Critical Reviews™ in Oncogenesis 23(5-6) 347–370 (2018)

Molecular Responses of Cancers by Natural Products: Modifications of Autophagy Revealed by Literature Analysis

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ABSTRACT: Although numerous bibliometric studies have examined various aspects of cancer research, the landscape of scientific studies focusing on natural products in cancer research has not been characterized. Using the Web of Science Core Collection online database, we identify and analyze scientific articles on natural products in cancer-related research. English is the language of publication for 99% of articles. In general, annual citation count of an article increases quickly after publication, reaches a plateau in the second year, stays in this plateau for 10 yr, and then begins to fall. The five most contributing journal categories are medicinal chemistry, contributing the most at 1890 articles (24% of 8012 articles); oncology (20%, with 1572 articles); pharmacology and pharmacy (19%, with 1557); biochemistry and molecular biology (15%, with 1225); and plant sciences (11%, with 883 articles). The United States and Spain yield a larger number of articles with high average citations, and China has been increasing since 2009. Apoptosis and cytotoxicity are the two most-frequently used keywords. Effects of natural products on autophagy with a relevance to cancer are mentioned in 69 publications. Our literature analysis reveals a dynamically evolving landscape and an increasing volume of research investigations that are focused on the study of natural products in the context of cancer. Curcumin, flavonoids, and resveratrol are the most-frequently mentioned natural products. Cancer of the breast, prostate, and colon are the most-frequently mentioned cancers.

KEY WORDS: autophagy, bibliometric, cancer, citation analysis, natural product, jasplakinolide, phytochemical

I. INTRODUCTION

Bibliometric studies using citation analysis and identification of most-cited articles enable readers to quickly understand the overall publishing landscape of a selected body of research, thus providing a general understanding of scientific impact.[1–4] In cancer research, bibliometric studies have reported on the impact of public policy regarding cancer research output and collaborations,[5] most-frequent types of cancers published,[6] and publishing trends of cancer molecular epidemiology[7] and cancer rehabilitation.[8] Recently, quantitative and qualitative assessments of scientific output have become more important as established methods for research policy decisions and for identification of the most relevant works in the booming literature.[9]

Currently, many natural products are already used in anticancer drugs or studied for potential cancer therapies.[10–13] However, the research landscape of natural products studied in the context of cancer investigations has remained largely unknown. Therefore, the current study aims to evaluate the existing literature on natural products in cancer research, discussing in particular most-contributing entities, popular research topics, and citation trends of highest-cited articles.

II. MATERIALS AND METHODS

We obtained bibliometric information of research reports from the online version of Science Citation Index Expanded (SCI-EXPANDED) databases in the Web of Science Core Collection of Clarivate Analytics (formerly known as Thomson Reuters and Institute for Scientific Information [ISI]). To identify natural-product research in cancer-related research reports, the keywords natural product, natural products, natural compound, natural compounds, natural molecule, natural molecules, phytochemical, phytochemicals, phytochemically, secondary metabolite, and secondary metabolites, in co-occurrence with cancer, cancers, cancerous, cancerogenesis, cancerogenic, malignant tumor, malignant tumors, malignant tumour, malignant tumours, malignant neoplasm, malignant neoplasms, adenomatous, adenoma, adenomas, carcinomoid, carcinoma, carcinomas, carcinomatous, carcinomatosis, onco, sarcoma, sarcomas, melanoma, melanomas, lymphoma, lymphomas, leukaemia, leukaemias, leukemia, and leukemias. All were searched in terms of topic (including title, abstract, author keywords, and *KeyWords Plus*) within publication years 1991 through 2016 based on SCI-EXPANDED (updated March 27, 2018). In total, we found 14,796 documents relating to natural-product research in cancer. We downloaded bibliometric information for all documents into Microsoft Excel 2016 spreadsheets and manually performed additional coding and filtering.[14,15] Once data were downloaded, we carried out another operation to exclude extraneously downloaded documents that might not be related to natural-product research in cancer but were included through the algorithm. We did this because *KeyWords Plus* supplied additional search terms extracted from article titles cited by authors in their bibliographies and footnotes in the ISI (now Clarivate Analytics) database, substantially augmenting title-word and author-keyword indexing. As a result, the search included articles that had little or no relevance to natural-product research in cancer.[15] Because the online version of Web of Science does not allow keyword searches without including *KeyWords Plus*, another filter, so-called "front page" criteria, was used.[16] This identified articles with topic keywords appearing on the article's front page, that is, article title, abstract, and author keywords. Articles that appeared only in *KeyWords Plus* searches were excluded. Finally, 10,367 documents (70% of 14,796 documents) related to natural-product research in cancer were defined.

In this research, we used country affiliation as an indicator. To ensure accuracy of the country's affiliation downloaded information required additional reclassification before it could be used for analysis. Due to changes in country or institution names over the years, we reclassified affiliations in England, Scotland, Northern Ireland, and Wales as being from the UK. Affiliations in Hong Kong were included in the China category, and affiliations in Czechoslovakia were classed in Slovakia.

Authorship information required editing before analysis as well. In the SCI-EXPANDED database, corresponding author was named as reprint author, but in this study, we used the term corresponding author. Only the first corresponding author was considered. When downloaded directly from Web of Science, in articles with only a single author, the institution's affiliation of the first author could be left blank in the downloaded database, possibly leading to underestimate first-authored articles. To resolve the problem, for a single-institution article, we reclassified the corresponding author's institution as the first author's institution as well.[17] In articles with multiple authors, in which first author and corresponding author were the same person, the author's institution affiliation could be misplaced. The affiliation information, thus, was rechecked manually to ensure accuracy.

We extracted journal impact factors (IF_{2016}) from *Journal Citation Reports* that were published in

2016, and six bibliometric indicators (total articles, independent articles, collaborative articles, first-authored articles, corresponding-authored articles, and singly authored articles) were tabulated.[18] Contributions from different institutions and countries were estimated by affiliation of at least one publication author. We determined collaboration type by author addresses, where the term single-country article was assigned if the researchers' addresses originated from the same country. The term internationally collaborative article was designated to those articles that were coauthored by researchers from multiple countries. The term single-institution article was assigned if all authors' addresses were from the same institution. The term interinstitutionally collaborative article was assigned if authors were from different institutions.

In addition to overall analysis, we specifically focused on effects of natural products on autophagy. As example of this is natural products that may have potential anticancerous properties. Thus, we searched included publications to analyze publication subgroup that had autophagy or autophagic in their author's keywords.

III. RESULTS AND DISCUSSION

A. Document Type and Language of Publication

We defined TC_{year} as the number of citations from the Web of Science Core Collection that referred to articles published to the end of the most recent year.[19,20] This indicator totals citations to be a constant that can be checked and reproduced. In addition, we calculated citations per publication ($CPP_{year} = TC_{year}/TP$).[14] Relationships between document types and citations per publication were evaluated.[21]

Table 1 shows characteristics of 14 document types, including 8013 articles (77% of the 10,367 documents) with the number of authors per publication (APP) of 6.3. This is larger than any other documents and citations per publication (CPP_{2016}) of 23. However, a review entitled *Designing a broad-spectrum integrative approach for cancer prevention and treatment*[22] had the largest number of authors (180). Documents of the type "notes" had the highest CPP_{2016} of 122, which could be attributed to the note entitled *Jasplakinolide, a cytotoxic natu-*

