UNIVERSITI PUTRA MALAYSIA

MOLECULAR SIMULATION BETWEEN AMYLOID BETA (1-42), A PEPTIDE ASSOCIATED WITH ALZHEIMER DISEASE, AND ZINC(II) ION

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By

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MOLECULAR SIMULATION BETWEEN AMYLOID BETA (1-42), A PEPTIDE ASSOCIATED WITH ALZHEIMER DISEASE, AND ZINC(II) ION

By

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June 2016

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Faculty : Science

Alzheimer's disease (AD) is a brain disorder resulting from the accumulation of amyloid-forming (both as amyloid-β and tau). Aβ peptide is present in everyone's brain, but the amyloid plaques found in AD's patients are abnormal, as they can degenerate nerve endings. The number of Alzheimer's patients is increasing rapidly while there are no specific solutions being reported yet to treat AD effectively. Amyloid-$\beta_{(1-42)}$ is a major fragment from amyloid precursor protein (APP) which tends to aggregate into mature amyloid fibrils through a number of intermediate structural forms, also called the oligomers or protofibrils. They are toxic to neurons. The mechanism by which Aβ aggregates in the brain is not fully understood, however there is increasing evidence that metal ions may play an important role in this aggregation process. In a healthy brain, the metal ion content is stringently regulated and the concentration of free metal ions is kept at a very low level.

Researchers nowadays are trying to uncover the neurodegenerative role of transition metals and the oxidative stress in AD which has been found to be responsible for major cellular problems. There are a vast number of experiment studies trying to shed some light on these processes but the lack of theoretical studies on this matter is quite visible. Here, we investigated the effect of zinc ion on $A\beta_{(1-42)}$ and its aggregation water and its mixture with hexafluoroisopropanol (HFIP) using molecular dynamics calculations. From our results, the amyloid-$\beta_{(1-42)}$ fragment and its aggregated structure showed good stability in both conditions which were with and without zinc in water based on the root mean square deviation and radius of gyration calculations over 1 μs and 100 ns simulation time for aggregation process. Besides that, $A\beta_{(1-42)}$ with and without zinc tend to produce more helical structures in solvent mixture, but no α-helix was detected in both Aβ-H_2O and Aβ-Zn-H_2O models.

The flexibility of $A\beta_{(1-42)}$ in solvent mixture was lower than $A\beta_{(1-42)}$ in water due to the length of its helical structure. In contrast, the presence of metal ion increased the flexibility of $A\beta_{(1-42)}$ when the peptide was placed in the solvent mixture, compared to its flexibility in water. Our aggregation study showed that 6Aβ-6Zn-HFIP-H_2O model had significant changes in secondary structures, compared to 6Aβ-6Zn-H_2O system. There was also a good correlation with the low flexibility of peptide in water. In addition, $A\beta_{(1-42)}$ with zinc in water produced less helical structure compared to $A\beta_{(1-42)}$ with zinc in mixed solvent. As shown in secondary structure analysis, the aggregation process occurred rapidly in water after 20 ns compared to solvent mixture where the fully spherical structure was not shown in the mixed solvent.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk Ijazah Master Sains

SIMULASI MOLEKUL DIANTARA AMILOID BETA (1-42), PEPTIDA YANG BERKAITAN DENGAN PENYAKIT ALZHEIMER DAN ION ZINK(II)

Oleh

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Penyakit Alzheimer merupakan penyakit gangguan otak yang disebabkan oleh pengumpulan amiloid yang terdiri daripada kedua-dua protein luar sel, amiloid beta (Aβ) dan intrasel (tau). Setiap manusia mempunyai peptida Aβ di dalam otak tetapi kandungan plak-plak amiloid yang ditemui pada pesakit Alzheimer adalah luar biasa kerana mereka boleh menyebabkan kemerosotan hujung saraf. Kuantiti pesakit Alzheimer semakin meningkat dengan mendadak sedangkan tiada penyelesaian yang spesifik dilaporkan untuk merawat AD secara efektif. $A\beta_{(1-42)}$ merupakan pecahan utama yang terhasil daripada amiloid pelopor protein (APP) yang tercenderung untuk berkumpul (agregat) kepada gentian amiloid matang melalui sebilangan bentuk struktur pertengahan yang juga dikenali sebagai oligomer atau protofibril. Ia merupakan racun kepada neurons.

