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Neuroprotection through adiponectin receptor agonist: an updated meta-analysis of preclinical Alzheimer's disease studies

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Abstract

Background Alzheimer's disease (AD) is a leading cause of dementia, imposing a substantial burden on individuals and society. While existing therapies can reduce the symptoms of AD, they do not offer genuine therapeutic effectiveness. Adiponectin Receptor Agonist (ADN-R Ag) has been proposed as a novel therapeutic agent for AD. This study aims to evaluate its efficacy in treating AD model mice.

Methods A systematic search of PubMed, Scopus, Cochrane Library, and Web of Science was conducted up to May 3, 2025. Research investigating the impact of ADN-R Ag on cognitive performance and associated molecular pathways in Alzheimer's disease models, specifically APP/PS1, P301S, and 5XFAD mice, was incorporated. The Alzheimer's disease models in the study were male and ranged in age from 5.5 to 8 months. Studies evaluating the effect of ADN-R Ag on AD model mice through cognitive function tests and related molecular mechanisms were included. Methodological quality assessment was performed using the CAMARADES tool for animal studies. The meta-analysis was performed following Cochrane guidelines.

Results Six articles were included for the review. ADN-R Ag significantly improved cognitive function in the meta-analysis. The weighted mean difference of ADN-R Ag was 21.75 (95% CI: 16.61–26.88; $p < 0.001$) for alternation rate percentage in the Y-maze, 20.46 (95% CI: 11.41–29.51, $p < 0.001$) for novel object exploration time percentage in the novel object recognition (NOR) test, -15.83 (95% CI: -23.33 to -8.32, $p < 0.001$) for escape latency in the Morris water maze (MWM), and 13.89 (95% CI: 8.84–18.94; $p < 0.001$) for target quadrant time in the probe test. Additionally, ADN-R Ag was reported to mitigate AD pathology by reducing Aβ depositions through inhibition of GSK3β/BACE1/NF-κB pathway, suppressing neuronal inflammation by suppressing microglial and astrocytes activity and reducing and IL1β and TNFα levels, enhancing autophagy, and improving mitochondrial function with significant involvement of the AMPK pathway.

Conclusion Based on the current study, ADN-R Ag has therapeutic effects on AD. However, considering the complex underlying molecular mechanisms and limited prior studies, further research is needed.

Keywords Adiponectin receptor agonist, Alzheimer, Neuroprotection, Meta-analysis

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the loss of cognitive functions [1]. As the leading cause of dementia, AD poses a significant challenge to both individuals and public health systems [2]. Extracellular β-amyloid (Aβ) plaque deposition and neurofibrillary tangles (NFT) accumulation are two main pathological hallmarks of AD [3]. Although current treatments, such as acetylcholinesterase inhibitors (AChEIs) and memantine, are used to help AD patients with their symptoms, there remains a significant gap in treatments focused on reversing the course of the disease and its underlying pathology [4]. Adiponectin, a peptide hormone secreted by adipose tissue, exerts regulatory effects on glucose and lipid homeostasis in the body [5]. Adiponectin can be found in cerebrospinal fluid due to its ability to cross the blood–brain barrier [6]. Additionally, AdipoR1 and AdipoR2, two adiponectin receptors, are found in various brain regions, including the hippocampus, cortex, and hypothalamus [7]. These receptors regulate cellular functions via AMPK and PPAR-α signaling [8]. This has been the basis for previous studies investigating the potential role of adiponectin and its pathway in the treatment of AD. Recent research has highlighted the efficacy of AdipoRon (ADN-R Ag) in AD. Zhao et al. [9] reported the ameliorating effect of ADN-R Ag on diabetic mice with AD. ADN-R Ag activated the AMPK/mTOR pathway and restored cognitive deficits in treated mice. In another study, ADN-R Ag increased Aβ clearance by promoting autophagy in AD mice. This autophagy was promoted via the GAPDH/SIRT1 pathway in neuronal cells. Furthermore, ADN-R Ag-treated mice showed improved performance in behavioral tests such as Novel Object Recognition (NOR), Y-maze, and Morris Water Maze (MWM) [10]. ADN-R Ag has also been shown to rescue neural stem cell proliferation in Aβ deposited areas of the brain in AD transgenic mice through an AdipoR1/AMPK-mediated mechanism [11]. While earlier research has explored the influence of ADN-R Ag on Alzheimer's disease, a systematic review offers a more thorough perspective on its underlying molecular mechanisms and possible effects on cognitive abilities. In this work, we systematically review the molecular interactions of ADN-R Ag within Alzheimer's pathology and perform a meta-analysis to assess its impact on cognitive outcomes in AD models, thereby evaluating its potential as a therapeutic intervention.

Methods

Data sources and searches

In accordance with the Cochrane Handbook of Systematic Reviews, a systematic search of the published literature was conducted to obtain the articles. Scopus, Cochrane Library, Web of Science, and PubMed (http://www.ncbi.nlm.nih.gov/pubmed), along with the reference list of the obtained articles, were searched until May 2025 according to the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. Medical Subject Headings (MeSH) and keywords such as "Adiponectin receptor agonist"," AdipoRon" and "Alzheimer Disease" were employed to search and filter CAMARADES included articles. All the retrieved articles were transferred to EndNote X9, where duplicates were removed. The initial screening involved reviewing titles and abstracts to discard irrelevant studies. Subsequently, a full-text review was conducted on the remaining articles. Those that were either irrelevant or lacked accessible full texts were also omitted. Supplementary Table 1 contains the full search approach and filters used. The protocol is listed in the PROSPERO registry (http://www.crd.york.ac.uk/PROSPERO) with the registration number PROSPERO 2025: CRD42025589440.

Eligibility criteria and study selection

Two independent researchers selected the eligible articles by screening titles and abstracts. Studies that investigated the effect of ADN-R Ag on animals with induced Alzheimer were included, and Non-Experimental Studies, like observational studies, case reports, or studies lacking experimental intervention, were excluded. The full-text papers were obtained following initial screening and article selection based on inclusion and exclusion criteria. ADN-R Ag's impact on the results of behavioral tests, including Y-maze, NOR, and MWM tests, was included in the selected studies, with review of underlying mechanisms in addition.

Data extraction

First Author (year), species, sex, disease modeling, Treatment group/dose and route and duration, Control group, behavioral tests, biochemical tests were extracted and checked by three authors.

