ROLE OF METAL NANOPARTICLES AS ARTIFICIAL CHAPERONES IN MODULATING THE AGGREGATION PROPENSITY OF β-AMYLOID (Aβ40) POLYPEPTIDE

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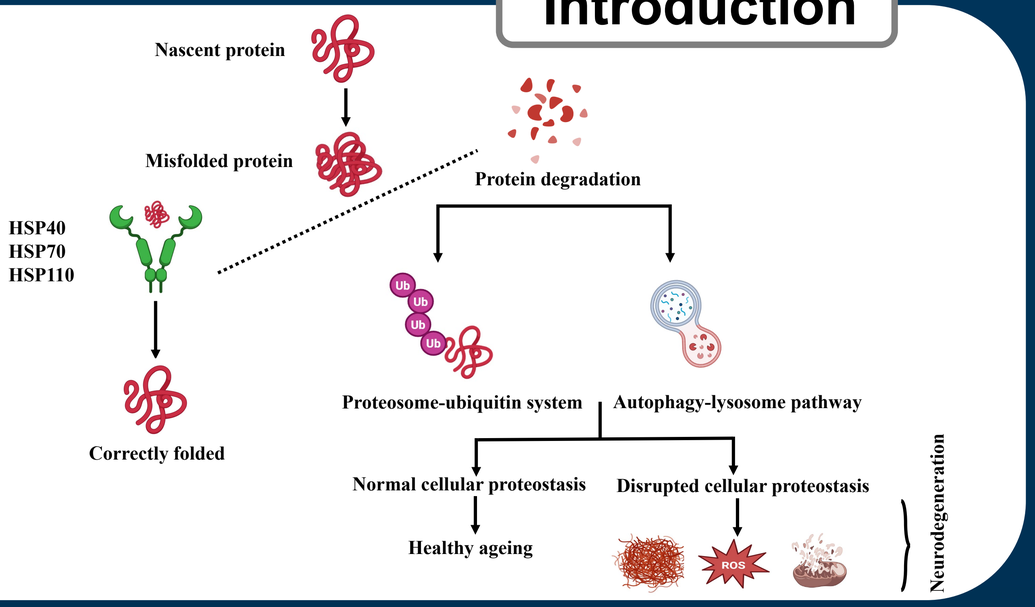
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Abstract

The abnormal cleavage of Amyloid Precursor Protein (APP), and the subsequent aggregation of the cleaved fragments, i.e. beta-Amyloid Polypeptides (Aβ40/42), are linked to the pathogenesis of Alzheimer's disease (AD)(1). Although molecular chaperones of the proteostasis network look after the fragments and consequent aggregates, they become inefficient with age and stress that result in the accumulation of Aβ40/42 peptides(2,3). Herein, by combining different techniques, we report the impact of metal nanoparticles (MNPs), including Zinc Oxide (ZnO), Cerium Oxide (CeO), and Gold (Au), as artificial Chaperones to modulate the aggregation propensity of Aβ40, the relatively abundant fragment found in the AD patients(4). The binding analysis revealed that the Aβ40 enthalpically binds with ZnONP and CeONP, whereas no binding is observed with AuNP. The binding resulted in flocculation of the complex, trapping Aβ40 monomers into non-amyloid aggregates with the native-like random coil conformation, compared to Aβ40 alone or with AuNP where the peptide adopted fibrillary morphology, which was also confirmed using amyloid-specific thioflavin T fluorescent dye. In conclusion, our results highlight the efficacy of the ZnONP interface in sequestering Aβ40 monomers and preventing their pathological self-assembly, underscoring its potential as a platform to modulate amyloid aggregation.

