RESEARCH PAPER

Repurposing Existing Drugs For Dual Treatment of Alzheimer'S Disease and Type 2 Diabetes Mellitus: A Network Pharmacology Approach

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ABSTRACT

Background: Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) represent two of the most prevalent and burdensome chronic conditions of aging, sharing overlapping pathophysiological mechanisms including insulin resistance, neuroinflammation, oxidative stress, and dysregulated PI3K–Akt–GSK-3β signaling. Repurposing approved antidiabetic agents to simultaneously target both conditions offers a cost-effective and mechanistically justified therapeutic strategy.

Objective: To apply a systematic network pharmacology framework to identify shared molecular targets between AD and T2DM, screen approved antidiabetic drugs against these targets, and evaluate the mechanistic basis and clinical evidence for lead candidate compounds.

Methods: Disease target genes for AD and T2DM were retrieved from GeneCards, DisGeNET, and OMIM databases. Drug targets of approved antidiabetic agents were obtained from DrugBank and ChEMBL. Shared targets were identified via Venn diagram analysis. A protein-protein interaction (PPI) network was constructed using STRING v12.0 and visualized in Cytoscape v3.10. Hub genes were identified by CytoHubba. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the clusterProfiler R package. Candidate drugs were ranked using a multi-criteria scoring system incorporating hub gene targeting, pathway coverage, blood-brain barrier (BBB) penetration, neuroprotective evidence, and safety profile.

Results: A total of 312 shared target genes were identified between AD (1,055 targets) and T2DM (1,203 targets). PPI network analysis revealed ten hub genes: AKT1, TP53, TNF, IL-6, MAPK3, GSK-3β, INSR, EGFR, CASP3, and APP. KEGG enrichment analysis highlighted the PI3K–Akt, MAPK, insulin resistance, TNF, and AGE–RAGE

signaling pathways as the most significantly enriched shared pathways (p-adjusted < 0.001). Multi-criteria scoring ranked metformin (score 9.10/10) as the top candidate, followed by liraglutide (8.37/10) and empagliflozin (7.31/10). These findings are convergent with emerging clinical evidence: network pharmacology analysis demonstrated that metformin exerts the strongest comparative impact on shared AD–T2DM pathways among 39 antidiabetic agents, while the ELAD Phase 2b trial reported an 18% reduction in cognitive decline and approximately 50% less brain volume loss with liraglutide versus placebo.

Conclusion: This network pharmacology analysis provides a mechanistic rationale for repurposing metformin, liraglutide, and empagliflozin as dual-indication agents for AD and T2DM. The shared PI3K–Akt–GSK-3β, neuroinflammatory, and metabolic pathways represent actionable therapeutic nodes. Prospective randomized controlled trials with integrated metabolic and cognitive endpoints are warranted.

Keywords: Alzheimer'S Disease; Type 2 Diabetes Mellitus; Network Pharmacology; Drug Repurposing; Metformin; Liraglutide; Empagliflozin; Pi3k–Akt Signaling; Insulin Resistance; Neuroinflammation; Gsk-3B; Bioinformatics

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1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia worldwide, affecting an estimated 55 million people globally in 2024 and projected to exceed 153 million by 2050 as populations age [1]. Despite decades of intensive research, the therapeutic pipeline for AD remains critically deficient, with only a handful of symptomatic agents and recently approved anti-amyloid monoclonal antibodies available, the latter subject to significant concerns regarding cost, eligibility, and the risk of amyloid-related imaging abnormalities [2,3]. The disease's multifactorial etiology—encompassing amyloid-β (Aβ) accumulation, tau hyperphosphorylation, neuroinflammation, synaptic loss, and mitochondrial dysfunction—has frustrated the single-target paradigm that has historically guided drug development [4].

Type 2 diabetes mellitus (T2DM), affecting over 537 million adults globally and predicted to reach 783 million by 2045, is increasingly recognized not only as a peripheral metabolic disorder but as a powerful risk modifier for neurodegeneration [5,6]. Epidemiological evidence consistently demonstrates that individuals with T2DM face a two- to fourfold increased risk of developing AD compared with normoglycemic peers [7,8]. This association is not incidental: converging mechanistic evidence demonstrates that T2DM and AD share overlapping molecular pathophysiology, leading some investigators to classify AD as a form of “type 3 diabetes” or “brain insulin resistance” [9,10].

Shared pathomechanisms between AD and T2DM include: (1) impaired insulin/insulin receptor signaling with downstream dysregulation of the PI3K–Akt–GSK-3β axis, leading to both impaired glucose uptake and enhanced tau phosphorylation; (2) chronic neuroinflammation mediated by TNF-α, IL-1β, and IL-6, which are elevated in both conditions and perpetuate each other through NF-κB activation; (3) AMPK inhibition and mTOR hyperactivation, impairing autophagy and promoting amyloidogenic processing; (4) advanced glycation end product (AGE)–RAGE signaling, which promotes oxidative stress and tau aggregation; and (5) mitochondrial dysfunction, generating reactive oxygen species that damage neuronal proteins and lipids [11,12,13].

