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Icariin Research Trends: Bibliometric Analysis

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Abstract: Icariin is a compound with various pharmacological effects, such as anti-osteoporosis, cardiovascular protection, anti-inflammatory, antitumor, immunoprotection, and sexual dysfunction improver. Over the past decades, several publications and literatures have studied the compound and its potential effects. This is a bibliometric analysis of academic studies related to icariin compounds, and their productivity. Therefore, this research aims to comprehensively analyse the findings of several articles related to icariin globally. The articles used were obtained from the Scopus database using the keywords "icariin" OR "icariine" OR "epimedii". Meanwhile, one of the inclusion criteria for the selection was articles published between 2010 and 2021. A total of 1,116 publications were then obtained from the search process, and the data were analyzed using VOSviewer, R-Studio (Biblioshiny). The results showed that the major contributing countries were China, South Korea, India, the United States, and Hong Kong, with a total of 844, 40, 26, 23, and 21 publications, respectively. Furthermore, the literatures were primarily published in pharmacology, chemistry, oncology, and biochemistry journals. The most mentioned compounds were icaritin, epimedium, flavonoids, icariside, and epimedin, which appeared in 41, 33, 29, 22 and 16 literatures, respectively. In the last 5 years, published research article focused on icariin's effects on osteoporosis, inflammation, Alzheimer, oxidative stress, and osteoarthritis. Different formulation technologies, such as solid dispersion, liposomes, nanoparticles, microemulsion, cyclodextrin inclusion complex, self-microemulsifying drug delivery system, nanoemulsion, and pH-sensitive nanoparticles, have been explored.

Keywords: Bibliometric; icariin; pharmacology; scopus; VOSviewer

Introduction

Epimedi plant has been used as a traditional herbal medicine for decades, and its main component is icariin, which contains C-3 glucosyl, C-4 methoxy, C-8 position isopentenyl, and C-7 rhamnosyl group (Shindel et al., 2010). Furthermore, Chinese Pharmacopoeia reported that icariin ($C_{33}H_{40}O_{15}$) has a molecular weight of 676.67 g/mol, and is the main compound present in the five Epimedii species, namely Epimedii brevicornum Maxim, Epimedii koreanum Nakai, Epimedii sagittatim Maxim, Epimedii pubescens Maxim, and Epimedii wushanense T. S. Ying (He et al., 2020).

The compound is known for its potential ability to prevent and treat sexual disorders, such as erectile dysfunction by inhibiting cGMP phosphodiesterase-5 (PDE5) (Dell'Agli et al., 2008). Several studies have also reported that it has a wide range of pharmaceutical effects, such as anti-osteoporosis (X. F. Li et al., 2013), cardiovascular protection (Zhou et al., 2014), antitumor (W. Li et al., 2014; Fang et al., 2019), immunoprotection (Sun et al., 2013), anti-inflammatory (Tao et al., 2013)(Xiong et al., 2016)(Kong et al., 2015), sexual dysfunction improver (Liu et al., 2011)(Ding et al., 2018), anti-oxidant (Song et al., 2016), and antidepressant (X. Zhang et al., 2017).

Meanwhile, numerous publications and studies have explored the field of icariin over the past few decades (Hui et al., 2020). They play an important role in bridging the knowledge gap as well as increasing knowledge absorption and application (Wiysonge et al., 2013). Professionals with a common interest in a

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particular field can collaborate to increase people's trust (Beshyah & Beshyah, 2019; Julkowska et al., 2017). Bibliometric analysis is an effective statistical method for quantifying global, national, organizational, and individual academic research on a specific topic using mathematical tools (Yu et al., 2020). Recently, it has been used across a wide range of disciplines to comprehensively identify scientific developments, as well as research hotspots and directions, which lays a foundation for future investigations (Pasin & Pasin, 2021).

