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REVIEW ARTICLE

Global landscape of biflavonoid bioactivity studies (1992–2024): A bibliometric and mechanistic overview

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Abstract

Biflavonoids are a unique class of polyphenolic compounds known for their diverse biological activities, including antioxidant, anti-inflammatory, anticancer and antimicrobial effects. Recent years have seen a surge in research investigating the therapeutic potential and molecular mechanisms of biflavonoids. This bibliometric review provides a comprehensive overview of the research landscape surrounding biflavonoids and their biological activities. Ultimately, this bibliometric analysis guides future research directions, pinpoints gaps in the literature and underscores the growing importance of biflavonoids in medicinal and pharmaceutical science. This study employs a bibliometric analysis of 742 publications on biflavonoid activity from 1992 to 2024, utilising data from multidisciplinary sources. The results reveal an annual growth rate of 5.06 %, with a peak in publications in 2022. Research output in this field spans ten primary disciplines, with the highest contributions from medicinal chemistry, pharmacology and biochemistry, indicating its multidisciplinary nature. Keyword analysis indicates that biflavonoid research has evolved from early studies focused on isolation and structural characterisation toward advanced investigations emphasising antioxidant activity, gene regulation, apoptosis and neuroprotective mechanisms. The co-occurrence network analysis identifies six thematic clusters, emphasising areas such as antioxidant mechanisms, anti-inflammatory pathways and neurodegenerative protection. This bibliometric analysis provides a comprehensive overview of the research landscape, highlighting the dynamic growth, collaborative networks and emerging trends in biflavonoid research, paving the way for further investigations into their therapeutic potential.

Keywords: biflavonoids; biological activities; collaboration network; literature article; oxidative stress

Introduction

Biflavonoids, as secondary metabolites, are dimer molecules of monomeric flavonoids, specifically flavone, chalcone, flavonol, flavanone or flavanol, which differ in the oxygenation patterns of their monomers at C-2/3/5/6/8/2′/3′/4′ in the A, B and C rings, including functional groups such as -OH, -OCH_3, etc (1). These include the C-O-C linked biflavonoids, such as ochnaflavone, delicaflavone, hinokiflavone and isocryptomerin and the C-C linked, such as robustaflavone, amentoflavone, sumaflavone, taiwaniaflavone and 2′,8″-biapigenin (2). Due to their unique structural features, biflavonoids have garnered significant attention in pharmacological research for their broad spectrum of biological activities, making them a rich source of novel therapeutic agents.

Biflavonoids exhibit significant pharmacological properties, including antioxidant, anti-inflammatory and anticancer activities (3). These compounds play a crucial role in modulating oxidative stress, inhibiting inflammatory pathways and inducing apoptosis in cancer cells. For instance, amentoflavone has been shown to inhibit amyloid-β (Aβ) aggregation, making it a promising candidate for Alzheimer's disease treatment by preventing fibrillisation and promoting the disaggregation of preformed fibrils (4). Isoginkgetin, a biflavonoid isolated from *Ginkgo biloba*, has been reported to suppress the proliferation and migration of hepatocellular carcinoma (HCC) cells by inducing autophagy-mediated cell death (5). Sciadopitysin enhances cell survival and reduces oxidative stress by activating the phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB or Akt)/glycogen synthase kinase 3-beta (GSK-3β) pathway, which regulates various cellular processes (6). Furthermore, biflavonoids exhibit antifungal, antibacterial and enzyme-inhibitory activities, including α-glucosidase inhibition, which highlights their potential as drug candidates for metabolic disorders such as diabetes (7–9).

Despite their promising bioactivities, challenges remain in understanding the specific molecular mechanisms and pathways by which biflavonoids exert their effects. The key questions include which signalling pathways are involved in the activity of biflavonoids and how these compounds interact with cellular targets. Although

numerous review articles have addressed the biological activities of biflavonoids, most focus primarily on specific bioactivities rather than the overall evolution and research landscape of the field. However, there are still only a limited number of writings that discuss the journey of research on biflavonoids, the activities discovered from the beginning to the present and their mechanisms. While many reviews focus on the biological activities of biflavonoids, there is still no comprehensive account that maps the chronological evolution of research output, thematic shifts and mechanistic understanding in this field. Therefore, this study employs bibliometric analysis to systematically examine the trajectory of biflavonoid research and its scientific evolution.

Bibliometric analysis offers a robust and reproducible approach for assessing scientific output, intellectual structure and research evolution within a specific domain. By applying quantitative methods to large-scale bibliographic data, bibliometric studies can identify influential authors, institutions, countries, research themes and knowledge gaps, thereby supporting evidence-based decision-making and future research planning (10–12). Nevertheless, to date, there has been no dedicated bibliometric analysis focusing on biflavonoids and their associated biological activities.

To address this gap, the present study aims to conduct a comprehensive bibliometric analysis of research on biflavonoid activity using data retrieved from the Web of Science (WoS) database. Several scientific literature databases are commonly used for bibliometric studies, including Scopus, PubMed, Web of Science (WoS) and Google Scholar, each notable for its own strengths and limitations. In this study, WoS was selected as the primary data source due to its access to the Science Citation Index Expanded (SCI-Expanded) and its reputation as a particularly comprehensive database that indexes the most influential and relevant journals in the field (13). In addition, WoS applies a rigorous journal selection process and provides highly standardised and curated citation data with extensive historical coverage. By emphasising quality over quantity, WoS ensures the reliability and consistency of bibliometric results. Moreover, its well-structured citation network enables robust analyses of research impact, co-citation patterns and long-term scientific trends, making it a widely recognised and trusted database for high-quality bibliometric studies (14).

This study provides a comprehensive bibliometric analysis of trends in biflavonoid research over the past three decades, offering critical insights into their biological activities and therapeutic applications. By mapping key signalling pathways associated with biflavonoids, it lays the foundation for future drug development strategies targeting oxidative stress, inflammation and apoptosis-related diseases. This study also identifies research gaps, particularly in bioavailability optimisation and mechanistic pharmacology, highlighting potential areas for further investigation. Additionally, these findings serve as a valuable resource for researchers, policymakers and the pharmaceutical industry in prioritising biflavonoid-related drug discovery and development. Through this approach, the study aims to fill research gaps in biflavonoid pharmacology and provide valuable insights into their development as effective targeted therapies, particularly in cancer treatment.

Materials and Methods

A standard bibliometrix workflow for science mapping involves five steps (10), which are depicted in Fig. 1. This approach enables a systematic evaluation of publication trends, research themes and collaboration patterns, thereby providing an overview of the current research landscape on biflavonoids and their biological activities while identifying potential directions for future studies.