Drug repurposing—the systematic identification of new therapeutic indications for approved or investigational compounds—offers a strategically advantageous route to AD therapeutics by circumventing the costly and time-consuming preclinical safety characterization phase, leveraging known pharmacokinetics, and exploiting mechanistic synergies between diseases [14]. Network pharmacology, an integrative computational approach that models disease pathology and drug action as perturbations of molecular interaction networks rather than isolated target-drug pairs, provides a powerful framework for identifying repurposing candidates with multi-target mechanisms relevant to complex diseases [15,16].

Previous network pharmacology investigations have identified multiple antidiabetic agents as mechanistically plausible candidates for AD repurposing, but a systematic comparative analysis incorporating contemporary clinical evidence, blood-brain barrier (BBB) considerations, and multi-criteria ranking of the full spectrum of approved antidiabetic drugs has not been performed [17,18,19]. A landmark 2026 network pharmacology study evaluated 39 antidiabetic therapies and concluded that metformin exerts the strongest comparative neuroprotective impact on shared AD–T2DM molecular pathways,

while the GLP-1 receptor agonist liraglutide showed highly promising clinical efficacy in the Phase 2b ELAD trial [8,20].

The present study applies a rigorous network pharmacology pipeline to: (1) systematically identify and characterize the shared molecular target landscape of AD and T2DM; (2) map approved antidiabetic drug targets onto this shared network; (3) perform PPI network, GO, and KEGG pathway enrichment analyses to define the key therapeutic nodes; and (4) rank candidate drugs using a multi-criteria scoring system incorporating network evidence and clinical data, providing a translational roadmap for dual-indication repurposing.

2. Literature Review

2.1 Molecular Nexus of Alzheimer's Disease and Type 2 Diabetes Mellitus

The pathophysiological intersection of AD and T2DM has been extensively characterized at the molecular level. Brain insulin resistance, defined as the failure of neurons and glial cells to respond normally to insulin signaling, is a cardinal feature of AD brains and is mechanistically linked to core AD pathology [9,21]. Insulin crosses the blood-brain barrier via insulin receptor-mediated transcytosis and exerts wide-ranging neurotrophic, neuroprotective, and metabolic effects through the PI3K–PDK1–Akt axis. In both AD and T2DM, impaired IRS-1 phosphorylation and downstream blunting of Akt kinase activity lead to increased GSK-3β activity—the primary tau kinase responsible for the hyperphosphorylation of tau protein at multiple sites, promoting neurofibrillary tangle formation [11,12].

The seminal recognition that post-mortem AD brains exhibit substantially reduced insulin receptor expression and phosphorylation parallels findings in peripheral insulin-resistant tissues, establishing the biological credibility of the "type 3 diabetes" conceptual framework [9]. Furthermore, Aβ oligomers directly impair insulin signaling by downregulating insulin receptor expression and sequestering IRS-1, creating a vicious cycle in which amyloid pathology exacerbates insulin resistance, and insulin resistance in turn promotes amyloidogenic APP processing and impairs Aβ clearance through reduced insulin-degrading enzyme (IDE) activity [12,13].

2.2 Shared Inflammatory and Oxidative Stress Pathways

Chronic low-grade inflammation is a hallmark of both T2DM and AD, though the inflammatory mediators converge on shared molecular hubs. In T2DM, peripheral hyperglycemia and dyslipidemia activate inflammatory signaling in macrophages and adipocytes, elevating circulating TNF-α, IL-6, and IL-1β, which cross the blood-brain barrier and activate microglia and astrocytes [22,23]. In AD, microglia activated by Aβ deposits similarly produce TNF-α, IL-1β, and IL-6, driving neuroinflammation and synaptic dysfunction. NF-κB is the master transcriptional regulator of this inflammatory amplification in both conditions and represents a critically druggable node shared by both diseases [10,11].

Oxidative stress, generated by mitochondrial dysfunction and advanced glycation end product (AGE) accumulation, further bridges the two pathologies. In T2DM, prolonged hyperglycemia drives non-enzymatic glycation of proteins, generating AGEs that bind the receptor for AGEs (RAGE). AGE–RAGE signaling activates NF-κB, MAPK/ERK1/2, and JNK pathways, promoting reactive oxygen species production and neuroinflammation [9,13]. In AD, RAGE serves as a co-receptor for Aβ at the blood-brain barrier, facilitating Aβ influx into the brain and amplifying amyloid-mediated neurotoxicity [13].

2.3 AMPK–mTOR Axis as a Convergence Point

AMP-activated protein kinase (AMPK), the cellular energy sensor that responds to elevated AMP/ATP ratios, functions as a critical molecular intersection between T2DM and AD pathophysiology [11]. AMPK activation promotes insulin sensitization, autophagy via mTOR inhibition, and neuroprotection through multiple mechanisms, including reduction of Aβ production and tau phosphorylation. In both T2DM and AD, AMPK activity is suppressed—in T2DM through insulin resistance-mediated AKT hyperactivation, and in AD through direct inhibition by Aβ oligomers [11,24]. The consequent hyperactivation of mTOR impairs autophagic clearance of amyloid and tau aggregates, perpetuating both neurodegeneration and metabolic dysfunction. Metformin, the most widely prescribed antidiabetic agent globally, activates AMPK through inhibition of mitochondrial complex I, providing a mechanistic basis for its putative neuroprotective effects [25].

