# Citrus Anticancer Research: A Bibliometric Mapping of Emerging Topics

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**Abstract.** Research on the potential anticancer effects of citrus has been widely published in scientific journals. Still, a bibliometric analysis concerning this topic has not been executed. This study employed bibliometric mapping to analyze articles related to citrus anticancer from the Scopus Database and visualized the results using the VOSviewer. In this review, 442 papers published between 1995 and 2023 were selected. Jeju National University in South Korea is recognized as a top contributor. According to the analysis, apoptosis and anticancer are the two specific keywords in the field with the highest co-occurrence. The other keywords in the selected papers were hesperidin, naringenin, nobiletin, apoptosis, and flavonoids. We also found the following steps in this research area: formulation, synthesis, and *in vivo* preclinical studies. Research trends have shifted from the crude extract to practical applications of specific flavonoid compounds with structure modification to improve their anticancer properties. Still, clinical trials in humans are lacking in this research area and should be further investigated to embrace citrus flavonoids as an anticancer candidate. This analysis and mapping provide a comprehensive understanding of research on the potential anticancer effect of citrus.
**Keywords:** citrus, flavonoid, anticancer, bibliometric, VOSviewer

## 1 Introduction

Cancer is an intricate environment comprised of tumor cells that proliferate uncontrollably in the body, triggering immune system dysfunction and possibly leading to mortality [1]. It is a multistep process in which the genetic composition of individual cells is altered, transforming normal cells into aberrant cells, and driving the change towards malignancy [2]. Chemotherapy is a common technique for treating cancer in the initial stages [3], although it may have negative effects on normal cells and occasionally fails to manage the malignant type [4]. Given the adverse effects and lack of selectivity of synthetic medications, the development of innovative and natural chemotherapeutic agents is in great demand. In recent decades, there has been a rise in research focused on producing anticancer candidates from nature. The ideal option is to utilize natural products, which are rich in bioactive chemicals that provide significant health effects [5]. Citrus flavonoids and their structural derivates have been explored as possible anticancer drugs because of their high chemical variety [6, 7]. Several promising lead compounds have recently been found [8]; however, only a handful are in clinical trials [9].

Citrus is the world's fourth-most-produced crop and contains numerous nutrients that are beneficial to humans [8]. Individual citrus components, such as vitamins, hesperidin, naringin, limonene, quercetin, tangeretin, nobiliten, etc., all contribute to various pharmacological effects [8, 10–12], including anticancer properties. Citrus in its entirety, including peel [6], seed [13], and juice [14], is an invaluable source of secondary metabolites and bioactive compounds. The anticancer properties of these compounds include cytotoxicity, inhibition of proliferation [15], induction of apoptosis, retardation of metastasis [16], suppression of angiogenesis [17], and enhancement of chemotherapy [18]. Multiple studies, including those on breast cancer, colon cancer, and pancreatic cancer, have demonstrated that hesperidin [19] and naringenin [20] inhibit the proliferation of cancer cells. These flavonoids have tremendous potential as an alternative cancer prevention and treatment strategy. In addition, the effects of citrus consumption have been studied using a variety of experimental models, and an estimate of citrus' toxicity has been established [21]. Citrus-derived bioactive chemicals have also been utilized in numerous toxicological studies, which have demonstrated that their safety profile is comparable to that of other bioactive compounds. The potential for citrus to be developed as a novel anticancer agent provides an essential opportunity. However, only a couple of studies have described the next phase of the preclinical evaluation of citrus flavonoids as a potential anticancer agent.

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Despite extensive research and several review articles on citrus anticancer research, an absence of bibliometric studies came to light. With a recent surge in the number of citrus anticancer research, researchers have found it difficult to locate pertinent information. As a result, bibliometric analysis may be utilized to deal with this massive volume of data [22]. Bibliometric analysis may be used to discover research trends, assess the effect of individual publications, assess the productivity of academics and institutions, and find possible partners [23]. Furthermore, it could be used to provide information on how far research has progressed as well as to guide financing, policy, and strategy choices. Bibliometric tools, such as the Visualization of Similarities viewer (VOSviewer) [24], and scientific databases, such as Scopus, can be used to study and evaluate large volumes of scientific data. Using the Web of Science database, recent research presented a scientometric investigation of citrus flavonoids as an anticancer and neuroprotective drug. In the other investigations, a bibliometric analysis was successful in determining worldwide trends in triple-negative breast cancer nanomedicine research. This study employs a bibliometric technique to examine the citrus anticancer research trend using the Scopus Database to answer several questions on significant themes, most productive authors, leading institutions and journals, leading countries, co-occurrence of authors, organization, and keywords in the citrus anticancer research. From this study, we hope the findings can elucidate the research gap and the prospects for future research.

## 2 Methodology

### 2.1.Data Source and Search Query

Publications on anticancer research in citrus were retrieved on May 31, 2023, from the Scopus database using the following search query: TITLE-ABS-KEY ("citrus") AND TITLE-ABS-KEY ("anti-cancer") OR TITLE-ABS-KEY ("anticancer"). Search strategies were limited to: (Document type, "Article") AND (Source type, "Journal") AND (LANGUAGE, "English"). No year restriction was applied. Manual filtering by assessing abstract eligibility was used to improve the quality of the collected data. The bibliographic data of selected papers was exported in CSV format and continued to be analyzed using the VOSviewer software. The flowchart of the bibliometric analysis is summarized in Fig. 1.

### 2.2.Bibliometric Mapping and Data Analysis

VOSviewer [24] was used to search for bibliographical and author keywords in selected articles. The network of interest items in the selected articles, such as contributing countries, authorships, keyword occurrences, and citations, were also built by VOSviewer using full-counting methods; the total of an analysis is equal to the number of links obtained as a result of the analysis. A trend of publications by year was illustrated by a graph. The top 10 of most countries, institutions, authors, journals, papers, and keywords were displayed in a table to assess the influence and impact of the research conducted.

The terms (countries, authors, and keywords) are represented in a bubble, and the size of the bubble corresponds to the number of documents or occurrences of each term. Lines are used to connect each of the bubbles to the others. The distance that exists between two bubbles is a representation of the degree to which the words are associated in terms of co-authorship, co-occurrence, or bibliographic coupling. The category that the words are categorized into may be inferred from the color of the bubble.

