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Irisin: An unveiled bridge between physical exercise and a healthy brain

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ABSTRACT

Aims: Physical exercise has been widely recognized for its positive effects on health and well-being. Recently, the impact of exercise on the nervous system has gained attention, with evidence indicating improvements in attention, memory, neurogenesis, and the release of "happiness hormones." One potential mediator of these benefits is Irisin, a myokine induced by exercise that can cross the blood-brain barrier, reduce neuroinflammation, and counteract neurodegeneration. The objective of this study is to conduct a systematic review of animal trials to summarize the neuroprotective effects of Irisin injection in mitigating neuroinflammation and neurodegeneration.

Materials and methods: Two independent reviewers screened three databases (PubMed, Embase, and Google Scholar) in November 2022. Animal studies assessing the neuroprotective effects of Irisin in mitigating

Abbreviations: 4-HNE, 4-hydroxy-2-nonenal; AD, Alzheimer's Disease; Akt, Ak Strain Transforming; ALOX12, Arachidonate 12-Lipoxygenase; AMPK, Adenosine Monophosphate-Activated Protein Kinase; ASCL4, Long-Chain-Fatty-Acid—CoA Ligase 4; Aβ, amyloid-beta; Bax, Bcl-2-Associated X Protein; BBB, blood-brain barrier; Bcl-2, B-Cell Leukemia/Lymphoma 2 Protein; BDNF, Brain-derived neurotrophic factor; BMSCs, bone marrow stem cells; BWC, brain water content; C57, C57BL/6 J mice; CA1, Cornu Ammonis-1; CD68, Cluster of Differentiation 68; CLP, cecal ligation and puncture; CNS, Central Nervous System; CSF, cerebrospinal fluid; DA, dopaminergic; DAPT, Dual Antiplatelet Therapy; DM, Diabetes Mellitus; DMSO, Dimethyl Sulfoxide; DNA, Deoxyribonucleic Acid; EB, Evans Blue; EE, endurance exercise; ELISA, Enzyme-Linked Immunoassay; ERK1/2, the extracellular signal-regulated kinase 1/2; FJC, Fluoro-Jade C; FNDC5, fibronectin type III domain-containing protein 5; GFAP, Glial fibrillary acidic protein; GPX4, glutathione peroxidase 4; GSH, glutathione; GSH-PX, glutathione peroxidase; Hes 1, Hairy/Enhancer of Split; Htau, Htau transgenic mice that express six isoforms of human tau; HO-1, Heme oxygenase 1; I/R, ischemia/reperfusion; Iba-1, ionized calcium-binding adaptor molecule 1; ICH, Intracerebral Hemorrhage; IgG, Immunoglobulins G; IL-1, Interleukin 1; IL-10, Interleukin 10; IL-4, Interleukin 4; IL-6, Interleukin 6; KA, Kainic Acid; LPS, Lipopolysaccharide; MCAO, middle cerebral artery occlusion; MDA, Malondialdehyde; Mito/SOX, Mitochondrial Superoxide; Mk-2206, Active Allosteric AKT Inhibitor; MMP, Matrix Metalloproteinase; MMP-9, Matrix Metalloproteinase-9; MPO, Myeloperoxidase; MPTP, 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine; MyD88, Myeloid Differentiation Primary Response Protein 88; NA, not available; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NICD, Notch-1 intracellular domain; NO2− Tyr, nitro tyrosine; Notch1, Neurogenic locus notch homolog protein 1; NQO-1, NAD(*P*)H: Quinone Oxidoreductase; Nrf2, Nuclear factor erythroid 2-related factor 2; OGD, Oxygen Glucose Deprivation; P38, p38 mitogen-activated protein kinases; p-AMPK, Phospho-AMPK; PD, Parkinson's Disease; PE, physical exercise; PGC-1α, Peroxisome proliferator activated receptor gamma coactivator-1 alpha; PICO, Population, Intervention, Comparison, Outcome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Prospero, International prospective register of systematic reviews; ptau, phosphorylated tau; qRT-PCR, Real-Time Quantitative Reverse Transcription PCR; RCTs, randomized controlled trials; ROS, reactive oxygen species; SAE, Sepsis Associated Encephalopathy; SLC7A11, Solute carrier family 7 member 11; SNpc, substantia nigra pars compacta; SOD, Superoxide Dismutase; STAT3, Signal Transducer and Activator of Transcription 3; STZ, Streptozocin; SYP, synaptophysin; SYRCLE's, Systematic Review Centre for Laboratory animal Experimentation; TBI, Traumatic Brain Injury; TJ, tight junctions; TLR4, Toll Like Receptor 4; TNF-α, Tumor Necrosis Factor Alpha; TTD, Total time of descending in pole test; TUNEL, Terminal deoxynucleotidyl transferase dUTP nick end labeling; U0126, MEK/ERK Inhibitor; UCP2, Uncoupling protein-2; UCP2−/−, homozygous UCP2 deletion; ZO-1, Zonula occludens 1.

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neuroinflammation or counteracting neurodegeneration were included. The methodological quality of the included studies was assessed using SYRCLE's Risk of Bias tool.
Key findings: Twelve studies met the inclusion criteria. Irisin injection in rodents significantly reduced neuroinflammation, cytokine cascades, and neurodegeneration. It also protected neurons from damage and apoptosis, reduced oxidative stress, blood-brain barrier disruption, and neurobehavioral deficits following disease or injury. Various mechanisms were suggested to be responsible for these neuroprotective effects. Most of the included studies presented a low risk of bias based on SYRCLE's Risk of Bias tool. Irisin injection demonstrated the potential to alleviate neuroinflammation and counteract neurodegeneration in rodent models through multiple pathways. However, further research is needed to fully understand its mechanism of action and its potential applications in clinical practice and drug discovery.

1. Background (introduction)

Neuroinflammation, the inflammatory response within the brain and spinal cord, is a common pathophysiological feature shared by many neurological disorders. Microglia, the first line of defense in the brain, is the central players in neuroinflammation. Once activated by an infection or disease, they can migrate to sites of infection, have phagocytic activity, and produce cytokines and chemokines like IL-1, IL-6, TNF-α, and reactive oxygen species (ROS) [1]. Besides microglia, astrocytes also play an important role in neuroinflammation. Once activated, they secrete soluble mediators like IL-1, and TNF-α, and control blood-brain barrier permeability [2]. Acute neuroinflammation has a neuroprotective effect, however, chronic neuroinflammation is most often detrimental and damaging to nervous tissue. In fact, neuroinflammation plays a key role in the onset of neurodegenerative diseases as well as in their pathogenesis. Many of neurodegenerative diseases share the accumulation of misfolded proteins which triggers a permanent damaging neuroinflammation, leading to more neurodegeneration, creating a detrimental vicious circle [3].

Physical activity's beneficial effects on the human body have long been known and studied. Physical exercises (PE) like aerobic, resistance, and endurance exercises, were shown to prevent obesity and helps loose and maintain a healthy weight [4], to improve muscle strength and bone mineral density, preventing osteopenia and osteoporosis [5,6], and to improve cardiorespiratory fitness and cardiovascular health, thus preventing from chronic non communicable diseases, including cardiovascular disease, metabolic syndromes, diabetes, breast, colon and other cancers [7].

These benefits managed to reach the nervous system. By increasing heart rate, PE increase the cerebral blood flow, exposing the brain to more oxygen and nutrients [8]. Studies have shown that PE improves focus, attention, and concentration in both children and adults [9]. By regulating genes responsible for synaptic plasticity, PE plays a role in strengthening and maintaining existing connections between neurons and helps forming new ones, influencing long term potentiation, therefore enhancing memory [10,11]. In addition, exercise was shown to stimulate neurogenesis in the dentate gyrus of the hippocampus [12], and to affect the proliferation, size and function of astrocytes [13]. Furthermore, a number of chemical signals called neurotransmitters are released in the brain during PE, like endorphins and endocannabinoids [14], dopamine [15], serotonin [16] and norepinephrine [17].

PE's beneficial effect could be partially attributed to myokines [11]. Myokines are cytokines and peptides produced by muscle fibers during physical activity, they mediate the communication between skeletal muscles and other organs [18]. Irisin is an exercise-induced myokine discovered by Boström and colleagues in 2012 [19]. It is the secreted form of the fibronectin type III domain-containing protein 5 (FNDC5), a transmembrane glycoprotein highly expressed in skeletal muscle, heart, and brain [19]. The expression of FNDC5 is regulated by the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), which, in turn, is induced by physical activity [18]. FDNC5's cleavage at the ectodomain portion releases into the bloodstream the soluble irisin fragment, consisting of 112 amino acids [20]. Mice, rats and humans share 100 % identical irisin peptide sequence, which is highly conserved across mammals [19].

Targeting multiple organs, irisin stimulates thermogenesis and browning of adipose tissue, glucose and lipid uptake by in skeletal muscles and their development and regeneration, glucose increase and lipid metabolism in the liver, osteoblast differentiation and anti-apoptotic function in bone, and angiogenesis and protection against vascular dysfunction at the level of the vascular endothelium [3].

