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Bibliometric Analysis of Curcumin Based on CiteSpace: Landscapes, Hotspots, and Frontiers

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Abstract: Curcumin, the main active compound in turmeric, has garnered significant interest for its wide range of pharmacological properties. In this study, CiteSpace was used to visually analyze curcumin-related publications to elucidate the current landscape and explore emerging frontiers in curcumin research. In total, 23,184 publications on curcumin from January 1, 2014, to December 31, 2023, were scrutinized. The analysis revealed that publication volume consistently increased over time. The top 10 countries contributed 90.87% of the publications, highlighting the global significance of curcumin research. China generated 31.34% of the total corpus due to its strong research capabilities and traditional medicine culture. The top 10 institutions contributed 11.21% of the articles, revealing notable collaborations. Among the prolific authors, Amirhossein Sahebkar produced 246 publications, whereas Preetha Anand garnered the most citations. Keyword analysis revealed prevalent trends such as "fabrication", "combination", "extract", "natural products", "colorectal cancer", and "resveratrol". Reference analysis emphasized research on therapeutic and modulatory effects, anticancer potential, and interdisciplinary topics, such as molecular biology, chemistry, and nutrition. More importantly, we simplified cluster relationships by selecting the top 30% of cluster dependency paths. For instance, the references within the #1 polymeric micelle cite literature from the #2 anticancer potential, #3 modulatory effect, and #4 therapeutic effect, indicating that clusters 2, 3, and 4 serve as knowledge foundations for cluster 1. This interconnectedness highlights how the information in these clusters can contribute to the knowledge of curcumin in various studies. This study provides an overview of the research trends and critical themes related to curcumin, offering insights for future research directions and emphasizing the interdisciplinary and global scope of curcumin research.

Keywords: CiteSpace, visualization analysis, curcumin, therapeutic effect, drug delivery system

Introduction

Turmeric, scientifically known as *Curcuma longa* L., is an economically and medicinally significant plant of international importance that is classified under the Curcuma genus of the Zingiberaceae family. Turmeric is native to the Indian subcontinent and countries in Southeast Asia. This herb has been employed for millennia to treat a wide range of diseases in diverse traditional medical systems, such as Ayurveda, Siddha, and traditional Chinese medicine. Turmeric contains over 235 bioactive constituents, with curcuminoids being the most abundant, accounting for more than 89% of the total active components.[1] The remaining fraction consists of noncurcuminoids, which include turmerosaccharides, essential oils, tumerones, and dietary fibers. These components contribute to the multifaceted pharmacological properties of turmeric.

Curcumin is the primary curcuminoid responsible for most of the therapeutic properties associated with turmeric and is denoted by the molecular formula $C_{21}H_{20}O_6$, with a molecular weight of 368.38 g/mol. Curcumin was first extracted in impure form by Vogel and Pelletier in 1815 and first prepared in pure and crystalline form by Daube in 1870.[2] Remarkably, the Lancet published the first article in 1937 describing the application of curcumin for biliary disease.[3] In this pioneering study, 67 patients were treated with 300–800 mg daily of curcumin in increasing doses after meals for 3 weeks. Symptomatic relief was observed in all patients, as was radiologic improvement by cholecystogram in 18 patients. Increasing evidence indicates that curcumin possesses a wide range of pharmacological properties, including anti-inflammatory, antioxidant,

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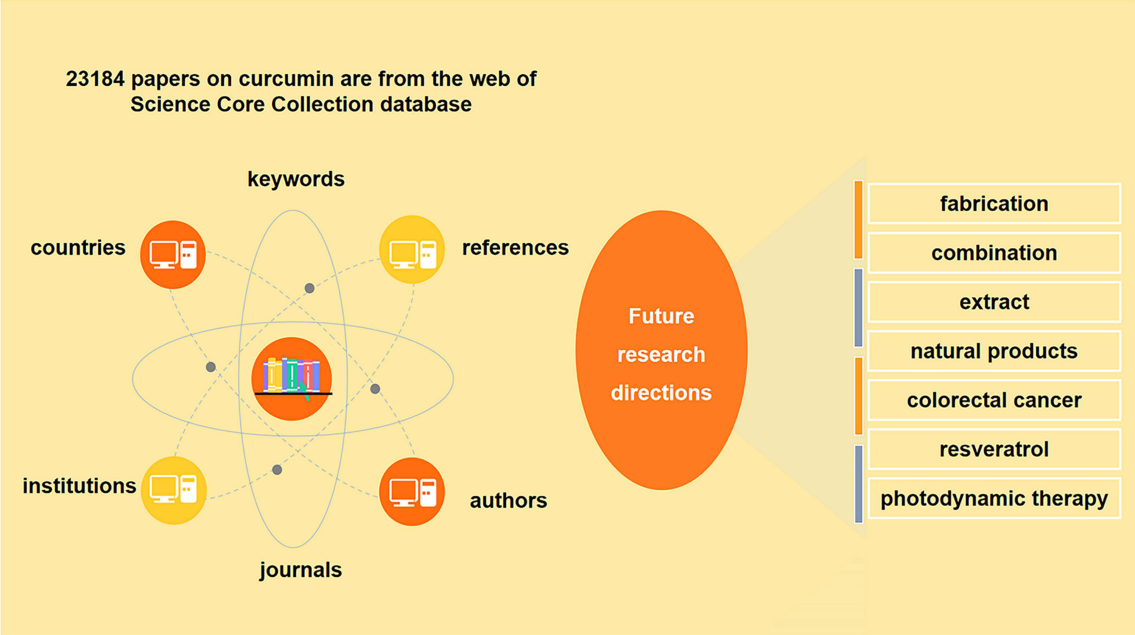
Graphical Abstract



lipid-regulating, antiviral, and anticancer effects, with low toxicity and minimal adverse reactions.[4] Interestingly, the US Food and Drug Administration labeled curcumin "generally regarded as safe", and this active ingredient is used in the United States as a preservative and coloring agent in mustard sauce, cheese, butter, chips, and other products.[5] Nevertheless, further research is needed to investigate the underlying mechanisms and verify the clinical efficacy of curcumin in medical practice.

Bibliometrics is an interdisciplinary field in which statistical techniques are applied to analyze published material, including books, journal articles, datasets, blogs, and the associated metadata, such as abstracts, keywords, and citations, to reveal and clarify the relationships among various scholarly publications.[6] CiteSpace is a Java-based, time-sharing, multivariable citation visualization analysis tool developed by Professor Chaomei Chen of the College of Computing and Informatics at Drexel University, USA.[7] The tool offers a promising approach to streamline complex tasks by identifying landmarks, pivots, and hubs. It is, thus, used to conduct bibliometric analyses of natural plants and their active ingredients.[8–10] Our study aims to provide a comprehensive and meticulous overview of the current landscape, theoretical underpinnings, principal research domains, and burgeoning trends within the field of curcumin research. This analysis encompasses a spectrum from foundational studies to clinical investigations, employing CiteSpace as a tool for visualizing and mapping the intellectual structure of the literature.

Materials and Methods

Search Strategy

By utilizing an "advanced search" strategy within the Web of Science Core Collection (WOSCC), we systematically searched for publications relevant to curcumin, as outlined in Figure 1. Only articles and reviews published from January 1, 2014, to December 31, 2023, were considered. The data collection was executed on February 5, 2024. After removing duplicate articles, a corpus of 23,184 papers was retained for further analysis.

