National Institute of Technology Rourkela

Synopsis Seminar

Seminar Title	: Optimization of surface-moderated zinc oxide nanoparticle-based αS nanoformulation for neuroprotective intervention in Parkinson's disease
Speaker	: Sonali Jena (Rollno : 519ls2014)
Supervisor	: Suman Jha
Venue	: LS Seminar Room
Date and Time	: 21 Jul 2025 (11:00 AM)
Abstract	: Alpha-synuclein (&alphaS) is an intrinsically disordered protein, predominantly found in neurons, and is pathologically linked to Parkinson&rsquos disease (PD). &alphaS has a tendency to misfold and aggregate into amyloid, which is known to exert cellular toxicity and consequently contributes to the PD pathogenesis. Despite extensive research using small molecules to modulate the &alphaS aggregation, none have been successful for the poor bioavailability across the blood-brain barrier (BBB). Therefore, the uses of BBB-permeable nanomaterial-based approaches have gained considerable interest as an alternative strategy to modulate &alphaS aggregation. However, the emerging evidence suggests that metal nanoparticles (NP) can significantly influence, either way, the protein conformation and aggregation propensity, i.e., it can act as a double-edged sword in protein aggregation, either inhibiting or inducing the aggregation, depending on the interacting interface. Nevertheless, the tunable physicochemical properties of the NPs give flexibility to modulate the NP interfacial interaction in the biological milieu, allowing precise control over the nanoparticle-based application. Hence, this thesis investigates the effects of zinc oxide NP (ZnONP) on the conformation and amyloidogenic propensity of &alphaS and explores the *in vitro* and *in vivo* therapeutic efficacy of the nanoparticle-based &alphaS nanoformulations obtained upon moderation of the surface physicochemical properties of the particle. Initially, the anti-amyloidogenic potential of surface-moderated ZnONPs was explored and compared with the bare nanoparticle, where the *in silico* and *in vitro* studies revealed that the moderated nanoparticle interfaces efficiently sequester the monomeric &alphaS (&alphaS M) into cytocompatible amorphous aggregates, referred to as &ldquoflocs&rdquo, as compared to the bare ZnONP. Interestingly, GC-MS analysis of green-synthesized ZnONP highlighted the efficacy of the heterogeneous phytochemicals&rsquo cocktail in sequestering &alphaS monomers than either the tyrosine functionalized or bare ZnONPs, against the protein amyloidosis. Next, to further evaluate the physiological relevance of these flocs, the differentiated SH-SY5Y neuronal cells and CHME3 cells were treated with the flocs. *In vitro* cellular assay demonstrated that flocs are neurocompatible in nature as compared to &alphaS fibril, and the gene expression analysis highlighted the therapeutic implications of these flocs. Lastly, the neuroprotective potential of the flocs was evaluated in &alphaS pre-formed fibril (PFF)-fed wild-type *Drosophila melanogaster*. Additionally, the uptake and biodistribution potentials of the green-synthesized nanoparticle platform to the brain, via the vagus nerve, with the surface-adsorbed phytochemicals and &alphaS were proved in the organism model. The flies administered with PFF exhibited typical PD-like phenotypes, including degeneration of dopaminergic (DA) neurons and impaired locomotor activity and molecular signatures. In contrast, the flocs did not show detrimental effects on the wild-type flies. Interestingly, when the PFF-induced PD flies were treated with flocs, significant restoration of locomotory behavior, life span, and basal gene expression in DA neurons were observed, compared to the untreated PD flies. Collectively, the thesis translated the therapeutic application of surface-moderated zinc oxide nanoparticle-based &alphaS nanoformulation in the restoration of PD pathology to normal in *Drosophila melanogaster*.