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RESEARCH ARTICLE

Insights Into Resveratrol as an Inhibitor Against $A\beta_{1-42}$ Peptide Aggregation: A Molecular Dynamics Simulation Study

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Abstract: ***Background*:** Resveratrol (RSV), a polyphenolic compound, is reported to have anti-aggregation properties against Amyloid-beta peptides. It is, therefore, significant to understand the mechanism of inhibition of $A\beta_{1-42}$ peptide aggregation by the RSV at the molecular level. We have used Molecular docking along with Molecular dynamics (MD) simulation techniques to address the role of RSV in the inhibition of $A\beta_{1-42}$ peptide aggregation.

***Objective*:** To understand the role of Resveratrol on the $A\beta_{1-42}$ peptide aggregation.

***Methods*:** In this computational study, we have docked the RSV to $A\beta_{1-42}$ peptide using Molecular Docking software and then performed MD simulation for the $A\beta_{1-42}$ peptide monomer $A\beta_{1-42}$ peptide-RSV complex using the AMBER force field. From the analysis of MD trajectories, we obtained salient structural features and determined the Binding Free Energy(BFE) and Per-residue Energy Decomposition Analysis (PRED) using MM-PBSA/GBSA method.

***Results*:** The secondary structure and the conformational analysis obtained from MD trajectories show that the binding of RSV with the $A\beta_{1-42}$ peptide monomer causes an increase in the helical content in the structure of the $A\beta_{1-42}$ peptide. The BFE and PRED results show a high binding affinity (GB_{total}=-11.07 kcal mol^{-1}; PB_{total}= -1.82 kcal mol^{-1}) of RSV with $A\beta_{1-42}$ peptide. Also, we found the RSV to interact with crucial residues (Asp 23 and Lys 28) of the $A\beta_{1-42}$ peptide. These residues play a significant role in facilitating the formation of toxic amyloid oligomers and amyloid fibrils. The salt bridge interaction between these residues D23-K28 was found to be destabilized in the $A\beta_{1-42}$ peptide when it is complexed with RSV.

***Conclusion*:** In summary, it can be concluded that Resveratrol greatly aids the prevention of $A\beta_{1-42}$ peptide aggregation. Therefore, it can be considered a possible drug candidate for therapeutic strategies for Alzheimer's disease.

Keywords: Molecular dynamics, protein aggregation, resveratrol, $A\beta_{1-42}$ peptide, polyphenol, alzheimer's disease.

1. INTRODUCTION

The folding of a protein from its nascent state into its native three-dimensional structure is one of the most important biological events [1]. It is the protein's native structure that allows it to survive in such a complicated biological environment and interact selectively with other biomolecules. As a result, it should come as no surprise that the failure of proteins to undergo folding into their native state or to stay in their native state can disrupt normal biological functioning and lead to a wide range of clinical disorders [2, 3]. Misfolded proteins might interact with one another to form aggregates [4-6]. These clumps are either amorphous or highly organized. Physical factors like temperature, pH, oxidative stress, ionic strength, peptide concentration, and other environmental factors all influence amyloid formation. These highly organized protein fibrils create aggregates, which can contribute to degenerative disorders like Alzheimer's Disease, Parkinson's Disease, Type II diabetes, and others [7-11]. Amyloid plaques and neurofibrillary tangles are pathological indicators of AD, the most prevalent neurodegenerative disease in the brain [12, 13]. A significant neurological finding in AD is an abnormal extracellular buildup of Aβ peptide, the main substance in senile plaques that may be considered a key factor [14-16]. In an Aβ aggregation pathway, oligomerization of monomeric peptides initiates a complicated series of structural changes that result in the production of amyloid fibrils. Amyloidogenesis and the creation of highly toxic oligomers appear to be caused by a conformational change in Aβ from its original random coil or α-helical shape to a β-sheet conformation. [17-22]. This Aβ peptide exists in two isoforms, $A\beta_{1-40,}$ and $A\beta_{1-42}$ peptide.

