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Potential effect of Irisin on sarcopenia: a systematic review

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Abstract

Objective Sarcopenia, a progressive musculoskeletal disorder associated with aging, is characterized by the deterioration of muscle mass, strength, and physical performance. This condition significantly increases the risk of debilitating consequences including functional impairment, diminished life quality, and increased mortality. With the progress of aging, it will affect a large number of people in the world and bring many problems. Despite its clinical significance, there are no medicine used to treatment sarcopenia by FDA approval in clinical. This systematic review synthesizes current evidence on the diagnostic and therapeutic potential of irisin—a myokine induced by exercise—in sarcopenia, aiming to address two key questions: (1) Can irisin serve as a reliable biomarker for sarcopenia diagnosis? (2) Does irisin hold promise as a therapeutic agent for sarcopenia management?

Methods A comprehensive literature search was conducted across multiple databases (Web of Science, PubMed, Cochrane Library, and Embase) to examine the relationship between irisin and sarcopenia. Eligible studies meeting our inclusion criteria underwent rigorous quality assessment.

Result 364 studies were identified, of which only 21 met the inclusion criteria—12 involving human studies and 9 involving animal and cell experiments. In human studies, irisin may serve as a potential diagnostic marker for sarcopenia in the elderly and postmenopausal women. In addition, as a myokine of exercise induced, increased circulating levels of irisin may enhanced skeletal muscle mass. Moreover, animal and cellular experiments suggest that increased levels of irisin help improve muscle mass.

Conclusion In conclusion, this review indicates that irisin has potential therapeutic effects for sarcopenia and may become a promising treatment for sarcopenia in the future. However, there is currently a lack of high-quality studies on the use of irisin in treating sarcopenia, and the relevant mechanisms of action are not yet clear. Therefore, more studies are needed to clarify the relationship between irisin and sarcopenia in the future.

Keywords Sarcopenia, Irisin, Systematic review, Treatment

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Introduction

Sarcopenia, first described by Rosenberg in 1989, is an age-related progressing disorder characterized by the loss of muscle mass and strength, and poor physical performance [1, 2]. Epidemiological studies reveal its prevalence increases substantially with age, affecting up to 29% of community-dwelling older adults and 11–50% of octogenarians [3]. It is projected that approximately 25% of Asia's population will be aged 60 years or older, with individuals aged 80 years and above comprising one-fifth of this demographic group [4]. These trends underscore sarcopenia as a critical public health challenge requiring urgent strategies for early detection and prevention. To standardize clinical management, the European Working Group on Sarcopenia in Older People (EWGSOP) established d consensus criteria in 2010 (EWGSOP1) and revised them in 2019 (EWGSOP2), emphasizing the integration of muscle mass, strength, and physical performance metrics [5, 6]. Pathophysiologically, sarcopenia arises from multifactorial mechanisms, including mitochondrial dysfunction, neuromuscular junction degeneration, age-related endocrine alterations and chronic low-grade inflammation. These mechanisms collectively contribute to detrimental clinical consequences including increased fall risk, functional disability, frailty progression, and elevated mortality [2]. Notably, no pharmacological treatments have yet received FDA approval for sarcopenia management, highlighting the need for effective interventions to support healthy aging [7]. Researchers are exploring exerkines like IL-6, TNF-α, FGF21and irisin for their potential to prevent muscle loss and boost physical performance [8]. Among these, Among these, irisin, a myokine derived from the cleavage of fibronectin type III domain-containing protein 5 (FNDC5), has emerged as a promising candidate [1]. A study revealed that aging is associated with reduced mRNA and protein expression levels of irisin and its precursor FNDC5 in skeletal muscle. Administration of recombinant irisin protein to aged or senescent mice demonstrated therapeutic efficacy against sarcopenia, as evidenced by improvements in grip strength, muscle mass, fiber size, and molecular phenotypes. These findings highlight the critical role of irisin in preserving muscle physiology and systemic energy homeostasis during aging, positioning it as a promising strategy for treating age-related metabolic disorders [9].

As an exercise-induced molecule, irisin has been proposed as a potential biomarker for sarcopenia and muscle damage due to its strong positive correlation with skeletal muscle mass and strength [10, 11]. Beyond its diagnostic potential, irisin enhances muscular energy metabolism, thereby improving contractile function and endurance [10]. It also exerts antioxidative effects, safeguarding skeletal muscle against oxidative damage—a critical mechanism for preserving muscle homeostasis and counteracting atrophy [10]. Experimental studies demonstrate irisin's regenerative capacity: In murine models of muscle injury, irisin activates satellite cells and regulates protein synthesis/degradation balance, facilitating tissue repair and hypertrophy [12]. Base on the relation between sarcopenia and irisin, these results indicate that irisin has a certain effect on the treatment of sarcopenia. However, the mechanism of action of irisin in the treatment of sarcopenia has not been fully elucidated. This review systematically evaluates current evidence from preclinical and clinical studies on the irisin-sarcopenia relationship, aiming to to address two key questions: (1) Whether irisin can be used as a reliable diagnostic biomarker for sarcopenia; (2) the potential role of irisin in the prevention or treatment of sarcopenia.

Materials and methods

This systematic review adhered to the 2020 PRISMA guidelines [11] to evaluate irisin's role in sarcopenia [13]. The study protocol was registered on the INPLASY platform (ID: CRD42025646670; accessible at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42025646670). No clinical trial number was applicable.

Literature search strategy

A comprehensive search was performed conducted across four databases (Web of Science, PubMed, Cochrane, Embase) from inception through November 2024. The search strategy combined Medical Subject Headings (MeSH) and keywords using Boolean operators, "OR" or "AND". The Mesh term and key words were follows: Sarcopenia, sarcopenia, FNDC5 protein, fibronectin type III domain-containing protein 5 and Irisin. Search details information in four databases are provided in supplementary 1.

Eligibility criteria

Inclusion criteria were (1) study involve irisin on sarcopenia (2) containing human or animal study in sarcopenia (3) aging-related sarcopenia(4)English literature. Exclusion criteria include (1) duplicate, review, letters, commentaries, editorials, conference abstracts, meta-analyses. (2) non-aging related sarcopenia, such as CKD, COPD et al. (3) full text that was inaccessible.

