REVIEW

Pharmacology Discovery 2024;4(3):17. https://doi.org/10.53388/PD202404017

Bibliometric analysis of 100 most-cited papers on Icariin

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Author contributions

Shen YF and Mao L contributed to data collection and verification. Huang XP contributed to the methodology. Zhu K contributed to data analysis. Shen YF and Zhu JL contributed to writing the original draft. Chang DG and You YD contributed to editing, and Yang DD contributed to the review.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This study was supported by the Natural Science Foundation of Sichuan Province (2023NSFSC1799), and the Science and Technology Development Fund of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (21ZS05, 23YY07).

Peer review information

Pharmacology Discovery thanks all anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations

AD, Alzheimer's disease; BMSCs, bone marrow mesenchymal stem cells; BMP2, bone morphogenetic protein-2; Cbfa1, Core binding factor a1; DA, dopamine; ERK, extracellular regulated protein kinases; LSP, Lipopolysaccharide; PD, Parkinson's disease; PDE5, Phosphodiesterase 5; Smad4, Recombinant Mothers Against Decapentaplegic Homolog 4; AKT, serine/threonine kinase; SN, substantia nigra; CMS, chronic moderate stress; HCC, hepatocellular carcinoma; HPA, hypothalamic-pituitary-adrenal.

Citation

Mao L, Shen YF, Zhu K, et al. Bibliometric analysis of 100 most-cited papers on Icariin. *Pharmacol Discov*. 2024;4(3):17. doi: 10.53388/PD202404017.

Executive editor: Ting Yu.

Received: 20 February 2024; **Accepted:** 02 September 2024; **Available online:** 04 September 2024.

Abstract

Icariin is the most prevalent component of the medicinal herb *Herba Epimedii*. Icariin exhibits many medicinal properties, including anti-cancer impact and osteoprotective and neuroprotective effects. The goal of this study was to use bibliometric analysis to find and describe the top 100 papers about Icariin that had received the most citations. The Science Citation Index-Expanded (SCI-E) of the Web of Science Core Collection was used to find publications on Icariin (WoSCC). Descriptive analysis was conducted using VOSviewer software. There were 1473 articles about Icariin in all. The top 100 papers were published between 1996 and 2024 and received citations in the range of 55 to 390. The country that has contributed the most to Icariin research is China (84). The most productive institution was Fudan University. The most published journal was Phytomedicine. The research hotspots of Icariin mainly focus on the following aspects: research on Icariin treatment of sex hormone-related osteoporosis and erectile function; The effect of Icariin on cells by regulating oxidative stress, apoptosis, and proliferation; the mechanism of Icariin in the treatment of cancer; the neuroprotective effect of Icariin in central nervous diseases, such as Alzheimer's disease, Parkinson's disease, and depression. Future research should focus on further elucidating Icariin's anti-tumor effects, its application in cartilage tissue engineering and orthopedic biomaterials, and developing novel drug delivery systems to enhance its bioavailability. This research contributed essential knowledge to the study of Icariin. These results may be used in new study areas and to direct drug development.

Keywords: Icariin; *Herba Epimedii*; VOSviewer; bibliometrics

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Background

Herba Epimedii is a significant medicinal plant that has been utilized for thousands of years in a variety of traditional Chinese formulations as well as in contemporary, patented traditional Chinese medicine products. It has a wide range of therapeutic applications, particularly for osteoporosis and sexual dysfunction. The majority of the more than 260 chemical moieties found in the genus Epimedium are flavonoids. The substance most prevalent in *Herba Epimedii* is icaridin. Icariin is pharmacologically bioactive and exhibits a wide range of therapeutic properties, including promoting reproductive health, osteoprotection, neuroprotection, cardiovascular protection, anti-inflammation, and anti-cancer activity. In particular, Icariin was a viable pharmacological option for bone tissue engineering due to its significant osteogenic impact [1]. It has been shown to outperform other flavonoids in promoting bone health by enhancing osteoblast maturation and combating osteoporosis [2, 3]. In clinical settings, Icariin adjunctively improves bone mineral density and alleviates pain, surpassing placebo effects in randomized controlled trials [4]. Neuroprotective, it inhibits key pathological processes in Alzheimer's disease and other neurodegenerative disorders, fostering improved cognitive function [5–7]. Icariin also demonstrates anti-inflammatory and anticancer activities, modulating various signaling pathways to reduce inflammation and hinder cancer progression [8]. Additionally, its estrogenic effects enhance sexual function and fertility by inhibiting PDE5 (phosphodiesterase 5) and boosting testosterone production [9]. Overall, Icariin's multifaceted therapeutic actions underscore its significant research value and vast therapeutic potential.