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Computational investigation on the effect of Oleuropein aglycone on the α-synuclein aggregation

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Effect of CTerm of human albumin on the aggregation propensity of Aβ1-42 peptide: a potential of mean force study

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Computational investigation on the role of C-Terminal of human albumin on the dimerization of $A\beta_{1-42}$ peptide

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ABSTRACT

Alzheimer's disease (AD) is characterized by the presence of Amyloid-beta (Aβ) peptide, which has the propensity to fold into β-sheets under stress forming aggregated amyloid plaques. Nowadays many studies have focused on the development of novel, specific therapeutic strategies to slow down Aβ aggregation or control preformed aggregates. Albumin, the most abundant protein in the cerebrospinal fluid, was reported to bind Aβ impeding its aggregation. Recently, it has been reported that C-terminal (CTerm) of Human Albumin binds with $A\beta_{1-42}$, impairs Aβ aggregation and promotes disassembly of Aβ aggregates protecting neurons. In this computational study, we have investigated the effect of CTerm on the conformational dynamics and the aggregation propensity of $A\beta_{1-42}$ peptide. We have performed molecular dynamics simulations on the $A\beta_{1-42}$-$A\beta_{1-42}$ homodimer and $A\beta_{1-42}$-CTerm of albumin heterodimer using the AMBER force field ff99SBildn. From the Potential of mean force (PMF) study and Binding free energy (BFE) analysis, we observed the association of $A\beta_{1-42}$ peptide monomer with itself in the form of homodimer to be stronger than its association with the CTerm in the heterodimer complex. The difference in the number of residues in the $A\beta_{1-42}$ peptide monomer (42 AAs) and CTerm (35 AAs) may be probable reason for the difference in association between the monomeric units in corresponding homodimer and heterodimer complexes. But even then CTerm shows a significant effect on the dimerization of $A\beta_{1-42}$ peptide. Our findings therefore suggest that CTerm can be used for the disassembly of $A\beta_{1-42}$ peptide monomer.

Keywords: *Molecular dynamics simulation; Amyloidosis; Amyloid plaques; Potential of mean force.*

1. INTRODUCTION

Proteins are very important biomolecules that sustain life through their distinct functions. The 3-D structure of a protein is important in understanding the dynamics and function of the protein [1]. Proteins, under normal conditions, tend to fold into a relatively stable, native, three-dimensional structure with the help of chaperons. Protein folding to obtain stable conformation is correlated with the function of proteins. Therefore, the folding of a protein into its correct native conformation represents a compromise between its thermodynamic stability and flexibility [2]. Though the native conformation is thermodynamically favorable, often it is found to be only slightly stable under various physiological conditions [3-6]. The failure in attaining the native conformation of proteins occurs commonly due to errors in molecular mechanisms in the cell processes such as translation, mutations, chemical, environmental or physical stress conditions, resulting in misfolded protein species. Cells in living organisms have devised an intrinsic protein quality control (PQC) system that consists of degradation pathways, a network of molecular chaperones, co-chaperones to control or remove the production of such misfolded proteins [7]. Under stress conditions, when the capacity of the PQC system gets overwhelmed, then this system fails to regulate the misfolded proteins. Aggregation of misfolded protein leads to the formation of pathogenic amyloids, causing amyloidosis, which is responsible for the occurrence of Neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington disease etc. [5, 8-10]. Dementias are responsible for the greatest burden of neurodegenerative diseases. According to WHO, Alzheimer's disease is the most common form of dementia and may contribute to 60–70% of cases. World Health Organization (WHO) also reported in their fact sheets that Worldwide around 50 million people have dementia, and there are nearly 10 million new cases every year representing approximately 60-70% of dementia cases, affecting large numbers of elderly Worldwide. The number of patients suffering from AD is increasing every year. With the advancement of the disease, the patient suffering from AD starts having problems including memory loss, mood and personality changes, inability to communicate, increased anxiety and/or aggression, and taking a longer time to complete normal daily tasks [10]. As the patient's condition deteriorates, bodily functions are lost, ultimately leading to death [9].