Study selection and evaluation

All records by search were imported into the software Endnote X9 to organize the related literature and removal duplicates reference. Two authors (YXC and YFG) independently evaluated the title and abstract, and those that met the inclusion criteria were eventually included in this analysis. Disagreements will be reached through discussion with a third author.

Risk of bias evaluation

The Agency for Healthcare Research and Quality (AHRQ) scale was used to assess the quality of human studies, focusing on five key aspects: selection bias, performance bias, attrition bias, detection bias, and reporting bias [14]. For animal studies, the risk of bias was evaluated using the Systematic Review Centre for Laboratory Animal Experimentation's (SYRCLE) tool [15].

Data collection and extraction

A standardized information form was used to collect and report all data from in vitro and in vivo studies. Key details such as author, year, subject, sample, groups, and main outcomes were extracted. One researcher extracted the record data (YXC), another researcher (YFG) checked the records quality according the inclusion criteria. Discrepancies were solved by discussion with a third researcher (XBW).

Results

Study selection

All records search results in 364 articles from PubMed ($n=48$), Cochrane ($n=11$), Embase = 215, Web of science ($n=90$). (Fig. 1). There are 122 duplicated records were removal, 163 of records excluded (e.g. review, letters Editorial, conference abstract). Next, 79 full-text articles were screened, of which 58 were excluded for not meeting the inclusion criteria. Ultimately, 21 studies qualified for inclusion in the systematic review.

Potential effect of Irisin involve human studies

Of the 21 screened articles, 12 were about human studies (Table 1), including Chang et al. 2017 [11]; Park et al. 2019 [16]; Park et al. 2021 [17]; Alsaawi et al. 2022 [18]; Baek et al. 2022 [19]; Wang et al. 2022 [20]; Yen et al. 2022 [21]; Liang et al. 2023 [22]; Dawson-Hughes et al. 2024 [23]; Luis et al. 2024 [24]; Liu et al. 2024 [25]; Mendez et al. 2024 [26]. Furthermore, in Table 2, we show the change values of irisin under different interventions. Although no statistically significant changes in irisin before and after the intervention were seen in these

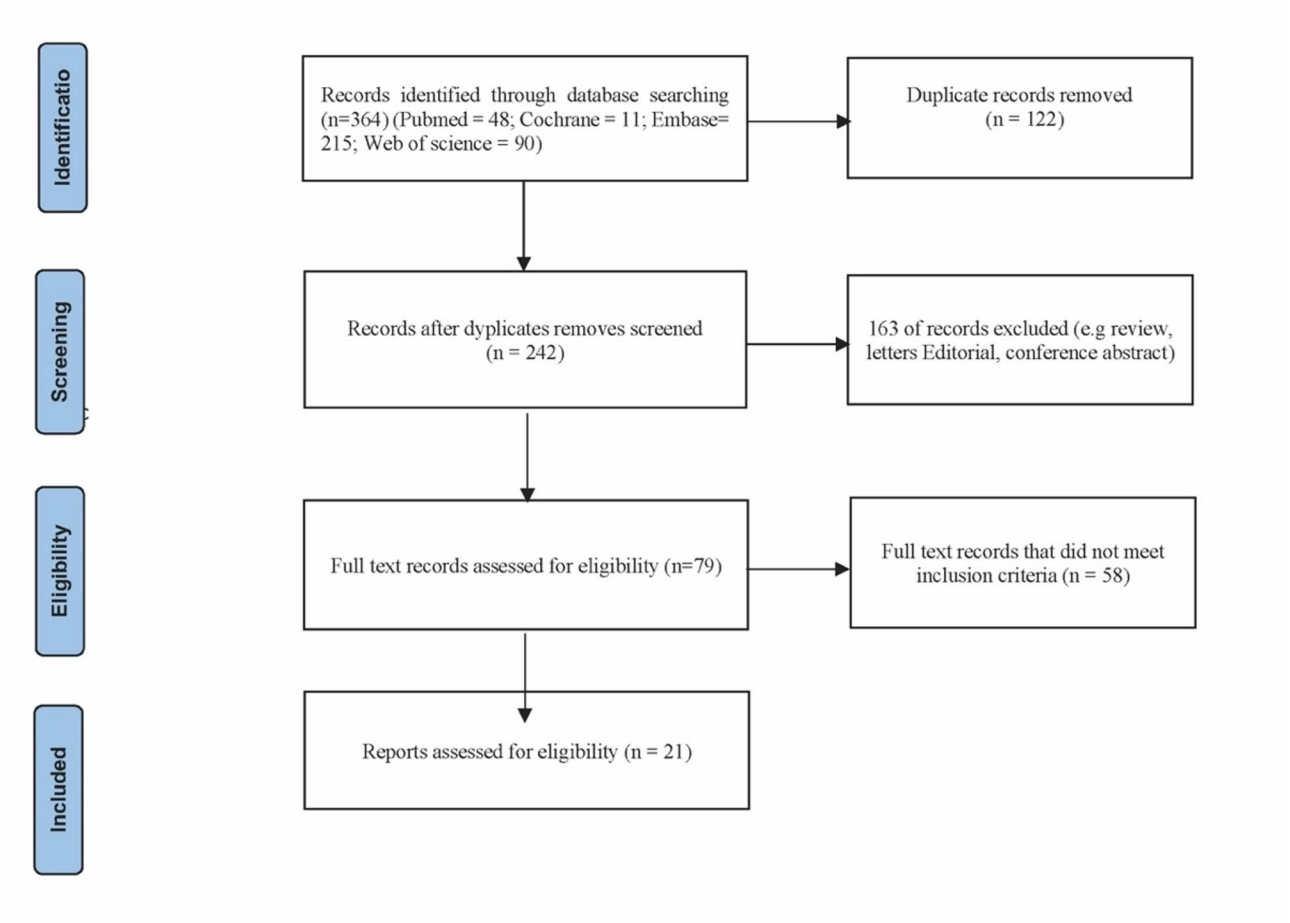

Fig. 1 The PRISMA flow chat describes the search process and literature screening process

