a linear combination of 4 statistical potential terms (estimated model reliability between 0-1). The pseudo-energies of the contributing terms are given below together with their Z-scores with respect to scores obtained for high-resolution experimental structures of similar size solved by X-ray crystallography. The QMEAN4 global scores of *E. tarda* OMP W is shown in Table 1 and the graphical representation is shown in Figure 5. The atomic empirical mean force potential ANOLEA was used to assess packing quality of the models. The graphical representation of packing quality of residues in the model is shown in Figure 6. Graphical representation of the analysis of conformations by GROMOS is shown in Figure 7.

In Figure 6 and 7, the Y -axis of the plot represents the energy for each amino acid of the protein chain. Negative energy values (in green) represent favorable energy environment whereas positive values (in red) represent unfavorable energy environment for a given amino acid. The Ramachandran plot visualizes energetically allowed regions for backbone dihedral angles ψ against φ of amino acid residues in protein structure. The Ramachandran plot developed for the OMP W of *E. tarda* is shown in Figure 8.

Nomenclature of torsion angles (Name check)

No errors were detected in valine, threonine, isoleucine, leucine, arginine nomenclature. Again No errors were detected in tyrosine torsion angle, phenylalanine torsion angle, aspartic acid torsion angle, glutamic acid torsion angle and phosphate group naming conventions. In the atom names for non-hydrogen atoms no errors were detected.

Normality of the local environment of amino acids (Coarse Packing Quality Control)

The packing quality control per amino acid Average was -0.598 which is considered within the permitted limit.

Table.1 QMEAN4 global scores

Scoring function term	Raw score	Z-score
C_beta interaction energy	31.15	-4.57
All-atom pairwise energy	-684.68	-3.43
Solvation energy	-0.26	-2.52
Torsion angle energy	-22.53	-2.16
QMEAN4 score	0.494	-3.84

Table.2 Antigenic peptides of *E. tarda* OMP W

Score	Sequence length	Residue position	Max score position	Sequence
1.255	37	5-41	9	KCSVALCLAAVLAPAAASAHQAGDVIV RAGAATVRPT
1.141	11	119-129	123	RPYLGVGVNYT
1.125	34	75-108	98	IELLAATPFRHKVSLGALGNIATVHQLPP TLMAQ
1.087	7	142-148	145	SLGLHDL
1.082	9	45-53	50	DNVLGLGEF
1.076	7	173-179	178	NASVWYI
1.075	10	156-165	159	VAGQAGLDYM
1.032	6	203-208	206	PWVFMF

Table.3 Peptide sequence with cytotoxic T lymphocyte in *E. tarda* OMP W

Sequence initial position	Peptide sequence
42	TSSDNVLGL
69	ATDNIGIEL
113	RAEDKLRPY
128	YTTFFNNSF
156	VAGQAGLDY
170	WMINASVWY
198	NTNINPWVF
204	WVFMFGAGY

