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SEQUENCE ANALYSIS AND HOMOLOGY MODELING OF MOUSE TRPV5 AND TRPV6 CHANNELS

AZREENA IZZATY ABD MANAN

FACULTY OF PHARMACY

MARA UNIVERSITY OF TECHNOLOGY (UiTM)

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APPROVAL FORM

I hereby recommend that the thesis prepared under my supervision by Azreena Izzaty Binti Abd Manan entitled ‘Sequence analysis and homology modeling of mouse TRPV5 and TRPV6 channels’ be accepted in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy from Faculty of Pharmacy, UiTM.

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(Date) (Dr. Siti Azma Yusof)

Supervisor

……. ……

(Date) (Professor Dr. Aishah Adam)

Dean Faculty of Pharmacy

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ABSTRACT

Transient receptor potential (TRP) channels are a group of cation channel that comprise of several sub-families which have important function in human body. One of the TRP channel sub-family, named transient receptor potential vanilloid (TRPV) channel especially TRPV5 and TRPV6 are associated with many diseases and cancers including breast and prostate cancers. Therefore, TRPV channels are expected to be very significant for future drug targets. In order to seek for new drugs that targeted on this type of ion channel, the structure, function and mechanism of this target protein need to be elucidated. Unfortunately, there is still no complete high-resolution structure available yet for TRPVs. Because of that, researchers only can predict the structure, function and mechanism of this protein through biochemical data and computational predicted models. Homology modeling method is significantly useful in developing a structure of the target protein. It is the initial part of the computational drug-design process that offers many advantages including cost and time efficiency compared to the former conventional method. The objectives of this study are to develop three-dimensional structures of mouse TRPV5 and TRPV6 channels using homology modeling method and to compare models of mouse TRPV5 and TRPV6 generated based on three multiple sequence alignments which are ClustalW, MAFFT and MUSCLE. In this study, a homology modeling method was used in order to construct and predict the atomic resolution models of mouse TRPV5 and TRPV6 protein channel. This study focused mainly on the construction of the transmembrane region (S1-S6) of both TRPV channels. In homology modeling method, the steps involved including selection of protein template, multiple sequence alignment of mouse TRPV5 and TRPV6 sequence with the protein template sequence by using the selected algorithms, transmembrane-domain prediction, model development and finally, model comparison and evaluation. In this study, Shaker family voltage dependent potassium channel (kv1.2-kv2.1 paddle chimera channel) (PDB ID 2R9R) was selected as the template .The results show that the models of mouse TRPV5 and TRPV6 generated based on ClustalW alignment are the best models due to the lowest RMSD values, the lowest z-score values viewed in ProSA plot and the highest percentage of residues in most favored region showed in the Ramachandran plot. Therefore, ClustalW is the best alignment that produces good quality models compared to MAFFT and MUSCLE algorithms.