Study design

The WoS database was selected as the repository for scientific literature in this bibliometric study. The analysis focuses on annual research trends in biflavonoid studies and their biological activities, with an emphasis on their relevance as potential lead compounds for drug discovery. The following research questions (RQs) guide this investigation:

RQ 1: How has research on biflavonoids and their biological activities evolved from 1992 to 2024 in terms of publication output and subject categories indexed in the WoS categories?

RQ 2: Which countries and institutions are the most productive contributors to biflavonoid research and how have global trends in publication output and collaboration changed over time?

RQ 3: What are the main collaboration networks among authors and institutions in biflavonoids research, as revealed by co-authorship analysis?

RQ 4: What are the dominant research themes and biological activity –related topics in biflavonoid studies based on keyword and citation analyses?

RQ 5: How do keyword co-occurrence and citation analyses reveal emerging trends and future research directions in biflavonoid research?

The author uses R packages and VOSviewer for data processing and analysis, facilitating the development of relevant discussions and conclusions.

Data collection

The data were retrieved from WoS, covering the period from 1992 to September 2024. The phrases "biflavonoid" and "activity" first appeared in 1992, according to a WoS search. The search utilised the following terms:biflavonoids (topic) OR dimeric flavonoids (topic) OR flavonylflavones (topic) AND activity (title). However, research into biflavonoid activity has remained limited, resulting in an incomplete search for articles over the years. The initial search returned 759 documents. The inclusion criteria were limited to documents classified as research articles and proceedings papers, with English set as the required language. These criteria were applied using the filtering tools available in the WoS platform to ensure data consistency and reliability for bibliometric analysis. Using the predefined search keywords within the selected time span, a total of 759 records were initially retrieved from the WoS Core Collection. In the first screening step, records were filtered by document type, excluding publication types other than articles and proceeding papers. This step resulted in 745 documents. In the second screening



Fig. 1. Workflow of the bibliometric research process.

step, language filtering was applied and publications written in languages other than English were excluded. As a result, three records were removed, yielding a final dataset of 742 documents for bibliometric analysis. This multilevel selection process enabled the identification of the most relevant records and facilitated a transparent and reliable bibliometric study of biflavonoids and their activities, 1992–2024.

Bibliometric analysis

We utilised applications including VOSviewer (version 1.6.20) and the R package Bibliometrix (version R. 4.4.1). The Bibliometrix R package facilitates a range of analyses, including publication status, scientific collaboration through authorship, citations, word clouds and topic trends. In addition, VOSviewer is used to construct co-occurrence networks utilising keywords, as well as collaboration networks among authors, institutions and countries. This tool demonstrates significant capabilities in scientific mapping. We imported thesaurus files from VOSviewer, which contained identical content to the anonymous lists used in the Bibliometric analysis, before developing co-occurrence networks with keywords.

Data visualisation

Visualisation techniques for representing science maps and analytical results include bi-dimensional maps, dendrograms, heliocentric maps and social network diagrams (10). In this study, the data are visualised using tables, bar and line charts, scatter plots, stacked bar charts, network maps, word clouds and thematic evolution maps.

Results

Dataset overview

From 1992 to 2024, there were 742 publications in the area of biflavonoid activity that met the inclusion and exclusion criteria. This total comprises journal articles, conference proceedings and review papers, as illustrated in Fig. 2. Research on the biological activities of biflavonoids first emerged in 1992, with seven articles published in that year. Since then, the field has exhibited a steady annual growth rate of 5.06 %. Publication output increased markedly after 2001, despite minor fluctuations over time. The highest publication volume was observed in 2022, accounting for 8.32 % of the total, followed by a slight decline in 2023.

The selected collection of publications is multidisciplinary and categorised into ten disciplines based on the WoS, as illustrated in Fig. 3. The top three disciplines are medicinal chemistry (212 publications), pharmacology and pharmacy (200 publications) and biochemistry and molecular biology (181 publications). This material has been published in 319 distinct sources, as shown in Table 1. The average age of these documents is 9.65 years and each document has an average of 26.51 citations, derived from a total of 22910 references. The primary collection contains 3913 keywords. In terms of author collaboration, there are seven publications authored by a single author, with an average of 6.74 co-authors per document. Notably, international co-authorship accounts for 25.88 % of the publications. The chosen documents include 734 articles and eight conference proceedings. These results indicate that biflavonoid research is highly multidisciplinary and characterised by moderate citation impact and substantial international collaboration, reflecting its broad scientific relevance.

The study assessed the h-index and g-index, metrics commonly used to evaluate scientific productivity and impact. Table 2 lists the ten leading sources contributing the most publications in this subject area. Among them, Phytochemistry has the highest publication output, with an h-index of 17 and a g-index of 28. At the same time, the Journal of Agricultural and Food Chemistry has accumulated 1583 citations since 2002, making it the most cited source in this context. In comparison, phytochemistry has received 949 citations since 1992. These findings indicate that both publication volume and citation impact are distributed across multiple leading journals within the field of biflavonoid research.

Examination of the output of scientific publications and the dynamics of global collaboration

Fig. 4 illustrates the classification of publication output into two categories: single-country publications (SCP) and multiple-country publications (MCP). China, Brazil and South Korea, with article counts of 170, 74 and 63, respectively, are the leading countries in the production of publications on biflavonoids and their activities, contributing a cumulative share of 41.21 %. China has the highest number of publications related to biflavonoid activity and also

Table 1. Key information regarding the datasets utilised

Description	Results
MAIN INFORMATION ABOUT DATA	
Timespan	1992:2024
Sources (Journals, Books, etc)	316
Documents	742
Annual Growth Rate %	5.06
Documents Average Age	9.65
Average citations per doc	26.55
References	22618
DOCUMENT CONTENTS	
Keywords plus (ID)	2125
Author's Keywords (DE)	2371
AUTHORS	
Authors	3913
Authors of single-authored docs	6
AUTHORS COLLABORATION	
Single-authored docs	7
Co-Authored per Doc	6.74
International co-authorships %	25.88
DOCUMENT TYPES	
article	734
article; proceedings paper	8

Table 2. Top ten journal sources in biflavonoid research based on publication output and bibliometric impact indicators (h-index, g-index and total citations (TC)

Sources	No Publication	h-index	g-index	TC	Articles
Phytochemistry	28	17	28	949	1298
Molecules	26	14	20	444	624
Natural Product Research	23	12	16	292	622
Journal of Natural Products	19	15	19	835	449
Fitoterapia	17	10	17	372	381
Journal of Agricultural and Food Chemistry	17	16	17	1583	376
Journal of Ethnopharmacology	17	10	17	510	355
Natural Product Communications	17	6	10	114	314
Planta medica	15	14	15	696	313
Bioorganic & Medicinal Chemistry Letters	14	5	5	217	206