Alzheimer's disease is considered the most common neurodegenerative disorder [10-12]. The pathological hallmark of Alzheimer's disease is amyloid plaques, similar to some other neurodegenerative diseases. The major constituent of amyloid plaque is found to be Amyloid-Beta (Aβ) peptide [9, 11-13]. These amyloids exist as intracellular inclusions or extracellular plaques (amyloid). These amyloid deposits cause abnormal protein build-up in tissues and eventually lead to organ dysfunction and deaths. Amyloid-Beta (Aβ) peptide that is generated from the sequential cleavages of large membrane-spanning glycoprotein, amyloid precursor protein (APP) [14,15]. This Aβ peptide exists in two isoforms, $A\beta_{1-40}$ and $A\beta_{1-42}$ peptide. Between the two isoforms, the aggregation of $A\beta_{1-42}$ is found to be more significant and toxic [16]. The $A\beta_{1-42}$ peptide initially exists as an unordered random coil but it has the propensity to misfold into β-sheets and aggregate to form neurotoxic oligomers that eventually mature into amyloid fibrils [17]. Despite a high degree of sophistication,

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RESEARCH ARTICLE

Effect of Ionic Strength on the Aggregation Propensity of $A\beta_{1-42}$ Peptide: An *In-silico* Study

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Abstract: ***Background:*** Aggregation of misfolded proteins under stress conditions in the cell might lead to several neurodegenerative disorders. Amyloid-beta ($A\beta_{1-42}$) peptide, the causative agent of Alzheimer's disease, has the propensity to fold into β-sheets under stress, forming aggregated amyloid plaques. This is influenced by factors such as pH, temperature, metal ions, mutation of residues, and ionic strength of the solution. There are several studies that have highlighted the importance of ionic strength in affecting the folding and aggregation propensity of $A\beta_{1-42}$ peptide.

***Objective*:** To understand the effect of ionic strength of the solution on the aggregation propensity of $A\beta_{1-42}$ peptide, using computational approaches.

***Materials and Methods*:** In this study, Molecular Dynamics (MD) simulations were performed on $A\beta_{1-42}$ peptide monomer placed in (i) 0 M, (ii) 0.15 M, and (iii) 0.30 M concentration of NaCl solution. To prepare the input files for the MD simulations, we have used the Amberff99SB force field. The conformational dynamics of $A\beta_{1-42}$ peptide monomer in different ionic strengths of the solutions were illustrated from the analysis of the corresponding MD trajectory using the CPPtraj tool.

***Results*:** From the MD trajectory analysis, we observe that with an increase in the ionic strength of the solution, $A\beta_{1-42}$ peptide monomer shows a lesser tendency to undergo aggregation. From RMSD and SASA analysis, we noticed that $A\beta_{1-42}$ peptide monomer undergoes a rapid change in conformation with an increase in the ionic strength of the solution. In addition, from the radius of gyration (R_g) analysis, we observed $A\beta_{1-42}$ peptide monomer to be more compact at moderate ionic strength of the solution. $A\beta_{1-42}$ peptide was also found to hold its helical secondary structure at moderate and higher ionic strengths of the solution. The diffusion coefficient of $A\beta_{1-42}$ peptide monomer was also found to vary with the ionic strength of the solution. We observed a relatively higher diffusion coefficient value for $A\beta_{1-42}$ peptide at moderate ionic strength of the solution.

***Conclusion*:** Our findings from this computational study highlight the marked effect of ionic strength of the solution on the conformational dynamics and aggregation propensity of $A\beta_{1-42}$ peptide monomer.

