Universe Scientific Publishing

# Global Advances and Frontiers of Phytochemicals in Tumor Research: A Bibliometric Study (2010-2023)

**Hao Zhu, Falin Wang, Juan Li, Tingting Yang, Jiaren Liu***

*** Corresponding author to Professor Jia-Ren Liu, MD, PhD**

**The Department of Clinical Laboratory, the 4th Affiliated Hospital of Harbin Medical University, Harbin 150001, China.**

***Abstract:*** Objectives: Analysis of advances, hotspots and frontiers of tumor-related phytochemicals by scientific bibliometric methods during 2012-2023. Background: Natural phytochemicals are abundantly found in nature and have a wide range of biological activities. Phytochemicals have been shown to provide both curative and preventive benefits on many chronic diseases such as cancers. Tumor research on phytochemicals is one of the fields with the greatest potential for expansion in the world. However, there is still much to explore about the action mechanism of phytochemicals, the efficacy and safety of application in vivo, and the value of clinical practice. Methods: A total of 6523 articles on tumor-related phytochemicals were identified from the Web of Science Core Collection (WOSCC) database for research on tumor-related phytochemicals. The bibliometric analysis was carried out using CiteSpace and the R package "Bibliometrix". Results: The analysis includes 6523 publications from 144 nations or regions, with China leading the way. The number of annual publications increased rapidly from 2012 to 2022 and reached a maximum in 2022. China published the most articles, followed by India and the United States. There is a wide range of collaborations between countries, with Saudi Arabia and Egypt being the closest partners. LI Y has produced the most research outputs, yet Prof. Liu RH has received the most local citations. Although MOLECULES has the most articles, FOOD CHEMISTRY is the journal with the highest H-index. The main topics include phytochemical mechanisms and clinical applications in carcinogenesis and development. "Secondary metabolite", "green synthesis", "functional food", and "degradation" all exhibit significant citation burstness between 2019-2023. Conclusions: This study is the first to apply bibliometrics to examine the development of phytochemicals in oncology research over the period 2010-2023, which gives researchers a brief overview of advances, hotspots, and potential future trends in the field.

***Keywords:*** Bibliometrics; Phytochemicals; Cancer; CiteSpace; Future Trends

## 1. Introduction

With rising levels of industrialization, the global burden of cancer mortality and incidence has been rising quickly in the past few decades. According to WHO Figures, cancer has surpassed cardiovascular disease as the leading cause of death before the age of 70 in 112 nations worldwide[1]. In 2023, it is anticipated that there will be 609,820 cancer deaths and 1,958,310 new cancer cases in the U.S[2]. Over the last several years, a great deal of study has been done on the pathogenesis and treatment principles of malignancies, yet traditional surgery, radiation therapy, and chemotherapy are likely to have some major adverse effects, possibly even endangering patient life. Therefore, the need for more effective, safe, and inexpensive treatment options is urgent. The biologically active substances known as phytochemicals support plant interactions with their environment during biological evolution. Numerous well-known phytochemicals exist today, including carotenoid, phytosterol, saponin, glucosinolate, polyphenol, etc. According to research, phytochemicals have a variety of biological functions, including anticancer, antioxidant, and immunomodulation. In order to provide creative research guidelines and choose logical clinical therapy regimens, it is crucial to comprehend the hotspots in the field of phytochemical research and predict future developments.

By statistically assessing a significant amount of literary data, bibliometric analysis is able to objectively analyze the hotspots, dynamics, and development trends in a variety of sectors. The technique has developed and is frequently applied in sectors that relate to medicine. However, none of the papers used bibliometric analysis in regard to the Phytochemicals for anti-tumor research. none of the article used bibliometric analysis in regard to the Phytochemicals for anti-tumor research. Based on previous studies, the major areas of interest for phytochemicals include their inhibitory effects on cancer cells[3-5], chemopreventive effects[6-8], synergetic effects[9, 10] and reverse growing clinical multi-drug resistance(MDR)[11]. The earlier induction and summary methods based on the Review have significant drawbacks, including a brief time period, subjective document selection, the ease with which crucial influencing elements can be missed, etc., which make it impossible to systematically examine the long-term dynamic development trends.

In any case, the aiticle aims to use bibliometric analysis to systematically investigate the advances in phytochemicals in tumor research.

## 2. Methods

### 2.1 Search Strategy and Data Source

Web of Science (http://www.webofknowledge.com), as a multidisciplinary worldwide academic information database, features the most comprehensive collection of international mainstream journals and rigorous retrieval patterns. All data for this study were obtained from the Web of Science Core Collection (WOSCC) database. On July 26, 2023, we used the advanced search to find publications about tumors and phytochemicals from 2010 to 2023, using the following search formula: TS= ((“Phytochemical*”) AND (“Tumo$r*” OR “Cancer *” OR “Oncology*” OR “Neoplasm*” OR “Carcinoma*”)). The Publication type was only restricted to article and the Language type is English. On July 26, we exported all eligible data in order to prevent bias brought on by database updates, obtaining a total of 6523 articles.

### 2.2 Statistics Analysis

To complete the bibliometric analysis, use the CiteSpce (version 6.1.R6) and the R package “Bibliometrix” (version 2.2.1), as well as Office 2019 for the correlation graphing. Scientific bibliometric software known as Bibliometrix is based on the RStudio. It can perform tasks like importing and converting texts, performing metrological analyses, creating matrices, normalizing data, creating networks, creating graphs, etc. Professor Chao-Mei Chen of the School of Computing and Intelligence at Drexel University created the visual literature analysis program called CiteSpace, which uses special algorithms to form co-occurrence networks and conduct clustering analyses. We used the Bibliometrix to show annual scientific production, average citations per year, countries scientific production and collaboration, most local cited authors, etc. CiteSpace was used to produce references co-cited and keyword co-occurrence networks, clustering, dual-map and citation bursts. The two pieces of software to jointly investigate the advances, hotspots and frontiers.

## 3. Results

### 3.1 General situation description

First, we selected 6523 articles from the WOS-core collection (WOSCC) that were particularly relevant to phytochemicals related to tumors. The selection process is shown in Figure 1. Figure 2A depicts the annual scientific production of Tumor-related phytochemicals from 2010 to 2022. 2023 is not shown in the statistics because it is only halfway through the year. The number of publication (NP) exhibits a general upward trend from 2010 to 2022, averaging around 300. Only 2018 (n=487, 7.41%) shows some the NP reduction, with rises in both 2011-2012 and 2018-2022 being particularly noticeable. The greatest NP was 2022 (n=1032, 15.82%). We created a polynomial regression equation, in Microsoft Office Excel 2019 to forecast the NP that will be published in 2023. The time prediction curve model was constructed by fitting the data with the equation (), which predicted that the NP in 2023 may reach approximately 980, and the fitted data were statistically well (). The average annual citations (AAC) of the papers in Figure 2B climbed quickly in 2010-2013, and despite some changes between 2013 and 2020, the total number of citations (TC) remained sTable. The maximum was attained in 2019 (n=3.31). Contrary to the yearly NP, the average annual citations from 2020 to 2023 showed a considerable decrease.