Assessment of methodological quality and risk of bias

To evaluate the risk of bias within the studies, the Collaborative Approach for Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) was employed [12]. Scores on a ten-point scale were used to assess the quality of the selected studies. The assessment was performed by two authors to address any discrepancies. The criteria used to do the assessment included: being published in a peer-reviewed journal; Random allocation; Compliance with animal welfare regulation; Blinded assessment of outcome; Sample-size calculation; Control of temperature; Appropriate animal model; Use of Anesthetic without Significant Neuroprotective Activity; Blinded Induction of Model; Statement of potential conflicts of interest. The scores were

calculated by allocating a score of 0 or 1 for each criterion. Only studies with a moderate to high quality were included. The studies were classified as low quality (1–4 points), moderate (5–7 points), and high quality (8–10 points).

Statistical analysis

The random-effect model was used to pool the included studies' results. The heterogeneity of included studies was assessed using Cochrane's Q test [13] (with a significant P-value < 0.1) and I-square test (I^2 greater than 50%, showing significant heterogeneity). Because of the small number of included studies, we are unable to conduct a subgroup analysis. Sensitivity analysis was performed to examine the impact of excluding individual studies on the overall effect size. The small-study effects were investigated using Begg's test and visually inspecting funnel plots. The meta-analysis was conducted using STATA 17.0 software (Stata Corp., College Station, TX), and statistical significance was set at P-value ≤ 0.05.

Results

Study selection

After removing duplicates, 89,498 articles were identified. Of these, 26,563 were excluded for not testing the efficacy of ADN-R Ag, 1,249 for testing efficacy on cell models of AD, and 55,768 due to publication type. After screening titles and abstracts, 5,796 articles were removed, and 122 articles were assessed through full-text review. Following this, 92 were excluded due to incomplete data, 8 for using inappropriate animal models, and 17 for combining ADN-R Ag with other interventions. Finally, 6 articles were included in the review, with 4 suitable for meta-analysis (Fig. 1).

Assessment of methodological quality of individual studies

In evaluating the methodological quality of the six studies chosen for the systematic review in animal research, the studies conducted by Ng et al. [14] and Khandelwal et al. [15] were categorized as having "high" methodological quality (Table 1). The other four studies were assessed to have a "medium" methodological quality [10, 11, 16, 17] (Table 1).

Animal models

5xFAD, APP/PS1, and P301S mice are three transgenic models of AD used in the included studies. 5xFAd mice carry five human gene mutations that lead to the overexpression and accumulation of Aβ and Amyloid Beta Precursor Protein (APP) [18]. APP/PS1 mice are double transgenic and express mutant APP, causing an early onset of AD in models [19]. P301S mice are mutant human tau transgenics and exhibit increased levels of tau protein accumulation, with accelerated neurodegeneration and dementia [20].

Study characteristics

Table 2 provides an overview of the principal features of the included studies. All six investigations utilized mouse models. The studies were conducted in China and India. In terms of experimental animal gender, all studies used male mice, except for two where gender was not specified. Among the mouse models employed, APP/PS1 was featured in four studies, while 5XFAD and P301S models were each used in the remaining two studies. Details regarding study characteristics, methodological quality, and potential publication bias are presented in Table 2.

Behavioral test analysis

Y-maze

The Y-maze can be used to assess short-term memory in mice. Mice tend to explore novel areas, and when put into a Y-maze, they successively alternate between different arms of the maze; however, each time they visit the recently visited arm with a lesser probability. Therefore, short-term memory function can be evaluated by the alternation rate for the novel arm entry [21]. According to the meta-analysis of three studies (Liu et al. [11], Khandelwal et al. [15], Sun et al. [10]), ADN-R Ag treatment significantly improved Y-maze performance compared to vehicle-treated Tg mice, with an overall effect size of 21.75 (95% CI: 16.61–26.88; $p < 0.001$) (Fig. 2A). No significant heterogeneity was observed among the studies (Cochran's $Q = 0.21$, $p = 0.901$; $I^2 = 0.0\%$) and Begg's test showed no evidence of publication bias ($p = 0.602$) (Fig. 3A). The sensitivity test showed that the results remained stable when each study was removed (Supplementary Fig. 1A).

Novel object recognition (NOR)

The NOR test is performed to assess the recognition memory of mice. Mice are presented with two identical objects in the first session, and in a second delayed session, one of the objects gets replaced with a novel object. As mice remember the familiar object, they spend more time exploring the novel object in the second session [22]. The pooled analysis from three studies (Ng et al. [14], Liu et al. [11], Sun et al. [10]) indicated a significant positive effect with an overall effect size of 20.46 (95% CI: 11.41–29.51, $p < 0.001$) (Fig. 2B). There was considerable heterogeneity among the studies (Cochran's $Q = 8.26$, $p = 0.016$; $I^2 = 75.8\%$), with no significant publication bias indicated by Begg's test ($p = 0.602$) (Fig. 3B). The overall effect size did not change significantly when any of the studies were excluded in the sensitivity analysis (Supplementary Fig. 1B).