Web of Science (WoS), Elsevier's Scopus (ES), Google Scholar (GS), as well as influential publishers, such as BioMed Central, Nature, Wiley, Frontiers, Elsevier and PLOS, are often used for publication data collection. This is because they have a wide range of literatures that provide comprehensive data for bibliometric analysis (Arshad et al., 2020)(Berlinberg et al., 2019). VOSviewer and R-Studio are also widely used for tabulation, charting, networking, and visualization to highlight the most influential countries, departments, authors, sources, and documents (van Eck & Waltman, 2010). Therefore, a bibliometric analysis was carried out to review publications and assess the current state of research relationship and. trends in drug icariin development. This research is expected to be useful to academic and clinical researchers as well as to serve as a guide for future studies.

Method

Literature Search

Literatures on icariin published between 2010 and 2021 were obtained from the Scopus database using the keywords "icariin" OR "icariine" OR "epimedii". Furthermore, the publications used were original article written in English, while the selected articles' data, such as the year of publication, language, journal, title, author, affiliation, keywords, document type, abstract, and the number of citations were exported into CSV format. The publications were extracted from the database on November 20, 2021, then, VOSviewer version 1.6.10 and R-Studio were used to analyze co-authorship, co-occurrence, citation, bibliographic coupling, co-citation, and themes. Visualization of similarities (VOS)" viewer software was used to graphically describe the bibliometric parameter by mapping networks, thereby aiding easy visualization (Sweileh et al., 2017).

Data Collection

The author filtered the selected literature and independently determined their eligibility. Publication data, such as authors, titles, abstracts, keywords, sources, languages, and citations, was downloaded in CSV format from the Scopus database.

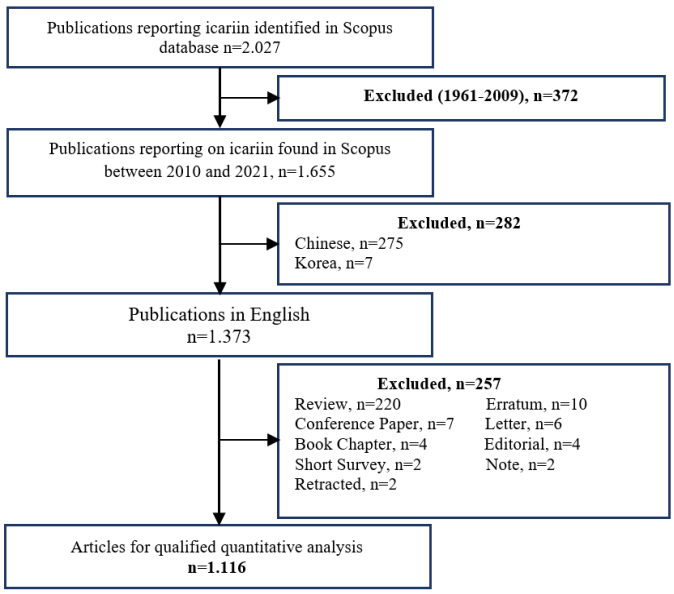

Figure 1. Publishing article selection flow diagram with Scopus

Bibliometric Analysis of Publication Output

A total of 1,116 publications met the predetermined inclusion criteria and were used for the quantitative analysis, as shown in Figure 1. Meanwhile, 282 documents written in other languages were excluded, including 25 Chinese and 7 Korean literatures. 257 publications, which comprise of 220 reviews, 10 errata, 7 conference papers, 6 letters, 4 editorials, 4 book chapters, 2 short surveys, 2 notes, and 2 retracted manuscripts, were also excluded as they were non-targets article type. Subsequently, analysis and data visualization was carried out on the selected publications using a variety of bibliometric applications and software, including MSExcel, VOSViewer, and Biblioshiny RStudio (http://bibliometric.com/). The analysis was conducted on the publication data obtained from Scopus, including the total number of documents, annual articles, countries, organizations, and authors as well as the distribution of research fields and the top-cited literatures.

Result and Discussion

Annual Publication Growth Forecast

The earliest articles on icariin indexed on Scopus were published in 1963 and 1984, and they examined its anti-progestational activity in the uterine endometrium as well as its function as an angiotensin-converting enzyme inhibitor (Kurouji, 1963; Inokuchi et al., 1984). A

total of 1,116 literatures published in 49 countries between 2010 and 2021 were obtained from the database. Meanwhile, exploration of the global geographic distribution of icariin articles showed that the top 5 contributors were China, South Korea, India, USA, and Hong Kong with a total of 844, 40, 26, 23, and 21 publications, respectively. China is the dominant country because it is an endemic place of epimedium plants (Dong et al., 2019).