Bibliometric analysis is frequently used in various sectors to assess and gauge the significance of published works or emerging trends on a particular subject. Bibliometric analysis involves the quantitative study of literature using statistical methods, allowing researchers to objectively assess the impact and influence of published works within a specific field. This methodical approach provides valuable insights into the intellectual structure of a subject, revealing patterns of research productivity, collaboration, and knowledge diffusion. By examining the most-cited papers on Icariin, we can identify the seminal works that have shaped the understanding of this compound and its applications. Furthermore, bibliometric analysis offers a comprehensive view of the historical development of Icariin research by tracing the evolution of publication numbers over time. The publication years can indicate periods of increased interest or breakthroughs in the field, while the distribution of articles across different journals reveals the disciplinary boundaries and interdisciplinary connections related to Icariin research. By integrating these bibliometric indicators, researchers can not only grasp the current state of Icariin research but also anticipate future trends and identify gaps in the existing literature. Such insights are instrumental in guiding the allocation of research resources, proposing new hypotheses, and fostering innovative research questions that can push the boundaries of current knowledge. Bibliometric analysis plays a pivotal role in deciphering the complex web of scientific literature, providing a roadmap for future explorations in the realm of Icariin research. Through a meticulous examination of the most-cited papers, this study aims to contribute to the collective understanding of Icariin's significance and potential, thereby advancing the scientific discourse and contributing to the discovery of new therapeutic applications.

In order to give a bibliometric analysis of the development of Icariin research, we undertook the current study with a focus on the 100 most cited publications and a thorough assessment of the citation classics devoted to Icariin.

Methods

Data source and retrieval

The last search was conducted on May 21, 2024, using the Science Citation Index-Expanded (SCI-E) of the Web of Science Core Collection (WoSCC). Icariin-related subjects were included in the data retrieval approach. The following are the search terms: (TS = Icariin) OR TS = (Icariine). The publishing type and language were unrestricted. The titles and abstracts of each included paper were examined independently by two researchers. The two reviewers' differences were settled through adjudication by a third party. There were determined the top 100 articles.

Statistical analysis

The descriptive analysis was conducted using VOSviewer. All documents published on Icariin and their annual publication numbers, and topics were first exported. We analyzed the general publication trend in this field and the number of published documents and cooperative relations in each country with VOSviewer. Then we use the website function of the WOS database to rank the literature by the number of citations and export the top 100 articles by the number of citations. The analysis of authors and journals was completed using the statistical function of VOSviewer, and this software was used for keyword analysis and clustering. Finally, we manually read titles and abstracts to summarize the research articles in the past three years and found possible future research directions.

Result

General trends in Icariin publications

The search results included 1473 articles on Icariin. In Figure 1 the publications of Icariin have been showing an upward trend, especially from 41 in 2011 to 208 in 2022, with a fast speed increase. China has the largest number of studies (1417), followed by the United States

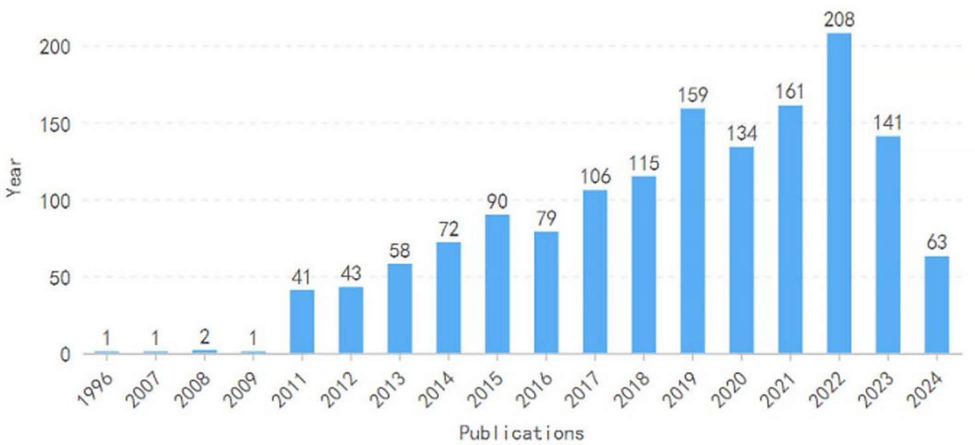

Figure 1 Annual number and trend of Icariin publications

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(78), and South Korea (51). The connection between countries shows China's close cooperative relationship with the United States, Japan, Australia, and South Korea. Research directions mainly involve pharmacology, chemistry and molecular biology. In addition, these studies include complementary and alternative medicine, oncology, neuroscience, endocrinology and metabolism, immunology, urology and nephrology, shown in Figure 2.

Distribution characteristics of the top 100 cited literature of Icariin

The top 10 cited articles and reviews are shown in Table 1. The top 100 papers were published between 2008 and 2022, and they received citations in the range of 55 to 390. Eighty-three original articles and seventeen reviews are included.

