

Irisin Research Landscape (2012–2024): A Bibliometric and Visual Analysis of Evolving Hotspots and Future Trends

Lijia Gao^{1,*}, Wen Sun^{1,*}, Hongwei Shi², Weijie Zhu³, Haidong Wang², Juan Wang¹

¹Department of Nephrology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China;

²College of Veterinary Medicine, Shanxi Agricultural University, Jinzhong, People's Republic of China; ³Department of Cardiology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Haidong Wang, College of Veterinary Medicine, Shanxi Agricultural University, No.1 Mingxian South Road, Jinzhong, Shanxi, 030801, People's Republic of China, Email wanghaidong@sxau.edu.cn; Juan Wang, Department of Nephrology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200080, People's Republic of China, Email wangdanwj@126.com

Purpose: Irisin, an exercise-induced myokine, promotes the browning of white adipose tissue. Over a decade of research has expanded its functions to include the amelioration of metabolic disorders and protection of neural, skeletal, muscular, cardiac, and renal systems. Exogenous administration of irisin has been demonstrated to mimic the beneficial effects of exercise, showing therapeutic potential for a range of conditions including obesity, diabetes, Alzheimer's disease, osteoporosis, sarcopenia, myocardial ischemia, and chronic kidney disease. Irisin emerges as a promising circulating biomarker for assessing health status. By offering a quantitative, data-driven perspective from macro to micro scales, bibliometrics serves as a crucial decision-support tool for irisin research. It facilitates the mapping of the intellectual landscape, pinpoints knowledge gaps and underinvestigated niches, and tracks the temporal evolution of research fronts, thereby guiding future investigative priorities.

Patients and Methods: Publications were retrieved from the Web of Science Core Collection (WoSCC) using the search strategy "Topic = irisin", covering the period from its discovery in 2012 to 2024. After applying language (English-only) and type (article/review) filters, VOSviewer, CiteSpace and R package "bibliometrix" was used to conduct the bibliometric analysis.

Results: This bibliometric analysis was conducted on a total of 2412 articles sourced from 78 countries. China emerged as the leading contributor, ranking first among the corresponding authors' countries. The primary research institutions identified were the Egyptian Knowledge Bank, Firat University, and Harvard University. The most locally cited authors were Mantzoros CS and Spiegelman BM, while Aydin S was recognized as the most relevant author. The most frequently occurring keywords included "exercise", "obesity", and "FNDC5". The latest trend topics identified were "neuroinflammation", "ferroptosis", "chronic kidney disease", and "cognition".

Conclusion: This bibliometric study delineates irisin's emerging clinical translational prospects, thereby providing evidence-based guidance for prioritizing research on irisin's therapeutic targeting and biomarker validation across multidisciplinary clinical contexts.

Keywords: irisin, FNDC5, exerkinases, myokines, skeletal muscle

Introduction

Irisin, a myokine, was first discovered in 2012 by a research team led by Bruce Spiegelman at Harvard Medical School.¹ The name "irisin" is derived from Iris, the Greek goddess who served as a messenger, symbolizing its role as a signaling molecule.^{1–3} Irisin is encoded by the fibronectin type III domain-containing 5 (FNDC5) gene and is primarily produced by skeletal muscle in response to exercise, particularly through the activation of peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α).^{1,4} Irisin is a cleaved and secreted fragment, comprising approximately 112 amino acids with a molecular weight of 12 kDa, which is proteolytically liberated from its transmembrane precursor protein FNDC5.^{4–6} Its bioactive structure is dominated by an N-terminal fibronectin type III domain, a characteristic

module frequently involved in protein-protein interactions, and it functions physiologically as a stable homodimer or oligomer, a quaternary conformation that is essential for its role in signaling and its capacity to induce the browning of white adipose tissue (WAT).^{5,7} Irisin exerts its biological functions through the $\alpha V/\beta 5$ integrin receptor, activating multiple signaling pathways including AMPK, ERK, p38, JNK, Wnt, RANK, and PI3K/AKT.^{8,9} It modulates various forms of cell death, such as apoptosis, autophagy, ferroptosis, and pyroptosis, ultimately leading to diverse biological effects.⁹ Irisin serves as a critical molecular mediator that conveys the systemic anti-aging benefits of exercise, making it a highly promising target for anti-aging research.¹⁰ It inhibits cellular senescence through multiple mechanisms, including reducing senescence-associated β -galactosidase (SA- β -gal) activity, alleviating oxidative stress, downregulating the expression of pro-inflammatory factors, stabilizing SIRT6 by attenuating its ubiquitination-mediated degradation, and activating autophagy.^{11,12}

Irisin is secreted into the bloodstream and exerts its effects on various tissues. In adipose tissue, irisin promotes the browning of WAT by upregulating uncoupling protein 1 (UCP1), enhancing thermogenesis and glucose homeostasis.^{13,14} Irisin interacts with adipokines and osteokines to form a complex intercellular signaling network.^{2,15,16} It suppresses the secretion of pro-inflammatory adipokines while promoting the expression of beneficial adipokines such as adiponectin. This modulation contributes to the amelioration of obesity-associated chronic low-grade inflammation and insulin resistance.¹⁷ Conversely, factors derived from adipose tissue may reciprocally regulate irisin; under obese and diabetic conditions, adipose tissue dysfunction and elevated inflammatory adipokines inhibit the expression and secretion of FND5/irisin, forming a vicious cycle.^{8,9} In bone metabolism, irisin inhibits sclerostin and enhances the expression of osteogenic markers, thereby promoting osteoblast differentiation. Furthermore, it modulates the RANKL/RANK/OPG system to suppress osteoclast differentiation and activity.^{9,17–19} Notably, cells of the osteoblast lineage can also express and secrete irisin (osteogenic irisin), indicating that bone tissue itself constitutes an important source of irisin, which may act in an autocrine or paracrine manner to regulate local bone metabolism and systemic functions. In skeletal muscle, it promotes hypertrophy and mitochondrial biogenesis, improving muscle health.²⁰ Irisin can cross the blood-brain barrier and directly act on brain regions such as the hippocampus, where it significantly upregulates the expression of brain-derived neurotrophic factor (BDNF), suppresses the overactivation of microglia, and alleviates neuroinflammation and neuronal apoptosis.^{21–25} Exogenous supplementation of irisin has been shown to effectively ameliorate conditions such as Alzheimer's disease (AD), depression, and ischemic stroke. Irisin exhibits potent anti-inflammatory properties by inhibiting the activation of the NLRP3 inflammasome and promoting the polarization of macrophages from the pro-inflammatory M1 phenotype toward the anti-inflammatory M2 phenotype.²⁶ This leads to a reduction in circulating levels of pro-inflammatory cytokines, including TNF- α , IL-6, and CRP. Furthermore, irisin improves pathologies such as atherosclerosis by suppressing vascular inflammation, reducing endothelial cell activation, and inhibiting macrophage foam cell formation.^{27,28} In the kidneys, it mitigates oxidative stress and inflammation, delaying chronic kidney disease (CKD) progression.^{29,30}