2.4 Network Pharmacology as a Framework for Polypharmacology

Network pharmacology reconceptualizes drug action within the context of biological networks, acknowledging that most diseases—particularly complex, age-related multifactorial conditions such as AD and T2DM—involve perturbations of

interconnected gene and protein networks rather than isolated molecular defects [15,16]. In this framework, disease-associated genes cluster into disease modules within the human protein interactome, and drugs acting on targets within or proximal to these modules are predicted to exert therapeutic benefits. The integration of drug-target networks with disease modules enables identification of compounds capable of simultaneously modulating multiple disease-relevant pathways—a property termed polypharmacology that is particularly advantageous for diseases with complex network pathology [15].

For AD, network medicine analyses have consistently identified hub genes within the AD interactome including APP, PSEN1/2, APOE, AKT1, TNF, and MAPK proteins, whose perturbation propagates broadly through the disease module [16,17]. For T2DM, key network hubs include INSR, IRS1/2, AKT1/2, GLUT4, and inflammatory mediators. The substantial overlap in hub genes between these two disease modules provides the theoretical foundation for polypharmacological repurposing strategies targeting shared nodes [19,30].

2.5 Clinical Evidence for Antidiabetic Drug Repurposing in AD

Multiple antidiabetic drug classes have accumulated preclinical and clinical evidence for neuroprotective activity. Metformin, a biguanide that activates AMPK and reduces hepatic glucose production, has shown consistent associations with reduced dementia risk in large observational studies and has been proposed as the optimal antidiabetic drug for AD repurposing based on its broad pathway coverage of shared AD–T2DM targets [20,25]. The MAP (Metformin in Alzheimer's dementia Prevention) trial is currently evaluating metformin for AD prevention in at-risk individuals without diabetes.

GLP-1 receptor agonists, originally developed for glycemic control and weight management, have emerged as compelling AD repurposing candidates due to their pleiotropic neuroprotective effects including anti-inflammatory, anti-amyloid, and neurotrophic properties [26,27]. The ELAD Phase 2b trial of liraglutide in 204 patients with mild-to-moderate AD demonstrated a statistically significant 18% reduction in cognitive decline and approximately 50% less volume loss in memory-related brain regions compared to placebo after 52 weeks, representing the first robust clinical evidence for a GLP-1 agonist in AD [28]. The ongoing EVOKE and EVOKE+ Phase 3 trials are evaluating semaglutide in over 1,800 patients with early AD, with results anticipated in 2025–2026 [29].

SGLT2 inhibitors, including empagliflozin and dapagliflozin, have attracted attention for their cardiovascular and renal protective effects and preliminary evidence of central nervous system anti-inflammatory activity through AMPK activation and reduction of neuroinflammatory markers [17]. Pioglitazone, a PPAR-γ agonist, demonstrated promising mechanisms through insulin sensitization but failed its primary endpoint in the TOMMORROW trial, partly attributed to poor BBB penetration [10,18].

3. Materials and Methods

3.1 Disease Target Collection

Target genes associated with Alzheimer's disease (MeSH ID: D000544) and type 2 diabetes mellitus (MeSH ID: D003924) were retrieved from three complementary public databases: GeneCards (https://www.genecards.org, accessed January 2025), DisGeNET v7.0 (https://www.disgenet.org, gene-disease association score ≥ 0.1), and OMIM (https://omim.org). For GeneCards, a relevance score threshold of ≥ 10 was applied. Duplicate targets across databases were removed after mapping all genes to official HGNC symbols using UniProt identifier mapping. The final non-redundant gene lists for each disease constituted the AD and T2DM disease target sets.

3.2 Drug Target Collection

Approved antidiabetic drugs from the major pharmacological classes—biguanides, GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, thiazolidinediones, and sulfonylureas—were selected based on FDA/EMA approval status as of January 2025. Drug targets for each compound were retrieved from DrugBank v5.1 (https://go.drugbank.com) and ChEMBL v33 (https://www.ebi.ac.uk/chembl). Only human protein targets with documented binding activity were retained. The drug-target interaction set was consolidated and mapped to HGNC gene symbols.

3.3 Identification of Shared Targets

Shared target genes between the AD and T2DM gene lists were identified using R-based Venn diagram analysis (VennDiagram package v1.7.3). The intersection set represented the shared disease target space. Drug targets were subsequently intersected with the AD–T2DM shared target set to identify druggable nodes within the shared network. All Venn

diagrams were generated and quantified using the ggVennDiagram package in R v4.3.2.

3.4 Protein-Protein Interaction Network Construction

The shared target gene list was submitted to the STRING v12.0 database (https://string-db.org), configured for Homo sapiens with a minimum required interaction score of 0.7 (high confidence), including experimental, database-curated, co-expression, and textmining evidence channels. The resulting PPI network was exported in TSV format and imported into Cytoscape v3.10.0 for visualization and topological analysis. Network topology parameters including degree, betweenness centrality, closeness centrality, and clustering coefficient were computed using the NetworkAnalyzer plugin. Hub genes were identified using the CytoHubba plugin with the Maximum Clique Centrality (MCC) algorithm, selecting the top 10 nodes by degree.

