

Review

Muscle-Brain Crosstalk in Alzheimer's Disease: Exercise-Associated FNDC5/Irisin Pathways in Preclinical Models – A Systematic Review

Rafael Aguiar Marschner^{1#,*}, Fernanda Marques da Silva^{1#}, Daisy Crispim^{2,3}, Carlos Alberto Saraiva Gonçalves¹

¹Program in Biological Sciences: Biochemistry, Institute of Basic Health Sciences, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil. ²Endocrine Division, Hospital De Clínicas De Porto Alegre, Porto Alegre, Rio Grande do Sul, Brazil. ³Faculdade de Medicina, Post-Graduate Program in Medical Sciences: Endocrinology, Universidade Federal do Rio Grande Do Sul, Porto Alegre, Rio Grande do Sul, Brazil.

[Received April 4, 2026; Revised May 15, 2026; Accepted May 16, 2026]

ABSTRACT: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive decline, synaptic dysfunction, neuroinflammation, and altered amyloid- β processing. Growing evidence suggests that physical exercise exerts neuroprotective effects partly mediated by myokines released from skeletal muscle. Among these, irisin, a cleavage product of fibronectin type III domain-containing protein 5 (FNDC5), has emerged as a potential component of muscle-brain communication involved in neuroplasticity and memory-related pathways. This systematic review summarizes evidence from preclinical in vivo studies investigating exercise-induced FNDC5 expression and irisin-related signaling pathways in experimental models of AD. A literature search was conducted in PubMed and EMBASE following PRISMA guidelines to identify studies evaluating the effects of physical exercise on FNDC5 expression, irisin-related pathways, and cognitive outcomes in animal models of AD. Ten preclinical studies met the inclusion criteria and were included in the qualitative synthesis, encompassing both behavioral and mechanistic evidence. Overall, the evidence indicates that physical exercise was associated with increased FNDC5 expression, activation of irisin-related pathways, and downstream neuroprotective mechanisms including PPARGC1A, AMPK, SIRT1, and BDNF signaling. These molecular adaptations were associated with improvements in synaptic plasticity, reductions in neuroinflammation and oxidative stress, and attenuation of amyloid-related pathology. Behavioral assessments across multiple paradigms also demonstrated improvements in learning and memory following exercise interventions. Collectively, the available preclinical evidence suggests that FNDC5/irisin-related signaling is associated with neuroprotective effects of physical exercise in experimental models of AD as part of a broader exercise-induced response. Further studies are needed to clarify the underlying mechanisms and translational relevance of this pathway in AD.

Keywords: Alzheimer's disease, Exercise, Irisin, Fndc5, Neuroinflammation, Muscle-brain axis

INTRODUCTION

Alzheimer's disease (AD) is characterized not only by β -amyloid (A β) accumulation and tau hyperphosphorylation, but also by persistent neuroinflammation, increasingly recognized as a central driver of progressive neurodegeneration [1, 2]. Chronic activation of microglia and astrocytes triggers the release

of pro-inflammatory cytokines, reactive species, and cytotoxic mediators, destabilizing the synaptic microenvironment, and exacerbating neuronal loss. This cascade promotes pro-degenerative gene expression and interacts with A β signaling, establishing a pathological loop that amplifies synaptic dysfunction and cognitive decline [3].

***Correspondence should be addressed to:** Dr. Rafael Aguiar Marschner, Department of Biochemistry, Universidade Federal do Rio Grande do Sul, 90035-003, Porto Alegre, Brazil. Email: rafamarschner@gmail.com. # These authors contributed equally to this work.

Copyright: © 2026 Marschner RA. et al. This is an open-access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Growing evidence indicates that muscle–brain communication critically modulates neuroinflammation [4, 5]. Physical exercise, a potent systemic intervention, alleviates neuroinflammation, enhances synaptic plasticity, and improves cognitive function in AD animal models [6, 7]. These benefits extend beyond local muscle effects and are mediated by myokines, among which irisin—produced via *Fndc5* cleavage—emerges as a key endocrine mediator [8, 9].

Exercise-induced PGC-1 α activation in skeletal muscle upregulates *Fndc5* and contributes to increased circulating irisin levels, which may influence central nervous system function after crossing the blood–brain barrier. Irisin has been associated with modulation of multiple AD-related processes, including glial neuroinflammation, NLRP3/caspase-1 signaling, microglial pyroptosis, BDNF expression, mitochondrial function, and A β clearance via neprilysin upregulation [10–12].

In parallel, exercise induces systemic metabolic adaptations—enhancing mitochondrial biogenesis, AMPK/SIRT1 activity, insulin sensitivity, and reducing peripheral inflammation—that converge on the neuroimmune axis [13–15]. Collectively, evidence suggests that the PGC-1 α –*Fndc5*–irisin axis may contribute to the interaction between exercise-induced muscle adaptations and neuroinflammatory mechanisms in AD.

Despite increasing evidence linking exercise to neuroprotection in AD, the molecular mediators underlying this muscle–brain communication remain incompletely understood. Irisin has emerged as a potential candidate, but evidence remains fragmented across experimental and clinical studies. Therefore, the aim of this systematic review was to synthesize current evidence regarding the role of irisin in the muscle–brain axis and its potential neuroprotective mechanisms in AD.

METHODS

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16] and was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD420251141572).

Study Objectives

The primary objective of this systematic review was to evaluate the effects of physical exercise on the modulation of the *Fndc5*/irisin axis in preclinical models of AD and

cognitive dysfunction. Specifically, we aimed to synthesize experimental evidence regarding how exercise-induced changes in *Fndc5*/irisin are associated with cognitive outcomes and neurobiological alterations in animal models of neurodegeneration.

Research Question and PECO Framework

To ensure a structured approach, the research question was formulated using the PECO framework:

Population (P): Preclinical experimental models of AD or cognitive dysfunction.

Exposure (E): Physical exercise interventions.

Comparison (C): Sedentary or non-exercise control groups.

Outcome (O): Modulation of *Fndc5*/irisin levels or expression, and/or molecular mechanisms related to neuroprotection and cognitive function.

Based on this framework, the guiding research question was defined as:

“How does physical exercise modulate the *Fndc5*/irisin axis in preclinical models of AD, and how are these changes associated with neuroprotective mechanisms and cognitive function?”

Eligibility Criteria

We included only original experimental studies conducted in preclinical in vivo models, including transgenic animal models of AD or neurodegeneration. Clinical (human) studies and in vitro experiments were excluded.

This restriction was adopted to ensure greater mechanistic consistency and internal validity across the included studies. Preclinical in vivo models allow controlled investigation of the integrated physiological effects of exercise-induced irisin on the central nervous system, including neuroinflammation, synaptic plasticity, and cognitive outcomes, which cannot be fully replicated in isolated cellular systems.

In vitro studies, although valuable for mechanistic exploration at the molecular level, do not capture the complex systemic interactions involved in muscle–brain crosstalk, particularly those mediated by endocrine and metabolic responses to physical exercise.

Similarly, clinical studies were excluded due to their inherent heterogeneity in terms of population characteristics, intervention protocols, and outcome measures, which could limit comparability and obscure mechanistic interpretation. By focusing on preclinical models, this review aimed to provide a more homogeneous and mechanistically grounded synthesis of the role of exercise-induced irisin in AD-related pathways.

Inclusion Criteria

- Studies that applied a physical exercise protocol as an intervention.
- Studies reporting direct or indirect measurements of irisin and/or Fndc5 (protein levels, gene expression, or related signaling pathways).
- Studies that assessed cognitive function using validated behavioral tests or provided mechanistic insights into FNDC5 expression and irisin-related pathways relevant to Alzheimer’s disease pathology (e.g., amyloid processing, neuroinflammation, mitochondrial function).
- Articles published in English or Spanish.

Exclusion Criteria

- Non-experimental studies (reviews, editorials, letters, conference abstracts, book chapters).
- Studies conducted in humans, in silico models, or non-neurodegenerative animal models.
- Studies that did not include physical exercise intervention.
- Studies that did not evaluate FNDC5 expression, irisin-related pathways, or AD-related molecular mechanisms.

Information Sources and Search Strategy

A comprehensive literature search was conducted in the PubMed and EMBASE databases to identify relevant studies published up to May 03, 2026.