TABLE 1: Characteristics of 14 document types

Document type	TP	TP*	%	AU	APP	TC_{2016}	CPP_{2016}
Article	8013	8012	77	50,414	6.3	182,250	23
Review	2014	2014	19	7705	3.8	94,442	47
Proceedings paper	336	336	3.2	1315	3.9	17,637	52
Meeting abstract	230	230	2.2	1009	4.4	37	0.16
Editorial material	74	74	0.71	171	2.3	1753	24
Book chapter	51	51	0.49	169	3.3	1705	33
Letter	9	9	0.087	33	3.7	34	3.8
Correction	8	8	0.077	29	3.6	2	0.25
News item	8	7	0.077	8	1.1	3	0.38
Note	6	6	0.058	30	5.0	731	122
Retracted publication	4	4	0.039	23	5.8	62	16
Biographical item	2	2	0.019	2	1.0	0	0
Reprint	2	2	0.019	2	1.0	156	78
Book review	1	1	0.010	1	1.0	0	0

APP, Number of authors per publication; AU, number of authors; CPP_{2016}, number of citations per publication ($CPP_{2016} = TC_{2016}/TP$); TC_{2016}, number of citations from Web of Science Core Collection since publication to the end of 2016; TP, total number of publications; TP*, total number of publications with author information in Web of Science.

ral product that induces actin polymerization and competitively inhibits the binding of phalloidin to F-actin,[23] with a TC_{2016} of 553. The average number of authors per article increased from 4.3 in 1991 to 7.1 in 2016.

Original articles were used for further analysis because they included original research ideas and results.[24] Of the 8013 articles, 99% were published in English. Several other languages also appeared: Chinese (13 articles), Portuguese (11), German (ten), Japanese (nine), Spanish (eight), Polish (five), French (five), Italian (two), and one each in Serbian and Turkish.

B. Article Citation Profile

For the 8013 articles that dealt with natural products in cancer research, we examined history of citations with CPP_{year} by article life. Overall, CPP_{2016} increased quickly after publication, reached a plateau in the second full year, and then stayed stable for 10 yr before decreasing; meanwhile, the fifth full year was the peak year, with the number of citations per publication at 4.6 (Fig. 1). Number of citations per year reached a maximum in a plateau 3–7 yr after publication, whereas a general maximum occurred at 2–3 yr.[25] Depending on research discipline, citation peak may be achieved at a slower rate, for example, during the third year in aerosol research,[26] fourth year in environmental law research,[27] fifth year in ocean circulation research,[28] and sixth year in contingent valuation research.[15] This current analysis suggests that articles dealing with natural products in cancer research may have prolonged scientific impact in terms of their being consistently cited by subsequent studies for an entire decade.

C. Analysis of Citation Trends

Figure 2 shows the distribution of 8013 articles dealing with natural products in cancer research and their citations per publication (CPP_{2016}). Annual output of research articles increased slowly from 27 articles in 1991 to 223 in 2006. After that, a sharper increase occurred and a peak was reached at 1067 articles in 2016. In particular, during 1992, which showed 21 articles and the highest CPP_{2016} of 129, this high CPP_{2016} was attributed to two frequently

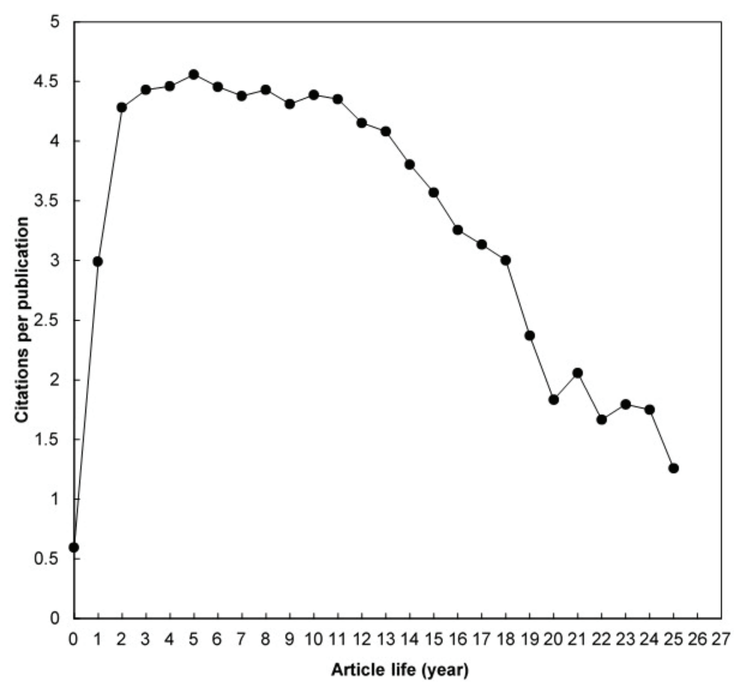

FIG. 1: Citations per publication by article life of natural products in cancer research

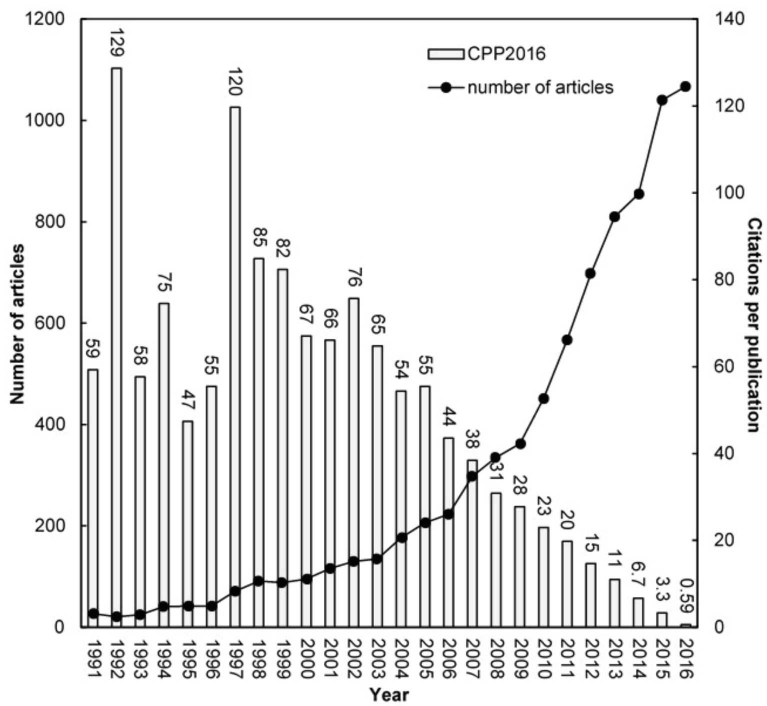

FIG. 2: Annual number of articles and citations per publication (CPP_{2016}) by year

cited articles, entitled *Modulation of activity of the promoter of the human* MDR1 *gene by Ras and p53*[29] and Fusarium moniliforme *and fumonisins in corn in relation to human esophageal cancer in Transkei,*[30] with TC_{2016}s of 752 and 513, respectively. In general, citation frequency is highly correlated with length of time since publication; newly published papers require time to accumulate citations.[31] According to what can be seen in Fig. 2, it takes CPPs about a decade to reach a plateau, similar to other evaluated scientific fields.[32,33] Therefore, we recommend that evaluating article impact should occur after citations have accumulated for at least one decade.[14] Chuang and Ho[32] concluded that regardless of the year of data, all articles show an approximate 10-yr period between time of data collection and peak output of highly cited papers. Therefore, it was reasonable to find a total of 5551 articles dealing with natural products in cancer research (69% of 8013 articles) that had no citation during the year of publication ($C_0 = 0$). Although an increasing number of journals have appeared in SCI-EXPANDED, the articles have actually had higher amounts of citations in the publication year during recent years.[18] This is consistent with current findings showing that among the top 100 articles in C_0, only 14% and 15% were among the top 100 articles in TC_{2016} and C_{2016}, respectively.

