THE EFFECTS OF DIFFERENT METALLIC NANOPARTICLES ON MODULATING THE AGGREGATION PROPENSITY OF AMYLOID BETA 42 (Aβ) POLYPEPTIDE: IMPLICATIONS FOR ALZHEIMER'S DISEASE

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Introduction: Alzheimer's disease (AD) is one of the most common neurodegenerative disorders. It is characterized by memory loss and cognitive decline. Extracellular amyloid beta (Aβ) plaques and intracellular neurofibrillary tangles of tau have been ascribed for the pathogenesis of AD. $A\beta_{40/42}$ polypeptides, a product of abnormal cleavage of amyloid precursor protein by β-secretases (BACE1) and γ-secretases, is known to follow nucleus-dependent aggregation kinetics, which leads to the formation of toxic Aβ oligomers and mature amyloid fibrils. Several reports suggest metal nanoparticle interfaces can be explored in modulating the aggregation of Aβ peptide.

Aim & objectives: To explore the anti-amyloidogenic propensity of metal nanoparticles, viz., gold (AuNPs), zinc oxide (ZnONPs), and cerium oxide (CeONPs) to modulate the aggregation dynamics of Aβ peptide.

Methods: The characterization of NPs was performed using UV-Visible spectroscopy, X-ray diffraction (XRD), and transmission electron microscopy (TEM). The cytocompatibility of NPs was determined against the SHSY5Y cell line by Alamar blue dye reduction assay. Protein purification was done through ion exchange chromatography. For studying NP-protein interactions, isothermal titration calorimetry (ITC) and endpoint Thioflavin T (ThT) assay were employed.

Results: Based on the thermodynamic parameters obtained from the ITC experiments, AuNPs showed stronger binding with Aβ peptide followed by CeONPs, whereas ZnONPs showed weaker binding. Later, in the ThT assay, a decrease in the amyloid fibrils growth was observed when Aβ peptide was incubated in the presence of AuNPs compared to Aβ peptide alone. On the contrary, no inhibition in the growth of fibrils was observed in the presence of CeONPs and ZnONPs.

Conclusion: To summarise, AuNPs showed stronger binding and prevented the fibrillation of Aβ peptide. Whereas CeONPs and ZnONPs showed no positive results. In conclusion, AuNPs could serve as a base for developing nanotherapeutics to mitigate AD's pathophysiology.

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Results: Based on the thermodynamic parameters obtained from the ITC experiments, AuNPs showed stronger binding towards Aβ 42 peptide followed by CeONPs, whereas ZnONPs showed weaker binding. Later, in the ThT assay, a decrease in the amyloid fibrils growth was observed when Aβ 42 peptide was incubated in the presence of AuNPs compared to Aβ peptide alone. On the contrary, no inhibition in the growth of fibrils was observed in the presence of CeONPs and ZnONPs.

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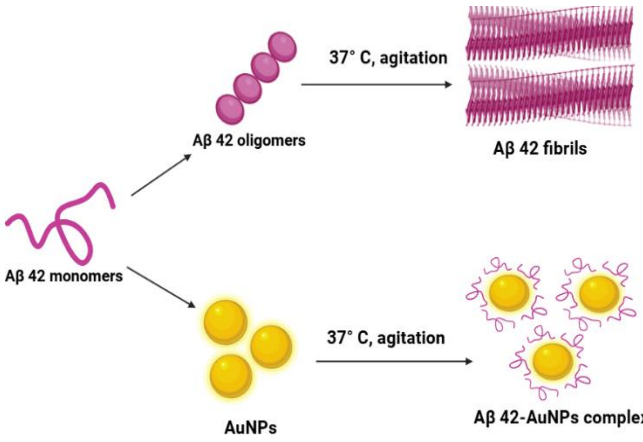

Figure 1. A schematic representation depicting adsorption of Aβ 42 monomer onto AuNP interface and render amorphous aggregates than toxic mature fibrils.