The search strategy combined controlled vocabulary terms (MeSH and Emtree) and free-text terms related to physical exercise, FNDC5 expression, irisin-related pathways, Alzheimer’s disease (AD), cognition, and exercise-related molecular pathways involved in muscle–brain communication and neuroprotection. To increase the sensitivity of the search strategy while maintaining specificity for FNDC5/irisin-related signaling, additional terms including “myokine”, “muscle-brain axis”, “PGC-1alpha”, and “BDNF” were incorporated into the search strategy. Boolean operators (AND/OR) were applied to optimize search sensitivity and specificity.

PubMed search strategy:

((‘Alzheimer Disease’[Mesh] OR ‘AD model’ OR Alzheimer*) AND (Irisin OR Fndc5 OR ‘fibronectin type III domain-containing protein 5 precursor’ OR ‘Fibronectin Type III Domain-Containing Protein 5’ OR ‘Irisin Hormone’ OR myokine* OR ‘muscle-brain axis’ OR ‘PGC-1alpha’ OR BDNF) AND (‘Exercise’[MeSH] OR ‘Exercise Therapy’[MeSH] OR exercise OR ‘physical activity’ OR training OR workout))

EMBASE search strategy:

((‘Alzheimer Disease’/exp OR Alzheimer*) AND (Irisin OR Fndc5 OR "Fibronectin Type III Domain-Containing Protein 5" OR ‘myokine’ OR ‘muscle-brain axis’ OR ‘peroxisome proliferator activated receptor gamma coactivator 1alpha’ OR ‘brain derived neurotrophic factor’) AND (‘Exercise’/exp OR ‘Exercise Therapy’/exp OR exercise OR ‘physical activity’ OR training))

Additionally, the reference lists of all included articles and relevant review papers were manually screened to identify any additional eligible studies.

The search was restricted to peer-reviewed articles indexed in PubMed and EMBASE. Grey literature, preprints, dissertations, and conference proceedings were not included in order to ensure the inclusion of studies with fully available methodological details and peer-reviewed quality.

All retrieved records were imported into EndNote 2025 (Student version), where duplicates were identified and removed using automated functions followed by manual verification prior to screening.

Study Selection

All records retrieved from the database search were imported into EndNote 2025 (Student version), where duplicates were identified and removed using a combination of automated detection and manual verification. After duplicate removal, titles and abstracts were independently screened by two reviewers (RAM and FMS) to identify potentially relevant studies. Abstracts that clearly did not meet the inclusion criteria or met any of the exclusion criteria were excluded.

Full-text versions of potentially eligible studies were independently assessed by the same reviewers. Disagreements were resolved through discussion and consensus, with a third reviewer consulted when necessary (CASG). The study selection process was documented using a PRISMA flow diagram, detailing the number of records identified, screened, included, and excluded, along with reasons for exclusion (Figure 1). No additional information was required during the data extraction process; therefore, corresponding authors were not contacted.

Data Extraction Process

Data extraction was independently performed by two reviewers (RAM and FMS) using a standardized data extraction form developed in Microsoft Excel. The following variables were extracted from each included study:

- **Study characteristics:** authors, year of publication, journal.
- **Animal model:** species, sex, age, weight, and AD induction method.
- **Experimental design:** number of groups, sample size per group, control conditions.
- **Exercise protocol:** type of exercise, intensity, frequency, and duration.
- **Behavioral outcomes:** cognitive assessments (e.g., Morris water maze, novel object recognition, Y-maze).
- **Main findings:** molecular and cognitive effects attributed to exercise.
- Any discrepancies in data extraction were resolved by consensus or by consultation with a third reviewer (CASG).

Risk of Bias and Quality Assessment

The methodological quality and risk of bias of the included studies were assessed using the SYRCLE's Risk of Bias tool, adapted for animal studies. The following domains were evaluated: sequence generation, baseline characteristics, allocation concealment, random housing, blinding of caregivers and investigators, random outcome assessment, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.

Each domain was rated as low, unclear, or high risk of bias. Discrepancies were resolved by discussion among reviewers.

Data Management

All references and extracted data were organized using EndNote 2025 and Microsoft Excel. Study characteristics and outcomes were tabulated for synthesis. The final dataset was reviewed for accuracy and completeness before analysis.

Data Synthesis

Given the expected heterogeneity among the included studies regarding experimental design, animal models, methods for assessing FNDC5 expression or irisin-related pathways, and cognitive evaluation protocols, only a qualitative synthesis was conducted.

In addition, a quantitative meta-analysis was not performed due to substantial heterogeneity across studies, including differences in animal species, experimental models, exercise protocols, intervention duration, behavioral assessments, and molecular endpoints. Effect sizes could not be consistently extracted due to variability

in data reporting and the lack of standardized outcome measures across studies.

Results were organized according to: (i) type of animal model (transgenic, pharmacological, or lesion-induced); (ii) characteristics of exercise intervention; (iii) molecular outcomes related to FNDC5/irisin; and (iv) cognitive and behavioral outcomes.

Key study characteristics and findings are summarized in tables to facilitate comparison across studies. The narrative synthesis focused on identifying consistent patterns and trends linking exercise-induced modulation of the FNDC5/irisin axis to cognitive function and neuroprotection in preclinical models of AD.

Ethical considerations

Ethical approval was not required for this systematic review, as it exclusively synthesized data from previously published animal studies.

RESULTS

A total of ten studies met the inclusion criteria and were included in the qualitative synthesis. Among these, seven studies included behavioral or cognitive assessments, whereas three provided supportive mechanistic evidence without behavioral evaluation.

The study selection process is presented in the PRISMA flow diagram (Fig. 1).

Risk of Bias Interpretation

The risk of bias assessment using the SYRCLE tool is summarized in Figure 2. Overall, most studies were classified as presenting an unclear risk of bias across several domains, particularly in sequence generation (D1), allocation concealment (D3), and blinding-related domains (D6–D7), reflecting insufficient reporting of key methodological procedures.

Baseline characteristics (D2) were generally well described and were predominantly rated as low risk, indicating acceptable group comparability across studies. In contrast, domains related to performance bias, especially blinding of caregivers and investigators (D5), were consistently classified as high risk, largely due to the inherent limitations of exercise-based interventions. Similarly, random housing (D4) was frequently rated as high or unclear risk, suggesting potential influence of environmental or cage-related factors.

Domains associated with data integrity, including incomplete outcome data (D8) and selective outcome reporting (D9), were consistently rated as low risk, indicating that most studies reported outcomes comprehensively and without evident attrition bias. The

domain of other sources of bias (D10) was predominantly classified as unclear, mainly due to the absence of sample

size calculations and limited reporting of additional methodological controls.