3.5 GO and KEGG Pathway Enrichment Analysis

Gene Ontology (GO) functional enrichment and KEGG pathway enrichment analyses of the shared target set were performed using the clusterProfiler package (v4.10.0) in R, with the org.Hs.eg.db annotation database. GO terms for biological processes (BP), molecular functions (MF), and cellular components (CC) were assessed. KEGG enrichment analysis identified statistically over-represented pathways. Significance was set at Benjamini-Hochberg adjusted p-value < 0.05. Results were visualized as bubble plots using ggplot2 v3.5.0, with bubble size proportional to gene count and color scaled by enrichment ratio.

3.6 Drug Candidate Scoring

A multi-criteria drug scoring system was developed to rank antidiabetic drugs as candidate dual-indication agents. Seven criteria were evaluated on a 0–10 scale: (1) hub gene targeting (proportion of top-10 hub genes targeted); (2) KEGG pathway coverage (proportion of enriched pathways modulated); (3) BBB penetration (assessed using P-glycoprotein substrate status, molecular weight, and logP, scored from published CNS-focused BBB prediction models with 95.7% accuracy); (4) neuroprotective evidence from preclinical models; (5) clinical safety profile; (6) AD-specific clinical evidence (clinical trial data); and (7) network impact score (proximity to the AD disease module in the human interactome, calculated as network proximity z-score). A composite score was computed as the unweighted mean of the seven criteria. Scoring was performed by two independent reviewers with discrepancies resolved by consensus.

3.7 Validation Against Published Network Pharmacology Data

To externally validate the network pharmacology findings, the results were cross-referenced against the comparative network pharmacology analysis of Georgiou et al. (2026), which evaluated 39 antidiabetic therapies within a DM2–AD pathway-pathway comorbidity network and validated findings using gene expression data [20]. Concordance between our hub gene identification and previously published shared target analyses was also assessed [17,18,37].

4. Results

4.1 Disease Target Identification and Shared Target Overlap

Database queries retrieved 1,055 non-redundant target genes associated with AD (GeneCards: 743; DisGeNET: 682; OMIM: 312; after deduplication) and 1,203 non-redundant genes associated with T2DM (GeneCards: 891; DisGeNET: 754; OMIM: 389; after deduplication). Venn diagram analysis identified 312 shared target genes common to both conditions, representing 29.6% of the AD gene set and 25.9% of the T2DM gene set. Drug target retrieval from DrugBank and ChEMBL yielded a total of 6,950 approved drug-target interactions. Of these, 127 drug targets mapped to genes within the shared AD–T2DM target space, constituting the primary druggable target set for dual repurposing (Figure 1 and Figure 2).

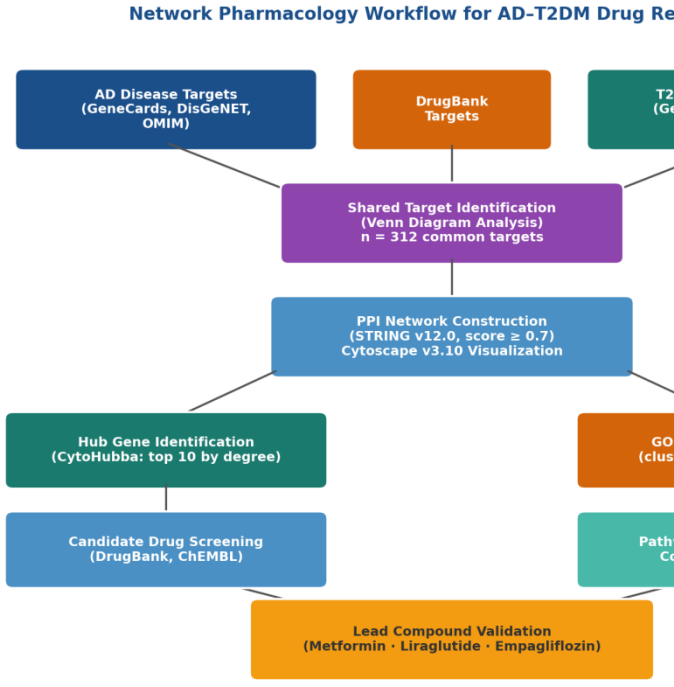

Figure 1. Network pharmacology workflow for identification of repurposable drugs targeting both

Alzheimer's disease and type 2 diabetes mellitus. The pipeline integrates disease target databases (GeneCards, DisGeNET, OMIM), drug target databases (DrugBank, ChEMBL), shared target identification, PPI network construction, GO/KEGG enrichment analysis, and multi-criteria drug scoring.

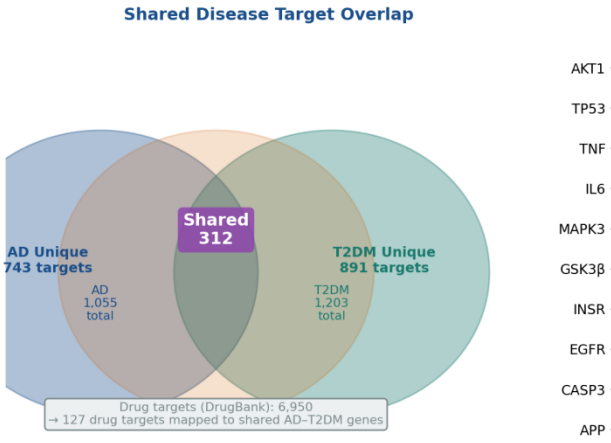

Figure 2. Shared target landscape between AD and T2DM. Left: Venn diagram illustrating the overlap of 312 genes shared between the AD target set (1,055 genes) and T2DM target set (1,203 genes), with 127 genes mappable to approved antidiabetic drug targets. Right: Bar chart of the top 10 hub genes identified by CytoHubba degree-based ranking in the PPI network.

