The Potency of Chalcone Derivatives as Anticancer Agents: A Five-Decade Bibliometric Overview

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Abstract. Cancer continues to pose a considerable global health challenge, as traditional therapies such as chemotherapy and radiotherapy are frequently constrained by drug resistance and detrimental side effects. Natural compounds such as chalcones have attracted interest for their potential as anticancer agents owing to their selective cytotoxicity. The chemical structure of chalcones can be readily modified to improve their biological activity. Chalcone derivatives exhibit anticancer properties via various mechanisms, such as apoptosis induction, reactive oxygen species generation, mitochondrial dysfunction, tubulin inhibition, and transcription factor modulation. Despite the increasing amount of research on chalcone derivatives, a comprehensive bibliometric analysis assessing research trends, hotspots, and international collaborations in this field is yet to be conducted. This study fills the gap by examining 1,269 articles from the Scopus database utilizing the keywords “chalcone derivatives” and “anticancer”. The data were analyzed using VOSviewer and Biblioshiny (RStudio) to investigate publication trends, keyword mapping, prolific journals, countries, institutions, and authors, also collaboration networks. Additionally, this study briefly reviews the synthetic approaches and mechanisms underlying the anticancer activity of chalcone derivatives. These findings aim to direct future research trends and enhance innovations in the development of chalcone-based anticancer therapies.

Keywords: Chalcone Derivatives, Anticancer, Bibliometric Analysis, Research Trends, Hotspot.

V. D. S. Handayani et al. (eds.), *Proceedings of the 6th International Conference on Bioinformatics, Biotechnology, and Biomedical Engineering (BIOMIC 2025)*, Advances in Health Sciences Research 94,
https://doi.org/10.2991/978-94-6239-762-0_31

1 Introduction

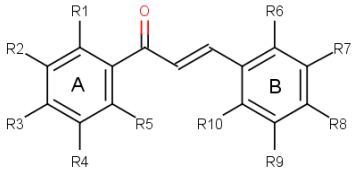


Fig. 1. General structure of chalcone showing potential modification sites.

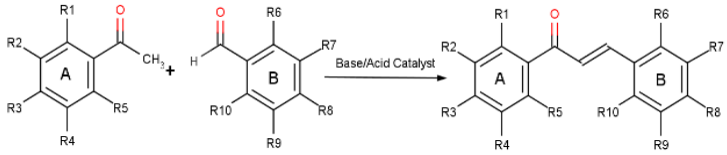


Fig. 2. General reaction of chalcone derivative synthesis via Claisen-Schmidt condensation.

Cancer is a leading cause of death worldwide and remains a major public health concern. Based on data from the Global Observatory Cancer (Globocan) for 2022, there are 19,976,499 cancer cases globally, with 9,743,832 deaths—accounting for more than 50% of the total cases. The highest incidence has been reported in countries across Asia, Europe, and Northern America [1]. To date, chemotherapy and radiotherapy remain the primary treatment options, although they have significant limitations such as toxicity and drug resistance [2]. This resistance is caused by the adaptation of cancer cells through a complex process upon repeated exposure to drugs, known as multidrug resistance (MDR) [3]. These limitations result in suboptimal cancer treatment outcomes. Thus, the development of new anticancer drugs is necessary to address these shortcomings, and to offer safer and more effective alternative therapies.

Natural compounds have shown promising potential as alternative or adjuvant cancer therapies because of their low toxicity, one of which is chalcone [4]. Chalcones demonstrate selectivity toward cancer cells and exhibit synergistic effects with conventional cancer therapies by enhancing their cytotoxic effects (chemosensitivity and radiosensitivity) [5]. Structurally, chalcone is an open-chain flavonoid consisting of two aromatic rings (A and B) connected by a three-carbon α,β-unsaturated carbonyl system [6]. The basic structure of chalcone and possible modification sites on rings A and B are illustrated in Fig. 1.

Chalcones, which are precursors of flavonoids and isoflavonoids, can be easily synthesized into various derivatives. The structural modification of chalcones can enhance their pharmacological efficacy [7]. These derivatives have been extensively developed through diverse structural modifications to enhance their biological activity. They can be synthesized via aldol condensation or Claisen–Schmidt condensation (Fig. 2) using microwave irradiation [8] or conventional stirring techniques [9]. In addition, various other techniques have also been employed, such as ultrasound irradiation,

grinding technique, ionic liquid catalysis, ZnO nanoparticle catalysis, Suzuki reaction, Julia–Kocienski olefination, and Wittig reaction [10].

The chalcone family has been shown to possess anticancer potential both in vitro and in vivo through various mechanisms, such as cell cycle disruption, autophagy regulation, apoptosis induction, and modulation of immunological and inflammatory mediators [11]. Specifically, chalcone derivatives such as pyrazolinone chalcones have been found to induce apoptosis and cell death by inhibiting the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway through reactive oxygen species (ROS) formation [12].

In addition to being used as individual drug candidates, chalcone derivatives can also be combined with nanoparticles to further enhance their biological activities. Mezoughi et al. (2024) reported that chalcone derivatives substituted with hydroxy and methoxy groups combined with silver nanoparticles showed potential as antioxidant agents [13]. This combination may represent a breakthrough in anticancer agent development, as the antioxidant activity of chalcone derivatives contributes to reducing oxidative stress or inhibiting ROS, which are key factors in DNA damage and tumor initiation [14, 15].

In recent years, based on the Scopus database, the number of publications related to chalcone derivatives as anticancer agents has increased, indicating growing interest in this field. Utilizing the keywords ‘chalcone derivatives’ and ‘anticancer’, illustrate this growth, with publications increasing from approximately 1 in 1975, to 63 in 2015, and reaching over 149 in 2024. However, to date, no bibliometric analysis has been conducted to map the development trends, research hotspots, and collaborative networks in chalcone-based anticancer research. Bibliometric methods help researchers analyze and manage large volumes of scientific literature efficiently and comprehensively, facilitating the identification of new research areas, emerging focal points, and increasing research impact [16, 17]. This approach includes keyword analysis to identify the most popular topics, highly influential articles, contributing countries, and long-term citation dynamics [18].

Therefore, this study aims to explore trends in anticancer research on chalcone derivatives using the Scopus database to identify research hotspots, journals, countries, institutions, authors, keywords, and collaborative relationships among entities. In addition, a brief review of synthetic approaches and the anticancer mechanisms of chalcone derivatives is presented. This study is expected to clarify existing research gaps and open future research opportunities, enabling a more focused and collaborative direction in this field.

2 Materials and Methods

Literature data for bibliometric analysis were acquired from the Scopus database (https://www.scopus.com/). The search queries were used according to TITLE-ABS-KEY (“chalcone derivatives” AND “anticancer”) AND (LIMIT-TO (DOCTYPE, “ar”) OR LIMIT-TO (DOCTYPE, “re”)), to calculate the relevance of article titles, abstracts, author keywords, and detailed scientific information. The publication data were specifically selected from English-language original research and review articles with

no restrictions on the publication year. Database collection was conducted until March 29, 2025. The final search yielded 1,269 articles related to the chosen keywords.