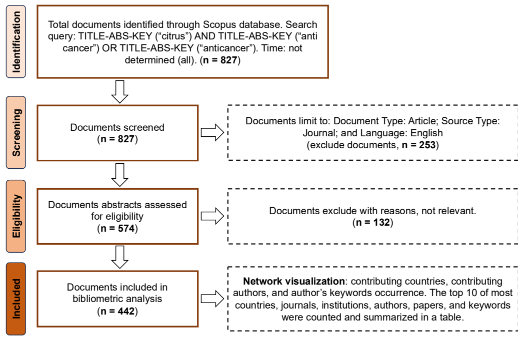


**Fig. 1.** Flowchart of the study.

## 3 Results

### 3.1 Trends of Publications by Year

For 28 years (1995–2003), a total of 442 research articles on citrus as an anticancer agent were published (Fig. 2). As of 1995, the first publication by the *British Journal of Cancer* revealed the apoptosis induction of the citrus flavone tangeretin against HL-60 leukemia cell lines [25]. The latest paper published by Amalina et al. [26] in the *Journal of the Egyptian National Cancer Institute* demonstrates the in vitro synergistic effect of citrus flavonoid hesperidin to enhance the efficacy of doxorubicin against 4T1 metastatic breast cancer cell lines.

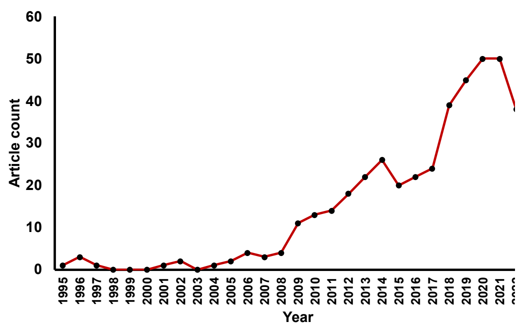


**Fig. 2.** Publication trends by year of citrus in the field of anticancer activities (n = 442).

The trend of publications by year has been relatively increasing over time, though from 1995 to 2008, related research on citrus anticancer was noted in under five publications per year. In 2009, the number of publications increased to eleven from four in 2008. The annual growth rate (AGR) climbed by 90% in 2009 and more than doubled between 2013 and 2014. Our graph showed that the overall number of publications decreased from 2015 to 2017, fluctuating around 20 publications, but showed a rebound in 2018 to double the previous and reach its peak in 2021 (n = 50). More than 50% of the publications published after 2018 (n = 250). In addition, the vast majority of articles published in the Biochemistry, Genetics, and Molecular Biology; Pharmacology, Toxicology, Pharmaceuticals; and Medicine subject areas We believed that the annual publications of citrus anticancer still became a challenging topic to explore and may continue to gain traction among researchers in the near future.

### 3.2 Assessment of Contributing Journals

The top 10 most productive journals are shown in Table 1. A total of 442 selected papers were published by 160 different journals, and the majority published their papers within the past five years. The top 10 journals contributed 5% of the total number of selected papers. The most productive journal in publishing citrus anticancer research is *Molecules* (n = 14), with an average number of citations (AC) of 33.36%. In second and third place are the J*ournal of Agricultural and Food Chemistry* and *Nutrition and Cancer*, which come out with 11 and 10 publications, with AC values of 59.18% and 79.90%, respectively. Although in third place, *Nutrition and Cancer* has the most cited paper with 799 citations. This data could help academics and researchers find the most credible journal both for literature searching and submitting their research on those specific topics. In brief, the *Molecules* could potentially be selected as a popular journal destination for publishing research on citrus anticancer. On the other hand, based on the latest articles published by the top 10 journals, studies on citrus anticancer have progressed to the anticancer exploration of specific flavonoid compounds from *Citrus sp.*, such as tangeretin, hesperetin, hesperidin, nobiletin, and sinensetin. The research being carried out is no longer directed towards the use of crude extracts but rather

**Table 1.** Top 10 Journals with the most papers

| No. | Journal | Number of papers | Number of Citations | AC[1] per paper | The title of the latest paper (year of publication) |
|---|---|---|---|---|---|
| 1 | Molecules | 14 | 467 | 33,36 | Metabolomic Analysis of Phytochemical Compounds from Ethanolic Extract of Lime (*Citrus aurantifolia*) Peel and Its Anti-Cancer Effects against Human Hepatocellular Carcinoma Cells (2023) |
| 2 | Journal of Agricultural and Food Chemistry | 11 | 651 | 59,18 | Identification and Quantification of Both Methylation and Demethylation Biotransformation Metabolites of 5-Demethylsinensetin in Rats (2022) |
| 3 | Nutrition and Cancer | 10 | 799 | 79,90 | Evaluation of the Effects of Nobiletin on Toll-Like Receptor 3 Signaling Pathways in Prostate Cancer In Vitro (2021) |
| 4 | International Journal of Biological Macromolecules | 9 | 286 | 31,78 | Construction and antitumor activity of selenium nanoparticles decorated with the polysaccharide extracted from *Citrus limon* (L.) Burm. f. (Rutaceae) (2021) |
| 5 | International Journal of Molecular Sciences | 9 | 138 | 15,33 | Acetylation Enhances the Anticancer Activity and Oral Bioavailability of 5-Demethyltangeretin (2022) |
| 6 | Phytomedicine | 8 | 168 | 21,00 | Nobiletin inhibits breast cancer cell migration and invasion by suppressing the IL-6-induced ERK-STAT and JNK-c-JUN pathways (2023) |
| 7 | Plos One | 8 | 345 | 43,13 | Experimental, molecular docking and molecular dynamic studies of natural products targeting overexpressed receptors in breast cancer (2022) |
| 8 | Bioorganic and Medicinal Chemistry Letters | 7 | 330 | 47,14 | Isolation and biological activity of agrostophillinol from kaffir lime (*Citrus hystrix*) leaves (2020) |
| 9 | Food and Function | 7 | 289 | 41,29 | Hesperetin ameliorates hepatic oxidative stress and inflammation: Via the PI3K/AKT-Nrf2-ARE pathway in oleic acid-induced HepG2 cells and a rat model of high-fat diet-induced NAFLD (2021) |
| 10 | International Journal of Oncology | 7 | 231 | 33,00 | Hesperetin induces apoptosis in A549 cells via the Hsp70-mediated activation of Bax (2022) |

towards single compounds and their formulations. The latest papers published by *Molecules* (2023) reported the metabolomic analysis of citrus peel extract and its cancer activity towards hepatocellular carcinoma [27]. The superior anticancer effect of citrus peel extract likely results from hesperidin and limonin, the major compounds in *Citrus aurantifolia* peel. Another recent paper published by Phytomedicine (2023) revealed an inhibitory effect on breast cancer metastasis of nobiletin, one of the interesting flavonoid compounds contained in *citrus sp.*, through *in vitro* and *in vivo* elucidation [28]. The results verified the safety and efficacy of metastasis inhibition by downregulating the ERK-STAT and JNK-c-JUN pathways, indicating the potential of nobiletin as an anticancer agent. From this analysis, it can be summarized that the research on citrus anticancer is increasingly directed toward exploring in depth specific compounds from citrus on their molecular pathways.