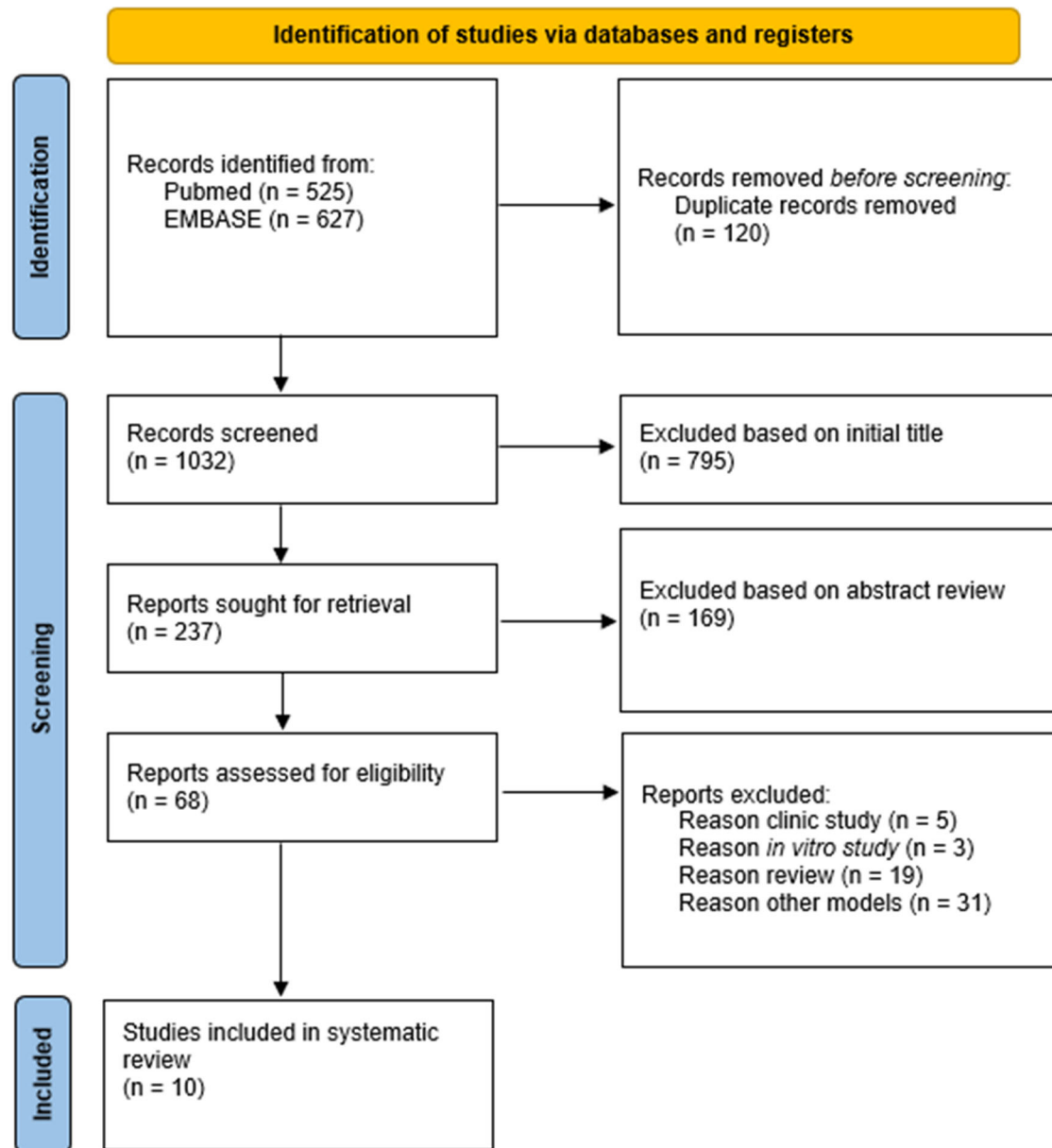


Figure 1. PRISMA flow diagram of study selection process. A total of 1,152 records were identified through database searching (PubMed, $n = 525$; EMBASE, $n = 627$). After removal of duplicates ($n = 120$), 1,032 records were screened by title, resulting in the exclusion of 795 studies. Subsequently, 237 reports were selected for abstract screening, of which 169 were excluded. Sixty-eight full-text articles were assessed for eligibility, and 58 studies were excluded for the following reasons: clinical studies ($n = 5$), in vitro studies ($n = 3$), review articles ($n = 19$), and studies using other experimental models ($n = 31$). Ultimately, 10 studies met the inclusion criteria and were included in the qualitative synthesis.

Collectively, these findings indicate an overall moderate methodological quality, with the main limitations related to insufficient reporting of randomization procedures and blinding. These factors should be considered when interpreting the strength and reliability of the evidence.

Experimental Models of the Included Studies

The main methodological characteristics of the experimental models are detailed in Table 1.

This systematic review included ten preclinical studies published between 2018 and 2026 [9, 17-24]. The

experimental evidence was predominantly derived from rodent models, with a clear predominance of Wistar rats, while a smaller number of studies employed mouse models, including NMRI mice and transgenic C57BL/6

strains. Sample sizes varied substantially across studies, ranging from 24 to 72 animals, or from 5 to 20 animals per group depending on the experimental design.

Manuscript	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Azimi et al., 2018	!	+	!	!	!	!	!	+	+	!
Lourenço et al., 2019	!	+	!	-	!	!	+	+	+	!
Dehghan et al., 2021	!	+	!	!	!	-	!	+	+	!
Islam et al., 2021	!	+	!	-	-	!	!	+	!	!
Hegazy et al., 2022	!	+	!	-	-	!	!	+	+	!
Nogueira Godinho 2022	!	+	!	!	-	!	!	+	+	!
Okudan et al., 2025	!	+	!	!	-	!	!	+	+	!
Puoyan-Majd et al., 2025	+	+	!	!	-	!	!	+	+	!
Kim T et al., 2025	+	+	!	!	!	!	+	+	+	+
Belviranlı et al., 2026	+	+	!	-	-	!	!	+	+	!

Low risk	+
Unclear risk	!
High risk	-

Figure 2. SYRCLE risk of bias assessment across the included preclinical studies. D1 - Sequence Generation; D2 - Baseline characteristics; D3 - Allocation concealment; D4 - Random housing; D5 - Blinding of caregivers & investigators; D6 - Random outcome assessment; D7 - Blinding of outcome assessor; D8 - Incomplete outcome data; D9 - Selective outcome reporting; D10 - Other bias.

The included studies investigated a range of experimental paradigms that can be broadly categorized into three main groups. The first group comprised chemically or experimentally induced models of Alzheimer's disease or cognitive impairment, including intracerebroventricular administration of amyloid- β peptides (A β 1–40 or A β 1–42) [20, 22, 25], intracerebroventricular streptozotocin (ICV-STZ) [17], and combined neurotoxic or aging-related protocols such as D-galactose alone or in combination with aluminum chloride (AlCl₃) [19, 21, 23]. These models were predominantly conducted in Wistar rats and represent most of the included evidence.

The second group consisted of transgenic mouse models of AD, as reported by Lourenço et al. [9], including APP/PS1 Δ E9 and APP/PS1 M146L strains, as well as the triple transgenic AD (3xTg-AD) mouse model evaluated by Kim et al. [24]. These models allow the investigation of amyloid related pathology in a genetically controlled context and were also combined with acute A β oligomer administration in some experimental conditions.

The third group included studies conducted in healthy animals, such as the work by Dehghan et al. [17], which

evaluated the isolated effects of physical exercise and FND5/irisin-related pathways on brain function and molecular pathways associated with neuroplasticity, independent of a disease model.

Overall, there was a predominance of sporadic and metabolically induced models of AD, particularly those involving insulin resistance in the brain (e.g., ICV-STZ) or systemic aging-related stressors (e.g., D-galactose). These approaches highlight a strong experimental focus on the interplay between metabolic dysfunction and neurodegeneration. In contrast, transgenic models provided complementary mechanistic insights into amyloid-driven pathology, while studies in healthy animals contributed to understanding the baseline neurobiological effects associated with exercise-induced FND5 expression and irisin-related pathways.

Summary of Experimental Findings

The main results of the included studies are summarized in Table 2 and 3.

Table 1. Overview of the preclinical studies included in this review.

Manuscript	Species	Model / Condition	Treatment	Dose / Intensity	Duration	Groups	Sample Size
Azimi et al., 2018 [25]	Wistar rats	Aβ1–42-induced AD	Treadmill exercise	10–15 m/min; 30–60 min	4 weeks	Intact; Sham; Aβ; Sham + exercise; Aβ + exercise	n = 70 (14 per group)
Lourenço et al., 2019 [9]	Mice	ICV Aβ oligomer; APP/PS1 models	Recombinant irisin; swimming	75 pmol/site; ~50–80% capacity	3–5 weeks	Control; AD; AβO; Fndc5 KD; OE; exercise	5–20 per group
Dehghan et al., 2021 [17]	NMRI mice (male)	Healthy (exercise/irisin)	Irisin; treadmill; ladder climbing	100 µg/kg; progressive; 200% BW	8 weeks	Control; resistance; endurance; irisin	n = 28 (7 per group)
Islam et al., 2021 [19]	Mice	APP/PS1; 5xFAD; Fndc5 KO	Irisin overexpression; Running	AAV8 (1 × 10 ¹⁰ GC); voluntary wheel running	Not specified	APP/PS1; 5xFAD; KO; APP/PS1-KO; exercise	6–14 per group
Hegazy et al., 2022 [18]	Wistar rats	ICV-STZ AD model	Carnosine; swimming	100 mg/kg; 1% load	5 weeks	STZ; STZ + exercise; STZ + carnosine	n = 30 (10 per group)
Nogueira Godinho et al., 2022 [20]	Wistar rats	Aβ1–42-induced AD	HIIT + Aβ1–42	Progressive HIIT	8 weeks	Sedentary Sham; Trained Sham; Sedentary AD; Trained AD	n = 48 (12 per group)
Okudan et al., 2025 [21]	Wistar rats	D-galactose + AlCl ₃	Treadmill exercise	Not reported	10 weeks	Control; AD; exercise; AD + exercise	n = 24 (6 per group)
Puoyan-Majd et al., 2025 [22]	Wistar rats	Aβ1–40-induced AD	HIIT ± CoQ10	~85–90% VO ₂ max; CoQ10 50 mg/kg	8 weeks	Control; AD; Q10; HIIT; HIIT + Q10; AD + Q10; AD + HIIT; AD + HIIT + Q10	n = 72 (9 per group)
Kim et al., 2025 [24]	Mice	3xTg-AD	Treadmill exercise	30 min/session, 5×/week	20 weeks	WT; WTEX; AD; ADEX	n = 40 (10 per group)
Belviranlı et al., 2026 [23]	Wistar rats	D-galactose + AlCl ₃	Treadmill exercise	~55–60% VO ₂ max	10 weeks	Control; AD; exercise; AD + exercise	n = 48 (12 per group)