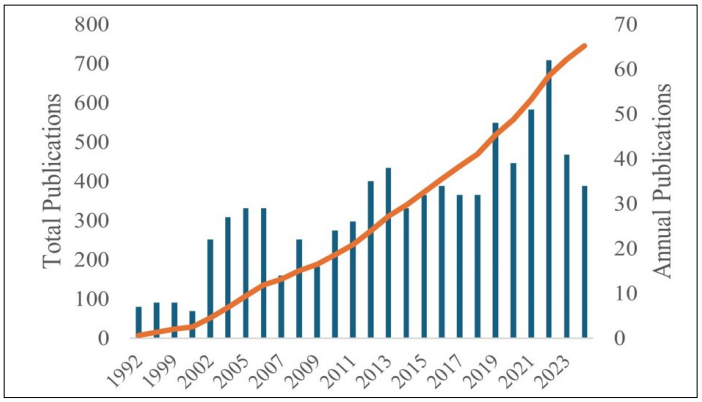


Fig. 2. Annual and cumulative publication trends on biflavonoids and their biological activities from 1992 to 2024.

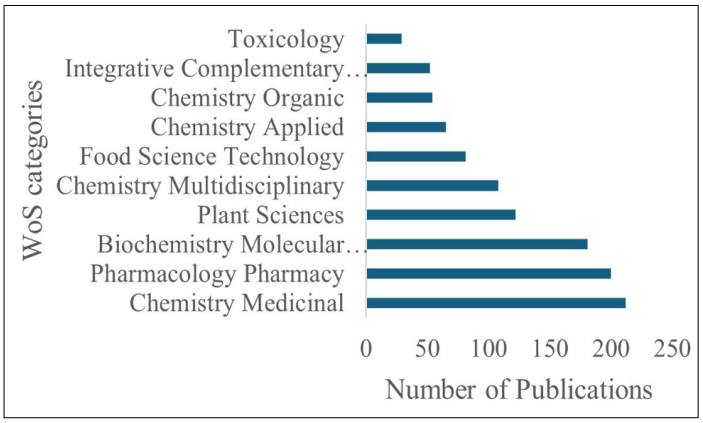


Fig. 3. Distribution of publications on biflavonoids and their biological activities across Web of Science categories.

demonstrates an extensive international collaboration network (red cluster), as shown in Fig. 5. Chinese authors initially established collaborative networks with researchers from South Korea, Japan, the United Kingdom and Canada. Nigeria also emerges as a prominent collaboration hub, with the green cluster encompassing countries from Africa (e.g., South Africa) and Asia (including Saudi Arabia, Turkey, India and Malaysia). Autorship network analysis identified 121 authors with at least 3 publications, as depicted in Fig. 6. The leading author in the network is Farombi EO (Green Group). Farombi EO engages in interdisciplinary collaborations to explore the activity of kolaviron. These collaboration patterns suggest that biflavonoid research is largely driven by countries with strong capacities in natural product research and is increasingly supported by international knowledge exchange.

Current trends and key terms in biflavonoid research

Research themes and trends in biflavonoid studies were analysed using keyword data extracted from 745 journals, with an emphasis on keyword frequency, as illustrated in Fig. 7. In the resulting visualisation, larger font sizes indicate higher keyword occurrence. The most frequently occurring keywords include biflavonoids and activity, which are commonly associated with terms such as flavonoids and bioflavonoids. Fig. 8 illustrates the trend of topic development across various periods. From 1992 to 2007, the predominant topics focused on separation techniques and the relationship between flavonoids and antioxidant activity. Between 2008 and 2013, biflavonoids emerged as a subject of study, with continued exploration from 2014 to 2018. During this latter period, research increasingly linked biflavonoids to flavonoids and oxidative stress, suggesting a relationship between biflavonoids and various biological activities. Between 2019 and 2021, biflavonoid complexes and biflavonoids attracted renewed attention, with increasing thematic associations with medicinal plants and antioxidant studies, reflecting their expanding relevance in the field. In the most recent period (2022–2024), biflavonoids maintained their prominence, with increasing associations with inhibitory activity and overexpression-related terms, reflecting a shift toward mechanistic and regulatory studies.

A keyword co-occurrence network analysis was conducted using 239 keywords with a minimum occurrence of five, as shown in Fig. 9. Five major clusters were identified and visualised using distinct colours. The red cluster corresponds to flavonoids, the blue cluster to dimeric flavonoids (biflavonoids) and the green cluster to biological and medical mechanisms. The yellow cluster primarily represents neuroprotective flavonoids, whereas the purple cluster-closely linked to the green cluster-focuses on the anti-inflammatory activities of specific biflavonoids.

Discussion

Global trends, collaboration networks and thematic evolution of biflavonoid research

Publications related to biflavonoids and their biological activities have shown a steady increase over time. Since 2001, an average of at least 10 publications per year has been recorded, with a continuous upward trend, peaking in 2022. This growth can be partially attributed to the COVID-19 pandemic, which intensified global research efforts on natural products, particularly those with antiviral, anti-inflammatory and immunomodulatory properties. Concurrently, the pandemic accelerated the use of integrated metabolomic and computational approaches, with metabolomics, network pharmacology and molecular docking increasingly applied to identify natural product-based adjunct therapies for urgent healthcare needs (15, 16). Although "computational research" did not appear as a dominant keyword (Fig. 7), the co-occurrence of terms such as inhibitors, proteins,