Table 1 Overview of the literature involving human studies

Author/Year	Subject/Sample	Detection method	Groups	Main outcome
Chang 2017 [11]	Community dwelling Koreans/715	ELISA	Sarcopenia group/normal group	The patient with sarcopenia exhibited lower circulating irisin levels, suggesting its potential utility as a predictive biomarker for this condition.
Park 2019 [16]	Postmenopausal women/153	ELISA	Postmenopausal women/ young women	In postmenopausal women, serum irisin could potentially function as a diagnostic biomarker for sarcopenia.
Park 2021 [17]	Women aged ≥ 60 with sarcopenia/19	ELISA	No OA group/ OA group	Combined exercise has positive changes in physiological and morphological factors in elderly women with sarcopenia combined with OA.
Alsaawi 2022 [18]	60–85 years with or without sarcopenia/131	ELISA	Sarcopenia group/normal group	The prevalence of sarcopenia was high in elderly Arab women (19.8%), and the level of irisin in sarcopenia patients was significantly lower.
Baek 2022 [19]	Community-dwelling Koreans/143	ELISA	Non-Sarcopenia/ Sarcopenia	There was no significant correlation between serum irisin level and clinical muscle parameters.
Wang 2022 [20]	Sarcopenia patiens/422	ELISA	Men / Women	Higher levels of serum vitamin D were independently associated with increased irisin in women with sarcopenia but not in men.
Yen 2022 [21]	≥ 40 years old/99	ELISA	Non-Sarcopenia / Sarcopenia	Lower levels of skeletal muscle protein biomarkers - particularly creatine kinase and irisin - were found to be significantly associated with sarcopenia.
Liang 2023 [22]	Postmenopausal women/128	ELISA	T1/T2/T3	In postmenopausal women, reduced serum irisin levels were associated with an increased risk of falls, diminished muscle strength, and elevated cortical porosity.
Dawson-Hughes 2024 [23]	≥ 50 years old and older/26	ELISA	Placebo/Anamorelin	The levels of irisin, IL-6, or hsCRP were not changes in sarcopenia patients treated with anamorelin.
Luis 2024 [24]	Disease-related malnutrition/108	MILLIPLEX	Non-Sarcopenia/ Sarcopenia	irisin concentrations were closely associated with sarcopenia in patients with DRM.
Liu 2024 [25]	inpatients aged ≥ 65 years/55	ELISA	Frailty/Pre-frailty/Robust groups	Irisin concentrations were significantly lower in pre-frailty and frailty groups than in healthy controls.
Mendez 2024 [26]	Postmenopausal women/14	ELISA	Control group/ Grape group	Chair-to-standing speed, gait speed, and irisin levels were significantly improve in the grape group compared with the control group.

Note: OA, osteoarthritis. DRM, disease-related malnutrition

Table 2 Changes of Irisin parameters before and after intervention

Study	Group	Exercise Type	Duration	Irisin change Pre-Intervention	Irisin change Pre-Intervention
Park [17]	OSEG SEG	Complex exercise	15 weeks	1.69 ± 0.18 1.86 ± 0.40	2.38 ± 0.38 2.64 ± 0.79
Mendez [26]	Group Grape	Postmenopausal	6 weeks	3800pmol/L 3600pmol/L	3700pmol/L 3900pmol/L

SEG, sarcopenia group. OESG, osteoarthritis with sarcopenia group

two studies, circulating levels of irisin increased after the intervention. In addition, the values are approximate because no specific values were given in Mendez's study.

Chang conducted a cross-sectional study involving 715 Korean participants, revealing that the study population exhibited aging-related muscle atrophy and weakness. The results demonstrated that irisin concentrations were associated with appendicular lean mass/height^2 and handgrip strength in both men and women. Notably, individuals with sarcopenia had significantly lower irisin levels compared to those in the normal group. These findings suggest that reduced circulating irisin may serve as a sensitive biomarker for muscle weakness and atrophy, potentially aiding in the prediction of sarcopenia [11]. Similarly, the study by Park examined 153 postmenopausal women and confirmed lower irisin levels in sarcopenia patients. This association This association remained significant even after adjusting for confounding variables, supporting the potential utility of irisin as a biomarker for early detection and staging of sarcopenia [16]. Consistent with these findings, both Alsaawi [18] and Yen [21] similarly identified irisin as a promising diagnostic indicator for sarcopenia. Additionally, Luis reported that diminished serum irisin concentrations were correlated with sarcopenia in patients suffering from disease-related malnutrition, further reinforcing

this biomarker's clinical relevance [24]. Beyond its diagnostic potential, irisin plays a significant role in muscle-bone crosstalk. For instance, Liang's work highlighted that postmenopausal woman with decreased irisin levels faced a greater likelihood of falls and muscle impairment. Moreover, higher serum irisin concentrations were associated to improved cortical volumetric bone mineral density (Ct. vBMD) while lower levels correlated with elevated cortical porosity—a possible contributor to fracture susceptibility [22]. Skeletal muscle derived myokines are closely related to frailty and sarcopenia. Bioinformatics analyses identified leptin, AMPK, irisin, decorin, and myostatin as candidate biomarkers for frailty [25]. A longitudinal study further revealed that pre-frail and frail individuals exhibited markedly reduced irisin levels, alongside elevated leptin, AMPK, and myostatin levels compared to their robust counterparts [25]. However. conflicting evidence exists. Beak's analysis failed to establish a definitive connection between irisin and sarcopenia, suggesting that irisin may not accurately predict sarcopenia in the elderly [19]. The authors proposed that the negative results observed between irisin and sarcopenia may stem from the lack of precise definitions and standardized assessment methods for sarcopenia, and the variability in how sarcopenia is defined could be the fundamental reason for this unclear association [19]. Additionally, Wang et al. investigated the relationship between serum vitamin D levels and irisin concentrations in older adults with sarcopenia. Higher serum vitamin D levels were independently associated with increased irisin levels in females with sarcopenia, but this correlation was absent in males [20].

Although no FDA-approved medications currently exist for sarcopenia treatment, several therapeutic approaches show promise in boosting irisin levels among affected individuals. Resistance training has emerged as a particularly effective intervention, with studies demonstrating its ability to reverse significant muscle function loss and slow age-related structural decline [27]. This exercise modality not only elevates circulating IGF-1, irisin, and the anti-inflammatory cytokine IL-10 but also suppresses myostatin expression. Notably, such training can increase thigh muscle cross-sectional area, potentially improving biochemical markers, anabolic processes, and functional capacity in elderly women with sarcopenia [17]. Nutritional interventions may also play a role, as evidenced by Mendez et al.'s double-blind pilot study. Postmenopausal women receiving grape powder supplements showed enhanced physical performance (measured by chair stand and gait speed tests) and elevated irisin levels after six weeks compared to controls [26]. However, not all interventions demonstrate consistent effects. For instance, research examining the growth hormone secretagogue anamorelin in osteosarcopenic patients found no significant alterations in irisin, IL-6, or hsCRP levels [23].