Irisin holds significant promise as a therapeutic agent mimicking the benefits of physical activity, positioning it as a potential “exercise mimetic” for clinical translation.¹⁰ However, clinical translation faces challenges such as the production of stable and bioactive recombinant irisin, determination of tissue-specific dosing regimens, and mitigation of off-target effects.^{3,31} The pleiotropic mechanisms underlying irisin's actions remain incompletely understood. Recent advancements, including the development of efficient irisin analogs and nanoparticle-based delivery systems, have enhanced its stability and bioavailability, supported by preclinical evidence of its efficacy in improving metabolic health, kidney diseases, and cognitive function.^{12,29,32} Exploring irisin's role in emerging areas such as aging and cancer could unlock new therapeutic avenues.^{10,20,33} Given irisin's paradigm-shifting potential in the treatment of chronic diseases, a bibliometric analysis of irisin-related literature is essential to identify research hotspots and trends, guiding future advancements in this emerging and impactful field.

Through metrics such as publication volume, citation frequency, collaboration networks, and keyword co-occurrence, this study employs quantitative and visualization methods to reveal the evolution of irisin research. By systematically mapping the evolution of research, uncovering key themes, and highlighting knowledge gaps, bibliometric analysis provides a strategic foundation for prioritizing research efforts, fostering innovation, and accelerating the translation of irisin's therapeutic potential into clinical applications.

Materials and Methods

Data Sources

By searching the Web of Science Core Collection (WoSCC), the retrieval strategy was set as: Topic = irisin, with a publication time range from January 1, 2012 (the year irisin was discovered) to December 31, 2024, resulting in 2926 studies identified. The literature types were filtered to include articles and reviews, and the language was restricted to English. After verification, a total of 2412 articles were obtained for subsequent bibliometric analysis. The raw data were downloaded from WoSCC, selecting complete records and cited references, and saved in plain text format. Each article included data on topics, authors, abstracts, keywords, titles, publication years, and references. Terms that were semantically equivalent but differed in case or form were unified. Compound terms were standardized to maintain consistency across the dataset.

Data Analysis

This study employed R package bibliometrix, VOSviewer (version 1.6.20), CiteSpace (version 6.3.1), and Excel (2021) to conduct a comprehensive analysis of literature related to irisin. R package bibliometrix is an open-source and freely available tool, distributed under the MIT license, used to analyze publication volumes and collaboration relationships among countries and institutions, as well as to identify highly cited and most relevant journals, documents, and authors.³⁴ VOSviewer is a bibliometric analysis software tool designed to construct and visualize co-authorship networks, keyword co-occurrence clusters, and citation relationships in scientific literature, enabling data-driven exploration of research trends and collaborative patterns in fields such as irisin studies.³⁵ It was utilized in this study for co-authorship, author keywords co-occurrence, bibliographic coupling, and co-citation analyses. CiteSpace is a Java-based scientometric tool developed by Chaomei Chen for analyzing temporal trends, detecting citation bursts, and mapping knowledge evolution through co-citation networks and timeline visualizations.^{36,37} It was applied in this study for journal overlay maps, keyword clustering, and temporal evolution analysis. Microsoft Excel 2021 was used to analyze the annual publication volume of irisin-related studies and predict future trends. The detailed research workflow is illustrated in Figure 1.

Results

Analysis of Publication Volume

The number of publications over time partially reflects the developmental speed and evolutionary trends of research in a specific field.³⁸ Since its discovery in 2012, studies on irisin have been increasingly emerging. Figure 2 illustrates the

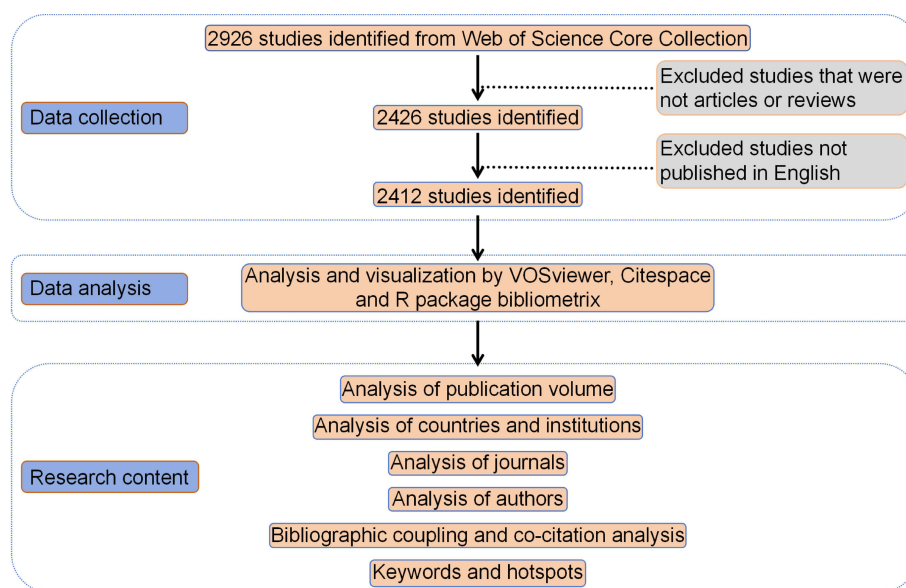


Figure 1 Workflow diagram of the bibliometric analysis on irisin-related literature.