Analysis Tools

The research employed CiteSpace (6.3. R1 Advanced), a convenient information visualization and analysis tool. Renowned for its meticulous literature-combining function and ability to apply multivariate, time-dependent, and visualization

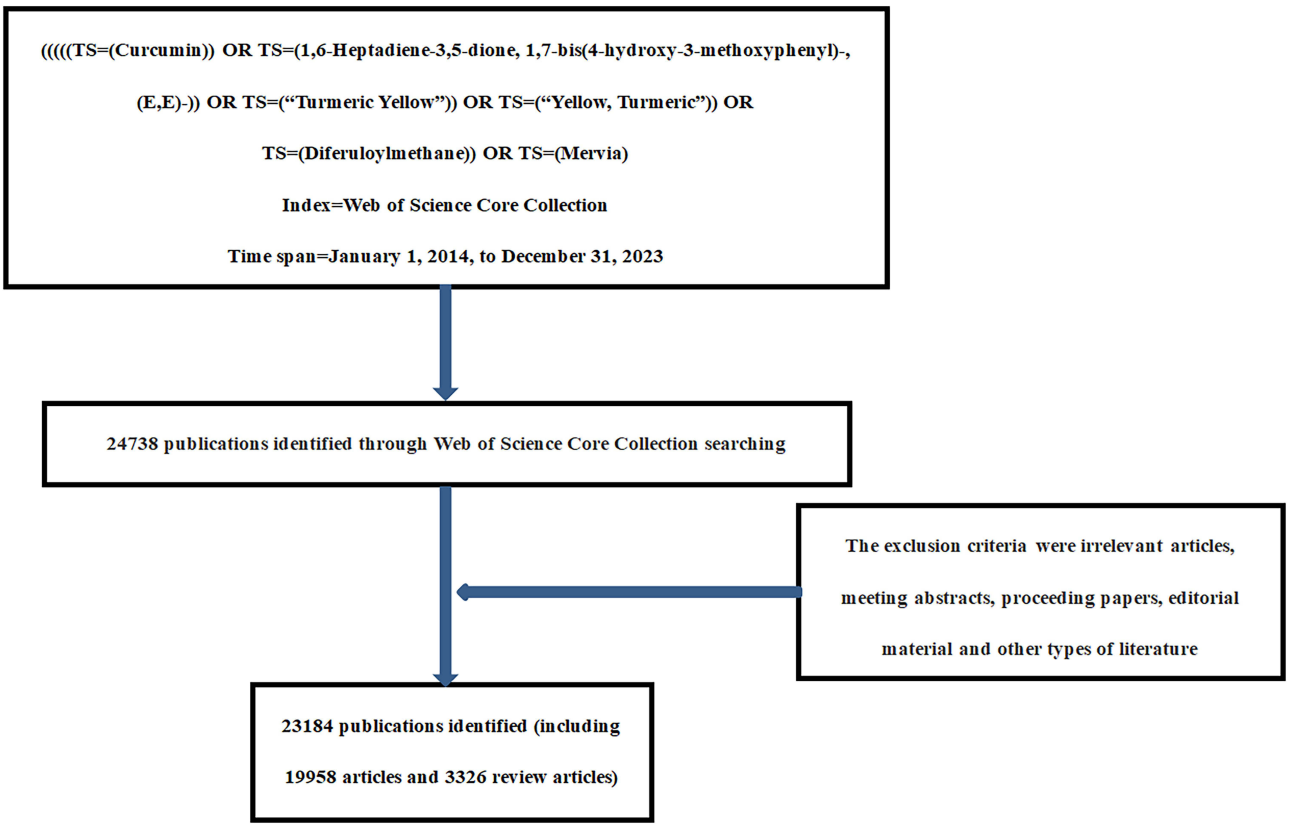


Figure 1 Search strategy.

techniques, this software automatically generates maps to explore research hotspots and development trends within a specified scientific field and timeframe.[11] Data from the literature published between January 1, 2014, and December 31, 2023, were analyzed, with a temporal range of 1 year. The "top N" was set to 50. Employing the network crop features, the output map was specifically refined by "Pruning sliced networks" and "Minimum Spanning Tree".

Typically, nodes outlined with a purple border indicate high betweenness centrality, which is generally considered when centrality is equal to or exceeds 0.1. Centrality, a graph theory attribute, assesses the significance of a node's position within a network. The formula is expressed as follows:

$$g(v) = \sum_{s \neq v \neq t} \frac{\sigma_{st}(v)}{\sigma_{st}}$$

Where $g(v)$ represents the centrality value of vertex v, $\sigma_{st}(v)$ signifies the number of shortest paths between s and t passing through v, and σ_{st} denotes the overall number of shortest paths between s and t. The burst-detection method is valuable for identifying sudden increases in research interest in a particular field.[12,13]

Results

Analysis of Papers by Publication Year

A total of 23,184 documents were gathered for examination. Figure 2 illustrates the fluctuations in the number of publications within the field of curcumin research. The X-axis represents the publication year, while the Y-axis corresponds to the number of papers published. Throughout the past decade, a consistent upward trajectory peaked in 2022, with the highest number of published papers recorded at 3,351. Importantly, owing to possible delays in WOS database updates, the data for 2023 may be incomplete and should be interpreted carefully. Notably, from 2014 to 2023, the annual publication count consistently exceeded 1000.

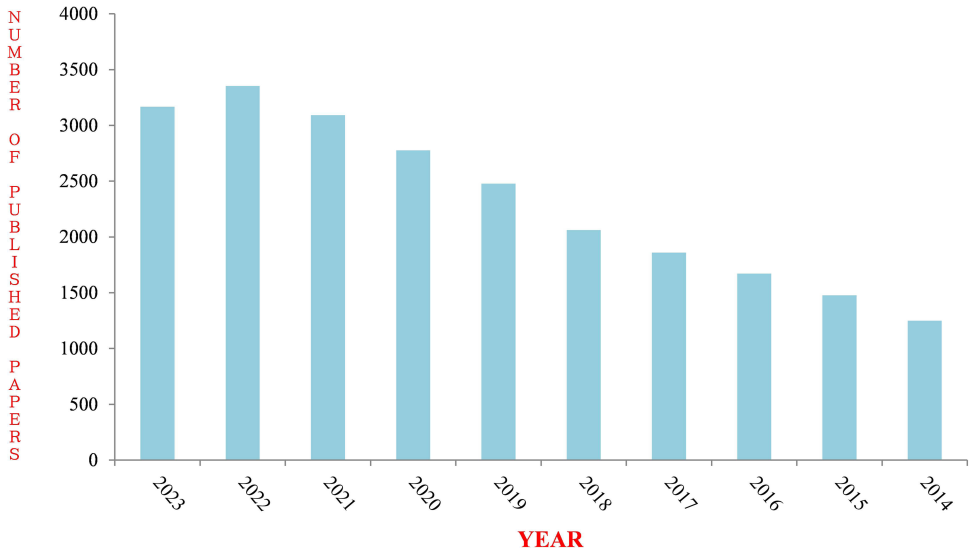


Figure 2 Visual analysis of papers by publication year.

Analysis of Countries and Institutions

Table 1 presents the distribution of contributions by the top 10 nations and institutions, totaling 21,068 articles (90.87%) and 2,599 articles (11.21%), respectively. China is the leading nation, with 7,267 publications, constituting 31.34% of the total. The Mashhad University of Medical Sciences ranks highest among institutions, with 438 articles (1.89%). Figure 3A visually represents 75 nodes and 339 links among nations. Nodes representing France, the US, and Saudi Arabia are highlighted in purple, signifying their significant centrality within the collaborative network. This visualization underscores the robust collaboration among these nations and others. Figure 3B illustrates cooperation between organizations. With 158 nodes and 387 connections, this figure portrays the extensive engagement of the Mashhad University of Medical Sciences within the collaborative landscape.