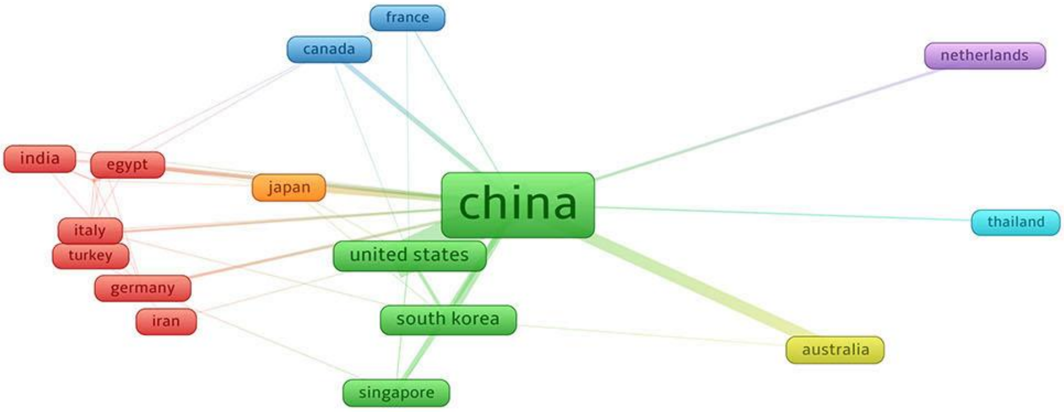

Figure 2 Research directions for icariin publications

Table 1 The top 10 cited articles and reviews of icariin

Type	Titles	First Author	Year	Journals	Citations
Article	Porous composite scaffold incorporating osteogenic Phyto molecule icariin for promoting skeletal regeneration in challenging osteonecrotic bone in rabbits	Lai, YX	2018	Biomaterials	200
Article	Icariin inhibits osteoclast differentiation and bone resorption by suppression of MAPKs/NF-κB regulated HIF-1α and PGE2 synthesis	Hsieh, TP	2011	Phytomedicine	156
Article	Icariin induces osteoblast proliferation, differentiation, and mineralization through estrogen receptor-mediated ERK and JNK signal activation	Song, LG	2013	The European Journal of Pharmacology	155
Article	ICARIIN EXERTS AN ANTIDEPRESSANT EFFECT IN AN UNPREDICTABLE CHRONIC MILD STRESS MODEL OF DEPRESSION IN RATS AND IS ASSOCIATED WITH THE REGULATION OF HIPPOCAMPAL NEUROINFLAMMATION	Liu, B	2015	Neuroscience	153
Article	Icariin is More Potent Than Genistein in Promoting Osteoblast Differentiation and Mineralization In vitro	Ma, HP	2011	Journal of Cellular Biochemistry	128
Article	Icariin and its derivative, ICT, exert anti-inflammatory, and anti-tumor effects, and modulate myeloid-derived suppressive cells (MDSCs) functions	Zhou, JM	2011	International Immunopharmacology	121
Article	Icariin alleviates osteoarthritis by inhibiting NLRP3-mediated pyroptosis	Zu, Y	2019	Journal of Orthopaedic Surgery and Research	120

Table 1 The top 10 cited articles and reviews of icariin (*continued*)

Type	Titles	First Author	Year	Journals	Citations
Article	Icariin and its Derivative Icariside II Extend Healthspan via Insulin/IGF-1 Pathway in C. elegans	Cai, WJ	2011	Plos One	104
Article	Colon-targeted oral drug delivery system based on alginate-chitosan microspheres loaded with icariin in the treatment of ulcerative colitis	Wang, QS	2016	International Journal of Pharmaceutics	102
Article	Potent inhibition of human phosphodiesterase-5 by icariin derivatives	Dell'Agli, M	2008	Journal of Natural Products	102
Review	Natural products for the treatment of osteoporosis: The effects and mechanisms on promoting osteoblast-mediated bone formation	An, J	2016	Life Sciences	390
Review	Anti-aging active ingredients from herbs and nutraceuticals used in traditional Chinese medicine: pharmacological mechanisms and implications for drug discovery	Shen, CY	2017	British Journal of Pharmacology	244
Review	Pharmacological effects and pharmacokinetic properties of icariin, the major bioactive component in *Herba Epimedii*	Li, CR	2015	Life Sciences	229
Review	Functions and action mechanisms of flavonoids genistein and icariin in regulating bone remodeling	Ming, LG	2013	Journal of Cellular Physiology	188
Review	The effect of icariin on bone metabolism and its potential clinical application	Wang, Z	2018	Osteoporosis International	186
Review	Pharmacological Effects of Active Components of Chinese Herbal Medicine in the Treatment of Alzheimer's Disease: A Review	Wang, ZY	2016	American Journal of Chinese Medicine	136
Review	Neuroinflammation in Alzheimer's Disease	Onyango, IG	2021	Biomedicines	119
Review	"Sweet Flavonoids": Glycosidase-Catalyzed Modifications	Slámová, K	2018	International Journal of Molecular Sciences	117
Review	Antidepressant active ingredients from herbs and nutraceuticals used in TCM: pharmacological mechanisms and prospects for drug discovery	Wang, YS	2019	Pharmacological Research	111
Review	Chinese herbal medicine for Alzheimer's disease: Clinical evidence and possible mechanism of neurogenesis	Yang, WT	2017	Biochemical Pharmacology	111

Countries and institutions distribution of top 100 cited literature of Icariin

Figure 3 displays the 100 most cited articles' publication years and country/region distribution. Table 2 lists the top 5 regions/countries and institutes on icariin research. The top 100 articles cited are from Seventeen different nations. China (82 publications and 6742 citations) and the United States (8 publications and 634 citations) are the two countries that have contributed the most resources to icariin research in rank.