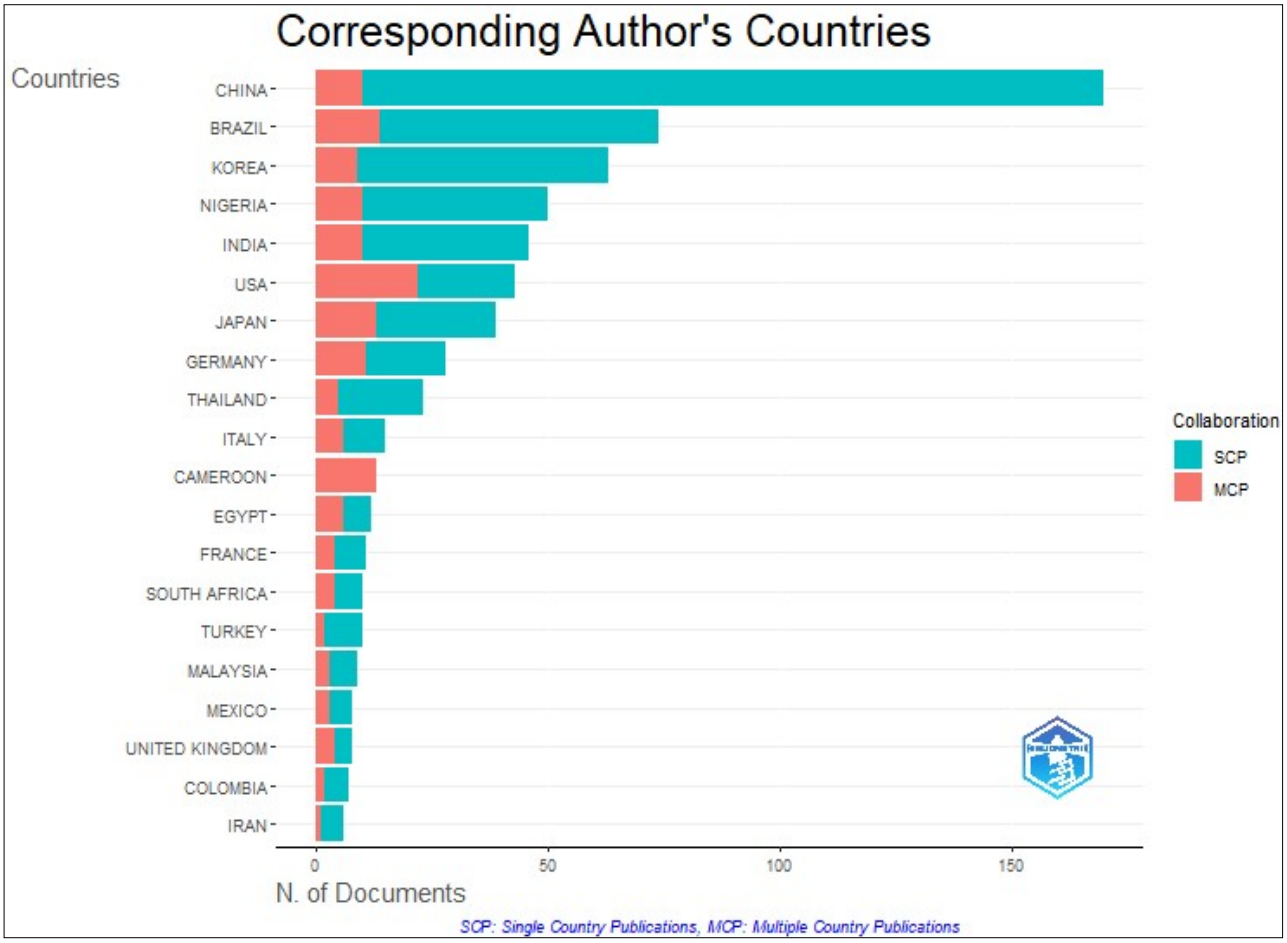


Fig. 4. Distribution of single-country publications and multiple-country publications (MCP) by the corresponding author's country.

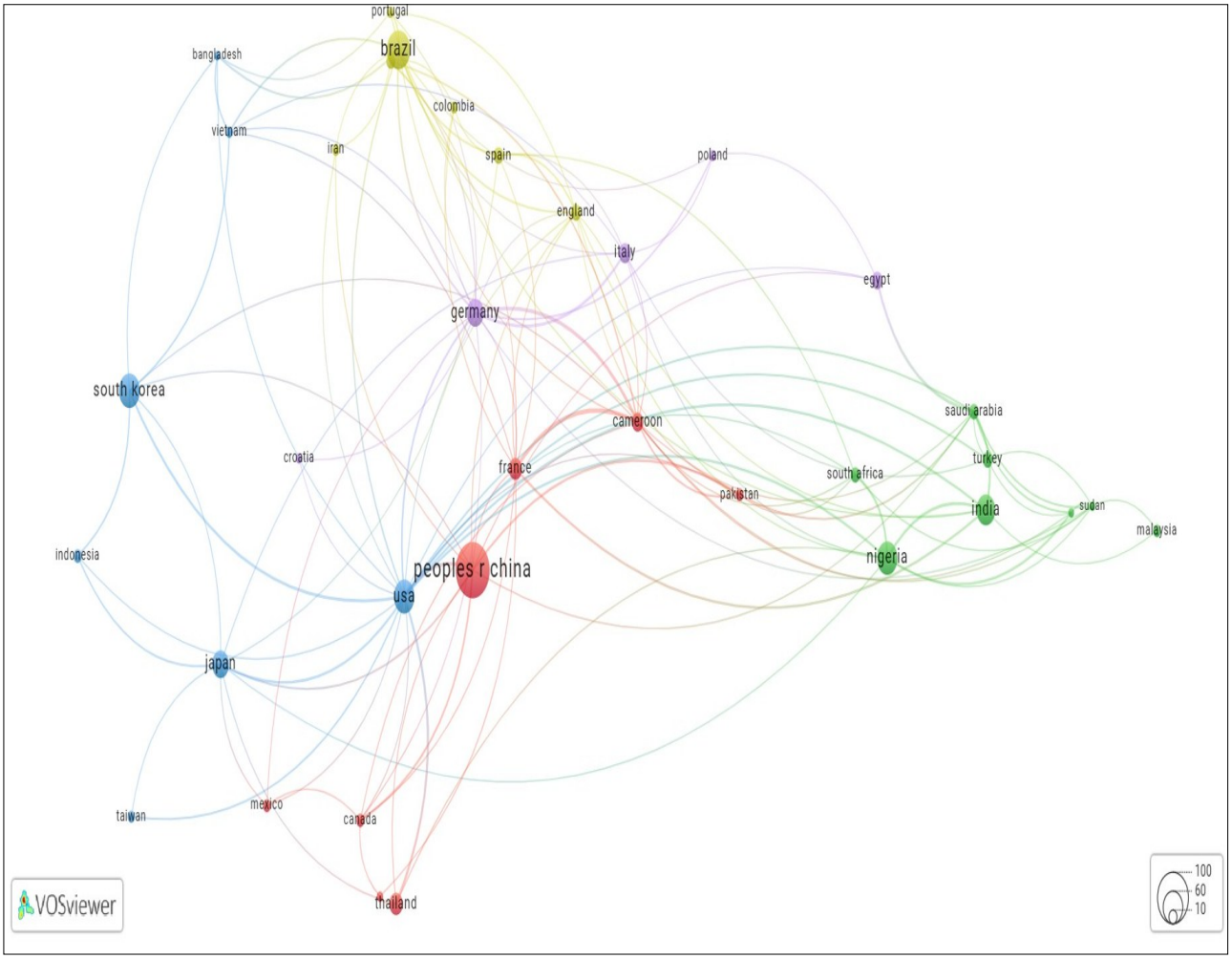


Fig. 5. International country collaboration network in biflavonoid research.