Fig.1 Sequential diagram for homology modeling

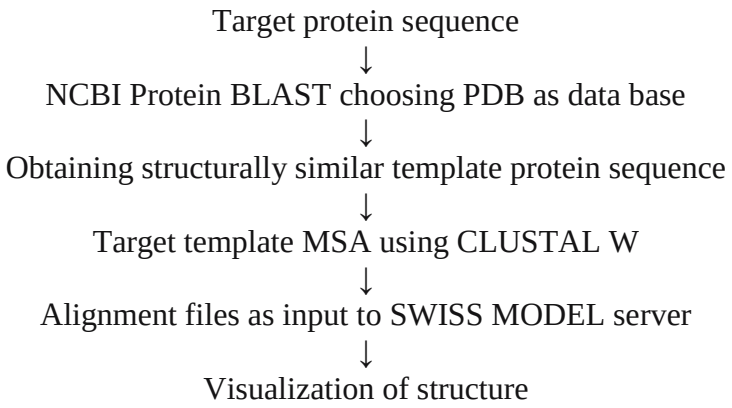


Fig.2 Amino acid sequence of D0ZH93

MMMKKCSVALCLAAVLAPAAASAHQAGDVIVRAGAATVRPTTSSDNVLGLGEFSVDNNTQLGLTFGYMATDNI

GIELLAATPFRHKVSLGALGNIATVHQLPPTLMAQWYFGRAEDKLRPYLGVGVNYTTFFNNSFDQNATSLGLHDLK

ATDSWGVAGQAGLDYMVSENWMINASVWYINIDTKVKFRDSADNQHSINTNINPWVFMFGAGYRF

Fig.3 Target (*E. tarda* OMP) –Template (*E. coli* OMP) alignment

```
E.tarda         MMMKKCSVALCLAAVLAPAAASAHQAGDVIVRAGAATVRPTTSSDNVLG-LGEFSVDNNT
E.coli          ----------------------HEAGEFFMRAGSATVRPTEGAGGTLGSLGGFSVTNNT
                                       *:**:.::***:****** .:...** ** *** ***

E.tarda         QLGLTFGYMATDNIGIELLAATPFRHKVSLGALGNIATVHQLPPTLMAQWYFGRAEDKLR
E.coli          QLGLTFTYMATDNIGVELLAATPFRHKIGTRATGDIATVHHLPPTLMAQWYFGDASSKFR
                ****** ********:***********:.  * *:*****:************ *..*:*

E.tarda         PYLGVGVNYTTFFNNSFDQNATSLGLHDLKATDSWGVAGQAGLDYMVSENWMINASVWYI
E.coli          PYVGAGINYTTFFDNGFNDHGKEAGLSDLSLKDSWGAAGQVGVDYLINRDWLVNMSVWYM
                **:*.*:******:*.*:::... ** **. .****.***.*:**::..:*::* ****:

E.tarda         NIDTKVKFRDSADNQHSINTNINPWVFMFGAGYRF------
E.coli          DIDTTANYKLGGAQQHDS-VRLDPWVFMFSAGYRFHHHHHH
                :***..::: .. :**.  ..::******.*****
```