A total of 123 institutions were included in the literature. Among the top 5 publications institutions, most are Chinese universities and research institutes, Fudan University (9 publications and 814 citations) ranked first, followed by Shanghai Jiao Tong University (7 publications and 756 citations). It shows China's dominant status in the field of icariin research has accelerated cooperation with other countries and regions.

Author and journal distribution of top 100 cited literature of icariin

A total of 539 authors were included. The most productive writers are shown in Table 3. Gong, Qi-Hai and Shi, Jing-Shan published four articles that were ranked top. Chen, Ke-Ming and Xian, Cory J got the most significant total citations (370). Only ten writers published three or more publications on icariin. The most frequently cited paper, which has been referenced 390 times, introduces the research progress of active compounds with potential anti-osteoporosis effects in traditional Chinese medicine such as icariin in osteoporosis, published by Jing An in 2016.

Ten journals published three or more studies on icariin, which together accounted for 43% of all the papers in our analysis (Table 3). Phytomedicine published the most articles (10), followed by European Journal of Pharmacology (6). 30% of the journals in the ranking belong to the JCR1 region, 50% of the journals belong to the JCR2 region, and 20% belong to the JCR3 region. The period with the highest impact factor is Phytomedicine (IF = 7.9) and the journal with the lowest impact factor is Asian Journal of Andrology (IF = 2.7).

Keywords distribution of top 100 cited literature of icariin

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Figure 3 Country/region collaboration map for icariin publications

Table 2 Distribution of top 100 cited literature of icariin across different countries and institutions

Country/Region	Count	Citations	Institute	Count	Citations
China	82	6742	Fudan Univ	9	814
United States	8	634	Shanghai Jiao Tong Univ	7	756
Australia	6	602	Jilin Univ	6	451
South Korea	5	300	Chinese Acad Sci	6	724
Canada	2	176	Capital Med Univ	6	547

Table 3 Author and journal distribution of top 100 cited literature of icariin

Authors	Documents		Journals	Documents	Citations	2023 impact factor	2023 JCR partition
Gong, Qi-Hai	4	301	Phytomedicine	10	1033	7.9	Q1
Shi, Jing-Shan	4	301	The European Journal of Pharmacology	6	705	5.0	Q2
Chen, Ke-Ming	3	370	International Immunopharmacology	4	340	5.6	Q2
Chen, Ming-Hong	3	334	Journal of Chromatography A	4	327	4.1	Q2
Dong, Jingcheng	3	256	Journal of Pharmaceutical and Biomedical Analysis	4	290	3.4	Q2
Guo, B. L.	3	235	Asian Journal of Andrology	3	221	2.9	Q2
Sheu, Shiow-Yunn	3	334	Journal of Ethnopharmacology	3	231	5.4	Q1
Sun, Jui-Sheng	3	334	Pharmacology Biochemistry and Behavior	3	253	3.6	Q1
Wu, Qin	3	211	Planta Medica	3	211	2.7	Q3
Xian, Cory J.	3	370	Biochemical and Biophysical Research Communications	3	278	3.1	Q3

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The top 30 keywords in publications on icariin are listed in Table 4. The most common keywords were icariin, in-vitro, expression, flavonoids, activation, cells, osteogenic differentiation, osteoporosis, differentiation, and marrow stromal cells. The cluster analysis of keywords found that the top 100 cited icariin literature mainly focused on the following research directions in Table 5: (1) Research on icariin treatment of sex hormone-related osteoporosis and erectile function; (2) The effect of icariin on cells by regulating oxidative stress, apoptosis, and proliferation; (3) The mechanism of icariin in the treatment of cancer; (4) The neuroprotect effect of icariin in central nervous diseases, such as Alzheimer's disease, Parkinson's disease and depression. Figure 4 illustrates the clustering and linkages between the keywords in the study, and Figure 5 shows the heat trends of the keywords in the study over time.