The table presents the animal species, experimental models/conditions, treatment protocols, exercise or intervention intensity, duration, experimental groups, and sample size. The included models comprise intracerebroventricular streptozotocin (ICV-STZ), amyloid-β (Aβ1–40 or Aβ1–42) administration, D-galactose-induced aging, transgenic AD models, and healthy animals subjected to exercise or irisin-related interventions. AD, Alzheimer's disease; Aβ, amyloid-beta; ICV, intracerebroventricular; STZ, streptozotocin; AlCl₃, aluminum chloride; HIIT, high-intensity interval training; KD, knockdown; OE, overexpression; KO, knockout; WT, wild-type; 3xTg-AD, triple transgenic Alzheimer's disease mouse model.

Among the ten included studies, seven directly assessed cognitive or behavioral outcomes, whereas three studies did not include behavioral assessments. These three studies were retained as supportive mechanistic evidence because they investigated FNDC5/irisin-related molecular pathways relevant to AD pathology, including neuroinflammation, mitochondrial function, amyloid-related changes, and neuroplasticity. Therefore, these studies were not interpreted as direct evidence of cognitive benefit, but rather as complementary evidence supporting the biological plausibility of FNDC5/irisin involvement in exercise-related neuroprotection.

Across the included studies, experimental designs typically comprised control, disease (AD or AD-like), and intervention groups involving physical exercise and/or irisin-related approaches [9, 17–25]. Some studies further incorporated molecular manipulation strategies, including Fndc5 knockdown or overexpression [9], as well as pharmacological interventions such as carnosine [18] and coenzyme Q10 [22].

Exercise interventions were implemented using different modalities, including treadmill running [17, 21,

23, 25], swimming protocols [9, 18], voluntary wheel running [19], ladder-climbing exercise [17] and high-intensity interval training (HIIT) [20, 22]. Exercise intensity ranged from moderate (~50–60% VO₂max) [23] to high intensity (~85–90% VO₂max) [22] or was progressively increased depending on the protocol [9, 17, 18, 20, 21, 25]. Intervention durations varied between 3 and 20 weeks [9, 17–25], with long-term treadmill exercise protocols also being evaluated in transgenic AD models [24]. In addition to exercise, some studies administered recombinant irisin [9] or induced its overexpression using viral vectors [19] either alone or in combination with exercise.

Behavioral assessments were widely employed to evaluate cognitive and functional outcomes. Spatial learning and memory were most frequently assessed using the Morris Water Maze (MWM) [18–20, 23–25]. Recognition memory and associative learning were evaluated using tests such as novel object recognition (NOR) [9, 18, 19]. Contextual fear conditioning (CFC) [9, 19] and radial arm water maze (RAWM) [9]. Additional behavioral paradigms, including elevated plus maze

(EPM), open field test, rotarod, grip strength, tail suspension test (TST), spontaneous alternation behavior (SAB), and gait analysis, were used to assess anxiety-like behavior, locomotor activity, and motor performance [9, 18, 19, 23–25].

Table 2. Summary of experimental studies investigating the effects of physical exercise and/or irisin in animal models of AD.

Manuscript	Irisin assessment	Causal evidence	Behavioral outcomes	Molecular outcomes	Pathology outcomes
Azimi et al., 2018 [25]	Indirect (FNDC5 expression)	No	MWM (acquisition, probe, visible platform)	↑ AMPK; activation of PGC-1 α /Fndc5/BDNF	Improved spatial learning and memory
Lourenço et al., 2019 [9]	Direct (recombinant irisin administration)	Yes	NOR; CFC; RAWM; Open field	↑ Fndc5/irisin; cAMP–PKA–CREB activation; ↓ A β oligomer binding to neurons	Preservation of synaptic plasticity; improved memory
Islam et al., 2021 [19]	Direct (viral irisin overexpression)	Yes	MWM; NOR; CFC; Barnes maze; motor and anxiety-related tests	↑ neurogenesis; ↓ glial activation; modulation of FNDC5/irisin-related pathways	Improved cognition; abolished effect in knockout
Hegazy et al., 2022 [18]	Direct (serum irisin + FNDC5/irisin protein assessment)	No	MWM; NOR; passive avoidance; marble burying	↑ Fndc5/irisin; ↑ BDNF; ↑ insulin signaling	↓ A β ; ↓ tau; improved cognition
Nogueira Godinho et al., 2022 [20]	Indirect (FNDC5 expression)	No	MWM	Activation of PGC-1 α –Fndc5/irisin; ↑ ITGB5	Prevention of cognitive impairment
Kim et al., 2025 [24]	Indirect (FNDC5 expression)	No	MWM; locomotor and anxiety-like behavior	↑ PGC-1 α and FNDC5 expression; ↑ BDNF/TrkB/PI3K/Akt; ↓ NF- κ B and pro-inflammatory cytokines; ↓ glial activation	↓ A β plaques; ↓ tau phosphorylation; ↓ neuroinflammation and myelin damage
Belviranlı et al., 2026 [23]	Indirect (FNDC5 expression)	No	MWM; EPM	AMPK/SIRT1/PGC-1 α ; Fndc5/irisin/BDNF	Improved cognition; neuroprotection

The table summarizes the experimental groups, intervention protocols, exercise intensity or irisin dose, intervention duration, behavioral assessments, main biomarkers evaluated, proposed molecular targets/mechanisms, and principal outcomes reported in each study. Abbreviations: A β , amyloid-beta; AD, Alzheimer’s disease; BDNF, brain-derived neurotrophic factor; *Fndc5*, fibronectin type III domain-containing protein 5; HIIT, high-intensity interval training; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator-1 α ; SIRT1, sirtuin 1; STZ, streptozotocin; SOD, superoxide dismutase; LTP, long-term potentiation; MWM, Morris water maze; RAWM, radial arm water maze; NOR, novel object recognition test; CFC, contextual fear conditioning; CFC-DL, contextual fear conditioning–discrimination learning; SAB, spontaneous alternation behavior; EPM, elevated plus maze; OFT, open field test; TST, tail suspension test.

At the molecular level, the included studies consistently reported associations with activation of the PGC-1 α –Fndc5/irisin-related axis [9, 17–25], with downstream involvement of AMPK [23, 25], SIRT1 [23], BDNF [18, 22–25], PI3K/Akt signaling [24] and cAMP–PKA–CREB signaling pathways [9]. These changes were associated with improvements in mitochondrial function [21, 24], reductions in neuroinflammatory markers [21, 24], attenuation of amyloid- β accumulation [9, 18, 22, 24], modulation of insulin signaling pathways [18], and reductions in tau-related pathology and glial activation [24].

However, these molecular adaptations were primarily observed in response to exercise interventions, and their direct relationship with FNDC5 expression or irisin-related pathways was only evaluated in a limited number of studies [9, 17, 19].

Overall, the findings consistently showed that exercise interventions and molecular changes associated with FNDC5 expression or irisin-related pathways were associated with improvements in cognitive performance,

particularly in spatial learning and memory [9, 18–20, 23–25], as well as enhanced synaptic plasticity and neuroprotective-related outcomes in experimental models of AD [9, 17, 22].

Nevertheless, most studies reported associative relationships between exercise, FNDC5/irisin expression, and downstream molecular pathways. Only a subset of studies employing direct experimental manipulation, such as FNDC5 knockdown or irisin administration [9, 17, 19], provided evidence supporting a potential causal role of FNDC5/irisin-related pathways.

Irisin expression in the Brain

Tissue-Specific Expression of FNDC5/irisin in Experimental Models of Alzheimer’s Disease

The main characteristics and outcomes of the studies investigating FNDC5 expression and irisin-related pathways in experimental models of AD are summarized in Table 2 and Table 3.

Table 3. Summary of study-level mechanistic evidence from included studies that did not assess cognitive outcomes.