Fig.4A *E. tarda* OMP W revealing the centre porous region

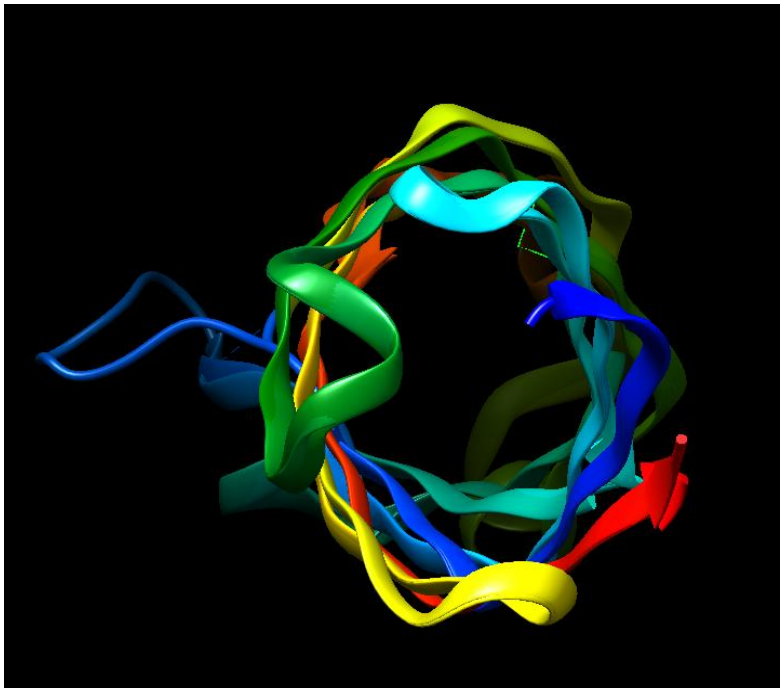


Fig.4B 3D Structure of *E. tarda* OMP W depicting the anti-parallel beta strands

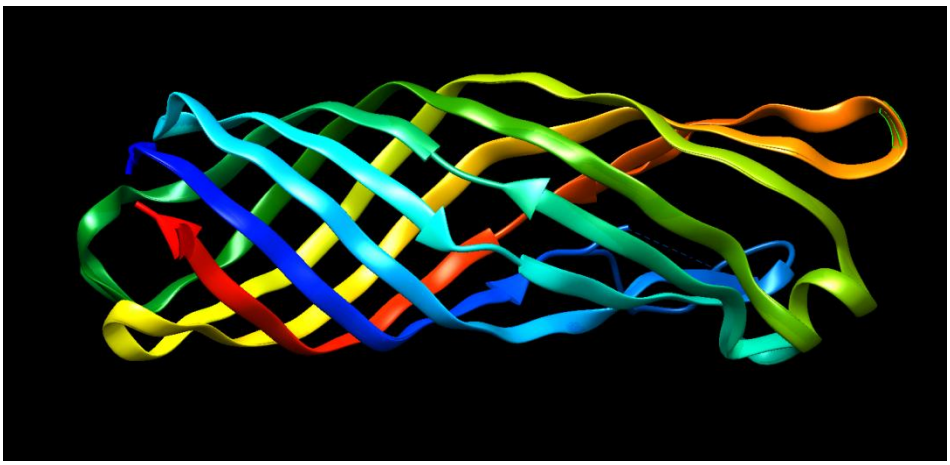


Fig.5 Graphical representation Q means score of each residue of *E. tarda* OMP W