D. Web of Science Categories and Journals

As mentioned above, a total of 8013 analyzed articles were published in journals listed in SCI-EXPANDED that were distributed in 123 Web of Science subject categories. In total, 5088 articles (64% of 8012 articles with Web of Science information) were published in five categories including medicinal chemistry with 60 journals, contributing to the most articles (1890 or 24% of 8012 articles), oncology with 217 journals (1572 or 20% of 8012 articles), pharmacology and pharmacy with 256 journals (1557 or19%), biochemistry and molecular biology with 286 journals (1225 or 15%), and plant sciences with 211 journals (883 or 11%). It should be noticed that journals could be classified in two or more categories in the Web of Science, for instance, *Journal of Natural Products* was listed in categories of plant sciences, medicinal chemistry, and pharmacology and pharmacy; thus, the sum of percentages is higher than 100%. To understand the interactions among Web of Science categories, distribution of subject categories for a research topic was studied using a trend figure.[34] Figure 3 shows the number of publications per year from the top five categories. Publications high in the category of oncology can be found in earlier years but ranked third since 2011. Conversely, medicinal chemistry started gaining momentum recently and has been ranked highest since 2011. Plant sciences may be a new category for natural-product studies in the context of cancer research. An article entitled *Horseradish peroxidase: A modern view of a classic enzyme*[35] published in the category of plant sciences was one of the highest-impact articles, with a C_{2016} of 61 and a rank of ninth.

In total, the 8013 articles were published in a wide range of 1231 journals in SCI-EXPANDED. Among these, 558 journals (45% of 1231 journals) contained only one article, 219 (18%) contained two, and 88 (7.1%) contained three. A total of 7785 articles were published in 1128 journals, with IF_{2016} information, and 228 articles were published in 103 journals that had no IF_{2016}. Six journals published more than 100 articles on natural products in cancer research. *Phytochemistry Letters*, with an IF_{2016} of 1418, published the most articles with 220 (2.7% of 8013 articles), followed by *PLoS One* with an IF_{2016} of 2.806 (195; 2.4%), *Journal of Natural Products* with an IF_{2016} of 3.281 (178; 2.2%), *Bioorganic & Medicinal Chemistry Letters* with an IF_{2016} of 2.454 (161; 2.0%), *Bioorganic & Medicinal Chemistry* with an IF_{2016} of 2.930 (147; 1.8%), and *Journal of Agricultural and Food Chemistry* with an IF_{2016} of 3.154 (122; 1.5%). The percentage of the top productive journals in natural products in cancer research was low, with only 2.7%, indicating the breadth of article distribution as well as the broad interest in natural products in cancer research from various research angles such as substance abuse, psychiatry, clinical psychology, and public, environmental, and occupational health areas. The

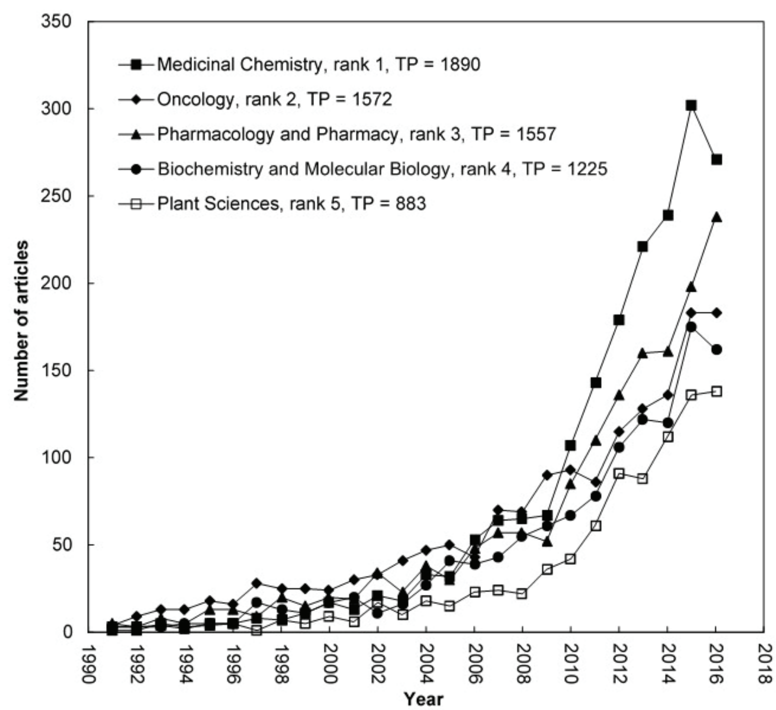

FIG. 3: Comparison of development trend for the top five categories

journal with the highest IF_{2016} was *Journal of the American Medical Association* with one article (IF_{2016} = 44.405), followed by *Nature Biotechnology* with two articles (IF_{2016} = 41.667), and *Nature* with eight articles (IF_{2016} = 40.137). In addition, the top article with TC_{2016} and C_{2016} was published in *Science* (IF_{2016} = 37.205).

E. Country and Institution

We applied six publication indicators[18, 24] including total publications (TP), independent publications (IP), collaborative publications (CP), first-authored publications (FP), corresponding-authored publications (RP), single-authored publications (SP), and number of citations per publication (CPP_{2016} = TC_{2016}/TP) to compare publications of countries and institutions, respectively. It is generally accepted that the first author is the person who contributes most to the work/writing of the article.[36] Corresponding-author responsibilities include supervision of study planning and execution, along with writing .[37] At the institutional level, the determined institution of the corresponding author might be the home base for the study or the origin of the paper.[38]

The Web of Science had six articles without affiliations. Of 8007 articles with author affiliations from 120 countries, 5897 (74% of 8007 articles) were single-country articles from 78 countries, and 2110 (26%) were internationally collaborative articles from 116 countries. The top 20 countries published at least 100 articles and are listed in Table 2 with the six publication indicators and citation indicator. Six European countries, nine Asian countries, three American states, and one for each of Oceania and Africa were ranked in the top 20 of publications. The US dominated all six publication indicators, whereas Spain and the US had higher CPP_{2016}, of 41 and 40, respectively. Spain had the highest CPP_{2016}, which can be attributed to the article entitled *Cancer chemopreventive activity of resveratrol, a natural product derived from grapes*[39] by authors from Spain and the UK, ranking at the top in both TC_{2016} and C_{2016} with 3187 and 151, respectively.

The top eight countries by number of articles from 1991 to 2016 are shown in Fig. 4. It is clear that the US dominated the natural products in cancer research publishing landscape from 1991 to 2013, showing the greatest counts of publications in the world, followed distantly by other countries. After 2009, China presented a rapid growth rate and caught up to the US in 2017. China could potentially dominate the number of publications in natural product in cancer research in the future. However, China held a low CPP_{2016} of 11, much lower than that of Spain (CPP_{2016} = 41), the US (40), the UK (34), Japan (25), Canada (25), Switzerland (25), and France (20) (Table 2). In addition, India also displays a sharp increasing trend after 2010, but it also had a low CPP_{2016} of 10.

Of the 8007 articles with author addresses in SCI-EXPANDED, 2848 articles (36% of 8007 articles) were institute-independent articles and 5159 (64%) were interinstitutionally collaborative articles, including 2110 (41% of 5159 articles), which were international collaborations, and 3049 (59%), which were national collaborations. The top ten institutions are listed in Table 3. Among these, six derived from the US, and one each came from China, Germany, South Korea, and Taiwan, respectively. Two of the ten institutions are nonuniversity institutions, and others are universities. Results in Table 3 demonstrate that nonuniversity institutions such as the Chinese Academy of Sciences in China and the National Cancer Institute in the US had strong collaborative relationships with other institutions in the scientific area of natural products in cancer research. A bias appeared in the Web of Science Core Collection because the Chinese Academy of Sciences has more than 100 branches in different cities. Seoul National University in South Korea and the University of Illinois in the US published the same number of articles. The University of Illinois also published the most institutional-independent articles. The Institute of Food Research in the UK published the most single-author articles, with six. Okezie I. Aruoma from OICA International, West Indies Associated States, and King's College London in the UK published the most-frequently cited single-author article, entitled *Free radicals, oxidative stress, and antioxidants in human health and disease*,[40] with a TC_{2016} of 617.