Manuscript	Irisin assessment	Causal evidence	Behavioral outcomes	Molecular outcomes	Pathology outcomes
Dehghan et al., 2021 [17]	Direct (irisin measurement by ELISA)	No	Not assessed	Activation of antioxidant pathways; proteostasis; energy metabolism	Neuroprotection; improved synaptic function
Okudan et al., 2025 [21]	Indirect (FNDC5 expression)	No	Not assessed	↓ NF-κB; ↓ IL-1β; ↑ mitochondrial biogenesis	Attenuation of neuroinflammatory responses
Puoyan-Majd et al., 2025 [22]	Direct and indirect (irisin and Fndc5 expression)	No	Not assessed	Activation of pathways associated with Fndc5/irisin and BDNF	↓ Aβ; Improved hippocampal neuroplasticity

The table presents information on irisin/FNDC5 assessment (direct or indirect), evaluation of causal relationships (e.g., genetic or pharmacological manipulation), and reported molecular and pathology-related outcomes in experimental models of AD. These studies were included to provide complementary mechanistic insights into FNDC5 expression, irisin-related pathways, and its association with AD-related processes, such as neuroinflammation, mitochondrial function, and amyloid-β (Aβ) pathology, despite the absence of behavioral assessments. FNDC5, fibronectin type III domain-containing protein 5; AD, Alzheimer's disease; Aβ, amyloid-β; NF-κB, nuclear factor kappa B; IL-1β, interleukin-1 beta.

Several studies included in this review evaluated the expression of *Fndc5*, the precursor of irisin, in brain regions associated with cognitive function. Among the selected studies, several specifically assessed *Fndc5* expression in brain tissue, with the hippocampus emerging as the most frequently analyzed region, along with ocular samples [9, 18, 19, 21–25].

Although most studies focused on brain regions such as the hippocampus, some investigations also evaluated ocular tissues. This approach is based on the shared embryological origin and physiological similarities between the eye and the central nervous system, supporting the use of ocular samples as a proxy to investigate neurodegenerative and neuroinflammatory processes associated with Alzheimer's disease.

Increased *Fndc5* expression in the brain following exercise interventions was consistently reported across experimental models of AD [18, 19, 21–25]. Exercise protocols used in these studies included treadmill running, swimming, and high-intensity interval training (HIIT), which were linked to activation of pathways involving PGC-1α and increased *Fndc5* expression in hippocampal tissue and ocular samples.

In addition to *Fndc5* expression, several studies reported increased hippocampal expression of brain-derived neurotrophic factor (*Bdnf*) following exercise interventions [18, 19, 23–25]. In particular, Kim et al., 2025 [24] demonstrated increased activation of the BDNF/TrkB/PI3K/Akt signaling pathway in a 3xTg-AD mouse model following long-term treadmill exercise. Furthermore, improvements in cognitive performance were observed in behavioral assessments, particularly in the MWM [18, 19, 22–25].

In experimental models involving amyloid-β induction, modulation of the FNDC5/irisin pathway and its effects on molecular markers in brain tissue were investigated by Lourenço et al., 2019 [9], who

demonstrated that manipulation of FNDC5/irisin pathways influenced molecular pathways associated with AD pathology and cognitive performance in animal models.

Irisin and Neuroinflammation in Alzheimer's Models

The relationship between FNDC5 expression, irisin-related pathways, and neuroinflammatory processes in experimental models of AD was investigated in a limited number of included studies. Overall, the assessment of inflammatory markers was heterogeneous across studies, with only a subset directly evaluating classical pro-inflammatory mediators [21, 24].

Exercise interventions were associated with modulation of neuroinflammatory-related pathways in different experimental contexts. Notably, Okudan et al., 2025 [21] directly assessed inflammatory markers, reporting alterations in nuclear factor kappa B (NF-κB) and interleukin-1β (IL-1β) expression in ocular tissues of an AD model following exercise intervention.

Similarly, Kim et al., 2025 [24] reported reductions in several neuroinflammatory markers, including NF-κB, TNF-α, IL-1β, and IL-6, in a transgenic AD mouse model following long-term treadmill exercise. The study also described reduced glial activation and attenuation of tau-related pathology, supporting an association between exercise-induced FNDC5 signaling and modulation of neuroinflammatory processes.

In contrast, most other studies did not directly quantify classical cytokines such as TNF-α or IL-1β in brain tissue. Instead, they reported indirect evidence of neuroinflammatory modulation based on broader molecular or pathological outcomes, including changes in signaling pathways, amyloid-related pathology, or markers associated with neuronal function.

For example, studies such as Puoyan-Majd et al., 2025 [22] and Belviranlı et al., 2026 [23] described molecular adaptations consistent with reduced neuroinflammatory burden, although specific inflammatory mediators were not directly quantified. Similarly, Lourenço et al., 2019 [9] demonstrated mechanistic effects of FNDC5/irisin modulation on synaptic and pathological features of AD, including processes linked to neuroinflammation, without directly measuring classical inflammatory cytokines.

Overall, the available evidence suggests that exercise and molecular changes associated with FNDC5 expression or irisin-related pathways may be linked to modulation of neuroinflammatory processes in experimental models of AD. However, direct mechanistic evidence specifically connecting these anti-inflammatory effects to functional FNDC5/irisin pathway modulation remains limited, and the findings should be interpreted with caution.

Molecular Insights: Exercise, Irisin, and Neuroprotection in Alzheimer's Disease

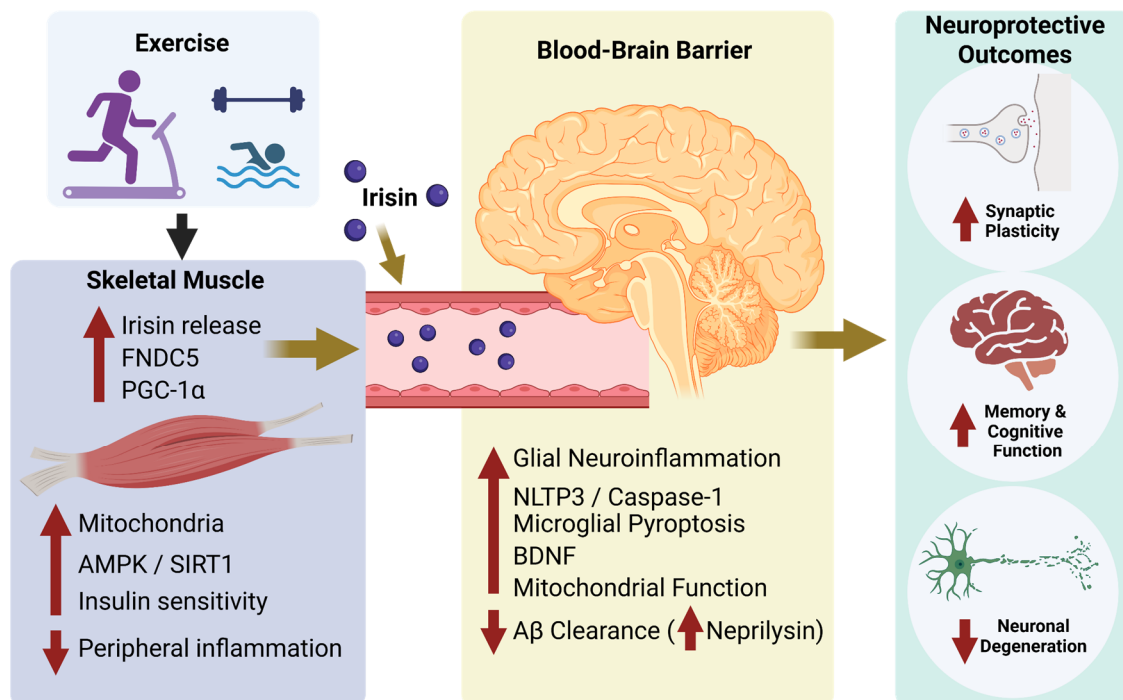


Figure 3. Proposed mechanisms linking physical exercise, irisin signaling, and neuroprotection in experimental models of Alzheimer's disease. This schematic illustrates the integrative pathways identified in experimental studies connecting physical exercise, skeletal muscle adaptations, and central neuroprotection. Exercise activates PGC-1α in skeletal muscle, increasing *Fndc5* expression and circulating irisin. Circulating irisin may cross the blood–brain barrier and has been associated with molecular and neuroprotective changes in the central nervous system, reducing glial neuroinflammation, NLRP3/caspase-1 signaling, and microglial pyroptosis, while enhancing BDNF expression, mitochondrial function, and Aβ clearance via neprilysin. Exercise also promotes systemic metabolic adaptations, including increased mitochondrial biogenesis, AMPK/SIRT1 activation, improved insulin sensitivity, and reduced peripheral inflammation, which collectively reinforce neuroprotective effects. These molecular and cellular changes contribute to improved synaptic plasticity, enhanced memory and cognitive function, and reduced neuronal degeneration. Abbreviations: PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator-1 alpha; *Fndc5*: Fibronectin type III domain-containing protein 5; BDNF: Brain-derived neurotrophic factor; Aβ: β-amyloid.