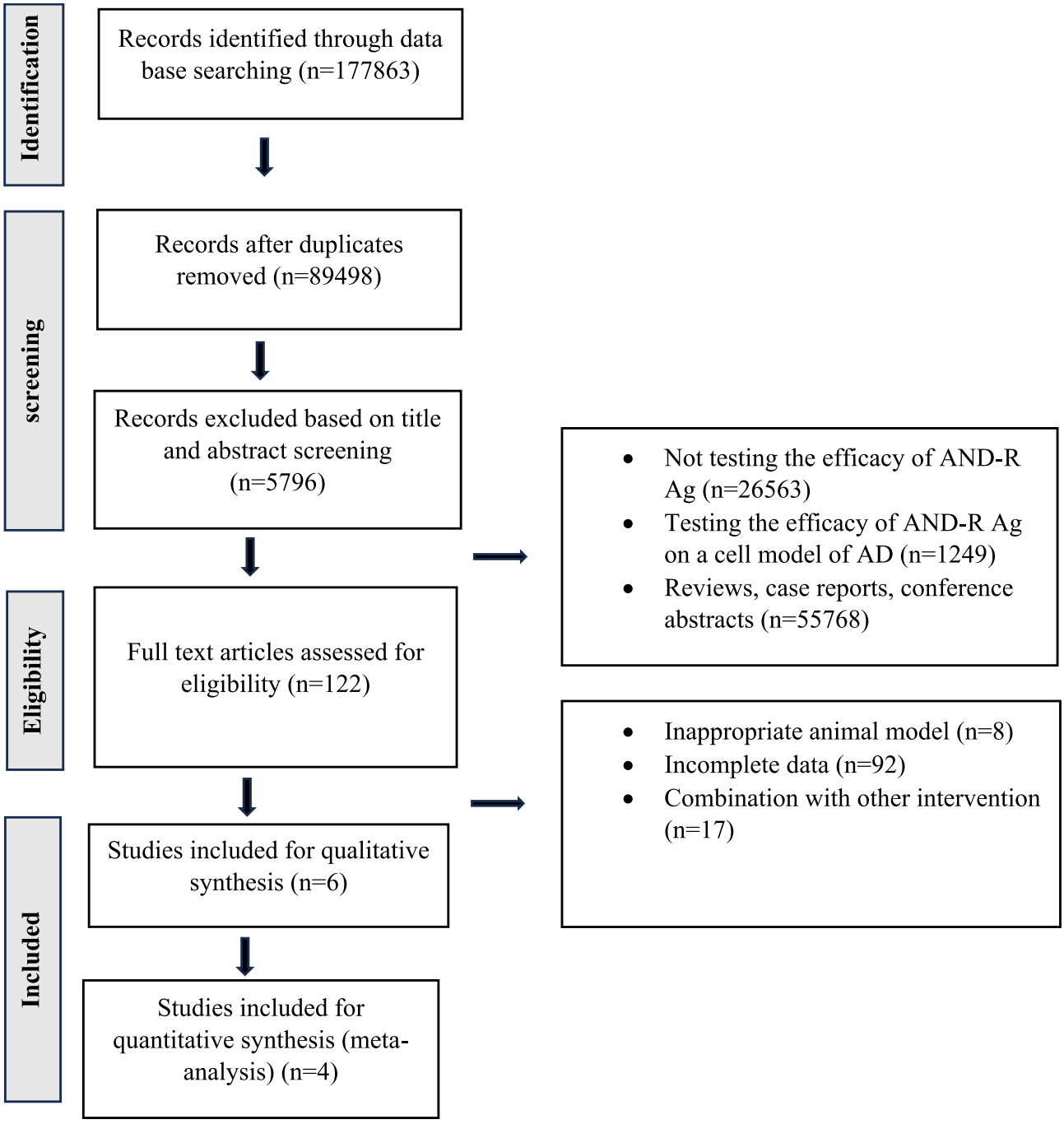

Fig. 1 Identification of studies via databases and registers

MWM and probe test

To evaluate memory and spatial learning in rodents, MWM and probe tests are used in the included studies. These tests show how fast mice learn their way to a submerged hidden platform in a water pool surrounded with visual cues (MWM test), and how much time they spend in the target quadrant if the platform is removed after the learning phase (Probe test) [23]. For the MWM test, Meta-analysis of four studies (Ng et al. [14], Liu et al. [11], Wang et al. [16], Sun et al. [10]) demonstrated a significant reduction in escape latency time, with an overall effect size of −15.83 (95% CI: −23.33 to −8.32, $p < 0.001$) (Fig. 2C). Heterogeneity was high among the studies (Cochran's Q = 21.53, $p < 0.001$; I^2 = 86.1%), and publication bias was not detected (Begg's test $p = 0.497$) (Fig. 3C). Sensitivity analysis demonstrated consistent results after the removal of each study (Supplementary Fig. 1C). In the probe test, analysis of two studies (Ng et

Table 1 Methodological quality assessment performed using the CAMARADES tool for animal studies

Author, year	Published in a peer-reviewed journal	Random allocation	Compliance with animal welfare regulation	Blinded assessment of outcome	Sample-size calculation	Statement of potential conflicts of interest	Control of Temperature	Appropriate Animal Model	Use of Anesthetic without Significant Neuroprotective Activity	Blinded Induction of Model	Total
Chun-Laam Ng et al. 2020	*	*	*	*	*	*	*	*	* (ketamine and xylazine after behavioral tests)	*	10
Liu B et al. 2020 [11]	*	0	*	*	0	*	*	*	0 (chloral hydrate)	0	6
He et al. 2021 [17]	*	*	*	0	0	*	0	*	NA	0	5
Khandelwal M et al. 2022 [15]	*	*	*	*	0	*	*	*	*(ketamine and xylazine after behavioral tests)	*	9
Wang et al. 2023 [16]	*	0	*	0	0	*	*	*	NA	0	5
Sun F et al. 2024 [10]	*	0	*	*	0	*	*	*	* (sodium pentobarbital before behavioral tests)	0	7

al. [14], Khandelwal et al. [15]) demonstrated a significant improvement following treatment, with an overall effect size of 13.89 (95% CI: 8.84–18.94; $p < 0.001$) (Fig. 2D). No significant heterogeneity was detected (Cochran's $Q = 0.33$, $p = 0.568$; $I^2 = 0.0\%$).

Molecular mechanisms

In addition to the behavioral features of ADN-R Ag, five articles examining its neuroprotective mechanisms in AD models were included in the systematic review. ADN-R Ag was found to induce its neuroprotective effects in mice through six processes: (1) Mitigation of Aβ depositions and Plaques, (2) Neuronal protection, (3) Autophagy enhancement, (4) improved Insulin sensitivity. (5) Enhanced Mitochondrial dynamics (6) AMPK pathway.

Adiponectin receptors

Adiponectin receptors, notably AdipoR1 and AdipoR2, belong to the family of G-protein coupled receptors (GPCRs) and are responsible for mediating the actions of adiponectin, a hormone predominantly produced by adipose tissue. These receptors are also distributed across several brain regions, such as the hippocampus, cortex, and hypothalamus, suggesting their involvement in cognitive processes and the regulation of energy balance. The roles of AdipoR1 and AdipoR2 have attracted significant attention in relation to Alzheimer's disease (AD), owing to their participation in metabolic regulation, modulation of inflammation, and neuroprotective mechanisms. Adiponectin itself has demonstrated neuroprotective properties, which may contribute to reduced neuronal injury and enhanced cell survival in neurodegenerative conditions. Experimental models have shown that upregulation of adiponectin receptor signaling can alleviate cognitive impairments and diminish hallmark pathological features of Alzheimer's disease. Furthermore, studies indicate that adiponectin and its receptors may facilitate the removal of amyloid-beta (Aβ) plaques, a defining feature of AD pathology. There is also supporting evidence that adiponectin signaling can modulate tau phosphorylation [24].

