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Research Paper

Nano-engineered nerolidol loaded lipid carrier delivery system attenuates cyclophosphamide neurotoxicity – Probable role of NLRP3 inflammasome and caspase-1

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Highlights

- Cyclophosphamide (200 mg/kg, i.p.) induced significant neurotoxicity. in hippocampus and cortex of Swiss Albino mice
- Nerolidol nanoformulation (NR-NLC 200) and nerolidol suspension (NR-200) at the dose of 200 mg/kg, p.o. were evaluated for neuroprotective effect.
- Molecular docking study revealed potential interaction profile of nerolidol in the binding pockets of NLRP3 and TLR-4
- NR-NLC 200 was found effective in reversing CP-induced neurotoxic manifestations in these mice.

Abstract

Neuroinflammation is one of the most common etiology in various neurological disorders and responsible for multi-array neurotoxic manifestations such as neurodegeneration, neurotransmitters alteration and cognitive dysfunction. NR (Nerolidol) is a natural bioactive molecule which possesses significant antioxidant and anti-inflammatory potential, but suffers from glitches of low solubility, low bioavailability and fast hepatic metabolism. In the current study, we fabricated nano-engineered lipid carrier of nerolidol (NR-NLC) for its effective delivery into the brain and explored its effect on neuroinflammation, neurotransmitters level and on dysfunctional behavioral attributes induced by CYC (cyclophosphamide). The binding affinity of nerolidol with NLRP3 and TLR-4 was performed which showed stong interaction between them. NR-NLC was prepared by the ultrasonication methods and particle size was determined by Zeta-sizer. Swiss Albino mice were divided into 5 groups ($n = 6$), assessed for behavioral dysfunction, and sacrificed on the fifteenth day following cyclophosphamide treatment. Brains were then removed and used for biochemical, histopathological, immunohistochemical and fluorescence microscopic analysis. Biochemical analysis showed increased levels of MDA, TNF-α, IL-6, IL-1β, acetylcholine esterase, BDNF, 5-HT and dopamine, and reduced levels of SOD, CAT, GSH, IL-10, along with significant behavioral dysfunction in cyclophosphamide-treated animals. Significant neuronal damage was also observed in the histological study. Immunohistochemical analysis demonstrated increased expression of NLRP3 and caspase-1. Fluorescence microscopic analysis showed significant availability of NR-NLC in the hippocampus and cortex region. In contrast, treatment with NR-NLC effectively mitigated the aforementioned neurotoxic manifestation as compared to NR suspension. Our results showed potent neuroprotective effect of NR-NLC via modulation of oxidative stress, NLRP3 inflammasome, caspase-1 and neurotransmitter status.

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Keywords

Nanotechnology; Drug delivery system; Inflammasome; Nerolidol; Cyclophosphamide; Microglia and Morris water test

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