Impact on Cognition and Spatial Memory

Cognitive and behavioral outcomes were assessed in seven studies included in this review, which investigated learning and memory performance in experimental models of AD or cognitive impairment in relation to physical exercise interventions and molecular changes

associated with FNDC5 expression or irisin-related pathways.

Lourenço et al., 2019 [9] evaluated hippocampus-dependent memory and synaptic plasticity in experimental models involving experimental manipulation of FNDC5/irisin-related pathways and reported behavioral assessments of cognitive

performance. Three studies additionally reported exercise-based interventions combined with behavioral assessments to evaluate learning and spatial memory in trained animals [18, 19, 23].

Belviranlı et al., 2026 [23] evaluated cognitive responses to exercise intervention and reported improvements in behavioral measures of learning and memory in an experimental model of neurodegeneration. Consistent with these findings, Nogueira Godinho et al., 2022 [20] also assessed cognitive performance in exercised animals, demonstrating enhanced memory-related outcomes.

In the included studies, cognitive function was primarily assessed using hippocampus-dependent behavioral paradigms, including the MWM and NOR.

Summary of Molecular Insights: Exercise, irisin, and Neuroprotection in AD

The included studies identified convergent molecular pathways linking reduced irisin availability, synaptic dysfunction, and cognitive impairment in experimental models of AD. Physical stimuli, such as regular exercise, can increase irisin availability via skeletal muscle PGC-1 α activation, which upregulates *Fndc5* expression and reduces soluble A β oligomers. Circulating irisin crosses the blood–brain barrier and exerts direct effects on the central nervous system, modulating glial neuroinflammation, suppressing NLRP3/caspase-1 signaling, and reducing microglial pyroptosis.

Exercise also promotes systemic metabolic adaptations including enhanced mitochondrial biogenesis, AMPK/SIRT1 activation, improved insulin sensitivity, and reduced peripheral inflammation that converge on the neuroimmune axis and further potentiate neuroprotective effects. Within the brain, irisin increases BDNF expression, improves mitochondrial function, and facilitates A β clearance via neprilysin upregulation, collectively enhancing synaptic plasticity and cognitive performance while mitigating neuronal loss.

Figure 3 illustrates the integrative muscle–brain axis as a central network linking peripheral exercise-induced adaptations to molecular and functional neuroprotection in AD.

DISCUSSION

This systematic review summarizes evidence indicating that physical exercise is associated with modulation of FNDC5 expression, irisin-related pathways, and improvements in cognitive and molecular outcomes in experimental models of AD. Overall, the included studies consistently demonstrated that physical exercise was associated with increased expression of *Fndc5* and, in

some studies, increased irisin levels in peripheral tissues and brain regions associated with cognition, particularly the hippocampus. These changes were associated with reductions in neuroinflammatory markers, modulation of amyloid-related pathology, and improvements in learning and spatial memory. Collectively, the available evidence suggests that FNDC5 expression and irisin-related pathways may contribute to the neuroprotective effects associated with physical exercise in experimental models of AD.

However, the available evidence should be interpreted with caution regarding causality. While most included studies demonstrate consistent associations between exercise-induced changes in FNDC5 expression, irisin-related pathways, and improvements in cognitive and molecular outcomes, only a limited number of studies directly tested the causal involvement of this pathway through genetic or pharmacological manipulation (FNDC5 knockdown or irisin administration) [9, 17, 19]. Therefore, FNDC5/irisin should be considered a candidate mediator within the broader exercise-induced neuroprotective response, rather than a definitively established causal mechanism.

In addition, it is important to consider that physical exercise induces a wide range of systemic adaptations, including changes in neurotrophic factors, metabolic pathways, inflammatory responses, and mitochondrial function. Therefore, FNDC5 expression and irisin-related pathways should be interpreted as one component within this complex network, rather than an isolated or dominant mediator of exercise-induced neuroprotection.

One of the most consistent observations across the included studies was increased *Fndc5* expression and activation of molecular pathways associated with FNDC5 expression and irisin-related signaling following physical exercise. However, direct assessment of irisin levels was performed only in a subset of studies. Irisin is generated through the proteolytic cleavage of *Fndc5* and has been widely described as a myokine released during muscle contraction [9, 17, 19, 26]. Importantly, experimental evidence indicates that circulating irisin can cross the blood–brain barrier, allowing peripheral exercise-derived signals to influence central nervous system function [27].

In the analyzed studies, FNDC5 expression and irisin-related molecular pathways were associated with the upregulation of neuroprotective mechanisms, including activation of BDNF, a key regulator of synaptic plasticity, neuronal survival, and memory formation [27].

An important aspect to consider is the heterogeneity of the experimental models used across the included studies. These models represent different biological dimensions of Alzheimer's disease, including amyloid-driven pathology in transgenic models (e.g., APP/PS1, 5xFAD), metabolically induced dysfunction (e.g., ICV-

STZ), and aging- or chemically induced alterations (e.g., D-galactose or D-galactose combined with AlCl_3).

Importantly, these models do not reflect the same underlying mechanisms of AD. Transgenic models provide stronger evidence for amyloid-related pathology and disease progression, whereas chemically induced or aging-related models primarily capture aspects such as oxidative stress, metabolic dysfunction, or cognitive impairment without fully reproducing the complexity of AD pathology.

Therefore, the strength of evidence should be interpreted accordingly. Findings derived from transgenic models, including APP/PS1, 5xFAD, and 3xTg-AD mice, may provide more direct insights into AD-related mechanisms, particularly those associated with amyloid and tau pathology. In contrast, results from chemically induced or aging-related models should be interpreted with caution and considered complementary evidence rather than equivalent representations of AD pathology.

Importantly, studies that did not assess behavioral outcomes should be interpreted as supportive mechanistic evidence rather than direct evidence that FND5/irisin modulation improves cognitive outcomes.

An important limitation of the current evidence relates to the methodological quality of the studies included. Although many studies reported beneficial effects associated with physical exercise, increased FND5 expression, or irisin-related pathways, the overall confidence in these findings is limited by incomplete reporting and frequent unclear or high risk of bias in key domains, particularly regarding randomization and blinding procedures.

These methodological limitations may lead to an overestimation of the reported effects and should be carefully considered when interpreting the results. Furthermore, not all studies contribute equally to the strength of the evidence, and findings from studies with lower risk of bias and more rigorous experimental design should be considered more robust.

The modulation of neuroinflammatory processes also emerged as a central mechanism through which irisin may exert neuroprotective effects. Chronic neuroinflammation is widely recognized as a key contributor to the pathophysiology of AD [18, 28], involving sustained activation of microglia and the release of pro-inflammatory cytokines. Direct assessment of inflammatory markers was limited across the included studies. Okudan et al. [21] evaluated NF- κ B and IL-1 β expression in ocular tissues following treadmill exercise in a D-galactose/ AlCl_3 -induced model, reporting reductions in both markers after exercise intervention. Kim et al. [24] assessed inflammatory and glial-related markers in brain tissue from a transgenic 3xTg-AD mouse model subjected to long-term treadmill exercise,

demonstrating reduced expression of NF- κ B, TNF- α , IL-6, and decreased glial activation. Importantly, these anti-inflammatory effects were associated with exercise interventions rather than direct pharmacological manipulation of irisin-related pathways.

In contrast, most of the remaining studies did not directly quantify classical inflammatory cytokines or inflammatory mediators in brain tissue. Instead, anti-inflammatory effects were inferred from broader molecular and pathological findings associated with FND5 expression, irisin-related pathways, mitochondrial function, amyloid-related pathology, or neuroprotective signaling mechanisms.