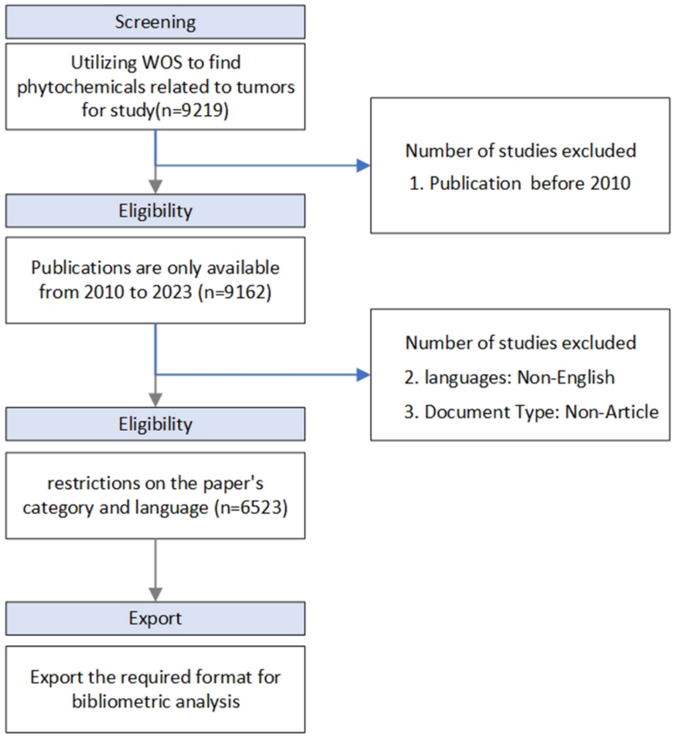



Figure 1 Document retrieval flow chart based on WOSCC

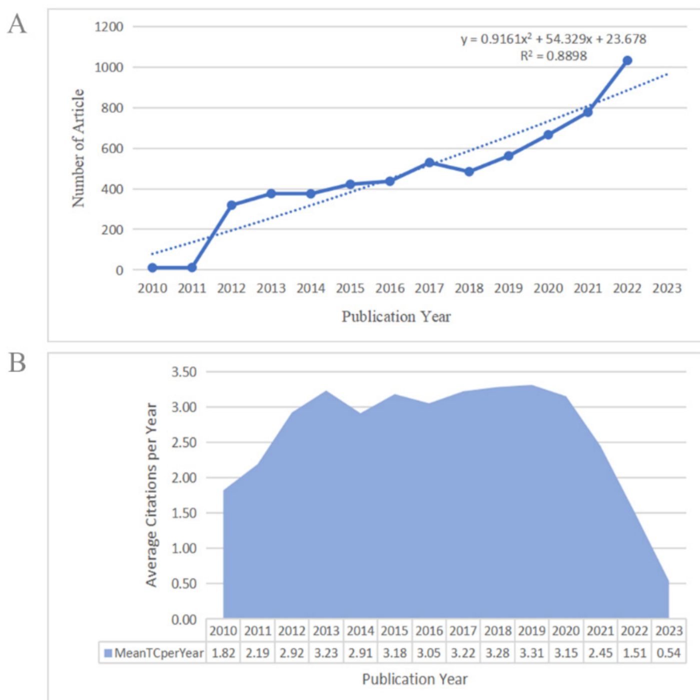



Figure 2 (A) Annual scientific production and polynomial regression modeling (B) Average citations per year during 2010 to 2023

## 3.2 Countries/regions analysis

In Figure 3, which compares the frequency of publications and national collaboration networks across 144 nations or regions, China (n=1197, 18.35%), India (n=930, 14.25%), the United States (n=520, 7.97%), and South Korea (n=384, 5.88%) are shown as the highest NP countries. There has been a great deal of international cooperation, with Saudi Arabia and Egypt collaborating the most closely (Freq=185). India and Saudi Arabia (Freq=136) as well as China and the United States (Freq=172) followed after this. Table 1 lists the Top15 countries/regions according to the Total Citations (TC). China has the most NP (n=1197) and TC (n=20599) internationally, followed by the U.S and India. We were shocked to see that SYRIA (n=96.00), SWEDEN (n=31.80), and the U.S (n=31.60) had the most Average Article Citations (AAC) internationally. The Countries with the greatest NP and TC worldwide, China and India, are only ranked 26th (n=17.2) and 40th (n=14.9) in the AAC rankings, respectively.