Mekanisme untuk Aβ bergumpal di dalam otak masih belum difahami sepenuhnya, walaubagaimanapun, terdapat banyak bukti ion-ion logam yang juga memainkan peranan dalam proses agregat ini. Otak yang sihat mempunyai kandungan ion logam yang spesifik dan kepekatan bagi ion logam yang bebas berada pada tahap yang sangat rendah. Para penyelidik pada masa kini sedang mencuba membongkar peranan neurodegeratif logam peralihan dan tekanan oksidatif yang merupakan punca bagi masalah selular secara keseluruhan. Pelbagai ujikaji telah dilakukan untuk mencari sinar dalam proses ini tetapi kekurangan ilmu dalam bidang teori dalam kajian ini kelihatan jelas. Di dalam penyelidikan ini, kami mengkaji tentang kesan ion zink terhadap $A\beta_{(1-42)}$ dan penggumpalannya dalam air serta larutan bercampur yang mengandungi air dan larutan hexafluoroisopropanol (HFIP) dengan menggunakan kaedah pengiraan dinamik molekul.

Keputusan kami menunjukkan bahawa struktur amyloid-β dan pengumpulan $A\beta_{(1-42)}$ menunjukkan kestabilan yang baik untuk semua keadaan iaitu dengan zink dan tanpa zink di dalam air berdasarkan varians sisihan punca min kuasa dua (RMSD) dan jejari legaran (R_g) untuk 1 μs and 100 ns untuk proses penggumpalan masa simulasi. Selain itu, $A\beta_{(1-42)}$ dengan zink dan tanpa zink menghasilkan kuantiti alfa-helik yang banyak di dalam larutan bercampur tetapi tidak kelihatan alfa-helik langsung pada model Aβ-H_2O dan Aβ-Zn-H_2O. Fleksibiliti $A\beta_{(1-42)}$ di dalam larutan bercampur adalah rendah berbanding dengan $A\beta_{(1-42)}$ dalam air disebabkan oleh alfa-helik yang panjang. Sebaliknya, kehadiran ion logam meningkatkan fleksibiliti $A\beta_{(1-42)}$ apabila peptida itu diletakkan dalam larutan bercampur berbanding dengan fleksibilitinya di dalam air.

Kajian kami dalam proses pengumpulan telah menunjukkan bahawa model 6Aβ-6Zn-HFIP-H_2O mempunyai perubahan yang ketara dalam struktur sekunder berbanding dengan sistem 6Aβ-6Zn-H_2O. Terdapat korelasi yang baik dengan peptida yang mempunyai fleksibiliti rendah dalam air. Tambahan pula, $A\beta_{(1-42)}$ dalam larutan bercampur dengan zink ion dalam air menghasilkan struktur helik yang rendah berbanding dengan $A\beta_{(1-42)}$ dan zink ion di dalam larutan bercampur. Proses penggumpalan berlaku dengan pantas di dalam air iaitu selepas 20 ns tetapi pembentukan sfera tidak dapat ditunjukkan sepenuhnya di dalam larutan bercampur.

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I certify that a Thesis Examination Committee has met on 09 June 2016 to conduct the final examination of Nur Syafiqah binti Abdul Ghani on her thesis entitled "Molecular Simulation Between Amyloid Beta (1-42), a Peptide Associated With Alzheimer Disease, and Zinc(Ii) Ion" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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Name of Member of Supervisory Committee: Prof. Dr. Mahiran Basri

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
APP	Amyloid Precursor Protein
APS	Aggregation Prone Structure
ATB	Automated Topology Builder
Aβ	Amyloid Beta
AβPP	Amyloid Beta Precursor Protein
CD	Circular Dichroism
CHC	Hydrophobic Core
CNS	Central Nervous System
CPU	Central Processing Unit
CQ	Compound Dioquinol
CSHA	Canadian Study of Health and Aging
DMD	Discrete Molecular Dynamics
DOPS	Dioleoylphosphatidylserine
DPPC	Dipalmitoylphosphatidycholine
DSSP	Definition of Secondary Structure of Protein
ESR	Electron Spin Resonance
EURODEM	European Community Concerted Action on Epidemiology and Prevention of Dementia
HFIP	Hexafluoroisopropanol / 1,1,1,3,3,3-hexafluoropropan-2-ol
IAPP	Islet Amyloid Polypeptide
LMW	Low Molecular Weight
MD	Molecular Dynamics