Mitigation of Aβ depositions and plaques

ADN-R Ag was reported to mitigate Aβ depositions and Plaques in the included studies. Chun-Laam Ng. et al. [14] reported the reduction of Aβ loading and number of deposits in the cerebral cortex and hippocampus of 5xFAD mice. ADN-R Ag also decreased soluble and oligomeric forms of Aβ in the hippocampus of the mice and soluble Aβ in the cortex, though the reduction of oligomeric Aβ in the cortex was not significant. ADN-R Ag was reported to decrease Aβ burden by decreasing its production and processing through inhibition of GSK3β/BACE1/NF-κB pathway, rather than by activating

Table 2 Characteristics of the included studies

First Author (year)	Controls (*n*)	Cases (*n*)	Age & sex	Treatment dose, route and duration	Behavioral tests	Behavioral test results	Biochemical test results
Chun-Laam Ng et al. 2020 [14]	*n* = 7 (5XFAD + vehicle for NOR test) *n* = 12 (for other cognitive tests)	*n* = 7 (5xFAD + ADN-R Ag for NOR) 14 (5xFAD + ADN-R Ag for other cognitive tests)	5.5-month-old	ADN-R Ag (50 mg/kg), oral gavage, 3 months	MWM, NOR, Fear-conditioning test	↓ anxiety levels ↑ the spatial learning and memory functions MWM, NOR task and hippocampus-dependent learning and memory functions (CFC tests) Did not improve performance in the cued fear-conditioning task	↓ IRS-1, ↑pAkt and ↑ pGSK3βS9 ↑insulin sensitivity ↓hippocampal CA1 axonal swelling ↓Aβ-associated dystrophic neurites ↑hippocampal CA1 stained neurons ↑layer V neurons ↑dendritic spine of the hippocampal CA1 pyramidal neurons ↑Spinophilin (but not synaptophysin) ↓Aβ loading ↓number of deposits in both hippocampus and cerebral cortex ↓soluble Aβ and ↓oligomeric Aβ in hippocampus ↓oligomeric Aβ not significantly in cortex ↓BACE1, sAPPβ, and βCTF levels ↓Aβ deposition by lowering ↓BACE1 level and decreasing ↓APP processing via the amyloidogenic pathway ↓activation of microglia and astrocytes (Iba1 and GFAP staining) ↓neuroinflammation and IL1β and TNFα levels ↓microglia around Aβ plaque ↑microglia phagocyte activity (Iba1 and Aβ containing) no significant difference in the number of astrocytes surrounding a plaque
Liu B et al. 2020 [11]	*n* = 9 (APP/PSI + vehicle)	*n* = 9 (APP/PS1 + AND-R Ag)	male-7-month-old	ADN-R Ag (1 µg in 2 µl vehicle), Intracerebroventricular injection, 7 days	NOR, Y maze, MWM	↑cognitive function, NOR, YM and MWM test but it did not improve locomotor activity	↓Aβ deposition ↓BACE1 ↑neural stem cell proliferation ↑ total dendritic length and dendritic complexity↓ ↓Aβ-induced injury via AMPK pathway ↑mitochondrial function (ΔΨm) via AMPK pathway ↑NSCs' proliferation against Aβ through AdipoR1 (but not AdipoR2) ↑NSCs' proliferation against Aβ via AMPK/CREB pathway
He et al. 2021 [17]	*n* = 4	*n* = 4 (APP/PS1 + AND-R Ag)	6-month-old	AND-R Ag (50 mg/kg), oral gavage, 2 months	NA	NA	↓toxic Aβ1–42 accumulation ↑autophagy-related gene (ATGs): Beclin-1, ATG5, ATG7, and LC3-II ↑AMPK-mTOR pathway ↓autophagy inhibitors, including 3-MA and CQ ↓pro-inflammatory cytokines (TNF-α, IL-1β, IL-10, IL-6) ↑AdipoR1 and APPL1 expression ↓neuroinflammatory state and GFAP and IBA-1 levels

Table 2 (continued)

First Author (year)	Controls (*n*)	Cases (*n*)	Age & sex	Treatment dose, route and duration	Behavioral tests	Behavioral test results	Biochemical test results
Khandelwal M et al. 2022 [15]	*n* = 14 (APP/PSI + vehicle)	*n* = 14 (APP/PS1 + ADN-R Ag)	male	ADN-R Ag (50 mg/kg), oral gavage, 30 days	NOR, Y-maze, MWM	↑behavioral performance in Y maze test ↑performance in probe test and retained memory ↓ thigmotaxic behavior but did not affect swimming speed ↑learning in reaching the platform during learning trails	↑insulin sensitivity in GTT and ITT tests did not affect body weight and food intake ↓RIPA (soluble) and guanidine (insoluble) Aβ42 levels ↓plaque burden, Aβ42 plaque area, and number occupied by Aβ plaque ↓reactive astrocytes (reduction of GFAP) ↑insulin signaling, phosphorylation of AKT ↑phosphorylation of AMPK (Thr 172) and its downstream targets ACCα and ACCβ did not change IRβ and insulin levels ↓astrocytosis (GFAP) and microgliosis (Iba-1) and phosphorylation of JNK ↑GLUT 4 (insulin sensitive), GLUT 1 (insulin independent), but not GLUT 3 did not affect expression of insulin receptor (INSR) and adiponectin receptors (AdipoR1 and AdipoR2) ↑ fatty acid metabolism genes ACCA, PGC1α, and PPARα ↓BACE 1 (involved in Aβ42 formation) and APP ↓ Tau phosphorylation ↓ mRNA expression of the transcription factor Sp1, BACE 1& Egr1 levels remain unchanged ↑ efflux and clearance of Aβ ↑expression of APOE, LDLR, and neprilysin ↑Aβ efflux did not affect Levels of IDE-1 and RAGE ↑ PSD-95 and synaptophysin
Wang et al. 2023 [16]	*n* = 11 (P301S + vehicle)	*n* = 11 (P301S + AND-R Ag)	male-6-month-old	ADN-R Ag (50 mg/kg), oral gavage, 4 months	NOR, MWM	↑MWM test, learning deficit, finding hidden latency, spatial memory, escape latency, and long-term memory deficits in NOR	↑ (PSD95, SYP, dendritic spines density and synapse loss ↑mitochondrial fusion relative proteins (Mfn2, OPA1) Did not affect fission protein (DRP1) ↑mitochondrial function by AMPK/SIRT3 pathway ↓tau phosphorylation and levels of p-Tau and p-Tau ↑hippocampal protein level of p-GSK3β Did not affect PP2Ac (Y307 site) and CDK5
Sun F et al. 2024 [10]	*n* = 5–9(APP/PSI + vehicle)	*n* = 5 to 9 (APP/PS1 + AND-R Ag)	male-8-month-old	ADN-R Ag (1 µg per mouse), Intracerebroventricular injection, 7 days	NOR, Y maze, MWM	↑cognitive dysfunction through the activation of autophagy ↑NOR, Y-Maze and MWM ↑cognitive dysfunction by the AMPK/SIRT1 pathway	↑Autophagy, the number of autophagic puncta in neurons, autophagosomes ↑ LC3II ↓p62 ↑autophagic flux ↑neurogenesis and Aβ clearance ↑autophagosomes through the AMPK pathway ↑cell viability by AMPK pathway ↑The nuclear intensity of GAPDH ↑interaction of SIRT1 with GAPDH ↓Aβ plaques by SIRT, EX527 ↓Aβ deposition ↑neurogenesis through the AMPK/SIRT1 pathway

