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Research Article

The Aβ_{16-22} hexamer's aggregation under a co-effect of EGCG compound and low-pH concentration

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ABSTRACT

One of the most common forms of dementia is Alzheimer's disease (AD), and its relationship with β-amyloid plaques. The deposition of amyloid beta (Aβ) oligomers is proved to be a damage cause for AD patients in which the mechanism of Aβ_{16-22} fragments is believed to keep an important role in the fibrils' aggregations due to its' β-contents. Many previous searches showed that the more β-contents formed the more Aβ-fibrillary conformations created. In a previous study, the Aβ_{16-22} hexamer configuration under the inhibition of the epigallocatechin-3-gallate (EGCG) compound, which attenuated the production of β-sheet structure formation, was successfully constructed. However, the environment controlled 6Aβ_{16-22} association change was neglected. So, in this scheme we are motivated to make an atomistic investigation via two molecular dynamic simulations (MD): Aβ_{16-22} hexamer and EGCG complex, one in normal condition pH = 7.0 and the other in lower one pH = 5.5, respectively. The received data provides evidence to determine, the environmental difference does not change the number of H-bond between EGCG and Aβ fragment in which asserted that EGCG becomes a potential prospect in treating AD. Besides that, the results of simulations by using the DSSP tool of Gromacs package demonstrated that the averaging number of random-coil structure didn't change too much and received similar values of 24.4 and 24.6, and the decreasing of β-contents under the co-operative interaction of low pH and EGCG inhibitor. The Aβ_{16-22} free energy has slightly increased from -14,3 kcal.mol^{-1} to -13,8 kcal.mol^{-1} when pH concentration is reduced from normal pH = 7.0 to low on pH = 5.5. Finally, the computational results are in agreement with the experimental investigation, our observation adds a physical insight into the picture of the computational aided drug design in Aβ treatment.

Key words: Aβ oligomers, epigallocatechin-3-gallate, condition pH, β-contents

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INTRODUCTION

Protein aggregation is an inherent feature of polypeptides that lies behind and responds to a wide range of human pathologies, including Alzheimer's and/or Parkinson's diseases or type II diabetes. Alzheimer's Disease (AD) has been known as one of the most common Neurodegenerative Diseases (NDs) worldwide and the most common cause of dementia in elderly patients[1,2]. Science has proved that AD relates to the progressive accumulation of Aβ fibrils, especially by the aggregation of Aβ_{1-42}. Thus, for a long time ago, amyloid-beta protein (Aβ) has become the most promising target for one trying to develop a treatment for AD. However, up to now, only five drugs are approached by FDA to treat AD so finding disease-modifying AD therapies continuously remains urgent[3]. This makes the search for a new compound always challenging. In this context, the epigallocatechin-3-gallate (EGCG) compound has been remarkably studied for its therapeutic potential not only for AD but also for NDs[4,5].

The efficacy of EGCG is currently impressive. One of the first investigations on the benefits of EGCG, early in the 2000s, was performed by Choi YT *in vitro*[6]. The polyphenol EGCG of natural green tea was inserted into an Aβ-induced neurotoxicity model using cultured hippocampal neurons. EGCG compound significantly attenuated the production of β-sheet structure formation[7]. Besides that, via a study in 2010, EGCG inhibitor mediates remodel the β-sheet-rich amyloid structures and caused the formation of smaller protein aggregates that are nontoxic to mammalian cells[8].

Widely, the therapeutic potential of EGCG for AD was firstly demonstrated in 2005 using Swedish mutant APP-overexpressing mice (Tg APPsw) in which the intraperitoneal injection (20 mg/kg) of EGCG remarkably decreased Aβ levels and Aβ plaques in the brain[10]. Moreover, the ability of EGCG to reduce memory deficits and cognitive deterioration has been proved in these mice using the low (5 mg/kg) and high doses (15 mg/kg) of EGCG[11,12]. Researchers also reported that EGCG performed the Aβ amyloid fib-