Data analyses and visualization were performed using VOSviewer software (https://www.vosviewer.com/) version 1.6.20 and the bibliometrix app by RStudio version 2024.12.0 build 467. The literature database was extracted from Scopus in bib or .csv format and imported into the Biblioshiny domain. The domain was initiated by running the ">bibliometrix::biblioshiny()" code [19]. The combination of VOSviewer and RStudio was used to obtain a comprehensive analysis of the database metrics and visualizations. The presented score values were calculated based on information provided in the Scopus database.

3 Result and Discussion

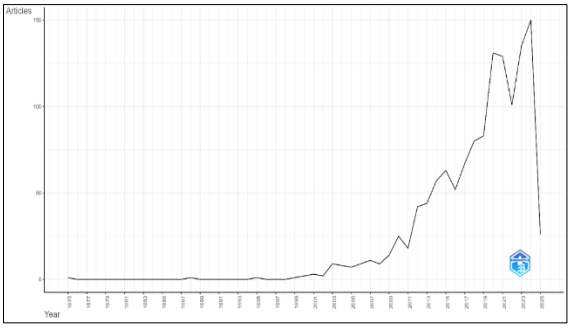


Fig. 3. Publication trends by year of chalcone derivatives as anticancer (n = 1269).

3.1 Publication Trend by Year

The publication trend, with no year restrictions, provides a five-decade overview spanning 1975-2025. A total of 1,269 research articles on chalcone derivatives as anticancer agents were published based on the Scopus database (Fig. 3). The first publication was recorded in 1975, marking the beginning of research interest in this field. Prescott B. published the first publication in the International Journal of Clinical Pharmacology Therapy and Toxicology revealing thiosemicarbazones and hydrazones of α-methylchalcone as potential chemotherapeutic agents, that showed inhibitory activity against Walker 256 carcinosarcoma and L1210 leukemia in mice [20]. The latest paper published by Al-Ghamdi et al. in the International Journal of Molecular Sciences describes the Synthesis and Anticancer Evaluation of O-Alkylated (E)-Chalcone Derivatives: A Focus on Estrogen Receptor Inhibition [21]. The average number of citations per publication and trends in the publishing data are displayed in Table 1. The trend of publications by year has been relatively increasing over time,

although from 1975 to 2002, related research on chalcone derivatives as anticancer agents was noted in less than five publications per year. In 2003, the number of publications increased from two to nine in 2002. The highest number of publications was observed in 2024 with 149 articles, followed by 2023 with 134 articles and 2020 with 129 articles. This trend indicates growing interest in the subject, with fluctuating publication rates across different years.

In terms of citations, the year with the highest citation rate was 1999 with an average of 24.59 citations per year, followed by 2002 with 10.75 citations per year and 2006 with 9.61 citations per year. High citation numbers suggest that certain publications have a significant impact on subsequent research. Citation counts are increasingly used as indicators of research influence and academic impact. The data presented indicate a growing academic interest in chalcone derivatives as anticancer agents, with fluctuations in annual publications. Recent publications naturally exhibit lower citation averages due to limited exposure time.

Table 1. Publication data trend by year.

Year	Number of Articles	Mean Total of Citations per Year	Mean Total of Citations per Article	Citable Years
1975	1	0.14	7	51
1988	1	1.63	62	38
1995	1	2.71	84	31
1999	1	24.59	664	27
2000	2	2.63	68.5	26
2001	3	1.25	31.33	25
2002	2	10.75	258	24
2003	9	7.96	183	23
2004	8	5.24	115.38	22
2005	7	3.77	79.14	21
2006	9	9.61	192.22	20
2007	10	6.22	118.1	19
2008	9	9.28	167	18
2009	14	4.16	70.79	17
2010	24	5.56	88.92	16
2011	18	8.19	122.78	15
2012	42	4.51	63.19	14
2013	44	4.94	64.16	13
2014	56	5.55	66.62	12
2015	63	5.55	61.03	11

Year	Number of Articles	Mean Total of Citations per Year	Mean Total of Citations per Article	Citable Years
2016	51	3.03	30.33	10
2017	67	5.12	46.06	9
2018	78	4.56	36.44	8
2019	83	6.85	47.98	7
2020	129	4.84	29.02	6
2021	128	5.61	28.05	5
2022	100	4.46	17.85	4
2023	134	2.34	7.01	3
2024	149	1.18	2.35	2
2025	26	0.38	0.38	1

3.2 Analysis of Contributing Sources

Table 2. The Most Productive Journals.

Rank	Sources	Documents
1	European Journal of Medicinal Chemistry	68
2	Molecules	50
3	Bioorganic Chemistry	40
4	International Journal of Molecular Sciences	38
5	Anti-Cancer Agents in Medicinal Chemistry	33
6	Bioorganic And Medicinal Chemistry	26
7	Bioorganic And Medicinal Chemistry Letters	24
8	Journal of Molecular Structure	23
9	Medicinal Chemistry Research	22
10	Archiv Der Pharmazie	18

Table 3. Source Impact and Citations.

Sources	h-index	Total Citations (TC)	Number of Papers (NP)
European Journal of Medicinal Chemistry	43	6,003	68
Bioorganic Chemistry	23	1,602	40
Molecules	22	1,694	50
Bioorganic and Medicinal Chemistry Letters	19	926	24
Anti-Cancer Agents in Medicinal Chemistry	13	825	33

Bioorganic and Medicinal Chemistry Letters	19	926	24
Current Medicinal Chemistry	14	2,803	18
International Journal of Molecular Sciences	14	1,288	38
Anti-Cancer Agents in Medicinal Chemistry	13	825	33
Medicinal Chemistry Research	13	413	22

The top ten most productive journals are listed in Table 2. A total of 1,269 selected papers were published in 407 journals. Among these, the European Journal of Medicinal Chemistry emerged as the most prolific source, contributing 68 articles to the field. The second most productive source was Molecules (50 articles), followed by Bioorganic Chemistry (40 articles).

The most highly cited sources, as indicated in Table 3, include the European Journal of Medicinal Chemistry with 6,003 citations and an impressive h-index of 43, showcasing its significant influence on the field. The Bioorganic and Medicinal Chemistry journal has also demonstrated considerable citation impact, with 2,177 citations and an h-index of 23. Notably, the Journal of Molecular Structure, with a more recent start date (2019), exhibits strong influence within a short period, having published 23 documents with 313 citations and an h-index of 9.

Table 3 shows that the European Journal of Medicinal Chemistry holds a leading position not only in terms of the number of publications but also in terms of citation impact. Additionally, journals such as Molecules and Bioorganic Chemistry are also making substantial contributions to the field, indicating a trend toward multidisciplinary research in medicinal chemistry, with a strong emphasis on bioorganic and medicinal chemistry applications.

The associations between the author's country (AU_CO), sources/ journals (SO), and affiliation (AU_UN) are shown in Fig. 4. The top 20 sources, top 20 authors, and top 20 affiliation used in published works where the focus of this study is the gray lines connecting the three regions. The length of the rectangle indicates the number of related items in each box. The length of the rectangle and number of items in each box become increasingly apparent as the rectangle elongates. Based on inflow analysis, the source with the greatest correlation in the dataset is the European Journal of Medicinal Chemistry, which has published articles from authors affiliated with multiple institutions worldwide. This indicates that the journal plays a crucial role in disseminating research on medicinal chemistry, particularly on chalcone derivatives as anticancer agents.