### 3.3 Analysis of Contributing Countries and Their Collaborations

The present study revealed that the top 10 countries with the most papers contributed to the growth of citrus anticancer research globally (Table 2). The selected articles (n = 442) came from 55 different countries. About 38% of publications were contributed by China and India, indicating that these two countries are key players in the progress of citrus anticancer research. With 91 papers, China was the most productive country, followed by India (n = 80) and South Korea (n = 68). Although China was the most productive country based on paper count, South Korea had a greater impact in terms of AC per paper (48.48), followed by Italy with an AC value of 32.53. The other 8 countries contribute

**Table 2.** Top 10 countries with the most papers.

| No. | Country | Number of papers | Number of citation | AC[1] per paper |
|---|---|---|---|---|
| 1 | China | 91 | 2263 | 24,87 |
| 2 | India | 80 | 1788 | 22,35 |
| 3 | South Korea | 68 | 1929 | 28,37 |
| 4 | United States | 61 | 2957 | 48,48 |
| 5 | Japan | 28 | 747 | 26,68 |
| 6 | Iran | 27 | 652 | 24,15 |
| 7 | Egypt | 26 | 691 | 26,58 |
| 8 | Taiwan | 22 | 607 | 27,59 |
| 9 | Italy | 17 | 553 | 32,53 |
| 10 | Saudi Arabia | 14 | 290 | 20,71 |

[1]AC: average number of citations

equally, with an AC value of ± 20. We then analyse the collaboration between countries with at least one publication in collaboration (Fig. 3a). China, India, the United States, and South Korea displayed a big bubble compared to other countries. The size of the bubble represents the number of publications, and the thickness of the line between countries indicates the strength of collaboration. From the visualization, China showed strong collaboration with the United States, and the United States showed equal collaboration with Taiwan. India was the top country with the most collaboration networks (19 countries), followed by the United States (15 countries). China and South Korea showed collaboration with a similar linkage of 12 countries. In the overlay visualization (Fig. 3b), the green bubbles displayed that China (average publication year 2018) was the most up-to-date country compared with South Korea (average publication year 2015), the United

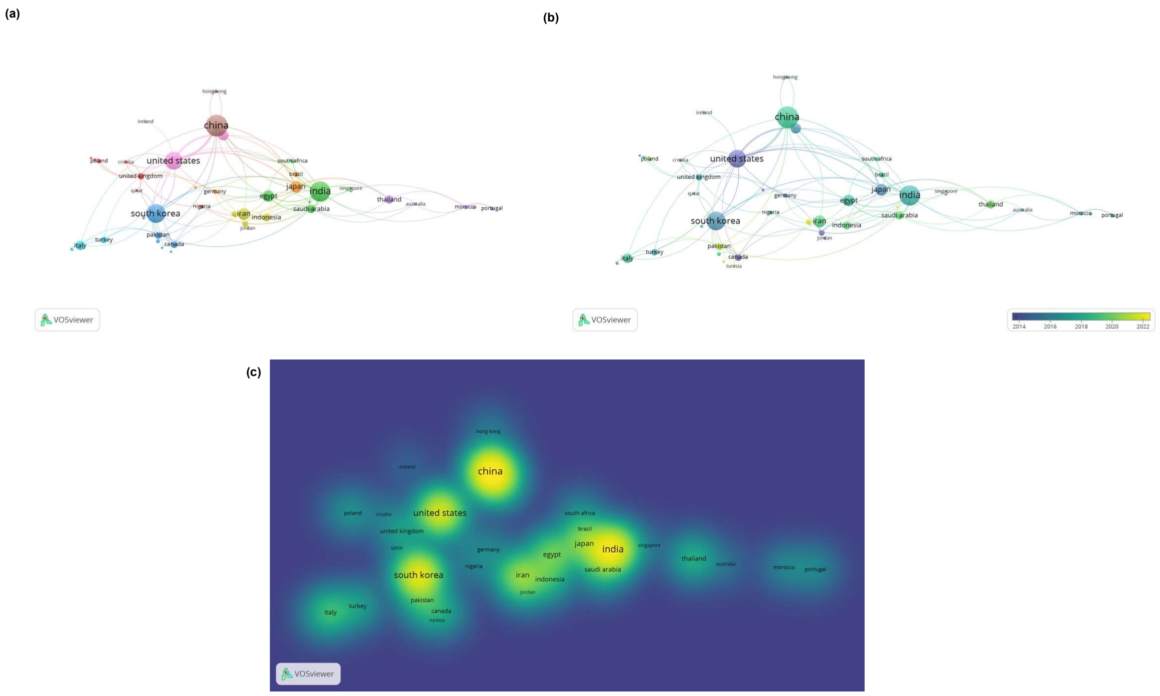


**Fig. 3.** Network visualization (a), overlay visualization (b), and item density visualization (c) of contributing countries.

States (average publication year 2014), and India (average publication year 2017) in publishing citrus anticancer research. These results are in line with item density visualization that showed China, India, the United States, and South Korea were the most productive countries with a large number of publications on this topic, indicated by a stronger yellow color intensity (Fig. 3c).