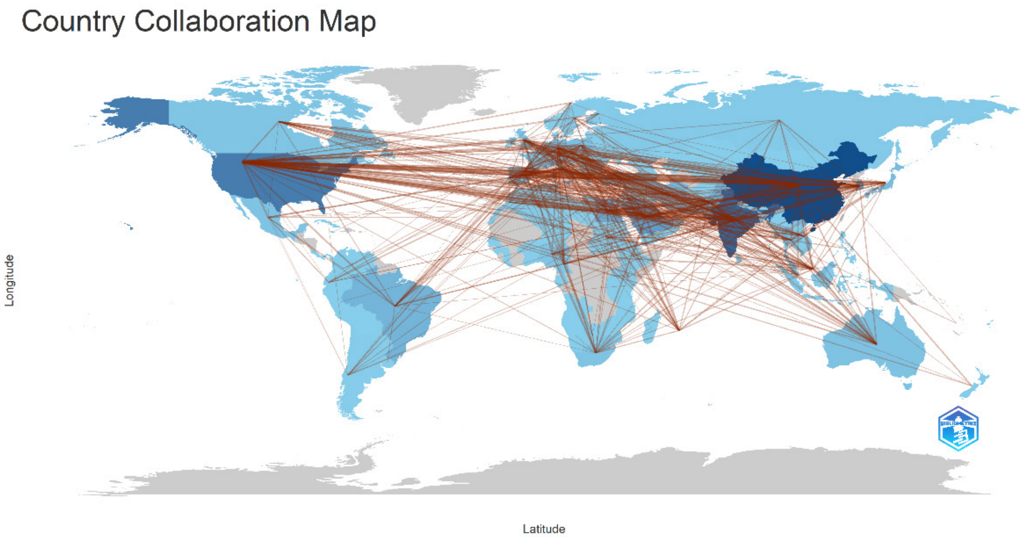



Figure 3 National/Regional Publications And International Cooperation Networks

Table 1 Top 15 Countries/Regions In Terms Of Total Citations

| Rank | Country | NP | TC | Average Article Citations |
|---|---|---|---|---|
| 1 | CHINA | 1197 | 20599 | 17.20 |
| 2 | USA | 520 | 16573 | 31.60 |
| 3 | INDIA | 930 | 13845 | 14.90 |
| 4 | KOREA | 384 | 5937 | 15.50 |
| 5 | ITALY | 283 | 5918 | 20.90 |
| 6 | GERMANY | 108 | 2778 | 25.70 |
| 7 | PAKISTAN | 228 | 2769 | 12.10 |
| 8 | BRAZIL | 230 | 2428 | 10.60 |
| 9 | SAUDI ARABIA | 239 | 2393 | 10.00 |
| 10 | IRAN | 177 | 2376 | 13.40 |
| 11 | MALAYSIA | 149 | 2313 | 15.50 |
| 12 | EGYPT | 197 | 2105 | 10.70 |
| 13 | JAPAN | 114 | 1821 | 16.00 |
| 14 | SPAIN | 75 | 1695 | 22.60 |
| 15 | POLAND | 116 | 1629 | 14.00 |

### 3.3 Author analysis

A total of 25103 authors were involved in the papers on tumor-related phytochemicals. Table 2 shows the Top15 authors with the most local citations, along with other relevant information including H-index, TC, and NP. Liu RH was ranked first (n=52). Additionally, individuals named EFFERTH T, KUMAR S, KONG ANT, SU ZY, and KUBATKA P had more than 35 local citations. Top10 authors' NP and the TC are depicted in Figure 4A (represented by the size of the circle and the darkness of the circle's color, respectively). In 2012, each author had published a various number of papers, particularly is LI Y, the top-ranked author, first published in 2010 (n=2), who produced the most significant NP (n=12) and TC (n=57.14) in 2017. 2022 was the most prolific year for the 10 authors overall, with a total of 78 publications. In Figure 4B, co-authors' nationalities can be analyzed to reveal how well they collaborate internationally, it can be found that the countries with the greatest number of the multiple country publications (MCP) are India (n=228), China (n=199), Saudi Arabia (n=173), the United States (n=160), and Pakistan (n=117). However, Saudi Arabia had the highest percentage of the MCP in the total NP (n=173, 72.38%). China and India had MCP rates of 10.65% and 24.51%, respectively.

Table 2 The Top15 Authors' Local Citations

| Rank | Author | Local Citations | H-index | NP | TC |
|---|---|---|---|---|---|
| 1 | LIU RH | 52 | 20 | 28 | 2103 |
| 2 | EFFERTH T | 47 | 14 | 33 | 593 |
| 3 | KUMAR S | 46 | 15 | 35 | 662 |
| 4 | KONG ANT | 37 | 11 | 13 | 618 |
| 5 | SU ZY | 36 | 7 | 9 | 412 |
| 6 | KUBATKA P | 35 | 8 | 9 | 305 |
| 7 | KELLO M | 34 | 9 | 9 | 328 |
| 8 | MOJZIS J | 34 | 9 | 9 | 328 |
| 9 | ADAMKOV M | 32 | 7 | 7 | 271 |
| 10 | BEALE P | 32 | 7 | 10 | 161 |
| 11 | FERREIRA ICFR | 31 | 15 | 35 | 876 |
| 12 | ZENGIN G | 30 | 13 | 40 | 415 |
| 13 | KAJO K | 29 | 6 | 6 | 203 |
| 14 | MAHOMOODALLY MF | 29 | 10 | 25 | 307 |
| 15 | PEC M | 28 | 7 | 8 | 269 |

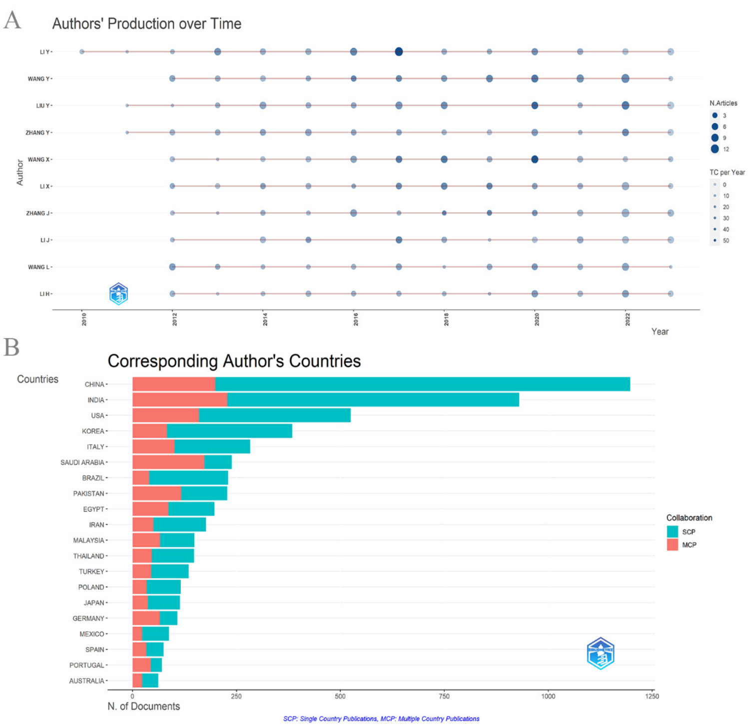



Figure 4 (A) Top10 authors' annual publications and total citation over time. (The size of the circle represents the NP, and the color of the circle represents the TC) (B) Percentage of co-authorship by authors of different nationalities

### 3.4 Journal analysis

The 6523 articles were published in a total of 969 distinct journals, and Figure 5 depicts the annual NPs variation in the top 10 journals. The most papers were published in MOLECULES (n=299, 4.58%), and the number of publications in this journal exhibited an upward trend each year, reaching peak in 2022 (n=90). Similarly, NATURAL PRODUCT RESEARCH, PLANTS-BASEL and SOUTH AFRICAN JOURNAL OF BOTANY follow the peaking, the maximum NP, trend as MOLECULES. Additionally, PHYTOCHEMISTRY LETTERS saw a dramatically increase between 2012 and 2016, and the NP decreases sharply after reaching the peak in 2017. The top 15 journals according to H-index are shown in Table 3, with FOOD CHEMISTRY journal having the highest H-index (n=40). Some journals are second only to it, including BMC COMPLEMENTARY AND ALTERNATIVE MEDICINE, PLOS ONE, and JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, etc.