Introduction



Results

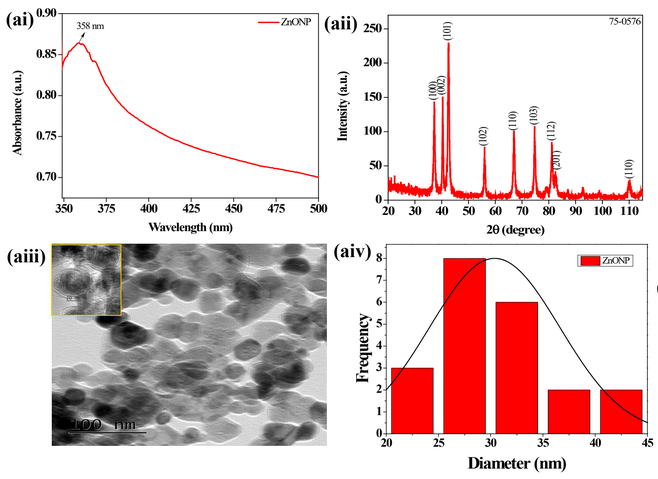


Table: Zeta potential of different NPs by Zeta analyzer.

Nanoparticles	Zeta (mV) ± S.D.
ZnONP	36.6 ± 4.14
CeONP	39.4 ± 6.32
AuNP	-24.8 ± 6.98

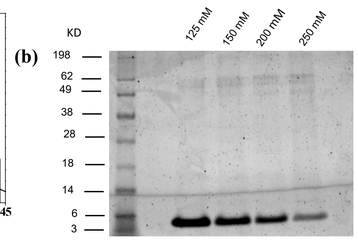


Fig.: (a) Characterization of ZnONP using (ai) UV-Visible spectra, (aii) XRD spectra, (aiii) TEM micrographs in 100 nm range and HRTEM insets, and (aiv) Size distribution. (b) A 15% SDS gel showing the bands of Aβ40 eluted in gradient NaCl eluents.

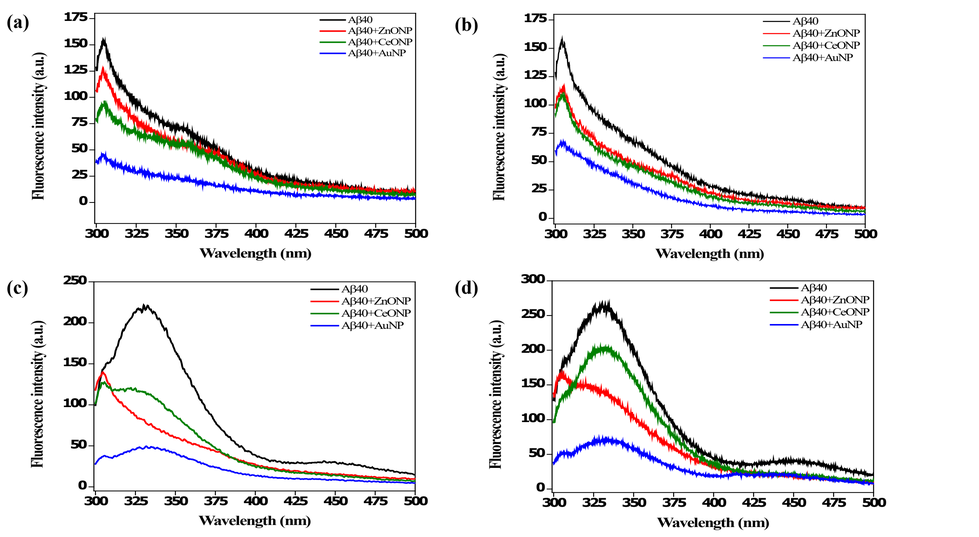
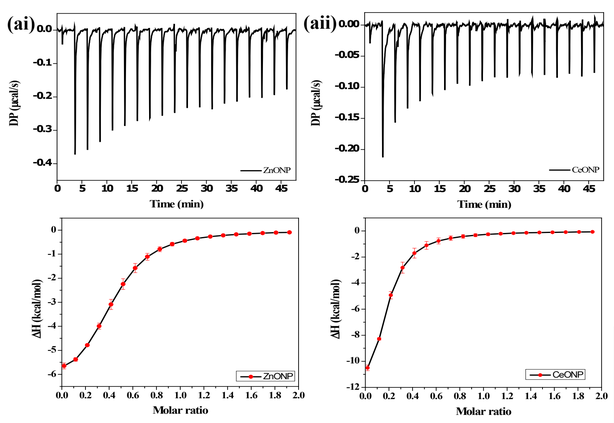
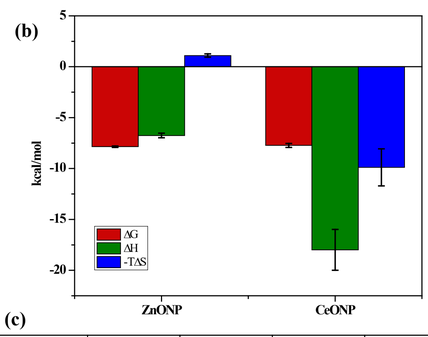