### 3.4 Institution Partnerships

A total of 442 selected papers were contributed by 160 institutions, which contain 1362 different organizations. A country can have several institutions, and an institution can consist of more than one organization. We summarized the top 10 institutions with the most papers and citations (Table 3). The most productive institution worldwide in citrus anticancer research was Jeju National University, which ranked as the top institution with 22 publications. This data correlated to the fact that Jeju Island was famous for its special citrus, the Jeju Tangerine and Jeju Mandarin [29]. Besides, Gyeongsang National University and Kyung Hee University from South Korea are in the third and fifth positions, respectively, and influenced 16 and 10 publications, respectively. In the second and fourth positions were Ruthers University-New Beunswick, United States, and the National Research Centre, Egypt, which contributed 19 and 12 publications, respectively. The other five institutions were China Medical University, the University of Madras, the University of Massachusetts Amherst, Texas A&M University, and Chiang Mai University, which contributed 10, 10, 9, 9, and 8 publications, respectively. Interestingly, tough contributed 9 publications, Texas A&M University ranked first with an AC value 64.78, indicates that their publication topics more influential and became a reference than other institutions. The publication of citrus anticancer research in 2014 from Texas A&M University demonstrated that obacunone, a unique compound from lemon seeds, inhibits estrogen-responsive breast cancer by activating apoptosis, aromatase enzymes, and inflammatory pathways [30]. Whereas Jeju National University, as the most productive institution, contributed their last papers in 2022 about the involvement of eriodictyol, a plant-derived flavonoid found in citrus fruits, in regulating phosphorylation of JNK, ERK, and FAK/AKT in SNU213 and Panc-1 pancreatic cell lines [31].

**Table 3.** Top 10 institutions with the most papers

| No. | Institutions | Country | Number of Papers | Number of Citations | AC[1] per paper | The title of the latest paper (year of publication) |
|---|---|---|---|---|---|---|
| 1 | Jeju National University | South Korea | 22 | 417 | 18,95 | Eriodictyol induces apoptosis via regulating phosphorylation of JNK, ERK, and FAK/AKT in pancreatic cancer cells (2022) |
| 2 | Ruthers University-New Beunswick | United States | 19 | 437 | 23,00 | Acetylation Enhances the Anticancer Activity and Oral Bioavailability of 5-Demethyltangeretin (2022) |
| 3 | Gyeongsang National University | South Korea | 16 | 590 | 36,88 | Pectolinarigenin induced cell cycle arrest, autophagy, and apoptosis in gastric cancer cell via PI3K/AKT/mTOR signaling pathway (2018) |
| 4 | National Research Centre | Egypt | 12 | 206 | 17,17 | Synthesis, characterization and cytotoxic activity of naturally isolated naringin-metal complexes (2019) |
| 5 | Kyung Hee University | South Korea | 10 | 323 | 32,30 | Hesperidin ameliorates benign prostatic hyperplasia by attenuating cell proliferation, inflammatory response, and epithelial-mesenchymal transition via the TGF-β1/Smad signaling pathway (2023) |
| 6 | China Medical University | Taiwan | 10 | 379 | 37,90 | Systematic analysis of the mechanism of aged citrus peel (Chenpi) in oral squamous cell carcinoma treatment via network pharmacology, molecular docking and experimental validation (2022) |
| 7 | University of Madras | India | 10 | 444 | 44,40 | Cytotoxic and apoptotic effect of citrus flavonoid naringin in treating pa-1 ovarian cancer cells (2020) |
| 8 | University of Massachusetts Amherst | United States | 9 | 375 | 41,67 | Identification of Xanthomicrol as a Major Metabolite of 5-Demethyltangeretin in Mouse Gastrointestinal Tract and Its Inhibitory Effects on Colon Cancer Cells (2020) |
| 9 | Texas A&M University | United States | 9 | 583 | 64,78 | Obacunone exhibits anti-proliferative and anti-aromatase activity in vitro by inhibiting the p38 MAPK signaling pathway in MCF-7 human breast adenocarcinoma cells (2014) |
| 10 | Chiang Mai University | Thailand | 8 | 221 | 27,63 | Sesame extract promotes chemopreventive effect of hesperidin on early phase of diethylnitrosamine-initiated hepatocarcinogenesis in rats (2021) |

[1]AC: average number of citations

According to the title of the most recent paper from the top ten institutions, hesperidin is a popular citrus flavonoid that has been explored for its anticancer activity. Hesperidin has been reported to attenuate benign prostate hyperplasia through the TGF-B1/Smad signaling pathway [32]. Nowadays, the study of anticancer drugs has reached the molecular mechanisms that are specifically targeted by compounds.

### 3.5 Assessment of Influential Authors

The 442 selected papers were contributed by 2125 authors from several organizations, institutions, or countries. The number of papers produced by an author reflects the author's contribution and engagement in this topic, as well as the contribution of the institution and country. Table 4 outlines the most prolific citrus anticancer authors from three countries, including the United States (1 author), South Korea (8 authors), and India (1 author). Interestingly, though China was crowned the most productive country with the most papers produced, China's authors were not included in the top ten productive authors. This can be explained by the possibility that, indeed, many authors from China published research on anticancer citrus, but they did not dedicate themselves to researching this topic totally and continually. The most productive author was Ho c.-t. from the United States, who contributed 15 papers. In second until ninth position, authors came from South Korea, named Kim g.s., Hong g.e., Kim g.e., Lee w.s., Lee h.j., Cho s.k., Ngappan a., and Choi y.h., each with 10, 9, 9, 9, 9, 9, 8, and 7 papers, respectively. The last author in the top ten list was Yumnam s. from India, who contributed seven papers. However, their latest papers were published before 2020, except for Ho c.-t., who published his latest paper in 2022. As the most productive author with the most papers produced, Ho c.-t. is also known to have the highest H-index value of 103. A high H-index value can indicate that the author was productive in producing papers and that the papers were highly cited by other papers.