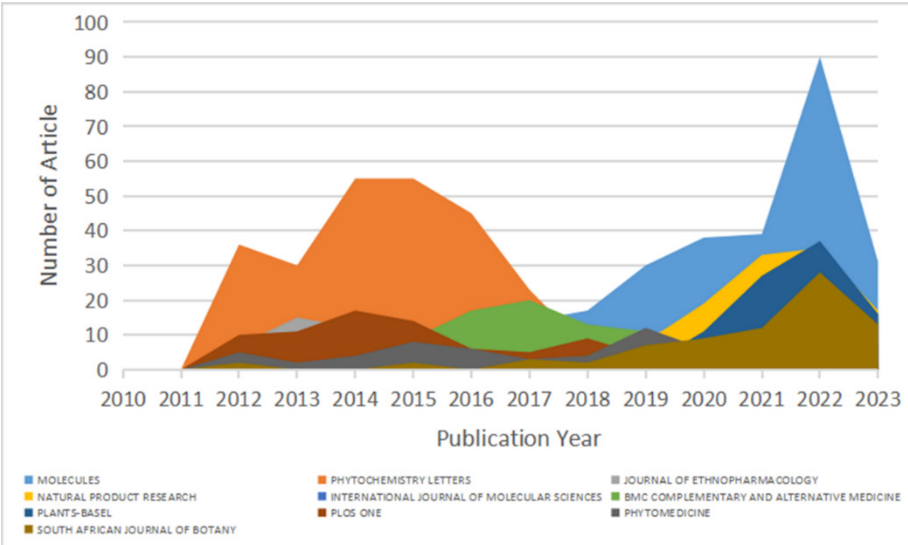



Figure 5 The cumulative number of publications of the top 10 journals

Table 3 Top15 journals impact by H-index

| Rank | Element | H-index | G-index | TC | NP |
|---|---|---|---|---|---|
| 1 | FOOD CHEMISTRY | 40 | 62 | 3934 | 73 |
| 2 | BMC COMPLEMENTARY AND ALTERNATIVE MEDICINE | 32 | 44 | 2642 | 94 |
| 3 | PLOS ONE | 31 | 50 | 2933 | 88 |
| 4 | JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY | 30 | 45 | 2209 | 62 |
| 5 | MOLECULES | 30 | 42 | 3431 | 299 |
| 6 | SCIENTIFIC REPORTS | 27 | 35 | 1512 | 68 |
| 7 | JOURNAL OF ETHNOPHARMACOLOGY | 26 | 34 | 2295 | 154 |
| 8 | PHYTOMEDICINE | 26 | 37 | 1694 | 79 |
| 9 | FOOD AND CHEMICAL TOXICOLOGY | 25 | 39 | 1682 | 53 |
| 10 | PHYTOCHEMISTRY LETTERS | 24 | 31 | 3430 | 276 |
| 11 | JOURNAL OF NATURAL PRODUCTS | 22 | 33 | 1239 | 51 |
| 12 | BIOMEDICINE \& PHARMACOTHERAPY | 21 | 34 | 1381 | 61 |
| 13 | INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES | 21 | 30 | 1211 | 102 |
| 14 | JOURNAL OF FUNCTIONAL FOODS | 20 | 31 | 1107 | 49 |
| 15 | INDUSTRIAL CROPS AND PRODUCTS | 19 | 30 | 981 | 44 |

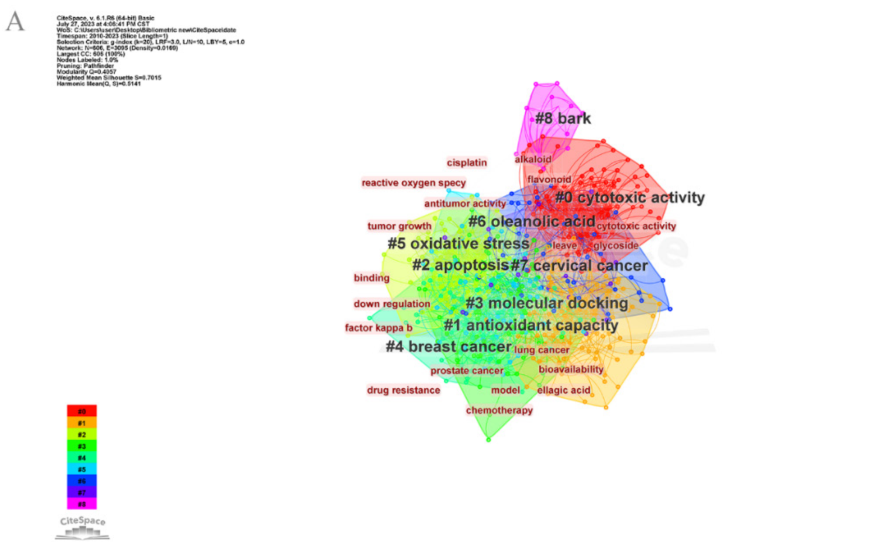
### 3.5 References analysis

With one year as the time slice, Figure 6A shows the co-cited network of references with high mediational centrality. There are 864 nodes and 1593 connecting lines in total. The reference was divided into 22 distinct clusters based on the co-cited network using the Log-Likelihood (LLR) clustering method in order to identify common themes among related references. The three clusters with the highest number of references found by this research were #0 withaferina, #1 drug combination, and #2 anti-inflammatry, with a Weighted Mean Silhouette value of 0.9368 suggesting that the results of the clustering were incredibly impressive.

Table 4 shows the three co-cited papers with the highest centrality (n=0.38) published in the CA-CANCER J CLIN (United States, IF=74.575), Siegel RL et al. provided 2021 global cancer burden statistics[12]. A 2018 reference by Chikara S et al. demonstrates how different phytochemicals affect oxidative stress and associated signaling pathways in cancer[13]. The sources and functions of phytochemicals that have been successfully applied as anticancer drugs in the clinic are summarized by Seca AML et al[14]. Shukla S et al. summarized the epigenetics regulation by phytochemicals in tumor chemoprevention[15].

