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3D Structure of NT-3 Protein (Neurotropin 3) of Pigeon (*Columba livia*) using Server-Swiss Model

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Abstract

The NT-3 protein plays an important role in the development and differentiation of neurons, and is unique in the neurotropin family, that it can bind to 3 Trk receptors, namely TrkC, TrkA and TrkB. This study aimed to analyze the characteristics and three-dimensional structure of NT-3 protein in Columba livia. The target protein was obtained from Uniprot server with the access code of PKK30025.1 using template 3buk.1A (PDB-ID) analyzed in-silico through homology method using SWISS-MODEL server. The results showed that the three-dimensional structure of the target NT-3 protein with a template formed a β-sheet and loop structure, which was composed of 304 amino acids, with the highest amino acid composition was serine at 8.88 mol polar, and the lowest amino acid was tryptophan at 1.32. moles which was relatively nonpolar. The analysis results of the structural quality revealed an identity value of 98.20%, QMEAN of 0.8, QMQE of 0.25, and the analysis on the Ramachandran plot presented an outlier value of 0.92%; the most favored region value was 94.5%, with good structural quality. The results of the 3-dimensional structure of the NT-3 Columba livia protein are expected to be useful for further research to determine the active side and interactions of proteins in carrying out their functions.

Keywords*: NT-3 Protein, 3-Dimensional Structure, Homology, In-silico, Columba livia*

INTRODUCTION

The nervous system comprises neurons and neuroglia (glia cells), which protect and maintain the liquid homeostasis around neurons, and to transmit signals from one cell to another (Djuwita et al., 2012). The previous studies have reported that the central nervous system (CNS) is highly sensitive to various injuries, including oxidative stress and mechanical trauma (Lee et al., 2002). CNS's injuries and

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neurodegenerative diseases may cause various levels of neuron death, axon and dendrite degenerations, which can inhibit impulse channeling (Jackson et al., 2010).

Johnsen et al. (2015) reported that there is one protein that plays an important role in neuron differentiation, axon growth, and synapsis development, which is called as NT-3 protein. NT- 3 is a protein expressed by NTF3 gen (Maisonpierre et al., 1991). NT-3 protein has an exclusive characteristic in functioning its role, which can bind to several Trk receptors, i.e TrkC, TrkB dan TrkA (Ryde'n & Ibanez, 1996).

The understanding of NT-3 protein, especially in the molecular level, is very vital in determining its nature and characteristics. Wijaya & Hasanah (2016) explained that the knowledge and comprehension of 3D protein structure can provide information in understanding the nature and protein function in molecular level.

NT-3 protein in Columba livia is rare enough in research, especially about its structure and biochemical function. The lack of information sources concerning this protein on Columba livia results in difficulties of elaborating the problems encountered in molecular level. The in-silico analysis (computerised) is one of the methods that can be used to solve this situation, by reconstructing the 3D structure of a protein through homology approach. This approach is conducted based on the protein sequence template which is homolog with the protein target (Lukitaningsih, 2015). Waterhouse et al., (2018) described that the homology modelling is the distinctive technique in structural biology. The objective of this study was to analyse the characteristics and structure of NT-3 protein in Columba livia, that is not found yet its 3D structure. The identified 3D structure is later useful for determining its characteristics, which makes us easy to understand its nature and function in molecular level

METHODS

This study used a descriptive method with parameters as follows: the composition of polar and non-polar amino acids and the image of NT-3 protein structure in Columbia livia, which was built from the results of modelling of the target and template protein, including the structural assessment based on the Ramadchandran plot.

Tools

This study utilized a computer (laptop) connected to internet connection, with its specification of Intel(R) Celeron(R) 3205U @ 1.5GHz 1.50 GHz. RAM of 4 GB, system 64-bit, and the operation system of windows 8, server UniProt (http://www.uniprot.org,serve), ProteinDataBank (http://www.pdb.org/pdb/home/home.do,server), server SWISS MODEL expacy (http://swissmodel,expasy.org/) and Bioedit version 7.2.5.

Materials

This study used a protein sequence of NT-3 Columba livia (Pigeon), which was obtained from the Uniprot server with the access code of PKK30025.1, with a template arose from "search" on the "upload target sequence file", then continued for

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selecting the menu "search for template". Kiefer et al. (2008) elaborated that the template determination is the key step to reconstruct the structure of protein targets.