The collaboration among the authors is visualized by the co-authorship analysis visualization generated from VOSviewer. The minimum number of documents for an author was one paper. Among 2125 authors, only 691 constituted the largest set of linked authors in 31 clusters (Fig. 4a). From the overall (Fig. 4b) and density (Fig. 4c) visualizations, we noted that most of the authors published their work between 2015 and 2022,

**Table 4.** Top 10 authors with the most papers

| No. | Author name | Country | H-index | Number of Papers | Number of Citations | AC[1] per paper | The title of the latest paper (year of publication) |
|---|---|---|---|---|---|---|---|
| 1 | Ho c. -t. | United States | 103 | 15 | 333 | 22,20 | Acetylation Enhances the Anticancer Activity and Oral Bioavailability of 5-Demethyltangeretin (2022) |
| 2 | Kim g.s. | South Korea | 32 | 10 | 378 | 37,80 | Pectolinarigenin induced cell cycle arrest, autophagy, and apoptosis in gastric cancer cell via PI3K/AKT/mTOR signaling pathway (2018) |
| 3 | Hong g.e. | South Korea | 16 | 9 | 293 | 32,56 | Korean Byungkyul -*Citrus platymamma* Hort.et Tanaka flavonoids induces cell cycle arrest and apoptosis, regulating MMP protein expression in Hep3B hepatocellular carcinoma cells (2017) |
| 4 | Kim e.h. | South Korea | 19 | 9 | 362 | 40,22 | Pectolinarigenin induced cell cycle arrest, autophagy, and apoptosis in gastric cancer cell via PI3K/AKT/mTOR signaling pathway (2018) |
| 5 | Lee w.s. | South Korea | 32 | 9 | 309 | 34,33 | Pectolinarigenin induced cell cycle arrest, autophagy, and apoptosis in gastric cancer cell via PI3K/AKT/mTOR signaling pathway (2018) |
| 6 | Lee h.j. | South Korea | 9 | 9 | 326 | 36,22 | Pectolinarigenin induced cell cycle arrest, autophagy, and apoptosis in gastric cancer cell via PI3K/AKT/mTOR signaling pathway (2018) |
| 7 | Cho s.k. | South Korea | 33 | 9 | 217 | 24,11 | Supercritical Fluid Extraction of *Citrus iyo* Hort. ex Tanaka Pericarp Inhibits Growth and Induces Apoptosis Through Abrogation of STAT3 Regulated Gene Products in Human Prostate Cancer Xenograft Mouse Model (2017) |
| 8 | Nagappan a. | South Korea | 21 | 8 | 274 | 34,25 | Proteomic analysis of selective cytotoxic anticancer properties of flavonoids isolated from *Citrus platymamma* on A549 human lung cancer cells (2016) |
| 9 | Choi y.h. | South Korea | 70 | 7 | 104 | 14,86 | The reactive oxygen species/AMP-activated protein kinase signaling pathway's role in the apoptotic induction of MCF-7 human breast cancer cells caused by the ethanol extract of *Citrus unshiu* peel (2018) |
| 10 | Yumnam s. | India | 17 | 7 | 235 | 33.57 | Korean Byungkyul -*Citrus platymamma* Hort.et Tanaka flavonoids induces cell cycle arrest and apoptosis, regulating MMP protein expression in Hep3B hepatocellular carcinoma cells (2017) |

[1]AC: average number of citations

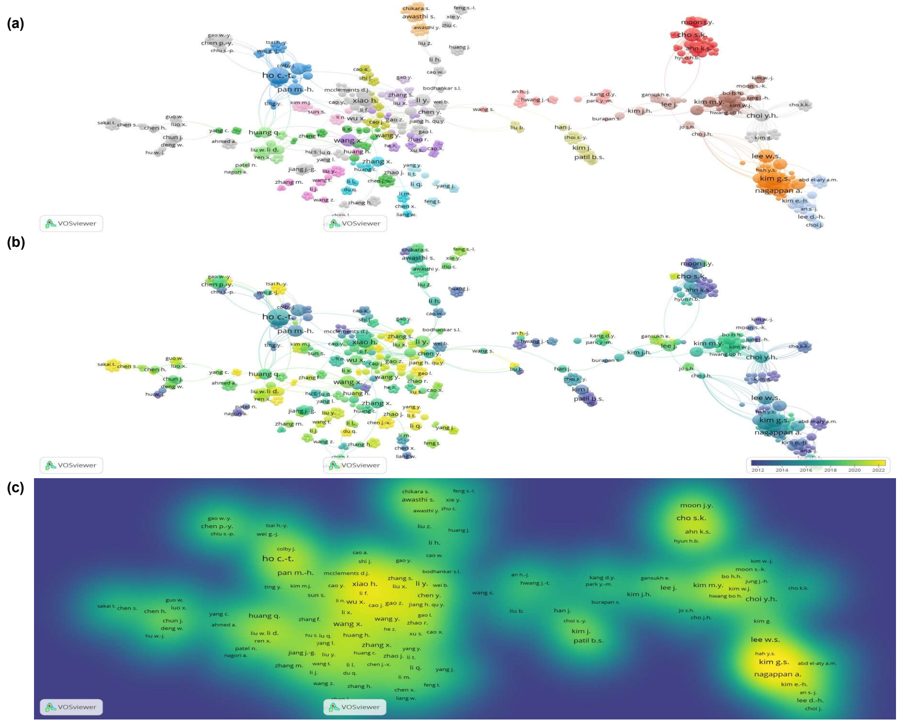

**Fig. 4.** Network visualization (a), overlay visualization (b), and item density visualization (c) of contributing authors.

and they had similar color density, which means that overall authors produced a similar number of articles. The most collaborative partner was Ho c.-t., displayed by the highest link strength of 64. The link strength reflects the number of papers co-authored by two authors. The latest publication from Ho c.-t. reported the effect of acetylation on 5-Demethyltangeretin's (5-DTAN) anticancer activity and oral bioavailability [33]. The acetylation contributed to G2/M phase arrest stimulation, cancer cell migration suppression, and a higher maximum concentration (Cmax) and area under the curve (AUC) in plasma. This research goes beyond the anticancer activity examination of natural flavonoids from citrus but goes more deeply into how structural modifications can be made to increase the anticancer activity. The latest papers from the top ten authors showed overall research in citrus anticancer had been done on various kinds of flavonoids, but none had led to formulation or clinical trials. This data showed a research gap: there was no research bridging citrus to be developed as a dosage form and directed to clinical trials.