Table 4 Top 30 keywords of top 100 cited literature of Icariin

No.	Keywords	Count	No.	Keywords	Count	No.	Keywords	Count
1	Icariin	344	11	Marrow stromal cells	65	21	Pathway	40
2	*In-vitro*	143	12	Postmenopausal women	63	22	Rank	40
3	Expression	122	13	Nf-kappa-b	56	23	Model	39
4	Flavonoids	88	14	Apoptosis	53	24	Proliferation	38
5	Activation	81	15	Alzheimers-disease	52	25	Estrogen	36
6	Cells	72	16	Herba-epimedium	50	26	Inflammation	35
7	Osteogenic differentiation	70	17	Icariin	49	27	Nitric-oxide synthase	35
8	Osteoporosis	66	18	Mice	45	28	Inhibition	34
9	Differentiation	65	19	Rats	44	29	Mesenchymal stem cells	34
10	Marrow stromal cells	65	20	Osteoblast	43	30	Dependent osteoblastic functions	33

Table 5 Top 100 keyword cluster analysis of top 100 cited literature of Icariin

Cluster	Keywords
1	osteogenic differentiation, marrow stromal cells, postmenopausal women, herba-epimedium, osteoblast, mesenchymal stem-cells, dependent osteoblastic functions, epimedium, bone, cbfa1 expression, estrogen-receptor-alpha, herba epimedium, mcf-7 cells, chondrocytes, er-xian decoction, osteoblast differentiation, total flavonoids, ipriflavone, regeneration, vivo, erectile function, mass-spectrometry, cells, osteoporosis, osteoblasts, genistein, bone loss, isoflavones, phosphodiesterase-5
2	expression, flavonoids, apoptosis, icariin, proliferation, nitric-oxide, phytoestrogens, osteoprotegerin, osteoclast, cardiomyocyte differentiation, cytokine, reactive oxygen species, desmethylicaritin, hippocampus, icariside ii, oxidative stress, antioxidants, induced apoptosis, mechanism
3	in-vitro, differentiation, rankl, estrogen, nitric-oxide synthase, controlled trial, gene expression, cancer, phosphorylation, flavonol glycosides, breast cancer, receptor, bmp-2, growth, kinase, assay, alpha, angiogenesis, berberidaceae
4	icariin, alzheimers-disease, mice, model, inflammation, protein, embryonic stem cells, extract, stress, memory, learning and memory, pathways, human endothelial cells, lipopolysaccharide, accumulation, alzheimer's disease, pathogenesis, depression, activation, nf-kappa-b, rats, pathway, inhibition, neuroprotection, damage, involvement, Parkinson's disease, neurotoxicity, microglia, regulator, sirt1, oxygen, protects

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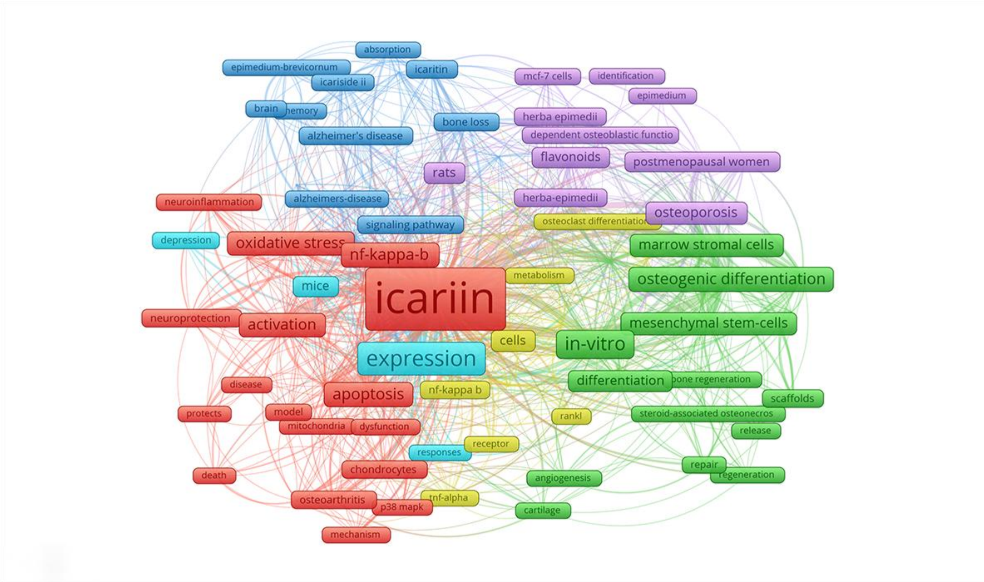

