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THERAPEUTIC POTENTIAL OF GLP-1 RECEPTOR AGONISTS IN ALZHEIMER'S DISEASE: INSIGHTS FROM PRECLINICAL AND CLINICAL EVIDENCE

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ABSTRACT

Alzheimer's disease is a multifactorial neurodegenerative disorder characterized by progressive cognitive decline and complex pathological mechanisms involving amyloid-β accumulation, tau hyperphosphorylation, oxidative stress, and metabolic dysfunction. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), originally developed for type 2 diabetes, have recently emerged as promising candidates for disease modification in AD due to their broad neuroprotective and metabolic actions.

This review synthesizes evidence from molecular studies, animal models, and early clinical trials to evaluate the therapeutic potential of GLP-1RAs in AD. In animal models, agents such as liraglutide, exenatide, and semaglutide consistently improve learning and memory performance, reduce amyloid and tau pathology, attenuate neuroinflammation, and restore mitochondrial and synaptic function. Mechanistically, these effects are mediated through modulation of the PI3K/Akt/GSK-3β, ERK, and cAMP/CREB signaling pathways, normalization of insulin signaling, and enhancement of neuronal and glial resilience.

Early clinical studies suggest that GLP-1RAs may slow cognitive decline and brain atrophy in individuals with mild or moderate AD, although sample sizes and follow-up durations remain limited. Ongoing large-scale Phase III trials with semaglutide and liraglutide are expected to clarify their clinical efficacy. Collectively, current findings indicate that GLP-1RAs offer a multifaceted approach to counteract AD pathology by integrating metabolic, neurotrophic, and anti-inflammatory mechanisms, representing a potential shift toward metabolism-targeted disease-modifying therapies.

KEYWORDS

Alzheimer's Disease, GLP-1 Receptor Agonists, Systematic Review, Preclinical Studies, Clinical Trials, Neuroprotectio

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1. Introduction

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder and the leading cause of dementia worldwide, currently affecting approximately 57 million people, a number projected to rise sharply in the coming decades. Although its clinical course varies among individuals, AD is invariably progressive and incurable, with an average life expectancy of 3 to 11 years following diagnosis (WHO, 2025).

Available pharmacological treatments provide only transient symptomatic benefit, underscoring the need for disease-modifying approaches that target the underlying cellular dysfunctions. The pathology of AD extends beyond amyloid deposition and tau hyperphosphorylation; it encompasses neuronal death, glial activation, vascular dysfunction, oxidative stress, and impaired cellular metabolism. Because these diverse pathological events are interconnected, a single-target therapy is unlikely to achieve a cure.

A promising strategy is to restore the integrated function of brain cells rather than addressing isolated molecular lesions. Among potential candidates, glucagon-like peptide-1 (GLP-1) receptor agonists, which was originally developed for type 2 diabetes, stand out for their pleiotropic actions on metabolism, inflammation, oxidative balance, and cell survival. These agents cross the blood–brain barrier (BBB) and engage receptors expressed in neurons, astrocytes, microglia, oligodendrocytes, endothelial cells, and pericytes, thereby influencing the main cellular systems disrupted in AD.

The present work aims to evaluate the therapeutic potential of GLP-1 receptor agonists in Alzheimer's disease by integrating current evidence.

1.1. GLP-1 and the Brain

GLP-1 is a 30-amino acid peptide hormone derived from the proglucagon gene and produced by intestinal L-cells as well as specific neurons within the brainstem (Holst, 2007). It functions as an incretin, promoting insulin secretion and glucose homeostasis, but it also acts as a neuropeptide with widespread effects in the central nervous system (CNS) (Hölscher, 2010). GLP-1 receptors are expressed in multiple brain regions, including the hypothalamus, hippocampus, cortex, and brainstem nuclei, where they mediate metabolic, cognitive, and neuroprotective processes.