Analysis of Authors and Cocited Authors

In Figure 4A, the coauthor network is depicted, with 597 nodes representing authors and 526 connections indicating cooperation between the authors. The authors' collaboration is visually represented by the lines connecting the nodes, with the colors of these lines indicating the first year of collaboration. Nodes with purple borders are absent in the graph, indicating a relatively lower centrality of the nodes and a potential lack of collaboration among authors. Figure 4B shows the depicted cited author graph, which indicates a network of 112 nodes interconnected by 259 lines. This graphical

Table 1 Top 10 Countries and Institutions with the Greatest Numbers of Articles

Rank	Count	Country	Count	Institution
1	7267	PEOPLES R CHINA	438	Mashhad Univ Med Sci
2	3508	INDIA	330	Univ Tehran Med Sci
3	3020	USA	318	Islamic Azad Univ
4	2137	IRAN	241	King Saud Univ
5	1161	ITALY	237	Wenzhou Med Univ
6	937	BRAZIL	226	Tabriz Univ Med Sci
7	898	SOUTH KOREA	210	Chinese Acad Sci
8	841	SAUDI ARABIA	208	Zhejiang Univ
9	710	EGYPT	200	Univ Sao Paulo
10	589	AUSTRALIA	191	China Med Univ

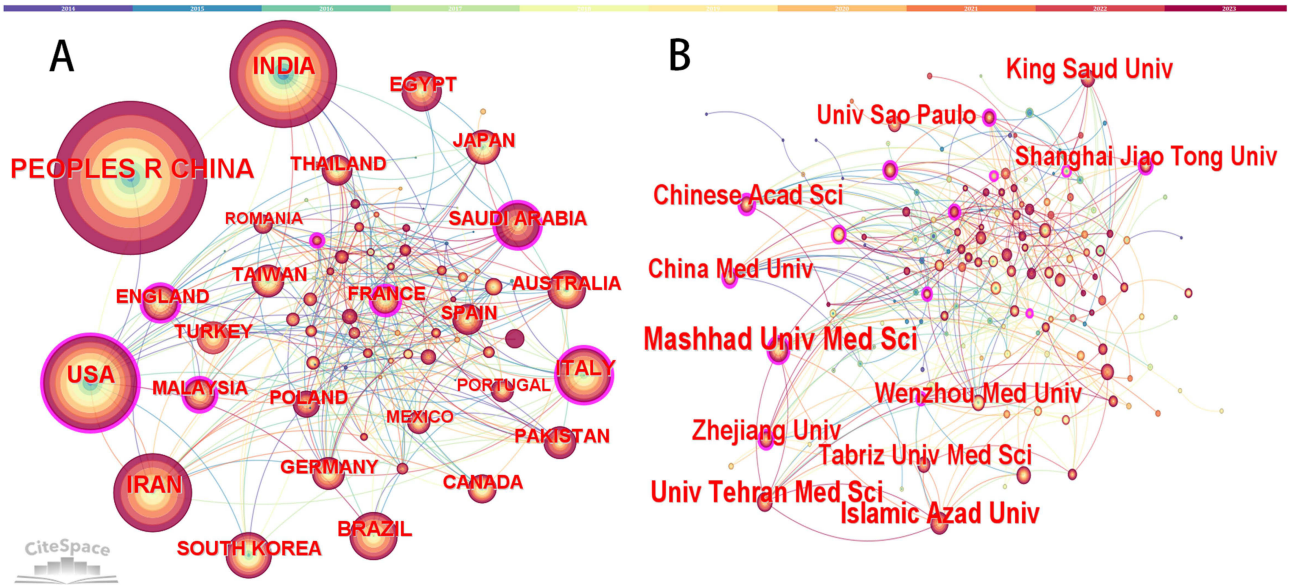


Figure 3 (**A**) Map of countries. (**B**) Map of institutions.

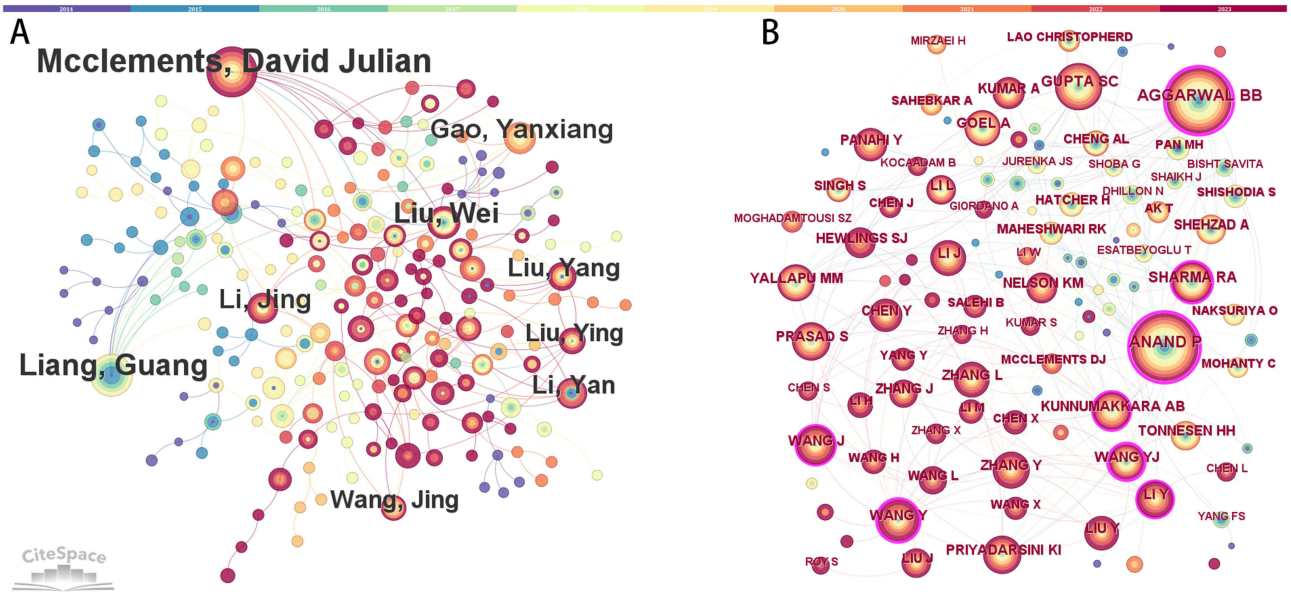


Figure 4 (**A**) Map of the authors. (**B**) Map of cocited authors.

representation helps illustrate the distribution of highly cited authors and facilitates identifying influential figures within the domain of curcumin research. The nodes representing Preetha Anand and Bharat B Aggarwal have purple boundaries and high betweenness centrality, so these authors collaborated closely with other authors.

The tabulated data in Table 2 provide insights into the top 10 authors and cocited authors. These authors are arranged on the basis of their publication frequency, with the top 10 contributors collectively presenting 753 articles (3.25% of the total). Amirhossein Sahebkar, the most prolific author, published 246 manuscripts, accounting for 1.06% of the overall literature. The cited authors are listed in descending order of their citation count, indicating their influence within the field. Preetha Anand leads this ranking with 3290 citations, reflecting her significant impact and recognition.