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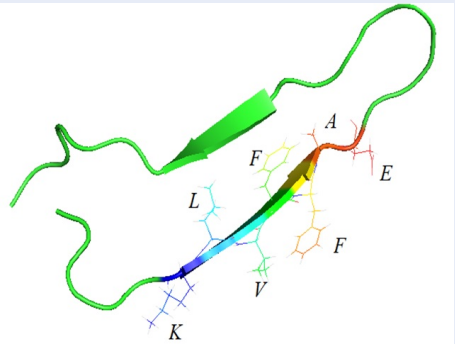

Figure 1: A full length oligomer (in green) and the secondary β – formation of a central hydrophobic core ($A\beta_{16-22}$ fragment) in the rainbow segment. Seven amino acids Lys-16 (K), Leu-17 (L), Val-18 (V), Phe-19 (F), Phe-20 (F), Ala-21 (A), Glu-21 (E) is named. The image is plotted by using the data from our previous study [9].

rils and oligomers. The mechanisms of EGCG–Aβ interactions can be explained by the interference of the EGCG compound with the aromatic hydrophobic core of Aβ, forming nontoxic Aβ oligomers and the nontoxic aggregates produced in the presence of EGCG [8]. The result was obtained by using magic angle spinning solid-state NMR spectroscopy [13]. *In silico*, studies focusing on understanding the mechanism of EG have been early proceeded [14-16] and researchers provided convincing evidence that the interventions of EGCG can prevent Aβ monomers to aggregate. Furthermore, there was proved through computational studies that EGCG preferentially binds to the hydrophobic region of Aβ peptides [9]. Briefly, evidence that the presence of EGCG is capable to inhibit the mechanism of the amyloid beta aggregation strongly supports EGCG to become a potential candidate in AD treatment.

Many environmental conditions, such as temperature, ionic strength, pH, temperature, protein concentration, and excipients concentration, play important roles in bimolecular aggregations. Solution pH can affect the macromolecular structure and colloidal stabilities, dictates the charge distribution on the protein surface, and then modulates intra-molecular and/or inter-molecular interactions [16]. The stabilization of EGCG compound and the amyloid beta protein [17] under low/high pH concentration was independently reviewed somewhere. Low pH significantly stabilizes the fibrillar aggregation of amyloid β, which is associated with Alzheimer's disease. The stabilizing effect is pronounced at pH 6.0 [17]. Moreover, one states that the stability of amyloid fibrils is highly dependent on pH with mild acidification enhancing the production of fibril-derived nonnative oligomers that disrupt membranes and alter cellular function [18]. A deep atomistic understanding of the pH-dependent Aβ deposition was first introduced by Telow and co-authors [19,20]. According to these, at physiological pH concentration $A\beta_{1-40}$ forms small oligomers, whereas, at acid pH below 3.4, it forms larger mass oligomers aggregating into beaded protofibrillar chains [21]. There has been also commented that at pH = 2.0, peptides may coexist with sphero-cylindrical micelles that act as nuclei for fibrillogenesis. Furthermore, Bhowmik et al. in 2014 [22] found that pH changes the aggregation tendency of amyloid-β without altering the monomer conformation. Between pH 10.5 and 5.5, the alpha-helical character of the peptide remains unchanged and the amyloid aggregation can be performed without significant conformational changes [22].

In another independent observation, Hortdchansky [23] reported the amyloid Beta protein aggregation at low pH concentration. The total fibril $6A\beta_{1-40}$ counted at pH = 4.5-6.5 is 2 or 3 times lower than pH = 7.0-7.5 [23]. This motivated us to do this scheme in which we will make clearer the inherent physical picture of the amyloid beta- sheet breakers under a cooperative effect including the environment (low pH concentration) and EGCG inhibitor. Although we want to make as much as possible in many different conditions, however, due to the limitation of the computing resources in this study we only try to perform two molecular dynamic simulations to explore the influence of pH-concentration on the stabilization of $6A\beta_{16-22}$ peptide. The $6A\beta_{16-22}$ conformation contains the lowest free energy which was obtained from our previous replica exchange molecular dynamic (REMD) simulation [9] is used as the initial structure. The kinetic of the molecular system, including $6A\beta_{16-22}$ hexamer and EGCG, will be performed in normal condition pH = 7.0 concentration and low pH = 5.5, respectively. Several hydrogen bonds between EGCG and AB will be counted; this helps us to evaluate the interaction between amyloid beta peptides and inhibitors in two different conditions. The conformational changes will be studied by comparison of protein secondary structure and through these; the detailed mechanism of the pH-induced conformational change will be observed.