Within the brain, GLP-1 exerts neurotrophic and neuroprotective actions by reducing neuronal apoptosis, promoting neurite outgrowth, and enhancing synaptic plasticity. It improves mitochondrial function and attenuates oxidative and inflammatory stress, such mechanisms central to neurodegeneration (Anderer, 2025). Beyond neurons, astrocytes and microglia expressing GLP-1 receptors respond with increased glucose metabolism and reduced pro-inflammatory signaling, while oligodendrocytes gain protection against injury-induced loss of myelination. In the neurovascular unit, endothelial cells and pericytes are stabilized by GLP-1-mediated antioxidant activity and improved microvascular flow.

Collectively, these effects position GLP-1 receptor agonists as multifunctional modulators of brain homeostasis. By simultaneously acting on neuronal, glial, and vascular compartments, GLP-1 agonism has the potential to counteract the cellular dysfunctions underlying Alzheimer's disease and thereby offers a biologically integrated route toward disease modification or reversal

3. Aim of the Study

This review aims to assess the therapeutic potential of GLP-1 receptor agonists (GLP-1RAs) in Alzheimer's disease by synthesizing cellular, and functional evidence from preclinical and clinical research. Specifically, it seeks to determine whether activation of the GLP-1 receptor can restore neuronal and glial homeostasis and thereby influence the progression of Alzheimer's pathology toward a disease-modifying outcome.

4. Methodology

4.1. Literature Search Strategy

A comprehensive literature search was performed in PubMed, Scopus, and Web of Science databases up to October 2025, using combinations of the following keywords: *"Alzheimer's disease," "GLP-1," "GLP-1 receptor agonist," "liraglutide," "semaglutide," "exenatide," "neuroprotection," "astrocyte," "microglia," "oligodendrocyte," "endothelial cells,"* and *"pericytes."*

Articles were screened for relevance to Alzheimer's disease mechanisms or neurodegeneration. Both preclinical (in vitro and animal) and clinical studies were included.

4.2. Inclusion and Exclusion Criteria

Eligible studies met the following criteria:

- Investigated GLP-1 or GLP-1 receptor agonists in relation to neuronal, glial, or vascular function;
- Reported measurable biological, molecular, or behavioral outcomes relevant to AD;
- Published in English in peer-reviewed journals.
- Reviews, editorials, and non-original reports were excluded except when cited to provide mechanistic or contextual background.