Figure 4 Key words collaboration of top 100 cited literature of icariin

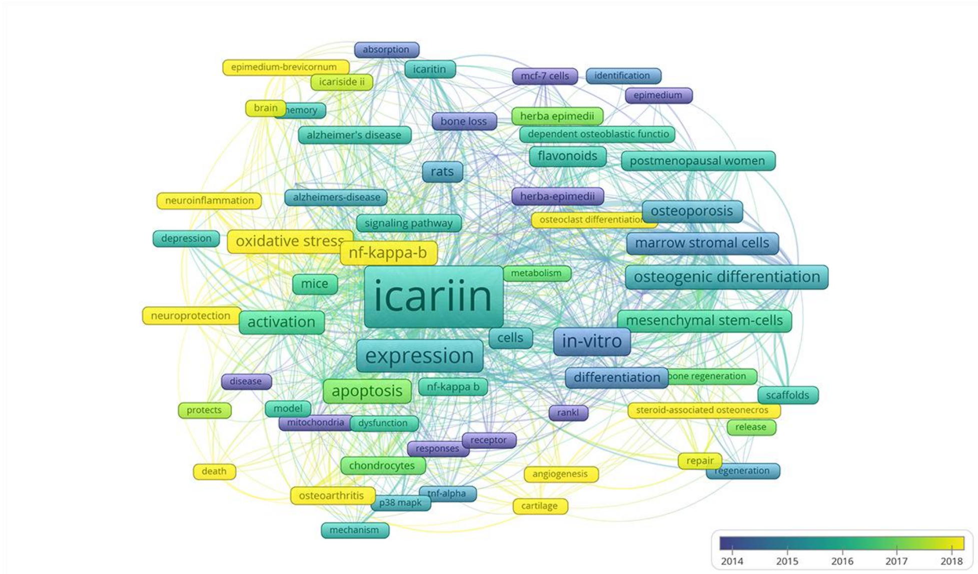

Figure 5 Key words time distribution of top 100 cited literature of Icariin

Discussion

Overview of Icariin research landscape

In this study, we have comprehensively identified and ranked the top 100 publications on icariin, providing the first bibliometric analysis of this field. Our analysis has allowed us to recognize significant developments and identify foundational works that have shaped the understanding of icariin. The quantitative data presented in this article, including information on nations, organizations, authors, journals, co-cited journals, and keywords, serves as a valuable resource for physicians and scientists looking to understand current trends and plan future research directions.

Bibliometric analysis and ranking of key papers

Our bibliometric analysis has revealed that the paper by Jing An et al., which The article focuses on osteoblasts and reviews the detailed research progress of active compounds with potential anti osteoporosis effects in traditional Chinese medicine such as icariin, as well as their molecular mechanisms promoting osteoblast mediated bone formation, with a maximum of 390 citations. The year 2022 saw the release of the majority of the most-cited articles, with a significant number also published in 2019, 2021, and 2023, indicating a period of heightened research activity in this field. The geographical distribution of publications is also noteworthy, with over 80% of the top 100 papers originating from China, likely because Epimedium, the source of icariin, is extensively utilized in traditional Chinese medicine and has been developed historically in China.

Global collaboration and contributions

The analysis of international collaboration reveals that China has made essential contributions to icariin research and has engaged in significant partnerships with the United States, Japan, Australia, and South Korea. Fudan University stands out as the most prolific institution in icariin-related research, significantly impacting other organizations. Ten journals have published three or more papers on icariin, with the majority focusing on pharmacology. Notably, Phytomedicine has published ten papers, and the European Journal of Pharmacology has six, highlighting icariin's status as a globally studied herb involved in various therapeutic processes.

Key research areas and findings

The keyword distribution suggests that research on icariin revolves around several key areas (Figure 6).

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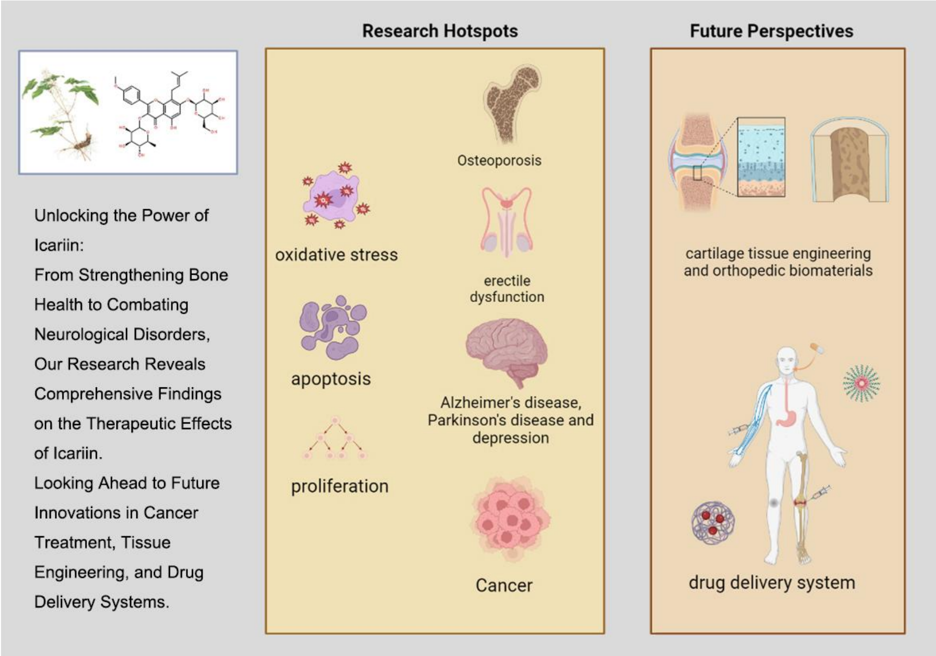