Table 2 The Top 10 Authors and Cocited Authors

Rank	Count	Authors	Count	Cocited Authors
1	246	Amirhossein Sahebkar	3290	Anand P
2	111	David Julian Mcclements	3203	Aggarwal BB
3	75	Guang Liang	1799	Gupta SC
4	59	Muhammed Majeed	1377	Sharma RA
5	50	Wei Liu	1277	Yallapu MM
6	47	Digambara Patra	1237	Wang Y
7	47	Prashant Kesharwani	1232	Kunnumakkara AB
8	41	Yanxiang Gao	1197	Goel A
9	40	Jing Li	1188	Priyadarsini KI
10	37	Tannaz Jamialahmadi	1140	Prasad S

Analysis of Keywords and Keyword Clusters

Keywords serve as concise summaries of the primary research themes within a body of literature, offering insight into their essential content. Through co-occurrence analysis, key patterns and focal points within a specific research domain can be identified. Table 3 presents the keywords with the highest frequency and centrality. Among the top 10 keywords, the most frequently encountered were curcumin (6439 occurrences, centrality: 0.72), in vitro (2913 occurrences, centrality: 0.28), oxidative stress (2763 occurrences, centrality: 0.36), nanoparticles (2487 occurrences, centrality: 0.27), and expression (1973 occurrences, centrality: 0.13), which are listed in descending order of frequency.

The keyword map generated by CiteSpace comprises 91 nodes connected by 229 connections (Figure 5A). The resulting cluster map revealed the following distinct clusters: drug delivery, apoptosis, oxidative stress, antioxidant, antioxidant activity, and in vitro (Figure 5B). The evaluation of the clustering effect relies on two key indicators: the cluster module value Q and the average contour value S. Typically, a Q value exceeding 0.3 indicates a significant cluster community structure. Moreover, a higher Q value signifies a denser network within the community, indicating a more effective clustering outcome. Similarly, the clustering is considered reasonable if S surpasses 0.5, whereas a value exceeding 0.7 denotes highly reliable clustering results. Analysis of the clusters within this map revealed that all clusters presented S values greater than 0.7 and Q values exceeding 0.3, confirming the rationality of the clusters. Consequently, the six knowledge clusters accurately reflect the distribution of research topics within the analyzed literature.

Keywords with the Most Robust Citation Bursts

"Keywords with citation bursts" denote a notable surge in keyword usage within a brief timeframe. By detecting and analyzing these burst keywords, research frontiers can be depicted during a specific period, along with their trajectory over time, enabling predictions of forthcoming research trends and trajectories (Figure 6). The blue lines delineate specific periods, whereas the red lines demarcate periods characterized by keyword bursts. Notable burst keywords

Table 3 Top 10 Keywords Related to Curcumin

Rank	Frequency	Keywords	Centrality	Keywords
1	6439	Curcumin	0.72	Curcumin
2	2913	in vitro	0.36	Acid
3	2763	Oxidative stress	0.36	Oxidative stress
4	2487	Nanoparticles	0.31	Apoptosis
5	1973	Expression	0.28	in vitro
6	1933	Apoptosis	0.27	Nanoparticles
7	1845	Drug delivery	0.16	Antioxidant
8	1776	Delivery	0.16	Stability
9	1434	Inhibition	0.13	Expression
10	1420	Cells	0.12	Drug delivery

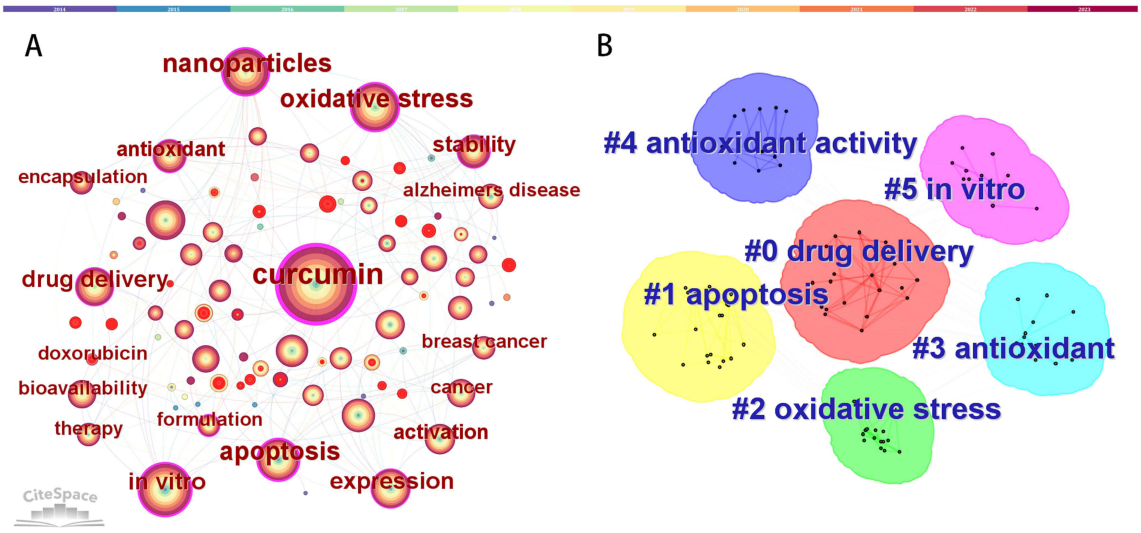


Figure 5 (**A**) Map of coreferenced keywords. (**B**) Map of the coreferenced keyword clusters.

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2014 - 2023
mice	2014	80.07	**2014**	2018	
cancer cells	2014	68.7	**2014**	2018	
rats	2014	62.78	**2014**	2018	
in vivo	2014	61.26	**2014**	2018	
lipid peroxidation	2014	52.9	**2014**	2016	
analogs	2014	46.7	**2014**	2016	
factor kappa b	2014	41.16	**2014**	2015	
binding	2014	29.54	**2014**	2015	
induction	2014	29.37	**2014**	2015	
down regulation	2014	17.03	**2014**	2017	
pathway	2015	24.49	**2015**	2018	
signaling pathway	2016	50.94	**2016**	2017	
prostate cancer	2014	33.98	**2016**	2017	
disease	2014	12.85	**2016**	2017	
doxorubicin	2017	35.75	**2017**	2019	
micelles	2018	64.7	**2018**	2020	
cytotoxicity	2014	22.92	**2018**	2019	
drug	2019	22.19	**2019**	2020	
fabrication	2020	67.39	**2020**	2023	
combination	2020	52.03	**2020**	2023	
extract	2017	38.36	**2020**	2023	
natural products	2021	56.53	**2021**	2023	
colorectal cancer	2021	52.57	**2021**	2023	
resveratrol	2019	46.23	**2021**	2023	
photodynamic therapy	2019	39.81	**2021**	2023	

Figure 6 Top 25 keywords with the strongest citation bursts.

observed up to 2023 include “fabrication”, “combination”, “extract”, “natural products”, “colorectal cancer”, “resveratrol”, and “photodynamic therapy”. However, it should be noted that the data for 2023 may be incomplete, so interpretations of these burst keywords should be made with caution.

Analysis of References

The 10 references with the highest citation frequencies and centralities are shown in Table 4. The most frequently cited study is the 2017 review by Nelson,[14] which examined the foundational pharmaceutical chemistry of curcumin and its clinical trial assessments. In this manuscript, Nelson elucidated the inherent instability, reactivity, and limited bioavailability of curcumin, which are characteristics that diminish the viability of curcumin as a primary lead compound. Furthermore, this review meticulously discusses potential novel trajectories for exploring curcuminoid compounds in research. A study by Kanai et al[15] assessed the safety and viability of coadministering curcumin with gemcitabine for the treatment of pancreatic cancer. Twenty-one gemcitabine-resistant pancreatic cancer patients were treated with 8 grams of oral curcumin daily alongside gemcitabine chemotherapy. Phase I investigations revealed no dose-limiting toxicity, confirming the safety of oral curcumin. In Phase II trials, none of the patients exhibited intolerance to combined therapy consisting of daily oral curcumin (8 grams) and gemcitabine chemotherapy. The median survival time posttreatment initiation was 161 days, validating the feasibility of the regimen. However, further research is needed to evaluate the efficacy of this combined therapy.