The outflow analysis further reveals that the European Journal of Medicinal Chemistry and Molecules is among the most internationally collaborative sources, publishing articles from multiple countries, including India, China, Egypt, and Turkey. These journals serve as central hubs for researchers in this field, contributing to their broad international reach and influence. Additionally, Bioorganic Chemistry and the Journal of Molecular Structure also demonstrate strong global connections, with contributions from researchers affiliated with universities and institutions across Asia, Europe, and the Americas. This underscores the interdisciplinary and international nature of the research on chalcone derivatives and medicinal chemistry.

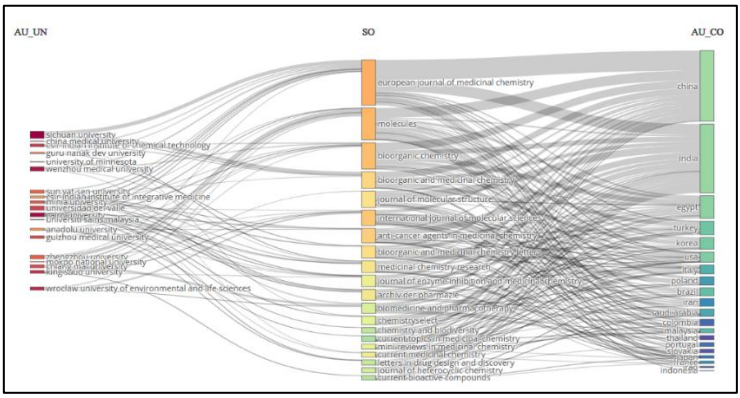


Fig. 4. Three-fields plot between author affiliations (AU_UN), sources (SO), and author countries (AU_CO).

3.3 Analysis of Contributing Country

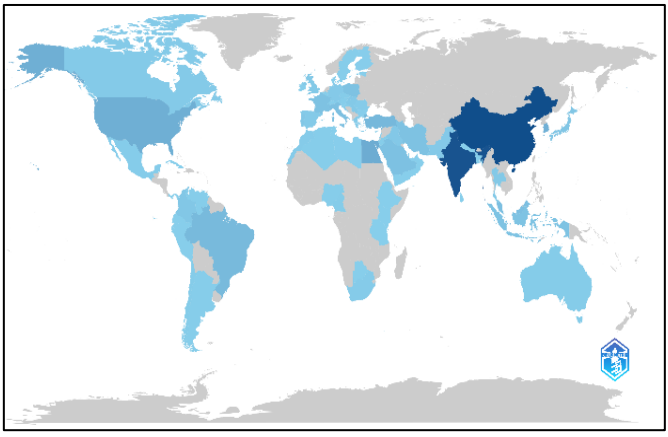


Fig. 5. Country production and collaboration heatmap of articles discussing chalcone derivatives as anticancer.

Table 4. The most productive countries.

Rank	Region	Frequency
1	India	844
2	China	763
3	Egypt	318
4	USA	207

5	South Korea	200
6	Turkey	180
7	Saudi Arabia	119
8	Brazil	104
9	Iran	101
10	Malaysia	96

The analysis of contributing countries provides insights into global participation and regional leaders in publishing research. The data were sourced from Scopus and covered a wide range of articles. Using the publication data, we created a heatmap representing the countries that contributed to the research studies. Countries with higher occurrence frequencies are shown in darker blue shades, indicating their dominance involvement to the field (Fig. 5). From the analysis (Table 4), it is evident that India is the highest frequency of contribution (844), followed by China (763) and Egypt (318). These high frequencies reflect strong and repeated involvement of authors from these countries in chalcone-based anticancer research.

In addition to the total number of publications, citation count was also considered to evaluate the influence of each country in the field. The citation rate provides insights into the impact and relevance of the research produced by each country. From the data on citations (Table 5), India stands out with 10,842 total citations, followed by China with 8,479 citations, and the USA with 3,823 citations. Despite having a lower number of publications, the USA demonstrates a significantly higher citation average (85 citations per article), indicating that research produced in the USA has a greater impact and recognition in the academic community. Furthermore, Canada, with an average citation rate of 182.1, is another prominent contributor with significant influence in the field. Hong Kong (232.8 average citations) also shows exceptionally high citation averages, suggesting that its research is highly regarded within the academic community. The citation analysis suggests that countries such as India, China, and the USA not only produce large volumes of research but also contribute high-quality, impactful publications in the field.

Based on Table 5, Hong Kong exhibits the highest average citation score (232.8), despite contributing only five articles. This suggests that although the volume of publications was low, each article had a significant scholarly impact—likely due to being published in high-impact journals or addressing highly relevant research topics. In contrast, China ranks second in total citations (8,479) and produces a much higher number of articles (218), yet its average citation score (38.9) is lower than those of Canada (182.1) and Italy (59.2). This indicates that while China dominates in quantity, the average impact per article may be lower, possibly due to a broader range of publication quality. A similar pattern can be observed in Canada, which produced only 11 articles but achieved a remarkably high average citation score (182.1), reflecting a strong emphasis on quality and impactful research output.

Table 5. The most cited countries.

Rank	Country	Total Citation (TC)	Number of Articles (NA)	Average Article Citations (TC/NA)
1	India	10,842	290	37.4
2	China	8,479	218	38.9
3	USA	3,823	45	85
4	Canada	2,003	11	182.1
5	Iran	1,865	23	81.1
6	Egypt	1,836	78	23.5
7	Italy	1,361	23	59.2
8	Korea	1,340	50	26.8
9	Malaysia	1,229	37	33.2
10	Hong Kong	1,164	5	232.8

3.4 Analysis of Contributing Institution

Table 6. The institutions with the highest number of publications.

Rank	Institution	Country	Articles
1	Cairo University	Egypt	46
2	National Research Centre	Egypt	35
3	China Medical University	China	32
4	Chiang Mai University	Thailand	31
5	Universitas Gadjah Mada	Indonesia	24
6	Kaohsiung Medical University	Taiwan	23
7	Minia University	Egypt	21
8	Ataturk University	Turkey	19
9	Guizhou Medical University	China	19
10	Al-Azhar University	Egypt	18

The contribution of institutions provides valuable insight into the global spread of research activity and highlights the institutions that are leading the way in terms of scientific output. A total of 1,269 selected papers were contributed to by 2,003 institutions. Table 6 summarizes the top 10 institutions with the highest number of papers and citations. Cairo University has 46 publications, making it the most productive institution in this field, followed closely by the National Research Centre and China Medical University.

While countries such as India, the USA, South Korea, and Malaysia are among the highest contributors at the national level (Section 3.3), their research output is more distributed across numerous institutions, resulting in no single institution surpassing the publication thresholds highlighted in this table. Conversely, countries such as Egypt, China, Thailand, and Indonesia have individual institutions with distinctly higher publication counts, allowing them to appear more prominently in institutional rankings. This indicates a correlation where national research dominance (e.g., India, USA) does not always translate into institutional centralization, whereas in countries such as Egypt or Indonesia, publication efforts tend to be concentrated in a few leading academic centers.

