

Neuroprotective Potential Of PAHSAs In Alzheimer’s Disease And Diabetes-Associated Cognitive Impairment

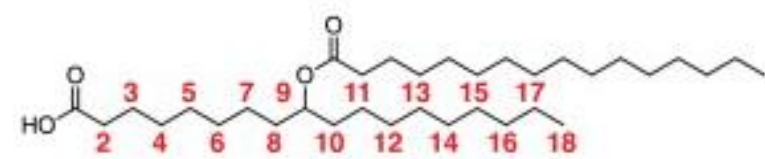
¹Rida Khan, OMS-3, ¹Mayur S. Parmar, PhD

¹Nova Southeastern University Dr. Kiran C. Patel College of Osteopathic Medicine, Fort Lauderdale, Florida,

²Nova Southeastern University Dr. Kiran C. Patel College of Osteopathic Medicine, Clearwater, Florida

Background

- Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline.
- Increasing evidence links AD to metabolic dysfunction, with emerging research indicating lipid-signaling disruptions contributing to neuroinflammation and neuronal vulnerability.
- Fatty acyl esters of hydroxy fatty acids (FAHFAs) are a class of bioactive lipids have shown metabolic benefits in type 2 diabetes (T2D).
- Within the FAHFA class, palmitic acid hydroxy stearic acids (PAHSAs) exhibit neuroprotective properties in preclinical studies, suggesting a therapeutic potential in AD and diabetes-associated cognitive impairment (DACI).



Formula: C₃₄H₆₆O₄
Mass of Negative Ion: 537.4888

Image:
Yore et al., 2014
Cell

Objective

The objective of this literature review is to investigate the studies that have researched FAHFAs and PAHSAs in mitigating cognitive decline in AD and DACI.

Method

- Data was collected through the Embase and PubMed databases.
- Review articles were selected based on the keywords “effects of FAHFAs,” “FAHFA and Alzheimer’s Disease,” “PAHSA and Alzheimer’s Disease,” “FAHFA and DACI,” and “PAHSA and DACI.”
- The articles utilized were primary research articles published in academic journals between 2014 and 2025.

Literature Findings

Study (PMID)	Objective / Model / Intervention	Key Findings (FAHFAs/PAHSAs & AD/DACI relevance)
Yore et al., 2014 (PMID: 25303528)	Lipidomic profiling of adipose tissue to identify endogenous lipids	- Discovered a new lipid class: FAHFAs, including PAHSAs - Multiple regioisomers (5–13-PAHSA) identified Reduced PAHSA levels in insulin-resistant humans - PAHSAs improved glucose tolerance and insulin secretion → strong metabolic relevance linked to AD risk
Wang et al., 2024 (PMID: 38332538)	S-9-PAHSA (S9P) treatment in HFD mice and PC12 cells ; role of CAIII	- S9P reduced oxidative stress and apoptosis in brain and PC12 cells - Improved metabolic parameters (glucose, LDL-C, insulin) - Neuroprotection partly mediated via CAIII - CAIII knockdown attenuated S9P effects (suggesting mechanistic involvement)
Huang et al., 2025 (PMID: 40325622)	S9P in HFD-induced DACI mice ; behavioral, neuronal, and gut-brain analyses	- Improved cognitive function (MWM, Y-maze) - Reduced astrocyte activation (↓GFAP, ↓C3) and restored synaptic integrity (↑SYN) - Increased dendritic complexity and reduced neuronal damage - Improved glucose/lipid metabolism - Restored gut barrier integrity, supporting a gut–brain axis mechanism
Lu et al., 2025 (PMID: 40275795)	S9P in 5xFAD AD model ; behavioral and post-mortem brain analysis	- Improved learning and memory (MWM, Y-maze) - Reduced Aβ plaque burden (hippocampus, cortex) ↓ Aβ1–40 and Aβ1–42 levels - Reduced neuronal apoptosis - Enhanced mitochondrial function and autophagy - Increased neuronal viability (Nissl-positive cells)

Conclusion and Future Directions

- PAHSAs and FAHFAs, especially the S-9-PAHSA (S9P) stereoisomer, demonstrate promising metabolic and neuroprotective effects in preclinical models of T2D, AD, and DACI.
- Human evidence remains limited to metabolic outcomes and associations with insulin resistance; direct clinical data in AD or DACI are currently lacking.
- Future research should prioritize elucidation of molecular mechanisms (e.g., CAIII-mediated neuroprotection and gut–brain axis) and validation of PAHSAs as biomarkers.
- Long-term efficacy/safety studies, structure–activity optimization of FAHFA isomers, and early-phase clinical trials in at-risk populations are essential to establish therapeutic potential.