Table 1 shows the total number of articles published annually, with trends of 40 articles in 2010 and 140 articles in 2020. Furthermore, an average of 93 articles were published annually, and the number icariin literature between 2010 and 2021 increased yearly. As of November 20, 2021, 127 articles were published in 2021. Figure 2 shows the distribution of countries studying the compound.

Table 1. Publication output Number of Icariin Research Annual Publications 2010-2021

Year	Articles
2010	40
2011	45
2012	67
2013	67
2014	69
2015	107
2016	78
2017	114
2018	123
2019	139
2020	140
2021	127

The top five Scopus data area subject categories are Biochemistry, Genetics and Molecular Biology (n = 514; 46.0%), Pharmacology, Toxicology and Pharmaceutics (n = 425; 38.0%), Medicine (n = 394; 35.3%), Chemistry (n = 216; 19.6%), and Agricultural and Biological Sciences (n = 92; 8.2%).

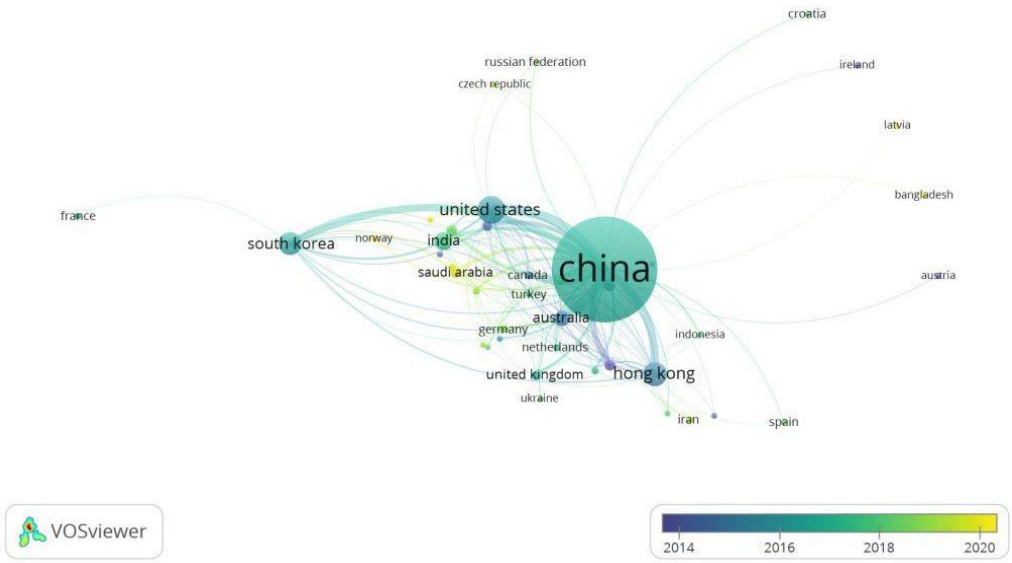

Figure 2. Map of the country network where the research is icariin

Publisher's Journal Distribution

There are 1,116 published academic journals related to icariin, and figure 3 shows the top 20 journals. Evidence-Based Complementary and Alternative Medic (H-Index 2021 = 13) had the highest number of publications (32 articles, 2.9%; 430 citasi), followed by Molecular Medicines Report (H-Index 2021 = 13; 29 publications; 2.6%, 366 citasi), Journal of Ethnopharmacology (H-Index 2021 = 14; 28 publications; 2.5%; 479 citasi), Biomedicines and Pharmacotherapy (H-Index 2021 = 13; 27 publications; 2.4%; 404 ideals), and Molecules (H-Index 2021 = 14; 24 publications; 2.2%, 511.