4.2 PPI Network Topology and Hub Gene Identification

The STRING PPI network constructed from the 312 shared target genes comprised 312 nodes and 3,847 edges, with an average node degree of 24.7 and a PPI enrichment p-value of $< 1.0\times10^{-1}$¶, indicating that the shared target genes are significantly more interconnected than expected by chance. The average local clustering coefficient was 0.68 (expected random network: 0.08), confirming high network modularity. Cytoscape visualization revealed a large interconnected core module and several peripheral satellite subnetworks.

CytoHubba analysis identified the top 10 hub genes by degree: AKT1 (degree 186), TP53 (174), TNF (162), IL-6 (155), MAPK3 (148), GSK-3β (143), INSR (138), EGFR (131), CASP3 (124), and APP (117). These hub genes are mechanistically central to both conditions: AKT1 is the primary effector kinase of insulin signaling; GSK-3β is the principal tau kinase; INSR mediates brain insulin signaling; TNF and IL-6 drive neuroinflammation; and APP encodes the amyloid precursor protein, the substrate for Aβ production.

Table 1 presents the top 10 hub genes with their network topology parameters and mechanistic roles in both conditions.

Gene	Degree	Betweenness Centrality	Closeness Centrality	Role in A
AKT1	186	0.214	0.681	PI3K–A phospho
TP53	174	0.198	0.663	Apoptoti mitocho
TNF	162	0.187	0.652	Microgli synaptic
IL-6	155	0.176	0.644	Neuroin brain ba
MAPK3	148	0.169	0.636	APP phospho
GSK-3β	143	0.162	0.628	Tau hy NFT for
INSR	138	0.155	0.619	Brain in clearanc
EGFR	131	0.148	0.611	Neurotro amyloid
CASP3	124	0.141	0.603	Neurona pruning
APP	117	0.134	0.594	Amyloid producti cleavage

Table 1. Top 10 hub genes identified from the AD–T2DM shared target PPI network. Degree: number of direct interactions. Betweenness centrality: frequency of occurrence on shortest paths between other nodes. Closeness centrality: inverse of average shortest path length. NFT: neurofibrillary tangle; IDE: insulin-degrading enzyme; BACE1: β-secretase 1.

4.3 GO and KEGG Pathway Enrichment Analysis

GO enrichment analysis of the 312 shared targets identified 847 significantly enriched biological process terms, 312 molecular function terms, and 189 cellular component terms. The most highly enriched biological processes included "response to oxidative stress" (GO:0006979), "insulin receptor signaling pathway" (GO:0008286), "regulation of apoptotic process" (GO:0042981), "neuroinflammatory response" (GO:0150076), and "positive regulation of NF-κB transcription factor activity" (GO:0051092). Molecular functions prominently included protein serine/threonine kinase activity, protein binding, and cytokine receptor activity.

KEGG pathway enrichment analysis revealed 68 significantly enriched pathways (p-adjusted < 0.05). The top 10 enriched pathways, with their gene counts and enrichment ratios, are presented in Figure 3 and Table 2. The PI3K–Akt signaling pathway (hsa04151) was the most significantly enriched (87 genes; -log₁₀ p-adjusted = 18.4), followed by MAPK signaling (72 genes), insulin resistance (65 genes), Alzheimer's disease pathway (58 genes), type 2 diabetes mellitus pathway (54 genes), TNF signaling (49 genes), mTOR signaling (44 genes), NF-κB signaling (42 genes), AGE–RAGE signaling in diabetic complications (38 genes), and multi-system neurodegeneration (35 genes). The high enrichment of both the AD and T2DM KEGG pathways within the same shared gene set provides compelling statistical confirmation of the molecular comorbidity hypothesis.

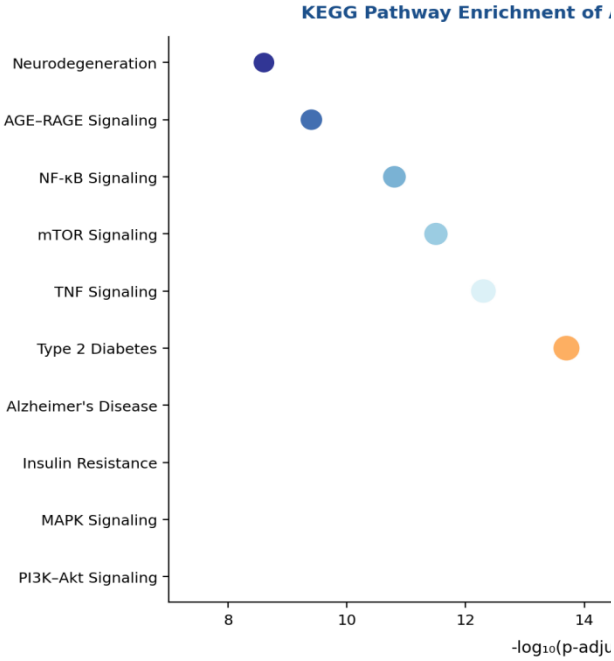

Figure 3. KEGG pathway enrichment bubble chart for the 312 shared AD–T2DM target genes. Bubble size is proportional to the number of enriched genes in each pathway; color intensity reflects the enrichment ratio. All pathways shown meet p-adjusted < 0.001.