Fig.: Time-dependent intrinsic fluorescence spectra of 25 µM Aβ40 incubated at 37 °C with 50 µg/mL of ZnONP, CeONP, AuNP at (a) 0 h, (b) 24 h, (c) 48 h, and (d) 72 h.





(c)

25 µM Aβ40 and 50 µg/mL of nanoparticles	Dissociation constant (K_D), µM	Enthalpy change (ΔH), Kcal/mol	Entropy change (TΔS), Kcal/mol	Free energy change (ΔG) Kcal/mol
ZnONP	1.77 ± 0.44	-6.75 ± 0.23	1.103 ± 0.15	-7.85 ± 0.07
CeONP	2.31 ± 0.70	-17 ± 2	-9.88 ± 1.81	-7.72 ± 0.19

Fig.: (a) Thermograms showing isothermal titration curves for 25 µM Aβ40 titrated with 50 µg/mL (ai) ZnONP, and (aii) CeONP at 25 °C in water. (b) Signature plot calculated by applying 1:1 binding model. (c) Calculated thermodynamics parameters.

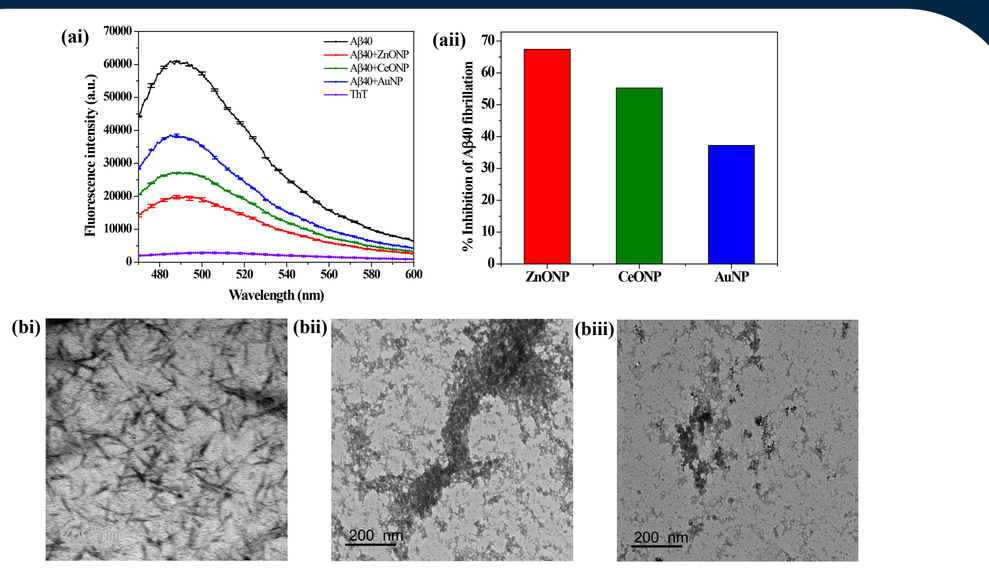


Fig.: (ai) Thioflavin T spectral scan upon excitation at 440 nm, and emission in the range of 470-600 nm, recorded for 25 µM Aβ40 incubated at 37 °C with 50 µg/mL of ZnONP, CeONP, and AuNP at 72 h. (aii) % inhibition of Aβ40 fibrillation in the presence of NPs bar graph. (b) TEM micrograph of (bi) 25 µM Aβ40 only (bii) 25 µM Aβ40 in presence of 50 µg/mL ZnONP (biii) 25 µM Aβ40 in presence of 50 µg/mL CeONP.