MATERIAL AND METHODS

In the situation of limited computing resources, it's proved that a short peptide $A\beta_{16-22}$ fragments are

useful for one who needs to investigate the behavior of the full-length amyloid beta protein. Containing the central hydrophobic, the $A\beta_{16-22}$ with 7 amino acids plays an important role in forming the β-sheet conformation which reveals the appearance of Aβ oligomers (Figure 1). From our previous performance, the preventative structure of $6A\beta_{16-22}$ in complex with EGCG compound is implemented as a beginning conformation.

With the Gromacs package version 2016.5[24], the initial conformation of protein will be simulated with Charmm-27 force field[25] and TIP3P water model[26]. The solvated box is set to ensure that the smallest distance between the protein and the boundary was large enough so that the protein does not interact with itself. The ligand conformation was submitted to the SwissParam23 server (http://www.swissparam.ch) to create its topology file. After optimization, the system including the receptor-ligand complex, counter ions, and solvents will be equilibrated through three steps: energy minimization, 500ps simulation in the NVT (number of particles, volume, and temperature), and 500 ps simulation in the NPT (number of particles, pressure, and temperature). The temperature and the pressure in our simulation are 300 K and 1atm. Up to now, setting a pH concentration consists of setting the solute protonated groups to the states that they would have in a solution at the intended pH, based on that the molecular mechanics/molecular dynamics (MM/MD) simulations can be performed. Fortunately, this is easier when the PDB2PQR server helps us to prepare the initial molecular dynamic structure, which contains a chosen pH concentration. In this work, we perform 100 (ns) molecular dynamic simulation (MD) for each environmental condition, pH = 5.5 and pH = 7.0.

RESULTS AND DISCUSSION

The molecular dynamic simulations at pH = 7.5 and pH = 5.5 are all stable after 100 ns

To analyze typical MD data, we calculated *the root mean square deviation* (RMSD) and *the radius of gyration* (Rg) of the Cα atoms via the equations below. Initial conformations were used as the reference structure.

$$RMSD(t) = \left[\frac{1}{M}\sum_{i=1}^{N} m_{i\,i}(t) - r_i^{ref}\Big|^2\right]^{1/2}$$

$$Rg = \left(\frac{\sum_i {}_i|^2 m_i}{\sum_i m_i}\right)^{1/2}$$

According to the time-dependent curve in Figure 2a, Figure 2b, both the protein RMSDs and Rgs after 100 ns simulation under the normal and low pH don't have much difference except for the first 20 ns duration time. This is caused by systematic bias. From now, only the last 50 ns simulated data is used for analysis to ignore the bias. Overview, RMSD receives the averaged value of 0.38 nm and 0.36 nm at normal and low pH concentrations, respectively. Rg is averaged at 1.1 nm for normal pH and 1.08 nm for a low one. Full data are listed in Table 1.

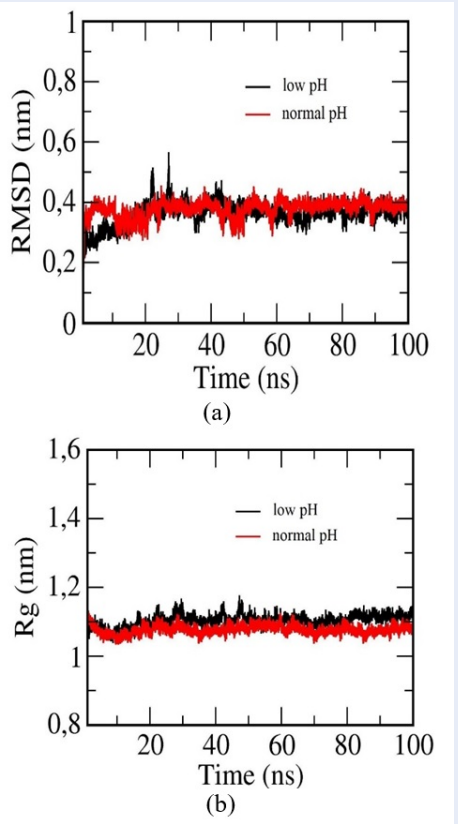

Figure 2: a. The root mean-square deviation (RSMD) in the dependence of time; b. The radius of gyration (R_g) in the dependence of time.