Recently, irisin's existence was detected and confirmed in various brain regions, like the hippocampus, cerebrum, and cerebrospinal fluid, and is thought to be responsible for the neuroprotective effect of physical exercise [20]. Exercise, specifically resistance and aerobic exercise, elevates circulating irisin levels which then reaches the brain by crossing the blood-brain barrier. By inducing FNDC5 expression in the hippocampus, irisin was able to alter specific gene expression in neurons and glial cells [21], influencing the neuronal differentiation of embryonic stem cells, activating the brain-derived neurotrophic factor BDNF and other neuroprotective genes, promoting synaptic plasticity, neuronal differentiation, and neuronal health, thus counteracting neurodegeneration, as a result of the activation of the PGC-1α/FNDC5/BDNF axis [22] (Hashemi et al., 2013).

Multiple studies have also shown that Irisin can mitigate neuroinflammation by reducing the number of activated microglia, reducing astrocyte activation and the expression of IL-6 and TNF-α, reducing oxidative stress and protecting neuronal cells against oxygen/glucose deprivation (OGD) and apoptosis [3].

These findings together may open new doors for researchers to use this naturally-produced myokine, to find new therapeutic strategies to treat, even prevent neuroinflammation, which is the leading cause of many neurodegenerative diseases, and highlight the importance of physical exercise, especially in sedentary communities and elderly population.

Before proceeding to clinical practice, animal models are usually used to test the effectiveness of therapeutic approaches [23]. Since this myokine is recently discovered, emerging animal trials are being constantly conducted and published. This calls for the need for updated reviews to summarize their latest findings to produce a reliable and accurate conclusion about irisin's neuroprotective effect and translate it to clinical practice. Therefore, this systematic review assessing the effects of the injection of irisin on the brain of rodent animal models, will be the first to tackle irisin effects on the brain, neuroinflammation, and neurodegeneration.

2. Objectives

In this study, we aim to conduct a systematic review in order to summarize all previous animal trials about the neuroprotective effect of the injection of the myokine irisin on the brain, specifically on mitigating neuroinflammation, and neurodegeneration in a reliable and accurate way to provide evidence for further investigations and potential treatment ideas for humans.

- **Primary objective**: systematically review the scientific literature for all published rodent animal studies addressing the neuroprotective effect of irisin's injection on the brain.

- **Secondary objectives:**

1. Present the main molecular pathways responsible for irisin's neuroprotective effect.
2. Evaluate implications of irisin levels in neurodegenerative diseases and its potential usage to develop new therapeutic strategies to prevent and treat them.

Highlight the importance of physical exercise to maintain a healthy brain.

The research question to be answered is formulated based on the PICO approach:

Does the myokine irisin have a neuroprotective effect on the brain? Is irisin injection able to reduce neuroinflammation and alleviate neurodegeneration in rodent animal models?

- **P (Population):** rodent animal models suffering from neuroinflammation/neurodegenerative diseases.
- **I (Intervention):** irisin injection.
- **C (Comparison):** controls, no injection of irisin.
- **(Outcome):** neuroprotection.

3. Methods

3.1. Study design

This study is a systematic review assessing the neuroprotective effect of the injection of the myokine irisin in the brain of rodent animal models, mitigating neuroinflammation and providing the latest findings on the application of this newly discovered myokine in neurodegenerative diseases. It was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, which consist of a 27-item checklist and a four-phase flow diagram [24].

This study protocol was registered on Prospero with the following registration number CRD42023396245.

3.2. Search strategy and databases

Two independent reviewers conducted a comprehensive literature search in November 2022 by searching the following databases, PubMed, Google Scholar, and Embase. The search strategy was performed using Keywords, Medical Subject Headings (mesh), and combinations related to irisin, brain, neuroinflammation, and neurodegeneration (Table 1). Keywords were combined using the Boolean operators OR AND as follows:

"Irisin" AND ("Brain" OR "Neuroplasticity" OR "Neurogenesis" OR "Neuron" OR "Hippocampus" OR "BDNF") AND ("Neuroinflammation" OR "Immune Response" OR "Microglia" OR "Astrocytes" OR "Chemokines" OR "Cytokines" OR "Interleukin-6" OR "TNF-α" OR "Neurodegenerative Diseases" OR "Alzheimer's disease" OR "Parkinson's disease" OR "Huntington's disease" OR "Amyotrophic lateral sclerosis" OR "Dementia" OR "Aging").

Table 1
The keywords used in this systematic review.

Search protocols	Mesh terms	Keywords
Irisin	"FNDC5 protein"	Irisin OR FNDC5
Brain	"Brain"	Brain OR Neuroplasticity OR Neurogenesis OR Neuron OR Hippocampus OR BDNF.
Neuroinflammation	"Neuroinflammatory Diseases"	Neuroinflammation OR Immune Response OR Microglia OR Astrocytes OR Chemokines OR Cytokines OR Interleukin-6 OR TNF-α.
Neurodegeneration	"Neurodegenerative Diseases"	Neurodegenerative Diseases OR Alzheimer's disease OR Parkinson's disease OR Huntington's disease OR Amyotrophic lateral sclerosis OR Neuroinflammation Dementia OR Aging.

Keywords and terms used were modified according to each database's searching protocol. There were no restrictions, filters, or search limits used in this step.

All the references identified with the databases were imported into Mendeley, a free reference management software, and the duplicates were removed.

3.3. Screening and study selection

The four-step PRISMA flow diagram (identification, screening, eligibility, and inclusion) was followed to select relevant studies.

The screening phase was done manually and consisted of two steps. First, titles and abstracts were screened to remove irrelevant articles, then full texts of the remaining articles were checked to assess their eligibility, and studies that didn't meet the inclusion criteria or met at least one of the exclusion criteria were excluded. Finally, the full texts of the selected articles were retrieved for data extraction, quality assessment, and qualitative synthesis. Reference lists of retrieved articles were also checked for relevant articles to spot any missing publications.

These mentioned steps were conducted by two independent reviewers (F.E and A.A), and any disagreement was discussed and resolved via consensus.

3.4. Eligibility criteria

Studies were included if they met the following criteria: (1) Published between 2012 and 2022 (2) Animal studies (3) Intervention is irisin injection (4) Published in English (5) Should include the neuroprotective effect of irisin (6) Performed on healthy brains or brains dealing with neurological conditions like neuroinflammation and neurodegeneration.

Studies were excluded if they met the following criteria: (1) Not published, not found or only abstract available (2) Published in a language other than English (3) Published as Reviews, reports, newspaper articles, books (4) non-animal studies (5) Animal studies where another intervention is used (sport, genetic manipulation, etc.) (6) Studies focused on psychological conditions, behavioral outcomes, or memory, without including any neuroprotective effect of irisin (7) Irisin treatment is combined with other drugs or approaches (8) Single arm studies.

3.5. Data extraction

The first author independently extracted data about (1) source details: the title and authors of the study, year of publication, country, and study design, (2) characteristics of the population: species used (mice/rats), sample size, sex, months of age, body weight and experimental groups, (3) details about the intervention and methodology: origin of irisin, its administration route, the dosage used, frequency of the injection, and parameters assessed, and finally (4) the outcomes and the conclusion stated by authors.

3.6. Quality assessment

Since the systematic review only included animal studies, the SYRCLE's Risk of Bias tool was employed to assess the methodological quality and potential biases in those studies [25].SYRCLE's Risk of Bias tool is an adapted version of the Cochrane Risk of Bias tool for clinical trials, that takes into consideration differences in design between RCTs and animal studies. It is composed of the following 10 items: sequence generation, baseline characteristics, allocation concealment, random housing, caregivers blinding, random outcome assessment, outcome

assessor blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. These entries are related to the following types of biases: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. This tool doesn't contain a numerical score, instead, a risk of bias ranging between a High, Low, or Unclear bias was attributed for each entry.

Two independent reviewers (F.E and A.A) critically appraised the quality of included studies, and any disagreement was discussed with third reviewer (N.S) and resolved via consensus.

3.7. Data synthesis and analysis

A qualitative analysis of the data was conducted in order to provide an in-depth understanding of the neuroprotective effects of irisin's injection in animal models. A qualitative description was performed to summarize the characteristics and findings of the included studies. All studies were grouped according to the disease or condition studied, and statistical significance was indicated by P-values <0.05.

4. Results

4.1. Identification of relevant studies

After conducting a search in three databases (PubMed, Embase, and Google Scholar), a total of 162 potentially relevant studies were identified (40 from PubMed, 77 from Embase, and 45 from Google Scholar). After removing 27 duplicates, 114 studies were excluded based on title and abstract screening. Subsequently, 21 full-text articles were carefully evaluated for eligibility, and their reference list was checked. As a result, 12 studies that met the predefined criteria were included for data extraction and qualitative synthesis in this review. The study selection process is visually represented in Fig. 1 of the PRISMA flow diagram.

4.2. Characteristics of studies included in the analysis

The characteristics and results of the studies included were summarized in Tables 1 and 2.