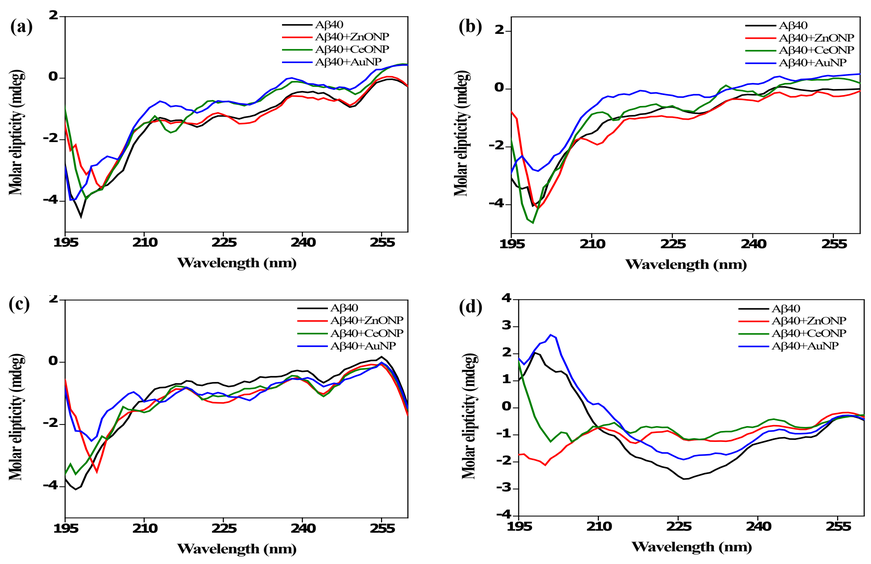


Fig.: Far-UV spectra of 25 µM Aβ40 incubated at 37 °C with 50 µg/mL of ZnONP, CeONP, AuNP at (a) 0 h, (b) 24 h, (c) 48 h, and (d) 72 h.

Conclusion

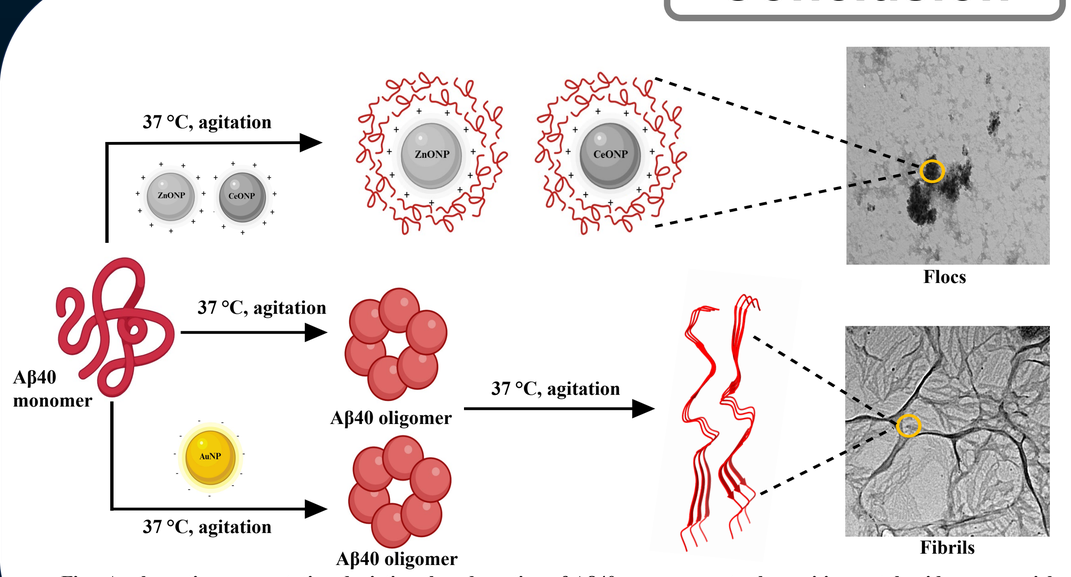


Fig.: A schematic representation depicting the adsorption of Aβ40 monomer onto the positive metal oxide nanoparticles interface leading to the formation of thermodynamically stable amorphous aggregates (flocs) instead of the amyloid fibril.

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