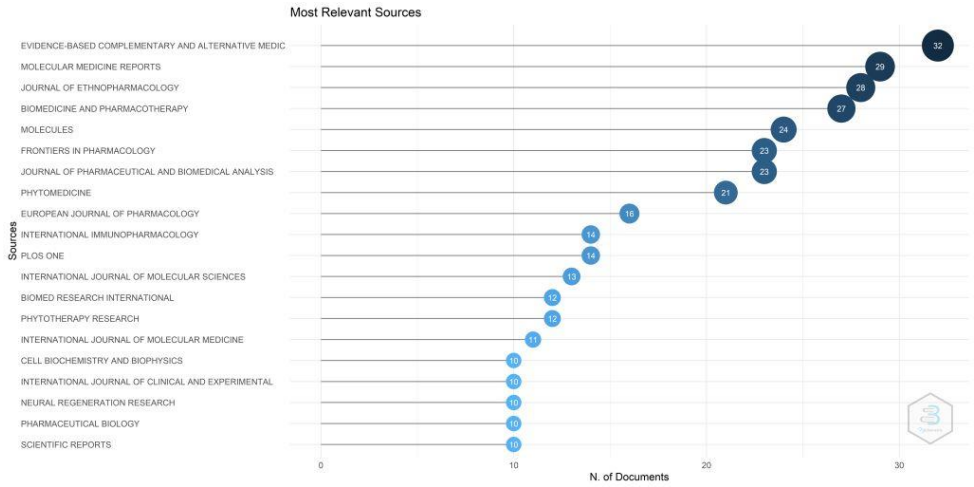

Figure 3. Top 20 contributor journals

Author or Researcher Actively Related to Icariin

Map of authors or researchers provides. information about research groups. and potential collaborators. This helps researchers find potential collaborators (Liang et al., 2017).

At least 3,224 authors contributed 1,116 articles related to Icariin research. Figure 4 shows a network of authors, while table 2 shows the top 10 active authors. Top-ranked Zhang Y. with 79 articles focused on atherosclerosis and diabetes (Y. Zhang et al., 2021; Jia Z et al., 2021). Meanwhile, Wang Y., the second top researcher, focused on improving osteogenic function (Wang et al., 2018).

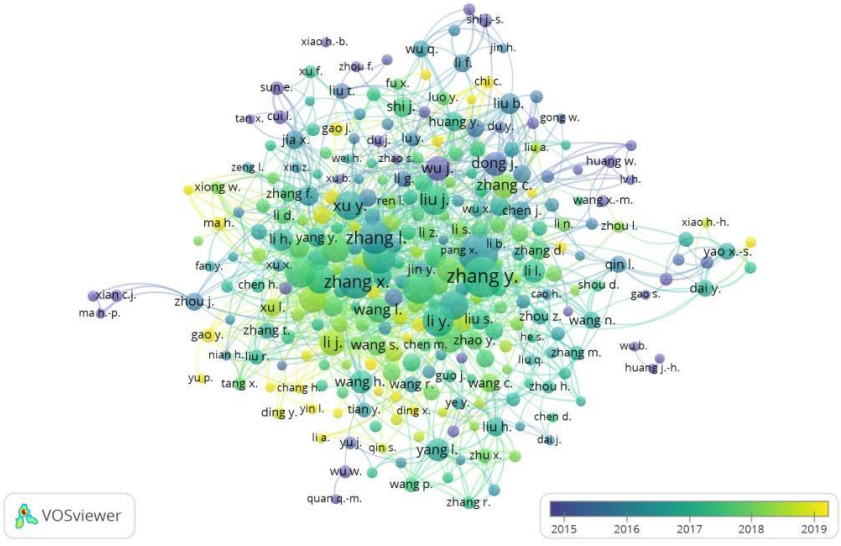

Figure 4. Network of authors contributes to icariin research

Figures 5 shows the top 5 institutions studying icariin, namely Fudan University, Jinan University, Zunyi Medical University, Huazhong University of Science and Technology, and Beijing University of Chinese Medicine, with a total of 269, 161, 159, 141, and 127 publications, respectively.

Figure 6 shows the result of visual analysis carried out with VOSviewer on the words used by the author and Scopus. In the analysis and visualization, keywords appeared at least 5 times in each literature (n = 115; 4.2%). The word size indicates how often a word appears, and when it appears multiple times in a manuscript, it counts as one. Meanwhile, the colour of the bubble represents the average year quote of the term. Icariin was the most reoccurring keyword used by the authors.