TABLE 2: Twenty most-productive countries (TP ≥ 100)

Country	TP	TPR (%)	IPR (%)	CPR (%)	FPR (%)	RPR (%)	SPR (%)	CPP_{2016}
USA	2666	1 (33)	1 (30)	1 (44)	1 (27)	1 (27)	1 (41)	40
China	1377	2 (17)	2 (16)	2 (20)	2 (15)	2 (15)	6 (3.4)	11
India	590	3 (7.4)	3 (7.3)	8 (7.6)	3 (6.3)	3 (6.3)	12 (1.3)	10
South Korea	488	4 (6.1)	4 (5.8)	9 (6.9)	4 (5.2)	4 (5.4)	6 (3.4)	18
Germany	485	5 (6.1)	7 (3.3)	3 (14)	5 (4.3)	5 (4.4)	3 (6.0)	19
Japan	452	6 (5.6)	5 (4.5)	6 (9.0)	6 (4.0)	7 (4.1)	4 (4.7)	25
Italy	415	7 (5.2)	6 (3.7)	4 (9.3)	7 (4)	6 (4.1)	9 (2.6)	19
UK	315	8 (3.9)	10 (2.0)	5 (9.2)	10 (2.4)	10 (2.4)	2 (8.6)	34
Taiwan	264	9 (3.3)	8 (3.1)	15 (3.9)	8 (2.8)	8 (2.9)	12 (1.3)	17
France	250	10 (3.1)	12 (1.5)	7 (7.7)	11 (1.8)	12 (1.8)	9 (2.6)	20
Brazil	237	11 (3)	9 (2.6)	16 (3.8)	9 (2.5)	9 (2.5)	20 (0.86)	8.6
Canada	213	12 (2.7)	11 (1.8)	12 (4.9)	12 (1.8)	11 (1.8)	5 (3.9)	25
Spain	199	13 (2.5)	13 (1.4)	11 (5.6)	15 (1.4)	13 (1.5)	12 (1.3)	41
Australia	161	14 (2.0)	14 (1.3)	14 (4.0)	14 (1.5)	15 (1.4)	8 (3.0)	12
Egypt	157	15 (2.0)	24 (0.42)	10 (6.3)	22 (0.7)	23 (0.69)	20 (0.86)	7.8
Malaysia	153	16 (1.9)	16 (1.3)	17 (3.7)	13 (1.5)	13 (1.5)	N/A	6.9
Thailand	134	17 (1.7)	15 (1.3)	21 (2.8)	16 (1.2)	16 (1.2)	25 (0.43)	14
Saudi Arabia	108	18 (1.3)	37 (0.24)	13 (4.5)	23 (0.65)	21 (0.71)	25 (0.43)	7.8
Iran	107	19 (1.3)	17 (1.2)	29 (1.7)	17 (1.2)	17 (1.2)	25 (0.43)	8.1
Switzerland	100	20 (1.2)	21 (0.56)	18 (3.2)	20 (0.74)	20 (0.77)	20 (0.86)	25

CPP_{2016}, Number of citations per publication ($CPP_{2016} = TC_{2016}/TP$); CPR (%), rank and percentage of international collaborative articles; FPR (%), rank and percentage of first-authored articles; IPR (%), rank and percentage of single-country articles; N/A, not available; RPR (%), rank and percentage of corresponding-authored articles; SPR, rank and percentage of single-authored articles; TP, total number of articles; TPR (%), rank and percentage of total articles; UK, United Kingdom; USA, United States of America.

F. Highly Cited Articles with TC_{2016} > 500

The total number of citations (TC_{2016}) is an indication that an article has high impact or visibility in the research community. Highly cited articles provide interesting and useful as insight into those authors and topics that influence a research discipline over time.[3,41–43] However, article impact may not always be high since publication.[38] Therefore, the number of citations in the most recent year (C_{year}) of an article was also considered for high-impact articles.[38] We found that top articles in TC_{year} and C_{year} were never the same.[38,44] The top articles in number of citations in the most recent year (C_{year}) might be an indicator that helps researchers understand recent research in a field.[14] The 13 most-frequently cited articles with $TC_{2016} \geq 500$ are shown in Table 4. Among these 13, three were published in the *Journal of Agricultural and Food Chemistry* (IF_{2016} = 3.154), two in *Proceedings of the National Academy of Sciences of the United States of America* (IF_{2016} = 9.661), two in *Science* (IF_{2016} = 37.205), and one each in six other journals. R.H. Liu from Cornell University in the US published five of the 13 most-frequently cited articles, including two first-author articles, five corresponding-author articles, and two single-author articles. In the area of natural products applied in cancer research, Liu published 43 articles, including seven first-author articles, 29 corresponding-author articles, and three single-author articles. Fourteen

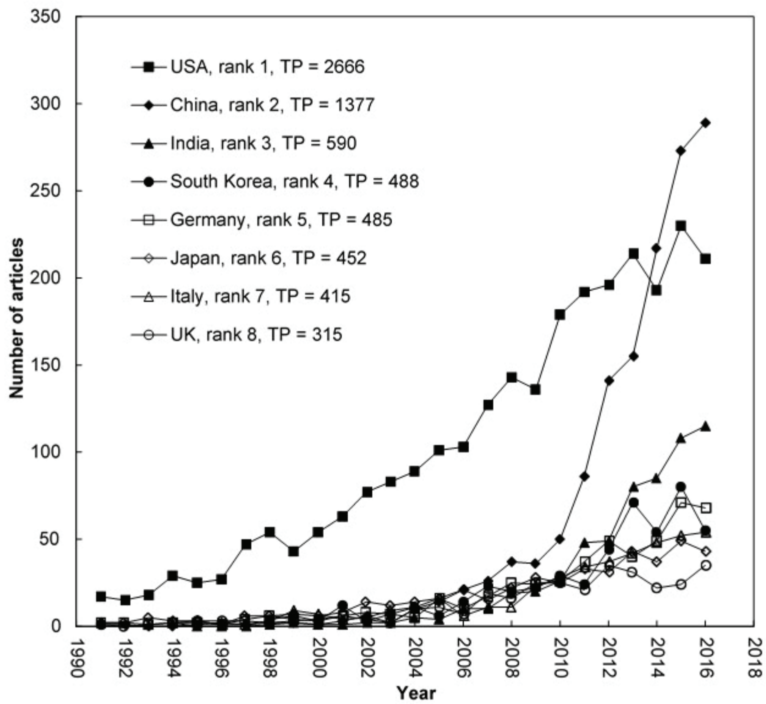

FIG. 4: Comparison of growth trends for the top eight countries

of the 43 articles were highly cited, with $TC_{2016} \geq 100$. Professor Liu and his team have been focusing on diet and cancer, effects of functional foods/nutraceuticals/phytochemicals on chronic disease risks, and antioxidant and antiproliferative effects of bioactive ingredients in natural sources. These topics are highly relevant to potential cancer-treatment strategies. Meanwhile, the 13 most-frequently cited articles mainly focused on two topics: antioxidants and genes. Most of them reported and discussed either the mechanisms of genetic modulations of cancers using cell or animal models or antioxidant properties of selected natural products using chemical assays. None were assessed in a clinical trial.