Composition Analysis of Amino Acid

Analysis of amino acid composition used server bioedit, which was offline accessed. Inserting the protein target on the bioedit, then clicking the sequence tab on menubar. After that, selecting sub menu "Protein", and continuing with the option of sub menu "Acid Amino Composition". Ultimately, the data of amino acid composition of protein target was resulted.

3-Dimentional Structure

The 3D structure of NT-3 protein target was built using the homology methodology. Khanfar et al. (2013) stated that homology modelling was done using server Swiss-Model. The homology methodology has been proved as the chosen approach to assemble an accurate 3D model from proteins based on amino acid sequences (Reddy et al., 2015). This methodology reconstructs the 3D structure of protein target based on the template of protein structure that is registered and stored in the PDB server. Rajendran et al. (2016) reported that the structure of protein target is made based on the template obtained from the protein sequences of other organisms that are homolog and available in the PDB server.

The 3-dimentional structure of NT-3 protein was developed using the SWISS MODEL server (Ayupov & Akberova, 2016). Handayani et al. (2017) suggested that the server is helpful in predicting the protein structure, with the following steps: selecting menu "user template" on "workspace", inserting the protein target sequences on the menu "upload target sequence file", uploading the coordinate template on the menu "add template file", and ultimately clicking the menu "build model".

Evaluation of 3D Structure

Structural evaluation in the assessment of 3D structure of NT-3 protein utilized the SWISS MODEL server, with the "structural assessment" step on the display of model results. The assessment of structural quality was determined from the values of seq identity, QMEAN, QMQE, and MolProbity Results in Polts Ramachandran. Lakhlili et al. (2015) revealed that the model accuracy is evaluated using the map calculation of Ramachandran.

RESULTS AND DISCUSSION

Protein Target

The searching results of protein target on the NCBI server exhibited 3 items of NT-3 protein in Columba livia, i.e proteins with the access code of XP_005510574.1, PKK30025.1 and ACF34521.1 (Figure 1), which have different sequences of amino acids.

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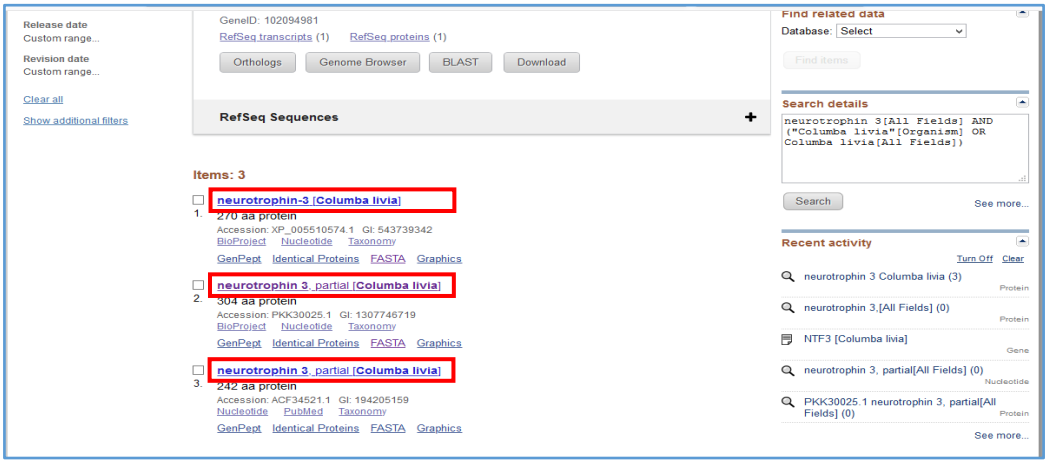

Figure 1. The searching results of NT-3 Protein of *Columba livia* in NCBI database

The results on the PDB *server* from the three protein access codes showed that the access code of PKK30025.1 was unidentified with "*no results were found matching your query*" (Figure 2). This finding indicated that proteins with that access code were not registered in the server, and yet built its 3D structure. The unregistered proteins in this PDB *server* may become a protein target to build the 3D protein structure (Wijaya & Hasanah, 2016).