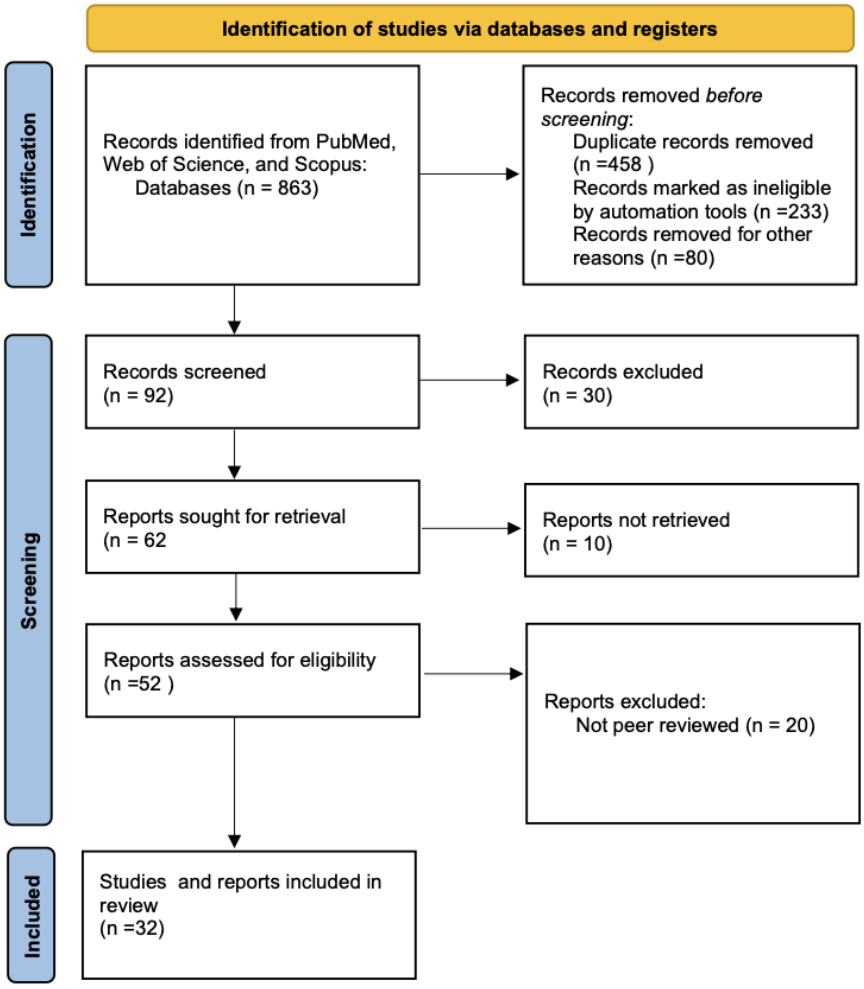

Fig. 1. *Flow diagram illustrating the study selection process.*

5. Results

There is robust evidence from both animal studies and early human clinical trials supporting the neuroprotective effects of GLP-1 receptor agonists in Alzheimer's disease models.

5.1. Evidence from Preclinical Animal Studies

Preclinical studies in transgenic animal models of Alzheimer's disease (AD) have demonstrated that GLP-1 receptor agonists, including liraglutide, exenatide, semaglutide, and dulaglutide, can significantly improve learning and memory performance. Treatment with these agents consistently leads to a reduction in amyloid-β (Aβ) plaque burden and phosphorylated tau accumulation, the two neuropathological hallmarks of AD (Urkon et al., 2025).

Beyond their effects on amyloid and tau pathology, GLP-1 agonists have been shown to attenuate neuroinflammation, reduce oxidative stress, and enhance neuronal survival. Several studies also report a restoration of impaired insulin signaling within the brain, suggesting that GLP-1–mediated neuroprotection may involve normalization of metabolic and synaptic pathways disrupted in AD.

A summary of key findings from preclinical animal studies is presented in Table 1.

Table 1. Summary of outcomes from animal studies.