NFTs	Neurofibrillary Tangles
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
NPT	Number of particle, Pressure, Temperature
NVT	Number of particle, Volume, Temperature
PBN	Phenyl-tert-butyl-nitrone
PBS	Phosphate-Buffered Saline
PCDs	Protein Conformational Disorders
PDB	Protein Data Bank
POPG	Palmitoyloleoylphosphatidylglycerol
REMD	Replica Exchange Molecular Dynamics
RMSD	Root Means Square Deviation
RMSF	Root Means Square Fluctuation
ROS	Reactive Oxygen Species
SASA	Solvent Accessible Surface Area
SDS	Sodium Dodecylsulfate
SPC	Simple Point Charge
TEM	Transmission Electron Microscopy
TFE	Trifluoroethanol
ThT	Thioflavin-T
VMD	Visual Molecular Dynamics
Zn	Zinc

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CHAPTER 1

INTRODUCTION

The most regular basis of dementia in aging individuals all over the world is Alzheimer's disease (AD). As a person gets older, AD becomes a more critical and ever-growing public health problem. AD is known as a type of prion-related illness that shows up in various diseases, for example Creutzfeldt-Jakob, bovine spongiform encephalopathy and Mad Cow. Statistically, in 2010, 5.1% of the US community was older than 65 years and about 454,000 AD cases were recognized, followed by a 10% boost up to 2,000 numbers each year (Abbott, 2011). There are no medicine, efficient approaches or powerful precautionary part for AD but younger generations may take some drugs to improve the cholinergic system, such as galantamine (Razadyne), donepezil (Aricept), tacrine (Cognex) and rivastigmine (Exelon) to avoid the risk of developing AD (Mancuso *et al*., 2011). The AD consequences on the mind are widely manifested over the failure of cholinergic neurons.

AD causes around 66.67% of extensive crisis of dementia (Pasture and Onkia, 1994). There are two well-known groups which analyse the risk factors of AD; the European Community Concerted Action on Epidemiology and Prevention of Dementia (EURODEM), and the Canadian Study of Health and Aging (CSHA) association. The EURODEM stated that smoking might raise the danger of AD (Launer *et al*., 1999), but there were no specific studies to observe the relationship between smoking and the onset of AD (Hebert *et al*., 1992, Wang *et al*., 1999; Dol *et al*., 2000).

EURODEM also reported that sex and low educational level were highly associated with the AD cases. However, they were not considered as possible aspects that triggered AD in other researches (Cobb *et al*., 1995; Yoshitake *et al*., 1995). On the other hand, the CSHA performed an enormous study of dementia towards aging people by concentrating on its popularity (Posture and Onkia, 1994), incidence (McDowell *et al*., 1994) and risk factors (McDowell *et al*., 1994; Lindsay *et al*., 1997; Hébert *et al*., 2000). It was found that, either the amyloid-β precursor protein (AβPP) or some enzymes for example, presenilin-1 from the metabolism process had contributed about 5% of the AD cases.

Both neural oxidative stress and neuroinflammatory events are crucial factors in the neurodegenerative landscape of AD. AD is regularly defined and distinguished by the existence of both Aβ-rich plaques (neuritic) and neurofibrillary tangles (NFTs) in the range of the entorhinal cortex, hippocampus and isocortex, that combined with synapse loss and clinical dementia (Duyckaerts *et al*., 2009). Aβ plaques have been effectively investigated for almost three decades and have been carefully analyzed. The 40-42 amino acids of Aβ peptides which are produced from a classic single-pass type 1 transmembrane protein called the amyloid precursor protein (APP) can form neurotoxic oligomers, to be ultimately restored in the hightly hydrophobic extracellular deposits, also known as plaques.

These plaques tend to concentrate over time and eventually, they become a dense core or neuritic structures in the advanced stages of disease (D'Alton *et al.*, 2011; Karran *et al.*, 2011). The pathological modification of amyloid precursor protein towards the uncontrolled quantity of Aβ in numerous forms (monomers. oligomers, protofibrils and fibrils) will lead to precipitation in the downstream processes, including the neuroinflammatory activation of microglia and neuritic pathology. Then, it will induce tangles' formation and cell death. Aβ has also been linked to the initiation of other AD pathophenomena. In addition, some studies propose that the oligomeric Aβ is more toxic than the Aβ fibrils themselves (Glabe *et al.*, 2005). The NFTs are usually found in the neocortical grey matter parenchyma. They are produced from proteins (MAPs) and many other components that have been identified using immunohistochemistry, immunoprecipitation and laser capture microdissection-mass spectrometry methods (Wang *et al.*, 2005; Duyckaerts *et al.*, 2009).