The EGCG - 6Aβ16-22 interactive picture under the environment change.

We count the number of hydrogen bonds to elucidate the interactive picture between the inhibited compound and the amyloid beta. A hydrogen bond will be determined when the hydrogen-donor-acceptor angle is larger than 135^0 and the donor-acceptor distance is longer than 0.36 nm. Under the normal pH = 7.0 condition, EGCG formed an average value of

Table 1: The averaged value of RMSD, Rg, number of hydrogen bonds, and Beta/Coil formed structures

pH concentration		7.0	5.5
RMSD (nm)		0.38 ± 0.03	0.36 ± 0.04
Rg (nm)		1.08 ± 0.01	1.10 ± 0.02
Hydrogen Bond	EGCG + 6Aβ_{16-22}	5.6 ± 0.9	5.5 ± 0.1
	Aβ_{16-22} + Aβ_{16-22}	16.6 ± 0.2	14.2 ± 0.2
Secondary structure	Beta	10.6 ± 1.4	8.7 ± 1.3
	Coil	24.4 ± 1.4	24.6 ± 1.5

5.6 of H-bond per one frame. Surprisingly, the same value of 5.5 number of H-bond per one frame was obtained when the concentration was decreased to pH = 5.5. Based on these, we found that the environmental change does not have a significant effect on the epigallocatechin-3-gallate of the 6Aβ_{16-22} association. So our result indicates again the ability of the EGCG compound to become a promised drug for AD treatment. Figure 3a, b below shows us the time dependence of hydrogen bond accounting between EGCG and the protein.

Low pH concentration decreases the 6Aβ_{16-22} aggregation via the number of inherent hydrogen bonds and the protein secondary structure.

In this study, we aim to count the number of inherent H-bond formed by 6Aβ_{16-22} when the complex was simulated under the low environmental pH condition. The averaged value of 16.6 of inherent H-bond was obtained when we set pH = 7.0 to the solution while it is 14.2 when the pH downed to 5.5. This result is in agreement with a previous study when one found that pH would change the propensity of the amyloid beta aggregation (23). The Aβ_{16-22} fragment containing six residues Lys-16 (K), Leu-17 (L), Val-18 (V), Phe-19 (F), Phe-20 (F), Ala-21 (A), Glu-21 (E) keeps an important role in the formation of Aβ prefibrils. The more β-contents the conformation have, the more fibrils will be formed. As we also try to analytical explore the secondary structure of 6Aβ_{16-22} by using the DSSP tool supported by the Gromacs package. Through this, not only the random-coil contents but also the β-contents are figured out. In Figure 4a, b, we plotted the counted random-coil and β-contents per time the 6Aβ_{16-22} formed under differ-

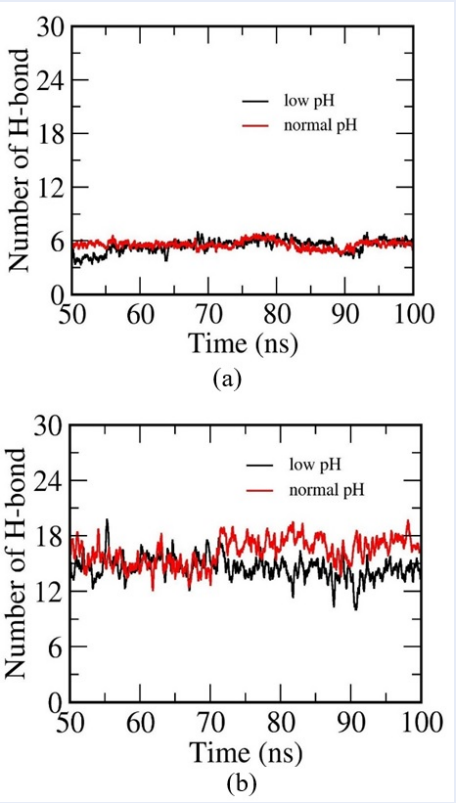

Figure 3: a. The time-dependent number of hydrogen bonds formed by the EGCG compound with Aβ16-22 fragments; b. The time-dependent number of hydrogen bonds inherently formed by 6Aβ_{16-22}.