In addition to the total number of articles published, the level of institutional collaboration can provide insight into how these institutions are engaging in global research efforts. Among the top institutions, Cairo University and the National Research Centre showed a high level of research output, which is indicative of their strong involvement in the field. The extensive publication records of Chiang Mai University, Universitas Gadjah Mada, and Kaohsiung Medical University suggest that these institutions are also leading contributors to the research community.

Several institutions actively collaborate across regions and contribute to global research efforts. For example, China Medical University and Guizhou Medical University in China, as well as Cairo University and the National Research Centre in Egypt, are key players in fostering cross-border collaborations. These partnerships are instrumental in driving innovation and knowledge-sharing in the scientific community.

3.5 Analysis of Influential Authors

A bibliometric analysis of 1,269 articles involving 5,672 authors in the field of chalcone derivatives as anticancer agents identified the most prolific contributors (Table 7). Wang Y. emerged as the most productive author with 22 publications, followed by Li Y. and Chen X., with 15 publications each. These high levels of contribution underscore the pivotal role of key researchers in advancing chalcone-related anticancer research. The leading authors also exhibited relatively high h-indices—for instance, Wang Y. with an h-index of 17—indicating that at least 17 of his publications have each been cited 17 times or more, which is a meaningful indicator of scholarly impact. This suggests that their work is not only quantitatively substantial but also frequently referenced by other researchers in this field.

The co-authorship network visualization (Fig. 6a), generated using VOSviewer, displays a tightly connected cluster of influential authors. Notably, Wang Y. and Zhang Y. were situated within the same dense collaborative group, indicating frequent joint publications. This close-knit collaboration reflects a high degree of scientific networking, which likely facilitates the accelerated progress in the development of chalcone derivatives as anticancer agents. Consistently, the author overlay visualization (Fig. 6b) shows increased involvement of newer researchers in recent years. For example, Zhang Y. appeared in more recent publication layers, suggesting that early-career researchers are becoming more active in contributing to the field. This trend points to a generational renewal and expansion of the scientific community, where

experienced senior researchers collaborate with emerging scholars, maintaining research continuity while incorporating fresh perspectives.

In the author density map (Fig. 6c), the brighter regions indicate higher concentrations of productive and influential authors. It is evident that authors from China dominate the map, which corresponds to the fact that the majority of top-ranking authors—including Wang, Chen, Li, Liu, and Zhang—are affiliated with Chinese research institutions. Among the top ten authors, only Kamal A. originated outside China (India). Despite the dominance of Chinese researchers in terms of quantity, individual contributions from countries such as India also hold considerable value. Kamal A., with an h-index of 13 and 14 publications, is known for his work on tubulin inhibitors and has demonstrated significant international influence, despite being affiliated with an institution not listed among the most productive.

A noteworthy correlation exists between influential authors and leading institutions (Table 6). The China Medical University, one of the top institutions with 32 publications, is likely home to several prominent Chinese authors, suggesting a convergence of individual and institutional productivity. Similarly, the dominance of Chinese authors aligns with the presence of several Chinese universities in the top ten institutions, such as China Medical University and Guizhou Medical University. In contrast, Cairo University and the National Research Centre in Egypt rank first and second, respectively, in total publication output but are not represented among the most influential individual authors. This indicates that research output in Egypt is achieved through collective contributions from numerous researchers rather than a few highly prolific individuals.

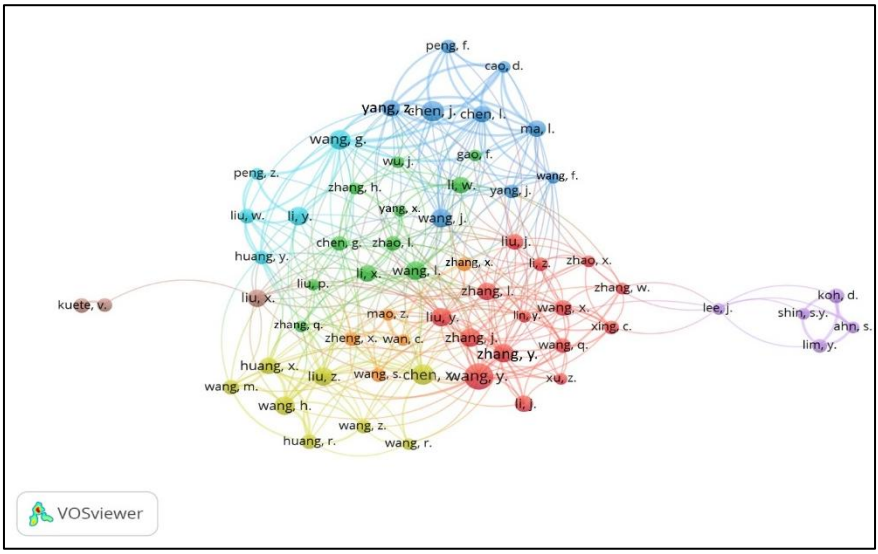
These observations highlight two distinct but complementary models of scientific contribution: one led by highly productive core research groups (as seen in China) and the other driven by broader institutional collaboration (as in Egypt and other countries). The synergy between these models ensures that research on chalcone derivatives as anticancer agents continues to evolve dynamically and is supported by key scientific figures and robust international collaboration networks.

Table 7. Top 10 authors with the most papers.

No.	Author	Country	h-index	Number of Papers	Number of Citations	Average Citation per Article	The title of the latest paper (year of publication)
1.	Wang Y.	China	17	22	895	40.68	Overexpression of the R2R3-MYB transcription factor GmMYB3a enhances isoflavone accumulation in soybean.
2.	Chen X.	China	10	15	640	42.67	Flavokawain C inhibits proliferation and migration of liver cancer cells through FAK/PI3K/AKT signaling pathway.
3.	Li Y.	China	12	15	572	38.13	In vitro anticancer effects in hepatocellular carcinoma (HCC) and protein interaction study of xanthoangelol.

No.	Author	Country	h-index	Number of Papers	Number of Citations	Average Citation per Article	The title of the latest paper (year of publication)
4.	Chen J.	China	11	14	668	47.71	Echinatin mitigates sevoflurane-induced neurotoxicity through regulation of ferroptosis and iron homeostasis.
5.	Kamal A.	India	13	14	836	59.71	An update on the development on tubulin inhibitors for the treatment of solid tumors.
6.	Wang G.	China	12	13	657	50.53	Current status of carbazole hybrids as anticancer agents.
7.	Liu Y.	China	7	12	804	67	Overexpression of the R2R3-MYB transcription factor GmMYB3a enhances isoflavone accumulation in soybean.
8.	Wang J.	China	7	12	589	49.08	Echinatin mitigates sevoflurane-induced neurotoxicity through regulation of ferroptosis and iron homeostasis.
9.	Wang L.	China	6	12	157	13.08	Licorice Extract Isoliquiritigenin Increased Cytosol Calcium and Induced Apoptosis in Colon Cancer Cells via Transient Receptor Potential Vanilloid-1.
10.	Zhang Y.	China	8	12	416	34.67	Overexpression of the R2R3-MYB transcription factor GmMYB3a enhances isoflavone accumulation in soybean.