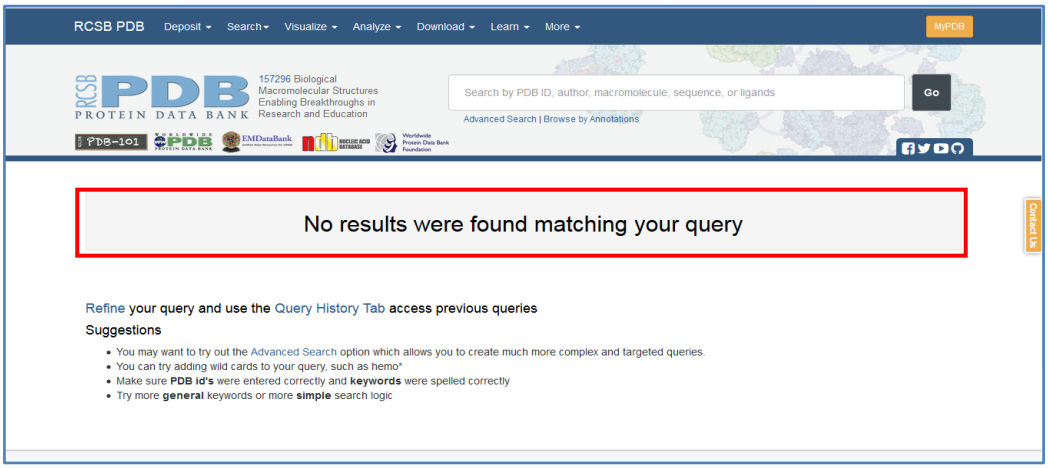

Figure 2. The finding of NT-3 Protein in PDB Database

The searching results of protein target sequences (Figure 3) exposed that NT-3 protein target has 304 amino acids, which are composed from 20 types of amino acids with different composition on each type, and has the molecular mass of 35,003 Dalton (Da). Molecular mass and amino acid composition in the protein polypeptides play a vital role in predicting a protein structure (Sugiyono, 2004).

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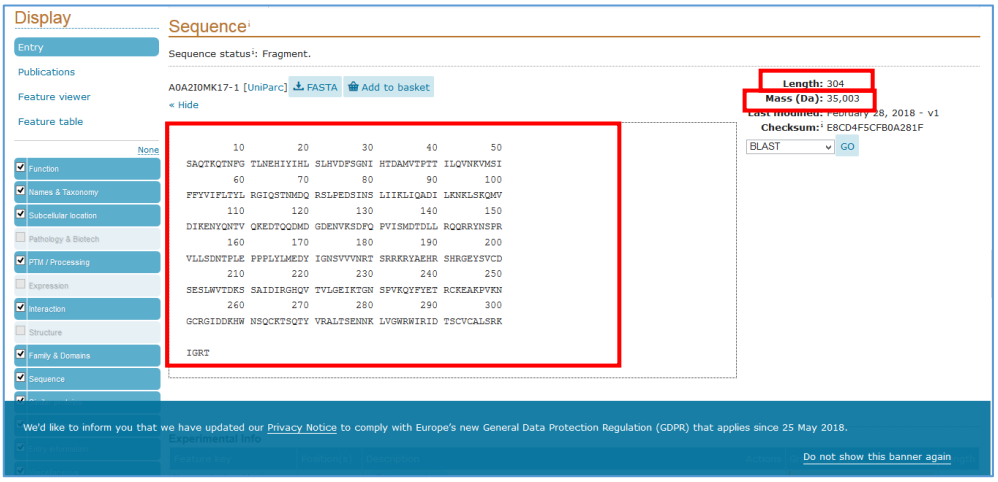

Figure 3. Protein Sequence of NT-3 of *Columba livia*

Amino Acid Composition

The analysis results revealed that NT-3 protein of *Columba livia* has the composition of amino acids as follows: alanine, cysteine, aspartate acid, glutamate acid, phenylalanine, glycine, histidine, isoleucine, lysine, leucine, methionine, asparagine, proline, glutamine, arginine, serine, threonine, valine, tryptophan, and tyrosine (Figure 4). Harti & Soebiyanto (2017) stated that the sequence, numbers, and combination of amino acids will help to construct the structure and function of proteins.

The highest number of amino acids made up of NT-3 protein was serine, with 8,88 mol and polar. The polarity of amino acids has hydrophilic property, in the folding process of amino acids this character tends to be outside of protein (Harti & Soebiyanto 2015). While, the amino acid composition with the lowest number was tryptophan, with 1.32 mol and non-polar. Non-polar amino acids have hydrophobic property (against water), in the folding process may tend to be inside the protein (Irianto, 2017). The hydrophilic and hydrophobic properties of amino acids are one of the main characters in the folding process of a protein in constructing their 3D structure.