Studies selected for this review were published between 2017 and 2022. Out of the 12 included studies, eight used mice models, including

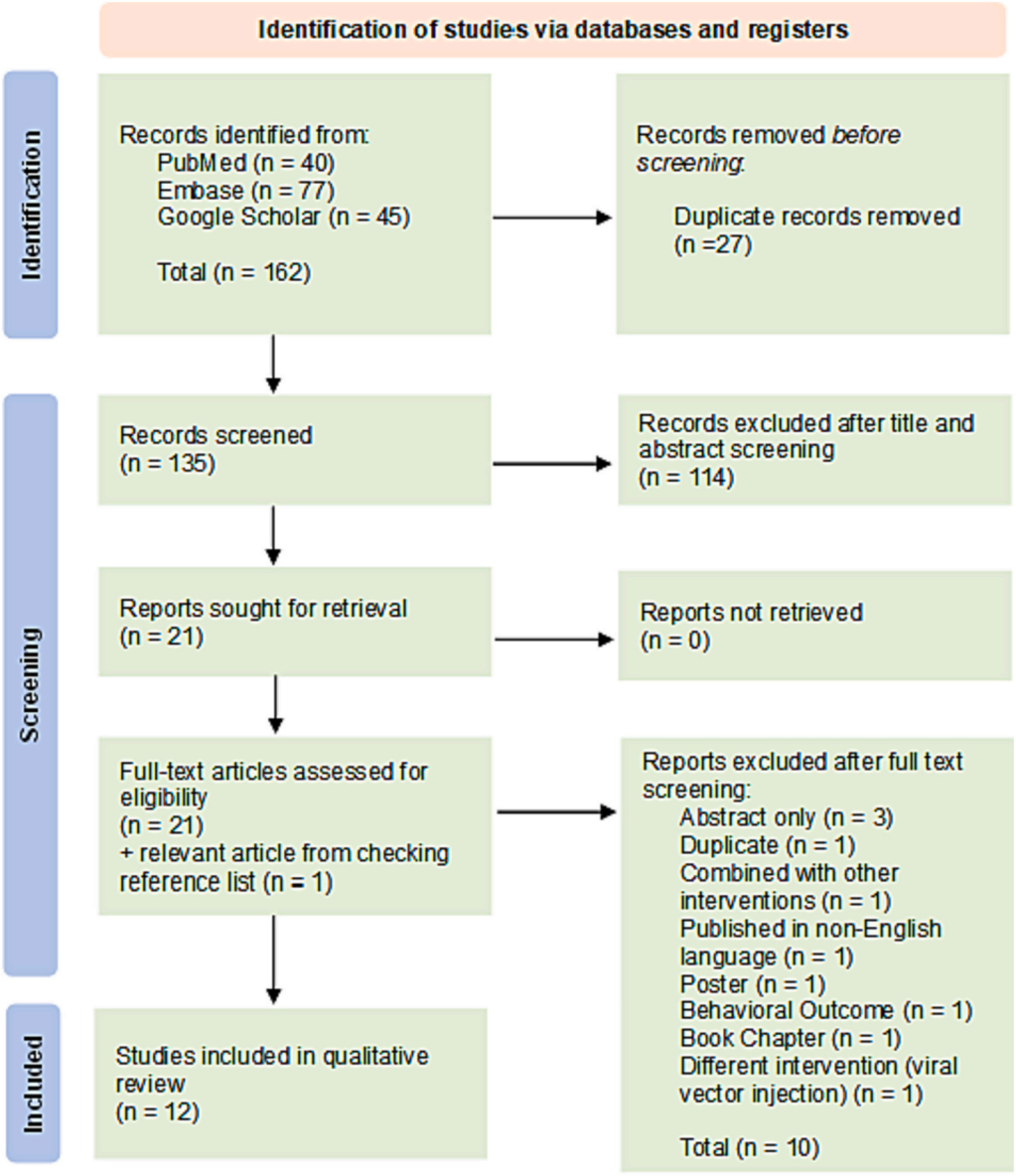

Fig. 1. Flow chart representing the search process based on PRISMA guidelines.

Table 2
Summary of characteristics and findings of included studies.

Reference	Author (year) Country Study design	Animal model Sample size/sex Months of age/body weight	Experimental groups	Origin of irisin/administration route/dosage/frequency	Outcomes
[27]	• Jin et al. (2019) • China • Randomized controlled study	• C57BL/6 mice • NA/male • Adult/20–25 g	1- Sham-operated control group 2- Global cerebral ischemia/reperfusion (I/R) group 3- Irisin-treated group 4- DAPT-treated group 5- Irisin/DAPT-treated group	NA/intravenously/10 μg/kg/once, 30 min after pretreatment	Irisin: ↓ Neurological function deficit * ↓ Neuronal damage induced by cerebral I/R injury * ↓ The value of BWC * ↓ Cerebral I/R-induced apoptosis * ↓ The levels of cleaved caspase-3 * ↓ Cerebral I/R-induced inflammation * ↓ Expression of inflammatory cytokines TNF-α and IL-1β * ↑ Expression of Notch1, NICD and Hes 1 *
[28]	• Wang et al. (2022) • China • Randomized controlled study	• C57BL/6 J wild-type mice (WT) and Nrf2-knockout mice (Nrf2 - /-) • NA/male • Eight-week-old, littermate/NA	1- Sham-operated control group 2- CLP (Sepsis caused by cecal ligation and puncture) 3- CLP+ Irisin 4- CLP + Irisin + Erastin	Phoenix Pharmaceuticals, Inc., Burlingame/intravenously via tail vein injection/250 μg/kg/once a day for 3 consecutive days	Irisin: ↑Survival rate and functional recovery after CLP * ↓ Sepsis-induced Cognitive Dysfunction and Neurological Deficits * ↓ Brain injury, neurodegeneration of hippocampal neurons * ↓ ROS, MDA, ASCL4 and ALOX12 in the hippocampus * ↑ expression of GPX4, SLC7A11, GSH and Nrf2 * ↓ Neuroinflammation, microglial activation, TNF-α, IL-1β and IL-6 level * ↓ CLP-induced blood brain barrier (BBB) disruption * ↓ The recruitment and chemotaxis of microglial cells induced by ferroptotic hippocampal cells * ↓ LPS-induced neurons ferroptosis and mitochondrial damage via Nrf2 pathway *
[31]	• Guo et al. (2021) • China • Randomized controlled study	• C57BL/6 J mice and UCP2 knockout mice with C57BL/6 J background • NA/male • Three-month-old adult/19–23 g	1- Sham-operated group 2- TBI group 3- Irisin-treated group 4- EE group (endurance exercise) 5- EE/IgG-treated group (nonimmune control IgG) 6- EE/NA-treated group (neutralizing antibody against irisin)	NA/intravenously/10 μg/kg/immediately after TBI impact	Irisin: ↓ BWC, EB content, and neurological damage after TBI * ↑ Expression of tight junction TJ-related proteins occludin, Claudin-5, and zonula occludens-1 ZO-1 * ↓ Damage of Ultrastructure of microvasculature * ↓ Levels of TNF-α and IL-1β * ↑ Levels of IL-4 and IL-10 * ↓ Inflammatory response 24 h after TBI * ↓ Oxidative stress, ROS production and MDA content * ↑ Antioxidative stress, the expressions of Nrf2 and its downstream proteins NQO-1, HO-1, SOD, and GSH-PX * ↓ Mitochondrial Apoptosis of vascular Endothelial Cells in the Brain Tissue after TBI * ↑ Protein expression of UCP2 * ↓ Mitochondrial membrane potential MMP * . These neuroprotective effects were not seen in UCP2−/− mice
[46]	• Wang et al. (2019) • China • Randomized controlled study	• C57BL/6 J mice • NA/male • 8-week-old/NA	1- Control 2- Control plus irisin 3- STZ (Streptozotocin-Induced Diabetic Mice) 4- STZ plus irisin	Sigma-Aldrich (MO, USA)/0.5 mg/kg/day/intraperitoneal injection/daily for three weeks	Irisin: ↓ STZ-induced spatial and nonspatial memory deficits * ↓Astrocyte activation and GFAP expression * ↓ Synaptic loss and the reduction of SYP (presynaptic vesicle protein synaptophysin) expression * ↓ Neuroinflammation and IL-1β and IL-6 Levels in Hippocampal Tissues and CSF * ↓ Activation of P38, STAT3, and NFkB Proteins *
[29]	• Guo et al. (2019)	• Sprague Dawley rats	1- Sham operation group 2- Focal cerebral ischemia/reperfusion	Cayman Chemical Company/10 μg/kg/intravenously/pretreatment 30 min before MCAO injury	Irisin: ↓ MCAO-induced neurological deficit * ↓ Brain water content *

(*continued on next page*)

Table 2 (*continued*)

