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**Nano-Oxyberberine Ameliorates the Cognitive Deficits in a Transgenic Mouse Model of Alzheimer's Disease**

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**Background and aims.** Alzheimer’s disease (AD) is one of the most prevalent neurodegenerative diseases. Oxyberberine (OBB), a berberine derivative, exhibits similar effects to berberine. However, its poor aqueous solubility and bioavailability have limited its therapeutic applications. OBB-hydroxypropyl-β-cyclodextrin (OBB-β-CD) was prepared to improve the water solubility and plasma concentration-effect relationship of OBB. In this study, we aimed to investigate the anti-AD effects of OBB-β-CD and action mechanisms in transgenic mouse model of AD.

**Methods.** Briefly, six-month-old female 3×Tg mice were orally administered with OBB or OBB-β-CD for 6 consecutive months, respectively. The neuropsychological functions of the mice were determined using Morris Water Maze test (MWMT), Open Field test (OFT) and Novel Object Recognition test (NORT). The brain and colon tissues were harvested for mechanistic studies.

**Results.** The morphology of OBB-β-CD were nearly spherical with an average diameter of 89.6 nm with an average ZP of -19.18 ± 0.90 mV. OBB-β-CD treatment markedly ameliorated the anxiety-like behavior, and improved the recognition memory and spatial learning ability of 3×Tg mice. OBB-β-CD was more effective than OBB in modulating the amyloid precursor protein (APP) processing. OBB-β-CD was also found to alleviate the Aβ plaque burdens in the brains of 3×Tg mice. Moreover, OBB-β-CD markedly inhibited the hyperphosphorylation of tau protein and neuroinflammation. Furthermore, OBB-β-CD restored the gut microbiota dysbiosis and inhibited the activation of CXCR3 in the brain and colon tissues of 3×Tg mice. Additionally, the fecal microbiota transplantation (FMT) experiment verified the role of gut microbiota on the anti-AD effects of OBB-β-CD.

**Conclusion.** OBB-β-CD was more potent than free OBB in improving cognitive impairments in 3×Tg mice via inhibiting Aβ deposition, tau hyperphosphorylation and neuroinflammation through suppressing the activation of CXCR3 and modulating the gut microbiota dysbiosis, indicating that OBB-β-CD has good potential for further development into therapeutic agent for AD treatment.

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