ent pH conditions. The averaging number of random-coil structure didn't change too much and received similar values of 24.4 and 24.6. However, the β-content is averaged at 10.6 (normal pH) and decreases to 8.7 (low pH). The detail is shown in Table 1. This gives us evidence to prove that a low pH concentration (from 5.5 to 7.0) will influence the amyloid-beta aggregation.

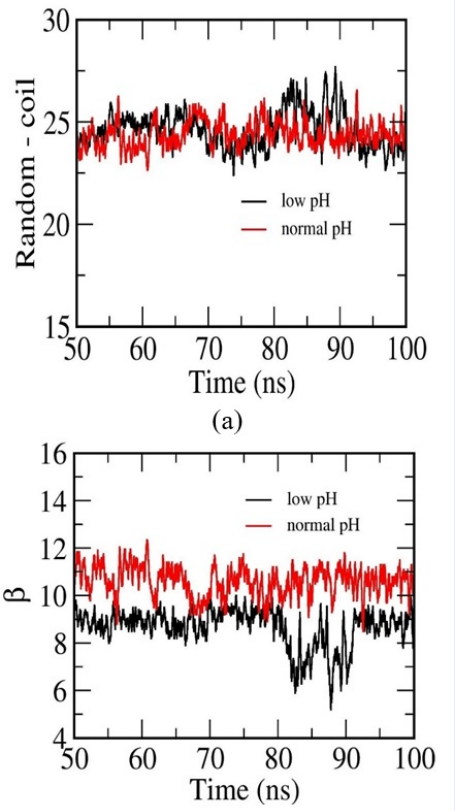

Figure 4: a. The number of random-coil contents the 6Aβ_{16-22} formed under the environmental condition; b. The number of β contents the 6Aβ_{16-22} formed under the environmental condition.

Protein's cluster and the free energy surface (FES)

In Figure 5 below, we 2D-plot the free energy landscape of the solvated Aβ_{16-22} hexamer under the effect of the EGCG compound and normal/low pH environment. Three presentative structures containing the largest probability in each performance are also generated. To analyze the obtained data we use the Gromacs tool, *gmx-sham*, in a combination with the *cluster method*.

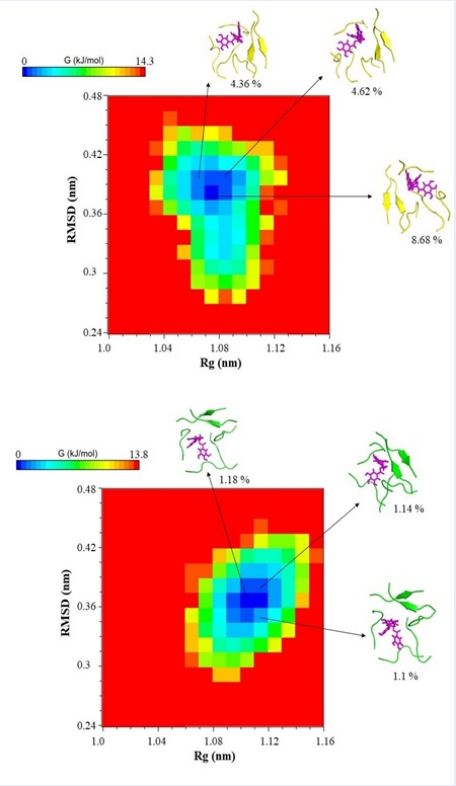

Figure 5: The protein free energy landscape: upper (normal pH 7.0) and lower (pH 5.5). EGCG compound in magenta.