(a)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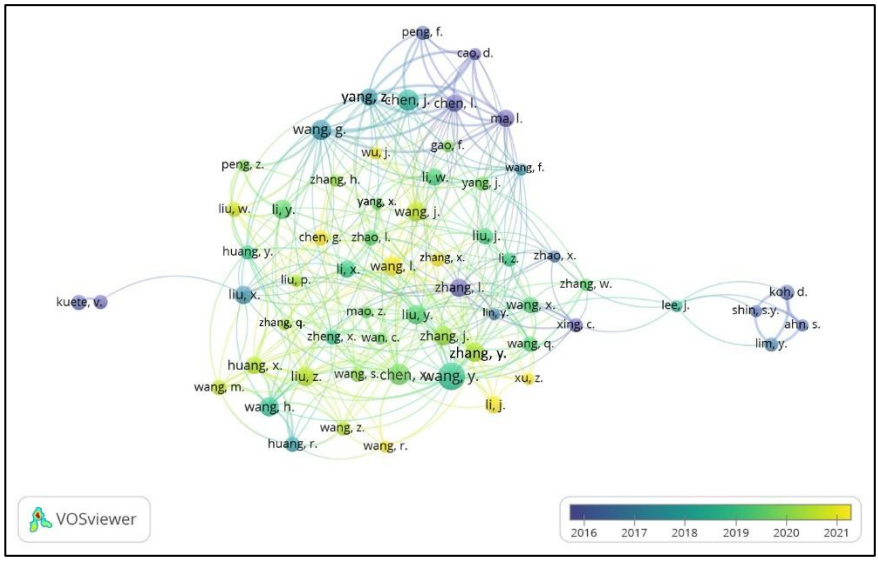
(b)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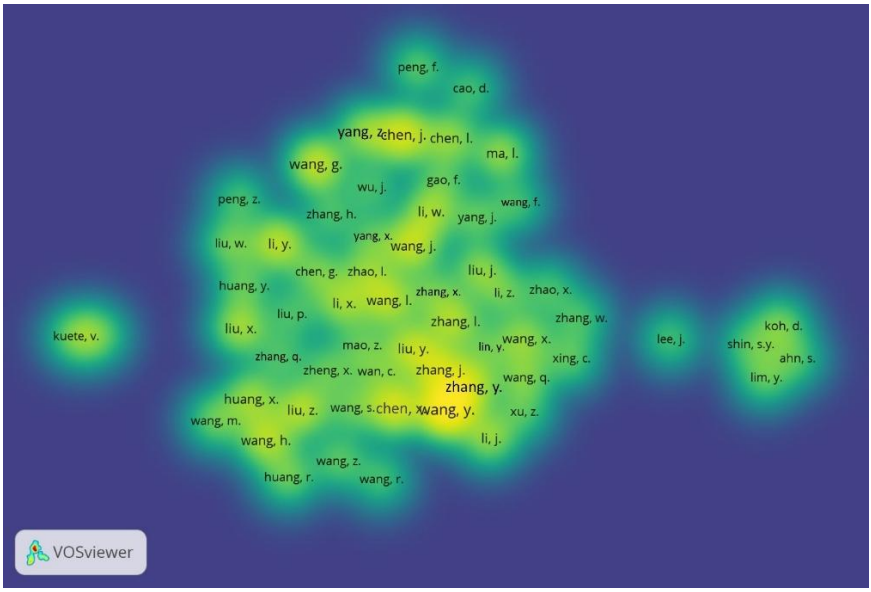
(c) 

Fig. 6. Three visualizations of contributing authors: (a) network visualization, (b) overlay visualization, and (c) item density map.

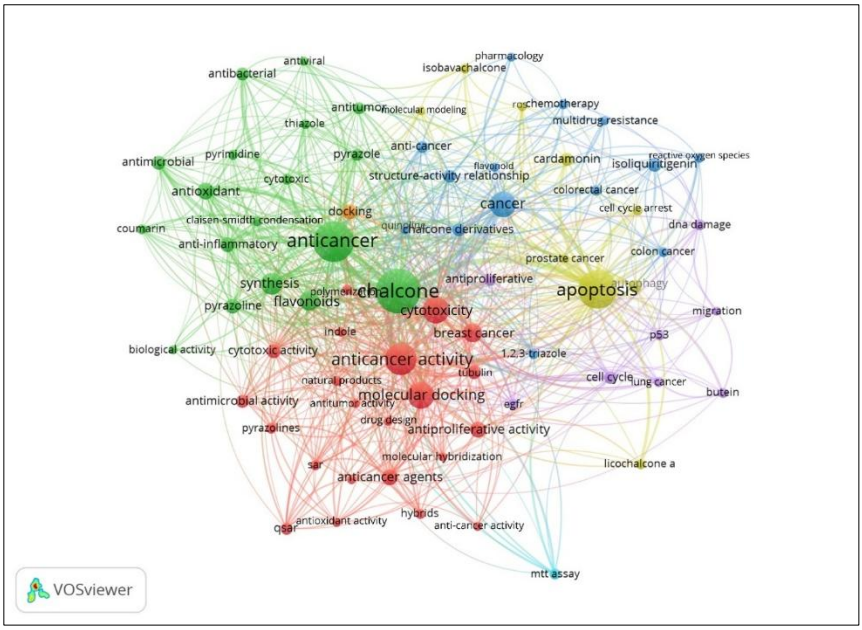
3.6 Keywords Co-occurrence Analysis

Keywords co-occurrence analysis was conducted to explore the main themes emerging from the literature on the development of chalcone derivatives as anticancer agents. The analysis revealed that the most prominent keywords were chalcone derivatives, anticancer activity, and apoptosis, indicating the significant role of apoptosis in the therapeutic application of chalcone derivatives in cancer treatment. Other frequently associated keywords include molecular docking, cytotoxicity, and flavonoids, suggesting that research in this field relies heavily on structure-based approaches for evaluating the cytotoxic effects of chalcone on cancer cells.

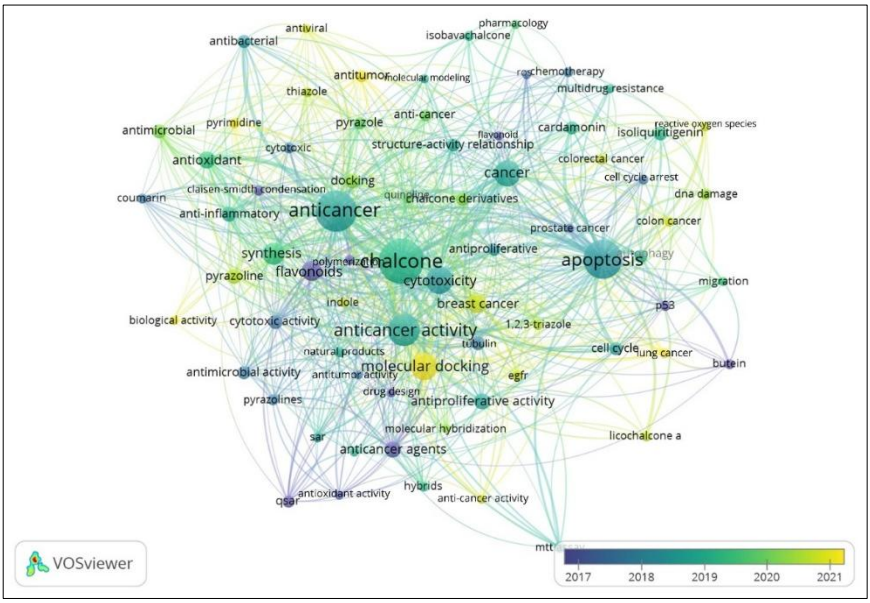
In the network visualization (Fig. 7a), it is evident that keywords such as ‘anticancer’ and ‘apoptosis’ form two major clusters that are closely linked to other terms, such as ‘molecular docking’ and ‘cytotoxicity’. This network visualization illustrates the strong connections between the fundamental mechanisms of cancer (apoptosis) and the application of chalcones in anticancer therapy. The keyword ‘molecular docking’ appears as a central node, connecting various aspects of chalcone research, highlighting its crucial role in mapping the interactions between chalcone compounds and cancer molecular targets.