We simplified the relationships among clusters by selecting the top 30% of cluster dependency paths, as shown in Figure 7, which helps researchers more clearly visualize and better understand the interdependencies among the clusters. Dependency among clusters refers to specific clusters that are constructed based on other clusters. For example, in Figure 7, the #1 polymeric micelle references literature within clusters #2 (anticancer potential), #3 (modulatory effect), and #4 (therapeutic effect), indicating that clusters 2, 3, and 4 serve as the knowledge foundation for cluster 1. This interconnectedness highlights how the information in these clusters can contribute to the knowledge of curcumin in various studies.

Journal Category Analysis

In an overlay map, the left side depicts the citing journal categories, which are connected to the cited journal categories on the right via the citation curve. The elliptic curve illustrates the ratio of authors to publications, with a longer horizontal axis indicating more authors and a lengthened vertical axis reflecting increased paper output by the journal. Cited literature is fundamental to the development of domains. Figure 8 illustrates that the citing atlas predominantly shows journals in molecular

Table 4 The Top 10 Cited References

Rank	Count	Cited Reference	Centrality	Cited Reference
1	612	Nelson KM, 2017, J MED CHEM, V60, P1620, DOI 10.1021/acs.jmedchem.6b00975	0.98	Kanai M, 2011, CANCER CHEMOTH PHARM, V68, P157, DOI 10.1007/s00280-010-1470-2
2	581	Hewlings SJ, 2017, FOODS, V6, P0, DOI 10.3390/foods6100092	0.95	Sahebkar A, 2014, PHYTOTHER RES, V28, P633, DOI 10.1002/ptr.5045
3	325	Gupta SC, 2013, AAPS J, V15, P195, DOI 10.1208/s12248-012-9432-8	0.94	Gupta SC, 2013, AAPS J, V15, P195, DOI 10.1208/s12248-012-9432-8
4	317	Giordano A, 2019, NUTRIENTS, V11, P0, DOI 10.3390/nu11102376	0.93	Trujillo J, 2013, REDOX BIOL, V1, P448, DOI 10.1016/j.redox.2013.09.003
5	313	Kunnumakkara AB, 2017, BRIT J PHARMACOL, V174, P1325, DOI 10.1111/bph.13621	0.93	Khalil NM, 2013, COLLOID SURFACE B, V101, P353, DOI 10.1016/j.colsurfb.2012.06.024
6	304	Tomeh MA, 2019, INT J MOL SCI, V20, P0, DOI 10.3390/ijms20051033	0.9	Gupta SC, 2013, BIOFACTORS, V39, the P2, DOI 10.1002/biof.1079
7	303	Naksuriya O, 2014, BIOMATERIALS, V35, P3365, DOI 10.1016/j.biomaterials.2013.12.090	0.88	Shehzad A, 2013, BIOFACTORS, V39, P56, DOI 10.1002/biof.1068
8	281	Kocaadam B, 2017, CRIT REV FOOD SCI, V57, P2889, DOI 10.1080/10.408.398.2015.1077195	0.87	Chuengsamarn S, 2012, DIABETES CARE, V35, P2121, DOI 10.2337/dc12-0116
9	277	Prasad S, 2014, CANCER RES TREAT, V46, the P2, DOI 10.4143/crt.2014.46.1.2	0.86	Panahi Y, 2014, COMPLEMENT THER MED, V22, P851, DOI 10.1016/j.ctim.2014.07.006

Abbreviations: WOSCC, Web of Science Core Collection; AD, Alzheimer's disease; PD, Parkinson's disease; Aβ, amyloid beta-peptide; fAβ, beta-amyloid fibrils; GSK-3β, glycogen synthase kinase-3β; IAPP, islet amyloid polypeptide; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; 5-ASA, 5-aminosalicylates; NF-κB, nuclear factor-κB; mTOR, mammalian target of rapamycin; IR, irradiation; COP, curcumin-loaded oleic acid-based polymeric; DFU, diabetic foot ulcer; HG, high glucose; FBN1, fibrillin-1; WP, whey proteins; WPC, WP concentrate; WPI, WP isolate; WPH, WP hydrolyzed; PBA, phenylboronic acid; OHA, oxidized hyaluronic acid.

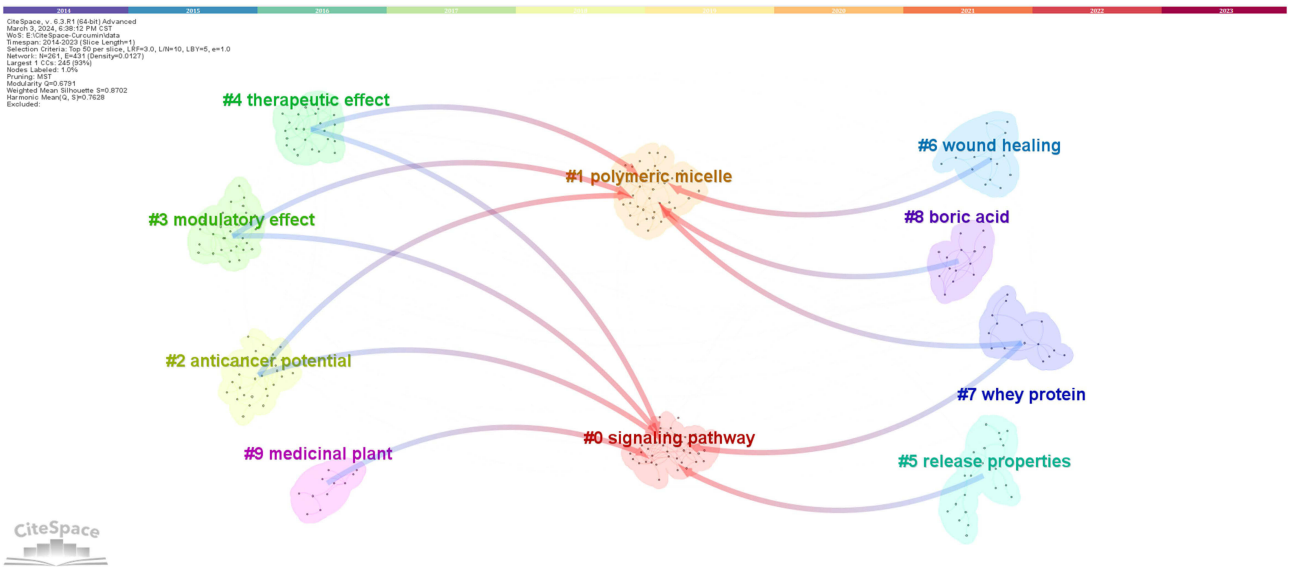


Figure 7 Cluster dependency map of the reference.