### 3.6 Keywords Co-occurrence Analysis

The analysis of keywords from selected papers was conducted to find the common terms and guide researchers in identifying the most popular subjects. Only keywords that appear at least five times are used in this visualization (Fig. 5a–c). Out of a total of 1239 keywords, only 49 meet the threshold. The selected forty-nine keywords were grouped into six clusters, with 250 links and a total link strength of 450. "Apoptosis" appeared as the most frequent keyword co-occurrence, displayed as the largest bubble size, the stronger intensity of the bubble yellow color (Fig. 5c), and the highest link value of 36. As the keywords used as queries in this bibliometric analysis, "anticancer", "anticancer activity", and "citrus" occupy the second, eighth, and ninth positions in the top ten keywords (Table 5). This is possible because many publications directly mention flavonoid compounds, for example "hesperidin", "naringenin', nobiletin", "naringin", "tangeretin", and "hesperetin", rather than mentioning "citrus". From the visualization, it is also noted that the anticancer activity from citrus flavonoids has been done against "colon cancer", "gastric cancer", "lung cancer", "colorectal cancer", "breast cancer", and "prostate cancer". Anticancer parameters that have been widely studied include "apoptosis", "anti-inflammation", "antiproliferative", "cytotoxicity", "oxidative stress", -

**Table 5.** Top 10 authors' keywords with the most co-occurrences.

| No. | Keywords | Co-occurrences |
|---|---|---|
| 1 | Apoptosis | 74 |
| 2 | Anticancer | 31 |
| 3 | Flavonoids | 28 |
| 4 | Cytotoxicity | 22 |
| 5 | Hesperidin | 21 |
| 6 | Naringenin | 20 |
| 7 | Nobiletin | 20 |
| 8 | Anticancer activity | 20 |
| 9 | Citrus | 19 |
| 10 | Antioxidant | 16 |

**Table 6.** Top 10 most cited papers.

| No. | Authors | Number of Citations | Title | Brief of studies |
|---|---|---|---|---|
| 1 | So f.v. et al. (1996) | 449 | Inhibition of human breast cancer cell proliferation and delay of mammary tumorigenesis by flavonoids and citrus juices | Aims: To assess two citrus flavonoids, hesperetin and naringenin for their effects on proliferation and growth of a human breast carcinoma cell line, MDA-MB-435. Results: Citrus flavonoids are effective inhibitors of human breast cancer cell proliferation in vitro, especially when paired with quercetin, which is widely distributed in other foods. |
| 2 | Mathey j.a. et al. (2002) | 331 | Antiproliferative activities of citrus flavonoids against six human cancer cell lines | Aims: To demonstrate the antiproliferative property of synthetic methoxylated flavones against additional human cancer cell lines. Results: The strong antiproliferative activities of the polymethoxylated flavones suggest that they may have use as anticancer agents in humans. |
| 3 | Morley k.l. et al. (2007) | 201 | Tangeretin and nobiletin induce G1 cell cycle arrest but not apoptosis in human breast and colon cancer cells | Aims: To evaluate the antiproliferative activity of tangeretin and nobiletin against human breast cancer cell lines MDA-MB-435 and MCF-7 and human colon cancer line HT-29. Results: Tangeretin and nobiletin could be effective cytostatic anticancer agents. Inhibition of proliferation of human cancers without inducing cell death may be advantageous in treating tumors as it would restrict proliferation in a manner less likely to induce cytotoxicity and death in normal, non-tumor tissues. |
| 4 | Hirano t. et al. (1995) | 191 | Citrus flavone tangeretin inhibits leukaemic HL-60 cell growth partially through induction of apoptosis with less cytotoxicity on normal lymphocytes | Aims: To observe the apoptosis induction of tangeretin. Results: Tangeretin inhibits growth of HL-60 cells in vitro, partially through induction of apoptosis, without causing serious side-effects on immune cells. |
| 5 | Zygmunt k. et al. (2010) | 182 | Naringenin, a citrus flavonoid, increases muscle cell glucose uptake via AMPK | Aims: To examine the direct effects of naringenin on skeletal muscle glucose uptake and investigated the mechanism involved. Results: Naringenin increases glucose uptake by skeletal muscle cells in an AMPK-dependent manner. |
| 6 | Poulose s.m. et al. (2005) | 161 | Citrus limonoids induce apoptosis in human neuroblastoma cells and have radical scavenging activity | Aims: To evaluate the apoptosis induction of citrus lumonoids and its radical scavenging activity. Results: Citrus limonoid glucosides are toxic to SH-SY5Y cancer cells through apoptosis by an as yet unknown mechanism of induction. Individual limonoid glucosides differ in efficacy as anticancer agents, and this difference may reside in structural variations in the A ring of the limonoid molecule. |
| 7 | Dudai n. et al. (2005) | 145 | Citral is a new inducer of caspase-3 in tumor cell lines | Aims: To investigate the anti-cancer potential of citral and its mode of action. Results: Citral induced apoptosis, accompanied by DNA fragmentation and caspase-3 catalytic activity induction. The apoptotic effect of citral depended on the α,β-unsaturated aldehyde group. |
| 8 | Chen j. et al. (1997) | 143 | Two New Polymethoxylated Flavones, a Class of Compounds with Potential Anticancer Activity, Isolated from Cold Pressed Dancy Tangerine Peel Oil Solids | Aims: To isolate citrus compounds and determined their biological activity. Results: Compounds II and VII are novel natural products; compounds IV, V, and VIII have been reported with significant activity against various strains of carcinoma cells; and compounds I and IV decrease erythrocyte aggregation and sedimentation in vitro. |
| 9 | El-Readi m.z. et al. (2010) | 128 | Inhibition of P-glycoprotein activity by limonin and other secondary metabolites from Citrus species in human colon and leukaemia cell lines | Aims: To investigate the effects of nine naturally occurring compounds isolated from *Citrus jambhiri* Lush and *Citrus pyriformis Hassk* (Rutaceae) for their potential to modulate the activity of P-gp in the multidrug-resistant human leukaemia cell line CEM/ADR5000. Results: The isolated Citrus compounds could be considered as good candidates for the development of novel P-gp/MDR1 reversal agents which may enhance the accumulation and efficacy of chemotherapy agents. |
| 10 | Celia c. et al. (2013) | 126 | Anticancer activity of liposomal bergamot essential oil (BEO) on human neuroblastoma cells | Aims: To evaluated the BEO liposomes on their anticancer activity in vitro against human SH-SY5Y neuroblastoma cells. Results: The results warrant further investigation of BEO liposomes for in vivo applications. |