Potential effect of Irisin involve animal and cellular

Table 3 summary data from 12 studies concentrating on animal and cellular research. Research by Iemura et al. revealed that orchiectomy-induced androgen deficiency (ORX) results in diminished muscle mass, impaired grip strength, and reduced muscle fiber diameter, accompanied by lower irisin expression in both soleus and gastrocnemius muscles. Interestingly, while these es occurred, ORX mice showed no alterations in the expression of genes associated with muscle differentiation or protein degradation. Notably, irisin appears to protect against the reduction in trabecular bone mineral density (BMD) but does not influence muscle mass [28]. The researchers concluded that while sarcopenia and osteoporosis can be induced in ORX mice, the decline in irisin production by skeletal muscle is not linked to muscle wasting in these mice. Zhou's findings corroborate these observations, indicating that androgen deficiency adversely affects bone and muscle microstructure and function, contributing to the development of both osteoporosis and sarcopenia. While the exact interplay between sclerostin and irisin in musculoskeletal pathophysiology requires further clarification, current evidence suggests their potential involvement in these degenerative conditions [29]. Experimental studies have identified Benzo[a]pyrene (BaP) as a detrimental factor for muscle integrity, as it can decrease irisin levels and increase myostatin levels both in vivo and in vitro, leading to conditions characteristic of sarcopenia [30]. Furthermore, aging causes muscle fiber atrophy and decreases AMPK phosphorylation, subsequently diminishing PGC-1α and FNDC5 expression in gastrocnemius tissue. Therapeutic interventions such as wheel running exercise appear to counteract these effects by stimulating the PGC-1α/FNDC5/AMPK cascade, which promotes VEGF upregulation and ultimately enhances muscle mass, functional strength, and motor coordination [31]. Complementary findings indicate that static resistance training similarly improves muscular endurance in sarcopenic models through activation of the PGC-1α/FNDC5/UCP1 signaling axis. Furthermore, static strength training elevates FNDC5 expression, which enhances circulating irisin levels and upregulates UCP1 expression, thereby preventing skeletal muscle atrophy and improving muscle mass [32]. Contradicting some previous findings, Han's et al. research observed that exercise intervention failed to significantly modify irisin levels in aged rats, despite the well-documented age-related decline in this myokine [33]. In contrast, the research by Guo demonstrated that intraperitoneal administration of recombinant irisin protein produced measurable improvements in sarcopenic

Table 3 Overview of the literature involving cellular and animal studies

Author/Years	Species/Cells	Sample	Group	Main outcome
Iemura 2020 [28]	C57BL/6	49	Control/sham, Control/ORX, Irisin/sham, Irisin/ORX	Irisin protects against androgen deficience-induced reduction in trabecular bone mineral density but not muscle mass in mice.
Young 2021 [31]	Rats	32	Young-age group, Young-age and wheel running exercise group, Old-age group, Old-age and wheel running exercise group.	Voluntary wheel-running exercise enhances the expression of VEGF through the activation of the PGC-1α/FNDC5/AMPK signaling pathway, which subsequently leads to increases in muscle mass, strength, and coordination.
Liu 2021 [32]	SD rat	40	PGC-1α siRNA, negative control sequence of PGC-1α (NC), static strength training, PGC-1αsiRNA + static strength training	Static resistance exercise enhances FNDC5 production, increasing circulating irisin which stimulates UCP1-mediated fat browning while protecting against muscle wasting, thus preserving lean mass.
Han 2021 [33]	Female SD rat	48	Young sedentary, old sedentary, moderate intensity continuous training, and high - intensity interval training	Exercise did not significantly alter serum irisin levels in aged rats, despite an age-related decline.
Wu 2022 [30]	344/NNarl / ratsC2C12	None	Control, exposure	BaP attenuated differentiation of myoblasts, triggered a series of responses. Ultimately, decrease irisin level and increase myostatin levels.
Zhou 2022 [29]	Rat	20	Sham, orchiectomy	Androgen deficiency adversely affects bone and muscle microstructure and function, resulting in osteoporosis and sarcopenia.
Guo 2023 [9]	C57BL/6	None	young and aged mice/ Wild-type and FNDC5/irisin knockout mice/ Irisin or control His-tag	Administration irisin can improves sarcopenia and muscle function in aging mice.
Wu 2023 [34]	Fibroblasts	None	G1: Control G2: D-gal 30 g/L G3: irisin 5 nM + D-gal G4: irisin 10 nM + D-gal G5: irisin 20 nM + D-gal G5: irisin 40 nM + D-gal	Irisin demonstrates anti-fibrotic and anti-senescence effects in D-galactose-induced models by restoring redox balance through PI3K/Akt signaling, suggesting therapeutic potential for sarcopenia.
Wu 2024 [35]	C2C12	None	G1: Control G2:D-gal + lv-NC G3:D-gal G4: D-gal + LV-FNDC5	Through caveolin-1-dependent Fas signaling, irisin modulates apoptosis in D-galactose-exposed muscle fibroblasts and C2C12 myoblasts.

parameters in aging mouse models, including enhanced grip strength, increased muscle mass, and improved molecular profiles. These results supporting the hypothesis that FNDC5/irisin signaling plays a crucial modulatory role in age-related muscle wasting and metabolic impairment [9]. Additional mechanistic studies reveal that irisin administration can mitigate D-galactose-induced skeletal muscle fibrosis and prevent apoptosis in C2C12 myoblasts. This protective effect is mediated through modulation of the PI3K/Akt signaling cascade and caveolin-1 expression. Collectively, these findings underscore irisin's potential as a promising therapeutic candidate for combating age-associated muscle atrophy and fibrotic degeneration [34, 35].

The risk of bias of the included studies

Human Study Bias Assessment can be seen in Fig. 2A and B. Of the 12 human studies analyzed, only one study exhibited low risk of selection, performance bias, and detection bias while the majority demonstrated high or unclear risks. Three studies showed high attrition bias from incomplete data collection. Notably, all studies demonstrated low reporting bias risk.