Overlay Visualization (Fig. 7b) revealed trends in the evolution of keywords over time. From this visualization, it is apparent that molecular docking has increasingly dominated the recent research landscape, reflecting its growing importance in understanding the interactions between chalcone derivatives and biological targets in cancer. The color changes observed in this visualization represent the emergence of

newer and increasingly important topics, such as molecular docking, which is advancing the design of more effective and selective anticancer compounds.



(a)



(b)

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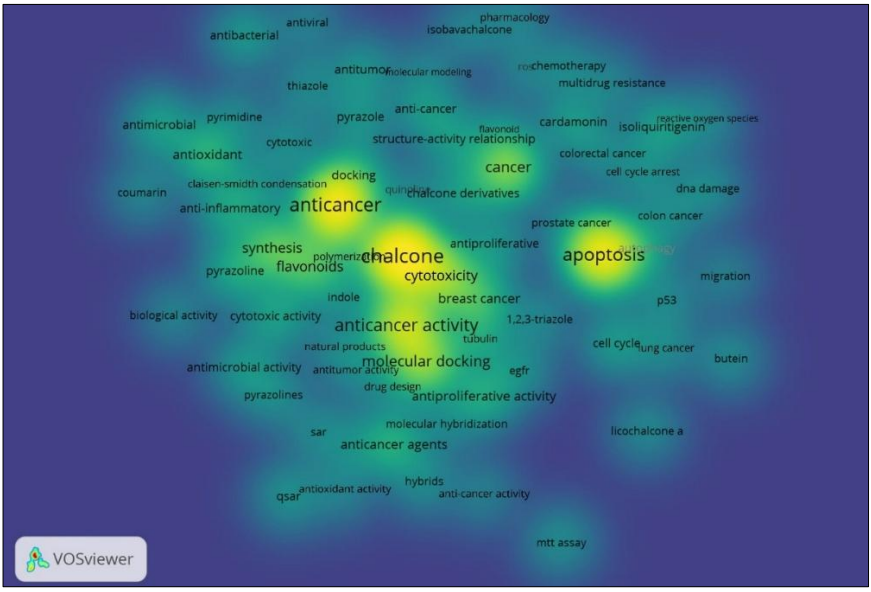


Fig. 7. Three visualizations of the co-occurrence of authors' keywords: (a) a network map, (b) an overlay visualization, and (c) a density map.

Additionally, further analysis using Density Visualization (Fig. 7c) emphasizes the prominence of keywords such as ‘chalcone’, ‘anticancer activity’, ‘apoptosis’, and ‘molecular docking’, which are notably bright and central to the visualization. This indicates that these topics not only frequently appear in the literature but also hold high density in the analyzed publications. The density of these keywords underscores their relevance and centrality in the current research on chalcone derivatives as anticancer agents.

In conclusion, the results of keywords co-occurrence analysis highlight the growing focus of research on molecular docking for the development of chalcone derivatives as anticancer agents. This approach offers deeper insights into the molecular interactions between chalcone derivatives and cancer targets, thereby providing a pathway for the development of more effective anticancer agents, particularly those inducing apoptosis. Moving forward, the application of molecular docking could be the key to improving the selectivity and efficacy of chalcone derivatives, leading to more targeted and efficient clinical applications.

3.7 Most Cited Papers

Table 8 lists the most cited original research articles in the domain of chalcone derivatives as anticancer agents. These studies are foundational and highly influential, providing both conceptual and methodological frameworks for subsequent investigations. Each article focuses on the synthesis of chalcone-based compounds and

their evaluation against cancer cell lines, with clear emphasis on elucidating the underlying mechanisms of anticancer action.

The top-cited work by Modzelewska et al. (2006, USA) introduced novel chalcone and bis-chalcone structures, highlighting their selective cytotoxicity, particularly through p53-dependent pathways. Bandgar et al. (2010, India) synthesized methoxylated chalcones, evaluated their anticancer, anti-inflammatory, and antioxidant properties, also identified key structural features for high bioactivity. Pingaew et al. (2014, Thailand) developed chalcone–coumarin hybrids using click chemistry, reporting dual antitumor and antimalarial activities, with microtubule inhibition as the primary mechanism.

Ducki et al. (2009, UK) focused on combretastatin-like chalcones that inhibit tubulin polymerization, demonstrating antivascular effects and mitotic arrest. Srinivasan et al. (2009, USA) explored Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) inhibition via structure–activity relationships of tetramethoxychalcones, linking transcriptional modulation with potent anticancer outcomes.

Collectively, these studies employed diverse synthetic routes such as Claisen–Schmidt condensation and triazole coupling, and targeted multiple mechanisms, including apoptosis induction, microtubule disruption, ROS generation, and suppression of pro-survival signaling pathways. Their high citation counts underscore their importance in shaping the trajectory of chalcone-based drug discovery and continue to serve as cornerstones in the field.

Table 8. Top cited papers on chalcone derivatives as anticancer.

No.	Authors	Number of Citations	Title	Country
1.	Modzelewska A. et al. (2006)	396	Anticancer activities of novel chalcone and bis-chalcone derivatives	United States
2.	Bangdar B.P. et al. (2010)	292	Synthesis and biological evaluation of simple methoxylated chalcones as anticancer, anti-inflammatory and antioxidant agents	India
3.	Pingaew R. et al. (2014)	211	Synthesis, biological evaluation, and molecular docking of novel chalcone-coumarin hybrids as anticancer and antimalarial agents	Thailand
4.	Ducki S. et al. (2009)	185	Combretastatin-like chalcones as inhibitors of microtubule polymerization. Part 1: Synthesis and biological evaluation of antivascular activity	United Kingdom
5.	Srinivasan B. et al. (2009)	172	Structure-activity relationship studies of chalcone leading to 3-hydroxy-4,3'.4',5'-tetramethoxychalcone and its analogues as potent nuclear factor κB inhibitors and their anticancer activities	United States

Table 9. Overview of synthesized methoxy-substituted chalcone derivatives and cell line testing.