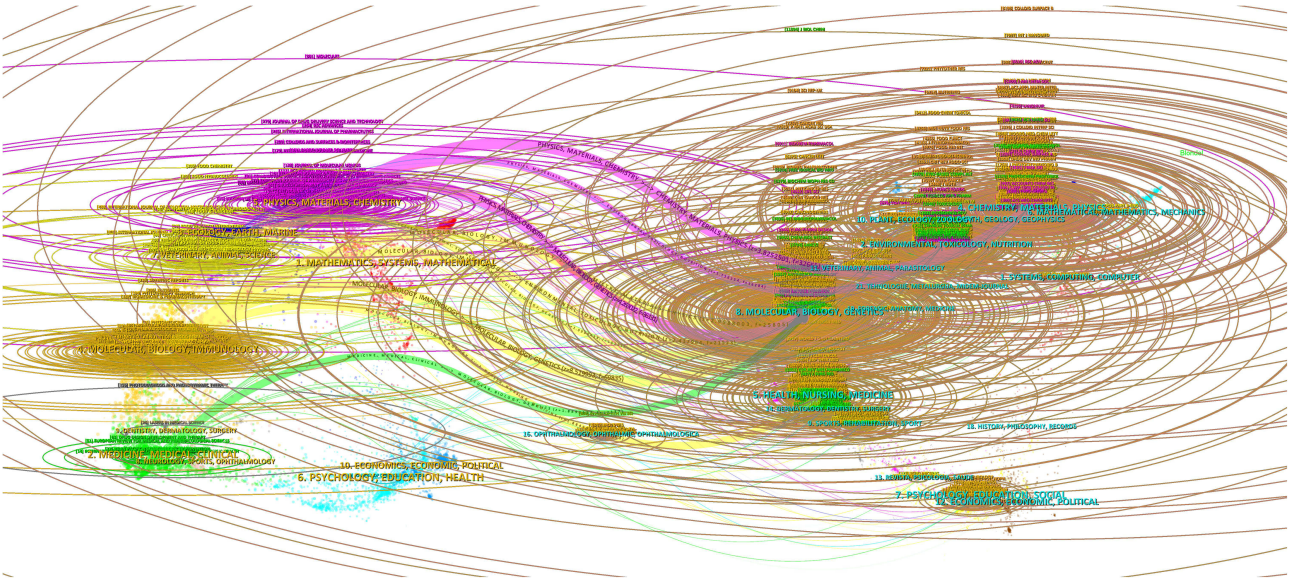


Figure 8 Overlay map of journals.

biology, biology, genetics, chemistry, materials science, physics, environmental studies, and nutrition. Correspondingly, the cited literature mainly originates from journals covering molecular biology, biology, immunology, medicine, clinical research, ecology, earth sciences, and marine studies.

Discussion

Using CiteSpace for visual analysis, this study examined the distribution of curcumin-related publications by countries, institutions, prolific authors, key terms, references, and journals. This study aimed to elucidate the current landscape, identify hotspots, and explore emerging frontiers in curcumin research.

General Information

23,184 publications from January 1, 2014, to December 31, 2023, were scrutinized, revealing a discernible upward trajectory in publication volume over time. The top 10 countries, which collectively contributed 21,068 articles and accounted for 90.87% of the corpus, underscore the global significance of curcumin research. With 7,267 articles, China represented 31.34% of the total corpus due to its abundant resources, robust research capabilities, flourishing pharmaceutical industry, and deep-rooted culture of traditional medicine. A closer examination of the top 10 organizations, which collectively contributed 2,599 articles (11.21%), revealed collaborative endeavors within and between countries and institutions at the institutional level. Among the cadre of prolific authors, Amirhossein Sahebkar is the most prolific, with 246 publications (constituting 1.06% of the total corpus), whereas Preetha Anand has the most citations. Keyword analysis uncovers prevailing trends and emerging areas of interest. Notably, terms such as "fabrication", "combination", "extract", "natural products", "colorectal cancer", "resveratrol", and "photodynamic therapy" garnered considerable attention in 2023. The cluster dependency map of the reference revealed that therapeutic effects, modulatory effects, and anticancer potential serve as foundational elements for research on polymeric micelles and signaling pathways. Moreover, the exploration of signaling pathways is further supported by studies on medicinal plants and their release properties. Research on polymeric micelles relies on investigations into wound healing and boric acid. The overlay visualization of journals highlights the interdisciplinary nature of curcumin research, with the top-cited publications spanning diverse fields, including molecular biology, biology, genetics, chemistry, materials science, physics, environmental research, and nutrition. Moreover, the referenced literature originates primarily from journals in molecular biology, biology, immunology, medicine, clinical research, ecology, earth sciences, and marine studies. The following text provides a concise overview of the significant areas of research and future development directions.

Emerging Topics

Therapeutic Effects of Curcumin

Curcumin has been scientifically proven to have various pharmacological effects and can potentially be a therapeutic agent for several diseases, including neurological disease, inflammatory bowel disease, metabolic disorders, autoimmune disease, and cancer.[16]

Neurological disorders are conditions that affect both the central and peripheral nervous systems. These disorders include Alzheimer's disease (AD), Parkinson's disease (PD), and epilepsy, which affect hundreds of millions of individuals worldwide. Blocking the accumulation of amyloid beta-peptide (Aβ) and the creation of beta-amyloid fibrils (fAβ) from Aβ, along with breaking down existing fAβ in the central nervous system, could be promising targets for AD treatment. Curcumin has been shown in in vitro studies to bind Aβ, impacting peptide aggregation and preventing fibril formation and elongation.[17] In a mouse model of AD, curcumin crossed the blood-brain barrier and reversed existing amyloid pathology as well as associated neurotoxicity.[18] Moreover, in a randomized controlled trial, plasma samples from participants taking curcumin (180 mg/day) for 12 weeks were examined for glycogen synthase kinase-3β (GSK-3β) and islet amyloid polypeptide (IAPP) levels.[19] Compared with the placebo, curcumin supplementation significantly reduced the levels of circulating GSK-3β ($p = 0.0068$) and IAPP ($p = 0.0163$) and insulin resistance ($p = 0.0142$), suggesting a novel mechanism by which curcumin could be employed to mitigate the risk of type 2 diabetes and AD. Curcumin may also be effective in treating PD,[20] Huntington's disease,[21] and major depression.[22] Furthermore, a series of randomized, double-blind, placebo-controlled studies support the antidepressant effects and safety of curcumin in people with major depressive disorder.[22–25] More research with larger sample sizes, longer treatment durations, and varying dosages of curcumin is needed.

Inflammatory bowel disease (IBD) is a chronic and relapsing illness characterized by inflammation of the gastrointestinal tract, whose two main types are Crohn's disease (CD) and ulcerative colitis (UC). Given the anti-inflammatory and antioxidant properties of curcumin in cell culture and animal studies, five patients with ulcerative proctitis and five with CD participated in an open-label study in which they received a pure curcumin preparation.[26] Unexpectedly, proctitis patients improved, with reduced use of medications in four patients, whereas four out of five CD patients experienced lower CD activity index (CDDAI) scores and sedimentation rates. The results of this pilot study emphasize the necessity of conducting double-blind, placebo-controlled follow-up studies. Moreover, a pilot trial was conducted in patients with mild-to-moderate distal UC via a double-blind, single-center design.[27] Forty-five patients were randomly

