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Unveilling Aucubin's Pharmacological Landscape: A Bibliometric Study on Antioxidant and Anti-Inflammatory Activities

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ABSTRACT
Aucubin is an iridoid glycoside known to have various pharmacological activities. Current research data shows that the pharmacological activities are very diverse and complex, so bibliometric analysis is used to facilitate understanding and provide references for further research directions. Publications related to the pharmacological activities of aucubin were obtained through the Web of Science Core Collection (WoSCC) database, which were then analyzed using Vosviewer 1.6.20 software. A total of 152 publications were obtained from the period 2013-2023, consisting of 142 articles and ten review articles. The articles came from 45 countries, 204 institutions, 862 authors, and 42 journals. Based on keyword analysis, the most frequently appearing pharmacological activities were "antioxidant" and "anti-inflammatory" that can be the primary development directions in the future.
Keywords: bibliometrics; aucubin; activity; pharmacology; keywords co-occurence

INTRODUCTION
Aucubin is an iridoid glycoside belonging to the cyclopentanone group of monoterpenes (Rahamouz-Haghighi, 2023). The compound was first isolated by Bourquelot and Harissey in 1905 from the leaves of Aucuba japonica, which belongs to the Cornaceae family. In addition, aucubin has also been isolated from other plant families such as Garryaceae, Orobanchaceae, Globulariaceae, Eucommiaceae, Scrophulariaceae, Plantaginaceae, and Rubiaceae (Abbasi et al., 2022; Khalaf et al., 2018; Sertić et al., 2015; Trim & Hill, 1952; Yang et al., 2018). The structure of aucubin can be seen in Figure 1. This compound can be found in almost all parts of plants, such as flowers, seeds, fruits, leaves, stems, and roots. Aucubin is included in the chemotaxonomic markers, and its presence helps explain many plant species whose classification is not yet clear (Kartini et al., 2023; Rahamouz-Haghighi, 2023). Some plants that are known to contain aucubin and have been used in traditional medicine in Asia and Europe include Plantago major, Eucommia ulmoides, Verbascum thapsus, and Ajuga reptans. The use of these plants is related to the pharmacological activities of aucubin, such as anti-inflammatory, antioxidant, hepatoprotective, and wound healing (Adom et al., 2017; Jan et al., 2022; Toiu et al., 2019).

Along with the increasing interest in natural medicine and the development of herbal medicines, research on aucubin has also increased. Currently, research on aucubin explores not only its pharmacological activities but also the molecular mechanisms underlying its various therapeutic effects. This reflects the growing interest in exploring the therapeutic potential of aucubin. Bibliometric analysis can be used to understand the trends and developments in research on the pharmacological activities of aucubin. Bibliometric analysis focuses on publications in a specific research field and can describe the distribution, research status, hotspots, and development trends, allowing researchers to easily access relevant scientific information and serve as useful references or guides for further research (Yan et al., 2024). Until now, no bibliometric analysis has been conducted on the pharmacological activity of aucubin. Therefore, this study conducted a bibliometric

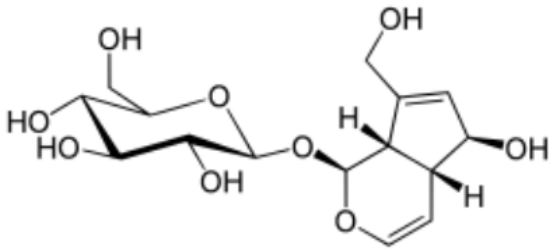

Figure 1. Aucubin structure

analysis to provide a comprehensive understanding of current conditions and trends, as well as to encourage further research on the pharmacological activity of aucubin.