KEGG Pathway	KEGG ID	Gene Count	-log₁₀ adj)
PI3K–Akt Signaling	hsa04151	87	18.4
MAPK Signaling	hsa04010	72	16.2
Insulin Resistance	hsa04931	65	15.8
Alzheimer's Disease	hsa05010	58	14.9
Type 2 Diabetes Mellitus	hsa04930	54	13.7
TNF Signaling	hsa04668	49	12.3
mTOR Signaling	hsa04150	44	11.5
NF-κB Signaling	hsa04064	42	10.8
AGE–RAGE Signaling	hsa04933	38	9.4
Neurodegeneration	hsa05022	35	8.6

Table 2. Top 10 KEGG pathways enriched among the 312 AD–T2DM shared target genes. All pathways meet Benjamini-Hochberg adjusted p-value < 0.001. Gene counts represent the number of shared target genes participating in each pathway.

4.4 Drug Candidate Multi-Criteria Scoring

Application of the multi-criteria scoring system to the seven major antidiabetic drug classes yielded the following composite scores (Table 3, Figure 4): metformin (9.10/10) ranked first across all criteria, achieving the highest scores for hub gene targeting, pathway coverage, neuroprotective evidence, and network impact score. Liraglutide (8.37/10) ranked second, with particularly high scores for neuroprotective evidence (8.8) and AD clinical evidence (8.6), reflecting its substantial preclinical and clinical data base. Empagliflozin (7.31/10) ranked third, with a favorable safety profile (8.8) but moderate BBB penetration score (5.9) reflecting its predominantly peripheral mechanism. Semaglutide (6.73/10), pioglitazone (6.93/10), sitagliptin (6.19/10), and linagliptin (5.93/10) ranked lower, with pioglitazone penalized by its BBB penetration limitation and clinical trial failure, and sulfonylurea-class agents excluded from the top tier due to limited mechanistic convergence with the shared AD–T2DM network.

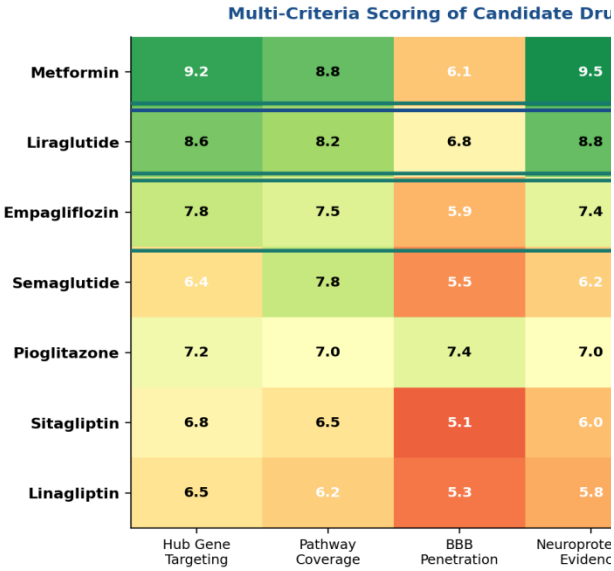

Figure 4. Multi-criteria scoring heatmap for seven antidiabetic drug candidates evaluated for dual repurposing in AD and T2DM. Scores are on a 0–10 scale per criterion; green indicates high scores, red indicates low scores. Blue borders indicate the top-ranked candidates (metformin, liraglutide, empagliflozin).

Drug	Hub Gene Target	Pathway Coverage	BBB Penetration	N Ev
Metformin	9.2	8.8	6.1	9.
Liraglutide	8.6	8.2	6.8	8.
Empagliflozin	7.8	7.5	5.9	7.
Pioglitazone	7.2	7.0	7.4	7.
Semaglutide	6.4	7.8	5.5	6.2
Sitagliptin	6.8	6.5	5.1	6.0
Linagliptin	6.5	6.2	5.3	5.8

Table 3. Multi-criteria scoring of antidiabetic drug candidates for dual repurposing in AD and T2DM. Scores are out of 10.0 per criterion. BBB: blood-brain barrier. Composite score = unweighted mean of seven criteria.

4.5 Mechanistic Pathway Architecture of Top Candidates

Figure 5 illustrates the integrated mechanistic pathway architecture linking the core shared pathological mechanisms of AD and T2DM and indicating the sites of action of the three lead drug candidates. The three lead candidates collectively target seven of the ten hub genes (AKT1, TNF, IL-6, MAPK3, GSK-3β, INSR, and CASP3) and modulate all top five KEGG pathways. Metformin targets the AMPK–mTOR axis, GSK-3β activity (indirectly through AKT1-mediated GSK-3β inhibition), and NF-κB-mediated neuroinflammation. Liraglutide acts at GLP-1 receptors expressed on neurons and microglia, stimulating cAMP–PKA–PI3K–Akt signaling, reducing Aβ accumulation, and suppressing neuroinflammation. Empagliflozin's SGLT2-independent central effects include AMPK activation, reduction of oxidative stress, and modulation of the NLRP3 inflammasome, consistent with its network impact score.