Figure 6 shows the most mentioned chemicals in the publications, including icaritin (n = 41), epimedium (n = 33), flavonoids (n = 29), icariside (n = 22) and epimedin c (n=16). Meanwhile, Figure 7 shows the chemical structure of icariin.

Table 2. Top 10 active authors in the field of icariin research

Author	Number of published articles	Number of citation
Zhang y.	79	984
Wang y.	76	1342
Zhang x.	54	903
Wang x.	52	730
Zhang l.	52	701
Liu y.	50	869
Wang j.	46	854
Li y.	46	558
Liu j.	43	653
Xu y.	41	868

Research Topic Trends

In the last five years, studies on icariin have explored its effects on tumors, inflammation, stem cells, testosterone and osteoarthritis. Figure 8 shows the trends in research topics between 2010-2021.

Scientific publications are an important tool for adding knowledge and information to new medical discoveries, as their analysis helps researchers to determine the quantity and quality of the research field. Meanwhile, bibliometric analysis is used to analyze publication data, such as citations, journals, authors, and various categories of information. This research is the first bibliometric analysis of icariin literature, hence, it is expected to lay the foundation for future studies. The research offers a general perspective of Icariin exploration in the 2010-2021.

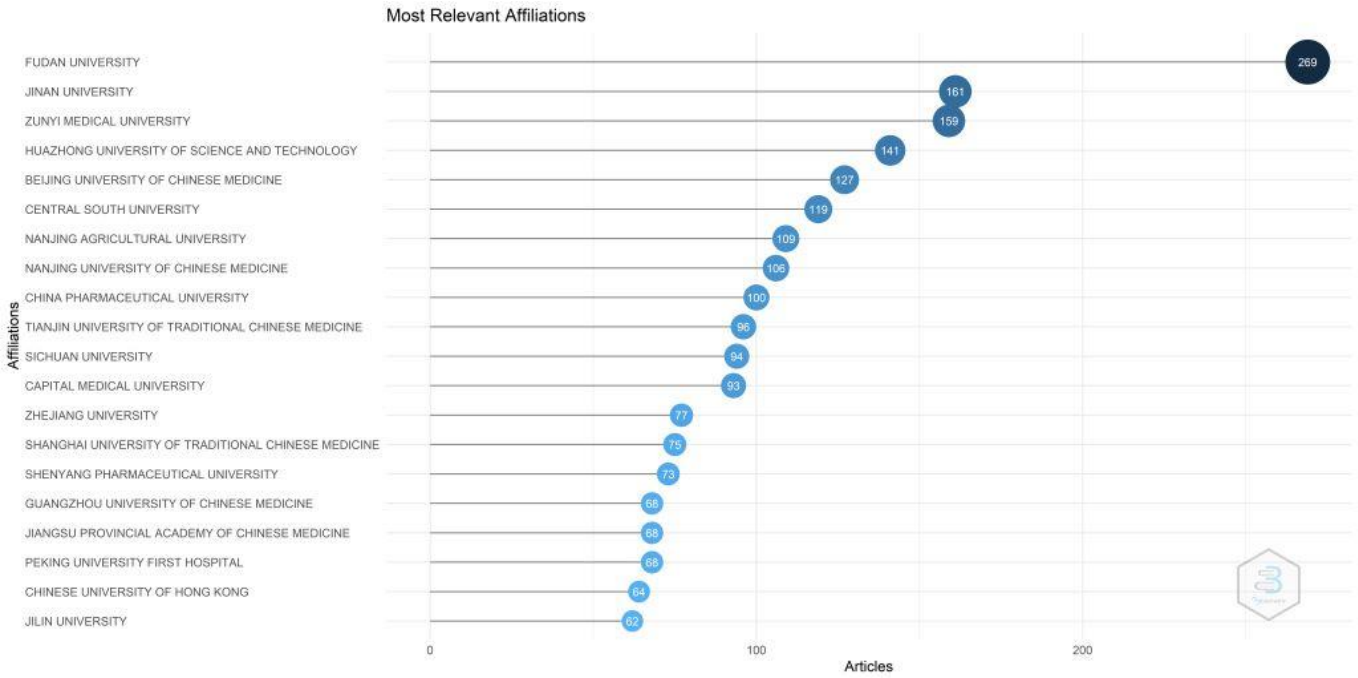

Figure 5. Top 20 contributor institutions

Relevant Keywords

Furthermore, the research summarized 1,116 publications obtained from Scopus, which provided insights on organizations, countries, authors, citations, keywords, and topic trends. The largest number of articles was written by Zhang Y, and most of the publications were written and published in English, followed by Chinese and Korean. Icariin is the active compound in epimedii plant that is widely found in China, hence, the country had the highest number of publications. Furthermore, the research of epimedii and icariin herbs should be expanded to create a network of cooperation and raise awareness about their potential, which creates sustainable economic growth. The majority of the research only explored certain areas, but when conducted in cooperation, it increases the scope of research.

Pharmacological Activity of Icariin