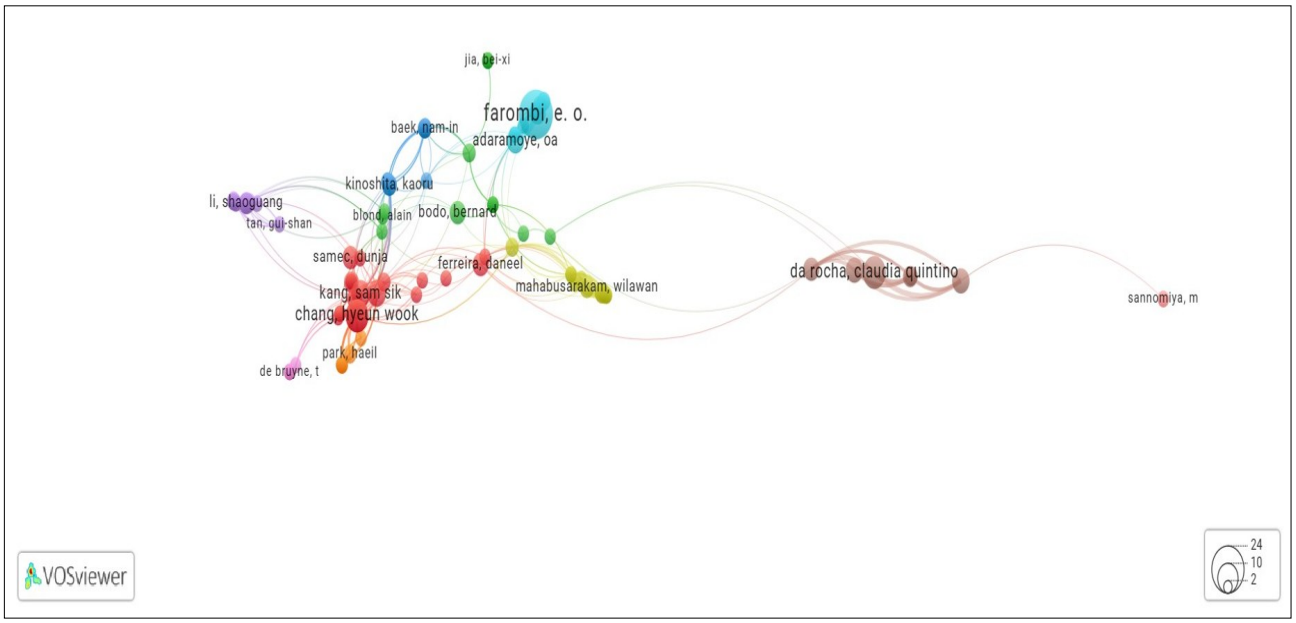


Fig. 6. Author collaboration network in biflavonoid research.

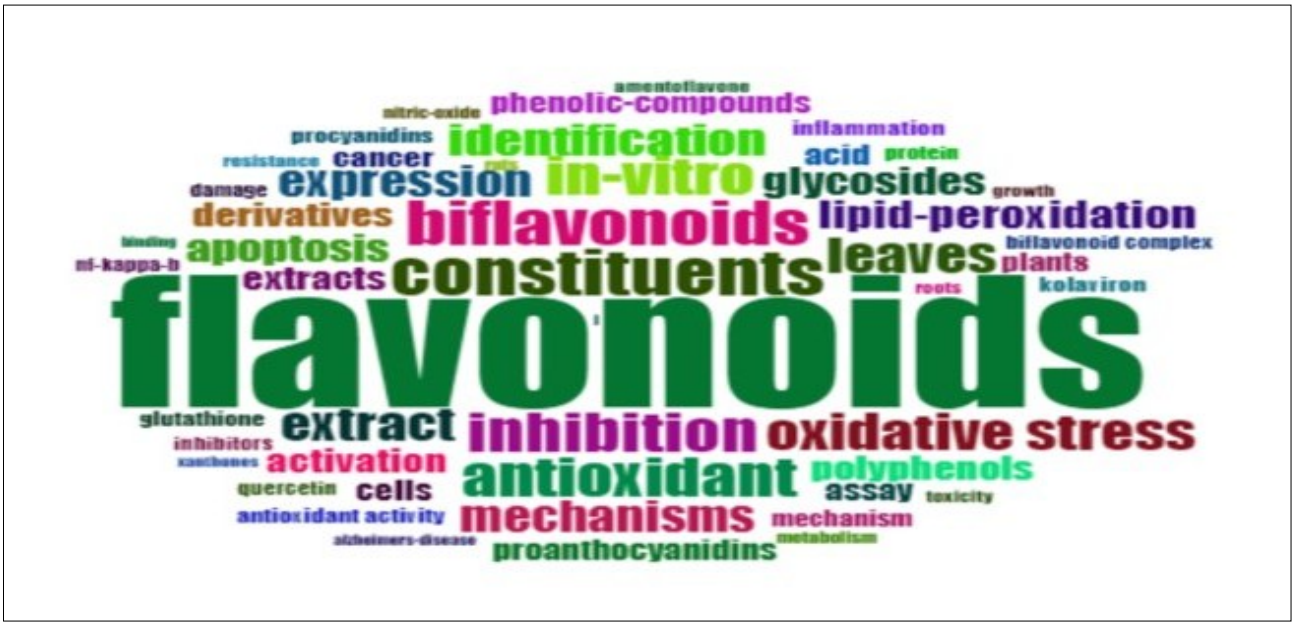


Fig. 7. Word cloud of keywords plus associated with biflavonoid research.