Figure 5 shows the top eight articles of TC_{2016}. As mentioned above, some with high TC_{2016} may not be cited as frequently anymore. For instance, Chin et al.[29] and Müller et al.[45] were infrequently cited in recent years, having only 7 and 5 C_{2016}, respectively, indicating that their findings were either outdated or assimilated as being common sense, without the need to cite the original articles.

G. Research Focuses and Trends

From Table 5, it can be observed that apoptosis and cytotoxicity were the two most-frequently used author keywords. These findings are consistent with the concept that natural products with potential therapeutic values target cancer cells by being selectively cytotoxic and induce apoptosis. Cancer of breast, prostate, and colon were the three most-frequently mentioned cancers, appearing in 233, 120, and 86 articles, respectively, as keywords. Breast cancer showed a consistent trend, appearing in approximately 3%–4% of articles in each of the 5-yr survey periods, whereas prostate cancer rose and reached the 3% mark during the 2007–2011 period and declined to 1.6% during 2012–2016. Colon cancer was stable at ~1%–2% in each 5-yr period. These three types of cancers were among the top five most-published cancers during the year 2007.[6] However, we did not see other commonly researched cancer types in Table 5, such as lung cancer and leukemia. These areas may represent future underexplored directions for natural-product application in cancer research. The low inter-

TABLE 3: Top ten most-productive institutions

Institution	TP	TPR (%)	IPR (%)	ICPR (%)	NCPR (%)	FPR (%)	RPR (%)	SPR (%)	CPP_{2016}
Chinese Academy of Sciences, China	208	1 (2.6)	3 (1.1)	2 (2.6)	1 (4.0)	1 (1.4)	1 (1.5)	44 (0.43)	13
National Cancer Institute, USA	193	2 (2.4)	2 (1.3)	1 (2.9)	2 (3.1)	2 (1.0)	3 (0.88)	3 (1.7)	64
Seoul National University, South Korea	115	3 (1.4)	4 (1.0)	5 (2.0)	5 (1.4)	4 (0.80)	2 (0.91)	14 (0.86)	29
University of Illinois, USA	115	3 (1.4)	1 (1.4)	7 (1.7)	7 (1.3)	3 (1.0)	4 (0.86)	2 (2.2)	74
University of California at San Diego, USA	79	5 (1.0)	9 (0.77)	13 (1.4)	16 (0.89)	6 (0.56)	6 (0.58)	14 (0.86)	53
Ohio State University, USA	77	6 (1.0)	8 (0.81)	17 (1.1)	10 (1.0)	5 (0.62)	5 (0.67)	44 (0.43)	38
University of Minnesota, USA	77	6 (1.0)	15 (0.56)	4 (2.0)	36 (0.59)	10 (0.50)	11 (0.45)	7 (1.3)	31
China Medical University, Taiwan	73	8 (0.91)	485 (0.035)	22 (1.0)	3 (1.7)	12 (0.44)	13 (0.44)	44 (0.43)	13
Harvard University, USA	69	9 (0.86)	26 (0.42)	11 (1.5)	17 (0.85)	22 (0.34)	18 (0.38)	7 (1.3)	46
Johannes Gutenberg University Mainz, Germany	66	10 (0.82)	N/A	3 (2.6)	83 (0.39)	17 (0.39)	13 (0.44)	N/A	14

CPP_{2016}, Number of citations per publication ($CPP_{2016} = TC_{2016}/TP$); FPR (%), rank and percentage of first-author articles; ICPR (%), rank and percentage of internationally collaborative articles; IPR (%), rank and percentage of single-institution articles; N/A, not available; NCPR (%), rank and percentage of nationally collaborative articles; RPR (%), rank and percentage of corresponding-authored articles; SPR (%), rank and percentage of single-author articles; TP, total number of articles; TPR (%), rank and percentage of total articles; USA, United States of America.

est in lung cancer studies involving natural products might be also influenced by the disappointing findings from supplementation of antioxidant vitamins in patients with this cancer.[46] Meanwhile, curcumin, flavonoids, and resveratrol were the most-frequently mentioned active ingredients of natural products. The former two were similarly frequently mentioned and cited in ethnopharmacology-related articles.[4] Moreover, flavonoids have been broadly studied in the context of cancer prevention,[13,47–49] whereas resveratrol was present in the title of two of the most highly cited articles identified in the current study (Table 4). Although many natural products are established for clinical chemotherapy, it is interesting to note that

TABLE 4: Thirteen most-frequently cited articles (TC_{2016} > 500)

Rank (TC_{2016})	Rank (C_{2016})	Article title (journal)	Reference
1 (3187)	1 (151)	*Cancer chemopreventive activity of resveratrol, a natural product derived from grapes* (*Science*)	Jang et al.[39]
2 (797)	48 (24)	*Total synthesis of Taxol* (*Nature*)	Nicolaou et al. (1994)
3 (752)	809 (7)	*Modulation of activity of the promoter of the human* MDR1 *gene by Ras and p53* (*Science*)	Chin et al.[29]
4 (710)	11 (48)	*Antioxidant and anti-proliferative activities of common fruits* (*J Agr Food Chem*)	Sun et al. (2002)
5 (685)	116 (18)	*Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor* (*Proc Natl Acad Sci USA*)	Gehm et al. (1997)
6 (617)	12 (45)	*Free radicals, oxidative stress, and antioxidants in human health and disease* (*J Am Oil Chem Soc*)	Aruoma[40]
7 (607)	4 (70)	*Potential synergy of phytochemicals in cancer prevention: Mechanism of action* (*J Nutr*)	Liu (2004)
8 (603)	1316 (5)	*Overexpression of the gene encoding the multidrug resistance-associated protein results in increased ATP-dependent glutathione S-conjugate transport* (*Proc Natl Acad Sci USA*)	Müller et al.[45]
9 (594)	8 (63)	*Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals* (*Am J Clin Nutr*)	Liu (2003)
10 (590)	21 (34)	*Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation* (*J Neurosci*)	Joseph et al. (1999)
11 (586)	4 (70)	*Antioxidant activity of apple peels* (*J Agr Food Chem*)	Wolfe et al. (2003)
12 (534)	6 (65)	*Antioxidant activity of grains* (*J Agr Food Chem*)	Adom and Liu (2002)
13 (513)	151 (16)	Fusarium moniliforme *and fumonisins in corn in relation to human esophageal cancer in Transkei* (*Phytopathology*)	Rheeder et al.[30]

TC_{2016}, Number of citations from Web of Science Core Collection since publication to the end of 2016; C_{2016}, number of citations in 2016.

the most studied compounds represent mainly dietary natural compounds studied for chemopreventive potential. Nevertheless, taxol, which is an established chemotherapy agent, was also mentioned in the title of one of the most-cited publications (Table 4). Examples of representative key compounds involved in the analyzed literature are listed in Fig. 6.