Reference	Author (year) Country Study design	Animal model Sample size/sex Months of age/body weight	Experimental groups	Origin of irisin/administration route/ dosage/frequency	Outcomes
	• China • Randomized controlled study	• 72/male • Adult/280–320 g	group 3- Irisin group		↓ Infarcted region volume and interstitial edema * ↓ BBB permeability and injury * ↓ Expression of MMP-9 *
[30]	• Yu et al. (2020) • China • Controlled study	• Sprague Dawley rats • 80/male • 20 months/190–240 g	1- Sham operation 2- Ischemia injury treated with saline - Ischemia injury treated with irisin at 3 different doses: 3- Irisin10 4- Irisin50 5- Irisin100	NA/intraperitoneally/3 different doses, 10, 50, and 100 mg/kg respectively/once per day for 3 days before surgery	Irisin only at a dose of 50 or 100 mg/kg not 10 mg/kg: ↑ Motor Function after I/R Injury ** ↓ Learning Defects after 3 days * and 4 days ** ↓ Infarct volume ** ↓ Hippocampal neurons in the CA1 region change and damage ** ↑ CA1 neuron number ** ↓ Expression of TLR4 ** and MyD88 * in hippocampus ↓ NF-Kb Activation *
[48]	• Cheng et al. (2021) • China • Randomized controlled study	• Sprague Dawley rat • 144/male • 8 weeks/300–310 g	1- Untreated 2- Kainic Acid + saline 3- Kainic Acid + irisin 4- Kainic Acid + Saline + Irisin 5- Kainic Acid + genipin + Irisin	Xingbao Biotechnology Co., Ltd., China/ injected into the lateral ventricle/49.5 mg/kg/30 min before KA injection	Irisin: ↑ The expression of BDNF and UCP2 in cortex and hippocampus ** ↑ Caspase-3 *** and Bcl-2 in cortex * and hippocampus *** ↓ Bax in cortex ** and hippocampus *** and activated caspase-3 in cortex ** and hippocampus *** ↓ Apoptosis and neuronal injury *** ↓ Mitophagic activity ** ↓ KA- induced oxidative stress *** These neuroprotective effects are reversed by UCP2 inhibitor genipin.
[42]	• Zarbakhsh et al. (2019) • Iran • Controlled study	• Wistar rat • 35/male • Adult/200–250 g	1- Control group 2- Parkinson's group 3- Parkinson's group + BMSCs 4- Parkinson's group + irisin 5- Parkinson's group + BMSCs + irisin	NA/intraperitoneally/50 nm/ml/for 7 days (1 week) after PD	Irisin: ↓ Total time of descending (TTD) in pole test evaluating the activity of basal ganglia and the DA system * ↓ Neuronal damage in SNpc * ↑ Migration and differentiation of the exogenous BMSCs into DA neurons in the injured site of the brain * ↑ Protection of SNpc from MPTP * ↓ Number of apoptotic cell and neuronal death *
[26]	• Bretland et al. (2021) • USA • Randomized Controlled study	• Htau mice on a C57BL/6 J background and C57BL/6 J (C57) mice • 30/Males and Females • 4 months/NA	1- Control htau 2- Control C57 3- Htau + irisin 4- C57 + irisin	r-irisin; #11451: Cayman Chemicals; Ann Arbor, MI/intraperitoneally/100 μg/kg/ four weekly injections	Irisin: ↓ Hippocampal ptau levels in female htau mice not in male htau mice * ↓ Hippocampal TNF-α and neuroinflammation in female htau mice * ↓ Peripheral inflammation in female htau mice * ↑ Neural and systemic inflammation in male htau mice * ↑ Serum circulating irisin levels *
[36]	• Li et al. (2017) • China • Controlled study	• C57BL/6 J mice • NA/Male • Eight- to 12-week-old/NA	1- Sham-operated 2- MCAO 3- MCAO + irisin 4- MCAO + irisin + U0126 and MK-2206 (inhibitors of Akt signaling pathway) 5- MCAO + exercise + irisin neutralizing antibody injection	PeproTech (Rocky Hill, NJ)/0.2 μg/g body weight/intravenously via tail injection/30 min after MCAO	Irisin: ↓ Brain infarct volume and neuronal injury * ↓ MCAO-induced neurological deficit * ↓ MCAO-induced decline in body weight * ↓ Microglia activation and infiltrating neutrophils * ↓ Expression of TNF-α and IL-6 * ↓ Oxidative Stress in peri-infarct brain tissues * ↓ Levels of NO2− Tyr, superoxide anion and 4-HNE * ↑ Phosphorylation of ERK1/2 and Akt * These neuroprotective effects were suppressed by Akt signaling pathway inhibitors (U0126 and MK-2206) and by

(*continued on next page*)

Table 2 (*continued*)

Reference	Author (year) Country Study design	Animal model Sample size/sex Months of age/body weight	Experimental groups	Origin of irisin/administration route/ dosage/frequency	Outcomes
					irisin neutralizing antibody injection post exercise.
[32]	• Asadi et al. (2018) • Iran • Randomized Controlled study	• Swiss albino mice • 91/Male • NA/(30–35 g)	3 series: 1- Control group 2–0.1 μg/kg irisin 3–0.5 μg/kg irisin 4–2.5 μg/kg irisin 5–7.5 μg/kg irisin 6–15 μg/kg irisin 1- Control group 2- Irisin immediately after ischemia 3- Irisin 1 h after ischemia 4- Irisin 3 h after ischemia 1- Sham operated 2- MCAO control 3- MCAO + irisin at a dose of 7.5 μg/kg	orb180476, Biorbyt, Cambridge, UK/0.1 μg/kg, 0.5 μg/kg, 2.5 μg/kg, 7.5 μg/kg, 15 μg/kg/into the right lateral ventricle/ immediately after ischemia (time 0), and 1 and 3 h after ischemia	Irisin: at 7.5 μg/kg immediately after MCAO (optimal dose and timing obtained) ↓ Infarct size *** ↑ Neurological deficit *** ↓ Brain edema formation ** ↓ MCAO Induced Apoptosis *** ↑ The expression of BDNF *** ↓ The expression of Bax and Caspase-3 Pro-apoptotic Proteins *** ↑ The expression of Bcl-2 Anti-apoptotic Protein *** Did Not Alter MCAO Induced BBB Interruption
[20]	• Wang et al. (2022) • China • Randomized Controlled study	• C57BL/6 mice • 285/male • 8-week-old/25–30 g	1- Sham 2- ICH 3- ICH + vehicle group 4- ICH+ 80 μg/kg irisin 5- ICH+ 250 μg/kg irisin 6- ICH+ 750 μg/kg irisin 7- Sham + irisin 8- ICH+ irisin + Cilengitide (integrin aVß5 receptor inhibitor) 9- ICH + irisin + DMSO 10- ICH + irisin + dorsomorphin	#100-65, Peprotech, USA/80 μg/kg, 250 μg/kg, and 750 μg/kg/intranasally/at 30 min after ICH induction	Irisin at 250 μg/kg: ↓ Neurofunctional deficit after ICH * ↓ Brain water content and brain edema after ICH * ↓ impairment of spatial learning and memory function * ↓ Neuronal apoptosis ** ↓ Expression of pro-apoptotic marker Bax * ↑ Protein levels of p-AMPK * ↑ Expression of pro-survival marker Bcl-2 ** ↓Neuroinflammation, the expression of Iba-1 **, MPO **, IL-1β ** and TNF-α * ↓ Peripheral neutrophil infiltration * ↑Microglia/macrophage phenotypic switch from pro-inflammatory to anti-inflammatory phenotypes * These effects were suppressed using integrin aVß5 inhibitor Cilengitide, or selective AMPK inhibitor dorsomorphin

Legend: ↓ Reduce ↑ Increase * P-value < 0.05 ** P-value < 0.01 *** P-value < 0.001 NA: not available.

six using C57BL/6 mice model, one Htau on a C57BL/6 J background mice model, and one Swiss albino mice, and four used rat models, including three using Sprague Dawley rats and one Wistar rat.

Selected articles inspected the following brain-affecting conditions: Ischemia/Reperfusion Injury (five), Sepsis-Associated Encephalopathy (one), Traumatic Brain Injury (one), memory and cognitive deterioration caused by Diabetes Mellitus (one), Status Epilepticus (one), Parkinson's Disease (one), Alzheimer's Disease (one), and Intracerebral Hemorrhage (one). Only one study [26] included female mice, while the remainder were all performed on male mice models. The included studies varied in the origin of irisin, treatment timing, frequency of injections, and optimal dose. For irisin's administration route, five studies used intravenous injection, four intraperitoneal, two into the lateral ventricle, and one intranasally.

4.3. Quality assessment

SYRCLE's risk of bias tool was used to assess the methodological quality of each included study [25]. Fig. 2 shows "traffic light" plots of the domain-level judgments for each result, to help visualize in each study the risk of bias of each of the 10 questions/domains evaluated by this tool, ranging between a high, low, or unclear bias whenever no information was provided by the authors. Fig. 3 shows a weighted bar plot of the distribution of risk-of-bias judgments within each bias domain. Randomization was mentioned in all studies except three, where Q. Yu, et al., D. Li, et al., and S. Zarbakhsh, et al. didn't provide any information describing a random component in the sequence generation process, whereas K. Bretland, et al., used body weight as a parameter to generate treatment groups, to ensure overall uniformity of subjects, but this could've led to a high bias during sequence generation, since parameters other than weight should also be considered during this step.

All studies included mentioned that baseline characteristics (weight, age, and gender) were similar between groups at the beginning, except for K. Wang, et al. that didn't provide enough information.

None of the studies provided information to know if the allocation to different experimental groups was concealed, if animals were randomly housed, or if outcomes were randomly assessed. Caregivers and investigators blinding was only mentioned in K. Bretland, et al. and P. Guo, et al.'s work. Seven studies have mentioned that the outcome assessor was blinded [20,27–32], and all studies were free from incomplete outcome data and selective outcome reporting bias as shown in Fig. 3.

4.4. Overview of outcomes

All the following mentioned results were significant, and a more detailed summary of these findings is provided below in Table 2.

