

BACKGROUND

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, amyloid- β ($A\beta$) plaque accumulation, tau hyperphosphorylation, oxidative stress, mitochondrial dysfunction, and neuroinflammation. Oxidative stress plays a central role in neuronal degeneration by increasing reactive oxygen species (ROS) levels, promoting lipid peroxidation, and inducing neuronal apoptosis. Idebenone, a synthetic analogue of coenzyme Q10, possesses potent antioxidant and mitochondrial protective properties; however, its clinical application is limited due to poor aqueous solubility, low bioavailability, and restricted penetration across the blood-brain barrier (BBB). Poly(lactic-co-glycolic acid) (PLGA) nanoparticles offer an effective drug delivery platform capable of enhancing drug stability, controlled release, and brain targeting.

METHODS

IB-PLGA nanoparticles were prepared using the nanoprecipitation (or emulsion-solvent evaporation) technique. The nanoparticles were characterised for particle size, zeta potential, polydispersity index (PDI), morphology, encapsulation efficiency, drug loading, in vitro drug release, antioxidant activity, cellular uptake, and cytotoxicity. The neuroprotective potential was assessed using SH-SY5Y neuronal cells exposed to hydrogen peroxide (H_2O_2) or amyloid- β peptides. Intracellular ROS generation, mitochondrial membrane potential, antioxidant enzyme activities, and cell viability were evaluated. In vivo efficacy was assessed in APP/PS1 transgenic mice (or $A\beta$ -induced AD rats) through behavioral tests, biochemical assays, and histopathological analysis.

RESULTS AND CONCLUSION

The optimized nanoparticles exhibited a particle size of approximately 150–200 nm with narrow size distribution (PDI <0.2), negative zeta potential, and encapsulation efficiency exceeding 80%. Sustained drug release was observed over 48–72 hours. In vitro studies demonstrated enhanced cellular uptake, significant reduction in ROS production, restoration of mitochondrial function, and improved neuronal viability compared to free idebenone. Animal studies showed improved spatial memory, decreased oxidative stress markers (MDA), increased antioxidant enzymes (SOD, CAT, GPx), reduced amyloid burden, and attenuated neuroinflammation.

REFERENCES

Hernández-Giottonini KY, Rodríguez-Córdova RJ, Gutiérrez-Valenzuela CA, Peñuñuri-Miranda O, Zavala-Rivera P, Guerrero-Germán P, Lucero-Acuña A. PLGA nanoparticle preparations by emulsification and nanoprecipitation techniques: effects of formulation parameters. RSC Adv. 2020 Jan 27;10(8):4218-4231. doi: 10.1039/c9ra10857b. PMID: 35495261; PMCID: PMC9049000.

Anand B, Wu Q, Nakhaei-Nejad M, Karthivashan G, Dorosh L, Amidian S, Dahal A, Li X, Stepanova M, Wille H, Giuliani F, Kar S. Significance of native PLGA nanoparticles in the treatment of Alzheimer's disease pathology. Bioact Mater. 2022 Jul 15;17:506-525. doi: 10.1016/j.bioactmat.2022.05.030. PMID: 36330076; PMCID: PMC9614411.

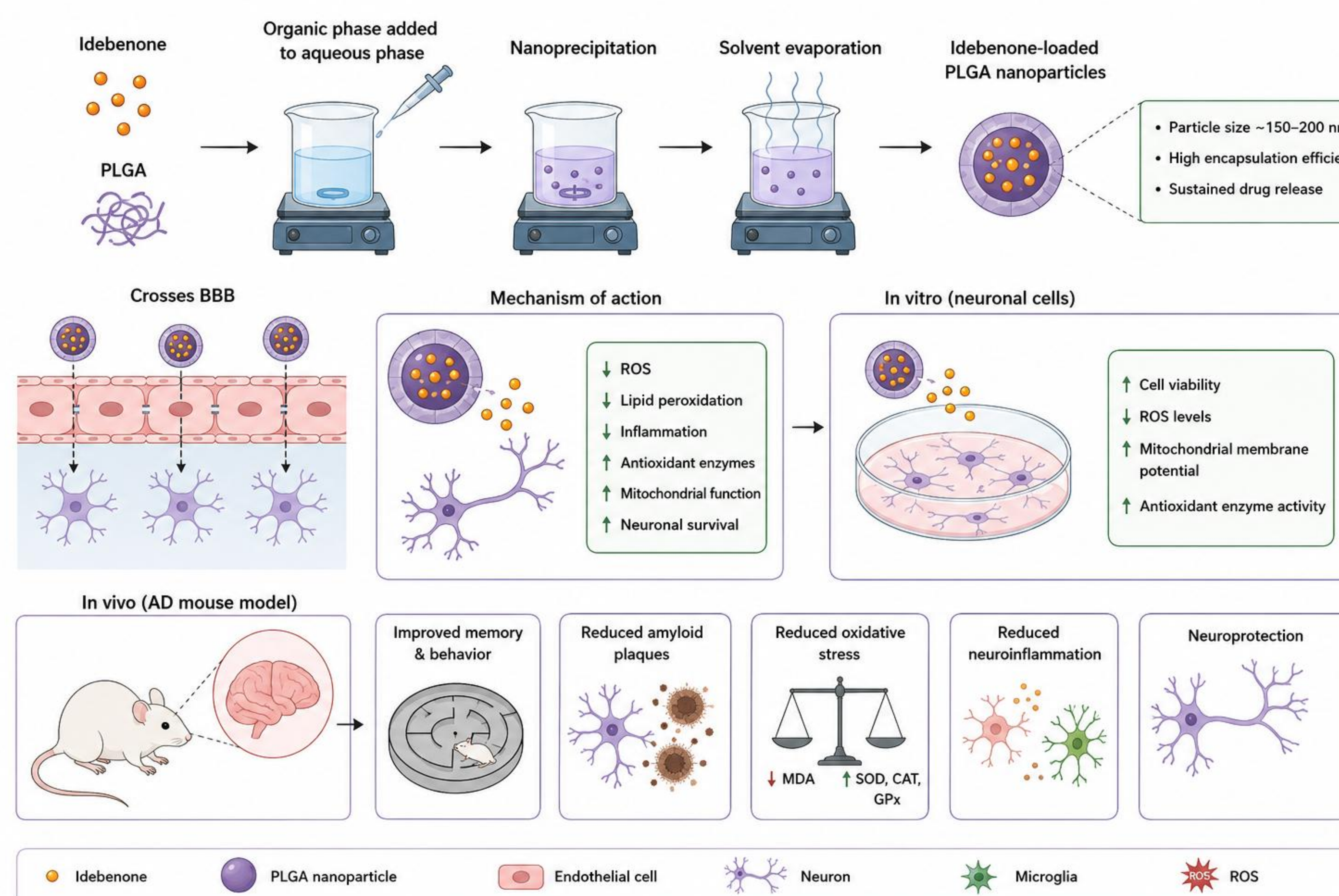


Figure 1. Proposed Mechanism of Idebenone-Loaded PLGA Nanoparticles Modulation and Neuroprotection in Alzheimer's Disease