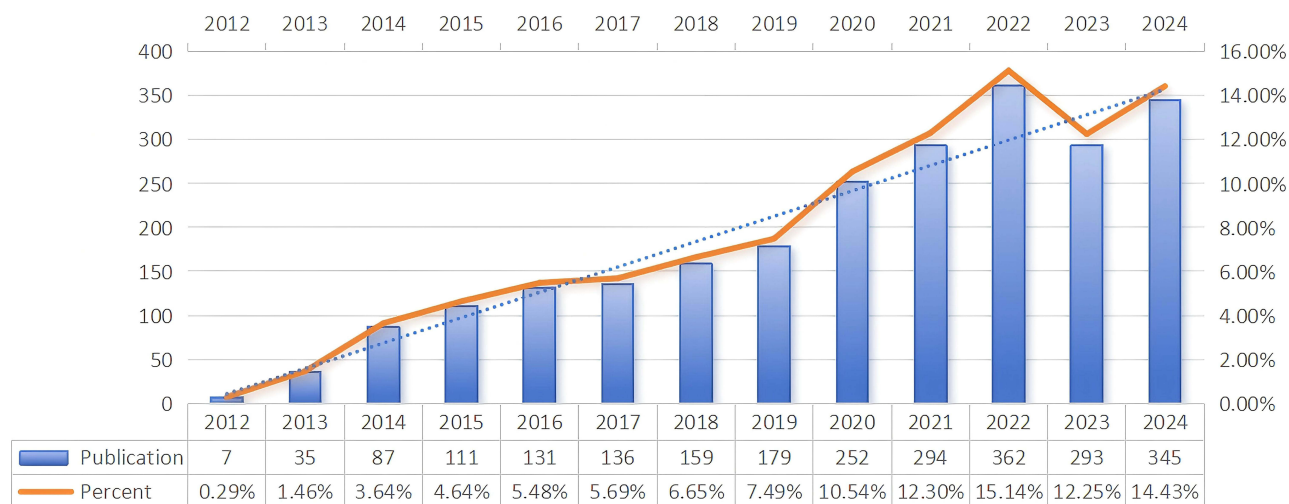


Figure 2 Annual publication volume and trend of irisin-related literature.

publication trend of irisin-related articles, starting with 7 articles in 2012 and reaching 345 articles in 2024, showing a clear upward trajectory. The peak number of publications occurred in 2022, with 362 articles. The number of publications is projected to continue increasing in 2025 and beyond. Based on the overall publication volume and trend, research on irisin represents an rapidly growing field, with substantial unexplored research potential and opportunities for further exploration.

Analysis of Countries and Institutions

The spatial distribution analysis of this research field reveals the extent of scientific contributions and the level of prioritization by individual countries/regions. A total of 77 countries/regions and 1893 institutions have published at least one article related to irisin, with 47 countries and 256 institutions publishing 10 or more articles. As depicted in [Figure 3A](#), China emerges as the leading contributor in terms of the number of publications related to irisin, followed by Turkey, the United States, Italy, and Poland. [Figure 3B](#) highlights that China and the United States serve as pivotal nodes in international collaborations, as illustrated in the country collaboration map. [Figure 3C](#) presents a co-authorship network diagram generated using VOSviewer, depicting collaborative linkages among 47 countries and highlighting the centrality of hub nations as well as the strength of international cooperation. [Figure 3D](#) identify Firat University as the institution with the highest number of publications in the irisin field. [Figure 3E](#) demonstrates that while the United States led in publication output following the discovery of irisin in 2012, China surpassed it in 2018 and has since experienced rapid growth, becoming the top publishing nation in this domain. [Figure 3F](#) indicates that Harvard University maintained its position as the leading institution in terms of annual publications from 2012 onwards, with consistent increases until it was overtaken by the Egyptian Knowledge Bank (EKB) and Firat University in 2023. EKB subsequently became the top publishing institution in 2024. [Figure 3G](#) shows that the most cited countries in irisin-related research are China and the United States, significantly outpacing other nations. Although China significantly surpasses the United States in the quantity of publications, the citations between the two nations remain comparable. This disparity underscores a gap in the level of academic innovation and leadership between China and the United States. As shown in [Figure 3H](#), the three most prolific affiliations in terms of publication output are EKB, Firat University, and Harvard University.

Analysis of Journals

Irisin-related publications have appeared in 877 journals, of which 32 have published 10 or more articles. [Figure 4A](#), the journal dual-map overlay, reveals that orange and green represent the primary paths, with Molecular/Biology/Genetics and Health/Nursing/Medicine journals being cited by Molecular/Biology/Immunology and Medicine/Medical/Clinical