The tau protein functions as a stabilizer by attaching the mictrotubules (MTs) to increase its rigidity along the length of axons (Obulesu *et al.*, 2011). Even though AD diagnosis generally needs a burden of plaques plus tangles, their mere presence do not always coincide with neuron loss or clinical dementia prior to death and autopsy (Green *et al.*, 2000; Price *et al.*, 2009). The human brain appears particularly vulnerable to oxidative stress. This necessitates the elaboration of complex antioxidant defenses in order to maintain oxidative balance. Vitamin A, C and E, glutathione and a several number of enzymes are the antioxidants that facilitate electron transfer to a nontoxic species such as catalase, superoxide dismutase and glutathione peroxidase. Each of them has been proven to decrease with age. Hence, the vulnerability of brain to oxidative stress originates from a number of various mechanisms.

In a healthy brain, the amount of metal ion is strictly standardized and the metal concentrations are kept at a very low level. The metal ions which are necessary for biological function and metal-binding of proteins (*i.e.* metalloproteins) constitute around one third of the proteome. The transition metals have a growing role of interactions on brain-related diseases because of their participation in biochemical reactions, forming free radicals. It is well known that oxidative stress is responsible for major cellular problems. The relationship between the AD disease and metals has been mostly studied by focusing on local accumulations of plaques in brain areas at high risk for AD (Squitti *et al.*, 2013). The hypothesis of Aβ-induced oxidative stress in AD patients (Markesbery *et al.*, 1997; Butterfield *et al.*, 2009) has been supported by Aβ-induced elevation of oxidative stress marker in brain and the subsequent neuronal degeneration (Frautschy *et al.*, 1991).

The research interest on the metal ions' position, specifically zinc, copper, aluminium, and iron in the neurobiological processes is growing rapidly. There are increasing evidences which demonstrate the interactions of zinc (II) and copper (II) ions with Aβ peptides and their effects towards fibrilization and toxicity. A lot of Zn^{2+} and Cu^{2+} ions are present in the synaptic area of the brain. It is possible that the age-related dyshomeostasis of these biometals are associated with the AD pathology. The assembly of Aβ into tinctoral aggregates as induced by Zn^{2+} ion was first reported by Bush and colleagues in 1994 where the aggregation was caused by sub-stoichiometric concentrations of Zn^{2+} (Bush *et al.*, 1994).

Tougu *et al*. (2011) also stated that $A\beta_{40}$ can aggregate in the presence of Zn^{2+} ions in a millisecond period (Noy *et al*., 2008). Previous studies reported two possible ways. First, the metal ions will attach to amyloid monomers and accumulate in the brain to form oligomers through the aggregation of metallated monomers. Next, they will connect the pre-formed apo-oligomers. Due to the various arrangements and distributions of the monomer and oligomer ensembles, these two pathways may eventually show different binding abilities of the metal ions that are connected to oligomers (Miller *et al*., 2012). The Alzheimer's cases are increasing rapidly in number worldwide, yet there is no exact medicine for AD to date. Several evidences have shown that the interaction of Aβ with transition metal ions can lead to the aggregation and toxicity (Bolognin *et al*., 2011). The mechanism of its action has been explained by a few experimental works but the data obtained are still limited (Nilsson, 2004; Takano, 2008; Vivekanandan *et al*., 2011).

The experimental results could not identify the necessary approach to figure out the direct protein-metal interactions at the single-molecular level. The problem faced in most experimental approaches is the direct observation of protein-protein and protein-metal interactions which require the proteins to be soluble and analyzed using several forqualitatic methods such as electrophoresis, mass spectrometry, and chromatography. Without a doubt, this will pose considerable challenges for those who adopt insoluble amyloid configuration in the direct analysis. In addition, X-ray crystallography and other related procedures depend upon protein crystallization in the first place which is not effective in describing heterogeneously sized oligomers, polymers and amorphous aggregates or insoluble amyloid proteins (Pedersen & Heegard, 2013). Nowadays, the amount of molecular biological data is increasing rapidly, thus the computer-based analysis of molecular interactions has become more and more practical.

Molecular modeling involves all theoretical methods and computational skills to model, predict or even mimic the routine of molecules. In this study, they were applied on Aβ peptide by treating the protein as the monomer to produce mechanistic and structural information of its aggregation processes, because Aβ peptide can aggregate very fast in water. However, using all-atom force field for full length MD simulations of $A\beta_{40}$ and $A\beta_{42}$ in aqueous solution is very challenging. Therefore, limited findings from MD have been reported. For example, Santini *et al*. (2004) and Rodziewicz-Motowidlo et al. (2008) simulated the hydrophobic core of $A\beta_{16-22}$ only, using implicit solvent model (Santini *et al*., 2004; Rodziewicz-Motowidło *et al*. 2008), while others used the coarse-grained MD approaches.