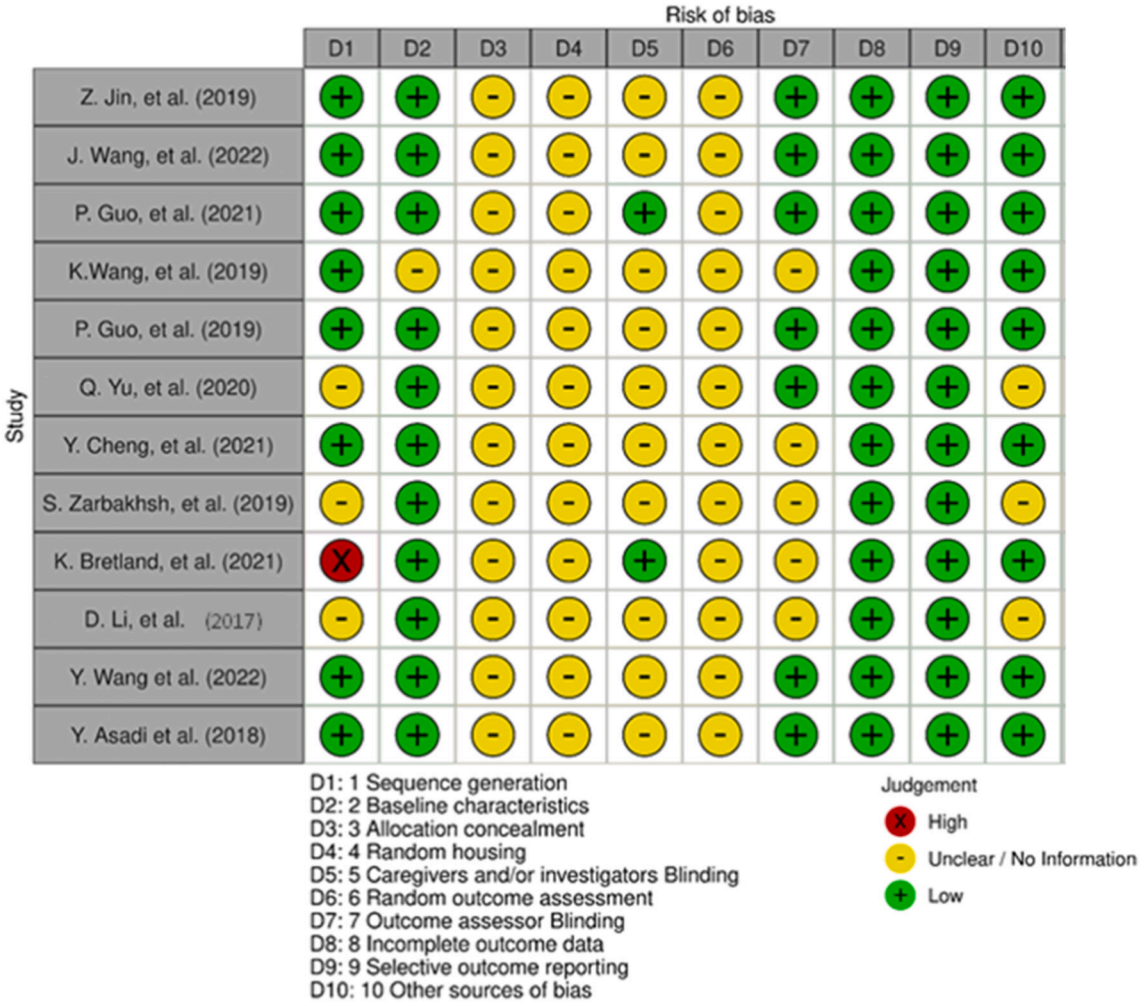

Fig. 2. "Traffic light" plots of the domain-level judgments for each individual result.

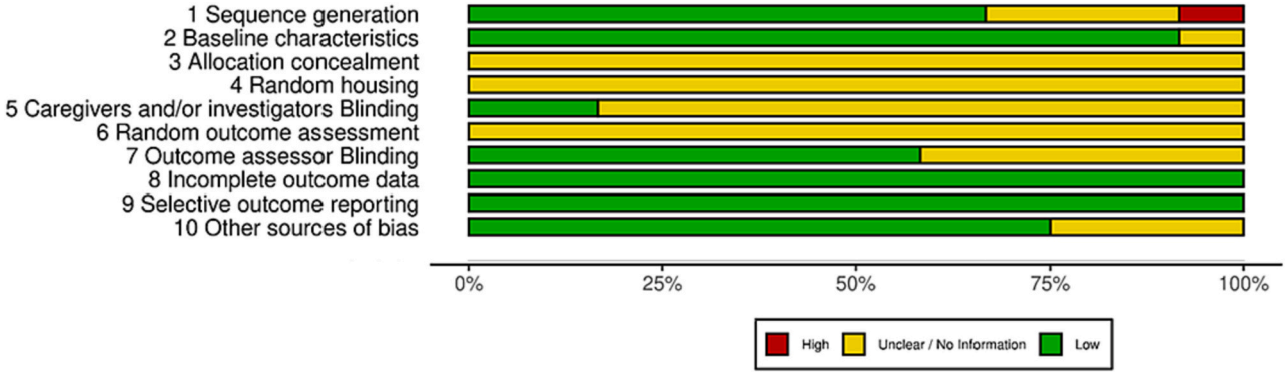

Fig. 3. Weighted bar plots of the distribution of risk-of-bias judgments within each bias domain.

4.4.1. Cerebral Ischemia

Cerebral Ischemic stroke is a serious condition frequently faced during perioperative period, cardiopulmonary resuscitation, and in elderly population [33]. Reperfusion after ischemia often leads to neuronal damage, incomplete restoration of blood flow to ischemic areas, BBB disruption increasing its permeability, which causes an increase in brain water content and brain edema [34]. Inflammation plays a crucial role in the ischemia/reperfusion (I/R) process, due to excessive activation and infiltration of immune cells and cytokines through the BBB, mitochondrial damage, oxidative stress, and cell apoptosis [35].

Q. Yu, et al. found that irisin injected once per day for three days before surgery of middle cerebral artery occlusion (MCAO), intraperitoneally at a dose of 50 or 100 mg/kg could promote motor and learning functions after I/R injury in Sprague Dawley rats It could also reduce MCAO-induced neuronal damage, and infarct volume, by down-regulating the expression of TLR4, MyD88, and NF-κB in the hippocampus which is activated after I/R injury [30].

Similarly, P. Guo, et al. found that 10 μg/kg of irisin injected intravenously in Sprague Dawley rats, once 30 min before MCAO, could reduce MCAO-induced neurological deficit, reduce brain water content,

infarcted region volume and interstitial edema, reduce BBB permeability and injury, and downregulate the expression of Matrix Metalloproteinase-9 MMP-9 whose activity contributes to BBB destruction in I/R injury [29].

Z. Jin, et al. also found that irisin injected intravenously in C57BL/6 mice at a single dose of 10 μg/kg 30 min after global cerebral ischemia/reperfusion (I/R) induction could attenuate the neurological function deficit and neuronal damage induced by cerebral I/R injury, decreased brain water content BWC, reduce cerebral I/R-induced apoptosis, cerebral I/R-induced inflammation and expression of inflammatory cytokines TNF-α and IL-1β while significantly enhancing the expression of Notch1, NICD, and Hes 1 [27].

Y. Assadi, et al. found that irisin injection into the lateral ventricle of Swiss albino mice, at an optimal dose of 7.5 μg/kg immediately after MCAO, was able to reduces infarct size and improves neurological outcomes, protects the brain against edema formation, reduces MCAO induced apoptosis in the cortex of cerebral ischemia, increases expression of BDNF, downregulates Bax and Caspase-3 pro-apoptotic proteins and upregulates Bcl-2 anti-apoptotic protein, but did not alter MCAO induced BBB interruption [32].

Finally, D. Li, et al. found that injecting C57BL/6 J mice intravenously, with 0.2 μg/g body weight of irisin, 30 min after MCAO protects against neuronal injury, reducing brain infarct, MCAO-induced neurological deficit and decline in body weight. Irisin Treatment was also found to inhibit post-ischemic neuroinflammation by reducing microglia activation, infiltrating neutrophils and downregulating the expression of TNF-a and IL-6, and reducing oxidative stress in the peri-infarct brain region. Interestingly, these effects were suppressed by Akt signaling pathway inhibitors (U0126 and MK-2206) and by the injection of irisin-neutralizing antibody post-exercise [36].

4.4.2. Intracerebral Hemorrhage (ICH)

The sudden rupture of blood vessels after ICH stroke leads to the formation of a huge hematoma, to intracranial hypertension and neurological deterioration [37]. As a result, red blood cells debris trigger a multitude of problems like neuroinflammation, oxidative stress, neuronal apoptosis, and BBB disruption [38].

Y. Wang, et al. administered 250 μg/kg of irisin (optimal dose) intranasally in C57BL/6 mice, 30 min after ICH induction. Irisin treatment could improve short and long-term neurobehavioral outcomes and reduce brain edema at 24 and 72 h after ICH. It alleviated neuronal apoptosis, reducing the levels of pro-apoptotic markers and increasing the levels of pro-survival markers. It attenuated neuroinflammation, since it could inhibit microglia and macrophage activation, neutrophil infiltration, and the expression of IL-1β, increasing the anti-inflammatory M2 phenotype of microglia/macrophage. These neuroprotective effects of irisin were abolished after the administration of Cilengitide, an integrin aVß5 inhibitor, or dorsomorphin, a selective AMPK inhibitor, leading them to conclude that irisin could act in part through the integrin αVβ5/AMPK signaling pathway after ICH [20].