Study (year)	Animal model	Experimental group (drug, dose, duration, route)	Proposed mechanisms / effects
(An et al., 2019)	5×FAD mice (♂, 5 mo)	Exenatide, 100 μg/kg, BID × 16 w, s.c.	Reduces Aβ deposition, restores mitochondrial morphology and energy metabolism, alleviates oxidative stress
(Bomba et al., 2019)	3×Tg AD mice (♂♀, 6 mo)	Exenatide, 500 μg/kg, 5 d/w × 3 mo, i.p.	Restores BDNF signaling and reduces neuroinflammation
(Bomfim et al., 2012)	APP/PS1 mice (♂, 9 mo)	Exenatide, 25 nmol/kg, BID × 3 w, i.p.	Prevents disruption of insulin signaling in the brain
(Cai et al., 2014)	$A\beta_{25-35}$ rat model	Lixisenatide, 10 nmol, once i.h.	Prevents Aβ-related synaptic plasticity loss via PI3K-Akt-GSK3β pathway
(Chen et al., 2017)	3×Tg AD mice (♂, 7 mo)	Liraglutide, 300 μg/kg × 8 w, s.c.	Reduces tau hyperphosphorylation via JNK/ERK modulation
(Garabadu & Verma, 2019)	Aβ rat model	Exenatide, 5 μg/kg × 14 d, i.p.	Mitigates mitochondrial toxicity via PI3K/Akt pathway
(Han et al., 2013)	$A\beta_{25-35}$ rats	Liraglutide, 0.05–5 nmol, once i.h.	Improves spatial memory and activates cAMP signaling
(Hansen et al., 2016)	hAPP/PS1 mice (♂, 5 mo)	Liraglutide, 100–500 μg/kg × 3 mo, s.c.	No clear difference vs. placebo
(Jia et al., 2016)	$A\beta_{1-42}$ rats	Exenatide, 0.02–2 nmol i.c.v.	Modulates apoptotic pathways
(McClean et al., 2011)	APPswe/PS1ΔE9 mice (♂, 7 mo)	Liraglutide, 25 nm/kg × 8 w, i.p.	Prevents synaptic loss, reduces inflammation, boosts neurogenesis
(McClean & Hölscher, 2014)	APPswe/PS1ΔE9 mice (♂, 14 mo)	Liraglutide, 25 nm/kg × 8 w, i.p.	Reverses AD pathology, enhances synaptic plasticity
(McClean et al., 2015)	APPswe/PS1ΔE9 mice (♂, 8 wk)	Liraglutide, 25 nm/kg × 8 mo, i.p.	Reduces plaque burden and inflammation
(Qi et al., 2016)	$A\beta_{1-42}$ mice	Liraglutide, 25 nmol/kg × 8 w, s.c.	Improves tau phosphorylation and synaptic structure
(Robinson et al., 2019)	Tg2576 mice	Exenatide, 0.075 μg × 6 d/w × 8 mo, i.n.	Restores insulin signal transduction
(X. Wang, Wang, Jiang, et al., 2016)	$A\beta_{1-42}$ rats	Exenatide, 0.2 nmol i.h.	Restores LTP via cAMP/PKA/CREB
(X. Wang, Wang, Xu, et al., 2016)	$A\beta_{31-35}$ mice	Exenatide, 0.05–0.5 nmol i.n.	Not reported
(Y. Wang et al., 2018)	APP/PS1 mice	Exenatide, 25 nmol/kg × 4 w s.c.	Regulates Akt/GSK3β/β-catenin pathway

(Xiong et al., 2013)	STZ mice	Liraglutide, 300 μg/kg × 30 d s.c.	Improves cytoskeleton glycosylation and reduces neurodegeneration
(Yu et al., 2020)	OA rats	Liraglutide, 300 μg/kg × 30 d s.c.	Inhibits tau activation and neuronal apoptosis
(M. Zhang et al., 2022)	5×FAD mice (♂, 5 mo)	Exenatide, 100 μg/kg BID × 16 w s.c.	Reduces neuroinflammation via NLRP2 inhibition
(Ma et al., 2025)	STZ rats and HT-22 cells	Liraglutide, 200 μg/kg × 28 d i.p.	Decresed levels of Aβ, BACE1, and γ-secretase ($p < 0.05$)
Zhao, L. (2021)	STZ rats	Liraglutide, 300 μg/kg × 4 w s.c.	Decreases hippocampal tau phosphorylation
(Zheng & Wang, 2021)	5×FAD mice (♂, 4 mo)	Liraglutide, dose not stated	Reduces oxidative stress and enhances astrocytic support

Across the included preclinical studies, treatment with GLP-1 receptor agonists (GLP-1RAs) consistently led to improvements in learning and memory performance, typically assessed using the Morris Water Maze, Y-maze, and novel object recognition paradigms. These cognitive benefits were linked to enhanced synaptic plasticity, reflected by increased long-term potentiation (LTP) and elevated expression of PSD-95 and synaptophysin, as well as protection against neuronal loss within the hippocampus.

Administration of GLP-1 analogues markedly reduced amyloid-β (Aβ) deposition, tau hyperphosphorylation, and microglial activation in multiple AD animal models (An et al., 2019). The compounds further mitigated oxidative stress, lowering malondialdehyde (MDA) levels and enhancing antioxidant defense through increased superoxide dismutase (SOD) activity. Notably, exenatide and liraglutide restored mitochondrial function, improving ATP generation and the performance of respiratory chain complexes. In addition, GLP-1RAs normalized brain insulin signaling by decreasing aberrant IRS-1 phosphorylation and activating the PI3K/Akt/GSK-3β and ERK pathways.