Protein: PKK30025.1 neurotrophin 3, partial [Columba livia]
Length = 304 amino acids
Molecular Weight = 35000.91 Daltons

Amino Acid		Number	Mol%
Ala	A	8	2.63
Cys	C	6	1.97
Asp	D	21	6.91
Glu	E	14	4.61
Phe	F	7	2.30
Gly	G	13	4.28
His	H	8	2.63
Ile	I	22	7.24
Lys	K	20	6.58
Leu	L	23	7.57
Met	M	7	2.30
Asn	N	19	6.25
Pro	P	10	3.29
Gln	Q	18	5.92
Arg	R	20	6.58
Ser	S	27	8.88
Thr	T	23	7.57
Val	V	22	7.24
Trp	W	4	1.32
Tyr	Y	12	3.95

Figure 4. Amino Acid Composition

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Protein Template (Neurotrophin-3)

The searching results of a template with the access code of 3buk.1A (PDB-ID) discovered the level of *seq identity* of 98,32%, with QMEAN at -0,82 (Figure 5). The higher identity score, the better the homology level produced, which reflected the high levels of similarity between the *sequence template* and protein target. Agung *et al*. (2016) described that a protein that is homolog will tend to have similarity in their characters, one of them is from the structure view. *Template* with high similarity levels is fundamental in the homology methodology in building a prototype of protein target (Biasini *et al*., 2014).

Figure 5. The Searching Results of Template using SWISS-MODEL *Server*

Dimentional Structure of NT-3 Protein

The 3D structure results of NT-3 protein showed a *β-sheet* (Figure 6a) and loop construction (Figure 6b), with the high levels of similarity between protein target and protein template.

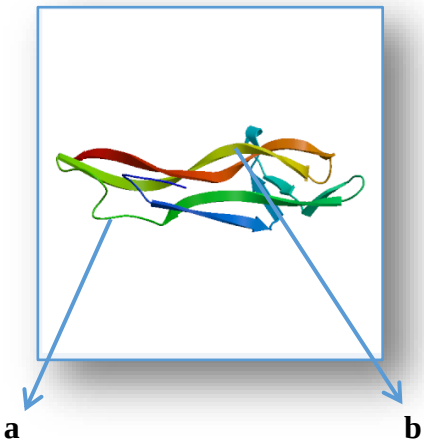

Figure 6. 3D NT-3 Protein (Target)

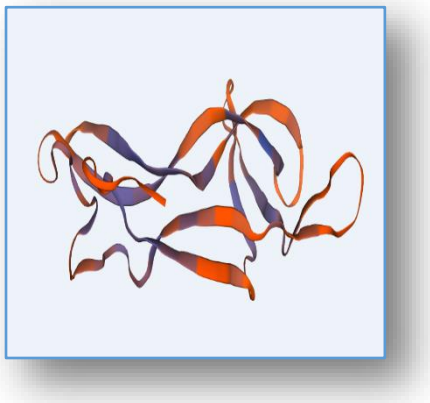

Figure 7. 3D Protein Template

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Structure of *β-sheet* and loop of NT-3 protein formation is the constituent part of secondary protein. As explained by Arjunan *et al*. (2001), the levels of secondary protein structure have constituent conformation consisting of alpha helix, *β-sheet* and loop. Loop structure is also called as non-regular, because CO and NH groups in the loop region do not form the hydrogen bonds (Arjunan *et al*., 2001). It is further explained that loop is a region from different length of protein chains and is located on the surface. The next formation of NT-3 protein is *β-sheet*, which is a sheet composed from a number of amino acid chains incorporated through hydrogen bonds between the CO groups from one peptide bond and the NH groups on another peptide bond that are closed and parallel so that established a multiple folding sheet (Irianto, 2017).

The structure form of 3D protein is determined by the composition of amino acid sequence (Arjunan *et al*., 2001). Each amino acid has a character or property that can distinguish one to another, which can help in predicting the structure formation of 3-dimension in the folding process of a protein. This process is vigorous for a protein to form a unique 3D structure in their biological function (Balchin *et al*., 2016). Tokheim *et al*. (2016) elucidated that functional proteins tend to fold establishing a 3-dimentional structure (3D). The formed 3D structure will learn the nature of functional proteins, in which each has their own specific structure.

Arjunan *et al*. (2002) disclosed that there is a correlation between structure and function in protein, in which a specific protein build-up reflects one function. Hence, the function of protein may be added or removed by changing their constructions in order to discover a required function. Besides that, the visualization results of 3D formation can expose the common shape of a protein, which is helix, sheet, and loop frame (Arjunan *et al*., 2002). Therefore, through this 3D protein structure, it can provide advantageous information in comprehending protein in molecular level (Wijaya & Hasanah, 2016).