Furthermore, some experimental findings suggested that irisin has been associated with reduced activation of the NLRP3 inflammasome, a multiprotein complex implicated in the amplification of neuroinflammation and neuronal damage [29]. Inhibition of NLRP3 signaling may contribute to reduced microglial activation and decreased pyroptosis, thereby attenuating neurodegenerative processes [30].

In addition to inflammatory pathways, several studies have reported associations between FND5 expression, irisin-related pathways, and changes in amyloid- β accumulation or amyloid-related toxicity, which are central components of AD pathology [9, 17, 19]. Experimental models involving amyloid peptide infusion or metabolic dysfunction have demonstrated that exercise-based interventions are associated with reduced amyloid burden and improved neuronal resilience [31]. These effects may occur through multiple mechanisms, including enhanced synaptic plasticity, improved mitochondrial function, and increased neurotrophic support [9, 17, 19, 32].

Furthermore, growing evidence suggests that exercise-associated irisin-related pathways may contribute to the regulation of amyloid clearance pathways. In particular, physical exercise has been associated with increased expression of neprilysin [31, 33], one of the major enzymes involved in amyloid- β degradation in the brain. Upregulation of neprilysin may facilitate the removal of toxic amyloid aggregates, thereby reducing plaque formation and attenuate neuronal damage [34, 35]. Through the combined modulation of amyloid degradation mechanisms and neuroprotective signaling pathways, the exercise–irisin axis may contribute to limiting the progression of amyloid-related pathology in experimental models of AD.

It is important to emphasize that the molecular and cellular changes observed in the analyzed studies were accompanied by improvements in behavioral outcomes. Most of the included studies reported enhanced performance in cognitive tests assessing learning and spatial memory, particularly the MWM. These findings

support the hypothesis that exercise-associated FNDC5 expression and irisin-related pathways may contribute to the preservation of cognitive performance in experimental models of neurodegeneration. The observed improvements in behavioral outcomes are likely mediated by the combined effects of reduced neuroinflammation, enhanced neurotrophic signaling, and improved synaptic integrity.

From a translational perspective, these findings highlight the potential relevance of exercise-induced FNDC5 expression and irisin-related pathways in the context of neurodegenerative diseases. However, the translational applicability of these findings to human populations remains uncertain. Physical exercise is already widely recognized as a non-pharmacological strategy capable of promoting brain health and reducing the risk of cognitive decline.

The identification of FNDC5 expression and irisin-related mechanisms as potential components of these effects suggests that modulation of this pathway may represent a promising avenue for future investigation in AD. Evidence derived from transgenic AD models has demonstrated associations between exercise-induced changes in FNDC5 expression and modulation of neuroinflammatory, neurotrophic, and amyloid-related pathways. Although emerging clinical studies suggest possible associations between exercise, irisin levels, and cognitive outcomes, the current human evidence remains limited and inconsistent.

Several important limitations should be considered when interpreting the translational potential of these findings. It remains unclear whether circulating irisin levels are consistently increased in response to exercise in older adults or in patients with Alzheimer's disease. Additionally, although experimental studies suggest that irisin can cross the blood–brain barrier, the extent to which this occurs in humans under physiological conditions is not well established.

Methodological concerns regarding the reliability and specificity of peripheral irisin assays have also been raised, which may affect the interpretation of circulating levels. Furthermore, it is not yet well established whether changes in irisin levels are consistently associated with cognitive improvements in clinical populations. Therefore, further well-designed longitudinal and mechanistic studies are required to determine the clinical relevance of FNDC5 expression and irisin-related pathways.

Despite the consistent findings observed across studies, the methodological quality of the evidence included should be carefully considered. The risk of bias assessment indicated an overall moderate methodological rigor, with most studies presenting unclear risk in domains related to randomization procedures and blinding.

Sequence generation and allocation concealment were frequently insufficiently reported, while performance bias associated with the lack of blinding of caregivers and investigators was consistently identified, reflecting inherent limitations of exercise-based interventions. Additionally, random housing conditions were often not described, representing a potential source of bias in animal studies. In contrast, domains related to outcome completeness and selective reporting were consistently classified as low risk, indicating that the reported findings were generally reliable and transparently presented. These methodological limitations do not invalidate the observed effects but highlight the need for improved experimental design and reporting standards in future preclinical studies.

Although exercise-induced irisin-related pathways represent a promising mechanism for neuroprotection, it is important to distinguish between the physiological effects of physical exercise and the administration of exogenous irisin as a therapeutic strategy. During physical exercise, expression of *Fndc5* in skeletal muscle is stimulated by metabolic regulators such as PGC-1 alpha, leading to the systemic release of irisin as part of a complex physiological response involving multiple organ systems [26, 27]. In this context, the observed neuroprotective effects likely reflect the integrated action of several exercise-associated factors, including improvements in energy metabolism, vascular function, and anti-inflammatory signaling.

In contrast, the administration of exogenous irisin represents a more targeted pharmacological approach aimed at reproducing some of the molecular effects associated with physical exercise. Although preclinical studies suggest that experimentally administered irisin may activate neurotrophic pathways and reduce neuroinflammation [9, 19, 36], it remains unclear whether this strategy can fully replicate the systemic benefits of physical exercise. Therefore, irisin based therapies may represent a promising complementary approach, but they are unlikely to replace the multifactorial effects of regular physical activity on brain health.

Taken together, the findings discussed here reinforce the potential relevance of exercise-associated FNDC5 expression and irisin-related pathways as a potential component of muscle–brain communication in experimental models of AD. The available evidence suggests that irisin may contribute to the integration of peripheral metabolic adaptations with central mechanisms related to neuroinflammation, synaptic plasticity, and cognitive function. However, important methodological limitations and heterogeneity across studies highlight the need for cautious interpretation. Future research using standardized protocols and translational approaches will be essential to further clarify the role of irisin in exercise-

induced neuroprotection and its potential relevance in the context of human neurodegenerative diseases.

Limitations

This review has some limitations that should be considered. The number of available preclinical studies investigating the relationship between physical exercise, FNDC5 expression, irisin-related pathways, and cognitive outcomes in AD models remains limited. Additionally, substantial heterogeneity was observed across studies regarding animal models, exercise protocols, and outcome measures, which may affect comparability.

Variability in the methods used to assess *Fndc5* and irisin, along with the lack of standardized assays, may also contribute to inconsistencies in the findings. Differences in cognitive testing protocols further limit direct comparisons of behavioral outcomes.

Moreover, the overall methodological rigor of the included studies was moderate, with limitations in reporting randomization and blinding procedures, as indicated by the risk of bias assessment. Finally, as this review is restricted to animal studies, the translational applicability to human AD remains uncertain.

Despite these limitations, the available evidence supports a potential role for the *Fndc5*/irisin axis in exercise-induced neuroprotection, highlighting the need for more standardized and translational research in this field.

Conclusions

In summary, this systematic review highlights the exercise FNDC5/irisin axis as a potential component associated with neuroprotective effects in diverse preclinical models of AD related pathology. The available preclinical evidence indicates that physical exercise is consistently associated with increased FNDC5 expression and, in some studies, increased irisin levels, which are consistently associated with reduced neuroinflammation, enhanced neurotrophic signaling particularly involving BDNF and modulation of amyloid-related pathways.

These findings support the concept that irisin may represent one of several biological mechanisms linking peripheral metabolic adaptations to central nervous system function, with potential relevance to cognitive outcomes in experimental models. However, as the current evidence is largely derived from animal studies, its translational applicability to human populations remains uncertain.

Future studies should focus on clarifying the molecular mechanisms underlying these associations and determining whether modulation of the FNDC5/irisin

pathway may contribute to exercise-related neuroprotective effects in the context of AD.

Author Contributions

Conceptualization, C.A.S.G., R.A.M. and F.M.S.; material selection, R.A.M. and F.M.S.; Writing—original draft preparation, R.A.M. and F.M.S.; writing—review and editing, C.A.S.G., D.C., R.A.M. and F.M.S.; All authors have read and agreed to the published version of the manuscript.

Conflicts Of Interest

The authors declare no conflict of interest.

Funding Statement

This study was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; grant number 171607/2023-6) and by the National Institutes of Science and Technology (INCT) programs Neuroprotection and Brain Health.