Compound	Starting Material(s)	Method	Yield	Tested Cancer Cell Line(s)	Reference
[Bbim]Br-DMC (Imidazolium conjugated with dimethylcardamonin)	DMC isolated; 1,4-dibromobutane; N-butylimidazole	Mixture at 50 °C for 24 h	91%	MDA-MB-231, TNBC, MCF-7	[23]
3,4,5-Trimethoxylated chalcone	3,4,5-trimethoxyacetophenone and substituted aldehydes	Claisen-Schmidt condensation via reflux	10-80%	HCT116, HT-29, DU145, PC3	[24]
Arylindolylpropenone (Indole hybrid chalcone)	Substituted 3-acetylindole and benzaldehyde derivatives; or substituted acetophenones and substituted indole-3-carboxaldehyde	Claisen-Schmidt condensation via stirring	55-81%	HCT116, HeLa, Jurkat, MDA-MB-231, MCF-7	[25]
1-Methoxyindole- and 2-alkoxyindole-based chalcones	3-acetyl-1-methoxyindole and substituted aldehydes; 1-methoxyindole-3-carboxaldehyde and acetophenones	Claisen-Schmidt condensation via reflux	26-32%	A549, Caco-2, HCT116, HeLa, MCF, MDA-MB-231, Jurkat	[26]
(E)-1-(2′-Hydroxy-4′,6′-dimethoxyphenyl)-3-(4-methylthio)phenyl)prop-2-ene-1-one (FLS)	4,6-dimethoxy-2′-hydroxyacetophenone and 4-(methylthio)benzaldehyde	Claisen-Schmidt condensation via stirring at room temperature	78.6%	MCF-7, MDA-MB-231, MCF-10A	[27]
3,5-Dibromo-4,6-dimethoxychalcones	3,5-dibromo-2-hydroxy-4, 6-dimethoxyacetopheno	Claisen–Schmidt condensation via	47-68%	MCF-7, A549	[28]

Compound	Starting Material(s)	Method	Yield	Tested Cancer Cell Line(s)	Reference
	ne and benzaldehyde derivatives	stirring at room temperature			
3,4,5-Trimethoxychalcone derivatives	3,4,5-trimethoxyacetohenone and benzaldehyde derivatives	Claisen–Schmidt condensation via stirring at room temperature	47.8-88.4 %	NCI-N87	[29]

3.8 Synthetic Approaches of Chalcone Derivatives

Research related to chalcone derivative compounds as anticancer candidates has seen significant developments over the years, both in terms of the compound sources (natural and synthetic) and the types of substituents used to enhance their biological activity. The research approaches have mostly involved in vitro methods to explore the cytotoxicity and mechanisms of chalcone derivative compounds.

Between 1975 and 2025, the chalcone derivative compounds studied included both isolated and synthesized compounds. One of the most frequently studied groups, which emerged as a recurring keyword, was the methoxy group. Methoxy-substituted chalcone derivatives have shown enhanced anticancer activity, especially against the A549 cancer cell line [23]. Examples of synthesized methoxy-substituted chalcone derivatives are shown in Table 9.

Based on the literature review summarized in Table 9, the methoxy group tends to be positioned on the ring, derived from ketones, and is sometimes combined with indole and imidazole groups. Most studies on chalcone derivative synthesis have focused on structural innovation to enhance biological activity, particularly in in vitro assays. The most commonly used cancer cell line in these studies was MCF-7. Most methoxy-substituted compounds are synthesized through the Claisen–Schmidt condensation reaction using conventional stirring or reflux methods.

In contrast, the microwave-assisted synthesis (MAS) method has been used to synthesize chalcone derivatives with other substituents. Kumar et al. (2014) successfully synthesized indole-based chalcone derivatives with a 96 % yield using the microwave method in just 5 minutes, whereas conventional methods produced only a 50% yield after 600 minutes [22]. MAS offers several advantages within the green chemistry framework compared with conventional methods, including shorter reaction times, higher yields, minimal solvent use, and reduced waste [30].

Several methoxy-substituted chalcone derivatives have demonstrated good and selective anticancer activity. Future research can focus on the optimization of their synthesis, including the selection of appropriate solvents and catalysts for MAS, to improve the reaction efficiency and further support green chemistry principles.

3.9 Mechanism of Anticancer Activity

Chalcones are crucial precursors in flavonoid biosynthesis and have gained significant attention owing to their diverse biological activities, particularly in cancer research. One of the compelling features of chalcones is their relatively simple structure, which permits easy structural modification to optimize their therapeutic potential. This structural versatility has enabled the development of various chalcone derivatives that target cancer through different molecular pathways. A prominent example is the chalcone-acridine hybrid 1C, which was investigated by Salanci et al. (2024) for its effects on ovarian cancer cells [31]. This compound exerts its anticancer action primarily through G2/M phase arrest, induction of apoptosis, and modulation of oxidative stress. Interestingly, 1C functions across both sensitive (A2780) and resistant (A2780cis) ovarian cancer cell lines, indicating its robust mechanism. What sets this derivative apart is its dynamic regulation of nuclear factor erythroid 2-related factor 2 (Nrf2), a key antioxidant transcription factor, that behaves differently in sensitive and resistant cells. Moreover, ROS generation plays a central role, as the presence of N-acetylcysteine (NAC), an ROS scavenger, diminishes 1C's efficacy, reinforcing the importance of oxidative stress in its anticancer mechanism. This ROS-centered mechanism was echoed in the work of chalcone derivative a14 [32]. This compound, tested on HepG2 liver cancer cells, also induced apoptosis via the ROS-mitochondrial axis, disrupted mitochondrial membrane potential (MMP), and altered the expression of key apoptosis regulators such as Bcl-2-associated X protein (Bax), B-cell lymphoma 2 (Bcl-2), and caspase 3. Similar to 1C, a14 causes G2/M phase arrest, indicating a shared mechanism across different cancer types where cell cycle blockade and mitochondrial stress act synergistically.

In another angle of exploration, SBD-2, a naturally derived prenylated chalcone from *Shuteria involucrata*, demonstrates potent anticancer effects against colorectal cancer cells by targeting the Akt pathway—a signaling cascade integral to cell survival. As shown by SBD-2's inhibition of Akt phosphorylation and downstream targets, such as Cyclin B1 and Bcl-2, its impact mirrors the synthetic derivatives by causing G2/M arrest and promoting mitochondrial apoptosis [33]. Collectively, these studies point to the G2/M checkpoint and mitochondrial pathways as consistent vulnerabilities that chalcones exploit in cancer cells. Beyond oxidative stress and mitochondrial dysfunction, DNA-interacting mechanisms have emerged as being critical. Ali et al. (2024) reported on a ciprofloxacin-chalcone hybrid (CP derivative 2) that directly targets topoisomerases I and II, which are essential enzymes for DNA replication. This inhibition leads to both cell cycle arrest and apoptosis, along with modulation of gene expression (upregulation of Bax and Caspase 9, downregulation of Bcl-2). This dual-targeting mechanism reinforces the potential of chalcone hybrids to disrupt DNA integrity and orchestrate cell death at the transcriptional level [34].