All seven animal studies presented unclear risk across multiple domains including selection bias, randomization outcome assessment, and blinding protocols. While all studies implemented random housing, and only one achieved low-risk status through proper blinding procedures. Importantly, no studies exhibited elevated risk for incomplete outcomes, selective reporting, or other potential biases.

Discussion

To our knowledge, this is the first systematic review integrating evidence from both human and animal studies to evaluate irisin's dual role in sarcopenia—as a diagnostic biomarker and a therapeutic target. Our analysis reveals that circulating irisin levels inversely correlate with sarcopenia severity, particularly in aging populations such as postmenopausal women (Table 1). For instance, cross-sectional studies demonstrated lower serum irisin concentrations in sarcopenic individuals compared to healthy controls [16, 36]. This association is supported by

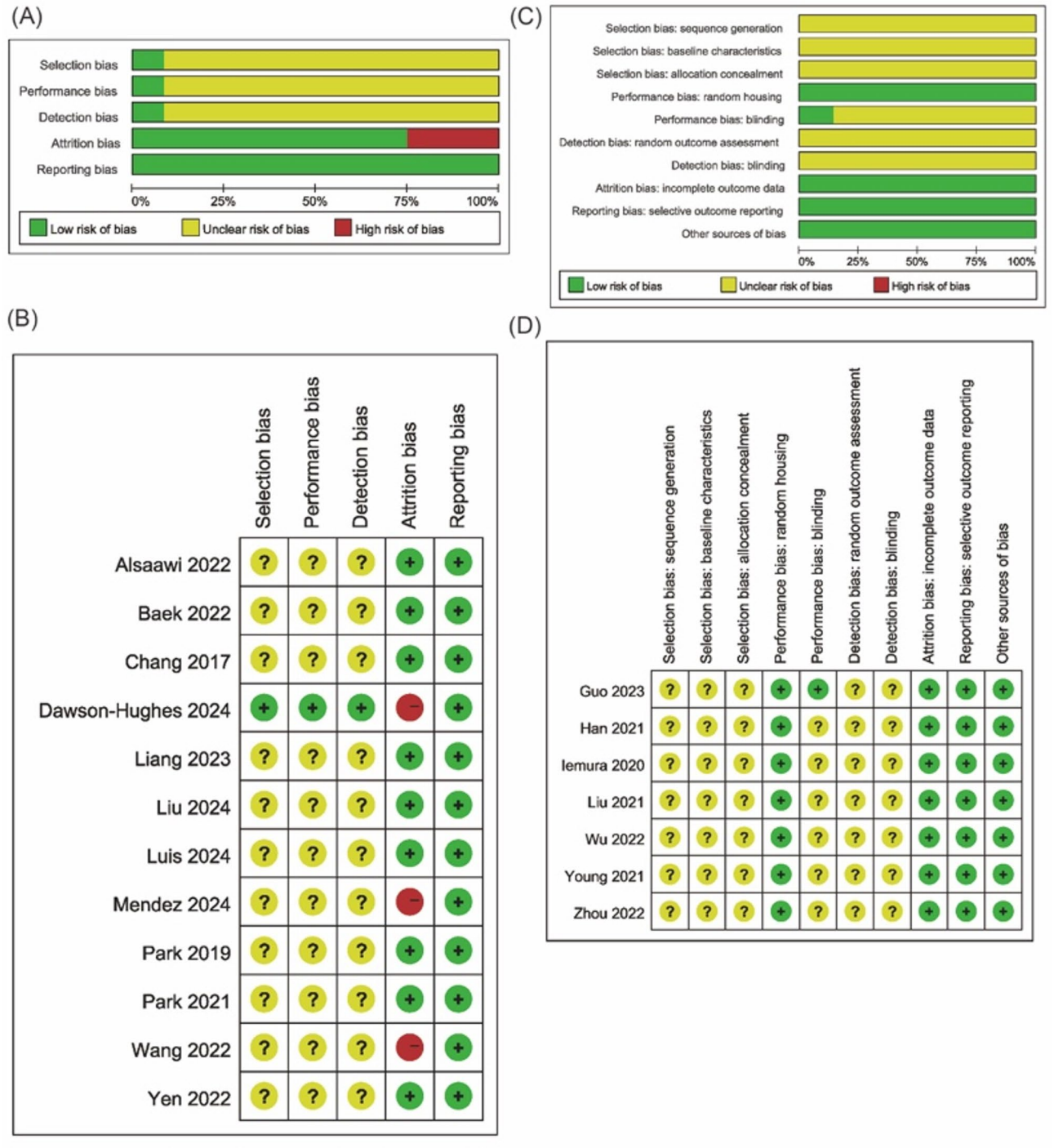

Fig. 2 AHRQ for human studies and SYRCLE risk of bias tool in animal. (**A**) Weighted bar plots of human; (**B**) Traffic-lights plots of human; (**C**) Weighted bar plots of animal; (**D**) Traffic-lights plots of animal

preclinical studies demonstrating that irisin administration improves muscle mass, strength, and mitochondrial function in aged models [9]. These findings collectively position irisin as a promising candidate for sarcopenia management, bridging molecular insights with clinical potential.

The global aging trend is expected to drive a significant increase in sarcopenia prevalence. Aging disrupts the catabolic balance of muscles, thereby compromising muscle health [37]. Muscle growth results from an imbalance between anabolic and catabolic processes, where protein synthesis exceeds breakdown. Mechanical stimuli like