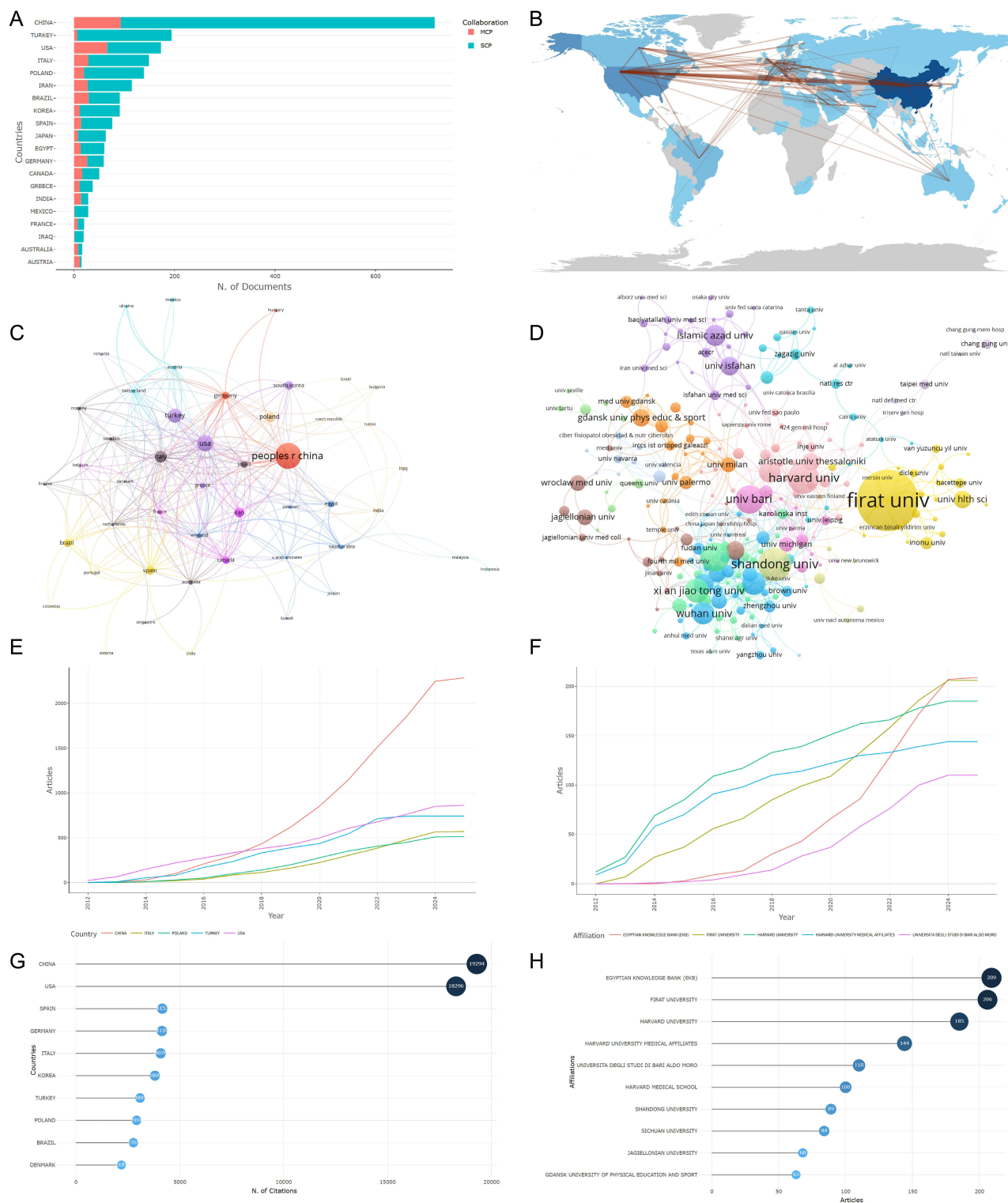


Figure 3 Analysis of the countries and institutions contributing to irisin-related literature. **(A)** Distribution of corresponding authors' countries. **(B)** Global country collaboration map. **(C)** Co-authorship analysis of countries, visualized as a network using VOSviewer. **(D)** Co-authorship analysis of institutions, visualized as a network using VOSviewer. **(E)** Line graph depicting country production over time. **(F)** Line graph depicting affiliations' production over time. **(G)** Ranking of the top 10 most cited countries in irisin research. **(H)** Ranking of the top 10 most relevant affiliations in the field of irisin research.

Abbreviations: SCP, Single Country Publications; MCP, Multiple Country Publications.

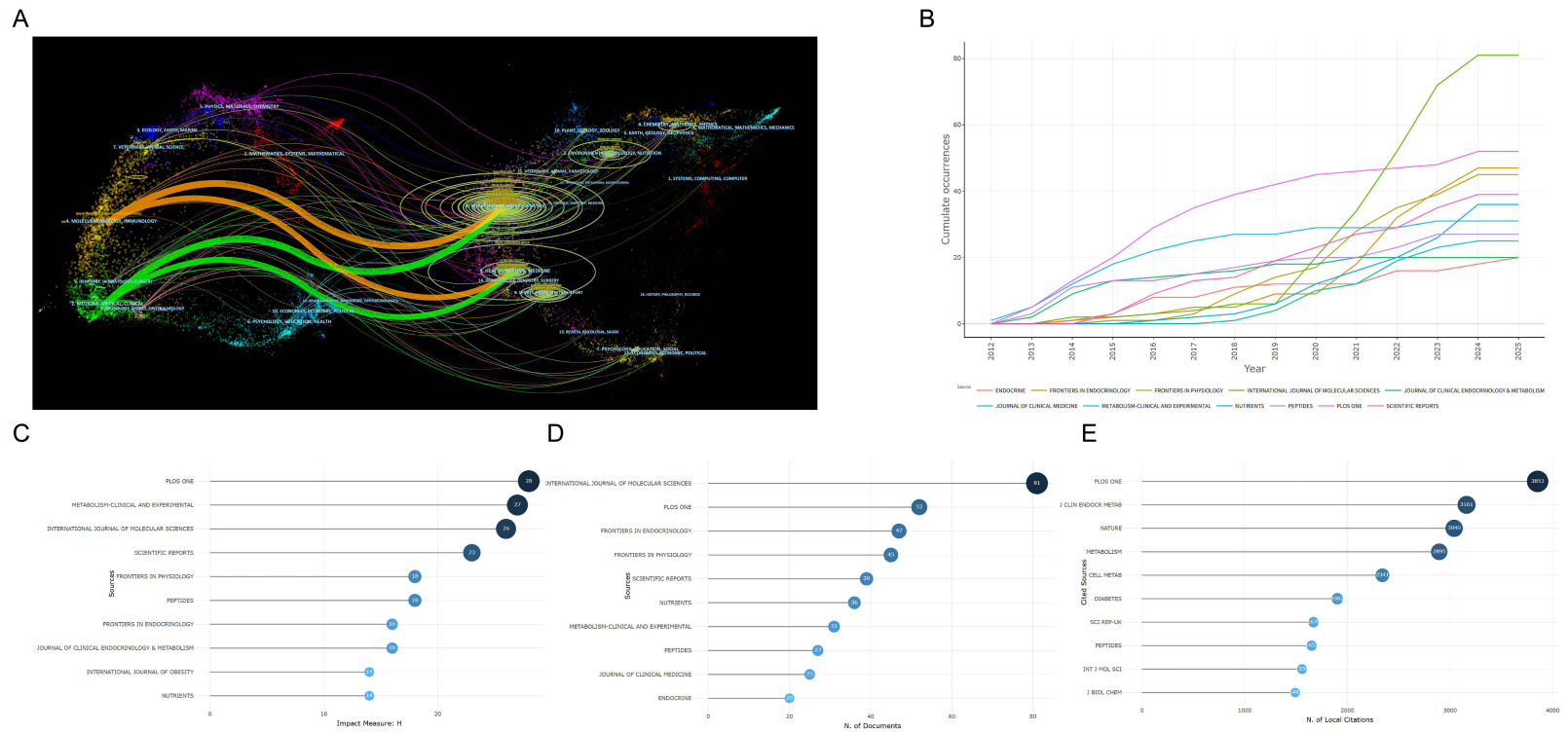


Figure 4 Analysis of sources publishing irisin-related literature. **(A)** journal dual-map overlay related to irisin. **(B)** Line graph depicting sources' production over time. **(C)** Ranking of the top 10 sources by local impact based on H-index. **(D)** Ranking of the top 10 most relevant sources in irisin research. **(E)** Ranking of the top 10 most locally cited sources.

journals. **Figure 4B** demonstrates that PLOS ONE (Q2, IF=3.2) experienced a significant increase in publication volume starting in 2014, becoming the leading journal in the irisin field. International Journal of Molecular Sciences (Q1, IF=5.7) saw a notable rise in publications beginning in 2020 and surpassed PLOS ONE in 2022 to become the top journal by publication volume. **Figure 4C** identifies PLOS ONE, Metabolism-Clinical and Experimental (Q1, IF=11.8), and the International Journal of Molecular Sciences as the top three journals based on Sources' Local Impact by H-index. **Figure 4D** highlights the International Journal of Molecular Sciences as the Most Relevant Source, followed by PLOS ONE and Frontiers in Endocrinology (Q1, IF=5.2). **Figure 4E** shows that PLOS ONE is the Most Local Cited Source, succeeded by the Journal of Clinical Endocrinology and Metabolism (Q1, IF=5.4) and Nature (Q1, IF=55).