Reference or Keywords with a high frequency of citations in a short amount of time are termed as citation bursts. Table 5 shows the Top20 citation bursts of references. The papers by LEE KW et al. and Hanahan D et al. both show the strongest bursts from 2012 to 2016, expressing the biology of phytochemicals in the progression of cancers[16] and the molecular targets of phytochemicals for cancer prevention[17], respectively. Several the bursts appearing after 2021 continue to be widely cited today, including the 2018 Global Cancer Statistics from GLOBALCAN[18], SwissADME, a web-based tool, for small molecule pharmacokinetics[19], and Choudhari AS et al. 2020 for an introduction to potential druggability and therapeutic uses[20].

Figure 6B is a dual-map overlay of bibliographic references in the tumor-related (2010-2023). With the distribution of journals where the citing articles is applied on the left and the corresponding cited articles on the right. We identified three sets of significant citation routes in total (three orange, two yellow, and one purple). Orange paths: VETERINARY, ANIMAL and SCIENCE; yellow paths: CHEMISTRY, MATERIALS and PHYSLCS; purple paths: CHEMISTRY, MATERIALS and PHYSLCS. The cited papers in the orange paths are typically published in Molecular, Biology and Immunology. It is interesting that all three sets of go-getters, major Journal Distribution of Cited references, with distinct colored paths have the most articles published in MOLECULAR, BIOLOGY, and GENATICS.



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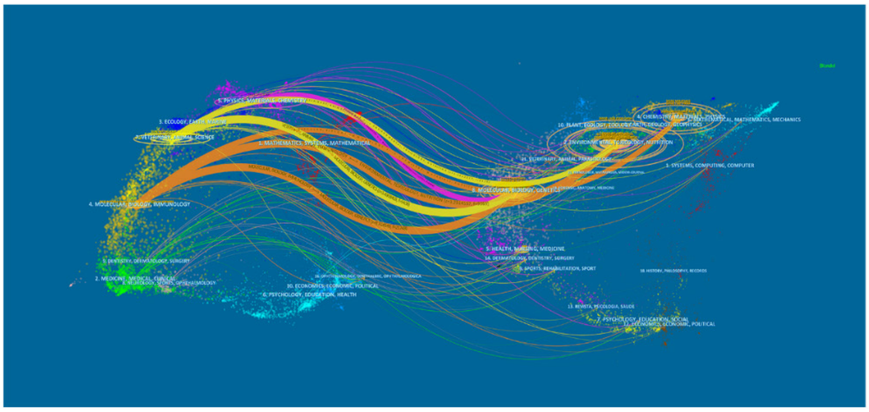

Figure 6 (A) The reference co-citation network and clustering analysis (B) Dual-map overlay plot concerning phytochemicals antitumor research

Table 4 Top15 co-citation reference based on the Betweenness Centrality

| Rank | Count | Centrality | Year | Author | Source | DOI |
|---|---|---|---|---|---|---|
| 1 | 198 | 0.38 | 2021 | Siegel RL | CA-CANCER J CLIN | 10.3322/caac.21654 |
| 2 | 42 | 0.24 | 2018 | Chikara S | CANCER LETT | 10.1016/j.canlet.2017.11.002 |
| 3 | 25 | 0.15 | 2018 | Seca AML | INT J MOL SCI | 10.3390/ijms19010263 |
| 4 | 62 | 0.12 | 2015 | Ferlay J | INT J CANCER | 10.1002/ijc.29210 |
| 5 | 18 | 0.12 | 2014 | Shukla S | CANCER LETT | 10.1016/j.canlet.2014.09.017 |
| 6 | 17 | 0.11 | 2010 | Shu LM | CANCER METAST REV | 10.1007/s10555-010-9239-y |
| 7 | 30 | 0.09 | 2011 | Hanahan D | CELL | 10.1016/j.cell.2011.02.013 |
| 8 | 24 | 0.09 | 2018 | Mohanraj K | SCI REP-UK | 10.1038/s41598-018-22631-z |
| 9 | 15 | 0.09 | 2016 | Anantharaju PG | NUTR J | 10.1186/s12937-016-0217-2 |
| 10 | 39 | 0.08 | 2011 | Lee KW | NAT REV CANCER | 10.1038/nrc3017 |
| 11 | 11 | 0.08 | 2016 | Ahmed S | J ADV RES | 10.1016/j.jare.2015.02.007 |
| 12 | 25 | 0.07 | 2012 | Newman DJ | J NAT PROD | 10.1021/np200906s |
| 13 | 24 | 0.07 | 2020 | Kopustinskiene DM | NUTRIENTS | 10.3390/nu12020457 |
| 14 | 60 | 0.06 | 2016 | Newman DJ | J NAT PROD | 10.1021/acs.jnatprod.5b01055 |
| 15 | 22 | 0.06 | 2015 | Greenwell M | INT J PHARM SCI RES | 10.13040/IJPSR.0975-8232.6(10).4103-12 |

Table 5 Top 20 References with the Strongest Citation Bursts

| References | Year | Strength | Begin | End | 2010 - 2023 |
|---|---|---|---|---|---|
| Lee KW, 2011, NAT REV CANCER, V11, P211, DOI 10.1038/nrc3017, DOI | 2011 | 17.15 | 2012 | 2016 | |
| Hanahan D, 2011, CELL, V144, P646, DOI 10.1016/j.cell.2011.02.013, DOI | 2011 | 13.16 | 2012 | 2016 | |
| [Anonymous], 2014, CA-CANCER J CLIN, V0, P0 | 2014 | 11.61 | 2014 | 2019 | |
| Shu LM, 2010, CANCER METAST REV, V29, P483, DOI 10.1007/s10555-010-9239-y, DOI | 2010 | 8.37 | 2012 | 2015 | |
| Newman DJ, 2012, J NAT PROD, V75, P311, DOI 10.1021/np200906s, DOI | 2012 | 10.79 | 2013 | 2017 | |
| Siegel R, 2012, CA-CANCER J CLIN, V62, P10, DOI 10.3322/caac.20138, DOI | 2012 | 7.77 | 2013 | 2014 | |
| Su ZY, 2013, TOP CURR CHEM, V329, P133, DOI 10.1007/128, 2012, 340, DOI | 2013 | 8.04 | 2014 | 2018 | |