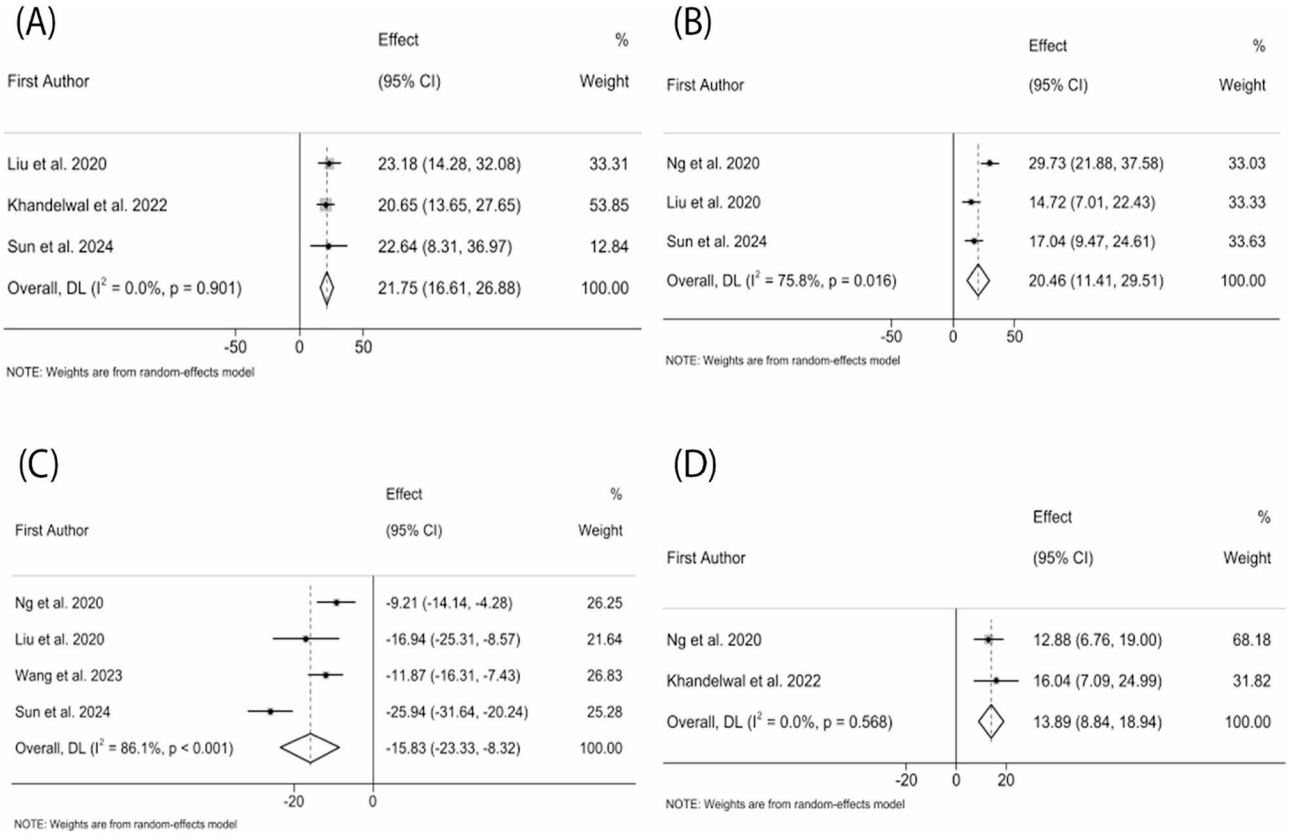

Fig. 2 Forest plot demonstrating the effect sizes of Adiponectin Receptor agonist (AND-R Ag) on Alzheimer's disease (AD) model mice in Y-maze **A**, Novel Object recognition (NOR) **B**, Morris Water Maze (MWM) **C**, and Probe test **D**. CI: Confidence interval

Aβ-degrading enzymes. Liu, et al. [11] reported a reduction of Aβ deposition in the cortex and hippocampus of APP/PS1 Tg mice after ADN-R Ag treatment. Additionally, ADN-R Ag was reported to decrease Aβ load through inhibition of amyloidogenic pathways and lowering amyloidogenic βsecretase (BACE1) levels. According to He et al.'s [17] study, AND-R Ag lowered Aβ plaque deposition in the cortex and hippocampus of APP/PS1 mice, as well as Aβ accumulation in vitro. However, the treatment did not alter the levels of proteins involved in amyloidogenesis, such as BACE1. In Khandelwal Ng et al.'s [14] study, ADN-R Ag reduced both soluble and insoluble Aβ42 levels, as well as Aβ42 plaque burden. Furthermore, SP1, a transcription factor for the BACE 1 gene, was decreased after ADN-R Ag treatment; however, the mRNA levels of the BACE 1 gene remained unchanged, suggesting a role for BACE 1 mRNA translation in reducing Aβ burden. ADN-R Ag also increased expression of APOE, LDLR, and neprilysin in brain tissue of model mice, as these proteins enhance clearance and efflux of Aβ. Sun et al. [10] reported that ADN-R Ag treatment increased the clearance of Aβ via autophagic pathways. Khandelwal et al. [15] and Wang et al. [16] demonstrated that ADN-R Ag decreases Tau hyperphosphorylation, a hallmark of Alzheimer's disease pathology. Additionally, ADN-R Ag inhibited the phosphorylation of JNK, which is involved in Tau phosphorylation [15].

Neuronal protection

The neuronal effects of ADN-R Ag were reported in the included studies. Chun-Laam Ng et al. [14] reported that ADN-R Ag reduced axonal swelling, rescued hippocampal CA1 neuron loss, and increased layer V neurons related to memory function in 5xFAD mice. ADN-R Ag was also able to enhance synaptic function by restoring spine deficits in hippocampal CA1 apical dendrites. In Addition, ADN-R Ag mitigated AD induced neuroinflammation by suppressing microglial and astrocytes activity and decreasing inflammatory factors such as IL1β and TNFα in 5xFAD mice brains. However, the activity of microglia was increased around Aβ plaques and number of astrocytes remained unchanged. In He et al.'s [17] study, AND-R Ag showed anti-neuroinflammatory effects by reducing both microglial activity and inflammatory markers, including TNF-α, IL-1β, IL-10, and IL-6. According to Liu et al.'s [11] study, the proliferation of neural stem cells was stimulated in the hippocampus of APP/PS1 TG mice after ADN-R Ag treatment. Furthermore, in their in vitro study, ADN-R Ag enhanced the total dendritic length and complexity of primary