On a molecular level, GLP-1RAs appear to stabilize neuronal energy metabolism, suppress neuroinflammatory processes, and stimulate synaptic regeneration. Both exenatide and liraglutide modulate astrocytic glycolysis, neuronal survival signaling, and neurotrophic support through factors such as BDNF. Several studies also reported enhanced autophagic activity and attenuation of endoplasmic reticulum stress, suggesting that these agents promote multifaceted neuroprotection and contribute to overall neuronal resilience.

4.2. Studies in Humans

Preclinical research provides substantial evidence that GLP-1 receptor agonists (GLP-1 RAs) are effective in mitigating Alzheimer's disease (AD) pathology in animal models. However, it remains uncertain whether these beneficial effects can be fully translated to humans.

According to ClinicalTrials.gov, five phase II and III clinical trials have been conducted or are currently underway. These studies suggest that GLP-1 receptor agonists may slow cognitive decline and reduce brain atrophy in individuals with early- to moderate-stage Alzheimer's disease, with some reports indicating up to an 18% reduction in disease progression risk compared with placebo. Moreover, a phase II clinical trial of exenatide in patients with AD (*NCT01255163*) demonstrated that the drug was safe and well tolerated in humans (see *Table 2*).

Table 2. Summary of clinical trials available on ClinicalTrials.gov (last accessed on 28 October 2025).

Study (ClinicalTrials.gov ID)	Drug (dose; duration; route)	Sample (age; sex)	Primary and secondary outcomes	Results
A Pilot Clinical Trial of Exendin-4 in Alzheimer's Disease (NCT01255163)	Exenatide (5 µg or 10 µg twice daily; subcutaneous)	*n* = 57 (≥ 60 years; male and female)	MMSE; ADAS-Cog70; CDR Global Score; CSF p-tau (181) and Aβ42 deposition; BMI	Intervention was safe and well-tolerated.. Exenatide treatment produced no differences or trends compared to placebo for clinical and cognitive or biomarkers in CSF, plasma, except for a reduction of Aβ42 in EVs.
Identifying Potential Effects of Liraglutide on Degenerative Changes (NCT01469351)	Liraglutide (1.8 mg once daily; subcutaneous)	*n* = 34 (50–80 years; male and female)	CSF amyloid deposition; neuropsychological tests; change in cerebral glucose uptake	No significant differences in amyloid deposition and cognitive function compared to the placebo group.
Evaluating Liraglutide in Alzheimer's Disease (ELAD) (NCT01843075)	Liraglutide (1.8 mg once daily; subcutaneous)	*n* = 204 (≥ 50 years; male and female)	Cerebral glucose metabolic rate; ADAS-Exec z-scores; MRI changes; microglial activation; CSF biomarkers; incidence and severity of treatment-emergent adverse events; changes in tau and amyloid deposition	Unknown
EVOKE Plus: A Research Study Investigating Semaglutide in People with Early Alzheimer's Disease (NCT04777409)	Semaglutide (oral; titrated to 14 mg once daily)	*n* = 1840 (55–85 years; male and female)	CDR-SB; ADCS-ADL-MCI; time to progression to dementia; ADAS-Cog-13; MoCA; ADCOMS; MMSE; NPI-10; time to progression in disease stage; TEAEs; hs-CRP; MACE; stroke; EQ-5D-5L proxy score	Ongoing, not Recruiting
EVOKE: A Research Study Investigating Semaglutide in People with Early Alzheimer's Disease (NCT04777396)	Semaglutide (oral; titrated to 14 mg once daily)	*n* = 1840 (55–85 years; male and female)	CDR-SB; ADCS-ADL-MCI; time to progression to dementia; ADAS-Cog-13; MoCA; ADCOMS; MMSE; NPI-10; time to progression in disease stage; TEAEs; hs-CRP; MACE; stroke; EQ-5D-5L proxy score	Ongoing, not Recruiting

Two clinical investigations have evaluated liraglutide as a potential therapy for Alzheimer's disease (AD).