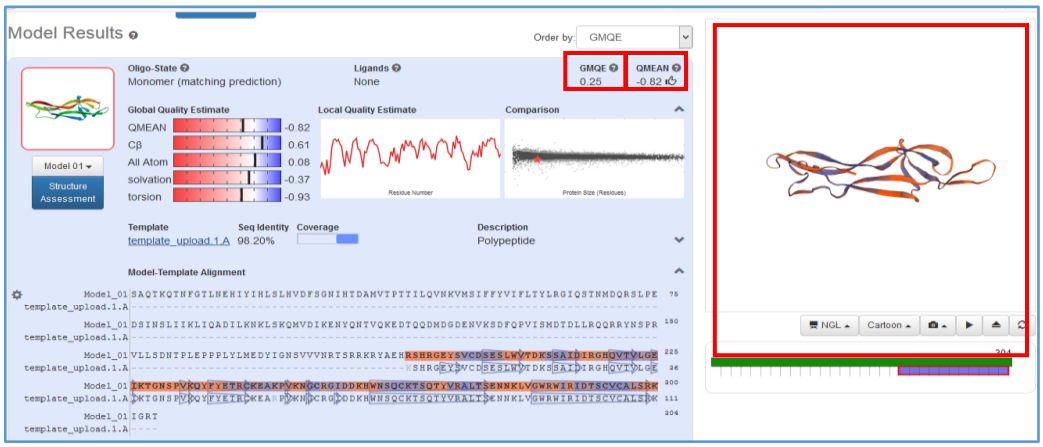

Figure 8. The Quality of Model Structure of Protein Target

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Structure Evaluation of NT-3 Protein Model

The results of structural evaluation of the built protein model were the crucial steps (Baker and Sali, 2001). The quality analysis results of NT-3 protein target observed the obtained values of QMEAN (*Quality Model Energy Analysis*), QMQE (*Global Model Quality Estimation*), and *identity* (Figure 8).

The results of *identity* values of NT-3 protein target and *template* were 98,20%. This percentage showed a high level similarity. The higher the percentage score (%) of sequence target *identity* and *template*, the closer the model structure to the real ones.

The analysis results obtained the 0.82 QMEAN of protein target. QMEAN is a combined function assessment based on the different geometric properties and provides an absolute quality prediction of the whole structure and each residues according to one single model. The good range of QMEAN score is 0,1 to 1 (Schwede *et al*., 2008). Based on this range, the obtained QMEAN score of this protein shape was good.

The result of QMQE (*Global Model Quality Estimation*) values of NT-3 protein target was 0,25. The GMQE scores with a range of 0-1 indicate the correspondence of residues on the target and *template* structures which reflects the expected accuracy of a model. Ekins *et al*. (2016) demonstrated that the results of the best homology models were elected according to GMQE and QMEAN.

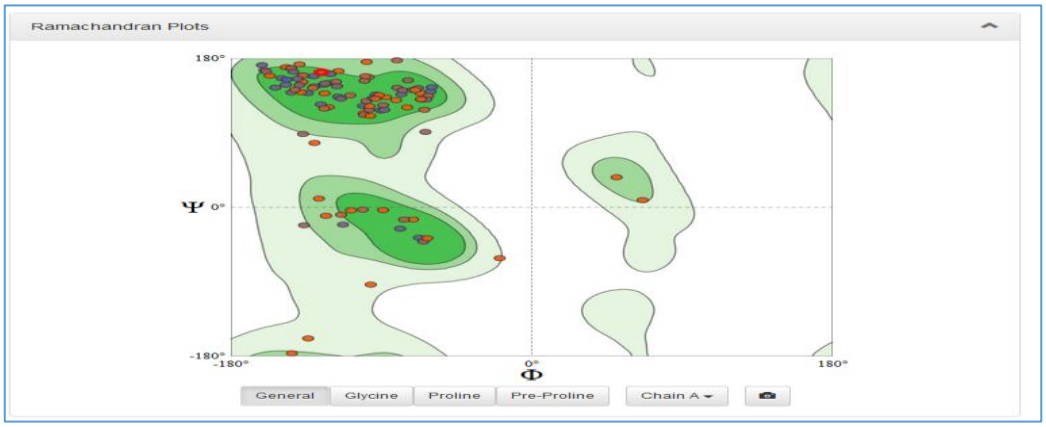

Figure 9. Ramachandran Plot

Ramachandran plot has an internal coordinate consisting of dihedral φ (phi) angles as x-axis, and ψ (psi) angles as y-axis (Figure 9). Ramachandran plot has 4 kinds of regions, i.e *most favoured*, *additional allowed*, *generously allowed*, and *disallowed region* (Kleywegt and Jones, 1996). Through this plot, it can be known that a protein structure has a good quality or not, by examining the residue percentages of non-glycine amino acids in the *outlier* areas and the residue of amino acids in the *most favoured region*. The residue of non-glycine in the *outlier* regions was less than 15%, and in the *most favoured region* was more than 90% (Gaffar