The *gmx-cluster* package classified the configuration based on the RMSD matrix. Thus, the number of similar structures in the same cluster was counted. The cut-off parameter was set at 0.3 nm. Figure 6 below shows us the first 20 clusters containing the highest distribution. At normal pH = 7.0 concentration, only 1091 clusters were found at normal pH and the three highest distributions are obtained of 8.68%, 4.62%, and 4.36%, respectively. In contrast to these, over two thousand clusters at pH = 5.5 are named and the first three biggest clusters only possess a small probability of 1.18%, 1.14%, and 0.11%, also from 5000 frames. It's easy to find that the low-concentration pH = 5.5 has dissipated the association of 6Aβ_{16-22} into more configurations. The lowest free energy of the system is observed at -14.3 kJ/mol and -13.8 kJ/mol in the case of pH = 7.0 and pH = 5.5, respectively. Figure 5 shows the free energy landscape and indicates to us the effect of low – pH concentration on the Aβ fragments' aggregation.

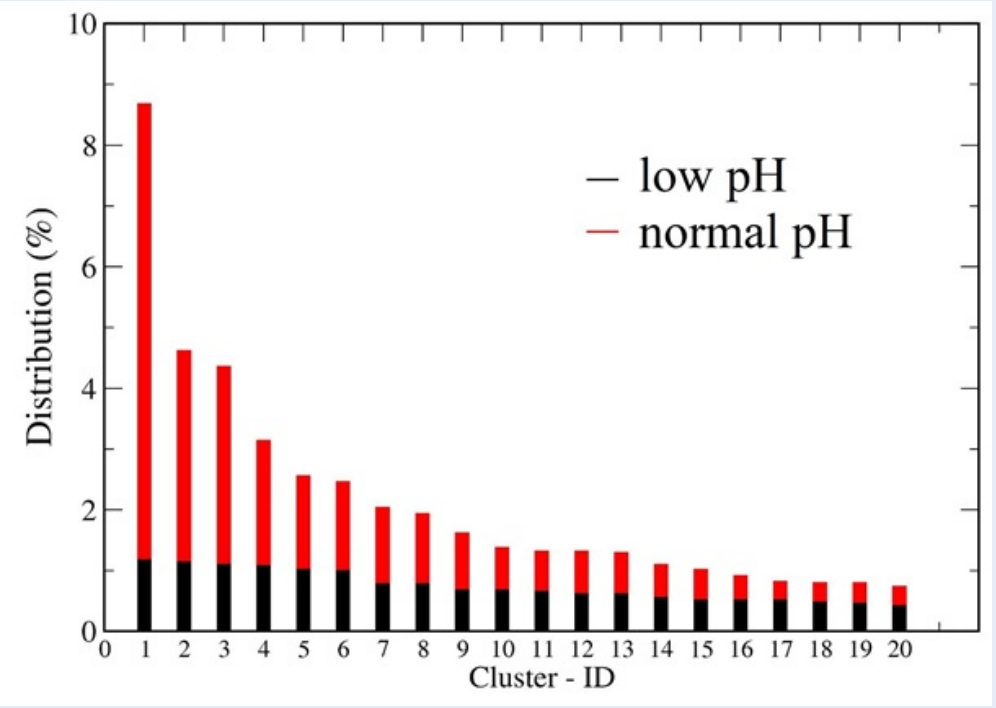

Figure 6: Population of the biggest 20th protein clusters in normal – pH concentration (pH = 7.0) and low – pH condition (pH = 5.5).

CONCLUSION

The two physical systems EGCG in two different pH conditions have been successfully simulated by Gromacs package version 2016.5. Based on the collected data, the environmental difference does not change the number of H-bond between inhibitor and Aβ fragment; this partly confirms the stability of EGCG in the relationship with Aβ. Our study encourages EGCG to become a potential prospect in treating AD. Besides that, we focus on analyzing the aggregation of Aβ_{16-22} under the dual interaction of environmental factors and potential inhibitors. Accordingly, the Aβ_{16-22} free energy has slightly increased from -14.3 kcal.mol^{-1} to -13.8 kcal.mol^{-1} when pH concentration is reduced from normal pH = 7.0 to low on pH = 5.5. A number of inherent H-bond and protein clusters also confirmed that Aβ aggregation was dissipated at pH = 5.5. Moreover, β-contents are also created in low pH- concentration less than in the normal one, thus Aβ fibrillary deposition will be smaller at pH = 5.5.

