

Preferential binding of fullerene and fullerenol with the N-terminal and middle regions of amyloid beta peptide: an in silico investigation

Vishal Pandya¹
Lokesh Baweja^{1,2}
Alok Dhawan^{1,2}

¹Division of Biological & Life Sciences, School of Arts & Sciences, (Formerly, Institute of Life Sciences), Ahmedabad University, Ahmedabad, Gujarat,

²Nanotherapeutics & Nanomaterial Toxicology Group, CSIR-Indian Institute of Toxicology Research, Mahatma Gandhi Marg, Lucknow, Uttar Pradesh, India

Abstract: Amyloid beta (A β) deposits are implicated in the pathogenesis of debilitating neurodegenerative disorders such as Alzheimer's disease. In the present study, the interactions of carbon-based nanoparticles (NPs) such as fullerene and fullerenol having different surface chemistry with A β were investigated using molecular dynamics simulations and docking studies. A detailed analysis of docking results showed that in 68% of the A β conformations, fullerene and fullerenol showed interactions with the N-terminal region of the peptide. However, the high-affinity binding site ($E=-48.31$ kJ/mol) of fullerene resides in the hydrophobic middle region of the peptide, whereas fullerenol interacts favorably with the charged N-terminal region with a binding energy of -50.42 kJ/mol. The above differences in binding could be attributed to the surface chemistry of fullerene and fullerenol. Moreover, the N-terminal and middle regions of A β play an important role in A β aggregation. Therefore, the binding of fullerene and fullerenol could inhibit amyloid aggregation. This information will be helpful in designing NPs for targeting amyloid-related disorders.

Keywords: fullerene, fullerenol

Introduction

The fast developing field of nanotechnology has made a significant impact on numerous areas of science and technology. Understanding the interaction between nanoparticles (NPs) and biomolecules^{1,2} is essential for NP-based biotechnology and biomedical applications such as gene delivery, inhibiting protein amyloidosis, tumor therapy, and cellular imaging. Carbon-based NPs such as fullerene and fullerenol have been proposed for inhibiting amyloid aggregation. However, the mechanism of interaction of fullerene and fullerenol with amyloid beta (A β) peptide is not well understood. Therefore, an attempt has been made to investigate the interaction of fullerene and fullerenol with A β using computational studies. This study will provide detailed insight into the interaction of fullerene and fullerenol with A β , which, in turn, would be useful for designing NPs for targeting amyloid-related disorders.

Materials and methods

The structure of A β (1–40) was obtained from the Protein Data Bank (1BA4). The A β was simulated further for 50 ns using GROMACS (Version 4.5.5) to generate an ensemble of A β conformations using g_cluster algorithm. Nineteen dominant conformations of A β were docked with fullerene and fullerenol using PatchDock server³ to predict the most probable binding site of fullerene and fullerenol in A β . Fullerene and fullerenol

Correspondence: Alok Dhawan
Nanotherapeutics & Nanomaterial
Toxicology Group, CSIR-Indian Institute
of Toxicology Research (CSIR-IITR),
Vishvgyan Bhawan, 31, M.G. Marg, PO
Box - 80, Lucknow, 226001, U.P., India
Email alokdhawan@iitr.res.in

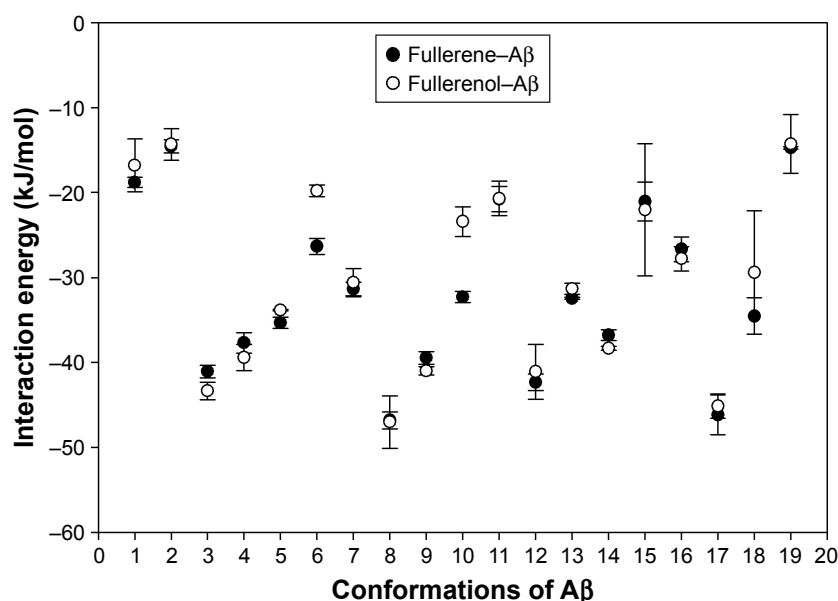


Figure 1 Interaction energy of fullerene and fullereneol with Aβ conformations.
Abbreviation: Aβ, amyloid beta.

were generated using GaussView. The docking results were analyzed using PyMOL and graphs were plotted using Σ (Sigma) plot.