[1]AC: average number of citations

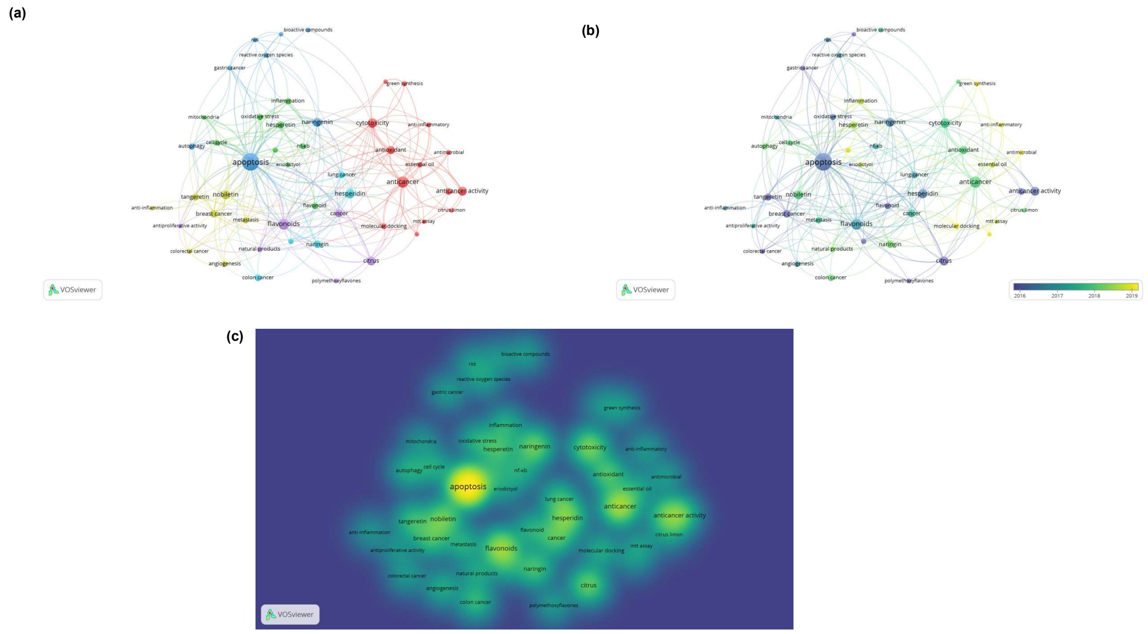

**Fig. 5.** Network visualization (a), overlay visualization (b), and item density visualization of authors' keywords co-occurrence

"autophagy", "cell cycle", "antioxidant", "metastasis", and "angiogenesis", as well as exploration using "molecular docking". All the selected author's keywords in visualization (Fig. 5b) tend to start being used around 2015. Topics marked in blue bubbles were popular at the start of around 2015, and topics marked in green bubbles were more popular between 2017 and 2018. In the year around 2019, topics in yellow bubbles dominated.

The terms "nanoparticle", "ultrasound", and "green synthesis", indicate that the citrus anticancer research also led to single compound development that focused on drug-delivery systems and advanced biotechnological approaches. From these findings, exploration of drug-delivery strategies may have future research promise in terms of enhancing molecular bioavailability[34, 35]. *In vivo* preclinical and clinical investigations can follow the drug-delivery strategy to elaborate on this specific issue.

### 3.7 Most Cited Papers

Among 442 selected citrus anticancer papers, we figured out the top ten most cited papers. The top 10 most-cited papers received 126 to 447 citations, with an average of 205.7 (Table 6). Only three papers from the top ten list were published after 2010. The most cited paper by So f.v. et al., [36] with 447 citations, was the oldest paper among the top 10. The research investigated the breast cancer suppression of orange juice and citrus flavonoids using *in vitro* and *in vivo* experiments. The results provide evidence of the anticancer properties of common fruits and orange juice, which contain several flavonoids that are effective inhibitors of cancer proliferation. The latest papers from the top 10 list were published by Celia c. et al., [37] and reported the anticancer properties of liposomal bergamot essential oil against human neuroblastoma cells. This finding showed that the formulation of citrus flavonoids or extracts to overcome physical and chemical limitations, such as poor water solubility, stability, and limited bioavailability, had been increasingly explored.

### 3.8 Top 10 citrus compounds

**Table 7.** Top 10 citrus compounds explored

| No. | Compounds |
|---|---|
| 1 | Hesperidin |
| 2 | Naringenin |
| 3 | Nobiletin |
| 4 | Naringin |
| 5 | Tangeretin |
| 6 | Hesperetin |
| 7 | Polymethoxyflavones |
| 8 | Pectin |
| 9 | Didymin |
| 10 | Diosmin |

We figured out the top ten explored citrus compounds to elucidate what the most promising compound is to develop as an anticancer agent [38]. Table 7 displayed that hesperidin, naringenin, and nobiletin were compounds widely explored as anticancer agents. The latest publication reported that hesperidin ameliorates benign prostatic hyperplasia through the TGF-β1/Smad signaling pathway [32]. Indeed, numerous studies have also highlighted the potency of hesperidin as an anti-breast cancer candidate, especially as a co-chemotherapeutic agent [26]. On the other side, naringenin and nobiletin, as an aglycon flavonoid from hesperidin, are also used as a co-adjuvant strategy in breast cancer [39]. Though not as deeply studied as the three compounds previously mentioned, the other citrus compounds have received greater attention in isolation and have been extensively explored for pharmacological activities besides anticancer.

### 3.9 Top 10 citrus species

**Table 8.** Top 10 citrus species explored

| No. | Species |
|---|---|
| 1 | *Citrus aurantifolia* |
| 2 | *Citrus limon* |
| 3 | *Citrus hystrix* |
| 4 | *Citrus reticula* |
| 5 | *Citrus sinensis* |
| 6 | *Citrus maxima* |
| 7 | *Citrus unshiu* |
| 8 | *Citrus limetta* |
| 9 | *Citrus bergamia* |
| 10 | *Citrus platymamma* |

Over 1000 species of citrus fruits grew all over the world, enriched with numerous kinds of hybridization results [21]. Despite the wide variety of citrus cultivars that are commercially accessible, the facilitation of resource allocation would be enhanced. However, it is essential to address this issue with particular attention due to the inherent diversity of their chemical constituents. We found out the top ten citrus species that have been extensively investigated for their pharmacological activities, including anticancer. Citrus aurantifolia, or key lime, is reported to be the most favorite species for anticancer research. The phytochemical composition of many different species would exhibit an appealingly consistent form, yet the proportions would vary. It serves to point out the importance of making precise determinations in research as a way to ensure the comprehensiveness and accuracy of the database [40].