H. Autophagy and Cancer

The role of autophagy in cancer is multidimensional. It is believed that autophagy is a suppressor during early stages of cancer development but becomes a promoter in cancers at advanced stages, and different cancer cells may have different responses.[50,51] Table 5 indicates that 69 publications had autophagy in their author keywords, and these 69 are listed in Table 6. Most were published after 2012 (Fig. 7). These publications have reported many promising preliminary experimental results that involve the use of natural products in the contexts of autophagy and cancer. For instance, the antibiotic elaiophylin isolated from *Streptomyces* bacteria may suppress tumor activity in human ovarian cancer cells by

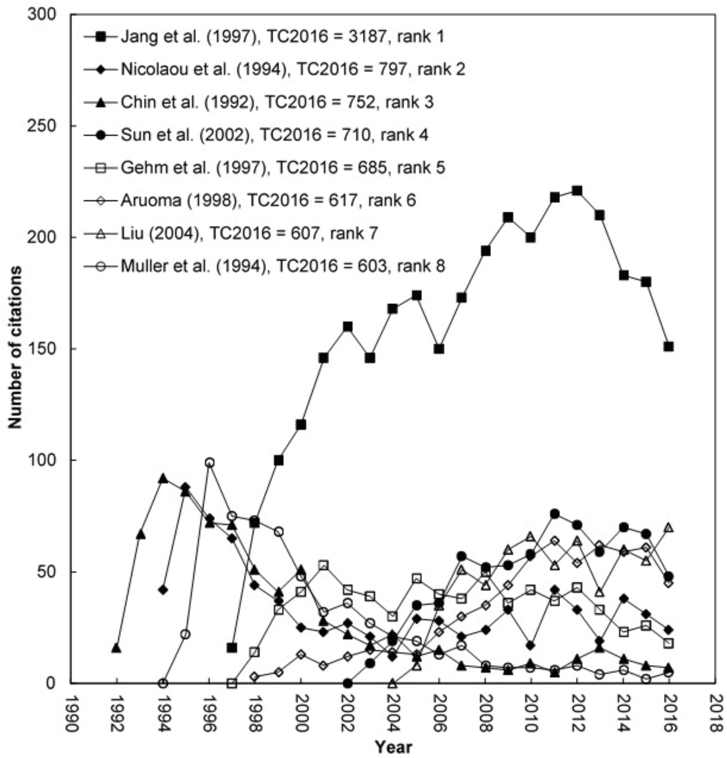

FIG. 5: Article lives of the top eight articles in TC_{2016}

TABLE 5: Top 30 author keywords

Author keywords	TP	1992–2016 Rank (%)	1992–1996 R (%)	1997–2001 R (%)	2002–2006 R (%)	2007–2011 R (%)	2012–2016 R (%)
Apoptosis	860	1 (15)	N/A	2 (7.9)	1 (14)	1 (14)	1 (16)
Cytotoxicity	531	2 (9)	9 (3.8)	8 (4)	5 (6.3)	3 (7.8)	2 (10)
Natural products	484	3 (8.2)	17 (2.5)	4 (7.6)	4 (7.1)	2 (10)	3 (8)
Cancer	397	4 (6.7)	5 (5.1)	2 (7.9)	2 (10)	4 (7.2)	4 (6)
Phytochemicals	240	5 (4.1)	17 (2.5)	1 (10)	3 (8)	7 (4)	9 (3.1)
Breast cancer	233	6 (4)	9 (3.8)	7 (4.3)	9 (3.2)	5 (4.3)	5 (3.9)
Chemoprevention	191	7 (3.2)	3 (6.3)	5 (6.5)	6 (4.6)	8 (3.8)	13 (2.5)
Anticancer	176	8 (3)	17 (2.5)	167 (0.36)	35 (1.3)	9 (3.6)	8 (3.2)
Curcumin	174	9 (3)	N/A	9 (3.2)	10 (3)	6 (4)	12 (2.6)
Cytotoxic activity	168	10 (2.9)	35 (1.3)	23 (1.8)	26 (1.6)	17 (1.9)	6 (3.5)
Natural product	168	10 (2.9)	35 (1.3)	42 (1.1)	18 (2)	15 (2.4)	7 (3.4)
Antioxidant	165	12 (2.8)	N/A	42 (1.1)	8 (3.9)	11 (3)	10 (2.7)
Flavonoids	165	12 (2.8)	35 (1.3)	21 (2.2)	7 (4.1)	11 (3)	11 (2.6)
Resveratrol	149	14 (2.5)	N/A	6 (4.7)	10 (3)	11 (3)	15 (2.1)
Cell cycle	136	15 (2.3)	35 (1.3)	13 (2.9)	12 (2.7)	15 (2.4)	14 (2.2)
Prostate cancer	120	16 (2)	N/A	42 (1.1)	14 (2.5)	10 (3.1)	17 (1.6)
Total synthesis	100	17 (1.7)	N/A	167 (0.36)	30 (1.4)	14 (2.5)	18 (1.6)
Colon cancer	86	18 (1.5)	N/A	23 (1.8)	15 (2.3)	18 (1.8)	29 (1.2)
NF-κB	83	19 (1.4)	N/A	78 (0.72)	35 (1.3)	21 (1.6)	20 (1.4)

TABLE 5: (*continued*)

Author keywords	TP	1992–2016 Rank (%)	1992–1996 R (%)	1997–2001 R (%)	2002–2006 R (%)	2007–2011 R (%)	2012–2016 R (%)
Multidrug resistance	82	20 (1.4)	1 (10)	13 (2.9)	42 (1.1)	25 (1.5)	35 (1.1)
Reactive oxygen species	81	21 (1.4)	N/A	42 (1.1)	35 (1.3)	22 (1.5)	23 (1.4)
Antioxidants	80	22 (1.4)	35 (1.3)	9 (3.2)	16 (2.1)	22 (1.5)	41 (1)
Antiproliferative activity	79	23 (1.3)	N/A	167 (0.36)	35 (1.3)	25 (1.5)	21 (1.4)
Angiogenesis	78	24 (1.3)	35 (1.3)	28 (1.4)	30 (1.4)	19 (1.7)	32 (1.1)
Inflammation	73	25 (1.2)	N/A	167 (0.36)	69 (0.71)	28 (1.3)	23 (1.4)
Marine natural products	72	26 (1.2)	N/A	N/A	26 (1.6)	28 (1.3)	27 (1.2)
Oxidative stress	71	27 (1.2)	N/A	78 (0.72)	35 (1.3)	39 (1)	25 (1.4)
Autophagy	69	28 (1.2)	N/A	N/A	N/A	183 (0.28)	16 (1.8)
Chemotherapy	69	28 (1.2)	9 (3.8)	21 (2.2)	312 (0.18)	28 (1.3)	32 (1.1)
Antioxidant activity	68	30 (1.2)	N/A	167 (0.36)	26 (1.6)	36 (1)	28 (1.2)