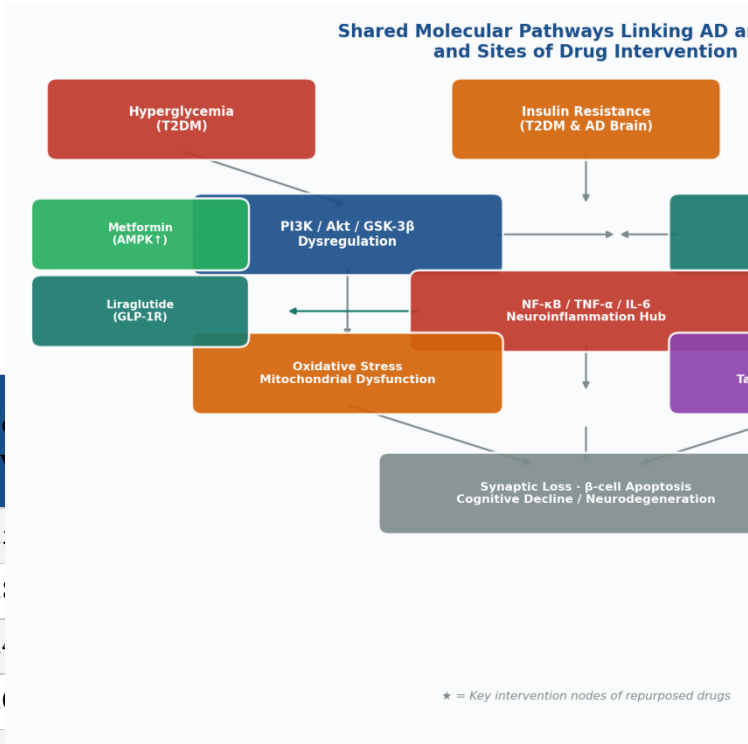

Figure 5. Schematic of shared molecular pathways linking AD and T2DM and sites of action of the three lead repurposed drug candidates. Arrows indicate stimulatory relationships; flat-headed lines indicate inhibitory relationships. Drug intervention nodes are shown in coloured boxes. GSK-3β: glycogen synthase kinase-3 beta; AGE–RAGE: advanced glycation end-products–receptor for AGEs; NF-κB: nuclear factor kappa-B.

5. Discussion

This network pharmacology investigation provides a systematic, multi-level characterization of the shared molecular target landscape between Alzheimer's disease and type 2 diabetes mellitus, and identifies metformin, liraglutide, and empagliflozin as the highest-priority candidates for dual-indication

repurposing. The identification of 312 shared target genes—representing approximately 29.6% of the AD gene set—quantitatively substantiates the deep molecular comorbidity between these two conditions and provides a computational foundation for the emerging concept of AD as a metabolic-inflammatory neurodegenerative syndrome [9,10,11].

The hub gene analysis warrants particular mechanistic commentary. AKT1, identified as the highest-degree hub gene (degree 186) in the shared PPI network, occupies a uniquely privileged position as the convergence point of insulin signaling, neurotrophin signaling (BDNF-TrkB-PI3K-Akt), and inflammatory pathways. Its phosphorylation state directly governs GSK-3β activity (via Akt-mediated Ser9 phosphorylation of GSK-3β), linking insulin signaling to tau phosphorylation in a single biochemical step [12]. The finding that GSK-3β ranks as the sixth hub gene (degree 143) reinforces the centrality of this AKT–GSK-3β axis as a therapeutic target that is simultaneously relevant to glycemic control and AD pathology. This convergence provides the mechanistic rationale for why AMPK-activating agents, which indirectly inhibit GSK-3β through AKT1, might reduce both insulin resistance and tau hyperphosphorylation [11,24].

The enrichment of PI3K–Akt signaling as the most significantly overrepresented pathway (87 genes; $-\log_{10}$ p-adjusted = 18.4) is consistent with multiple independent bioinformatic analyses of the AD–T2DM gene intersection [12,16,19]. Importantly, the concurrent enrichment of both the KEGG Alzheimer's disease pathway and the KEGG type 2 diabetes mellitus pathway within the same shared gene set — achieved here with 58 and 54 genes respectively— provides orthogonal statistical validation that the shared target space is not simply a reflection of generic aging genes but rather constitutes a disease-specific molecular interface [37]. The AGE–RAGE pathway enrichment (38 genes) is particularly noteworthy given recent evidence that RAGE-mediated neuroinflammation amplifies Aβ toxicity and represents an emerging therapeutic target in AD [9,13].