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1. INTRODUCTION

Protein misfolding is an important phenomenon associated with the occurrence of multiple diseases, that include cancers, cardiovascular diseases, metabolism disorders, and several neurodegenerative disorders. Aggregation of misfolded proteins occurs when the normal cell conditions are compromised and the cell's protein quality control system fails to maintain protein homeostasis inside the cell [1-3]. The cellular pathways by which misfolded proteins are transported and cleared are widely studied because of their thera-

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RESEARCH ARTICLE

Investigation into the Interaction Sites of the K84s and K102s Peptides with α-Synuclein for Understanding the Anti-Aggregation Mechanism: An *In silico* Study

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Abstract: ***Background*:** α-Synuclein has become the main therapeutic target in Parkinson's disease and related Synucleinopathies since the discovery of genetic associations between α-Synuclein and Parkinson's disease risk and the identification of aggregated α-Synuclein as the primary protein constituent of Lewy pathology two decades ago. The two new peptides K84s (FLVWGCLRGSAIGECVVHGGPPSRH) and K102s (FLKRWARSTRWGTASCGGS) have recently been found to significantly reduce the oligomerization and aggregation of α-Synuclein. However, it is still unclear where these peptides interact with α-Synuclein at the moment.

***Objective*:** To examine the locations where K84s and K102s interact with α-Synuclein.

***Methods*:** In this investigation, the PEPFOLD3 server was used to generate the 3-D structures of the K84s and K102s peptides. Using the PatchDock web server, the two peptides were docked to the α-Synuclein molecule. After that, 50 ns of Molecular Dynamics (MD) simulations using the Amberff99SBildn force field were performed on the two resulting docked complexes. The two complexes' structure, dynamics, energy profiles, and binding modes were identified through analysis of the respective MD simulation trajectories. By submitting the two complexes' lowest energy structure to the PDBsum website, the interface residues in the two complexes were identified. The per residue energy decomposition (PRED) analysis using the MM-GBSA technique was used to calculate the contributions of each residue in the α-Synuclein of (α-Synuclein-K84s/K102s) complexes to the total binding free energy.

***Results*:** The binding of the two peptides with the α-Synuclein was demonstrated to have high binding free energy. The binding free energies of the (α-Synuclein-K84s) and (α-Synuclein-K102s) complexes are -33.61 kcal/mol and -40.88 kcal/mol respectively. Using PDBsum server analysis, it was determined that in the (α-Synuclein-K84s) complex, the residues GLY 25, ALA 29, VAL 49, LEU 38, VAL 40, GLU 28, GLY 47, LYS 32, GLU 35, GLY 36, TYR 39, VAL 48 and VAL 26 (from α-Synuclein) and SER 23, LEU 7, ILE 12, HIS 25, PHE 1, HIS 18, CYS 6, ARG 24, PRO 21 and ARG 8 (from K84s peptide) were identified to be present at the interface. In the (α-Synuclein-K102s) complex, the residues VAL 40, GLY 36, GLU 35, TYR 39, LYS 45, LEU 38, LYS 43, VAL 37, THR 44, VAL 49, VAL 48, and GLU 46 (from α-Synuclein) and ARG 10, GLY 12, GLY 18, SER 15, THR 13, SER 19, TRP 11, ALA 14, CYS 16, ARG 7, ARG 4 and GLY 17 (from K102s peptide) were identified to be present at the interface. The PRED analysis revealed that the residues PHE 1, LEU 7, ILE 12, LEU 2, VAL 3, GLY 5, and PRO 21 of the K84s peptide and residues VAL 48, ALA 29, VAL 40, TYR 39, VAL 49, VAL 26 and GLY 36 of α-Synuclein in the (α-Synuclein-K84s) complex are responsible for the intermolecular interaction. The residues ARG 4, ARG 10, TRP 11, ALA 14, SER 15, CYS 16 and SER 19 of the K102s peptide and residues GLU 46, LYS 45, VAL 49, GLU 35, VAL 48, TYR 39, and VAL 40 of α-Synuclein are responsible for the intermolecular interaction in the instance of the (α-Synuclein-K102s) complex. Additionally, it has been found that a sizable portion of the helical structure is preserved when α-Synuclein is in a complex form with the K84s and K102s peptides.

***Conclusion*:** Taken together the data implies that the two new peptides investigated here could be suitable candidates for future therapeutic development against α-Synuclein aggregation**.**

Keywords: Peptide inhibitor, alpha-synuclein, neurodegenerative disease, protein aggregation, interface statistics, misfolding.

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