Unlocking Neuroprotection: How Chebulinic Acid Targets Protein Biomarkers and Lipid Imbalance in Alzheimer's Disease

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Alzheimer’s disease (AD), a neurodegenerative disorder causing cognitive deterioration, remains a leading cause of death. Previous research has not fully clarified the impact of amyloid-beta, apolipoprotein E4 (ApoE4), and lipopolysaccharide (LPS) on lipid droplet (LD) formation in AD. This study aims to determine the specific effects of these molecules and investigate the efficacy of chebulinic acid (CA), a natural plant-based chemical, as potential treatment for AD by addressing these mechanisms. This study included three phases. Phase one consisted of an in silico screening. Phase two involved in vitro biochemical assays on human neuronal and immune cells. Phase three involved the use of fruit flies as an in vivo model. Molecular docking revealed strong binding affinities for amyloid-beta with the acyl-CoA synthetase long-chain (ACSL) family, suggesting ACSL’s role in LD formation. CA reduced cell adhesion and therefore neuroinflammation induced by amyloid-beta and LPS. Both amyloid-beta and LPS caused an imbalance in LD formation. By reducing lipid production and LD formation, CA mitigated the harmful lipid dysregulation. Amyloid-bta and LPS further disrupted ApoE balance, differentially promoting harmful ApoE4 expression while decreasing production of other protective ApoE alleles. CA prevented the upregulation of ApoE4, restoring ApoE balance. In a Drosophila fruit fly model, both amyloid-beta and ApoE4 impaired locomotion, demonstrating lipid dysfunction, while CA improved movement, indicating broad therapeutic benefits. Overall, this study clarifies the specific roles of amyloid-beta, LPS, and ApoE4 in AD lipid dysregulation, highlighting CA as a promising candidate for AD treatment, counteracting multiple disease-promoting factors.

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