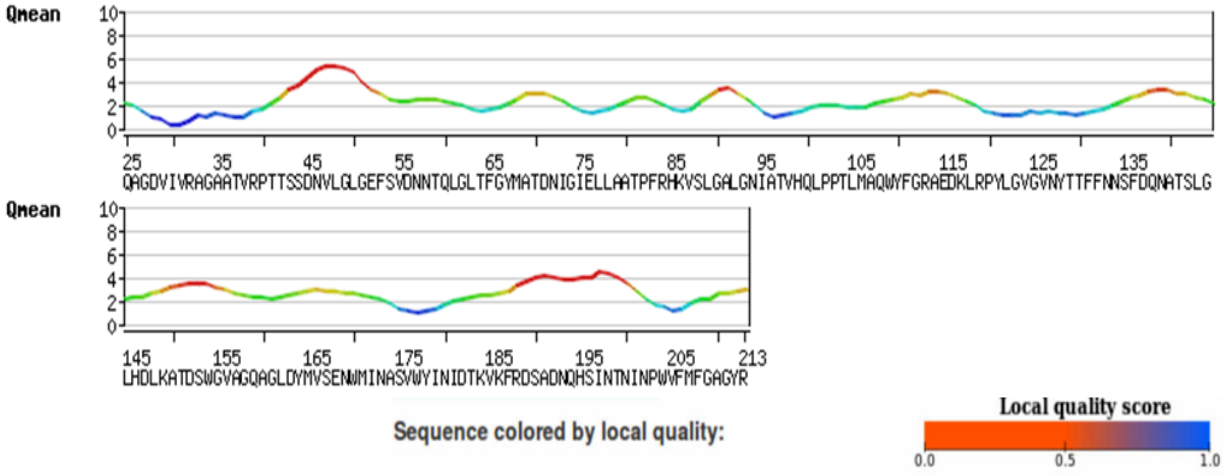


Fig.6 Packing quality of the homology based structure of *E. tarda* OMP W

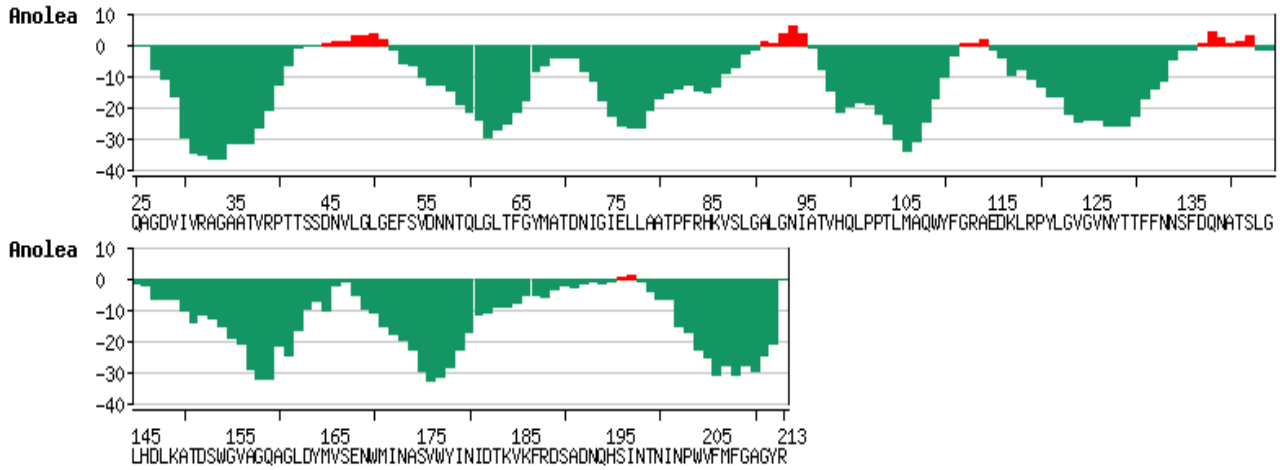


Fig.7 GROMOS results

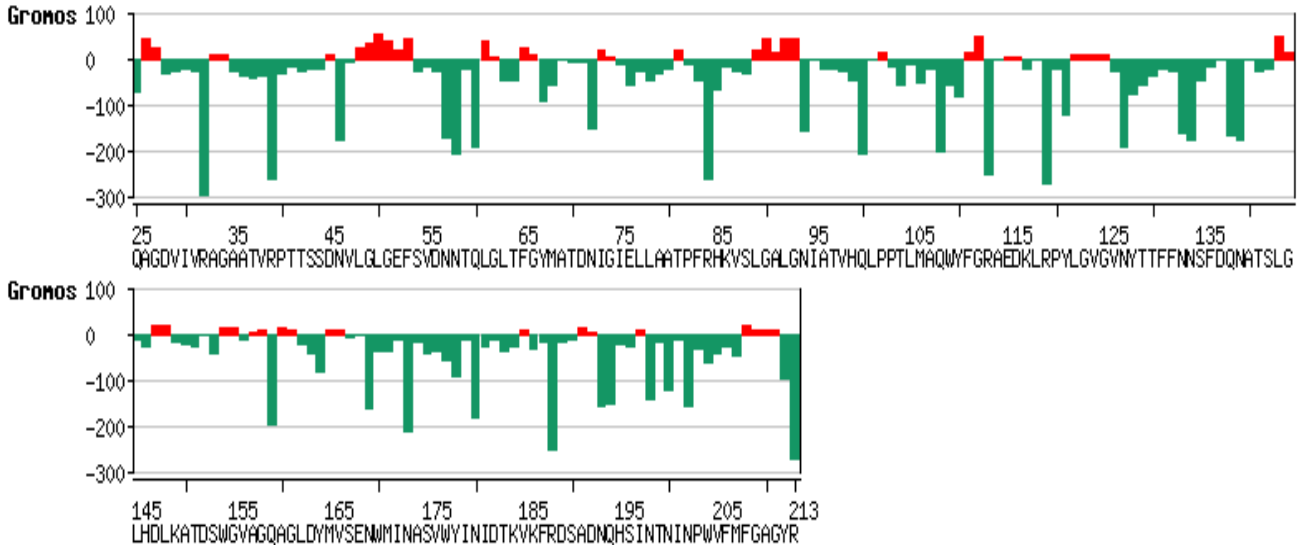
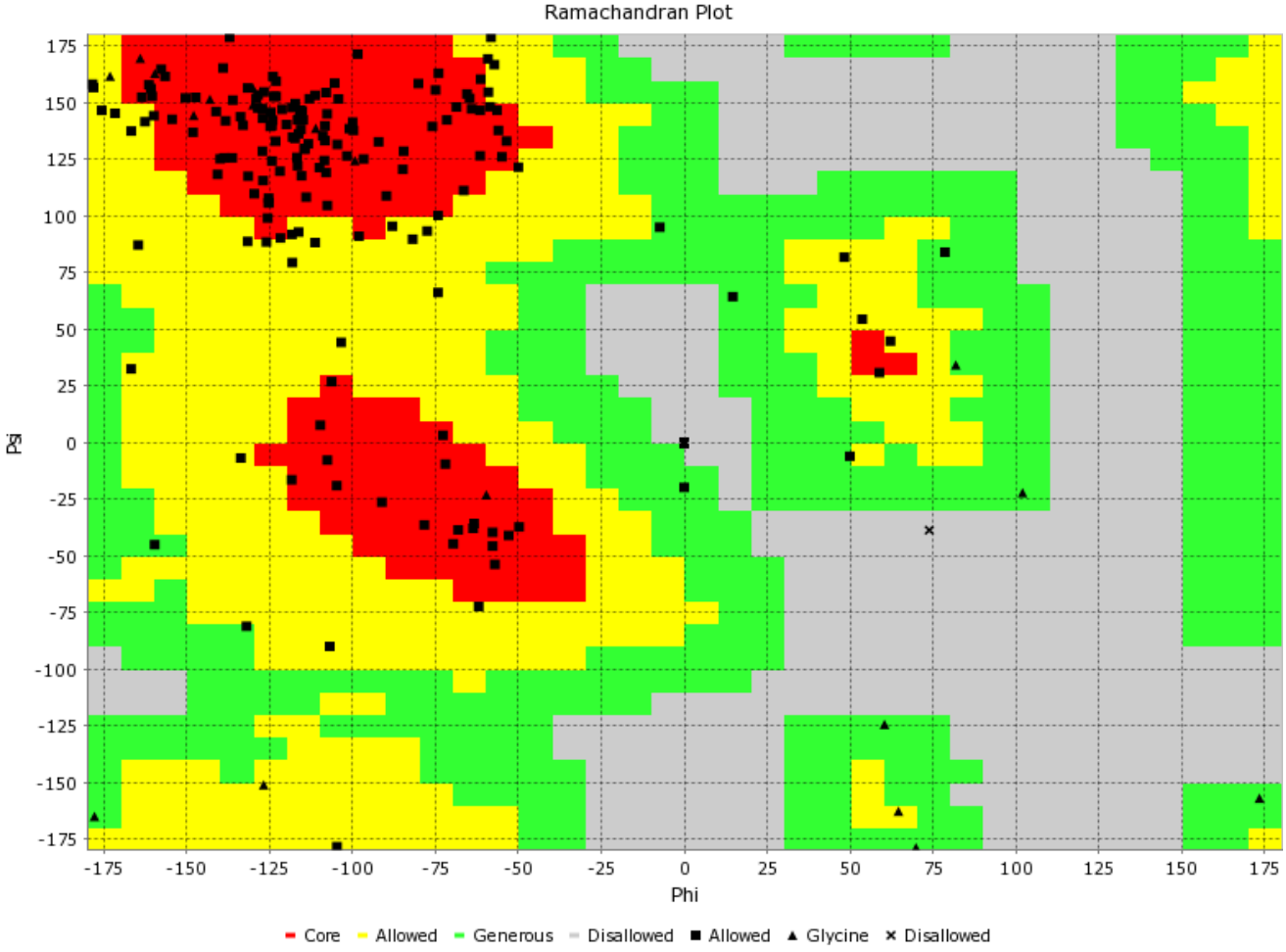


Fig.8 Ramachandran Plot of *E. tarda* OMP W



Anomalous bond lengths

The standard values and sigmas for the bond lengths of amino acid residues have been taken from Engh and Huber (1991). The bond lengths which deviated more than 4 sigma from standard bond lengths were considered unusual. In this model the bond lengths were found to deviate less than normal from the mean standard bond lengths.