| | | | | |
|---|---|---|---|---|
| Siegel RL, 2015, CA-CANCER J CLIN, V65, P5, DOI 10.3322/caac.21254, DOI | 2015 | 14.69 | 2015 | 2019 |
| Ferlay J, 2015, INT J CANCER, V136, PE359, DOI 10.1002/ijc.29210, DOI | 2015 | 19.13 | 2016 | 2020 |
| Newman DJ, 2016, J NAT PROD, V79, P629, DOI 10.1021/acs.jnatprod.5b01055, DOI | 2016 | 16.12 | 2017 | 2021 |
| Torre LA, 2015, CA-CANCER J CLIN, V65, P87, DOI 10.3322/caac.21262, DOI | 2015 | 9.87 | 2017 | 2020 |
| Kotecha R, 2016, ONCOTARGET, V7, P52517, DOI 10.18632/oncotarget.9593, DOI | 2016 | 8.53 | 2017 | 2021 |
| Zhang YJ, 2015, MOLECULES, V20, P21138, DOI 10.3390/molecules201219753, DOI | 2015 | 7.89 | 2017 | 2020 |
| Greenwell M, 2015, INT J PHARM SCI RES, V6, P4103, DOI 10.13040/IJPSR.0975-8232.6(10).4103-12, DOI | 2015 | 10.05 | 2018 | 2020 |
| Redza-Dutordoir M, 2016, BBA-MOL CELL RES, V1863, P2977, DOI 10.1016/j.bbamcr.2016.09.012, DOI | 2016 | 9.36 | 2019 | 2021 |
| Panche AN, 2016, J NUTR SCI, V5, P0, DOI 10.1017/jns.2016.41, DOI | 2016 | 8.97 | 2019 | 2021 |
| Atanasov AG, 2015, BIOTECHNOL ADV, V33, P1582, DOI 10.1016/j.biotechadv.2015.08.001, DOI | 2015 | 8.28 | 2019 | 2020 |
| Bray F, 2018, CA-CANCER J CLIN, V68, P394, DOI 10.3322/caac.21492, DOI | 2018 | 28.05 | 2021 | 2023 |
| Daina A, 2017, SCI REP-UK, V7, P0, DOI 10.1038/srep42717, DOI | 2017 | 17.3 | 2021 | 2023 |
| Choudhari AS, 2020, FRONT PHARMACOL, V10, P0, DOI 10.3389/fphar.2019.01614, DOI | 2020 | 10.78 | 2021 | 2023 |

### 3.7 Keywords analysis

Figure 7A depicts the keywords co-occurrence network with a time slice of 1 year, which consists of 606 nodes and 3095 connecting lines. Eight clusters were produced by Log-Likelihood (LLR), including #0 cytotoxic activity, #1 antioxidant capacity, #2 apoptosis, #3 molecular docking, #4 breast cancer #5 oxidative stress, etc. The Top15 keywords with the highest betweenness centrality in the phytochemicals research from 2010 to 2023 are clearly listed in Table 6. The emergence of “alkaloid” in 2010 with the highest centricity, in addition to “chemotherapy”, “antitumor activity”, and “ellagic acid”, all of which play crucial roles in the research and development of tumor-related phytochemicals.

The Top20 keywords with citation bursts are listed in Figure 7B. The blue lines denote time intervals, and the red lines depict keyword burst time periods. During 2012-2018, the keywords “chemoprevention”, “epithelial cell”, “in vivo”, “mice”, “phosphorylation”, and “free radical” came into view. In which the chemoprevention has the strongest citation bursts (STRENGTH=12.86). Additionally, researchers have continued to pay close attention to some keywords, such as “system”, “secondary metabolite”, “green synthesis”, “functional food”, “degradation”, etc. since 2019 or 2020 till now.

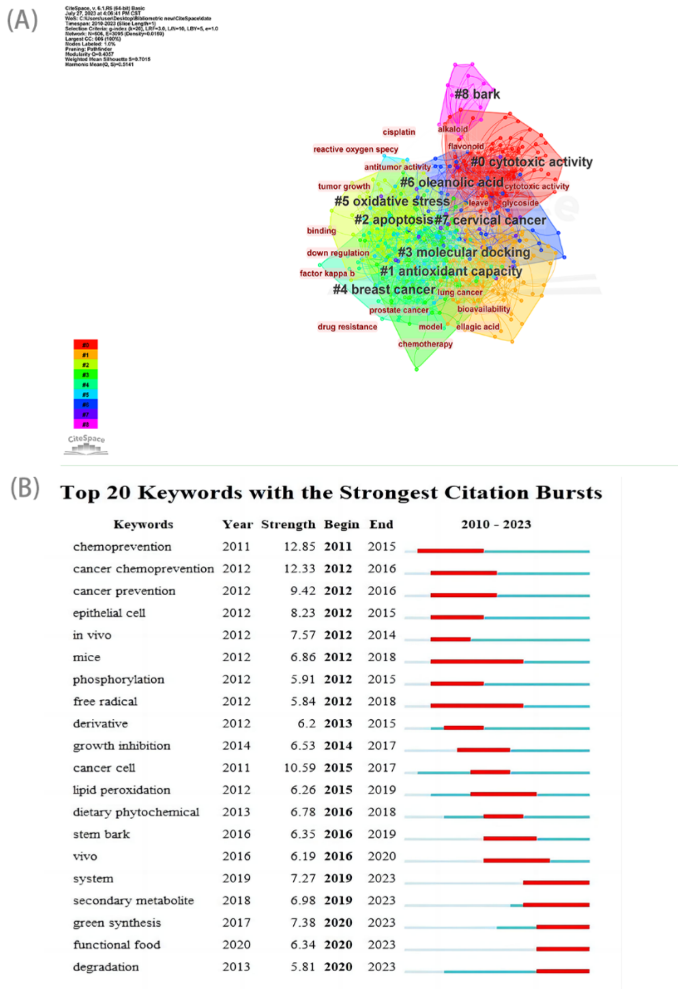


Figure 7 (A) Keyword co-occurrence mapping and clustering (different colors in the Figure represent different clusters and nodes). (B) Top20 keywords strength and time of occurrence with most citation bursts.

Table 6 Top15 co-occurring keywords by centrality

| Rank | Count | Centrality | Year | Keyword |
|---|---|---|---|---|
| 1 | 79 | 0.06 | 2010 | alkaloid |
| 2 | 63 | 0.06 | 2010 | chemotherapy |
| 3 | 84 | 0.05 | 2012 | antitumor activity |
| 4 | 67 | 0.05 | 2012 | ellagic acid |
| 5 | 408 | 0.04 | 2010 | flavonoid |
| 6 | 162 | 0.04 | 2010 | glycoside |
| 7 | 102 | 0.04 | 2012 | lung cancer |
| 8 | 88 | 0.04 | 2012 | bioavailability |
| 9 | 74 | 0.04 | 2012 | rat |
| 10 | 72 | 0.04 | 2012 | model |
| 11 | 48 | 0.04 | 2012 | alpha |
| 12 | 39 | 0.04 | 2012 | binding |
| 13 | 30 | 0.04 | 2013 | cisplatin |
| 14 | 434 | 0.03 | 2010 | constituent |
| 15 | 324 | 0.03 | 2010 | leave |

## 4. Discussion

Currently, with the incidence and mortality of cancer rising globally, how to overcome the toxic side effects as well as multidrug resistance (MDR) caused by conventional treatments, and develop safe therapeutic strategies has become a major problem for clinicians. Natural phytochemicals have demonstrated great therapeutic potential for a variety of chronic conditions, particularly in the chemoprevention and co-treatment of cancer. However, there are still several issues that need to be resolved before phytochemicals widely used, including the proper concentration, application methods, in vivo mode of action, and safety, etc. For these reasons, this study is the first bibliometric examination of the connection between phytochemicals and tumors, allowing researchers to easily grasp the research advances, hotspots, and frontiers.