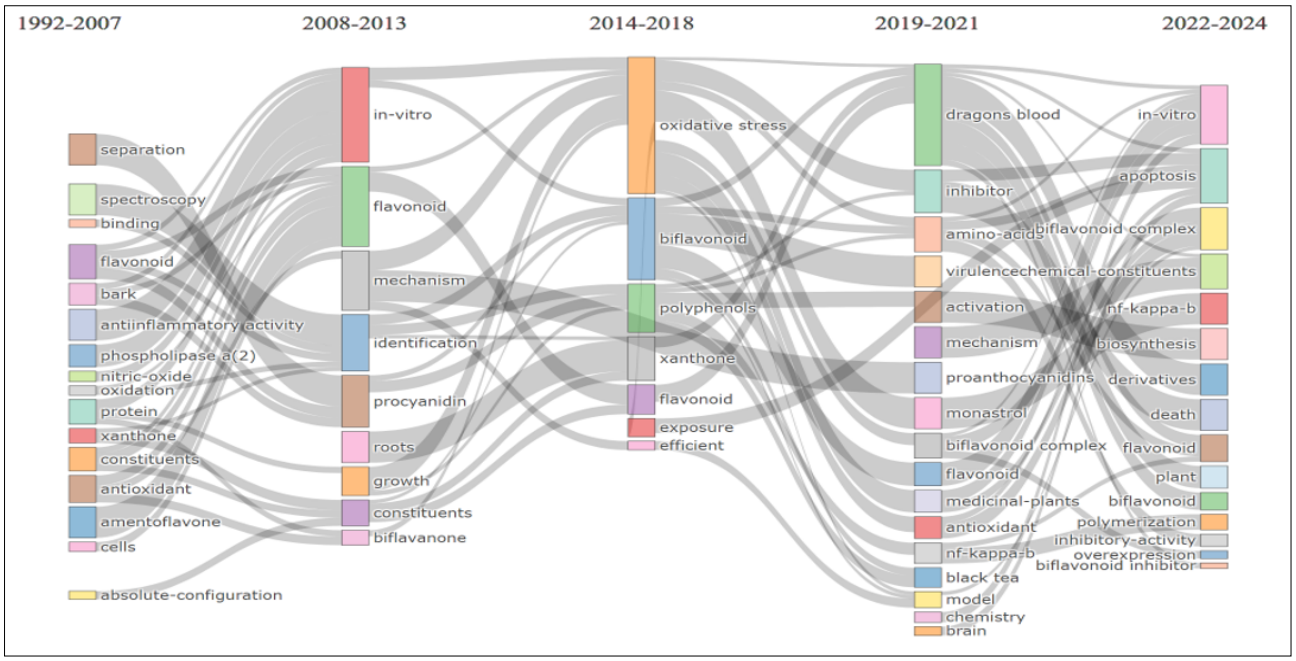


Fig. 8. Thematic evolution of biflavonoid research and associated biological activities (1992–2024).

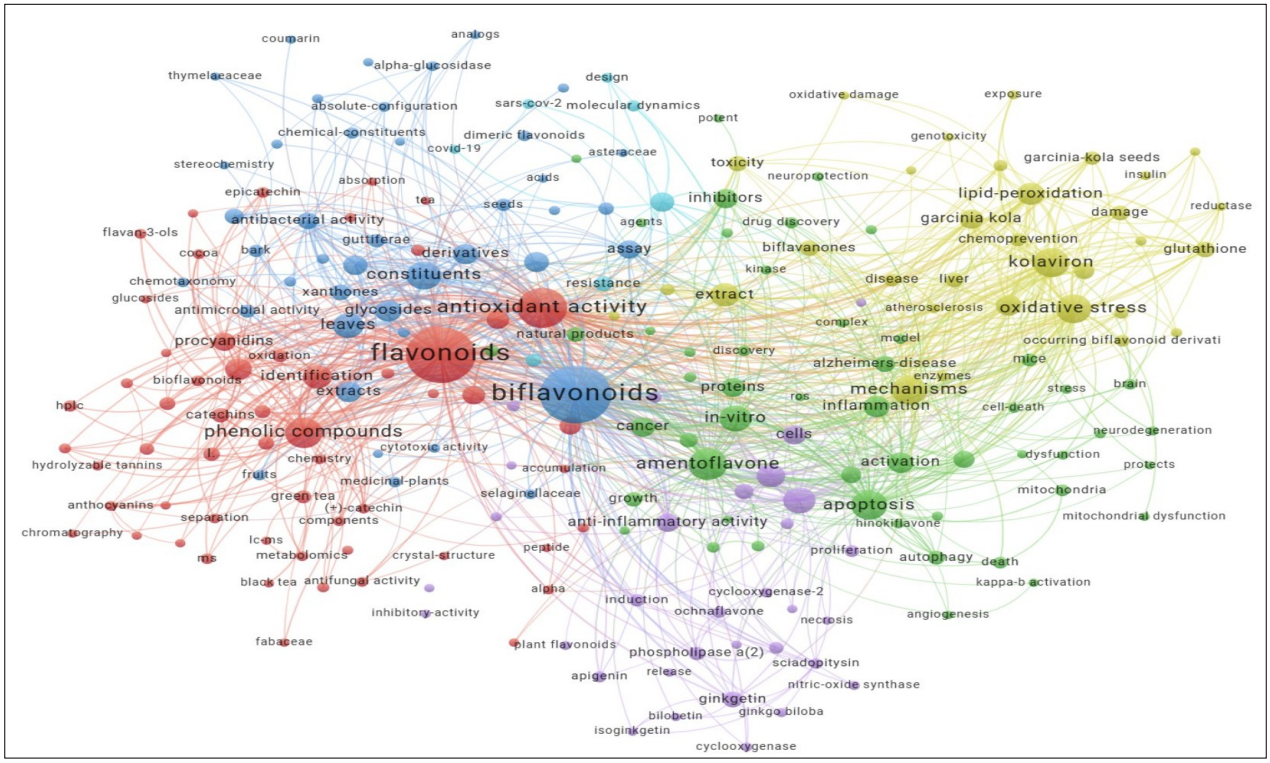


Fig. 9. Keyword co-occurrence network based on keywords plus in biflavonoid research.

enzymes, kinases and drug discovery indicates the emerging adoption of computational and target-based approaches in biflavonoid research. This pattern suggests a transition from activity-oriented studies to mechanistic and in-silico-assisted investigations.

Phytochemistry is the journal with the most publications on biflavonoid research, reflecting its strong focus on natural product chemistry. In contrast, the Journal of Agricultural and Food Chemistry represents the most highly cited primary source in this field. Its prominence can be attributed to its multidisciplinary scope, high publication output, increasing impact factor, proactive editorial policies and broad global reach (17). These findings underscore the pivotal role of the Journal of Agricultural and Food Chemistry in disseminating influential research on biflavonoids and their biological activities.