resistance training initiate the PI3K/Akt/mTOR cascade, stimulating myocyte growth pathways that ultimately increase muscle fiber size and mass [38]. For example, overexpression of irisin alleviated D-Gal-induced senescence, redox imbalance and fibrosis by regulating PI3K/Akt signaling pathway [34]. Another, Irisin prevents mitochondrial fission and increases mitochondrial fusion to reduce apoptosis, and reduces oxidative stress by activating the PI3K/AKT/mTOR axis [39]. These studies suggest that irisin can regulate the PI3K/Akt/mTOR signaling pathway. However, the relationship between irisin regulation and PI3K/Akt/mTOR signaling pathway in sarcopenia is still unclear, and further studies are needed to clarify in the future. Physical activity induces peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) upregulation, which in turn stimulates FNDC5 gene expression and subsequent irisin production [37]. This PGC-1α-dependent myokine, proteolytically cleaved from skeletal muscle, enters circulation where it modulates brown adipose tissue morphology and promotes vascularization, thereby supporting myocyte proliferation [40]. However, age-dependent disparity may reflect declining mitochondrial biogenesis capacity, as aging impairs PGC-1α-mediated activation of NRF1/NRF2/TFAM, thereby reducing mitochondrial DNA replication and muscle resilience. These alterations contribute to the decline in muscle strength and function, which are characteristic features of sarcopenia [41]. In this review, Young found that wheel running exercise enhance old rat the expression of VEGF by activating PGC-1α/FNDC5/AMPK which improving muscle mass and coordination in aged rodents. Consequently, PGC-1α may serve as a target for preventing aging-related muscle atrophy [31]. Similarly, high-intensity interval static training has been shown to regulate the PGC-1α/FNDC5/UCP1 cascade which prevents skeletal muscle atrophy and improve the motor function [32]. Furthermore, irisin is implicated in the regulation of sarcopenia through various signaling pathways. Murine studies indicate that recombinant irisin mitigates oxidative stress and fibrosis via PI3K/Akt signaling [12] while suppressing myostatin through ERK/IGF-1 crosstalk [42]. These dual mechanisms create an anabolic milieu conducive to muscle hypertrophy, highlighting irisin's pleiotropic potential.

Sarcopenia development involves both controllable and inherent risk factors. Lifestyle-related elements including sedentary behavior, poor nutrition, and vitamin D insufficiency can be modified, whereas age-related biological changes, genetic predisposition, and endocrine alterations constitute inherent risk parameters [43]. Current research suggests an important relationship between irisin and muscle homeostasis, with declining irisin levels potentially contributing to sarcopenic progression [37]. While one study reported no correlation between serum irisin and standard sarcopenia measures [19], multiple investigations have consistently observed reduced irisin concentrations in aging populations, particularly postmenopausal women [16, 18, 21]. The study by park suggested that each 1.0 ng/mL decrease of irisin was associated with 95% higher risk of having sarcopenia [16]. Another research demonstrated that low circulation level of irisin (< 118.0 ng/mL may increase the risk for sarcopenia [44]. These findings position irisin as a promising diagnostic indicator. However, there is no unified diagnostic criterion for circulating irisin at present, and further determination is needed in the future. Because the accuracy of detecting the circulation level of irisin also varies among different ELISA kits, this may lead to differences in the detection of irisin. Therapeutic interventions targeting irisin show considerable potential. Experimental studies demonstrate that recombinant irisin administration improves multiple sarcopenia parameters, including muscle morphology and strength [9]. Nutritional intervention,, such as grape powder supplementation, elevates circulating irisin in sarcopenic postmenopausal women whlie improving lower-extremity functional measures including chair sit-to-stand speed and gait speed [26]. Therefore, these studies illustrated that enhancing irisin expression levels may have therapeutic effects for sarcopenia.

Skeletal muscle is the largest organ responsible for the production and secretion of irisin. The synthesis and secretion of irisin also showed different results under different exercise [37]. Clinical trials reveal that acute exercise transiently increases circulating irisin levels, peaking at 24 h post-exercise (baseline: 9.0 ± 2.0 ng/mL; 24 h: 13.5 ± 2.5 ng/mL, $P < 0.001$). Young adults consistently exhibit higher irisin levels than middle-aged individuals across all time points (YA: 9.7 ± 1.7 to 14.5 ± 2.2 ng/mL vs. MA: 7.6 ± 1.6 to 11.8 ± 2.2 ng/mL, $P < 0.05$). These results highlight the critical role of acute exercise in counteracting age-related skeletal muscle mass loss and functional decline in both YA and MA populations [45]. A parallel study confirmed exercise-induced irisin elevation in both serum and saliva, with levels returning to baseline after 48 h of rest ($P \leq 0.05$) [46]. Notably, progressive resistance training has demonstrated efficacy in promoting muscle protein anabolism while improving muscle mass, strength and physical function in sarcopenic older adults [27]. Furthermore, the 2018 International Conference on Sarcopenia and Frailty Research strongly recommended progressive resistance exercise as a first-line therapeutic approach for sarcopenia, supported by a moderate level of evidence [43]. Beyond muscle benefits, resistance training enhances growth hormone secretion, myocyte development, and bone mineral density [47, 48]. Clinical investigations reveal consistent irisin upregulation following structured resistance programs, including an

8-week intervention in sarcopenic obese women [49] and a 15-week regimen in sarcopenia patient(with or without osteoarthritis), which also reduced myostatin expression [17]. However, exercise-induced irisin modulation appears context-dependent. Han et al. reported no significant serum irisin changes in aged rodents post-exercise, potentially reflecting interspecies differences, subject fitness levels, or protocol variations in training intensity and duration [33].

The strength of our conclusion depends on the methodological rigor of the included studies. As mentioned in Sect. 3.4, some studies in human research have shown unclear risk of selection bias, performance bias and detection bias. These limitations may weaken the reliability of irisin as a diagnostic biomarker. In animal studies, although some studies have demonstrated the therapeutic potential of irisin, in the selection bias, random outcome assessment and blinding is unclear which may have an impact on the therapeutic effect. Therefore, standardized schemes are urgently needed in future experiments to ensure repeatability.

There are some limitations in our review. Firstly, this review did not determine the mechanisms of irisin on sarcopenia which require more research to explanation. Secondly, although relevant searches were conducted in four databases, there may still be missing articles that were not included in this study. Thirdly, using the risk of bias tool to process quality assessment found that important information relates to design and conduct of the include research were missing. The detection standard of irisin has not been unified, and the detection standard of irisin is not summarized in this review. In the future, it is necessary to further clarify the detection standard of irisin to improve the detection reliability of irisin.

Conclusion

In this systematic review, we summarize the potential effect of irisin on sarcopenia in human and animal. While the role of irisin in sarcopenia remains ambiguous according to some studies, evidence suggests that irisin, whether induced by exercise or administered in vitro, exhibits promising therapeutic effects on sarcopenia. This positions irisin as a potential candidate for future pharmacological interventions targeting sarcopenia. Nevertheless, the current body of research is constrained by the limited number and quality of studies, leaving the mechanisms and therapeutic efficacy of irisin in sarcopenia insufficiently elucidated. Therefore, in order to further study the role of irisin in the human body and verify it as a potential therapeutic drug in the future, large-scale RCT trials need to be conducted further.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-08767-w.