4.4.3. Traumatic Brain Injury (TBI)

BBB disruption and cerebrovascular cells apoptosis caused by TBI can cause brain edema, oxidative stress, mitochondrial dysfunction and inflammatory response leading to more damage and injury in the brain [39].

P. Guo, et al. injected C57BL/6 J mice intravenously with 10 μg/kg of irisin, immediately after TBI impact. They found that irisin was able to reduce neurological damage after TBI and BBB destruction. It inhibited neuroinflammation by reducing proinflammatory cytokines and increasing anti-inflammatory cytokines, and oxidative stress by reducing reactive oxygen species ROS production, and enhancing anti-oxidative stress activity. It reduced mitochondrial apoptosis of vascular endothelial cells in the brain tissue, it increased the expression of Uncoupling proteins UCP2 which can regulate mitochondrial number, mitochondrial membrane potential (MMP), and the generation of oxygen free radicals. These neuroprotective effects of irisin were suppressed in UCP2 knockout mice UCP2−/−, leading to the conclusion that irisin could protect from BBB disruption and exert its neuroprotection by increasing the expression of UCP2 on the mitochondrial membrane [31].

4.4.4. Alzheimer's Disease (AD)

Major neuropathological hallmark of AD and other dementias are tauopathy, which is the hyperphosphorylation of tau, and its assembly into damaging neurofibrillary tangles, and the accumulation of misfolded proteins like extracellular amyloid beta (Aβ). This triggers neuroinflammatory response and exacerbates neuronal injury and degeneration [40].

K. Bretland, et al. administered four weekly injections of irisin at a dose of 100 μg/kg, intraperitoneally, in htau mice on a C57BL/6 J background. They found that irisin could reduce hippocampal ptau levels, TNFα levels, peripheral inflammation and neuroinflammation. These results were only seen in female htau mice, but not in male htau mice where irisin exacerbated both neural and systemic inflammation [26].

4.4.5. Parkinson's Disease (PD)

Parkinson's Disease is a chronic neurodegenerative disease manifested by the progressive deterioration of motor functions, due to dopaminergic neuronal loss in the substantia nigra pars compacta (SNpc), in addition to the accumulation of misfolded α-Synuclein, triggering neuronal dysfunction, neuroinflammation and ultimately neurodegeneration [41].

S. Zarbakhsh, et al. injected Wistar rats with 50 nm/ml of irisin, intraperitoneally, for 7 days after PD induction by MPTP toxin. They found that irisin was able to improve motor function related to the activity of basal ganglia and the dopaminergic system. It protected DA neurons from MPTP-induced damage, and reduced the number of apoptotic cells and neurodegeneration. It also promoted the migration of stem cells to the injured substantia nigra pars compacta (SNpc), and their differentiation to dopaminergic neurons [42].

4.4.6. Sepsis-Associated Encephalopathy (SAE)

Sepsis-associated encephalopathy (SAE) is the diffuse cerebral dysfunction caused by the inflammatory response to various infected bodies in the brain. It leads to changes in the BBB permeability, overproduction of reactive oxygen sepsis ROS, oxidative stress, neuroinflammation and neuronal damage [43].

J. Wang, et al. injected C57BL/6 J mice with 250 μg/kg of irisin, intravenously, once a day for 3 consecutive days. SAE was induced by cecal ligation and puncture (CLP). They found that irisin reduced sepsis-induced cognitive dysfunction and neurological deficits in CLP mice, protected against the degeneration of hippocampal neurons, and inhibited the production of ROS. It attenuated BBB permeability, microglial activation and neuroinflammation by inhibiting ferroptosis. This neuroprotective effect was dependent on the activation of Nrf2 which is a transcription factor implicated in mitochondrial oxidative stress and ferroptosis [28].

4.4.7. Diabetes Mellitus (DM)

Diabetes mellitus is a chronic metabolic disorder, where the liver produces more glucose, while the pancreas produces less insulin, resulting in hyperglycemia. This poor glycemic control has many effects on the brain, resulting in memory and attention deficit, and cognitive decline overtime [44]. Studies have shown that activated astrocytes induce a neuroinflammatory response in the hippocampus of diabetic mice, leading to neuronal damage [45].

K. Wang, et al. injected C57BL/6 J streptozotocin-induced diabetic mice intraperitoneally with 0.5 mg/kg/day of irisin, daily for three weeks. They found that irisin could improve the memory and cognitive deficiency in diabetic mice, inhibited the increase of GFAP (Glial

fibrillary acidic protein) related to astrocyte activation, and prevented synaptic protein loss. It was also able to attenuate neuroinflammation by reducing IL-1β and IL-6 levels, and finally reduced the activation of P38, STAT3, and NFκB proteins in the brain hippocampal tissues which are involved in the inflammatory cytokine cascade [46].

8. Status Epilepticus:

Epilepsy is a complex form of neuroencephalopathy characterized by neuronal injury, and an increased level of reactive oxygen species ROS due to mitochondrial dysfunction and oxidative stress, which in turn contribute to the formation of epileptic networks and cognitive damage [47].

Y. Cheng, et al. injected Sprague Dawley rats with 49.5 mg/kg of irisin into the lateral ventricle, 30 min before Kainic Acid administration, used to induce Status Epilepticus. Irisin was found to increase the expression of Brain-Derived Neurotrophic Factor BDNF and Uncoupling Protein 2 UCP2, a mitochondrial inner membrane known to have neuroprotective effects. It alleviated apoptosis and neuronal injury, by reducing pro-apoptotic markers. It also reduced mitophagy, ROS levels and oxidative stress. However, irisin's neuroprotective effects are reversed by the administration of Genipin, a UCP2 inhibitor, leading them to conclude that irisin exerts its neuroprotective effect through the BDNF/UCP2 pathway [48].

5. Discussion

This systematic review aimed to assess the neuroprotective effect of irisin injected in rodent animal models, specifically on mitigating neuroinflammation and counteracting neurodegeneration. The search was conducted following Prisma guidelines by searching the following three databases PubMed, Embase, and google scholar, using combinations related to irisin, the brain, neuroinflammation, and neurodegeneration. A total of 161 study was primarily identified, but only 12 met our eligibility criteria, and their results were therefore included and retrieved for qualitative synthesis.

Interestingly, all of the included studies shared the same expected outcome, which is summarized in Fig. 4. Irisin could significantly protect neuronal cells from different harmful conditions that will be developed later, by reducing inflammatory processes in the brain, like microglial and astrocyte activation, and the release of proinflammatory cytokines. It was also found to reduce oxidative stress, mitochondrial dysfunction, and the production of reactive oxygen species ROS. Furthermore, it corrected blood-brain barrier disruption resulting from injury and inflammation. As a result, irisin reduced neuronal damage and apoptosis and was shown to prevent neurotoxicity and neurodegeneration.

Traumatic brain and spinal cord injury, autoimmunity, infections, toxic metabolites, diseases, stress, and aging are all triggers that can activate these cells to start producing proinflammatory cytokines (IL-1, IL-6, and TNF-α), chemokines, reactive oxygen species ROS, and secondary messengers [39]. This response can have a plethora of immune, physiological, biochemical, and behavioral consequences, leading to the recruitment of more immune cells. This leads to an increase in the blood-brain barrier's permeability, causing brain edema, tissue damage, and eventually neuronal death [49,3]. The majority of the scientific literature focuses on the pathological consequences of neuroinflammation, due to its numerous detrimental negative outcomes. Nevertheless, neuroinflammation signaling can also have positive aspects, as it assures the functional communication between the immune and nervous systems via the secreted cytokines, it has a critical role in brain development, memory, and learning processes, and promotes tissue repair and recovery after a CNS injury [49]. However, whenever the balance between the resting and activated state of the brain's immune cells is disturbed, chronic permanent inflammation can take place. This can be seen in the case of neurodegenerative diseases, where the presence of misfolded proteins and other pathogenic metabolites can constantly trigger an increased activation of glial cells. This leads to an excessive release of immune mediators, which ultimately results in neurotoxicity, aggravating neuronal injury and apoptosis. This creates the famous never-ending vicious cycle where neuroinflammation leads to neurodegeneration, and in turn, neurodegeneration exacerbates neuroinflammation [3,49]. Therefore, a therapeutic strategy that can target both anti-inflammation and anti-apoptosis would be essential to improve the treatment of neurodegeneration and neuroinflammation.