METHOD

The data in this study were collected from the Web of Science Core Collection (WoSCC) database on August 22, 2024. The database search used the search formula TS=(aucubin) AND (TS=(pharmacology) OR TS=(pharmacological) OR TS=(activity)). This formula is used to obtain reliable and accurate information from articles with relevant keywords in the title, abstract, and author keywords. The types of publications selected were limited to "articles" and "review articles" during the period 2013-2023. A total of 152 publications were obtained for bibliometric analysis over the past ten years, consisting of 142 articles and ten review articles. Furthermore, the articles were downloaded and analyzed with VOSviewer 1.6.20.

RESULTS AND DISCUSSION

Quantitative analysis of annual publication distribution

The development of publications related to the pharmacological activity of aucubin can be seen in Figure 2A. The number of publications in 2013-2017 was relatively low, with the number of publications being less than 10. In general, research related to the pharmacological activity of aucubin increased after 2018. This indicates an increase in interest in research related to the pharmacological activity of aucubin. In addition, Elsevier ranked first in the number of publications (39), followed by Mdpi (20) and Springer Nature (16) as shown in Figure 2B.

Characteristics of distribution of countries/regions and institutions

Over the past ten years, 45 countries have contributed to publishing research on the pharmacological activities of aucubin. Asia, Europe, and North America are the top 10 countries with the most publications. Among the top 10 countries (Table I), China has the highest number of publications (n=61), followed by South Korea (n=15) and Germany (n=9). *Eucommia ulmoides*, widely used in TCM (Traditional Chinese Medicine), is known to contain aucubin. Easy access to native plants, ancient book records, noticeable therapeutic effects, and significant needs have led to many aucubin research in China (Xue et al., 2012). South Korea, Mexico, China, and Egypt are the top institutions with the most publications (Table I). The top ten contributing institutions published 45 articles, accounting for 29.60% of the total publications. Jeonbuk National University, South Korea, contributed the most (n=8), followed by Instituto Politecnico Nacional Mexico (n=6) and Northwest University Xi An (n=5).

Analysis of *top authors* and *co-cited authors*

The top five authors and the top five most cited authors are presented in Table II. based on the articles published by the authors. Seven authors (the minimum number of co-citation authors is equal to 20) were selected to describe the co-citation network (Figure 3). The analysis showed that Kim, Junghyun from Jeonbuk National University published the most articles related to the pharmacological activity of aucubin (n=5). Xue hy, Chang im, and Park ks have a significant influence on the pharmacological activity of aucubin.

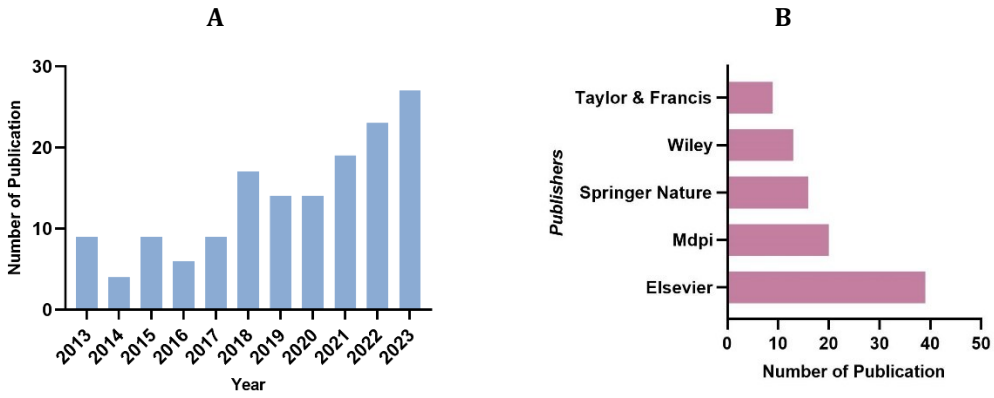

Figure 2. A Development of publications on the pharmacological activity of aucubin from 2013-2023. B Top 5 publishers

Table I. Top 10 countries and institutions contributing to publications on the pharmacological activities of aucubin