assigned to receive NCB-02 (standardized curcumin preparation) enemas and oral 5-aminosalicylate (5-ASA) or placebo enemas alongside oral 5-ASA. At week 8, clinical relief was recorded in 43.4% of patients in the NCB-02 group compared with 22.7% in the placebo group (p = 0.14). Additionally, 52.2% of patients in the NCB-02 group improved on endoscopy, whereas 36.4% of individuals in the placebo group improved (p = 0.29). A follow-up clinical study yielded consistent results.[28] This double-blind trial involving 70 patients with mild to moderate UC investigated the effects of curcumin (1,500 mg/day) versus placebo over 8 weeks. The results indicated that patients with UC who took 1,500 mg of curcumin per day for 8 weeks experienced clinical remission, improved clinical response, improved quality of life, and reduced levels of high-sensitivity C-reactive protein and erythrocyte sedimentation rates. Nevertheless, in a trial of CD surgery patients receiving thiopurine treatment, curcumin showed no additional effectiveness in preventing disease recurrence compared with placebo.[29] The study was halted because of futility after an interim analysis. The small sample size and absence of endoscopic evaluations were the main limitations of this study. Fortunately, curcumin dispersed with colloidal nanoparticles, Theracurmin®, has an absorption rate 27 times higher than that of natural curcumin powder,[30] and it functions as an inhibitor of nuclear factor-κB (NF-κB), which is responsible for the expression of inflammatory cytokines. Accordingly, its efficacy and safety in patients with CD were investigated in a randomized, double-blinded study performed at 5 independent medical centers in Japan.[31] For 12 weeks, patients with active mild-to-moderate CD were given either Theracurmin® (360 mg/day, n = 20) or a placebo (n = 10). The Theracurmin® group presented a significant decrease in clinical disease activity from week 0 to week 12 (p = 0.005). At weeks 4, 8, and 12, the clinical remission rates were 35%, 40%, and 40%, respectively. These rates were significantly higher than those in the placebo group, which had a remission rate of 0% (p = 0.033, p = 0.020, and p = 0.020, respectively). Furthermore, there was a reduction in the endoscopic severity of CD at week 12 and significant healing of anal lesions at week 8 in the Theracurmin® group (p = 0.032 and p = 0.017, respectively). Throughout the study, neither group recorded any serious adverse events. Larger dose-response trials are needed to evaluate the effects of curcumin on other inflammatory biomarkers before curcumin can be widely introduced into routine clinical practice for treating IBD. During the past decade, considerable advances have been made in our understanding of the biological activities of curcumin, which has promoted a series of clinical studies. In addition to neurological disorders and IBD, these pilot trials of curcumin administration have been conducted in patients with cardiovascular diseases,[32,33] metabolic disorders,[19,34,35] autoimmune diseases,[36,37] and cancer,[38] and promising clinical benefits have been reported.

Cancer is one of the leading causes of death worldwide. Curcumin is a highly effective compound against cancer, especially by inducing autophagy, and offers a promising new treatment option. An earlier study revealed that curcumin suppressed the growth of malignant gliomas by activating the extracellular signal-regulated kinase pathway, inhibiting the protein kinase B (Akt)/mammalian target of rapamycin (mTOR)/p70 ribosomal protein S6 kinase pathway, and hence inducing autophagy both in vitro and in vivo.[39] Moreover, curcumin effectively triggers apoptosis and induces autophagy in MG63 osteosarcoma cells.[40] Inhibiting apoptosis resulted in enhanced autophagy caused by curcumin through the upregulation of the c-Jun N-terminal kinase signaling pathway, offering critical insights into the interaction between autophagy and apoptosis in osteosarcoma cells. Furthermore, curcumin stimulates autophagy and enhances lysosomal function by inhibiting the Akt–mTOR signaling pathway and directly activating the transcription factor EB.[41] There is also in vitro evidence that curcumin induces autophagy, leading to ferroptosis in non-small cell lung cancer.[42] Many studies have demonstrated the antitumor properties of curcumin against colon cancer,[43] osteosarcoma,[44] ovarian cancer,[45] and uterine leiomyosarcoma.[46] More importantly, in a randomized phase IIa trial,[38] curcumin was demonstrated to be a well-tolerated and safe addition to folinic acid/5-fluorouracil/oxaliplatin chemotherapy in patients with metastatic colorectal cancer. These results underscore the potential of curcumin as a therapeutic candidate for oncological applications, warranting further investigation into its efficacy and safety in tumor treatment.

Wound Healing by Curcumin

Wound healing is a complex process that involves the synchronized efforts of diverse tissues and cell lineages. Tightly orchestrating cell migration and proliferation, extracellular matrix deposition and remodeling, and inflammation and angiogenesis are required in this process.[47] In the past 10 years, there has been significant research on the use of curcumin as a wound-healing agent.[48] In a previous study, the backs of rats were incised with full-thickness wounds, and curcumin was applied topically.[49] Interestingly, cellular proliferation and collagen synthesis at the wound site were enhanced by curcumin, as indicated

by the increase in DNA, total protein, and type III collagen in the wound tissues. Histopathological examinations also revealed that wounds treated with curcumin healed faster, with enhanced epithelialization, wound contraction, and tensile strength. Moreover, curcumin exhibited antioxidant properties that accelerated wound healing by decreasing lipid peroxides and increasing superoxide dismutase, catalase, and glutathione peroxidase levels. Another study examined how curcumin affects the healing of deep excision wounds in mice exposed to fractionated irradiation (IR), mimicking real-life clinical scenarios.[50] Histological analysis revealed a decrease in collagen deposition and fibroblast and vascular densities following fractionated IR. However, this decline was significantly blocked by curcumin pretreatment. A curcumin-loaded oleic acid-based polymeric (COP) bandage was formulated to maximize the healing potential of curcumin in a rat model.[51] The COP bandage increased wound reduction and cell proliferation by scavenging free radicals and reducing the inflammatory reaction mediated by the NF-κB pathway during wound healing. Surprisingly, this result resembles an earlier study in which dermal wound healing processes were evaluated with curcumin-incorporated collagen films.[52] Furthermore, a recent investigation indicated that curcumin enhances skin wound healing by stimulating the nuclear factor erythroid 2-related factor 2 signaling pathway and eliciting apoptosis in vivo.[53] In a recent study, a model of diabetic foot ulcer (DFU) in rats was established, along with a cell model of fibroblasts cultured in a high-glucose (HG) environment.[54] Moreover, venous blood was obtained from the elbows of 20 pairs of healthy people and patients suffering from DFU. In DFU patients, miR-152-3p was found to be overexpressed, whereas fibrillin-1 (FBN1) was underexpressed. Further investigation revealed that curcumin inhibited HG-induced fibroblast apoptosis and damage, promoted fibroblast proliferation and migration, and facilitated angiogenesis, thus accelerating wound healing in DFU rats by inhibiting miR-152-3p and activating the FBN1/transforming growth factor-β pathway.

Furthermore, 60 patients with oral cancer who had undergone radical surgery were recruited for a randomized, double-blinded, placebo-controlled trial.[55] The patients were randomly divided into three groups. Participants received either low-dose (1 g/day) or high-dose (1.5 g/day) bioenhanced turmeric formulation capsules or a placebo daily for 6 weeks during chemoradiotherapy. Interestingly, the use of turmeric formulations can lead to substantial reductions in severe oral mucositis, dysphagia, oral pain, and dermatitis resulting from chemoradiotherapy in oral cancer patients. In a separate clinical trial study, 50 patients were assigned to either the study or control group and underwent chemotherapy with or without head and neck radiotherapy.[56] During the 7-week study period, the study group took curcumin nanomicelle capsules (80 mg) twice daily, whereas the control group received a placebo. Researchers have measured the severity of and pain associated with oral mucositis. The control group had significantly greater oral mucositis severity than the study group at the first ($p = 0.010$), fourth ($p = 0.022$), and seventh ($p < 0.001$) weeks. In the seventh week, there was a significant decrease in pain levels in the study group compared with those in the control group ($p = 0.001$). These findings strongly suggest that curcumin could be an effective agent for wound healing, particularly when applied topically. Nevertheless, research on the utilization of curcumin in wound patients is scarce.