Analysis of Authors

A total of 12,236 authors have contributed to research on irisin, among whom 38 authors have published 10 or more articles. **Figure 5A** presents the co-authorship network we established, which includes 265 authors with a minimum of 5 publications used to construct the network, displaying 39 items connected to each other. **Figure 5B** illustrates authors' production over time, with Mantzoros C producing the highest annual output of 14 articles in 2014, while other authors in the figure continue to publish irisin-related articles up to 2024. **Figure 5C**, the Three-Field Plot, demonstrates the connections among 20 authors, cited references, and research keywords. **Figure 5D** shows that Aydin S ranks first among the most relevant authors with 50 documents, followed by Grano M and Colaianni G. **Figure 5E** displays the most global cited documents, among which *Bostrom P, 2012, Nature* and *Wu J, 2012, Cell* are foundational works in the irisin field, both originating from the laboratory of Professor Bruce M. Spiegelman.^{1,13} Notably, *Bostrom P, 2012, Nature*, published on January 26, 2012, was the first to discover irisin as a PGC1- α -dependent myokine.¹ **Figure 5F** highlights the most local cited documents, with *Bostrom P, 2012, Nature* leading significantly with 1709 local citations, far surpassing other articles.

Bibliographic Coupling and Co-Citation Analysis

Bibliographic coupling identifies thematic relationships between publications based on their shared references, enabling clustering of contemporary research themes in irisin studies, while co-citation analysis traces historical intellectual linkages by mapping frequently cited document pairs, revealing foundational works and knowledge evolution.³⁸

In the bibliographic coupling analysis, we set the minimum number of documents of a source to 6, resulting in 79 out of 877 sources meeting the threshold, which were used to construct the Bibliographic Coupling Sources network, as shown in **Figure 6A**. Among these, PLOS ONE served as a central hub in the early period around 2016, while the International Journal of Molecular Sciences emerged as a key hub in the later period around 2021, consistent with our earlier analysis of journals. We also set the minimum number of documents of an author to 8, with 71 out of 12,236 authors meeting the threshold, and the overlay visualization constructed is presented in **Figure 6B**. Key nodes in this network include Mantzoros C, Aydin S, Grano M, and Colaianni G, aligning with our previous findings. Additionally, we selected a minimum number of citations of a document as 120, with 117 out of 2412 documents meeting the threshold, and the constructed network is illustrated in **Figure 6C**. As depicted, articles from the initial two years following the discovery of irisin hold significant importance in the bibliographic coupling analysis. *Bostrom P, 2012, Nature* remains the most prominent key node, while *Pedersen BK, 2012, Nat Rev Endocrinol* also stands out prominently.^{1,2}

In the co-citation analysis, we set the minimum number of citations of a source to 300, resulting in 74 out of 8174 sources meeting the threshold. The resulting density visualization is shown in **Figure 6D**, with journals such as PLOS ONE, Nature, and Cell Metabolism (Q1, IF=33.4) exhibiting high density within the network. We also set the minimum number of citations of an author to 100, with 88 out of 53,103 authors meeting the threshold. The density visualization for this analysis is presented in **Figure 6E**, with prominent nodes including Bostrom P, Pedersen BK, Colaianni G, and Aydin S. Additionally, we selected a minimum number of citations of a cited reference as 130, with 45 out of 75,791 cited references meeting the threshold. The density visualization for this is illustrated in **Figure 6F**, where *Bostrom P, 2012, Nature* remains the most densely prominent key node.¹

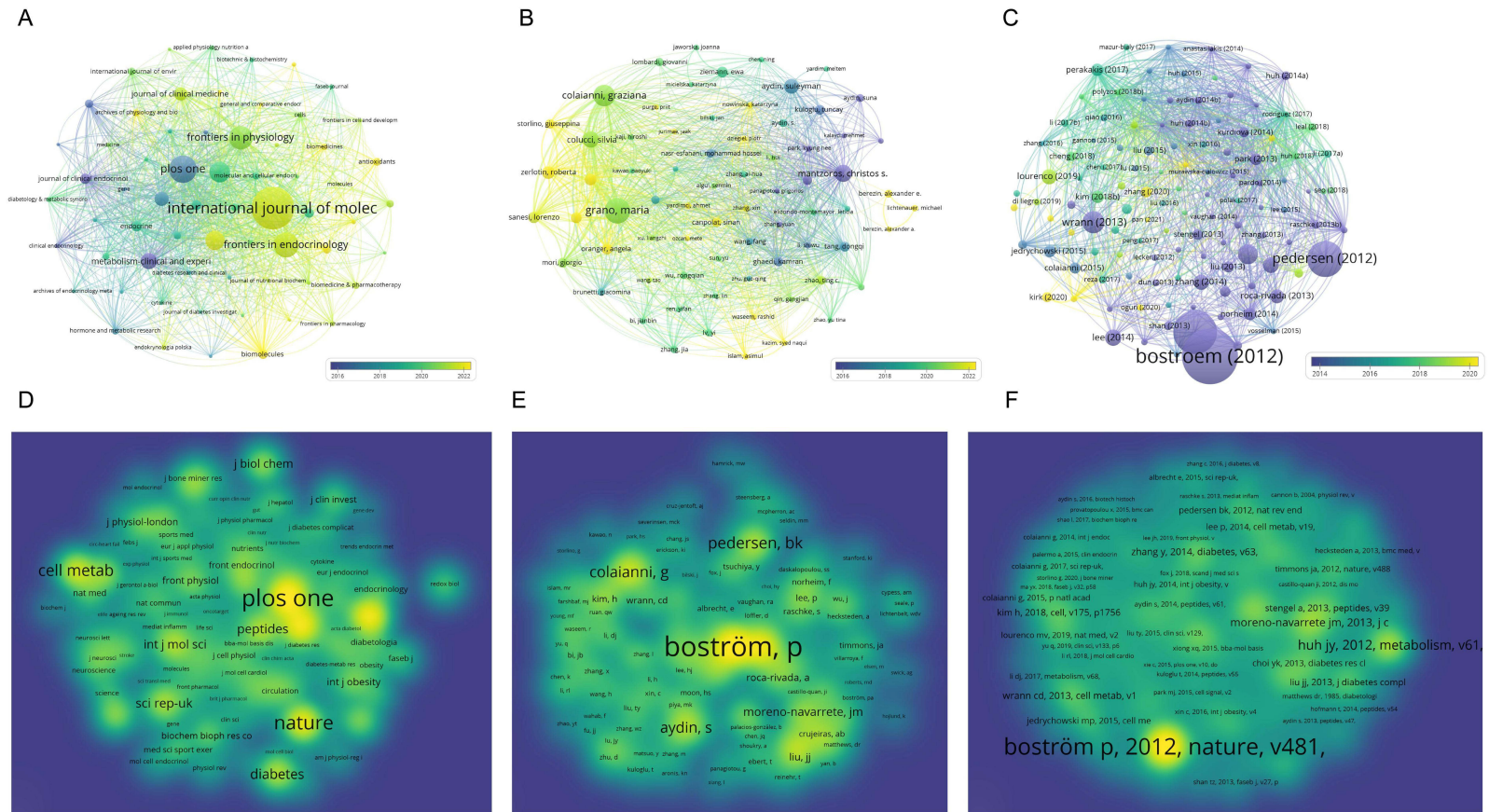


Figure 6 Bibliographic coupling and co-citation analysis of irisin-related literature. **(A)** Bibliographic coupling of sources, visualized as a network using VOSviewer. **(B)** Bibliographic coupling of authors. **(C)** Bibliographic coupling of documents. **(D)** Density visualization of co-citation of sources, constructed using VOSviewer. **(E)** Density visualization of co-citation of authors. **(F)** Density visualization of co-citation of documents.