The RMS Z-score given below is expected to be around 1.0 for a normally restrained data set. But in this model the RMS Z-score for bond lengths is 0.654 and the RMS-deviation in bond distances is 0.013 indicating that too-strong restraints might have been used in the refinement.

Planarity validation results

In the structure all of the atoms that are connected to planar aromatic rings in side chains of amino-acid residues are in the plane within expected RMS deviations. But the side chains of the residues ASP (137th position) and GLN (25th position) was found to deviate from planarity by more than 4.0 times the expected value. For an amino acid residue that has a side chain with a planar group, the RMS deviation of the atoms to a least squares plane was determined. The RMS value of ASP and GLN deviates 7.34 and 5.74 times standard deviation from the expected value.

Fine packing quality control

Structural validation for fine packing quality control of the Homology based model of *E. tarda* OMP showed that the average Z-score for all contacts (BB-BB, BB-SC, SC-BB and SC-SC) is 0.03, which confirms the structure is good. Here BB and SC is the minimal distance between the heavy atoms of the protein backbone and side chains of the two residues respectively.

Distribution of omega angles

The omega angles for trans-peptide bonds in a structure are expected to give a Gaussian distribution with the average around +178 degrees, and a standard deviation around 5.5. In the current structure the omega average and standard deviation values are 178.208 and 6.322 respectively which agrees with this expectation.

Proline puckering

Puckering amplitudes and puckering phases for all Proline residues are within normal ranges.

Anomalous bond angles

Except for the residues ASP (116), MET (165), VAL (185) and HIS (195) which has strange bond angles of 108.46, 92.08, 99.74 and 109.23 all other bond angles fall within the standard value described in Engh and Huber (1991). The RMS Z-score for bond angles was 1.053 and the RMS-deviation in bond angles was 1.928.

Solvent Accessible Regions

The solvent accessible regions of *E. tarda* as calculated by NetSurfP predicted 101 exposed residues in the peptide chain.

Prediction of antigenic peptides

The antigenic peptides as predicted by EMBOSS ‘antigenic’ shows that eight peptide sequences of the OMP are antigenic. The antigenic peptides and the score are shown in Table 2. Cytotoxic T lymphocyte (CTL) epitopes in OMP W of *E. tarda* identified by NetCTL 1.2 server is presented in Table 3.

The subcellular localization prediction by PSORTb V.3.0 confirmed that OMP W of *E.*

tarda is localized in the outer membrane of the bacteria. The CD search conducted to find the conserved domains in *E. tarda* OMP W showed that Surface antigen 2 super family domain is present. An Enterobacterial virulence outer membrane protein signature 2 was found in between residue 206 and 214 with the peptide sequence FMFGAGYRF by the Motif search. The different patterns associated with *E. tarda* OMP are N-glycosylation site, cAMP- and cGMP-dependent protein kinase phosphorylation site, Protein kinase C phosphorylation site, Casein kinase II phosphorylation site and N-myristoylation site as obtained from PROSCAN.

SEAPATH is linux based software, which classifies the proteins as adhesins or non adhesins based on the probability of adhesive (Pad) value. A protein with a Pad value ≥ 0.7 is an adhesin and could be considered as virulent. If the Pad value is ≤0.4, then it is a non adhesin. A value between 0.4 and 0.7 suggests that the protein is in the twilight zone i.e it could be an adhesin or a non-adhesin depending upon the proximity of the Pad value to the upper or lower limit. SEAPATH analysis confirmed *E. tarda* OMP W as an adhesin.

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