Supplementary Material 1

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Author contributions
All authors have read and agreed to the published version of the manuscript. Yixiao Chen: Writing-original draft, Conceptualization; Yufeng Ge and Min Qian: Conceptualization Visualization; Feng Gao and Qingnan Sun, Visualization; Guoqing Li and Yifei Sun: Methodology; Kangzu Peng: Investigation; Gang Liu: Writing-review & editing, Supervision; Minghui Yang: Project administration, Funding acquisition, Resources, Supervision; Xinbao Wu: Project administration, Funding acquisition, Resources, Supervision.

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Data availability
All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Falsetti I, Palmini G, Donati S, Aurilia C, Iantomasi T, Brandi ML. Irisin and its role in postmenopausal osteoporosis and sarcopenia. Biomedicines. 2024; 12(4).
2. Cho MR, Lee S, Song SK. A review of sarcopenia pathophysiology, diagnosis, treatment and future direction. J Korean Med Sci. 2022;37(18):e146.
3. Cruz-Jentoft AJ, Landi F, Schneider SM, Zuniga C, Arai H, Boirie Y, Chen LK, Fielding RA, Martin FC, Michel JP, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the international sarcopenia initiative (EWGSOP and IWGS). Age Ageing. 2014;43(6):748–59.
4. Chen LK, Arai H, Assantachai P, Akishita M, Chew STH, Dumlao LC, Duque G, Woo J. Roles of nutrition in muscle health of community-dwelling older adults: evidence-based expert consensus from Asian working group for sarcopenia. J Cachexia Sarcopenia Muscle. 2022;13(3):1653–72.
5. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. Age Ageing. 2010;39(4):412–23.
6. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16–31.