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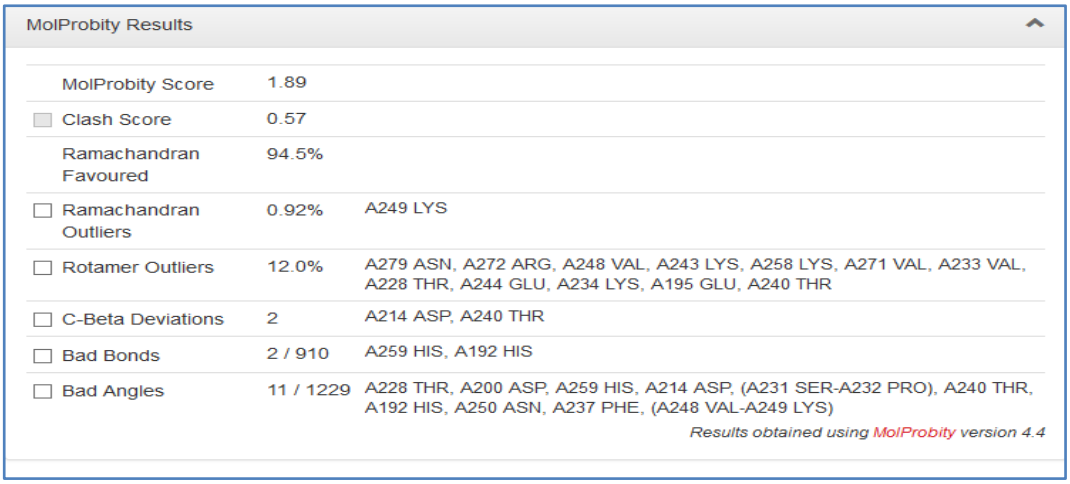
dkk., 2016), which indicated that protein structure has an excellent quality. The results of assessment analysis on the 3D structure of NT-3 protein on Ramachandran plot were elaborated on *MolProbality Results* (Figure 10). Based on these results, it was found that the residue numbers of amino acids in the *most favoured region* were 94,5%, and the residue numbers of amino acids in the *outlier* were merely 0,92%. This finding indicated that the 3-dimentional structure results of NT-3 protein has an excellent structural quality.



MolProbity Results

MolProbity Score	1.89	
Clash Score	0.57	
Ramachandran Favoured	94.5%	
Ramachandran Outliers	0.92%	A249 LYS
Rotamer Outliers	12.0%	A279 ASN, A272 ARG, A248 VAL, A243 LYS, A258 LYS, A271 VAL, A233 VAL, A228 THR, A244 GLU, A234 LYS, A195 GLU, A240 THR
C-Beta Deviations	2	A214 ASP, A240 THR
Bad Bonds	2 / 910	A259 HIS, A192 HIS
Bad Angles	11 / 1229	A228 THR, A200 ASP, A259 HIS, A214 ASP, (A231 SER-A232 PRO), A240 THR, A192 HIS, A250 ASN, A237 PHE, (A248 VAL-A249 LYS)

Results obtained using MolProbity version 4.4

Figure 10. *MolProbality Results* on Ramachandran Plot

CONCLUSION

The 3-dimentional structure of NT-3 protein in *Columba livia* used a protein target with the access code of PKK30025.1, and a *template* with the access code of 3buk.1A. The results of 3-dimensional structure suggested the *β-sheet* and loop construction with the highest amino acid composition of serine (8,88 mol) and the lowest amino acid composition of tryptophan (1,32 mol). The evaluation results of 3D structure of NT-3 protein exposed the values of *seq identity* at 98,20%, QMEAN at -0,82, QMQE at 0,25, with the structural quality on Ramachandran plot in the *outliers* was 0,92%, and in the *most favoured region* was 94,5%, which presented an excellent quality.

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