China's dominance in biflavonoid research output and international collaboration may be attributed to its rich biodiversity, extensive traditional use of medicinal plants and diverse ecological zones, which together provide abundant resources for biflavonoid exploration. Numerous studies have reported the isolation of biflavonoids from plant species native to China, such as *Camellia oleifera* (18), *Lonicera macranthoides* (19), *Daphniphyllum angustifolium* (20), *Cephalotaxus sinensis* (21) and *Artemisia frigida* (22). The isolation of compounds was motivated by the plant's traditional use as a therapeutic agent by local communities. For example, *Artemisia frigida* has historically been used in indigenous medicine to manage joint swelling, menstrual disorders, renal heat and carbuncles (22).

Nigeria also serves as a significant collaboration hub, linked to extensive research on *Garcinia kola*, a native medicinal plant rich in biflavonoids. Biflavonoids isolated from *G. kola*, particularly kolaviron, have been reported to exhibit a broad spectrum of biological activities, including antioxidant, anti-inflammatory and antidiabetic effects, as well as inhibitory activities against α-glucosidase and mitotic kinesin Eg5 (23–26). The prominence of Farombi EO within the collaboration network reflects sustained and focused research on kolaviron over nearly two decades (2002–2020). His position as a central node suggests that interdisciplinary and long-term collaboration has played a critical role in advancing mechanistic and pharmacological understanding of biflavonoids, particularly those derived from African medicinal plants.

Evolution of research themes and hotspots

The keyword analysis reveals that biflavonoid research has evolved from an early emphasis on compound isolation and antioxidant properties toward more complex biological and mechanistic investigations, as reflected in the thematic evolution shown in Fig. 8. Throughout this progression, antioxidant activity has consistently emerged as a central research focus, as evidenced by its persistent prominence across multiple time periods. This sustained focus can be attributed to the intrinsic structural features of biflavonoids, which are rich in phenolic hydroxyl groups, possess extensive conjugated systems and often exist as planar dimers. These features have consistently been highlighted in the literature as key contributors to the antioxidant potential of biflavonoids.

Beyond antioxidant-related studies, anti-inflammatory activity has emerged as the second most extensively explored research theme, indicating a broadening of scientific interest toward inflammation-associated biological processes. From a bibliometric perspective, the frequent co-occurrence of antioxidant- and anti-inflammatory-related keywords suggests a close thematic linkage between these two research directions, reinforcing the central position of biflavonoids within pharmacological and biomedical research. The sustained prominence of biflavonoids across multiple time periods underscores their central role in flavonoid research and their growing relevance in pharmacological studies.

The emergence of inhibitory activity and overexpression-related topics in the most recent period suggests a shift toward investigating the regulatory effects of biflavonoids on cellular and molecular pathways. This thematic transition indicates a growing research emphasis on target-oriented and mechanism-informed studies, reflecting increased interest in the roles of biflavonoids in

antioxidant defence, modulation of inflammatory responses, regulation of gene expression and induction of apoptosis-processes that are highly relevant to diseases such as cancer, inflammatory disorders and degenerative conditions.

Cluster analysis further supports this trend, showing a clear progression from chemical characterisation and structural analysis toward biologically oriented research themes. The presence of dedicated clusters related to neuroprotection and anti-inflammatory activity, as identified through keyword co-occurrence patterns, underscores the diversification of biflavonoid research into disease-specific applications. From a thematic standpoint, these clusters highlight emerging opportunities for future investigations, particularly involving under-explored plant sources and biologically relevant targets, which may guide subsequent mechanistic and translational studies.

Chronological development and mechanistic insights

Biflavonoids exert diverse biological effects through interconnected, multitarget mechanisms, as illustrated in Fig. 10. The trajectory of research on biflavonoid activity has evolved substantially, transitioning from foundational studies on anti-inflammatory properties to a broader exploration of their therapeutic potential, as summarised in Table 3. In the late 1990s, seminal studies identified compounds such as amentoflavone and ginkgetin as potential anti-inflammatory agents, laying the groundwork for subsequent pharmacological investigations (27–30). This early research phase established a critical foundation for understanding the role of biflavonoids in modulating inflammatory pathways. Amentoflavone, for example, has been shown to inhibit phospholipase A_2 (PLA_2) and cyclooxygenase (COX) enzymes, resulting in significant *in vivo* anti-inflammatory effects in oedema-induced models (27).

Following these early discoveries, studies in the early 2000s broadened the scope of biflavonoid research to include antiviral and anticancer applications, with compounds such as amentoflavone demonstrating inhibitory effects against HSV-1 (31–33). Concurrently, studies revealed that certain biflavonoids could suppress the activation of nuclear factor kappa B (NF-κB), a key signalling pathway implicated in cancer progression, thereby supporting their potential utility in anticancer strategies (33). This period marked a clear diversification of biflavonoid research, highlighting their multifaceted biological activities.

The subsequent decade witnessed intensified investigations into the antioxidant (23, 34) and antidiabetic (35, 36) properties of biflavonoids. Compounds such as kolaviron were found to exhibit chemopreventive effects against genotoxicity and oxidative stress, underscoring their antioxidant capabilities (23). Additionally, studies have demonstrated that biflavonoids can modulate carbohydrate-metabolising enzymes, offering potential benefits for the management of diabetes. Mechanistically, these effects have been attributed to multiple phenolic hydroxyl groups, which enhance enzyme binding and inhibit lipid peroxidation. Together, these findings expanded the therapeutic scope of biflavonoids to include metabolic disorders. Furthermore, antidiabetic effects have been associated with the inhibition of carbohydrate-metabolising enzymes such as α-glucosidase, thereby reducing postprandial hyperglycemia (35).

In more recent years, research attention has shifted toward the neuroprotective (37, 38) and antiparasitic potentials of biflavonoids. Amentoflavone and related compounds have been reported to inhibit β-site amyloid precursor protein cleaving enzyme 1 (BACE-1), a key enzyme involved in Aβ formation, suggesting potential therapeutic relevance for neurodegenerative disorders (38). In parallel, several studies have shown that biflavonoids can protect neuronal cells from ischemic damage, further supporting their neuroprotective relevance. From a structural perspective, the 3′–8″ interflavonoid linkage enables expanded molecular interactions within enzyme active sites, while hydroxyl substituents serve as hydrogen-bond donors, thereby increasing binding affinity and

Table 3. Key research publications on biflavonoid activities (1998–2019) ranked by local and global citation metrics, identifying landmark studies in biflavonoid research