7. Jimenez-Gutierrez GE, Martinez-Gomez LE, Martinez-Armenta C, Pineda C, Martinez-Nava GA, Lopez-Reyes A. Molecular mechanisms of inflammation in sarcopenia: diagnosis and therapeutic update. Cells. 2022; 11(15).
8. Najm A, Niculescu AG, Grumezescu AM, Beuran M. Emerging therapeutic strategies in sarcopenia: an updated review on pathogenesis and treatment advances. Int J Mol Sci. 2024; 25(8).
9. Guo M, Yao J, Li J, Zhang J, Wang D, Zuo H, Zhang Y, Xu B, Zhong Y, Shen F, et al. Irisin ameliorates age-associated sarcopenia and metabolic dysfunction. J Cachexia Sarcopenia Muscle. 2023;14(1):391–405.
10. Zhao C, Wu Y, Zhu S, Liu H, Xu S. Irisin protects musculoskeletal homeostasis via a mitochondrial quality control mechanism. Int J Mol Sci. 2024; 25(18).
11. Chang JS, Kim TH, Tuyet Thi N, Park K-S, Kim N, Kong ID. Circulating Irisin levels as a predictive biomarker for sarcopenia: A cross-sectional community-based study. Geriatr Gerontol Int. 2017;17(11):2266–73.
12. Reza MM, Subramaniyam N, Sim CM, Ge X, Sathiakumar D, McFarlane C, Sharma M, Kambadur R. Irisin is a pro-myogenic factor that induces skeletal muscle hypertrophy and rescues denervation-induced atrophy. Nat Commun. 2017;8(1):1104.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
14. Liu S, Li G, Xu H, Wang Q, Wei Y, Yang Q, Xiong A, Yu F, Weng J, Zeng H. Crosstalk between gut Microbiome dysbiosis and osteoarthritis progression: a systematic review. Front Immunol. 2023;14:1150572.
15. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14:43.
16. Park HS, Kim HC, Zhang D, Yeom H, Lim SK. The novel myokine Irisin: clinical implications and potential role as a biomarker for sarcopenia in postmenopausal women. Endocrine. 2019;64(2):341–8.
17. Park J, Bae J, Lee J. Complex exercise improves anti-inflammatory and anabolic effects in osteoarthritis-induced sarcopenia in elderly women. Healthcare. 2021; 9(6).
18. Alsaawi TA, Aldisi D, Abulmeaty MMA, Khattak MNK, Alnaami AM, Sabico S, Al-Daghri NM. Screening for sarcopenia among elderly Arab females: influence of body composition, lifestyle, Irisin, and vitamin D. Nutrients. 2022; 14(9).
19. Baek JY, Jang IY, Jung HW, Park SJ, Lee JY, Choi E, Lee YS, Lee E, Kim BJ. Serum Irisin level is independent of sarcopenia and related muscle parameters in older adults. Exp Gerontol. 2022;162:111744.
20. Wang Y, Gu Y, Huang J, Wu H, Meng G, Zhang Q, Liu L, Zhang S, Wang X, Zhang J et al. Serum vitamin D status and Circulating Irisin levels in older adults with sarcopenia. Front Nutr. 2022; 9:1051870.
21. Yen C-H, Chang P-S, Chang Y-H, Lin P-T. Identification of coenzyme Q10 and skeletal muscle protein biomarkers as potential factors to assist in the diagnosis of sarcopenia. Antioxidants. 2022; 11(4).
22. Liang H, Qi W, Jiajue R, Chi Y, Liu W, Wang O, Li M, Xing X, Yu W, Jiang Y et al. Serum irisin level is associated with fall risk, muscle strength, and cortical porosity in postmenopausal women. Front Endocrinol. 2023; 14:1096950.
23. Dawson-Hughes B, Konieczynski EM, Reitshamer E, Ceglia L. Effect of a GH secretagogue, Anamorelin, on serum Irisin and inflammation levels in osteosarcopenic adults. J Endocr Soc. 2024; 8(4).
24. de Luis D, Primo D, Izaola O, Gómez JJL. Role of Irisin and myostatin on sarcopenia in malnourished patients diagnosed with GLIM criteria. Nutrition. 2024; 120:112348.
25. Liu H, Li W, Zhu M, Wen X, Jin J, Wang H, Lv D, Zhao S, Wu X, Jiao J. Myokines and biomarkers of frailty in older inpatients with undernutrition: A prospective study. J Frailty Aging. 2024;13(2):82–90.
26. Mendez JL, Mackenzie G, Oteiza P, Holt R. Investigating the effects of daily grape powder consumption on sarcopenia in postmenopausal women. 2024.
27. Kirk B, Zanker J, Duque G. Osteosarcopenia: epidemiology, diagnosis, and treatment-facts and numbers. J Cachexia Sarcopenia Muscle. 2020;11(3):609–18.
28. Iemura S, Kawao N, Okumoto K, Akagi M, Kaji H. Role of Irisin in androgen-deficient muscle wasting and osteopenia in mice. J Bone Miner Metab. 2020;38(2):161–71.
29. Zhou BN, Zhang Q, Lin XY, Hu J, Zhao DC, Jiang Y, Xing XP, Li M. The roles of sclerostin and Irisin on bone and muscle of orchiectomized rats. BMC Musculoskelet Disord. 2022; 23(1).
30. Wu SE, Hsu JC, Chang YL, Chuang HC, Chiu YL, Chen WL. Benzo[a]pyrene exposure in muscle triggers sarcopenia through Aryl hydrocarbon receptor-mediated reactive oxygen species production. Ecotoxicol Environ Saf. 2022;239:113599.
31. Ko YJ, Ko IG. Voluntary wheel running exercise improves aging-induced sarcopenia via activation of peroxisome proliferator-activated receptor gamma coactivator-1α/fibronectin type Iii domain- containing protein 5/adenosine monophosphate-activated protein kinase signaling pathway. Int Neurourol J. 2021;25:S27–34.
32. Liu Y, Guo C, Liu S, Zhang S, Mao Y, Fang L. Eight weeks of high-intensity interval static strength training improves skeletal muscle atrophy and motor function in aged rats via the PGC-1α/FNDC5/UCP1 pathway. Clin Interv Aging. 2021;16:811–21.
33. Han C, Lu P, Yan SZ. Effects of high-intensity interval training on mitochondrial supercomplex assembly and biogenesis, mitophagy, and the AMP-activated protein kinase pathway in the soleus muscle of aged female rats. Exp Gerontol. 2022; 158:111648.
34. Wu Y, Wu Y, Yu J, Zhang Y, Li Y, Fu R, Sun Y, Zhao K, Xiao Q. Irisin ameliorates D-galactose-induced skeletal muscle fibrosis via the PI3K/Akt pathway. Eur J Pharmacol. 2023;939:175476.
35. Wu Y, Wu Y, Yu J, Zhang Y, Dai X, Chen J, Sun Y, Yang Y, Zhao K, Xiao Q. Irisin alters d-galactose-induced apoptosis by increasing caveolin-1 expression in C2C12 myoblasts and skeletal muscle fibroblasts. Mol Cell Biochem. 2025;480(1):577–88.
36. Chang JS, Kim TH, Nguyen TT, Park KS, Kim N, Kong ID. Circulating Irisin levels as a predictive biomarker for sarcopenia: A cross-sectional community-based study. Geriatr Gerontol Int. 2017;17(11):2266–73.
37. Wang YT, Zheng SY, Jiang SD, Luo Y, Wu YX, Naranmandakh S, Li YS, Liu SG, Xiao WF. Irisin in degenerative musculoskeletal diseases: functions in system and potential in therapy. Pharmacol Res. 2024;210:107480.
38. Bodine SC, Stitt TN, Gonzalez M, Kline WO, Stover GL, Bauerlein R, Zlotchenko E, Scrimgeour A, Lawrence JC, Glass DJ, et al. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. Nat Cell Biol. 2001;3(11):1014–9.
39. Liu JF, Su G, Chen LX, Zhou JP, Gao J, Zhang JJ, Wu QH, Chen W, Chen DY, Zhang ZC. Irisin attenuates apoptosis following Ischemia-Reperfusion injury through improved mitochondria dynamics and ROS suppression mediated through the PI3K/Akt/mTOR Axis. Mol Neurobiol. 2023;60(8):4261–72.
40. Rodriguez Lanzi C, Perdicaro DJ, Gambarte Tudela J, Muscia V, Fontana AR, Oteiza PI, Vazquez Prieto MA. Grape pomace extract supplementation activates FNDC5/irisin in muscle and promotes white adipose Browning in rats fed a high-fat diet. Food Funct. 2020;11(2):1537–46.
41. Joseph AM, Adhihetty PJ, Buford TW, Wohlgemuth SE, Lees HA, Nguyen LM, Aranda JM, Sandesara BD, Pahor M, Manini TM, et al. The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals. Aging Cell. 2012;11(5):801–9.
42. Consitt LA, Clark BC. The vicious cycle of myostatin signaling in sarcopenic obesity: myostatin role in skeletal muscle growth, insulin signaling and implications for clinical trials. J Frailty Aging. 2018;7(1):21–7.
43. Liu D, Wang S, Liu S, Wang Q, Che X, Wu G. Frontiers in sarcopenia: advancements in diagnostics, molecular mechanisms, and therapeutic strategies. Mol Aspects Med. 2024;97:101270.
44. Yen CH, Chang PS, Chang YH, Lin PT. Identification of coenzyme Q10 and skeletal muscle protein biomarkers as potential factors to assist in the diagnosis of sarcopenia. Antioxid (Basel). 2022; 11(4).
45. Tommasini E, Missaglia S, Vago P, Galvani C, Pecci C, Rampinini E, Bosio A, Morelli A, Bonanomi A, Silvestrini A et al. The time course of Irisin release after an acute exercise: relevant implications for health and future experimental designs. Eur J Transl Myol. 2024; 34(2).
46. Missaglia S, Tommasini E, Vago P, Pecci C, Galvani C, Silvestrini A, Mordente A, Tavian D. Salivary and serum Irisin in healthy adults before and after exercise. Eur J Transl Myol. 2023; 33(1).
47. Kozakowski J, Papierska L, Krassowski J, Zgliczynski S. [The effect of growth hormone replacement therapy on markers of bone formation and bone mineral density in elderly men]. Pol Arch Med Wewn. 1998;100(4):306–12.
48. Singh MA, Ding W, Manfredi TJ, Solares GS, O'Neill EF, Clements KM, Ryan ND, Kehayias JJ, Fielding RA, Evans WJ. Insulin-like growth factor I in skeletal muscle after weight-lifting exercise in frail elders. Am J Physiol. 1999;277(1):E135–143.

49. Jaeil C. Effects of resistance exercise interventions on the acute and Long-term Irisin expression and sarcopenia indices in sarcopenic obese Middle-Aged women. J Wellness. 2022;17(2):263–9.

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