ACKNOWLEDGMENT

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LIST OF ABBREVIATIONS

AD Alzheimer's Disease
EGCG Epigallocatechin-3-gallate
FDA Food and Drug Administration
Rg Radius of gyration
MD Molecular Dynamics
MM Molecular Mechanics
Aβ Amyloid Beta
NDs Neurodegenerative Diseases
APP Amyloid Precursor Protein
REMD Replica exchange molecular dynamic
NVT Number of particles, Volume, Temperature
NPT Number of particles, Pressure, Temperature
RMSD Root Mean Square Deviation
NMR Nuclear Magnetic Resonance

CONFLICT OF INTERESTS

The authors declare no competing financial interest.

AUTHOR'S CONTRIBUTION

Nguyen Quoc Thai and Huynh Quang Linh analyzed the results. Nguyen Quoc Thai and Huynh Quang Linh wrote the paper.

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Sự ngưng tụ của AB_{16-22} hexamer dưới ảnh hưởng kép của hợp chất EGCG và điều kiện môi trường pH thấp

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TÓM TẮT

Bệnh Alzheimer là một trong những bệnh mất trí phổ biến nhất, bệnh này có liên quan đến mảng amyloid beta (Aβ). Sự tích tụ Aβ dạng tiền sợi đã chứng minh là gây tổn thương cho những bệnh nhân mắc chứng suy giảm trí nhớ (Azheimer), cơ chế hoạt động của đoạn Aβ_{16-22} giữ vai trò quan trọng trong sự kết tập sợi Aβ dựa vào cấu trúc β. Các nghiên cứu trước đây chỉ ra rằng càng nhiều thành phần β thì càng nhiều cấu trúc dạng sợi được tạo ra. Trong một nghiên cứu trước đây, chúng tôi đã xây dựng được cấu hình hexamer của Aβ_{16-22} kết tập dưới sự ức chế của hoạt chất epigallocatechin-3-gallate (EGCG), đây là hợp chất có khả năng làm suy giảm sự hình thành cấu trúc β-sheet. Tuy nhiên, ảnh hưởng của môi trường lên sự kết tập chưa được xem xét. Vì vậy, trong nghiên cứu này, chúng tôi nghiên cứu ảnh hưởng của pH ở cấp độ nguyên tử bằng mô phỏng động lực học phân tử: cấu hình 6Aβ_{16-22}-EGCG dưới ảnh hưởng của pH = 7.0 và pH = 5.5. Phân tích dữ liệu cho thấy rằng số lượng liên kết Hydrogen giữa EGCG và đoạn Aβ không thay đổi ở các nồng độ pH khác nhau. Bên cạnh đó, kết quả mô phỏng được phân tích bằng công cụ DSSP của gói phần mềm Gromacs cho thấy số lượng trung bình của cấu trúc random-coil không thay đổi nhiều, có giá trị gần bằng nhau 24.4 (pH = 7.0), 24.6 (pH = 5.5), và có sự suy giảm nồng độ β dưới tương tác của nồng độ pH thấp và hoạt chất ức chế EGCG. Năng lượng tự do bề mặt của Aβ_{16-22} tăng nhẹ từ -14.3 kcal.mol^{-1} lên -13.8 kcal.mol^{-1} khi nồng độ pH giảm từ pH = 7.0 xuống thấp ở pH = 5.5. Kết quả nghiên cứu mô phỏng phù hợp với các kết quả của thực nghiệm. Những kết quả đạt được làm sáng tỏ một phần cơ chế vật lý, tương tác của phân tử trong lĩnh vực, và bức tranh về khoa học tính toán ứng dụng trong thiết kế thuốc điều trị bệnh Azheimer.

Từ khoá: A-beta oligomer, epigalocatechin galat (EGCG), điều kiện pH, hàm lượng beta

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