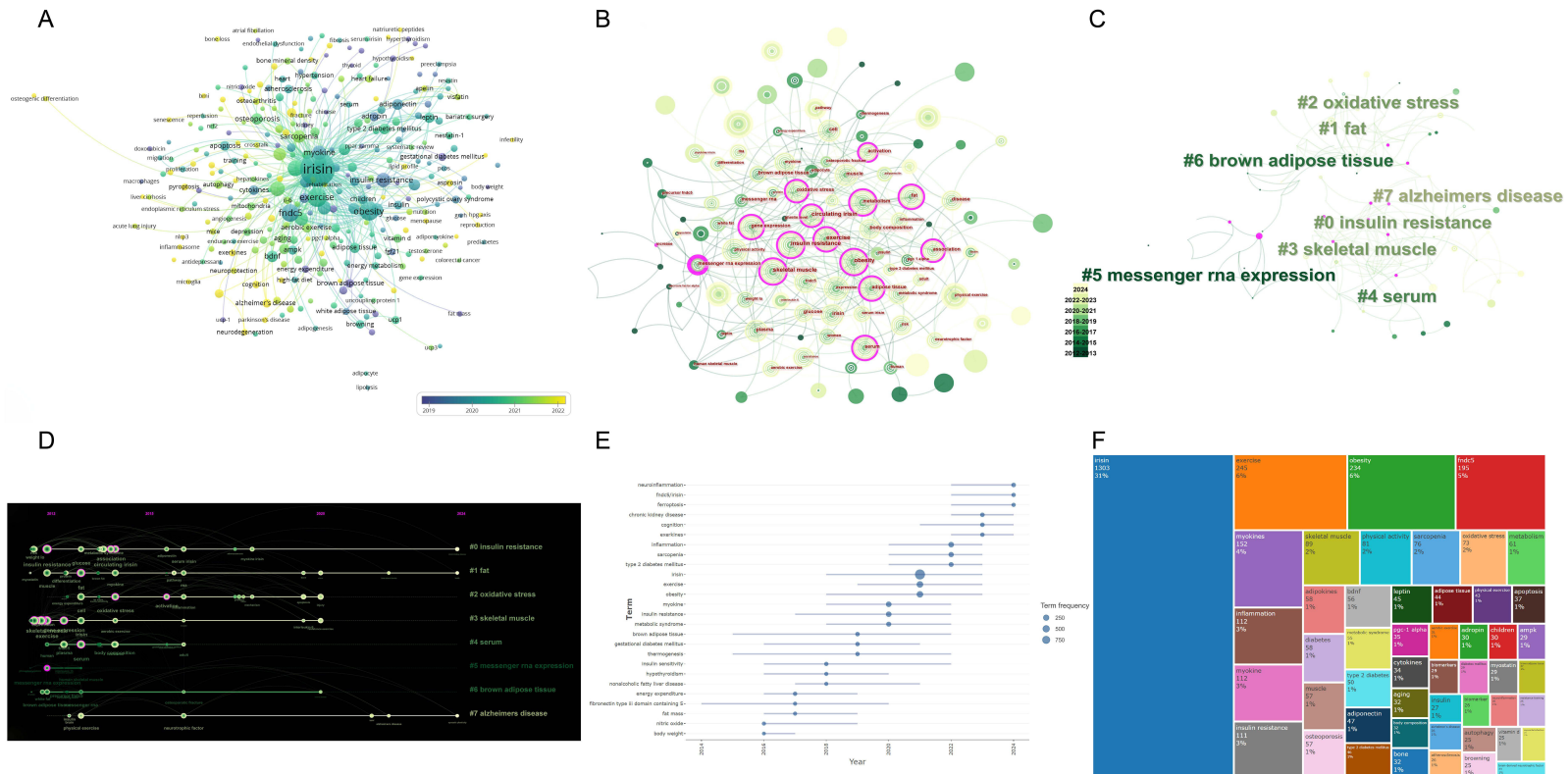


Figure 7 Analysis of keywords, hotspots, and trends in irisin-related literature. **(A)** Co-occurrence network of author keywords, constructed using VOSviewer. **(B)** Betweenness centrality analysis of author keywords using CiteSpace, with purple circles indicating nodes with centrality ≥ 0.1 . **(C)** Clustering of author keywords using CiteSpace, resulting in 8 clusters labeled #0 to #7. **(D)** Temporal evolution analysis of keywords, visualized as a timeline graph using CiteSpace. **(E)** Trend topics analysis of irisin-related literature from 2012 to 2024. **(F)** TreeMap visualization of author keywords in irisin-related literature.

A timeline graph of keywords was constructed, as shown in Figure 7D, revealing that clusters persisting until the end of 2024 included cluster #0 insulin resistance, cluster #1 fat, and cluster #7 Alzheimer's disease. This demonstrates that research on irisin in the metabolic field continues to thrive, while emerging research areas are increasingly focused on neurodegenerative diseases. Trend topics depicted in Figure 7E indicate a shift in irisin research from previous focuses on metabolic syndromes, obesity and T2DM, as well as musculoskeletal disorders like sarcopenia, towards the neurocognitive domain, particularly neuroinflammation, and CKD. Ferroptosis, a form of cell death, are gradually gaining attention within the irisin research field. Figure 7F visualizes a treemap generated from 50 author's keywords.