Figure 6 Hotspots and future directions of epimedium research

Osteoporosis and erectile dysfunction treatment. Studies indicate that icariin may prevent bone loss in postmenopausal women and enhance osteoblast growth, differentiation, and mineralization. Additionally, icariin's neurotrophic properties and its ability to inhibit phosphodiesterase type 5 make it a potential treatment for erectile dysfunction. Osteoporotic fractures develop in menopausal women as a result of the menopause's onset and the fast estrogen withdrawal [10]. It was discovered that icariin might prevent bone loss in late postmenopausal women without causing any discernible endometrial hyperplasia [11]. This icariin's antiosteoporotic action was also reported in ovariectomized rats and *in vitro* cell experiment [12, 13–16]. Icariin might promote osteoblast growth, differentiation, and mineralization by controlling the expression of BMP2(bone morphogenetic protein-2), SMAD4 (Recombinant Mothers Against Decapentaplegic Homolog 4), and Cbfa1 (Core binding factor a1), inhibit p38/JNK and active ERK/JNK signal pathway [17–19]. The treatment of erectile dysfunction using Epimedium species has long been used in Traditional Chinese Medicine. Icariin has neurotrophic properties and inhibits phosphodiesterase type 5 in rats with injured cavernous nerves, could improve erectile function of aged rats and castrated rats [20–22].

Cellular effects on oxidative stress, apoptosis, and proliferation. Icariin's anti-oxidative activities are linked to its role in inducing enzymes that scavenge free radicals. It also significantly influences cell migration, reduces apoptosis, and restores mitochondrial membrane potential in vascular endothelium cells. Icariin's anti-oxidative activities are linked to its inductive influence on endogenous enzymes that scavenge free radicals, and flavonoids' natural capacity to donate electrons [23]. The vascular endothelium is particularly sensitive to oxidative stress. Icariin significantly increased cell migration and capillary tube formation in vascular endothelium cells, significantly reduced hydrogen peroxide (H_2O_2)-induced apoptotic and autophagic programmed cell death that was associated with decreased intracellular reactive oxygen species levels, and restored mitochondrial membrane potential [24].

Cancer treatment mechanisms. *In vitro* and *in vivo* studies demonstrate icariin's anti-cancer activity against various cancer cells through mechanisms like apoptosis, cell cycle modulation, anti-angiogenesis, anti-metastasis, and immunomodulation. Icariin is particularly effective in targeting cancer stem cells and drug-resistant cancer cells. This activity is mediated by a variety of mechanisms, including apoptosis, cell cycle modulation, anti-angiogenesis, anti-metastasis, and immunomodulation. Notably, icariin is efficient at targeting cancer stem cells and drug-resistant cancer cells [25]. Icariin can regulate the proliferation and apoptosis of human ovarian cancer cells, human prostate cancer PC-3 cells, breast cancer cells and human liver cancer SMMC-7721 cells [26–29].

Neuroprotective effects on central nervous system disorders. Icariin shows promise in addressing neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, and depression. It enhances memory and learning processes, improves neuronal cell survival, and regulates multiple signaling pathways implicated in these disorders. Alzheimer's disease (AD) is a neurodegenerative condition marked by the formation of beta-amyloid proteins and the gradual death of neurons (A beta). Icariin may enhance memory and learning processes by enhancing NO/cGMP signaling and coordinating the induction of NOS isoforms, improve the rat cortical neurons' atrophies of the axons and dendrites caused by amyloid beta (1–42), reduce the hyperphosphorylation of tau protein and increase the survival of neuronal cells, lowered synthesis of AV's insoluble fragments by suppressing P-secretase expression in rats with AD caused by A beta (25–35) [30–33]. Parkinson's disease (PD) is one of the most common neurodegenerative diseases characterized by a gradual loss of midbrain substantia nigra (SN) dopamine (DA) neurons. Icariin could shield DA neurons from LPS- and 6-OHDA-induced neurotoxicity both *in vivo* and *in vitro* by inhibiting microglia-mediated neuroinflammation, regulating PI3K/Akt and MEK/ERK pathways [34, 35]. The hypothalamic-pituitary-adrenal (HPA) axis and the hypothalamus-pituitary-thyroid (HPT) axis are thought to be affected abnormally by chronic moderate stress (CMS). Icariin may help to correct these abnormalities, reduce the NLRP3-inflammasomes in the brain, and exhibit antidepressant-like characteristics by the neuroendocrine and neurochemical systems [36–38].

Future perspectives on Icariin research and development

In order to further understand the development trend of icariin in recent years, the critical literature related to icariin in the past three years was screened by reading abstracts one by one. We found that the future hot trends and development directions of icariin may focus on the following aspects (Figure 6).