Moreover, the significance of inflammatory and survival pathways such as NF-κB and signal transducer and activator of transcription 3 (STAT3) was underlined in the study by Papierska et al. (2024) on chalcone thio-derivatives in hepatocellular carcinoma (HCC) [35]. These compounds not only induce apoptosis and cell cycle arrest but also suppress NF-κB by inhibiting IKKα/β kinase activity and reducing STAT3 activation, two key pathways often upregulated in HCC. Of particular interest is the downregulation of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and tumor necrosis factor-alpha (TNF-α), indicating an anti-inflammatory contribution to their anticancer effect—further differentiating this mechanism from that of other chalcone analogs. All these findings emphasize that while individual derivatives may vary in their primary targets, such as ROS, tubulin, topoisomerases, or survival signaling pathways—most chalcone compounds converge on a few crucial outcomes: mitochondrial disruption, cell cycle arrest, and apoptotic signaling.

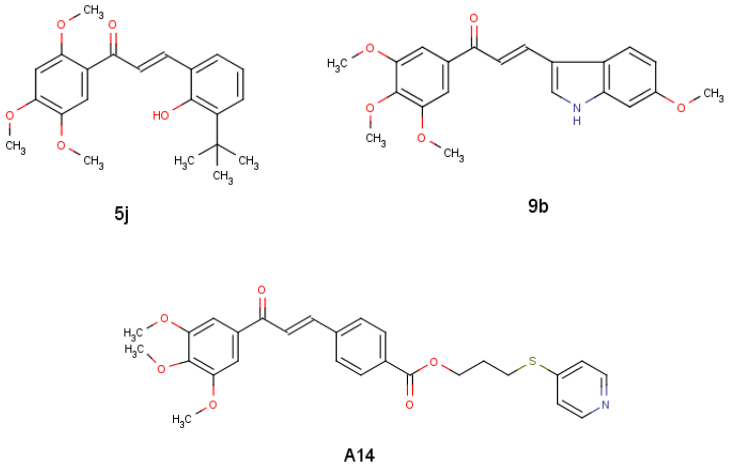
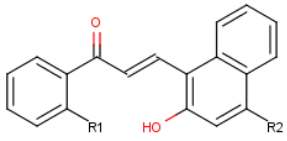


Fig. 8. Chalcone derivatives with trimethoxyphenyl (ring A) based resulting potent activity against breast cancer cells.



11: R1 = $O(CH_2)_5CH_3$, R2 = F
12: R1 = $O(CH2)_7CH_3$, R2 = F
13: R1 = $O(CH2)_9CH_3$, R2 = F
14: R1 = $O(CH2)_{11}CH_3$, R2 = F
15: R1 = $O(CH2)_{13}CH_3$, R2 = F

Fig. 9. Fluorinated chalcone 11-15 structure.

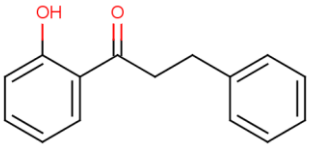


Fig. 10. 2'-Hydroxychalcone structure.

This mechanistic diversity is closely related to the structure-activity relationship (SAR). For instance, studies on ortho-hydroxy chalcones, indole-chalcones, and fluorinated chalcones have shown that structural modifications such as the introduction of hydroxy, methoxy, bromine, fluorine, or heterocyclic moieties can drastically enhance selectivity and cytotoxicity. The presence of three methoxy substituents on ring A and an ortho-hydroxy group on ring B was found to enhance the cytotoxicity of chalcone derivatives, with compound 5j showing the strongest activity (IC_{50} = 10.45 μM), and the addition of a methoxy group into the indole ring (compound 9b) improving its activity from 29.86 μM to 19.18 μM against MCF-7 [36]. Additionally, compound A14 has IC_{50} = 9.79 μM [37]. The structure of the trimethoxyphenyl-based chalcones is shown in Figure 8. Binding studies further confirmed these SAR findings, showing that certain derivatives strongly interact with tubulin at the colchicine site, thereby interfering with microtubule polymerization—a mechanism essential for mitotic inhibition and tumor suppression. Notably, fluorinated chalcones (11-15) (Fig. 9) exhibited greater cytotoxicity against breast cancer cells (4T1) and reduced toxicity to normal fibroblasts compared to cisplatin. These fluorinated chalcones induce apoptosis through mitochondrial dysfunction and caspase activation, modulating Bax and Bcl-2 levels [38].

To enhance anticancer efficacy and selectivity, structural modifications of chalcones have been explored extensively. Maadh et al. (2022) synthesized two series of chalcone derivatives targeting breast cancer cells MCF-7, particularly emphasizing microtubule inhibition via binding to the colchicine site on tubulin [39]. Derivatives such as 4c, 5j, and 6a demonstrated potent activity, and molecular docking revealed strong binding affinities with favorable free energy values. Substitutions with hydroxy, methoxy, and bromine groups improved cytotoxicity and specificity.

Against colorectal cancer cells (CRC) (HCT116), compound 4c, part of the dihydrochalcones (DHC) series, induced G2/M arrest via murine double minute 2 (MDM2) and p21 modulation and promoted Fas-mediated apoptosis, as confirmed through Fas knockdown experiments [40]. Molecular docking highlighted 4c's interaction with the Fas-associated death domain (Fas/FADD), while transcriptomic and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses emphasized the regulation of the p53 signaling pathway. The compound also inhibited CRC cell migration and invasion, indicating anti-metastatic potential.

In a recent in vivo study, the chalcone derivative 2'-hydroxychalcone was shown to suppress tumor growth and metastasis by inhibiting the NF-κB pro-survival pathway. This inhibition contributes to excessive accumulation of cellular ROS, endoplasmic reticulum stress (ERS), and autophagy-dependent apoptosis in breast cancer cells [41]. The chemical structure of 2'-hydroxychalcone is shown in Figure 10.

Chalcone derivatives exhibit multi-targeted anticancer potential through mechanisms such as apoptosis induction, ROS generation, mitochondrial dysfunction, tubulin inhibition, and transcription factor regulation underscoring the multi-targeted therapeutic potential of chalcone derivatives. Structural modifications have improved selectivity, potency, and pharmacological properties, making them versatile scaffolds for anticancer drug design. These findings advocate further preclinical and clinical development of chalcone-based therapeutics, especially for cancers with drug resistance or poor prognosis.

4 Conclusion

This bibliometric study showed an increase in publications on chalcone derivatives as anticancer agents over the past 51 years, with India and China being the major contributors. The most productive journal is the European Journal of Medicinal Chemistry, while the institution with the highest number of publications is Cairo University, and the most prolific author is Wang Y. from China. In addition, current research focuses on apoptosis, cytotoxic activity, and molecular docking approaches. The synthesis of chalcone derivatives is generally carried out using the Claisen–Schmidt method with conventional techniques. Many of the chalcone derivatives studied contain methoxy substituents on the A ring, which have been shown to enhance both activity and selectivity. The mechanisms of action of chalcone derivatives include induction of apoptosis, ROS generation, disruption of the cell cycle, and suppression of cancer signaling pathways. SAR supports the importance of structural modifications in enhancing anticancer activity. Overall, this overview confirms the potential of chalcone derivatives as cancer drug candidates. Future research should focus on optimizing synthetic methods using MAS to support green chemistry principles, conducting more in vivo and clinical evaluations, and expanding collaborative networks to accelerate clinical development.

Acknowledgments. This research did not receive funding from any organization.

Disclosure of Interests. The authors declare no conflict of interest.

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