## 4 Discussion

A bibliometric method was utilized in this study to examine the available literature on citrus anticancer, find trends in cancer research, and embark on a research agenda for the next few decades. Furthermore, this method analyzes authorship, article keywords, citations, and co-citations, which is a critical subject. The citation trend analysis enables us to comprehend how the subject of interest is related to other study areas [41]. Citations have long been used to assess the usefulness of a research work. Citation reflects a paper's academic value and the extent to which it is acknowledged by other academics. A bibliometric research essay differs from a review article in that it focuses on the most recent progress, challenges, and likely future directions of a certain field [42]. This goal has the ability to increase awareness as well as progress in the field of research. This study provides an in-depth examination of the anticancer properties of citrus and appeared as a research article in journals included in the Scopus database. Despite the fact that there are several review papers on the issue, there are no instances of bibliometric analysis in the literature. According to the findings, published research on citrus anticancer countermeasures began in 1995 and will continue through 2023. This study has been ongoing since 1995. The number of publications has steadily increased over the last five years, although this trend has not yet reached its pinnacle. In 2022, there was a slight decrease in the number of publications, which might be attributed to the COVID-19 pandemic [43] and the fact that the bulk of research is focused on immunotherapy [44]. If there is no compromise in investigating the mechanism of action, then the lack of research related to citrus anticancer may be attributed to the difficulty in developing anticancer drugs from natural components owing to the diversity of chemicals contained in citrus. Obtaining pure single-use chemicals from natural sources requires tremendous work and incurs major financial expense. In reality, in order for these substances to be transformed into pharmaceuticals, they must be produced in large quantities. As a consequence, efforts will be necessary in the future, from synthesis through formulation.

In a trend-topic scan, initial research was focused on crude extract [45, 46], total flavonoids [47], and cytotoxicity [25], but now it is focused more on single compounds, deeper mechanisms, and prospective action for overcoming physico-chemical limitations and improving anticancer properties, such as biosynthesized **[48–50]**, micronized [51, 52], and nanoformulation **[53–55]**. Research on citrus anticancer will continue to gain traction in the coming years because there are still many opportunities to reach as a result of this growth. Still, the research on citrus anticancer still stacks on the targeted mechanism exploration, and no compound continues to be clinically tested in humans. From these findings, we noted that there are no authors, organizations, or countries that are constantly focused on research on citrus anticancer. The most persistent author was Ho c.-t. from the United States, who focused on tangeretin's development as an anticancer candidate. The latest publication demonstrated the structure modification of tangeretin with acetylation to enhance its bioavailability *in vivo* as well as increase its anticancer properties [33]. Structure modification can be done to improve the physical and chemical limitations of natural compounds. It is different in formulation but has the same objectives. Structure modification would facilitate the dosage formulation and design of synthesis so that efficacy can be achieved with minimal cost.

In a bibliometric mapping, keywords may give immediate details on topics, emerging topics, and the core subject of research. Word analysis may reveal the topics on which a given research project focuses [56]. Apoptosis, anticancer, flavonoid, citrus, hesperidin, naringenin, tangeretin, and nobiletin were the most frequently used terms in our investigation during the previous decade. The bulk of these keywords were found in the center of a word network and were significant as core terms. Apoptosis has been recognized as an essential term since the majority of citrus flavonoid mechanisms as anticancer agents induce apoptosis. Then, we may use the general search phrase "citrus flavonoid" since the most often used terms in the recent decade may be selected by researchers to obtain citrus anticancer studies in this field. In our study, we evaluated the course of time to identify the keywords with the most citation bursts in the word network. Year-by-year trends in citrus anticancer research are revealed by keywords with high citation counts. Between 2016 and 2017, in the case of citrus flavonoid, the word hesperidin was used the most. Positive developments in citrus anticancer research over the past five years indicate the direction of the trend for citrus flavonoids in the field of structural modification. Further research can be directed toward in-depth exploration related to selectivity and efforts to improve compound limitations to be developed in dosage formulation, followed by in vivo preclinical and clinical studies.

At the end, citrus showed promising potential as anticancer agent, especially hesperidin, naringenin, and nobiletin. The challenges of the development of citrus as an anticancer candidate is also related to the many species that exist in the world, but it will give big advantages that people are presented with a powerful, high-value resource to be consumed daily. Indeed, for anticancer treatment, it needs a single compound to be isolated, purified, and established its mechanism of action with selective, effective, and targeted. From this bibliometric mapping, future direction of the research on citrus anticancer would-be developing dosage formulation to increase the chemical and biological effectivity. This study's limitations should be considered when evaluating results. We used Scopus database for relevant papers and did not examine items in non-Scopus journals. Another important factor is selecting research articles over conference papers, book chapters, reviews, etc. Despite these limitations, these studies contribute to citrus anticancer research mapping and provide basic understanding for the research gap and future direction of anticancer exploration.

## 5 Conclusion

This study gives significant data on the overall number of publications from 1995 to 2023 in the field of citrus anticancer research. There has been a rising tide of publications on the subject, especially after 2017. The examination of recent trends in the field of citrus anticancer demonstrates that scientists have been paying greater attention to the role of a certain flavonoid chemical in cytotoxicity, cell cycle, apoptosis, autophagy, and metastasis. The most fruitful countries are China and India, and the journal "Molecules" has the most articles on citrus's anticancer properties. The investigation has also uncovered the top institutions and emerging trends in the field.

Overall, the synthesis and formulation of citrus flavonoids (specific citrus compound), as well as *in vitro* preclinical trials, have advanced citrus anticancer research and became the future perspective of citrus anticancer. More clinical trials are required to determine the optimal dose of citrus flavonoids for treating cancer as well as address any safety issues that may arise from using these compounds. As an anticancer drug, citrus flavonoid still warrants investigation into its formulation technique, followed by *in vivo* preclinical and clinical studies.

At the end, research collaboration between leading countries and top journals in the publication of scientific articles on citrus anticancer research is urgently needed to speed up the research progress. Through publication on a relevant academic impact and thus establish an important channel to promote studies for the development of citrus anticancer research.

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## 7 Conflict of Interest

The authors have no conflict interest to disclose.

## 8 Ethical Approvals

This study does not involve experiments on animal or human subjects.

## 9 Author Contribution

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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