Irisin, is a novel myokine secreted by muscles during physical

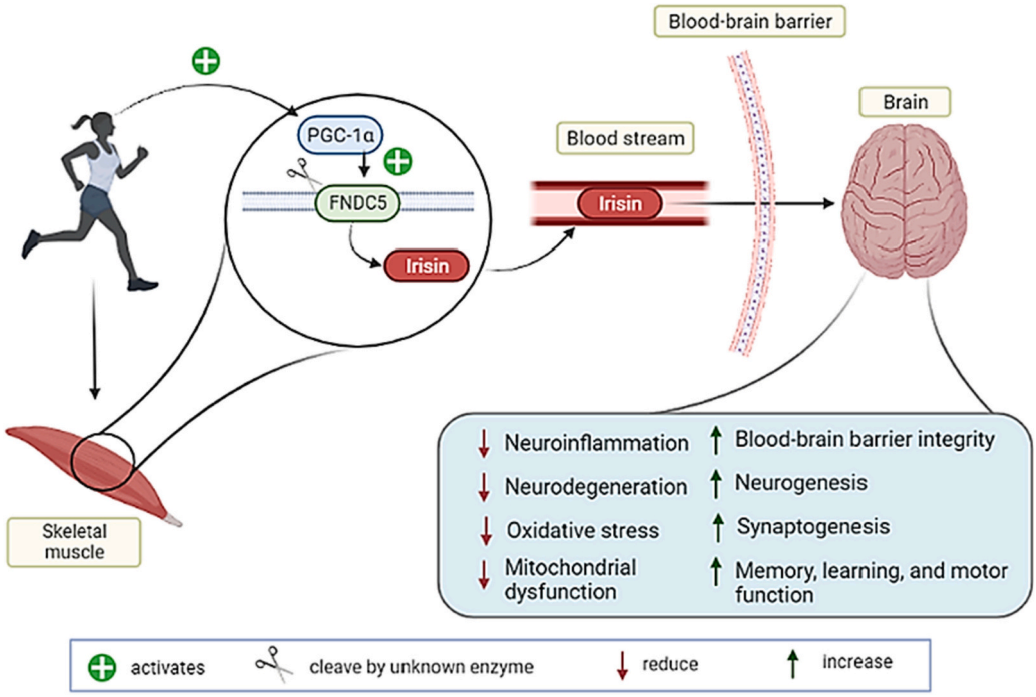

Fig. 4. Physical exercise induces PGC-1a activation in skeletal muscles, which in turn activates FNDC5 who's cleaved by an unknown enzyme to release irisin into the bloodstream. Once irisin has reached the brain by crossing the blood-brain barrier, it exerts its neuroprotective effect. (Created using Bio Render).

exercise. Physical exercise's beneficial impact on the brain has long been known and studied. It increases cerebral blood flow, promotes neuronal survival and synaptogenesis, and reduces neuroinflammation and the risk of developing neurological and neuropsychological disorders. In addition, it is one of the few known stimuli capable of inducing de novo neurogenesis [22,50,51].

Irisin peptide is highly conserved across mammals and is 100 % identical in mice, rats and humans [19]. That's why all of the experimental studies that matched our intervention (injection of exogenous irisin) were performed on rodents as a first step before preclinical and clinical application.

Neuroinflammation in the included studies was assessed mainly by measuring the levels of proinflammatory cytokines (IL-1, IL-6, and TNF-α) by Western Blot [20,26], ELISA [28,31,36,44,46,52–54], and qRT-PCR [27] Furthermore, microglial activation was assessed by immunofluorescence using antibodies against CD68 and Iba-1 [20,28], and astrocyte activation assessed using GFAP marker by western blot [46]. Data suggested that irisin could significantly mitigate neuroinflammation by reducing microglial and astrocytic activation, as well as the concentration of proinflammatory cytokines that can cause neuronal injury while increasing anti-inflammatory cytokines (IL-4 and IL-10) and protective switch to anti-inflammatory phenotype in glial cells. These results are supported by K. Wang's results in a study conducted on cultured neurons, where irisin was found to reduce neuroinflammation by regulating astrocytes [55] as well as Z. Jin et al.'s work where irisin could reduce the mRNA levels of TNF-α and IL-1β in the hippocampus after cerebral I/R injury and in HT22 cells after oxygen-glucose deprivation OGD challenge [27].

As a result, irisin was also shown to reduce neuronal apoptosis, which was assessed by TUNEL staining [20,27,32,42], Nissl and Fluoro-Jade C (FJC) staining [28,48] and by downregulating the expression of pro-apoptotic proteins (Bax and activated Caspase-3) measured by western blot [32,48], and upregulating anti-apoptotic proteins (Bcl-2 and caspase-3) [32,48]. Irisin could also attenuate neuronal damage, for example, the infarct size after Brain Ischemia was greatly diminished following irisin treatment [27,29,30,32,36], and prevent synaptic loss [46]. These results are supported by D. Li et al.'s result where irisin protected cultured neurons from oxygen-glucose deprivation OGD-induced injury in vitro [36], and Z. Jin et al. where irisin could reduce the number of apoptotic HT22 cells after OGD treatment [27].

In addition, irisin was found to protect the blood-brain barrier (BBB) from injury-induced disruption. It was assessed by quantifying the Evans Blue EB leakage into ischemic brain tissue [28,29,32], and by enhancing the expressions of key proteins that constitute BBB's tight junctions (occludin, claudin-5, and ZO-1) [31]. As a result of reducing BBB's permeability, irisin could also reduce brain edema, assessed by measuring the percent of brain water content (BWC%) [20,27,29,32]. These results are supported by a body of evidence that suggests that regular exercise is capable of reducing BBB permeability and improving cerebral endothelial function by promoting the stability of tight junctions TJ [56–58].

Furthermore, included data also supported that irisin significantly reduced oxidative stress and the production of ROS and the levels of NO2− Tyr, superoxide anion, 4-HNE, MDA, and Mito/SOX [28,31,48], and enhanced anti-oxidative stress assessed by quantifying the expressions of Nrf2 and its downstream proteins NQO-1, HO-1, SOD, and GSH-PX [28,31]. These results are supported by those of Y. Lu et al., where physical exercise, the inducer of irisin's production, was shown to suppress oxidative damage, reduced peroxynitrite production, lipid peroxidation, and oxidized DNA damage in rat models of sporadic Alzheimer's Disease [59].

Another interesting finding was that irisin could lower the levels of phosphorylated tau in the hippocampus of pre-symptomatic female htau mice [26], and protect dopaminergic neurons from MPTP toxicity in rat models of Parkinson's disease [42]. This highlights the importance of physical exercise for preventing and slowing down the onset of symptoms and progression of these neurodegenerative diseases. This was supported by A. De La Rosa's review summarizing physical exercise's protective effects on brain function, both in humans and animals, on modulating amyloid-beta turnover, reducing inflammation and neurodegeneration, stimulating production and release of neurotrophins, and improving cognition [60].

Additional studies support irisin's neuroprotective effect. As mentioned in M. Islam et al.'s study on mice, overall cognitive function was deteriorated in Fndc5/irisin knock-out (KO) mice, while elevating the levels of central irisin was capable of improving the cognitive deficit and neuropathology in AD mouse models [72]. It's also worth mentioning T. Kam et al.'s work on mice where irisin was shown to protect neuronal cells against neurodegeneration in PD, by preventing the accumulation of pathological α-synuclein [73].

5.1. Regulatory pathways

Many mechanisms were suggested by these studies to be responsible for this neuroprotective effect and, are summarized in Fig. 5.

First, data suggested that irisin's beneficial effect was derived from its ability to increase the expression of brain-derived neurotrophic factor BDNF in brain tissues [32,48]. BDNF is one of the most abundant neurotrophic factors, that supports the differentiation and survival of neuronal cells and microglia and regulates neuroplasticity, neurogenesis, and synaptogenesis [61]. This finding is supported by the study by Wrann et al. which showed that FNDC5, the precursor to irisin, increases BDNF gene expression in cortical cell cultures and mice's hippocampus after irisin's intravenous injection [62]. Thus irisin, by increasing BDNF's expression, promotes all of these properties suggesting a possible neuroprotective effect of the FNDC5/irisin/BDNF pathway.

Furthermore, BDNF regulates the expression of UCP2, one of its downstream proteins. UCP2 is a mitochondrial inner membrane protein and was also suggested to play a role in irisin's effect on the brain due to its known role in neuroprotection. It promotes the survival of mitochondria and neurons, sends out stress signals in case of injury, reduces mitochondrial membrane potential MMP, thus reducing the production of ROS and oxidative stress [63,64]. When Y. Cheng et al. used genipin, which is an inhibitor of UCP2, they found that irisin's beneficial effect was partially reversed. The same result was obtained by P. Guo et al. who found that irisin's neuroprotective effects were absent in UCP2 knockout mice [31,48]. This suggests that irisin could exert its neuroprotective effect by promoting the expression of UCP2 on mitochondrial membranes of neurons as a result of activating the FNDC5/irisin/BDNF pathway. The same results were found by Lourenco et al., where adenoviral-mediated expression of irisin increased the expression and accumulation of BDNF in hippocampal cell cultures [74].

The second mechanism proposed was via activation of the Akt and ERK1/2 signaling pathways. ERK1/2 (extracellular signal-regulated kinase 1/2) cascade and Akt signaling pathway regulate a wide range of cellular processes, primarily proliferation, differentiation, and survival, as well as apoptosis and stress responses [65,66]. D. Li et al. have found that irisin could enhance the phosphorylation of ERK1/2 and Akt in mice brain tissues, and that irisin's neuroprotective effect was reduced when they used specific inhibitors of Akt and ERK1/2 [36].