References

- [1] Heinonen O, Soininen H, Sorvari H, Kosunen O, Paljarvi L, Koivisto E, et al. (1995). Loss of synaptophysin-like immunoreactivity in the hippocampal formation is an early phenomenon in Alzheimer's disease. *Neuroscience*, 64: 375-384
- [2] Scheff SW, Sparks L, Price DA (1993). Quantitative assessment of synaptic density in the entorhinal cortex in Alzheimer's disease. *Ann Neurol*, 34: 356-361
- [3] Hampel H, Hardy J, Blennow K, Chen C, Perry G, Kim SH, et al. (2021). The Amyloid-beta Pathway in Alzheimer's Disease. *Mol Psychiatry*, 26: 5481-5503
- [4] Kostka M, Morys J, Malecki A, Nowacka-Chmielewska M (2024). Muscle-brain crosstalk mediated by exercise-induced myokines - insights from experimental studies. *Front Physiol*, 15: 1488375
- [5] Rai M, Demontis F (2022). Muscle-to-Brain Signaling Via Myokines and Myometabolites. *Brain Plast*, 8: 43-63
- [6] Mu L, Xia D, Cai J, Gu B, Liu X, Friedman V, et al. (2022). Treadmill Exercise Reduces Neuroinflammation, Glial Cell Activation and Improves Synaptic Transmission in the Prefrontal Cortex in 3 x Tg-AD Mice. *Int J Mol Sci*, 23
- [7] Wang M, Zhang H, Liang J, Huang J, Chen N (2023). Exercise suppresses neuroinflammation for alleviating Alzheimer's disease. *J Neuroinflammation*, 20: 76
- [8] Kim E, Tanzi RE, Choi SH (2025). Therapeutic potential of exercise-hormone irisin in Alzheimer's disease. *Neural Regen Res*, 20: 1555-1564
- [9] Lourenco MV, Frozza RL, de Freitas GB, Zhang H, Kincheski GC, Ribeiro FC, et al. (2019). Exercise-linked

- FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models. *Nat Med*, 25: 165-175
- [10] Kim E, Kim H, Jedrychowski MP, Bakiasi G, Park J, Kruskop J, et al. (2023). Irisin reduces amyloid-beta by inducing the release of neprilysin from astrocytes following downregulation of ERK-STAT3 signaling. *Neuron*, 111: 3619-3633 e3618
- [11] Lee JM, Sim TH, Kim SH, Choi YJ, Lee JH, Yeo SG, et al. (2025). Exercise-Induced FNDC5/Irisin Ameliorates Cognitive Impairment in Aged Mice, Associated with Antioxidant and Neurotrophic Responses. *Antioxidants* (Ba), 14
- [12] Zhang DQ, Li G, Fu ZD, Huang YS, Feng XL, Chen LJ, et al. (2025). Irisin ameliorates cognitive impairment in a lipopolysaccharide-induced neuroinflammation mouse model by inhibiting the NLRP3 inflammasome pathway in microglia. *Neuropharmacology*, 278: 110572
- [13] Kong J, Xie Y, Fan R, Wang Q, Luo Y, Dong P (2025). Exercise orchestrates systemic metabolic and neuroimmune homeostasis via the brain-muscle-liver axis to slow down aging and neurodegeneration: a narrative review. *Eur J Med Res*, 30: 475
- [14] Lin J, Zhang X, Sun Y, Xu H, Li N, Wang Y, et al. (2024). Exercise ameliorates muscular excessive mitochondrial fission, insulin resistance and inflammation in diabetic rats via irisin/AMPK activation. *Sci Rep*, 14: 10658
- [15] Zheng L, Rao Z, Wu J, Ma X, Jiang Z, Xiao W (2024). Resistance Exercise Improves Glycolipid Metabolism and Mitochondrial Biogenesis in Skeletal Muscle of T2DM Mice via miR-30d-5p/SIRT1/PGC-1alpha Axis. *Int J Mol Sci*, 25
- [16] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Rev Esp Cardiol (Engl Ed)*, 74: 790-799
- [17] Dehghan F, Zamani S, Barreiro C, Jami MS (2021). Irisin injection mimics exercise effects on the brain proteome. *Eur J Neurosci*, 54: 7422-7441
- [18] Hegazy MA, Abdelmonsif DA, Zeitoun TM, El-Sayed NS, Samy DM (2022). Swimming exercise versus L-carnosine supplementation for Alzheimer's dementia in rats: implication of circulating and hippocampal FNDC5/irisin. *J Physiol Biochem*, 78: 109-124
- [19] Islam MR, Valaris S, Young MF, Haley EB, Luo R, Bond SF, et al. (2021). Exercise hormone irisin is a critical regulator of cognitive function. *Nat Metab*, 3: 1058-1070
- [20] Nogueira Godinho WD, Vasconcelos Filho FSL, Pinto DV, Alves JO, de Souza Nascimento T, de Aguiar ID, et al. (2022). High-Intense Interval Training Prevents Cognitive Impairment and Increases the Expression of Muscle Genes FNDC5 and PPARGC1A in a Rat Model of Alzheimer's Disease. *Curr Alzheimer Res*, 19: 830-840
- [21] Okudan S, Sezer T, Tinkir Kayirbatmaz E, Belviranli M, Okudan N (2025). Effect of regular exercise on ocular inflammation and mitochondrial biogenesis in experimental Alzheimer's disease model. *Cell Mol Biol (Noisy-le-grand)*, 71: 117-123
- [22] Puoyan-Majd S, Parnow A, Rashno M, Heidarimoghadam R, Komaki A (2025). Effects of Pretreatment With Coenzyme Q10 (CoQ10) and High-Intensity Interval Training (HIIT) on FNDC5, Irisin, and BDNF Levels, and Amyloid-Beta (Abeta) Plaque Formation in the Hippocampus of Abeta-Induced Alzheimer's Disease Rats. *CNS Neurosci Ther*, 31: e70221
- [23] Belviranli M, Okudan N, Sezer T (2026). Exercise upregulates Mitsugumin 53 and ameliorates behavioral deficits and mitochondrial biogenesis in a sporadic Alzheimer's disease model in rats. *Arch Gerontol Geriatr*, 141: 106078
- [24] Kim T, Cho J, Kang H (2025). Exercise training-induced benefits for Alzheimer's disease are associated with modulation of the BDNF-TrkB signaling complex. *Sci Rep*, 15: 45130
- [25] Azimi M, Gharakhanlou R, Naghdi N, Khodadadi D, Heysieattalab S (2018). Moderate treadmill exercise ameliorates amyloid-beta-induced learning and memory impairment, possibly via increasing AMPK activity and up-regulation of the PGC-1alpha/FNDC5/BDNF pathway. *Peptides*, 102: 78-88
- [26] Bostrom P, Wu J, Jedrychowski MP, Korde A, Ye L, Lo JC, et al. (2012). A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*, 481: 463-468
- [27] Wrann CD, White JP, Salogiannnis J, Laznik-Bogoslavski D, Wu J, Ma D, et al. (2013). Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. *Cell Metab*, 18: 649-659
- [28] Zhang Q, Yang G, Luo Y, Jiang L, Chi H, Tian G (2024). Neuroinflammation in Alzheimer's disease: insights from peripheral immune cells. *Immun Ageing*, 21: 38
- [29] Guo P, Jin Z, Wu H, Li X, Ke J, Zhang Z, et al. (2019). Effects of irisin on the dysfunction of blood-brain barrier in rats after focal cerebral ischemia/reperfusion. *Brain Behav*, 9: e01425
- [30] Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, et al. (2013). NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature*, 493: 674-678
- [31] Adlard PA, Perreau VM, Pop V, Cotman CW (2005). Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *J Neurosci*, 25: 4217-4221
- [32] Pedersen BK, Saltin B (2015). Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports*, 25 Suppl 3: 1-72
- [33] Moore KM, Girens RE, Larson SK, Jones MR, Restivo JL, Holtzman DM, et al. (2016). A spectrum of exercise training reduces soluble Abeta in a dose-dependent manner in a mouse model of Alzheimer's disease. *Neurobiol Dis*, 85: 218-224
- [34] Iwata N, Tsubuki S, Takaki Y, Shirotani K, Lu B, Gerard NP, et al. (2001). Metabolic regulation of brain Abeta by neprilysin. *Science*, 292: 1550-1552

- [35] Nalivaeva NN, Beckett C, Belyaev ND, Turner AJ (2012). Are amyloid-degrading enzymes viable therapeutic targets in Alzheimer's disease? *J Neurochem*, 120 Suppl 1: 167-185
- [36] Muzaffar S, Tyagi A, Pugazhenti S (2025). Therapeutic Potential of Irisin in Neurodegenerative Diseases. *Int J Mol Sci*, 26