Delivery Systems for Curcumin

Curcumin is limited by its low water solubility, poor absorption, quick elimination from the body, degradation under alkaline conditions, and limited oral bioavailability. During the past decade, numerous vehicles, such as hydrogels, emulsions, nanoparticles, and liposomes, have been developed to address the constraints and obstacles of potent curcumin delivery systems. In recent research, curcumin-loaded κ-carrageenan hydrogel beads were further coated with scallop (*Patinopecten yessoensis*) male gonad hydrolysates via a combination of injection-gelation and coacervation techniques.[57] Forty-five percent of the curcumin was released in the small intestine medium, whereas 49.0% was released in the colon, suggesting a consistent and ongoing delivery of curcumin to the colon. Moreover, the beads maintained a high level of storage stability, with curcumin retention rates of over 90% even after 30 days of storage at 4 °C. Briefly, these methods possess the advantages of being both highly efficient in improving the release and biological activity of curcumin and low in toxicity, necessitating further clinical trials. Dahal and Janaswamy recently explored κ-carrageenan hydrogel beads as a curcumin delivery system, which achieved an encapsulation efficiency of 74.61 ± 3.2%.[58] Moreover, the melting point of curcumin in curcumin-κ-carrageenan beads increased by 25 °C, suggesting that carrageenan chains offer thermal protection to curcumin molecules. The release of curcumin from the beads in vitro indicates a sustained and pH-dependent pattern, and the release kinetics are consistent with the first-order and Korsmeyer–Peppas models. The results suggest the provision of value-added delivery systems for bioactive compounds, supporting the creation of innovative food and pharmaceutical uses.

Whey proteins (WPs), which contain β-lactoglobulin and α-lactalbumin and smaller amounts of bovine serum albumin, immunoglobulins, and lactoferrin, have superior biological value compared with egg protein.[59] They are also rich sources of essential and branched-chain amino acids and are thus well regarded as high-quality sources of nutrients. WP concentrate (WPC), WP isolate (WPI), and WP hydrolyzed (WPH) are the three forms of WP. By forming molecular complexes with WP, curcumin significantly improves its solubility, bioactivity, and bioavailability. In an initial study, nanofibrils were formed by heating a solution of WPI at pH 2.0 for 5 hours at 85 °C.[60] By complexing with WP nanofibrils, the water solubility of curcumin was enhanced by approximately 1200-fold. The primary mechanisms responsible for the formation of these complexes are hydrogen bonding and hydrophobic interactions. Moreover, high viscosity and significant antioxidant activity were observed in the nanocomplexes in vitro. In another study by the same team, microgel particles were prepared by heating a WP solution at pH 5.90, near its isoelectric point, and then loaded with curcumin.[61] The results revealed that the loading amounts of curcumin into the WP microgels and WPIs were 17.51 ± 0.46 and 1.84 ± 0.18 μg curcumin/mg protein, respectively. X-ray diffraction analysis revealed the amorphous form of the curcumin loaded in the microgels. In vitro, the curcumin-loaded WP microgels demonstrated potent antioxidant activity, and the release of curcumin was slower from the WP microgels than from WPIs under simulated gastrointestinal conditions. The utilization of WPC as a nanocarrier also shows promise for enhancing curcumin properties with a low economic cost compared to WPIs. Furthermore, the current understanding of the formation of complexes involving curcumin and WPC at different molar ratios and the nanostructure of these complexes suggest that WPC is a promising nanocarrier for curcumin.[62] More importantly, a recent study reported the fabrication and characterization of self-assembled WPI/short linear glucan core-shell nanoparticles for the sustained release of curcumin.[63] The nanocomplexes maintained a relatively stable state at high temperatures (60–70 °C), extreme pH values (2–4 and 8–10), and ionic strengths (<400 mm), allowing curcumin to be released continuously under simulated digestive conditions. Additionally, the nanocomplexes showed low cytotoxicity at high concentrations but significantly enhanced the 2.2-diphenyl-1-picryl-hydrazyl radical scavenging ability and reduced the power of curcumin. The findings of this study introduce a new paradigm for incorporating hydrophobic active compounds within core-shell nanocapsules.

Boronic acids are extensively employed in modern synthesis to create C–C and C–heteroatom bonds. Boronic acids possess a boron atom with a vacant p-orbital that easily forms reversible covalent bonds with oxygen and nitrogen nucleophiles and have been utilized to promote the precise transport of cytotoxic drugs, proteins, and gene vectors to cancer cells.[64] In a recent study, phenylboronic acid (PBA)-modified gelatin and oxidized hyaluronic acid (OHA) were crosslinked and transformed into GOHA-PBA through borate ester and Schiff base reactions.[65] Notably, GOHA-PBA had an exceptional curcumin loading efficiency that was 130,000 times greater than that of water, resulting in the formation of curcumin-laden GOHA-PBA. The pH- and glucose-responsive boronate ester bonds in the curcumin-laden GOHA-PBA enabled the controlled release of curcumin in diabetic wounds with high glucose and slightly acidic environments. Therefore, it exhibited outstanding antibacterial, antioxidant, and anti-inflammatory properties in vitro. The efficacy of the hydrogel in repairing chronic diabetic wounds was further evaluated via whole skin defect models on the backs of diabetic standard deviation rats. The results indicated that the hydrogel slowly released curcumin, which acts as an antiseptic, anti-inflammatory, and antioxidant treatment at the trauma site, thereby transitioning the healing process from inflammation to tissue remodeling. This study provides evidence that boronic acids have promising properties when designing therapeutic delivery systems for curcumin.

Research Prospects

Curcumin, a bioactive compound derived from turmeric, offers extensive therapeutic benefits across multiple applications. The potent anticancer effects of curcumin arise from its ability to modulate key signaling pathways that regulate autophagy and inhibit cancer progression. Additionally, curcumin has potent anti-inflammatory and antioxidant properties, which help treat chronic inflammation and oxidative stress and promote wound healing through NF-κB inhibition and cellular protection. Despite the diverse therapeutic potential of curcumin, its clinical use is limited by its poor solubility, low oral bioavailability, and rapid degradation. Advanced drug delivery systems, such as WP conjugation, offer solutions to these challenges. These systems increase the stability of curcumin, improve its water solubility, and ensure sustained and targeted release, allowing for more efficient absorption and prolonged therapeutic action. Integrating curcumin with these innovative delivery systems maximizes its effectiveness and opens new avenues for its application in clinical practice. Further research and optimization are needed to fully harness the multifaceted benefits of curcumin and develop novel treatment strategies for a range of conditions.

Conclusion

In our study, we employed CiteSpace to visually analyze 23,184 curcumin-related publications from 2014 to 2023, aiming to delineate the current state and emerging trends in curcumin research. The analysis revealed a sustained increase in publication volume, underscoring the increasing interest in the pharmacological potential of curcumin. Globally, the top 10 contributing countries accounted for 90.87% of the total publications, with China leading at 31.34%, reflecting its robust research capabilities and the influence of traditional medicine. The top 10 institutions contributed 11.21% of the articles, indicating significant collaborative efforts within the field. Amirhossein Sahebkar was the most prolific author, and Preetha Anand had the highest citation count, indicating their substantial impact on curcumin research. Keyword analysis identified vital research themes, including "fabrication", "combination", "extract", "natural products", "colorectal cancer", and "resveratrol". Reference analysis further highlighted the therapeutic effects, anticancer potential, and interdisciplinary relevance of curcumin in molecular biology, chemistry, and nutrition. We also refined our analysis by concentrating on the top 30% of cluster dependency paths, simplifying cluster relationships. For instance, the #1 cluster on polymeric micelles is underpinned by references from clusters #2 (anticancer potential), #3 (modulatory effect), and #4 (therapeutic effect), establishing these as foundational knowledge bases. This network of interconnections elucidates the integrated knowledge that these clusters contribute to the broader study of curcumin.

While our study offers valuable insights into the curcumin research landscape, it has limitations. The data utilized in this analysis were sourced exclusively from the WOSCC, which may have introduced a degree of selection bias into our findings. Additionally, the dynamic nature of bibliometric tools such as CiteSpace, which is sensitive to the temporal availability of data, could render parts of our analysis less current over time. Despite these constraints, our research presents a thorough synthesis of the current state of curcumin research, equipping researchers and stakeholders with the knowledge necessary to make evidence-based decisions and remain abreast of the most recent advancements in the field.

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Disclosure

The authors report no conflicts of interest in this work.

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