Figure 8 presents burst detection for both keywords and references.^{4,5,7,8,15,16,18,21,22,39–53} Keywords initially centered on adipocyte, leptin and energy expenditure, shifted focus to insulin sensitivity in 2014, then to cardiovascular aspects such as atherosclerosis in 2018, to skeletal system impacts in 2020, and finally to neurocognitive areas including BDNF and AD in 2022. Among the references, *Bostrom P, 2012, Nature* exhibits the strongest burst detection strength, indicating significant attention within the field.¹

Discussion

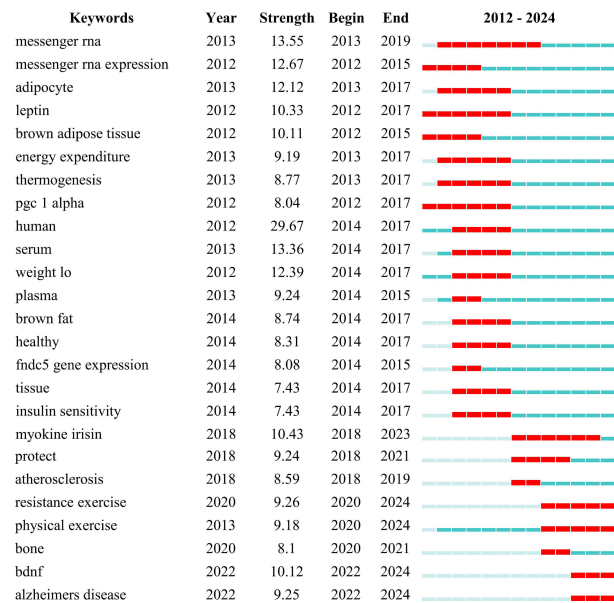
This study examined the evolution of publication output in the field of irisin research from its discovery in 2012 through the end of 2024. It analyzed the contributions of various countries and institutions, highlighting China and the United States as pivotal nodes in international collaborations. The most relevant affiliations identified include EKB, Firat University, and Harvard University. The research also evaluated the prominent journals, authors, and articles that have significantly influenced the irisin research domain. Through bibliographic coupling and co-citation analyses, the study further identified the core journals, authors, and articles within this field. The analysis included keyword and hotspot evaluations, employing measures such as betweenness centrality, clustering, temporal evolution analysis, and burst detection to track research hotspots and trends. This comprehensive approach aims to guide researchers in selecting pertinent areas of study and aligning with emerging trends, thereby facilitating the clinical translation of irisin-related findings.

A comprehensive review encompassing 1510 publications analyzed the literature on irisin from 2012 to 2021.⁵⁴ The study identified insulin resistance, inflammation, and circulating irisin levels in serum as prominent research hotspots. Additionally, it predicted that apoptosis, BDNF, and osteoporosis would emerge as key trends in the irisin research field, a forecast partially validated by recent publications. However, there remains a clear need for more up-to-date evidence to further substantiate these findings. Our study augments the existing body of literature by incorporating approximately 900 additional recent publications, thereby providing stronger evidence of irisin's significant role in metabolic regulation and its therapeutic potential in diverse areas such as neurodegenerative diseases, aging, and cancer. A bibliometric analysis of exercise-regulated myokines, which included 1405 relevant publications, explored various exercise modalities and their impact on biological processes such as oxidative stress.⁵⁵ This analysis predicted that irisin would become a focal point in future exercise-related research, emphasizing the need to investigate the crosstalk between irisin and various organ systems. This conclusion aligns closely with the findings of our study. Consequently, this article holds importance in guiding researchers in the irisin field beyond 2025, offering insights into emerging trends and research directions.

Current research on irisin spans a wide range of fields, demonstrating its multifaceted roles and therapeutic potential. In metabolism, exercise induces the accumulation of circulating extracellular vesicles irisin, which enhances adipose energy metabolism, thermogenesis, and WAT browning, leading to weight loss.¹⁴ In the musculoskeletal system, studies highlight irisin's importance in maintaining muscle physiology and systemic energy homeostasis during aging, proposing irisin administration as a therapeutic strategy against age-related sarcopenia and metabolic dysfunction.^{20,56,57} A recent finding indicated that irisin downregulates the TLR4/MyD88/NF- κ B pathway, reducing IL-6 production in adipocytes and enhancing bone marrow mesenchymal stem cells (BMSCs) osteogenesis, offering a potential target for alleviating obesity-induced osteoporosis.⁵⁸ In neurodegenerative diseases, irisin has been shown to mitigate A β pathology through exercise-induced mechanisms, providing new therapeutic avenues for AD.^{21,59} Additionally, irisin may optimize gut microbiota and metabolism to counteract aging-induced cognitive impairment, with cerebrospinal fluid irisin levels correlating with AD biomarkers and clinical dementia scores, suggesting potential for liquid biopsy applications.^{60–62} In cardiovascular research, irisin improves cardiac function in type 1 diabetes mellitus (T1DM) by inhibiting ferroptosis via the SIRT1-p53-SLC7A11/GPX4 pathway and alleviates hypertension and vascular remodeling by restoring calcium homeostasis and reducing

A

Top 25 Keywords with the Strongest Citation Bursts



B

Top 25 References with the Strongest Citation Bursts

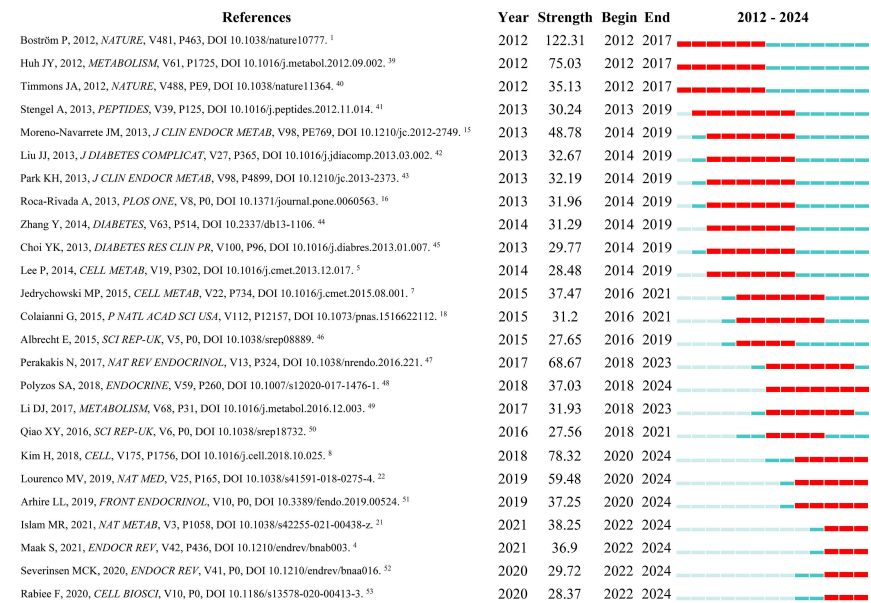


Figure 8 Burst detection of irisin-related literature and its keywords. **(A)** Top 25 keywords with the strongest citation bursts. **(B)** Top 25 references with the strongest citation bursts.