R, Rank; TP, total number of articles

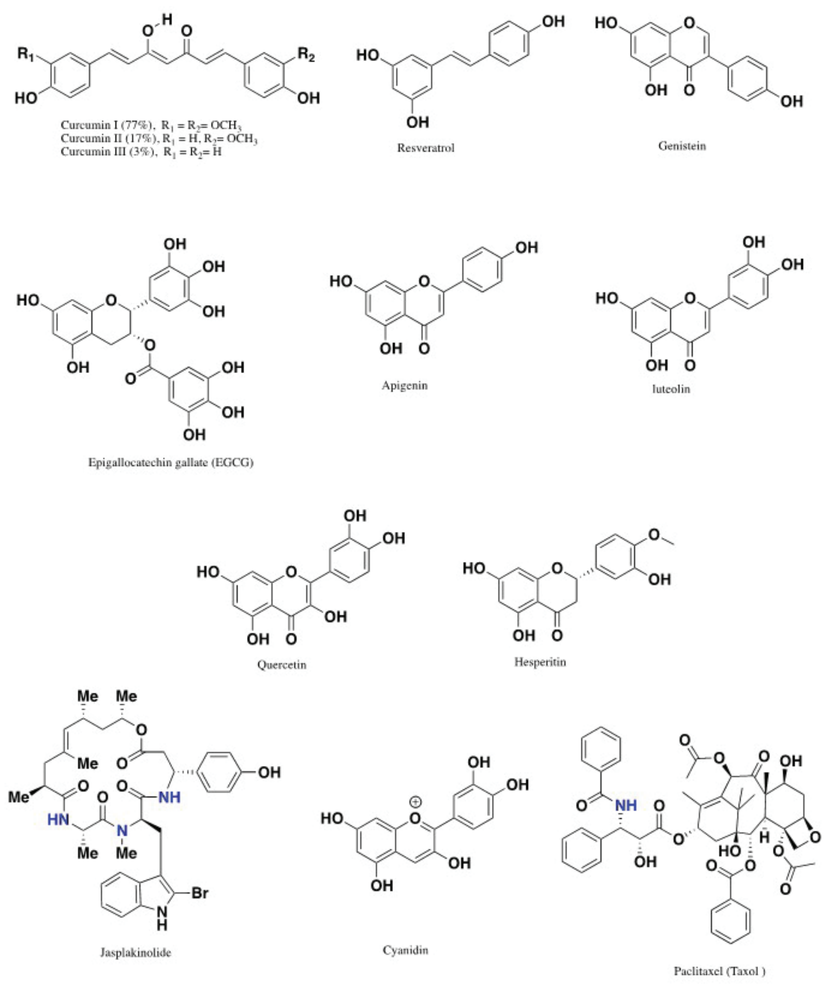

FIG. 6: Examples of representative key compounds from the analyzed literature

TABLE 6: The 69 publications with autophagy or autophagic in their author keywords[52–120]

Article title	Journal	Author keywords
Silvestrol induces early autophagy and apoptosis in human melanoma cells	*BMC Cancer*	Melanoma; silvestrol; autophagy; apoptosis
Coibamide A, a natural lariat depsipeptide, inhibits VEGFA/VEGFR2 expression and suppresses tumor growth in glioblastoma xenografts	*Investigational New Drugs*	Coibamide A; apratoxin A; cyclic depsipeptide; antiangiogenic; autophagy; glioblastoma
Reversal of muscle atrophy by Zhimu and Huangbai herb pair via activation of IGF-1/Akt and autophagy signal in cancer cachexia	*Supportive Care in Cancer*	Cancer cachexia; skeletal muscle atrophy; Zhimu and Huangbai herb pair; autophagy; IGF-1/Akt
Tangeretin derivative, 5-acetyloxy-6,7,8,4′-tetramethoxyflavone, induces G_2/M arrest, apoptosis and autophagy in human non-small-cell lung cancer cells in vitro and in vivo	*Cancer Biology & Therapy*	AKT; apoptosis; autophagy; G_2/M arrest; non-small-cell lung cancer cell; 5-acetyloxy-6,7,8,4′-tetramethoxyflavone
A novel microtubule depolymerizing colchicine analogue triggers apoptosis and autophagy in HCT-116 colon cancer cells	*Cell Biochemistry and Function*	Colchicine analogue; cytotoxicity; tubulin; reactive oxygen species; apoptosis; autophagy
Cryptotanshinone induces pro-death autophagy through JNK signaling mediated by reactive oxygen species generation in lung cancer cells	*Anti-Cancer Agents in Medicinal Chemistry*	Autophagy; cancer; cryptotanshinone; JNK; reactive oxygen species
Enhanced autophagic activity of artocarpin in human hepatocellular carcinoma cells through improving its solubility by a nanoparticle system	Phytomedicine	Artocarpin; autophagy; hepatocellular carcinoma; nanoparticle; solubility
The synergistic effect of resveratrol in combination with cisplatin on apoptosis via modulating autophagy in A549 cells	*Acta Biochimica et Biophysica Sinica*	Resveratrol; apoptosis; autophagy; cisplatin; non-small-cell lung cancer
Screening and target identification of bioactive compounds that modulate cell migration and autophagy	*Bioorganic & Medicinal Chemistry*	Cell migration; autophagy; filopodia; lamellipodia; target identification; 14-3-3; GLUT; VCP
16-Hydroxy-cleroda-3, 13-dien-16, 15-olide induced glioma cell autophagy via ROS generation and activation of p38 MAPK and ERK-1/2	*Environmental Toxicology and Pharmacology*	Autophagy; reactive oxygen species; antioxidant enzymes; p38 MAPK; 16-hydroxy-cleroda-3, 13-dien-16, 15-olide; brain tumor
3,3′-Diindolylmethane induces anti-human gastric cancer cells by the miR-30e-ATG5 modulating autophagy	*Biochemical Pharmacology*	3,3′-Diindolylmethane; gastric cancer; miR-30e; ATG5; autophagy
Reactivation of mutant p53 by capsaicin, the major constituent of peppers	*Journal of Experimental & Clinical Cancer Research*	p53; capsaicin; autophagy; apoptosis; natural compounds; p53 reactivation; mutant p53
Natural compound oblongifolin C inhibits autophagic flux, and induces apoptosis and mitochondrial dysfunction in human cholangiocarcinoma QBC939 cells	*Molecular Medicine Reports*	Oblongifolin C; cholangiocarcinoma; autophagy; mitochondrial dysfunction; apoptosis
Salvianolic acid B, a novel autophagy inducer, exerts antitumor activity as a single agent in colorectal cancer cells	*Oncotarget*	Salvianolic acid B; natural compound; autophagy; cell death; colorectal cancer

TABLE 6: (*continued*)

Article title	**Journal**	**Author keywords**
Expression, modulation, and clinical correlates of the autophagy protein Beclin-1 in esophageal adenocarcinoma	*Molecular Carcinogenesis*	Autophagy; esophagus; rapamycin; natural product
EHHM, a novel phenolic natural product from Livistona chinensis*, induces autophagy-related apoptosis in hepatocellular carcinoma cells*	*Oncology Letters*	EHHM; hepatocellular carcinoma; apoptosis; autophagy
The effects of Colchicum baytopiorum *on regulatory genes of apoptotic and autophagic cell death in HeLa cells*	*Current Pharmaceutical Biotechnology*	Apoptosis; autophagy; cancer therapy; cell death; *Colchicum baytopiorum*; HeLa cells
The peiminine stimulating autophagy in human colorectal carcinoma cells via AMPK pathway by SQSTM1	*Open Life Sciences*	Peiminine; autophagy; natural product; autophagic cell death; SQSTM1; AMPK/mTOC/ULK signaling pathway
Isocryptotanshinone, a STAT3 inhibitor, induces apoptosis and pro-death autophagy in A549 lung cancer cells	*Journal of Drug Targeting*	Apoptosis; autophagy; isocryptotanshinone; STAT3
Identification and characterization of anticancer compounds targeting apoptosis and autophagy from Chinese native Garcinia *species*	*Planta Medica*	*Garcinia*; Clusiaceae; autophagy; apoptosis; natural compound; caged prenylxanthones
Mechanisms underlying physiological functions of food factors via non-specific interactions with biological proteins	*Yakugaku Zasshi: Journal of the Pharmaceutical Society of Japan*	Cancer prevention; zerumbone; heat shock protein; proteasome; autophagy; stress
Psammaplin A induces Sirtuin 1-dependent autophagic cell death in doxorubicin-resistant MCF-7/adr human breast cancer cells and xenografts	*Biochimica et Biophysica Acta General Subjects*	Breast cancer; doxorubicin; drug-resistant; autophagy; SIRT1
Thymoquinone induces caspase-independent, autophagic cell death in CPT-11-resistant LoVo colon cancer via mitochondrial dysfunction and activation of JNK and p38	*Journal of Agricultural and Food Chemistry*	Apoptosis; autophagy; caspase-independent; CPT-11-R LoVo colon cancer cells; thymoquinone
Ursolic acid and resveratrol synergize with chloroquine to reduce melanoma cell viability	*Melanoma Research*	Autophagy; chloroquine; melanoma; phytonutrients
Natural autophagy regulators in cancer therapy: A review	*Phytochemistry Reviews*	Autophagy; cancer; natural products; drug discovery
Development and mechanism investigation of a new piperlongumine derivative as a potent anti-inflammatory agent	*Biochemical Pharmacology*	Piperlongumine; inflammation; mechanism; NF-κB; MAPK; autophagy
The natural product peiminine represses colorectal carcinoma tumor growth by inducing autophagic cell death	*Biochemical and Biophysical Research Communications*	Peiminine; autophagy; natural product; autophagic cell death
Ursolic acid protects hepatocytes against lipotoxicity through activating autophagy via an AMPK pathway	*Journal of Functional Foods*	Ursolic acid; lipotoxicity; autophagy; AMPK
Guttiferone K induces autophagy and sensitizes cancer cells to nutrient stress-induced cell death	*Phytomedicine*	Apoptosis; autophagy; guttiferone K; natural compound; starvation