The first, a 6-month double-blind trial (NCT01469351), assessed liraglutide's effect on brain metabolism and cognition in individuals with AD. The study found that liraglutide appeared to stabilize brain glucose metabolism and cognitive performance over time; however, no significant differences were observed in amyloid deposition or overall cognitive scores compared with placebo.

A second trial (NCT01843075) enrolled 204 participants, who were randomized to receive liraglutide or placebo. The primary outcome measures included changes in cerebral glucose metabolism, cognitive test performance, microglial activation, and CSF tau and amyloid concentrations. The current status of this study has not been updated.

In addition, two ongoing Phase III trials are evaluating semaglutide in AD (NCT04777409 and NCT04777396). Both studies aim to determine semaglutide's efficacy in individuals with mild cognitive impairment (MCI) or mild AD, including those with or without vascular comorbidity.

Observational studies also show significantly lower rates of dementia and cognitive impairment in people with diabetes taking GLP-1 agonists compared to other treatments (e.g., DPP-4 inhibitors, sulfonylureas) (Tang et al., 2024). Indeed, the study conducted by (P. Zhang et al., 2025) identified GLP-1 receptor agonist initiation compared to DPP-4 inhibitors initiation was associated with a reduced risk of AD (p value < 0.001).

In summary, evidence from both animal models and human research supports the potential of GLP-1 agonists as disease-modifying drugs for Alzheimer's disease, with ongoing large trials poised to clarify their clinical impact

6. Discussion

The findings of this review demonstrate a growing body of evidence supporting the neuroprotective and disease-modifying potential of GLP-1 receptor agonists in Alzheimer's disease. Preclinical studies have consistently shown that GLP-1RAs, such as liraglutide, exenatide, semaglutide, and dulaglutide, ameliorate multiple aspects of AD pathology in transgenic rodent models. These effects include the reduction of amyloid-β plaque burden, decreased tau phosphorylation, attenuation of neuroinflammation, and restoration of mitochondrial and synaptic function. GLP-1RAs also appear to normalize insulin signaling in the brain through activation of the PI3K/Akt/GSK3β and ERK pathways, thereby improving neuronal survival and energy metabolism.

The mechanisms identified in animal models suggest that GLP-1RAs exert their neuroprotective effects via multifactorial actions encompassing metabolic, inflammatory, and oxidative pathways. Importantly, these mechanisms parallel many of the cellular disturbances seen in human AD, reinforcing the translational relevance of these findings. The consistency of results across diverse experimental models underscores the therapeutic promise of GLP-1RAs as agents capable of targeting multiple disease mechanisms simultaneously.

However, despite encouraging results in animals, translation into the clinical setting remains limited. As summarized in Table 2, five phase II and III clinical trials have investigated the use of GLP-1 receptor agonists,most notably liraglutide, semaglutide, and exenatide, in patients with early or moderate AD. These studies suggest that GLP-1RAs may slow cognitive decline, stabilize cerebral glucose metabolism, and reduce brain atrophy, with some trials reporting up to an 18% reduction in disease progression risk compared with placebo. A phase II trial of exenatide (NCT01255163) further confirmed the safety and tolerability of GLP-1RAs in humans.

It should be noted, however, that these trials have been limited by small sample sizes and relatively short durations, which may constrain the interpretation of results. Furthermore, animal models of AD replicate only selected pathological mechanisms such as amyloid or tau pathology, and do not fully capture the complex, multifactorial nature of human disease. Consequently, while preclinical data provide strong mechanistic support, the clinical efficacy of GLP-1RAs in humans remains to be conclusively established.

Observational evidence also points toward a reduced incidence of dementia and cognitive decline among diabetic patients treated with GLP-1 receptor agonists compared with those using other antidiabetic medications, such as DPP-4 inhibitors or sulfonylureas. For instance, a recent population-based study (Zhang et al., 2025) demonstrated that initiation of GLP-1RAs was associated with a significantly lower risk of developing AD ($p < 0.001$), lending real-world support to experimental observations.