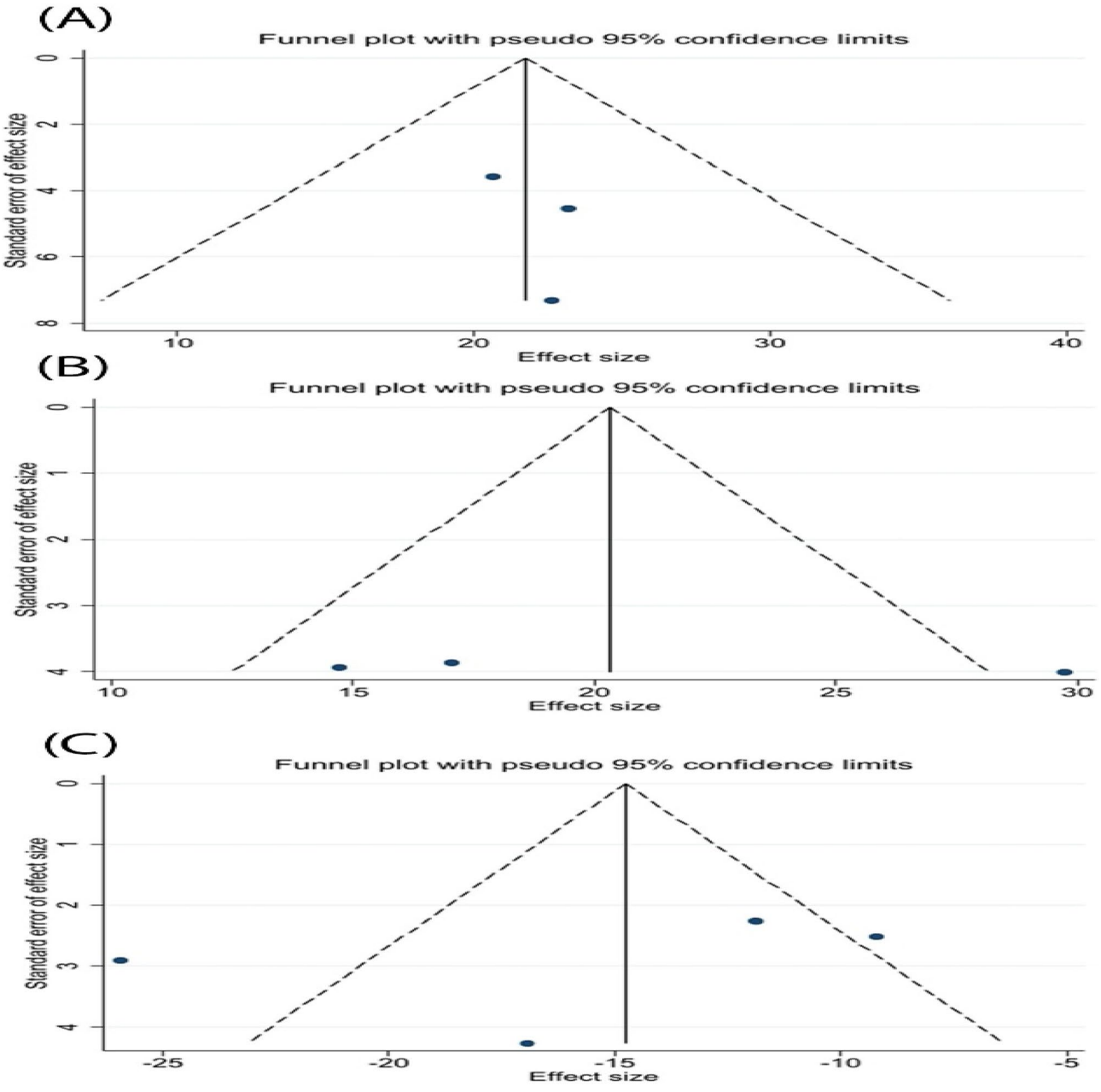

Fig. 3 Funnel plot of meta-analyzed studies in Y-maze **A**, Novel Object recognition (NOR) **B**, Morris Water Maze (MWM) **C** tests

neurons and also protected them from the cytotoxic effects of Aβ incubation via AdipoR1 receptors. ADN-R Ag also boosted the proliferation of neural stem cells in vitro, and reversed the adverse effects of Aβ incubation (Adipor1 and AMPK). Khandelwal et al. [15] demonstrated ADN-R Ag's anti-neuroinflammatory effects in AD model mice, marked by reduced activation of microglia and astrocytes. ADN-R Ag also enhanced synaptic function in TG mice, indicated by increased synaptic markers PSD-95 and synaptophysin. Wang et al. [16] reported that ADN-R Ag rescued synaptic function in P301S mice. ADN-R Ag treatment increased PSD-95 and synaptophysin and restored the density of the dendritic spine in mice. Furthermore, in Sun et al.'s [10] study, ADN-R Ag stimulated neurogenesis in the hippocampus of APP/PS1 Tg mice.

Autophagy enhancement

According to Chun-Laam Ng et al.'s [14] study, ADN-R Ag promoted the phagocytic activity of microglia around Aβ plaques, which was confirmed in vitro. He et al. [17] reported that AND-R Ag treatment stimulated autophagic activity in neuronal cells, as indicated by increased expression of autophagy-related genes (ATGs) and

decreased levels of autophagy inhibitors, including 3-MA and CQ. Sun et al. [10] conducted a more in-depth investigation of ADN-R Ag's neuroprotective role through phagocytic pathways. They demonstrated ADN-R Ag's neuroprotective role through phagocytic pathways in APP/PS1 Tg mice. ADN-R Ag treatment increased autophagic activity in neurons of the hippocampus and cortex of the model mice, but the increased autophagy was not evident in astrocytes or microglia. ADN-R Ag did not enhance autophagic activity in wild-type mice. It was also demonstrated that ADN-R Ag's neuroprotective and neurogenic effects were diminished upon suppression of autophagy, emphasizing an autophagy-dependent mechanism for ADN-R Ag's effectiveness. Additionally, ADN-R Ag was reported to exert its effects via the AMPK/SIRT1 pathway through AdipoR1 receptors.

Improved insulin sensitivity

ADN-R Ag has been studied for its ability to enhance insulin sensitivity, a potential factor in ameliorating AD symptoms. Chun-Laam Ng et al. [14] reported reduced insulin sensitivity in 5xFAD mice compared to WT mice; however, ADN-R Ag treatment restored insulin sensitivity, indicated by increased pAkt and pGSK levels. According to Khandelwal et al.'s [15] study, ADN-R Ag improved insulin sensitivity in APP/PS1 mice during the glucose tolerance test (GTT) and insulin tolerance test (ITT). ADN-R Ag was reported to increase pAkt and pGSK3β levels, but no change in IRβ was indicated. Furthermore, expression of metabolism-regulated genes, including ACCA, ACCB, PGC1α, and PPARα, was increased upon ADN-R Ag treatment in the brain of the APP/PS1 mice, unlike the expression of insulin receptor (INSR) and adiponectin receptors AdipoR1 and AdipoR2. In vitro, ADN-R Ag restored glucose uptake in neuronal cells by facilitating the translocation of the glucose receptor GLUT4 to the cell membrane.