Title	Activity	References	Year	LCS	GCS
Chemoprevention of aflatoxin B1-induced genotoxicity and hepatic oxidative damage in rats by kolaviron, a natural biflavonoid of *G. Kola* seeds	Antioxidant	23	2005	18	82
Amentoflavone, a plant biflavone: a new potential anti-inflammatory agent	Anti-inflammation	27	1998	18	91
Effects of ginkgetin from *G. Biloba* leaves on cyclooxygenases and in vivo skin inflammation	Anti-inflammation	28	2002	12	65
A cyclooxygenase (COX) inhibitory biflavonoid from the seeds of *Semecarpus anacardium*	Anti-inflammation	29	2004	9	64
Effects of anti-inflammatory biflavonoid, ginkgetin, on chronic skin inflammation	Anti-inflammation	30	2006	7	63
Antiviral activities of biflavonoids	Anti-vitral	31	1999	24	156
Anti-influenza virus activity of biflavonoids	Anti-vitral	32	2007	7	88
Inhibition of TNFα-induced cyclooxygenase-2 expression by amentoflavone through suppression of NF-κb activation in A549 cells	Anti-cancer (lung disease)	33	2002	13	86
Low-density lipoprotein (LDL)-antioxidant biflavonoids from *Garcinia madruno*	Antioxidant	34	2013	8	31
Hypoglycaemic and hypolipidaemic effects of fractions from kolaviron, a biflavonoid complex from *G. Kola* in streptozotocin-induced diabetes mellitus rats	Antidiabetic	35	2006	20	53
Kolaviron, a biflavonoid complex of *G. Kola* seeds modulates apoptosis by suppressing oxidative stress and inflammation in diabetes-induced nephrotoxic rats	Antidiabetic	36	2014	13	48
Kolaviron, a *G. Kola* biflavonoid complex, protects against ischemia/reperfusion injury: pertinent mechanistic insights from biochemical and physical evaluations in rat brain	Neuroprotective	37	2015	7	23
B-secretase (bace-1) inhibitory effect of biflavonoids	Neuroprotective	38	2010	7	50
Dimeric flavonoids from arrabidaea brachypoda and assessment of their anti-*Trypanosoma cruzi* activity	Antiparasitic	39	2014	15	56

LCS: local citation score; GSC: global citation score

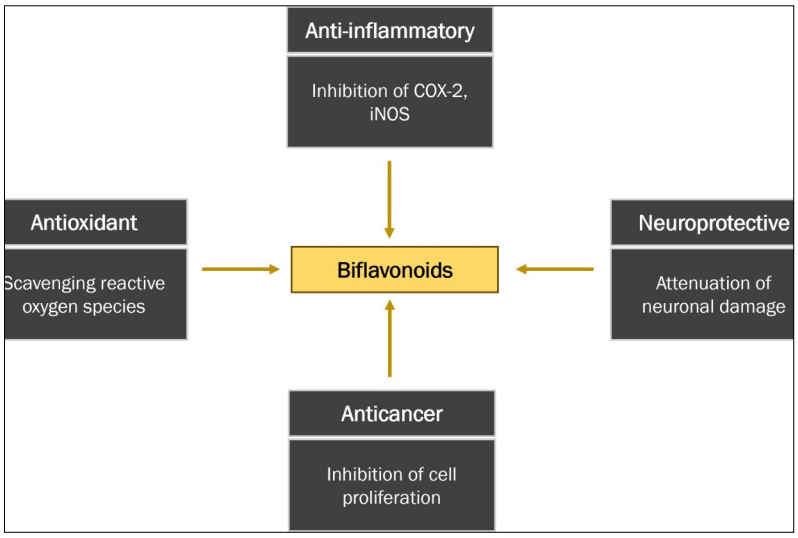


Fig. 10. Multifunctional biological mechanisms of biflavonoids, including antioxidant, anti-inflammatory, anticancer and neuroprotective activities.

inhibitory potency. Moreover, biflavonoids isolated from species such as *Selaginella bryopteris*, including brachydin B, have demonstrated antiplasmodial activity, underscoring their potential as promising leads for the treatment of parasitic infections (39).

Collectively, these chronological and mechanistic findings demonstrate that the diverse pharmacological activities of biflavonoids are strongly governed by their structural features, particularly interflavonoid linkages and hydroxylation patterns. A deeper understanding of these structure–activity relationships is therefore essential for guiding future drug discovery, structural optimisation and the rational development of biflavonoid-based therapeutic agents (3).

Challenges and future directions

The exploration of biflavonoid activities in the present study provides a foundation for future investigations to advance their therapeutic potential. To achieve a deeper understanding of biflavonoid bioactivity, future research should adopt structure-activity relationship (SAR)-guided design approaches.

Importantly, continued exploration and systematic characterisation of biflavonoids from diverse and under-investigated plant sources are essential to enrich existing biflavonoid databases. Expanding such databases will improve the chemical diversity and representativeness of biflavonoid scaffolds, thereby strengthening subsequent in silico screening and SAR analysis.

A comprehensive biflavonoid database should be established and systematically screened against multiple disease-relevant protein targets using in silico methods, including molecular docking and virtual screening. Structurally active biflavonoids identified from these analyses can then be further examined to elucidate key structural features governing their biological activities through SAR analysis.

Experimental validation of computational findings should subsequently be conducted using in vitro and in vivo models to confirm pharmacological efficacy and safety. In addition, chemical synthesis or semi-synthetic modification of promising biflavonoid scaffolds may enable structural optimisation and large-scale production. Considering the structural diversity and abundance of naturally occurring biflavonoids, these compounds represent a valuable reservoir for future drug discovery and development.

Conclusion

This bibliometric analysis provides a comprehensive overview of the global research landscape on biflavonoids from 1992 to 2024, revealing clear trends, thematic evolution and collaboration patterns in this field. The results indicate a steady increase in publications on biflavonoids, accompanied by a clear shift from early studies focused on compound isolation and antioxidant properties toward mechanistic and disease-oriented investigations, encompassing inflammation, cancer, metabolic disorders and neurodegenerative diseases.

The predominance of China in biflavonoid research publications can be attributed to the country's rich biodiversity, extensive availability of medicinal plant resources and well-established research infrastructure in natural product chemistry and pharmacology. These factors collectively enable systematic isolation, characterisation and biological evaluation of biflavonoids, thereby positioning China as a leading contributor to the field.

The knowledge gaps from this bibliometric study were that the structure-activity relationships of biflavonoids remain insufficiently explored. Addressing this gap is essential for elucidating the molecular basis of their bioactivities and for guiding rational design and optimisation of biflavonoid-based therapeutic candidates.

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Authors' contributions

EBT carried out the formulation, analysed the data and drafted the manuscript. AI participated in formulating, drafting and editing. STW guided the software analysis. AA carried out data curation and data validation. HME participated in developing ideas. PS conceptualised, reviewed and approved the final manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interest to declare.

Ethical issues: None

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