endoplasmic reticulum stress in vascular smooth muscle cells (VSMCs).^{27,63} While FNDC5/irisin shows promise in treating chemotherapy-induced cardiotoxicity, its protective effects are diminished in aged mice due to reduced cardiac FNDC5 expression.⁶⁴ In nephrology, innovative macrophage membrane-coated metal-organic framework (MCM@MOF) have been developed as nanocarriers for irisin, overcoming its short circulation time, limited renal targeting, and low membrane permeability. Irisin-loaded biomimetic nanotherapeutics protect mitochondrial function and modulate superoxide dismutase 2 (SOD2) levels in renal tubular epithelial cells, effectively mitigating acute ischemia-reperfusion injury.²⁹ Irisin also emerges as a key mediator of muscle-kidney crosstalk, inhibiting cGAS-STING signaling and preventing dsDNA leakage via integrin $\alpha V/\beta 5$, thereby reducing tubular injury and inflammation.⁶⁵ These findings position irisin as a promising predictive biomarker and preventive strategy for contrast-induced acute kidney injury. Collectively, these studies provide robust experimental evidence, significantly advancing the clinical translation of irisin.

Numerous cross-sectional studies have indicated that circulating irisin levels are significantly associated with the presence, severity, and progression of a range of chronic diseases, including obesity, T2DM, non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, AD, sarcopenia, osteoporosis, atherosclerosis, heart failure, and CKD. As a direct product of exercise, circulating irisin levels may objectively reflect an individual's physiological status.³⁹ Mechanistically, irisin is directly involved in core pathophysiological processes enhancing its biological relevance as a biomarker.^{3,39} However, heterogeneity in detection methods and insufficient antibody specificity, coupled with the lack of internationally standardized assays and reference ranges, have complicated the comparison and replication of findings across studies, impeding its clinical translation. While the association of irisin with numerous chronic conditions underscores its broad utility, this also constitutes a limitation: aberrant irisin levels lack specificity for any single disease and may instead serve as a global biomarker reflecting overall metabolic and inflammatory health.

Despite considerable progress in irisin research, numerous fundamental questions remain unresolved, including an unclear pharmacological mechanism, unconfirmed transmembrane receptor, and lack of human validation for the integrin $\alpha V/\beta 5$ complex hypothesis, along with tissue-specific signaling pathway variations and disparate AMPK activation efficiencies across tissues.⁶⁶ The mechanisms by which small peptides such as irisin signal through integrins remain poorly understood; however, recent work by Bruce M. Spiegelman's team has demonstrated that extracellular heat shock protein 90 α (eHsp90 α), secreted by muscles in response to exercise, activates integrin $\alpha V/\beta 5$, facilitating high-affinity irisin binding and signal transduction through the Hsp90 $\alpha/\alpha V/\beta 5$ complex.⁶⁷ Delivery system limitations, such as the short half-life of recombinant irisin (45–60 minutes) and insufficient blood-brain barrier penetration, could be potentially addressed in the near future through engineered exosome technologies.^{6,11,68–70} Safety concerns persist, with risks of antibody induction and arrhythmogenicity during long-term high-dose administration, while standardization of detection methods remains inadequate, evidenced by high coefficient of variation among commercial ELISA kits and significant discrepancies across platforms.⁷¹ Scalable production faces challenges, with *Pichia pastoris* expression systems yielding a relatively low concentration, requiring substantial cost reduction to achieve commercialization. Population heterogeneity further complicates application, as irisin bioactivity is diminished in obese individuals, with a reduction in receptor binding efficiency.^{72,73} Further research advancements are imperative to unlock the future clinical applications of irisin.

Furthermore, Future efforts should focus on developing more specific and accurate methods for quantifying bioactive irisin, conducting large-scale prospective cohort studies to establish its predictive value, constructing multi-marker panels integrated with machine learning algorithms for improved disease prediction and risk assessment, and employing Mendelian randomization to clarify causal relationships between irisin and various chronic diseases. Irisin remains a highly promising candidate biomarker and deepens our molecular understanding of the concept that “exercise is medicine”.

This study has several limitations, including its reliance solely on the WoSCC database, which disregards Scopus and Embase, as well as the exclusion of document types other than articles and review articles, which may limit the comprehensiveness of the literature coverage. Potential under-detection of relevant literature could arise from delayed updates in synonyms, abbreviations, or emerging terminology. The bibliometric analysis cutoff date of December 31, 2024, excludes the latest publications, while the restriction to English-language articles introduces geographic or linguistic bias. Cluster analysis may over-merge heterogeneous themes, and burst detection is susceptible to short-term hotspot interference. The study quantifies publication volume rather than research quality, unable to assess experimental design rigor or sample size adequacy, potentially allowing low-quality literature to influence results. Moreover, the

inability to analyze graphical data or negative findings may lead to partial conclusions. Future research should employ larger sample sizes, more comprehensive databases, and include unpublished data to ensure conclusions more accurately reflect the true state of the field.

Conclusion

Irisin holds significant research value and promising application prospects. The rapidly increasing number of publications indicates that irisin research is gaining growing attention from scholars worldwide. Leading countries in this field are China and the United States, yet collaboration and exchange among nations and institutions still require further enhancement. From its role in adipose and energy metabolism to its protective effects on the musculoskeletal, cardiac, renal, and nervous systems, irisin exhibits immense potential for clinical applications in the future. As an exercise-mimetic factor, irisin is poised to bring about a paradigm shift in the fields of public health and health management, offering interventions for aging and chronic diseases in a simple and accessible manner, thereby improving individual health and alleviating societal burdens. Moreover, the growing body of irisin-related research is progressively providing a robust theoretical foundation for the health benefits of exercise. It is hoped that an increasing number of researchers will dedicate their efforts to translating irisin research findings into clinical applications, ultimately benefiting patients.

Abbreviations

FNDC5, fibronectin type III domain-containing 5; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator 1- α ; WAT, white adipose tissue; UCP1, uncoupling protein 1; BDNF, brain-derived neurotrophic factor; AD, Alzheimer's disease; CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus; WoSCC, Web of Science Core Collection; BMSCs, bone marrow mesenchymal stem cells; T1DM, type 1 diabetes mellitus; VSMCs, vascular smooth muscle cells; MCM@MOF, macrophage membrane-coated metal-organic framework; SOD2, superoxide dismutase 2; eHsp90 α , extracellular heat shock protein 90 α .

Data Sharing Statement

The datasets utilized throughout this investigation can be obtained from the corresponding author Juan Wang upon a reasonable inquiry.

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Disclosure

The authors report no conflicts of interest in this work.

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