Third, the Notch signaling pathway was also suggested to be involved in irisin's effect. It is a receptor expressed mainly in the cortex and hippocampus. This signaling pathway regulates gliogenesis, neuronal differentiation, and microglial activation both in normal brain or pathological conditions, and in determining neuronal fate, proliferation, and apoptosis [67]. Z. Jin et al. found that irisin not only enhanced the expression of Notch but also of NICD, which is the Notch intracellular domain (NICD) cleaved by γ-secretase after Notch activation, as well as the expression of Hes 1, one of Notch's downstream proteins. They also found that irisin's neuroprotective effect was reversed after the application of a γ-secretase inhibitor which blocks

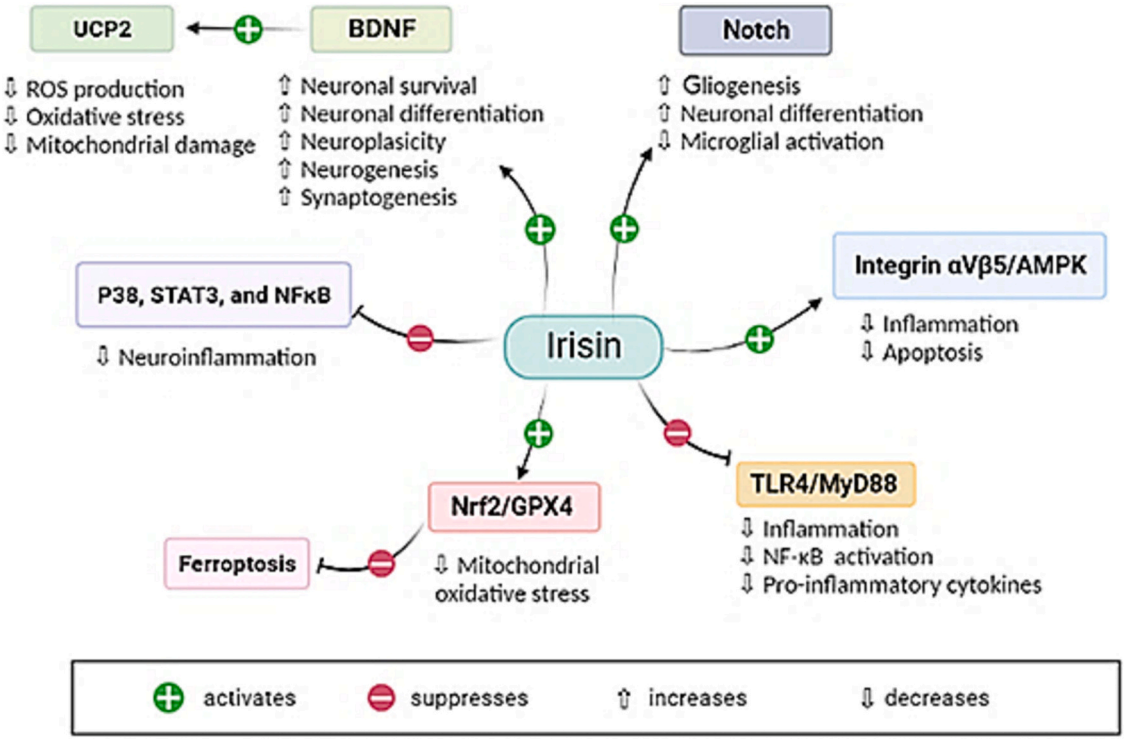

Fig. 5. Summary of suggested signaling pathways that could be involved in irisin's neuroprotection. (Created using Bio Render).

Notch activation and cleavage, confirming that the Notch signaling pathway is also involved in irisin's protective effect on the brain [27].

The fourth suggested pathway was integrin αVβ5/AMPK. Integrin αVβ5 was identified in osteocytes and intestinal epithelial cells as a functional receptor of irisin, and AMPK signaling is a downstream pathway targeted by irisin after binding to integrin αVβ5, which could regulate energy metabolism, mitigate apoptosis, and reduce inflammation in various pathological conditions [20]. Y. Wang et al. found that irisin significantly enhanced the expression of integrin αVβ5, p-AMPK following ICH, and its neuroprotective effects were abolished by both integrin αVβ5 inhibitor Cilengitide and AMPK inhibitor Dorsomorphin. Furthermore, they also found that irisin co-localized on microglia/macrophages with integrin αVβ5 and that they both shared a similar time course of expression, which led them to suggest that irisin could bind to integrin αVβ5 receptor and exert its effect via the αVβ5/AMPK signaling pathway [20].

The fifth mechanism of action was suggested by Q. Yu et al. through suppressing TLR4/MyD88 pathway. Toll Like Receptor 4 Toll/IL-1 receptor domain (TLR4) and myeloid differentiation factor 88 (MyD88) play a key role in the inflammatory response, they activate the transcription factors NF-κB, which would initiate the inflammatory cascade and the production of pro-inflammatory cytokines [68]. Q. Yu et al. found that irisin could reduce the expression of TLR4 and MyD88, and led to decreased activation of NF-κB, suggesting that irisin could reduce neuroinflammation by downregulate the TLR4/MyD88/NF-κB pathway [30].

Another suggested mechanism is suppressing ferroptosis via activation of the Nrf2/GPX4 signal axis. Ferroptosis is the accumulation and overload of iron in the cell, leading to its death. It's accompanied by glutathione (GSH) depletion, inactivation of glutathione peroxidase 4 (GPX4), lipid peroxidation, and mitochondrial damage [28]. On the other hand, Nrf2 is known to play a protective role against mitochondrial oxidative stress and ferroptosis [54]. J. Wang et al. found that Irisin could significantly promote the expression of GPX4, GSH, and Nrf2 while reducing hippocampus ferroptosis and microglial activation. Irisin-mediated anti-ferroptosis was suppressed in Nrf2−/− mice, which led them to suggest that irisin exerts its neuroprotective effect by suppressing hippocampus ferroptosis via the Nrf2/GPX4 signaling pathway [28].

The last mechanism suggested to be responsible for irisin's neuroprotective effect is related to P38, STAT3, and NFκB. The phosphorylation of P38 and STAT3 and the activation of NFκB are known to be closely involved in the inflammatory response and many cytokine cascades, including IL-6, IL-10, and TNFα [53,69]. In their study on diabetic mice, K. Wang et al. found that irisin could reduce the activation of p38, STAT3, and NFκB proteins in brain hippocampal tissues, suggesting that irisin could exert its neuroprotective effect by regulating the function of P38, STAT3, and NFκB [46].

Hence, not only does irisin target multiple organs, but it was also found to target multiple pathways and cellular mechanisms. This pleiotropic feature further expands its crucial importance in maintaining healthy cellular reactions as well as its potential therapeutic applications in managing a wide spectrum of conditions, including metabolic disorders, neurodegenerative diseases, and multifactorial diseases. However, these mechanisms need to be further clarified. For example, the enzyme that cleaves FNDC5 to release irisin, as well as irisin's receptor in the brain has yet to be discovered. The molecular pathways leading to irisin effect in gene modulation and protein phosphorylation are also not revealed. Therefore, future studies should focus on identifying these missing components, to better understand irisin's mechanism of action.

Together, these findings also suggest the potential application of irisin as a biomarker for the early identification of neurodegenerative diseases and other brain-related pathologies, as circulating irisin level was found to be significantly decreased in the serum and CSF of both human patients and animals suffering from these conditions, compared to normal controls [21,70].

This is the first systematic review summarizing the neuroprotective effect of irisin's injection in animal models, however, some included studies had certain limitations that could affect the reproduction and reliability of their results. For example, irisin's effect was mainly studied in the hippocampus, and all of the included studies focused on brain-related conditions and a limited number of neurodegenerative

diseases. Another limitation was that most of these studies were performed only on male animal models, yet sex differences are very well-known regarding the brain's physiology, physiological response to physical exercise, BDNF signaling, and irisin's sensitivity, which can all be affected by sex-hormone. Finally, as shown is Table 2, each study used a different dosage, route of administration, and frequency of irisin's injection, the studies were heterogenous which prohibited us from conducting a meta-analysis of extracted data.

Therefore, further studies should focus on finding the optimal dose and administration route of irisin. In addition, irisin's expression and effect in other important brain regions like the prefrontal cortex should also be addressed, as well as other types of injuries like spinal cord injury, Huntington's disease, and Amyotrophic lateral sclerosis. Females, as well as different age groups, should also be included.

Furthermore, studies with positive results tend to be published more than those with negative ones, which could've led to missing some publications. In addition, one of our inclusion criteria was that studies should be published in English, which could've also led to a publication bias, as one potentially relevant study published in another language (i.e., Chinese) was excluded [71]. Finally, some studies were only composed of an abstract and were therefore excluded too.

6. Conclusion

This systematic review demonstrates that irisin's injection can alleviate neuroinflammation and counteract neurodegeneration in rodent models by activating or suppressing a combination of pathways. It could also reduce oxidative stress, blood-brain barrier disruption, and the accumulation of misfolded proteins in neurodegenerative diseases like Alzheimer's and Parkinson's disease. Furthermore, it improved memory, learning, sensory and motor functions that could be impaired after an injury or disease.

However, many questions still need to be answered about its mechanism of action before translating it into clinical practice and drug discovery. Meanwhile, the neuroprotective effect of this novel exercise-induced myokine clearly emphasizes how physical exercise is a free natural remedy desperately needed in sedentary aging communities like ours.

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CRediT authorship contribution statement

Najwane Said Sadier: Conceptualization, Project administration, Writing – original draft. **Farah El Hajjar:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Amani Al Khayat Al Sabouri:** Investigation, Writing – review & editing. **Linda Abou Abbas:** Investigation, Writing – original draft, Writing – review & editing. **Natalia Siomava:** Investigation, Writing – original draft. **Abdulmajeed G. Almutary:** Investigation, Project administration, Writing – original draft. **Murtaza M. Tambuwala:** Conceptualization, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

Data will be made available on request.

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