Results and discussion

The interaction energy of Aβ–NPs complexes is represented in Figure 1. It can be observed from the figure that fullerene showed the highest affinity, with conformation number 17, whereas fullereneol showed high affinity with conformation number 8 of Aβ.

The snapshots of Aβ–fullerene and Aβ–fullereneol are represented in Figure 2. The high-affinity binding site ($E=-48.31$ kJ/mol) of fullerene resides in the hydrophobic

middle region of the peptide, whereas fullereneol interacts favorably with the charged N-terminal region with a binding energy of -50.42 kJ/mol. Aβ has three different regions, which are N-terminal, middle region, and C-terminal. Docking studies have shown that these NPs preferentially bind to the N-terminal and middle regions of the peptide (Figure 2). To confirm which portion of the peptide is actively involved in the interaction with fullerene and fullereneol, we calculated the occupancy of binding sites by NPs in Aβ. The results showed that fullerene and fullereneol occupied the N-terminal in ~68% of Aβ conformations and fullerene occupied the middle region in ~47% of Aβ conformations, whereas the C-terminal showed least occupancy by fullerene and fullereneol (Figure 3).

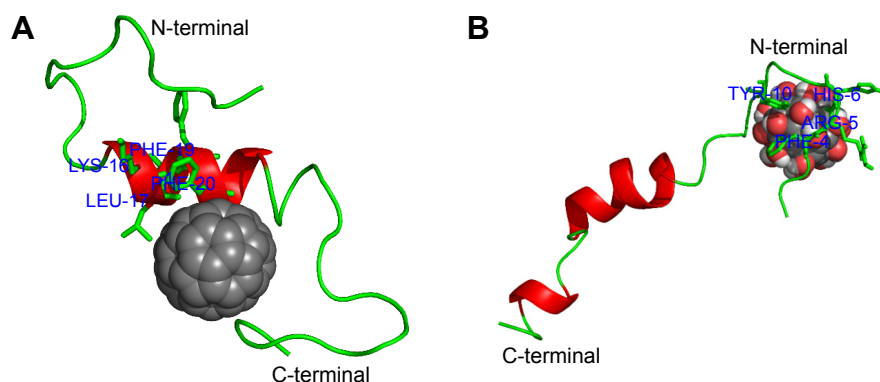


Figure 2 Interaction of fullerene and fullereneol with Aβ (1–40): **(A)** fullerene with Aβ; **(B)** fullereneol with Aβ.
Notes: The helical region in the peptide is shown in red color; fullerene and fullereneol are represented in gray color.
Abbreviation: Aβ, amyloid beta.

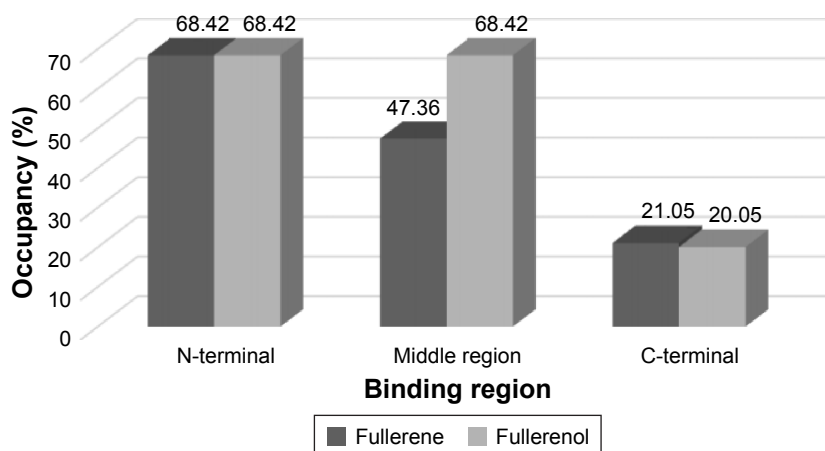


Figure 3 Most probable binding sites of peptide with fullerene and fullerenol.

We could infer that the C-terminal is not actively involved in the interaction as the other two regions of A β . The middle region of the peptide and specifically the residues 16–20 (KLVFF) are involved in A β polymerization/aggregation.⁴ The aromatic residues and the charged residues in these regions may form π – π , hydrogen bonding, and van der Waals interactions with fullerene and fullerenol.

Taking together, the above analysis showed that the binding of the NPs to A β may modulate their aggregation.

Conclusion

We investigated the effect of fullerene and fullerenol NPs on the A β (1–40) peptides by performing docking and simulation studies. Our docking studies demonstrated high-affinity binding of NPs with the peptide at the N-terminal and middle regions, which is in agreement with the previous experimental study results. These results provide novel insight into the inhibition mechanism⁵ of fullerene and fullerenol on the aggregation of A β (1–40). Further molecular dynamics simulations will be performed to validate our docking results.

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Disclosure

The authors report no conflicts of interest in this work.

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