Anti-Tumor potential of Icariin

Recent approvals and research highlight icariin as a promising anti-tumor agent. In January 2022, China approved the launch of Icaritin as an advanced liver cancer drug, which further confirmed the potential of icariin in the field of cancer. Icaritin may enhance immunomodulation in individuals with advanced, prognostically dire hepatocellular carcinoma (HCC) associated with the hepatitis B virus [39]. Icaritin showed good safety profiles and early sustained survival effects in patients with advanced HCC [40]. As a typical plant ingredient to enhance immunity, it is in line with the idea of "supporting righteousness" in traditional Chinese medicine [41]. Modern pharmacological studies have shown that icaritin has an anti-tumor effect, including inhibiting gastric cancer, pancreatic cancer, colon cancer, oral squamous cell carcinoma, lung cancer, breast cancer, cervical cancer and ovarian cancer [42–60].

Icariin in cartilage tissue engineering and orthopedic biomaterials

Preliminary research suggests icariin may play a significant role in cartilage tissue engineering. Icariin could inhibit autophagy and inflammation, increase chondrocyte vitality, and promote chondrogenic differentiation of cartilage cells [61–64]. It may be an alternative to using certain growth factors and a possible stimulating substance for cartilage tissue creation [65]. A potential strategy for osteochondral defect repair uses composite hydrogels and scaffolds supplemented with icariin [66]. This innovative icariin-loaded hydrogel's incorporation of bone marrow mesenchymal stem cells (BMSCs) suggests greater effectiveness than a single BMSC injection [67, 68]. Additionally, chitosan and icariin-conditioned serum, fibrin-icariin nanoparticles are loaded in the poly (lactic-co-glycolic acid) scaffold have also been reported as a repair strategy for articular cartilage [69, 70]. Icariin contains properties that prevent osteoporosis and promote bone regrowth, which may induce osteogenesis in pre-osteoblastic cells [71–73]. Icariin-functionalized materials can enhance osteogenic capacity compared to conventional materials [74–76]. Icariin-encapsulated polymeric scaffolds printed in 3D effectively encourage osteogenesis [77–79]. icariin can be effectively loaded and released by SF/MBGNs-ICA scaffolds for a considerable amount of time, and the sustained-release icariin can support BMSC proliferation and differentiation for a considerable amount of time [80]. The innovative hierarchical biofunctionalized porous Ti6Al4V 3D-printed scaffold containing icariin might improve osteoporotic osseointegration through immunotherapy [81].

Innovative drug delivery systems for enhancing Icariin bioavailability

Despite its high solubility in organic solvents, icariin's low water solubility and oral bioavailability present challenges. With an oral bioavailability rate of just 12.02%, strategies are being explored to improve its absorption and efficacy [82]. Pharmaceutical innovations, structural changes, and absorption boosters can improve icariin's bioavailability. Icariin's use is restricted by its poor oral bioavailability and inefficient brain distribution; however, icariin-NGSTH, when delivered intranasally, has a quick and potent antidepressant-like effect [83]. Through the trigeminal epineurium-brain dura route, intradermal injection of icariin-HP-beta-cyclodextrin reduced the effects of traumatic brain damage [84]. Icariin's FBS-derived exosomes may develop into a novel nanoscale medication formulation for treating conditions that cause bone loss [85]. In ovarian cancer cells, improved icariin phytosomes demonstrate improved cellular penetration and apoptosis-inducing activity [86]. Icariin's aphrodisiac properties might be enhanced by zein-stabilized nanospheres acting as nanocarriers [87].

Limitations

Our study still has some limitations. First, we only searched SCI databases. Other databases such as Scopus, Medline or Embase were not searched. However, the literature in the SCI database has a broad coverage and includes some well-recognized journals. This bibliometric study can reflect the research trend of icariin and the research interests of scholars. Second, due to the tendency of newly published literature to be under-cited compared to earlier literature due to time, this may cause some newly published high-quality articles to be excluded from our analysis. Third, bibliometric research cannot fully quantify the value of research and contributions to the field based on citation counts. Self-citation can also increase the presence of bias in research. Older articles tend to have higher citation counts, which may skew the analysis towards earlier studies. This citation advantage could be due to their longer availability, allowing more time to be cited. Future studies should consider normalizing citation counts by the number of years since publication to provide a more balanced view of research impact.

Conclusions

The bibliometric analysis of the top 100 most-cited papers on icariin has revealed that research on this compound is multifaceted, addressing various biological activities and therapeutic potentials. The analysis showed a significant increase in publications on icariin over the past two decades. A notable surge in recent years indicates growing interest and recognition of its therapeutic potential. The findings of this study provide a comprehensive overview of the current state of icariin research, highlighting its impact on inflammation pathways, among other key areas of investigation. This study highlights important trends in icariin research, emphasizing its growing significance in pharmacology and therapeutic development. The insights gained from this bibliometric analysis can guide future research priorities and support the development of icariin-based treatments, ultimately benefiting clinical practice and patient care. Future research should focus on translating the pharmacological properties of icariin into clinical applications. For instance, investigating its efficacy and safety in clinical trials could pave the way for developing new therapeutic agents for osteoporosis and neurodegenerative diseases. Additionally, understanding its mechanisms of action at the molecular level can help design more effective drug formulations.

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