Rank	Country	Publication	%	Rank	Institution	Publication	%
1	China	61	40,13	1	Jeonbuk National University	8	5,26
2	Korea Selatan	15	9,87	2	Instituto Politecnico Nacional Mexico	6	3,95
3	Jerman	9	5,92	3	Northwest University Xi An	5	3,29
4	Meksiko	9	5,92	4	Chinese Academy of Sciences	4	2,63
5	India	7	4,61	5	Instituto Mexicano Del Seguro Social	4	2,63
6	Itali	7	4,61	6	Seoul National University	4	2,63
7	Jepang	7	4,61	7	Shanghai University of Traditional Chinese Medicine	4	2,63
8	Pakistan	5	3,29	8	Universidad Autonoma del Estado de Moreles	4	2,63
9	Polandia	5	3,29	9	Beijing Forestry University	3	1,97
10	Thailand	5	3,29	10	Egyptian Knowledge Bank	3	1,97

Table II. Top five authors and co-cited authors in the research on the pharmacological activity of aucubin

Rank	*Authors*	Number	*Co-cited authors*	*Citations*
1	Kim, Junghyun	5	Xue, hy	57
2	Trejo-Tapia, Gabriela	4	Chang, im	39
3	Park, Su-Bin	4	Park, ks	35
4	Zamilpa, Alejandro	4	Venditti, a	24
5	Jung, Woo Kwon	4	Jin, l	22

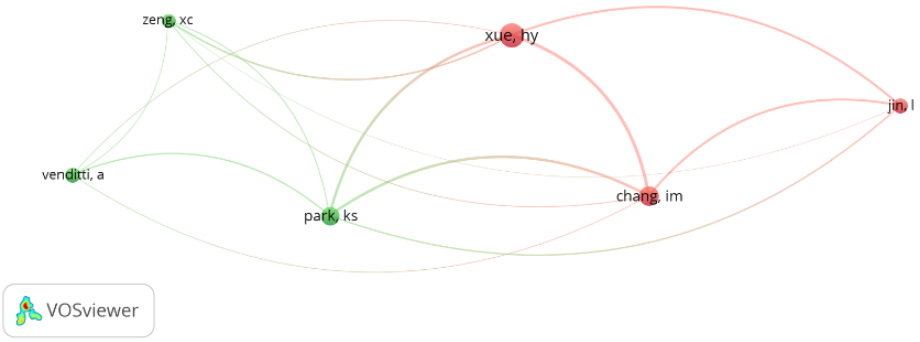

Figure 3. Visualization of co-citation authors network

Analysis of reference with co-citation

Co-citation references can indicate the most frequently cited papers (Li et al., 2020), represented in the co-citation network shown in Figure 4. The references were filtered to include only those with a minimum co-citation count of 15. Table III shows the top five co-cited references. The reference "Jin L, 2008, eur j pharmacol, v582, p162, https://doi.org/10.1111/jcmm.14293" is co-cited up to 22 times. (Shen et al., 2019).

Analysis of hotspots and frontiers

Hotspots are a crucial methodology in bibliometric analysis used to identify topics in a specific research area during a specific period (Yan et al., 2024). Keyword explosion patterns were detected to reveal active content in the pharmacological activities of aucubin through keyword co-occurrence analysis. Based on previous studies by (Yan et al., 2024), keywords with similar meanings were combined before analysis. Figure 5 shows the visualization of the keyword network, where the node size reflects the frequency of occurrence of keywords, and the distance between nodes indicates the strength of their association. Table IV shows the twenty keywords with the highest frequency of occurrence.