Here is a table of research related to pharmacological activities of icariin, including types of studies, findings, and their references:

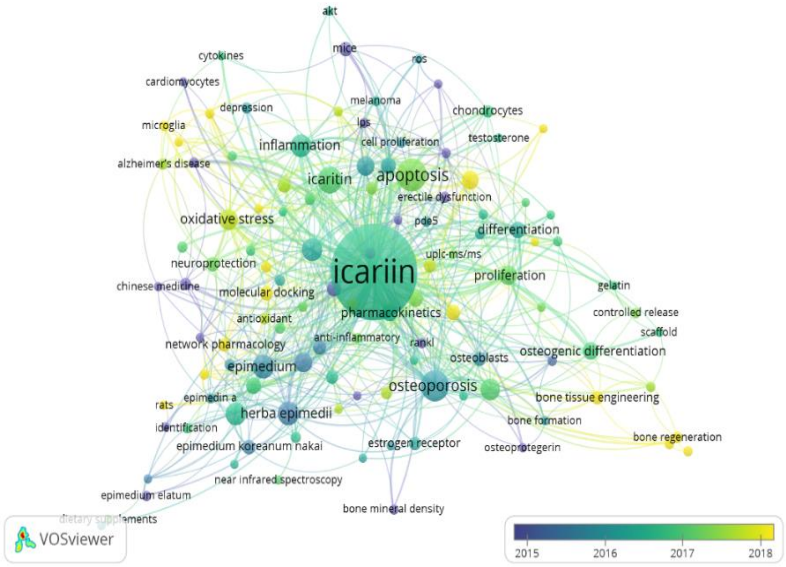

Figure 6. Bubble maps visualize keywords from 1,116 icariin publications

Table 3. Pharmacological Activity of Icariin

Pharmacological Activity	Types of Research	Result	Ref.
Antioxidant	In vitro	Lowers ROS and MDA levels, increases SOD and GSH	(Luo et al., 2004)
Anti-inflammatory	In vitro and in vivo	Inhibits the production of TNF-α, IL-1β, and IL-6, reduces infiltration of inflammatory cells	(Kong et al., 2015)
Osteogenesis	In vitro and in vivo	Improves the expression of Runx2, OCN, and Col1a1, increasing the density of trabecular bones	(Qin et al., 2013)
Neuroprotective	In vitro and in vivo	Icariin shows neuroprotective effects in 3 9 Tg-AD mice and may be a promising multitarget drug in the prevention/protection against AD.	(Chen et al., 2016)
		ICA pretreatment may promote autophagy by activating the ERα and ERβ pathways, thus reducing the apoptosis induced by HIBD and exerting a neuroprotective effect on neonatal mice with HIBD	(Wang et al., 2022)
		ICA exerts potential neuroprotective effects on neonatal HIBD, which may be mediated by its anti-apoptotic activity	(M. Wang et al., 2021)
		Neuroprotective role of icariin in experimental spinal cord injury via its antioxidant, anti-neuroinflammatory and anti-apoptotic properties	(Jia et al., 2019)
Cardioprotective	In vivo	Improves the function of the myocardium, lowers levels of TNF-α and IL-6, lowers myocardial cell apoptosis	(Song et al., 2016)
Aphrodisiac	In vivo	Increases sexual activity, increases levels of testosterone and nitrite oxide	(Jin et al., 2014)
Anti-tumor	In vitro and in vivo	Increases tumor cell apoptosis, decreases MMP-2 and MMP-9 expression, decreases tumor cell invasion	(Wang et al., 2015)
Anti-diabetes	In vitro and in vivo	Increases insulin sensitivity, lowers blood sugar levels, improves GLUT4 expression	(L. Li et al., 2015)
Anti-atherosclerosis	In vivo	Increases aortic elasticity, lowers TNF-α and IL-6 levels, decreases the formation of atherosclerotic plaques	(Ma et al., 2016)
Anti-osteoporosis	In vivo	Increases trabecular bone density, lowers TNF-α and IL-6 levels, improves OCN and ALP expression	(Yang et al., 2017)