General Information

Oncology and phytochemicals-related papers totaling 6523 were searched for and extracted from the WOSCC between 2010 and 2023, as the foundation for this bibliometric study. A time-series analysis of the annual NP and AAC is beneficial to understand the dynamic research progress in a field. In terms of annual NP, tumor-related phytochemicals have shown a general upward trend. Without a doubt, the two most noTable dates are 2012 and 2022. 2012 witnessed the beginning of research on tumor-related phytochemicals, and since then, both the annual NP and the average citations per year have grown rapidly. The NP peaked in 2022 with 1,032 articles appearing and increased by more than twice as much as in 2012. After 2020, however, the average annual citations decreased dramatically, which may be related to the delay in citations of newly published papers. Following 2012, a large number of studies clarified the chemopreventive and therapeutic potential of phytochemicals against preclinical models of a variety of cancers[21, 22], including the EGCG[23-25], Resveratrol[26, 27], and Curcumin[28]. In terms of mechanistic investigations, it has been demonstrated that phytochemicals inhibit tumor proliferation, invasion, and metastasis by down-regulating multiple pathways. Examples include PI3K/ Akt / mTOR[29, 30] , IL - 6 / JAK/ STAT3[31], NF - κB[11, 32], MAPK/ ERK[33]. These studies have contributed to the peak of publications, and the available evidence suggests that the research on tumor-related phytochemicals will continue to increase in the future.

China has the highest NP and TC in tumor-related phytochemicals research which is reflected in the country/region analysis (Table 1), which examines the popularity and output of a study in various nations and regions. This characteristic is also demonstrated in Figure 4A, where the authors of high-impact publications are virtually exclusively Chinese, with varying numbers of papers produced from 2012 onwards. This may be related to China's long history of dietary and traditional Chinese medicine culture. There is a strong cooperation between high-publishing countries, with Saudi Arabia and Iran being the most frequent partners, followed by China and the United States. Saudi Arabia is also the nation with the most co-authors of various nationalities. Surprisingly, SYRIA, SWEDEN, and the U.S are the top3 nations with the greatest average article citations internationally, with China and India being left out of the Top20. This indicates that the quality of papers from China and India needs to be improved, and more cross-national or cross-nationality collaborations should be carried out in the future. Statistics demonstrate a significant correlation between population density and the burden of tumors in China, India, and the United States, which may be one of the explanations for why these nations are more active in tumor-related phytochemical study.

When we used local citations to evaluate the influence of authors, Prof. Liu, Rui Hai from Shenyang Agricultural University attracted our attention the most, focusing on the antioxidant and antiproliferative activities of different phytochemicals in cancer. For example, Ursolic Acid inhibits the growth of breast cancer cells and induces death via the Nrf2 or p231/MAPK signaling pathways[34, 35]. Efferth Thomas from Johannes Gutenberg University of Mainz and Kumar Shashank from Central University of Punjab, both of Germany. The most publications about tumor-related phytochemicals are published in MOLECULES. The first open-access journal of MDPI, MOLECULES was established in 1996, which includes two main columns, "Materials Chemistry" and "Nanochemistry", and contains a wide range of articles in the fields of materials chemistry, biomedicine and nanomaterials. Food Chemistry (IF=8.8) in the subject of food science and technology in the United Kingdom, launched in 1976 and published as a semimonthly by Elsevier Press, has the highest H-index and TC. It offers complete open access and publishes a wide variety of original research papers in the fields of food chemistry and biochemistry. Although this journal does not appear in the Top10 journals in terms of number of articles issued (Figure 5), it has the most TC. Indicating that its excellent academic caliber has attracted greater attention and citations from scholars.

Knowledge Base

A reference's or a keyword's centrality is a reliable sign of how significant it is to the wider network. In this bibliometric analysis, we evaluated the Top15 references with the highest centrality (Table 4) to understand the research base of tumor-related phytochemicals. Along with the global cancer incidence and mortality rates provided by GLOBALCAN, the Global Cancer Burden Statistics published by Siegel RL et al. in 2021 had the highest centrality and number of citations, which underlined the necessity of antitumor research[12, 36]. A range of phytochemicals exert chemopreventive effects on cancer by lowering oxidative stress were reviewed by Chikara S[12, 36]. Natural phytochemicals still play a significant role in antitumor research due to their antioxidant properties. For instance, SAW CL et al. showed that Quercetin, Kaempferol, and Pterostilbene exert a synergistic antioxidant stress effect by activating the Nef2-ARE pathway and reducing intracellular levels of reactive oxygen species (ROS)[37]. In addition, the four highly centrality literature reviewed phytochemicals as anticancer medicines successfully applied in the clinic or in clinical trials[14, 38-40]. These phytochemicals are the cornerstone of research and keep advancing practically in fresh studies. For instance, in 2012, the FDA approved the use of sphingomyelin/cholesterol (SM/Chol) liposome vincristine (Marqibo®) for the treatment of relapsed acute lymphoblastic leukemia in adults[41]. Since then, novel pathways for the clinical use of Paclitaxel[42], Vincristine[43] and Homoharringtonine[44, 45] have been discovered, highlighting the enormous potential of phytochemicals for medical uses. Shukla S et al. revealed how plant chemicals can modify epigenetics to mediate anticancer effects[15]. In 2016, Anantharaju PG et al. introduced phenolic compounds to regulate vascular endothelial factors, cell cycle proteins, transcription factors, epigenetics and other effects[46]. The Top15 centrality keywords in Table 6 can also assist us in swiftly summarizing the fundamental information of studies on tumor-related phytochemicals. These keywords primarily include alkaloid, chemotherapy, antitumor activity, flavonoid, glycoside, lung cancer, and bioavailability, among others. Global cancer burden, processes of phytochemicals in carcinogenesis and development, and clinical applications make up the majority of the fundamentals on phytochemicals associated with tumors.