Keywords with closer distances are grouped into the same cluster, roughly reflecting the research field's main topics. Among these keywords, "Antioxidant" appears up to 43 times, indicating the main direction of research on the pharmacological activity of aucubin. The keywords "Iridoid glycosides", "iridoids", and "glycosides" are related to the bioactive compound group aucubin, which belongs to iridoid glycosides. As shown in Figure 4A, keywords in the red cluster such as "antioxidant", "cells", "toxicity", and "in-vitro" reflect the main direction of research in recent years. These keywords indicate studies on the antioxidant activity of aucubin conducted in vitro using cells. Keywords in the blue cluster, such as "antiinflammatory", "rat", and "oxidative stress" indicate studies on the anti-inflammatory activity of aucubin conducted in-vivo using mice. Keywords such as "inhibition", "tnf-alpha", "nrf2", "apoptosis" and "activation" describe the molecular mechanism of aucubin. These results indicate that research on the pharmacological activity of aucubin has focused on antioxidant and anti-inflammatory activities.

Compounds known as antioxidants can inhibit or decelerate cellular damage caused by oxidative stress. The process of oxidative stress in biological systems is intricate and is defined by an imbalance between the body's capacity to eliminate reactive species through the use of endogenous and exogenous antioxidants and the production of free radicals (FR) (Francenia Santos-Sánchez et al., 2019). Oxidative stress-induced damage to cells, tissues, and organ systems is leading to several severe diseases, including malignancies, cataracts, neurological disorders, and even the natural aging process (Finaud et al., 2006). Based on several studies that have already been conducted, aucubin has been shown to reduce oxidative stress in various medical conditions. These conditions include liver fibrosis, nonalcoholic fatty liver disease, diabetic nephropathy, gastric mucosal lesions, myocardial infarction, liver ischemia-reperfusion injury, traumatic brain injury, osteoarthritis, and male infertility (Duan et al., 2019; Ma et al., 2020; Zhang et al., 2020).

Aucubin has demonstrated the ability to effectively reduce the release of proinflammatory cytokines (MCP-1, PAI-1, and IL-6) by inhibiting the breakdown of IκBα and the movement of the p65

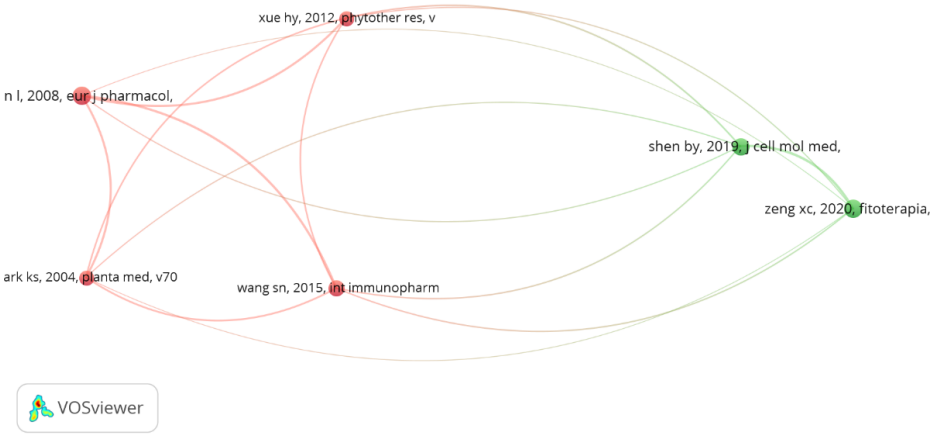

Figure 4. Visualization of reference co-citations in the pharmacological activity research of aucubin

Table III. Top five cited references regarding the pharmacological activities of aucubin

Rank	Reference	Number of citations
1	Jin l, 2008, eur j pharmacol, v582, p162, doi 10.1016/j.ejphar.2007.12.011	22
2	Zeng xc, 2020, fitoterapia, v140, doi 10.1016/j.fitote.2019.104443	21
3	Shen by, 2019, j cell mol med, v23, p4063, doi 10.1111/jcmm.14293	19
4	Wang sn, 2015, int immunopharmacol, v24, p408, doi 10.1016/j.intimp.2014.12.029	17
5	Xue hy, 2012, phytother res, v26, p369, doi 10.1002/ptr.3562	15