Enhanced mitochondrial dynamics

In AD, mitochondrial function is also altered. As reported by Lie et al. [11], in primary neurons with Aβ-induced impairment, ADN-R Ag enhanced mitochondrial function via the AMPK route. Furthermore, Wang et al. [16] demonstrated that ADN-R Ag restored mitochondrial activity by ameliorating AD-induced fusion disruption in P301S mice, again through the AMPK pathway.

AMPK pathway

As reported in the included studies, AMPK phosphorylation, a downstream component in ADN-R Ag's cascade, plays a key role in mediating ADN-R Ag's effects in mitigating AD pathology. The involvement of the AMPK pathway has been demonstrated in several processes. ADN-R Ag-induced AMPK activation has been reported as necessary for NSC proliferation (via AMPK/CREB activation), increased insulin sensitivity (via activation of AKT [Ser473] and inhibition of GSK3β [Ser9]), enhanced mitochondrial fusion (via AMPK/SIRT3 pathway activation), inhibition of tau hyperphosphorylation (via AMPK/GSK3β pathway), promotion of autophagy (via GAPDH and SIRT1 colocalization), improvements in neurogenesis and cognitive performance (both via the AMPK/SIRT1 pathway), and mitigating Aβ deposition [10, 11, 14–16].

Discussion

While conventional treatments minimize AD symptoms, they fail to affect disease progression or deliver sustained therapeutic outcomes. Following a systematic review of the published literature, we performed a meta-analysis to determine whether ADN-R Ag could be used as a potential therapeutic agent for AD. According to the meta-analysis, ADN-R Ag significantly improved cognitive function in behavioral tests in AD model mice. Furthermore, the included articles revealed that ADN-R Ag's therapeutic effect occurred through multiple processes and was not limited to a single pathway. The results of this study may provide insights that contribute to further research and human clinical trials.

AD is a major cause of dementia and impairs cognitive and neuronal functions in affected individuals. Therefore, cognitive behavioral tests such as the Y-maze and NOR are employed to assess ADN-R Ag's effects on cognitive and memory function in AD model rodents. Moreover, processes such as Aβ deposition, insulin sensitivity, neuronal impairments, and mitochondrial dysfunction are studied and reviewed to provide a broader understanding of the underlying mechanisms involved in ADN-R Ag treatment. Based on the meta-analysis, ADN-R Ag significantly improved cognitive functions in model mice across all tests, with considerable effect sizes in the Y-maze, NOR, MWM, and probe tests, indicating enhancements in short-term and recognition memory, as well as spatial learning. The heterogeneity was evident in the results, particularly for the NOR and MWM tests; however, the overall robust positive effect of ADN-R Ag on cognitive functions adds to its value as a therapeutic agent for AD. The heterogeneity among the studies was evident in the results, particularly for the NOR and MWM tests, which may be because of differences in treatment dose and duration of the included experiments. In addition, various animal models evaluated in the studies could impact the obtained results. Further research is required to conduct subgroup analyses to assess their effects on the findings.

As reported, ADN-R Ag was involved in multiple processes and pathways along its course of effect. It was demonstrated to mitigate the pathological hallmark of

AD, Aβ depositions and plaques, as well as seemingly less direct but related pathways such as mitochondrial dysfunction and insulin sensitivity. Regarding the formation of Aβ depositions, included studies reported contrasting findings: Liu et al. [11] reported that AND-R Ag lowered BACE1 levels in the cortex and hippocampus of APP/PS1 mice, but He et al. [17] found no such effect in the same brain regions and mouse model. Both studies used the same model; however, differences in animal age, drug delivery method (intracerebroventricular vs. oral), and group size may explain their conflicting results. Using more standardized experimental designs could help resolve such inconsistencies. Furthermore, considering the presence of adiponectin receptors in various tissues, the effects of ADN-R Ag may not be limited to the brain, as suggested by previous studies. Dhandapany et al. [25] reported the role of AdipoR1 in hypertrophic cardiomyopathy in mice. Furthermore, a study by Staiger et al. [26] indicated that AdipoR1 expression in skeletal muscle cells was related to glucose and lipid metabolism. Not being limited to a single pathway or tissue burdens the suggestion of ADN-R Ag as an overly promising drug for AD without further studies. However, considering the multifactorial nature of AD and its wide-ranging effects on overall health, such complexity may support the potential of ADN-R Ag as a valuable therapeutic candidate. The reviewed studies indicated a decreased number and activity of astrocytes and microglia, serving as markers of the anti-inflammatory effect of ADN-R Ag. As reported by Chun-Laam Ng et al. [14], in addition to reducing axonal swelling and restoring neuronal loss, ADN-R Ag reduced the number and activity of astrocytes and microglia. However, in contrast to this overall reduction, microglial activity increased around Aβ plaques following ADN-R Ag treatment. This paradox suggests that ADN-R Ag may exert its effects both by suppressing the global neuroinflammatory state in AD and by promoting Aβ clearance through localized glial activity. Nevertheless, with regard to the underlying mechanism, Sun et al. [10] reported that ADN-R Ag did not influence glial cell phagocytosis, implying that its effects on glial activation may involve alternative, phagocytosis-independent pathways. Consistent with these findings, APN knockout was found to suppress lysosomal activity in glial cells; however, it had no effect on glial phagocytosis [17].

By comparing the responses of mouse models to ADN-R Ag, Sun et al. [10] found that ADN-R Ag did not show protective effects in restoring neuronal numbers, autophagic puncta, autophagosomes, or autophagic flux in wild-type (WT) mice. This suggests that the function of ADN-R Ag may be dependent on the specific cellular or pathological environment. Alterations in the expression of adiponectin receptors, AdipoR1 and AdipoR2, may help explain this variability. Kim et al. [27] reported that the expression of AdipoR1, the primary mediator of ADN-R Ag's signaling cascade, is significantly altered in Alzheimer's disease (AD) model mice. Additionally, Pratap et al. [28] reported a marked upregulation of AdipoR2 expression in astrocytes within the 5XFAD mouse model of AD. While these changes in adiponectin receptor expression and interaction may help explain ADN-R Ag's varied efficacy across mouse strains, further research is needed to support more robust assumptions. The results of the present review indicate that the AMPK pathway is essential for multiple neuroprotective effects of ADN-R Ag. AMPK is a kinase enzyme that functions as a key regulator of cellular energy homeostasis. Elevated AMP/ATP ratios indicate a low-energy status and activate AMPK. AMPK activation modulates its downstream pathway toward an energy-saving, catabolic state and enhances processes such as glycolysis. This AMPK-induced catabolic state may increase the cell's ability to survive under stress conditions, such as oxidative stress [29].Previous studies have reported molecular pathways involved in AMPK's neuroprotective role. AMPK can directly phosphorylate and activate AKT, while it phosphorylates and inhibits GSK3β (both key regulatory kinases), leading to increased insulin sensitivity in neurons [30, 31]. Furthermore, GSK3β is known to promote Tau phosphorylation, increasing the formation of neurofibrillary tangles in the brain in AD. AMPK is believed to mitigate this process by phosphorylating and inhibiting GSK3β [32].