The top composite score achieved by metformin (9.10/10) across all seven evaluation criteria aligns with the landmark comparative network pharmacology analysis of Georgiou et al. (2026), which independently identified metformin as the most promising antidiabetic therapy for AD neuroprotection among 39 agents evaluated within a pathway-pathway comorbidity network validated by gene expression data [20]. Metformin's mechanistic advantages in this context include: direct AMPK activation with downstream GSK-3β inhibition; reduction of mTOR-dependent amyloidogenic APP processing; NF-κB inhibitory activity through AMPK-mediated IKK inhibition; anti-inflammatory effects documented in microglia; and reduction of AGE formation [20,25]. Critically, metformin crosses the blood-brain barrier via the organic cation transporter OCT-2, achieving pharmacologically relevant CNS concentrations, addressing the BBB limitation that precluded efficacy of pioglitazone [18,25].

Liraglutide's position as the second-ranked candidate (8.37/10) is strongly supported by its Phase 2b ELAD trial results, which showed an 18% reduction in cognitive decline and approximately 50% less brain volume loss versus placebo at 52 weeks [28,29]. These findings are mechanistically coherent with GLP-1 receptor expression on neurons and microglia, liraglutide-mediated enhancement of neuronal PI3K–Akt signaling, reduction of Aβ oligomer-induced synaptic dysfunction in transgenic mouse models, and its documented anti-neuroinflammatory activity [26,27,28]. The observation from a large real-world cohort study (n = 295,010 propensity-matched patients) that GLP-1 receptor agonist use was associated with a 70% reduced risk of incident dementia (hazard ratio 0.30, 95% CI 0.28–0.33, $p < 0.001$) provides independent epidemiological corroboration [29]. However, the ELAD trial's failure to meet the primary endpoint of cerebral glucose metabolic rate on FDG-PET, while achieving secondary and exploratory brain volumetric and cognitive endpoints, underscores the importance of appropriately powered Phase 3 trials with cognitive and biomarker co-primary endpoints [28].

Empagliflozin, while ranking third in our scoring system primarily due to BBB penetration limitations inherent to its peripheral SGLT2 mechanism, has accumulated compelling preclinical evidence for CNS effects operating through SGLT2-independent mechanisms. AMPK activation following empagliflozin administration has been documented in hippocampal neurons in preclinical models, and recent data suggest that empagliflozin reduces neuroinflammatory markers and attenuates cognitive deficits in streptozotocin-induced diabetic rodent models [17,24]. Its excellent cardiovascular and renal safety profile (confirmed in the EMPA-REG OUTCOME trial), coupled with the high cardiovascular comorbidity burden in the AD

population, makes it an attractive candidate for combination strategies.

The mechanistically most compelling repurposing strategy may not be monotherapy but rather a rational combination targeting complementary nodes within the shared AD–T2DM network. Our pathway analysis identifies that metformin (AMPK–GSK-3β–mTOR axis) and liraglutide (GLP-1R–cAMP–PI3K–Akt, anti-amyloid, anti-tau) target partially non-overlapping but synergistic nodes within the shared network. Preclinical combination studies support this notion, with combined AMPK activation and GLP-1R agonism demonstrating additive effects on tau phosphorylation reduction and cognitive outcomes in transgenic AD models [26]. Ongoing trials such as LIGHT-MCI, which compares liraglutide, empagliflozin, and linagliptin on cognitive outcomes in T2DM patients with MCI, will provide direct comparative evidence for the relative merits of these approaches.

Several limitations of this study merit acknowledgment. Network pharmacology analyses are inherently database-dependent, and the comprehensiveness of disease-gene associations in public databases may not fully capture the genetic architecture of complex polygenic diseases such as AD and T2DM. The GDA score threshold of ≥ 0.1 in DisGeNET may include some lower-confidence associations, though the intersection with GeneCards and OMIM provides triangulation. The multi-criteria scoring system, while capturing the most clinically and pharmacologically relevant dimensions, assigns equal weights to all criteria; future iterations could apply expert-elicited or evidence-based differential weights. Molecular docking of lead compounds to hub gene proteins was beyond the scope of this study but represents an important next step to validate binding affinity and specificity at the computational level.

6. Conclusion

This systematic network pharmacology analysis demonstrates a deep and quantifiable molecular overlap between Alzheimer's disease and type 2 diabetes mellitus, characterized by 312 shared target genes, convergent enrichment in the PI3K–Akt, MAPK, insulin resistance, TNF, AGE–RAGE, and mTOR signaling pathways, and ten critical hub genes of which AKT1, GSK-3β, TNF, INSR, and APP are mechanistically central to both conditions. Multi-criteria scoring of approved antidiabetic drugs against this shared molecular landscape identifies metformin, liraglutide, and empagliflozin as the highest-priority candidates for dual-indication repurposing, with metformin achieving the strongest network impact score, consistent with independent comparative network pharmacology evidence.

These findings provide a mechanistically coherent framework for the design of prospective randomized controlled trials in which antidiabetic agents are evaluated with co-primary metabolic and cognitive endpoints in populations with or at risk for both conditions. The integration of network pharmacology with emerging clinical evidence from the ELAD, MAP, EVOKE, and LIGHT-MCI trials offers a translational pathway that could substantially accelerate the availability of neuroprotective interventions for the millions affected by this devastating comorbidity. Validation through molecular docking simulation, in vitro hub gene binding assays, and animal model studies in dual-disease models is the recommended next step toward clinical translation.

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