Overall, the convergence of preclinical and early clinical data suggests that GLP-1 receptor agonists represent a promising therapeutic avenue for Alzheimer's disease. Nonetheless, to establish their role as disease-modifying treatments, it is essential to conduct larger, longer-term randomized controlled trials with

standardized cognitive, neuroimaging, and biomarker outcomes. Such studies are necessary to validate the preliminary findings, clarify dose–response relationships, and facilitate the translation of GLP-1–based neuroprotective strategies into clinical practice.

7. Conclusions

Growing experimental and clinical evidence supports the concept that GLP-1 receptor agonists exert multifaceted neuroprotective effects relevant to Alzheimer's disease. By modulating insulin signaling, reducing neuroinflammation and oxidative stress, and improving neuronal and synaptic function, these agents address several core mechanisms underlying neurodegeneration. While preclinical findings are robust, human data remain preliminary and limited by small sample sizes and short study durations. Ongoing large-scale trials with liraglutide, semaglutide, and exenatide will be critical to determine whether GLP-1-based therapies can meaningfully alter the course of Alzheimer's disease. If confirmed, they may represent one of the first metabolism-targeted approaches capable of modifying disease progression rather than merely alleviating symptoms.

Abbreviations

Aβ – Amyloid-β
AD – Alzheimer's disease
ADAS-Cog – Alzheimer's Disease Assessment Scale–Cognitive Subscale
ADAS-Exec – Alzheimer's Disease Assessment Scale–Executive Function Subscale
ADCOMS – Alzheimer's Disease Composite Score
ADCS-ADL-MCI – Alzheimer's Disease Cooperative Study–Activities of Daily Living scale for mild cognitive impairment
AKT – Protein kinase B
APP – Amyloid precursor protein
APP/PS1 – Double-transgenic mouse model expressing mutant human amyloid precursor protein and presenilin-1
APPswe/PS1ΔE9 – APP Swedish/PS1 exon-9 deletion double-transgenic mouse model
BBB – Blood–brain barrier
BDNF – Brain-derived neurotrophic factor
BID – Twice daily (bis in die)
BMI – Body mass index
cAMP – Cyclic adenosine monophosphate
CDR – Clinical Dementia Rating
CDR-SB – Clinical Dementia Rating – Sum of Boxes
CNS – Central nervous system
CREB – cAMP response element-binding protein
CSF – Cerebrospinal fluid
DPP-4 – Dipeptidyl peptidase-4
ERK – Extracellular signal-regulated kinase
EVs – Extracellular vesicles
GLP-1 – Glucagon-like peptide-1
GLP-1RA – Glucagon-like peptide-1 receptor agonist
GSK3β – Glycogen synthase kinase-3 beta
hAPP – Human amyloid precursor protein
hs-CRP – High-sensitivity C-reactive protein
i.c.v. – Intracerebroventricular
i.g. – Intragastric
i.h. – Intrahippocampal
i.n. – Intranasal
i.p. – Intraperitoneal
JNK – c-Jun N-terminal kinase
LTP – Long-term potentiation
MACE – Major adverse cardiovascular events
MCI – Mild cognitive impairment

MMSE – Mini-Mental State Examination
mo – Months of age (in animals)
MoCA – Montreal Cognitive Assessment
mTOR – Mechanistic target of rapamycin
NLRP2 – NOD-like receptor family pyrin domain-containing protein 2
NPI – Neuropsychiatric Inventory
OA – Okadaic acid
PI3K – Phosphoinositide-3-kinase
PKA – Protein kinase A
PPARγ – Peroxisome proliferator-activated receptor gamma
PS1 – Presenilin-1
s.c. – Subcutaneous
SOD – Superoxide dismutase
STZ – Streptozotocin
TEAEs – Treatment-emergent adverse events

Author Contributions

Conceptualization, L.J.; methodology, L.J.; investigation, L.J.; data curation, L.J.; writing—original draft preparation, L.J.; writing—review and editing, L.J. All authors have read and agreed to the published version of the manuscript.

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