Table IV. Twenty keywords with the highest frequency of occurrence

Rank	Keywords	Occur-rences	Total link strength	Rank	Keywords	Occur-rences	Total link strength
1	aucubin	74	208	11	flavonoid	13	48
2	antioxidant	43	133	12	activation	12	55
3	inhibition	26	93	13	iridoids	12	28
4	iridoid glycoside	26	65	14	rats	12	40
5	oxidative stress	21	73	15	expression	11	44
6	apoptosis	17	64	16	in-vitro	11	41
7	anti-inflammatory	15	61	17	acteoside	9	39
8	*eucommia ulmoiders*	15	41	18	secondary metabolites	9	27
9	constituent	13	37	19	cells	8	31
10	extract	13	33	20	leaves	8	25

subunit, resulting in the deactivation of NF-κB using 3T3-L1 adipocytes cultured with TNF-α-induced inflammation (Park, 2013). Aucubin abolished the phosphorylation of IKKα/β, IκBα, and p65 (IL-1β) and the translocation of p65 from the cytosol to the nucleus in murine chondrocytes. These inhibitory reactions effectively suppressed the production of inflammatory mediators such as MMP, iNOS, COX-2, NO, and others (Wang et al., 2015). Meanwhile, aucubin inhibited TNF-α, IL-6, IL-1β, and IFN-γ synthesis in THP-1 macrophages activated with LPS (Kartini et al., 2017).

Aucubin is a natural compound with notable biological activity that has shown promise in various therapeutic areas. The bibliometric analysis indicates that aucubin has demonstrated

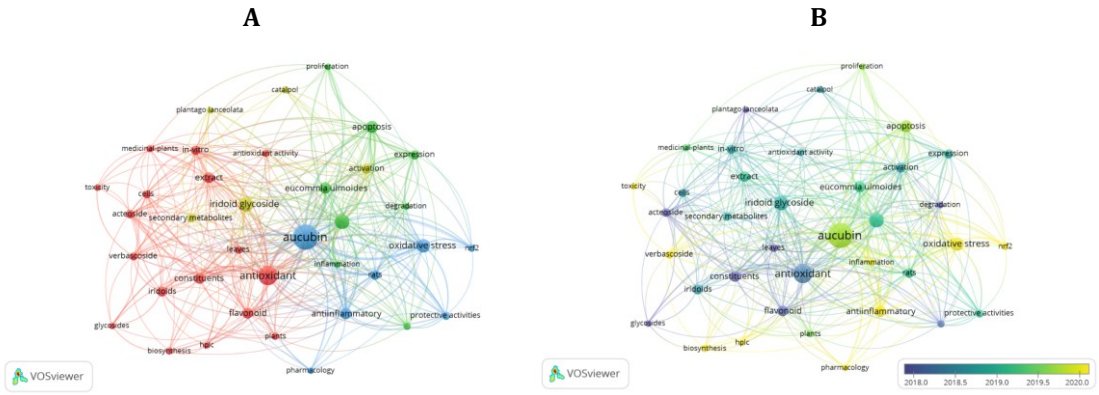

Figure 5. Hotspot analysis of aucubin pharmacological activity research. A author keyword network visualization and B author keyword overlay visualization.

significant effects in studies involving cellular pathways, particularly in inhibiting inflammation and oxidative stress. Moreover, aucubin has been evaluated in preclinical models, showing potential as a therapeutic agent in animal studies. However, more extensive clinical trials in humans still need to be conducted. Consequently, future research should focus on the investigation of human studies and other pharmacological activities.

CONCLUSION

The number of publications related to the pharmacological activity of aucubin has increased over the past ten years. Nearly half of the publications were published in China. Kim, Junghyun from Jeonbuk National University published the most articles related to the pharmacological activity of aucubin. Based on word frequency and burst detection, antioxidant and anti-inflammatory are the front lines and hot spots that can be the primary development directions in the future.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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