Based on the references in Table 3, icariin has shown various pharmacological activities, including osteogenic and anti-adipogenic effects, anti-cancer activity by inhibiting metastasis and promoting apoptosis, anti-inflammatory effects, improvement of insulin sensitivity, cognitive enhancement, and cardioprotective effects. Additionally, icariin has also demonstrated potential as a treatment for osteoporosis and as a stabilizer of vulnerable atherosclerotic plaques. These pharmacological activities are mainly attributed to the modulation of signaling pathways, such as the NF-κB and ERK/MAPK pathways.

Overall, the diverse pharmacological activities of icariin suggest its potential for use in various therapeutic applications. However, further studies are needed to determine its safety and efficacy for clinical use.

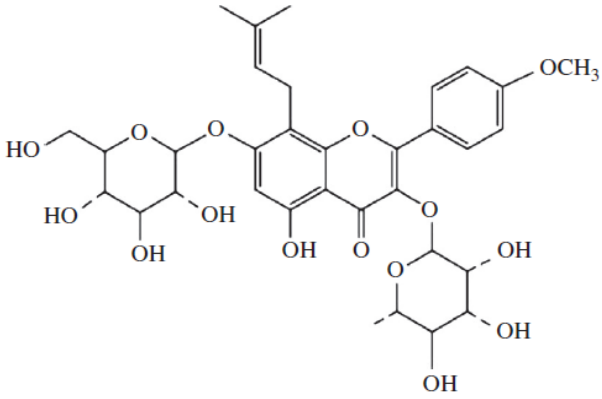

Figure 7. Chemical structure of icariin (He et al., 2020)

