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ORIGINAL RESEARCH

Transferrin-Modified Osthole PEGylated Liposomes Travel the Blood-Brain Barrier and Mitigate Alzheimer's Disease-Related Pathology in APP/PS-1 Mice

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Introduction: Osthole (Ost) is a coumarin compound that strengthens hippocampal neurons and neural stem cells against Aβ oligomer-induced neurotoxicity in mice, and is a potential drug for the treatment of Alzheimer's disease (AD). However, the effectiveness of the drug is limited by its solubility and bioavailability, as well as by the low permeability of the blood-brain barrier (BBB). In this study, a kind of transferrin-modified Ost liposomes (Tf-Ost-Lip) was constructed, which could improve the bioavailability and enhance brain targeting.

Methods: Tf-Ost-Lip was prepared by thin-film hydration method. The ability of liposomal formulations to translocate across BBB was investigated using in vitro BBB model. And the protective effect of Tf-Ost-Lip was evaluated in APP-SH-SY5Y cells. In addition, we performed pharmacokinetics study and brain tissue distribution analysis of liposomal formulations in vivo. We also observed the neuroprotective effect of the varying formulations in APP/PS-1 mice.

Results: In vitro studies reveal that Tf-Ost-Lip could increase the intracellular uptake of hCMEC/D3 cells and APP-SH-SY5Y cells, and increase the drug concentration across the BBB. Additionally, Tf-Ost-Lip was found to exert a protective effect on APP-SH-SY5Y cells. In vivo studies of pharmacokinetics and the Ost distribution in brain tissue indicate that Tf-Ost-Lip prolonged the cycle time in mice and increased the accumulation of Ost in the brain. Furthermore, Tf-Ost-Lip was also found to enhance the effect of Ost on the alleviation of Alzheimer's disease-related pathology.

Conclusion: Transferrin-modified liposomes for delivery of Ost has great potential for AD treatment.

Keywords: transferrin, osthole, liposomes, blood-brain barrier, Alzheimer's disease

Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disease, the clinical symptoms of which are cognitive and memory dysfunction accompanied by mental and behavioral disorders.[1] It affects approximately 50 million people worldwide, and, according to the 2018 World Alzheimer Report, the number of patients will increase exponentially every 20 years.[2] The pathological features of AD include β-amyloid polypeptide (Aβ) deposition, hyperphosphorylated tau aggregation, synapses and neuronal loss, and neuroinflammation, among others.[3] In recent years, listed drugs have been found to only alleviate the disease, and there are no