Hot Topics and Frontiers

Reference and keyword citation bursts are frequently used to highlight trending themes over time. We can understand the research hotspots of tumor-associated phytochemicals by combining the keywords bursts (Figure 7B) with the corresponding clustering maps. Between 2012 and 2016, the impacts of cancer chemotherapy were incredibly prevalent in citation bursts. For instance, Nitidine, a STAT3 pathway inhibitor, inhibits Janus kinase 2 / STAT3 signaling and STAT3 DNA binding activity in endothelial cells to mediate angiogenesis suppression and apoptosis[47]. SHAN et al. demonstrated for the first time that Sulforaphane (SFN) mediates EMT inhibition in bladder cancer through the mir-200c/ZEB1 pathway[48]. Picrasidine induces apoptosis in cholangiocarcinoma cells by activating mitochondria-dependent pathways through induction of Cystatinase activation, regulation of bcl2/Bax expression and inactivation of the PI3K/AKT pathway[49]. According to these research, phytochemicals, as modulators of important cell signaling pathways, interact with cancer targets to have chemopreventive. Interestingly, Sulforaphane and Nitisin, two chemical compounds with nitrogen, are included in the most centrality term "Alkaloid" that are frequently found in nature. Subsequently, new findings on the regulation of epigenetics by phenolic chemicals continue to emerge. For instance, EGCG induces RKIP expression by histone modification in AsPC-1 pancreatic cancer cells, which reduces invasive and metastatic activities[23]. Resveratrol reduces the risk of breast tumors caused by exposure to aromatic hydrocarbon receptor agonists (AhR) during pregnancy by inhibiting CpG methylation of the BRCA-1 gene[26]. The keywords "in vivo" and "mice" have the longest time span between 2012 and 2020, since in vivo animal experiments, such as nude mouse transplanted tumor models, may better imitate the complex in vivo environment and are one of the most widely used techniques for anticancer drug screening. Between 2015 and 2019, lipid peroxidation got a lot of attention, particularly in anticancer investigations involving oxidative stress and Ferroptosis. For instance, colon cancer cells treated with Saffron extracts CST and CTA dramatically reduced hydrogen peroxide-induced ROS generation and MDA levels (a recognized LPO marker)[50]. In 2017, Tamara Y et al. showed that strawberry extracts enriched with anthocyanin fractions modulated lipid metabolism, modulated ROS and Thiobarbituric Acid (TBARs) production to improve the redox status of HepG2 cells[51]. Ferroptosis is primarily triggered by LPO, which has three primary stages: initiation, propagation, and termination[52]. Numerous phytochemicals have been demonstrated to have anticancer effects when they target NRF2 to induce LPO and iron-deficiency anemia[53]. In present, some keywords from 2019 continue to have a large audience, including secondary metabolite, green synthesis, functional food, and degradation.

In addition, some other hotspots also deserve our attention. Withaferin A (WFA) is one of the most important herbs in Ayurvedic system in India[54]M.</author></authors></contributors><auth-address>School of Systems Biology, George Mason University, Manassas, VA, United States.</auth-address><titles><title>Evaluating anticancer properties of Withaferin A-a potent phytochemical</title><secondary-title>Front Pharmacol</secondary-title></titles><periodical><full-title>Front Pharmacol</full-title></periodical><pages>975320</pages><volume>13</volume><edition>2022/11/08</edition><keywords><keyword>Ashwagandha</keyword><keyword>Withaferin A</keyword><keyword>Withania somnifera</keyword><keyword>apoptosis</keyword><keyword>cancer</keyword><keyword>cancer treatment</keyword><keyword>withanolides</keyword><keyword>commercial or financial relationships that could be construed as a potential</keyword><keyword>conflict of interest.</keyword></keywords><dates><year>2022</year></dates><isbn>1663-9812 (Print, and it has the most linked articles in the cluster mapping of literature co-citation network. Several preclinical studies have shown that it has potent anticancer action[55]. For example, WFA, for example, reduced tumor growth in 80% of ovarian epithelial carcinomas when combined with cisplatin[56]. The combination of phytochemicals and chemotherapeutic drugs, which ranked second in the cluster mapping, has long been used to reverse MDR and chemotherapeutic sensitization. Teng et al. (2016) revealed that β-carotene inhibited P-gp transcription by stimulating ATPase activity in a variety of drug-resistant tumor cells and improved doxorubicin, paclitaxel, and mitoxantrone chemosensitivity[57]. Allicin and 5-FU can exert a synergistic effect in a variety of cancers, including lung, liver, and colorectal cancers, promoting tumor cell morphology transformation and inhibiting tumor cell invasion and migration[58]. After 2015. New approaches to tumor therapy are made possible by the quick development of materials chemistry. In 2017, Javid et al. created Nanoparticles made from PLGA/PEG copolymers for the first time to construct nanoparticles with a combination of Curcumin and Chrysin, which successfully reduced hTERT expression, sped up the inhibition of caco-2 cells, and lessened harmful side effects[59].

Table 5 shows that the research interest in oncology-related phytochemicals from 2021-2023 is focused on drug development based on naturally derived phytochemicals[60], computer model assessment of pharmacokinetics and drug similarities[19], and clinical application of phytochemicals in cancer therapy[20]. Surprisingly, these topics are extremely similar to the research base and the drugability and clinical translation may become a central topic for future research.

Limitation

Since we used the WOSCC database to gather all the data for this research, it’s possible that we left out certain articles. Additionally, our analysis only included English-language articles, some non-English writing, reviews, and other kinds of studies were omitted. Due to word count restrictions, there are only a limit number of graphs and Tables that can be provided in the bibliometric analysis.

## 4. Conclusion

In oncology, phytochemicals have important research value and clinical application potential. Since 2012, the NP and the average annual citations have been rising quickly, peaking in 2012, which has drawn significant interest from academics and institutions all around the world. Although China has the greatest NP and TC in the world, there is still room to improve international collaborations. The closest collaborations are between Saudi Arabia and Egypt, with Saudi Arabia having the most publications written with authors of other nationalities. The author with the most scientific contributions is LI Y, whereas Prof. RH Liu has the most local citations. The journal with the greatest H-index and most referenced articles was Food Chemistry, however Molecules had the most papers published in it. Chemoprevention, anti-tumor mechanisms, and clinical applications are the key topics of interest in the development of phytochemicals related to tumors. We should combine computational and materials chemistry approaches with fundamental research in the future to promote additional therapeutic applications of anti-tumor phytochemicals.

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## Conflict of interest

Authors declare that no conflicts of interest are declared in this study.

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