The combination of coarse-grained atomic representations and the enhanced computational power, has allowed us to perform the simulations of biological complex systems within microsecond or millisecond time frame (Tozzini, 2005). Moreover, the timescales accessible to simulation coincide with the particular that is reachable using high advanced spectroscopic techniques. Therefore, it is possible to directly compare MD observations with the experimental results, for example, the complex aggregation of soluble proteins into fibrillar species (Wu and Shea, 2011). The coupling of powerful computers and molecular modeling approaches such as molecular docking and MD makes computational chemistry an exciting area for groundbreaking researches with lots of capabilities (Karplus and Kuriyan, 2005).

1.1 Objectives

The main objectives of this study were to identify the amyloid-$\beta_{(1-42)}$ peptide interaction with zinc ion in water and its mixture with hexafluoroisopropanol (HFIP) followed by exploring the aggregation process of this peptide in the presence of metal by using MD simulation technique. Therefore, these specific objectives were selected:

- To simulate the interaction of $A\beta_{(1-42)}$ peptide with zinc ion in different solvent conditions.
- To model the aggregation process of $A\beta_{(1-42)}$ peptide in the presence of zinc ion in different solvent conditions.
- To determine the dynamics, flexibility and structural changes of both model systems after interacting with metal.

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BIODATA OF STUDENT

Nur Syafiqah Binti Abdul Ghani was born on 31st August 1989 and received her first educational at Sek. Ren. Rantau Panjang at Melaka and continued for secondary level at Sek. Men. Sultan Alauddin also in Melaka. After SPM she got offered to continue studied in Johor Matriculation College, Tangkak, Johor for one year and further her high level education in Universiti Putra Malaysia on 2008. She graduated with a major of Bachelor of Science (Hons.) Petroleum Chemistry in 2011 and her final year project was in organic field which entitled "Chemical Consistuent in *Cratoxylum Arborescens*" under supervision Prof Gwendoline Ee Cheng Liang. Before she started her studies as a Master student, she was working as a Material Engineer at Shah Alam, Selangor. Almost one year working, she got an offered from her supervisor, Dr. Roghayeh Abedi Karjiban who is looking a master student in computational of theoretical and chemistry on March 2012. She thought this was the best opportunity to further her studies in computational field and she also wants to learn something new because she preferred chemistry in her life more. She worked as research assistant for six months before continued as official master student under supervision Dr Roghayeh and co-supervisor, Prof Mahiran Basri. On the way to complete her worked, in the middle of the end of semester she was married with her husband, Nor Irman Yajis on 14th of June 2014. Right now in the middle of writing her thesis, she was pregnant and got delivered on 27th August 2015 her son was coming out and the name was Muhammad Iqbal.

LIST OF PUBLICATIONS

Published

Nur Syafiqah Abdul Ghani, Roghayeh Abedi Karjiban, Mahiran Basri, NurHana Faujan and Lim Wui Zhuan. Unveiling Amyloid-$\beta_{(1-42)}$ interaction with Zinc in water and mixed hexafluoroisopropanol solution in Alzheimer's disease. International Journal of Peptide Research and Therapeutics. DOI: 10.1007/s10989-016-9570-4 (Accepted)

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Zarina bt Ahmad, Roghayeh Abedi Karjiban, Nur Syafiqah Abdul Ghani (2015). Comparison of Amyloid-$\beta_{(1-42)}$ in Different Solvent and Temperature. 18th Industrial Chemistry Seminar, 9 June, Cyberview Resort & Spa, Cyberjaya, Malaysia.

Nur Syafiqah Abdul Ghani, Roghayeh Abedi Karjiban, Mahiran Basri (2014). Structural Comparison Between $A\beta_{(1-42)}$ and $A\beta_{(1-42)}$-Zn in Water. 18th Malaysian International Chemical Congress (18MICC) 2014, PWTC, 3-5th November, Kuala Lampur, Malaysia.

Nur Syafiqah Abdul Ghani, Roghayeh Abedi Karjiban, Mahiran Basri (2014). A Comparison between the Structure of Amyloid-$\beta_{(1-42)}$ without and with Zinc in Mixed Solvent. The Fundamental Science Congress (FSC 2014), 19-20th August, Auditorium Jurutera, Universiti Putra Malaysia, Malaysia.

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Nur Syafiqah Abdul Ghani, Roghayeh Abedi Karjiban, and Mahiran Basri (2013). Computational Simulation of Amyloid-$\beta_{(1-42)}$ in the Mixed Solvent. 38th Annual Conference of the Malaysian society for Biochemistry and molecular Biology, Putrajaya Marriot hotel & spa, Putrajaya, 28-29th August, Malaysia.