Results

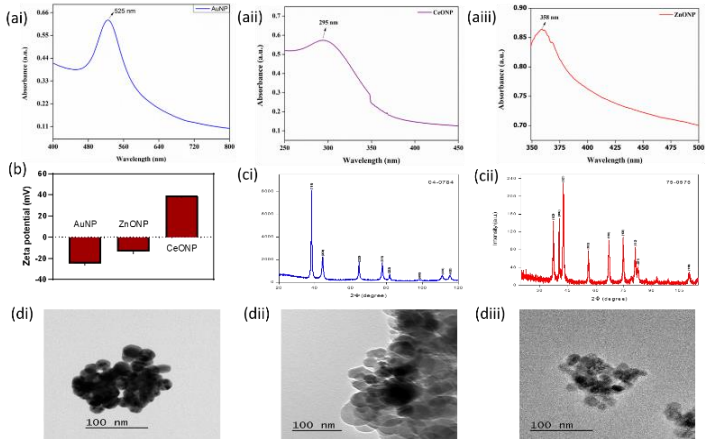

Figure 2. Characterization of synthesized nanoparticles: UV-visible spectra of (ai) AuNPs, (aii) CeONPs, and (aiii) ZnONPs; (b) Zeta potential; XRD spectra of (ci) AuNPs, and (cii) ZnONPs; TEM micrograph of (di) AuNPs, (dii) CeONPs, and (diii) ZnONPs.

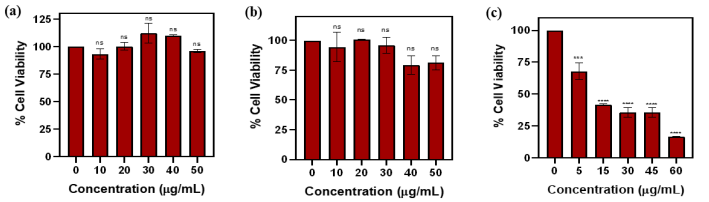

Figure 3. Cell viability assay SHSY-5Y cell line in varying concentrations of metallic nanoparticles (0-60 µg/mL): (a) AuNPs, (b) CeONPs, and (c) ZnONPs using Alamar blue dye reduction assay.

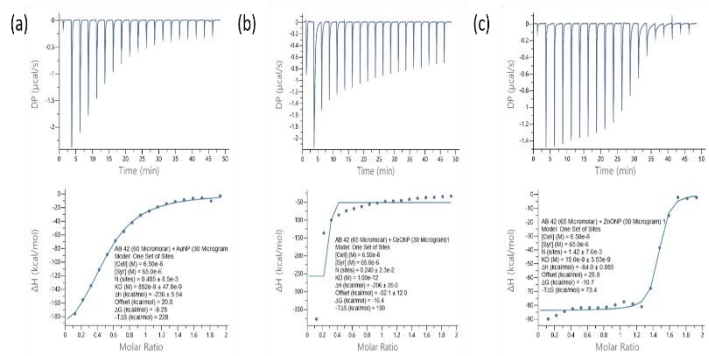

Figure 4. Thermograms showing isothermal titration curves of Aβ 42 peptide (65 µM) titrated with nanoparticles (30 µg/mL): (a) AuNPs, (b) CeONPs, and (c) ZnONPs.

Nanoparticles	Stoichiometry (N)	Enthalpy change (ΔH) Kcal/mol	Entropy change (ΔS) Kcal/mol	Free energy change (ΔG) Kcal/mol
AuNP	0.485	-236	-228	-8.28
ZnONP	0.240	-84	-73	-10.7
CeONP	1.42	-206	-190	-16.4

Table 1. Thermodynamic parameters obtained for the interaction between Aβ 42 peptide and metallic nanoparticles as investigated by isothermal titration calorimetry.

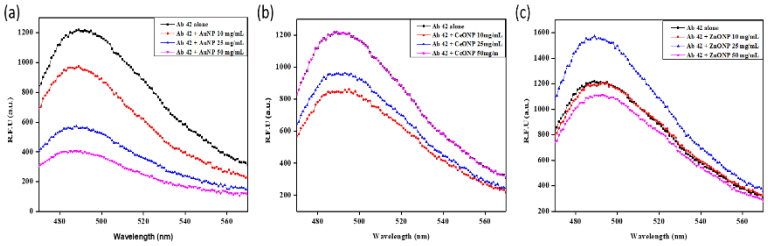

Figure 5. Comparative endpoint ThT assay of Aβ 42 peptide (25 µM) in the presence of varying concentrations (10-50 µg/mL) of metallic nanoparticles at 37 °C for 24 h: (a) AuNPs, (b) CeONPs, and (d) ZnONPs.

Inferences

AuNPs and CeONPs were found to be cytocompatible, while ZnONPs showed cytotoxicity towards the SHSY-5Y cell line.

AuNPs exhibited stronger binding affinity towards Aβ 42 peptide, followed by CeONPs and ZnONPs as investigated by ITC.

Further, AuNPs was found to inhibit Aβ 42 peptide fibrillation propensity at higher concentration compared to the CeONPs and ZnONPs.

Taken all together, AuNPs could be fabricated further to reduce the aggregation propensity of Aβ 42 peptide.

Acknowledgement

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