CREB is another downstream component of the AMPK pathway and functions as a transcription factor. CREB is reported to be directly phosphorylated and activated by AMPK and it exerts its effects in AD by regulating the expression of various neuroprotective factors and enhancing NSC proliferation [33]. Furthermore, AMPK is reported to be neuroprotective via the SIRT1 pathway. SIRT1 is a protein involved in regulating cellular stress resistance, metabolism, autophagy, neurogenesis, and cognitive performance. However, its activity is indirectly modulated by AMPK via markers such as NAD^+ (nicotinamide adenine dinucleotide), rather than through direct phosphorylation [34]. It is important to note that AMPK-related processes, similar to most cellular pathways, can be context-dependent and may have bidirectional roles. For instance, although AKT is generally considered to be a downstream of AMPK, it can also exert regulatory effects on AMPK activity through feedback loops [35]. Moreover, the AMPK pathway is a broadly involved signaling cascade that is not specific to ADN-R Ag. According to Li et al.'s [36] study, Graphene oxide decreased Aβ deposition and improved AD in mice through the AMPK pathway. In another study, the AMPK pathway was found to be involved in the neuroprotective and neurogenesis effects of TBG096, a lead compound, in

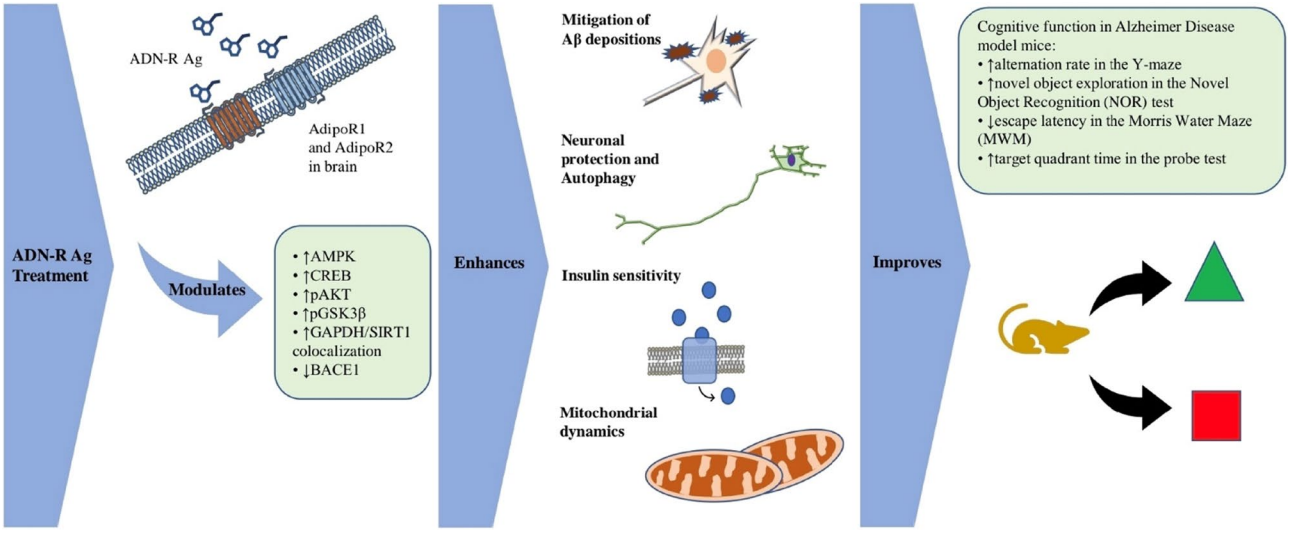

Fig. 4 Schematic representation of the Adiponectin Receptor Agonist (AND-R Ag), adiponectin receptors (AdipoR1 and AdipoR2), their associated molecular mechanisms, and the effects of receptor agonists in the context of Alzheimer's disease model mice and their cognitive function

AD model mice [37]. Huang et al. [38] demonstrated the role of the AMPK pathway in mitigating hypoxia-induced injuries in neuronal cells. Kornelius et al. [39] report that AMPK activation by mevastatin, a reductase inhibitor used to treat dyslipidemia, enhances insulin resistance and mediates neuroprotection against Aβ-induced toxicity. Furthermore, AMPK activation has been reported to restore mitochondrial dynamics in hepatocytes following drug-induced injury, emphasizing the complex nature of ADN-R Ag's downstream components [40].

Limitations

This study has some limitations. First, the mouse models of AD were not consistent across studies included in the meta-analysis, which might have introduced additional heterogeneity to the results. Second, diverse outcome measures and molecular pathways were employed to assess the efficacy of ADN-R Ag, limiting the feasibility of performing a meta-analysis. Third, a limited number of articles with small sample sizes were included in the current study, which could reduce the reliability of the findings.

Conclusion

The present study demonstrated that ADN-R Ag significantly enhanced cognitive functions in AD model mice. The findings also revealed multiple pathways involved in ADN-R Ag's neuroprotective effects, highlighting its potential as a therapeutic agent for AD (Fig. 4). However, some limitations and gaps remain in the literature. As reported, the downstream effects of ADN-R Ag are diverse and cannot be measured by single-metric approaches. Additionally, contrasting findings, particularly in the Aβ formation processes, neuroinflammation, and phagocytosis, suggest a need for more focused research. Future studies and clinical trials may help address these issues and further investigate the therapeutic potential of ADN-R Ag in AD.

Supplementary Information

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Supplementary Material 1. Supplementary Figure 1. The overall effect size did not change significantly when any of the studies were excluded in the sensitivity analysis (A, B, C).

Supplementary Material 2. Supplementary Table 1. Search strategy table.

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Authors' contributions

HS and TN conceived and designed the study. TN, AP and AA selected the articles and extracted and cross-checked the data. RM, TN, AA, and LA contributed to the statistical analysis. AA, AP and TN wrote the first draft of the manuscript. HS revised and discussed the final edition. All authors read and approved the final manuscript.

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Data availability

Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate

The study was approved by the Tabriz University of Medical Sciences Institutional Ethics Committee under the code IR.TBZMED.REC.1403.955.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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