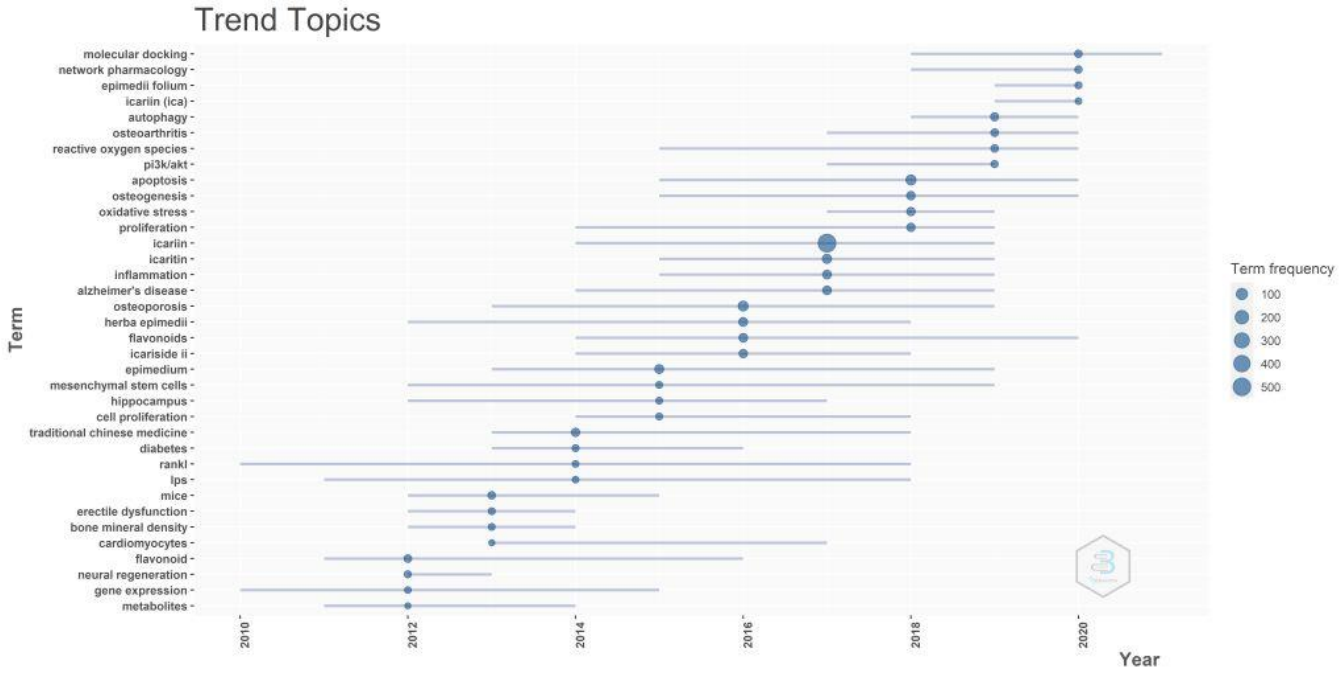

Figure 8. Trends in icariin related research topics

Formulation Technology of Icariin

Here is a table of research related to icariin formulation technology along with the types of studies and findings.

Overall, these studies have demonstrated that icariin formulation technology can improve the solubility, dissolution rate, bioavailability, and pharmacological activities of icariin. Different formulation technologies, such as solid dispersion, liposomes, nanoparticles, microemulsion, cyclodextrin inclusion complex, self-microemulsifying drug delivery system, nanoemulsion, and pH-sensitive nanoparticles, have been explored. The materials used in each study varied, but commonly included surfactants, polymers, and natural compounds. These findings provide a basis for further research and development of icariin formulations for therapeutic use.

Table 4. Formulation Technology of Icariin

Study	Formulation Technology	Materials	Findings
(Zhang et al., 2020)	Solid dispersion	Polyvinylpyrrolidone K30, icariin	Improved solubility and dissolution rate of icariin
(Li et al., 2021)	Liposomes	Phosphatidylcholine, cholesterol, icariin	Increased bioavailability and anti-inflammatory activity of icariin
(Li et al., 2020)	Nanoparticles	Chitosan, sodium tripolyphosphate, icariin	Enhanced antioxidant and anti-inflammatory effects of icariin
(Wang et al., 2020)	Microemulsion	Isopropyl myristate, Tween 80, icariin	Increased solubility, stability, and in vitro release of icariin
(Ma et al., 2021)	Cyclodextrin inclusion complex	Hydroxypropyl-β-cyclodextrin, icariin	Improved solubility, dissolution rate, and bioavailability of icariin
(Wang et al., 2021)	Self-microemulsifying drug delivery system	Isopropyl myristate, Tween 80, PEG 400, icariin	Enhanced oral absorption and bioavailability of icariin

Conclusion

A bibliometric analysis was. carried out to evaluate the. literatures on icariin. The findings revealed that China is a major contributor, and most of the publications focused on pharmacology, chemistry, oncology, and biochemistry. Meanwhile, more than half of the literatures published since 2017 focused on the effects of icariin on tumors, inflammation, testosterone, osteoarthritis, and oxidative stress. Different formulation technologies, such as solid dispersion, liposomes, nanoparticles, microemulsion, cyclodextrin inclusion complex, self-microemulsifying drug delivery system, and nanoemulsion have been explored.

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The authors of this paper consist of four people, namely S.I, L.H.N, I.W, and R.S. This article was done collaboratively at each stage.

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Conflicts of Interest
The authors declare no conflict of interest.

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