TABLE 6: (*continued*)

Article title	Journal	Author keywords
Cucurbitacin B induces DNA damage and autophagy mediated by reactive oxygen species (ROS) in MCF-7 breast cancer cells	*Journal of Natural Medicines*	Cucurbitacin B; ROS; DNA damage; autophagy; breast cancer
Synergistic anticancer effects of combined γ-tocotrienol and oridonin treatment is associated with the induction of autophagy	*Molecular and Cellular Biochemistry*	γ-Tocotrienol; autophagy; breast cancer; Beclin-1; LAMP-1; cathepsin-D
Analysis of autophagic flux in response to sulforaphane in metastatic prostate cancer cells	*Molecular Nutrition & Food Research*	Autophagy; cancer; flux; prostate; sulforaphane
Honokiol inhibits melanoma stem cells by targeting Notch signaling	*Molecular Carcinogenesis*	Cancer stem cells; autophagy; cell cycle arrest; Notch-1; Notch-2
Elaiophylin, a novel autophagy inhibitor, exerts antitumor activity as a single agent in ovarian cancer cells	*Autophagy*	Antitumor; autophagy; cell death; elaiophylin; natural compound; ovarian cancer
Polyphyllin I induced-apoptosis is enhanced by inhibition of autophagy in human hepatocellular carcinoma cells	*Phytomedicine*	Polyphyllin I; autophagy; apoptosis; antiproliferation; human hepatocellular carcinoma cell
Cellular stress responses and cancer: New mechanistic insights on anticancer effect by phytochemicals	*Phytochemistry Reviews*	Cancer; endoplasmic reticulum stress; unfolded protein response; autophagy; phytochemicals
Inhibition of autophagy augments the anticancer activity of α-mangostin in chronic myeloid leukemia cells	*Leukemia & Lymphoma*	α-Mangostin; chronic myeloid leukemia; chloroquine; apoptosis; autophagy
Cryptotanshinone induces G_1 cell cycle arrest and autophagic cell death by activating the AMP-activated protein kinase signal pathway in $HepG_2$ hepatoma	*Apoptosis*	AMPK; cryptotanshinone; cell cycle arrest; autophagy; $HepG_2$ hepatoma
Tanshinone IIA induces autophagic cell death via activation of AMPK and ERK and inhibition of mTOR and p70 S6K in KBM-5 leukemia cells	*Phytotherapy Research*	Autophagy; tanshinone IIA; ERK; p70 S6K; AMPK; LC3 II; mTOR
The natural compound oblongifolin C inhibits autophagic flux and enhances antitumor efficacy of nutrient deprivation	*Autophagy*	Oblongifolin C; autophagy; lysosome; apoptosis; cancer; natural product
Oleanolic acid induces protective autophagy in cancer cells through the JNK and mTOR pathways	*Oncology Reports*	Oleanolic acid; autophagy; cancer; mammalian target of rapamycin; c-Jun N-terminal kinase
The pro-apoptotic role of autophagy in breast cancer	*British Journal of Cancer*	Autophagy; LC3B expression; tissue microarray; growth inhibition; natural compound and breast cancer
Stimulation of autophagic activity in human glioma cells by anti-proliferative ardipusilloside I isolated from Ardisia pusilla	*Life Sciences*	Ardipusilloside I; natural compound; triterpenoid saponin; *Ardisia pusilla*; human glioblastoma; autophagy; apoptosis

TABLE 6: (*continued*)

Article title	Journal	Author keywords
Hydroxychavicol, a betel leaf component, inhibits prostate cancer through ROS-driven DNA damage and apoptosis	*Toxicology and Applied Pharmacology*	Hydroxychavicol; reactive oxygen species (ROS); apoptosis; DNA damage; autophagy; prostate cancer
Mollugin induces tumor cell apoptosis and autophagy via the PI3K/AKT/mTOR/p70S6K and ERK signaling pathways	*Biochemical and Biophysical Research Communications*	Mollugin; apoptosis; autophagy; PI3K/AKT/mTOR/p70S6K; ERK
Oleanolic acid inhibits proliferation and invasiveness of Kras-transformed cells via autophagy	*Journal of Nutritional Biochemistry*	Oleanolic acid; autophagy; Akt; cancer prevention; natural compounds
Turmeric toxicity in A431 epidermoid cancer cells associates with autophagy degradation of anti-apoptotic and anti-autophagic p53 mutant	*Phytotherapy Research*	Skin cancer; phytochemicals; autophagy; apoptosis; rapamycin; p53R273H
Celastrol inhibits gastric cancer growth by induction of apoptosis and autophagy	*BMB Reports*	Apoptosis; autophagy; celastrol; chemotherapy; gastric cancer
Bioactivity of Fragaria vesca *leaves through inflammation, proteasome and autophagy modulation*	*Journal of Ethnopharmacology*	*Fragaria vesca* leaves; polyphenols; inflammation; nitric oxide scavenger; ubiquitin-proteasome system; autophagy
Renal cancer-selective Englerin A induces multiple mechanisms of cell death and autophagy	*Journal of Experimental & Clinical Cancer Research*	Englerin A; apoptosis; autophagy; necrosis; renal cell carcinoma
Natural products targeting autophagy via the PI3K/Akt/mTOR pathway as anticancer agents	*Anti-Cancer Agents in Medicinal Chemistry*	Natural products; PI3K/Akt; autophagy; cancer stem cell; stemness; cell death; anticancer drugs
Akebia saponin PA induces autophagic and apoptotic cell death in AGS human gastric cancer cells	*Food and Chemical Toxicology*	Akebia saponin PA; autophagy; apoptosis; mTOR; MAPKs
Allicin induces anti-human liver cancer cells through the p53 gene modulating apoptosis and autophagy	*Journal of Agricultural and Food Chemistry*	Allicin; apoptosis; autophagy; *p53*; reactive oxygen species
Piperlongumine induces autophagy by targeting p38 signaling	*Cell Death & Disease*	Piperlongumine; autophagy; p38; reactive oxygen species
Autophagy triggered by magnolol derivative negatively regulates angiogenesis	*Cell Death & Disease*	Autophagy; angiogenesis; hypoxia; vascular endothelial growth factor receptor 2; light chain protein 3
The marine natural product Manzamine A targets vacuolar ATPases and inhibits autophagy in pancreatic cancer cells	*Marine Drugs*	Manzamine A; vacuolar ATPase; lysosome; autophagy; pancreatic cancer
Autophagy mediates anti-melanogenic activity of 3′-ODI in B16F1 melanoma cells	*Biochemical and Biophysical Research Communications*	Autophagy; melanogenesis; 3′-ODI; α-MSH; B16F1 cells

TABLE 6: (*continued*)

Article title	**Journal**	**Author keywords**
Enhancement of apoptotic and autophagic induction by a novel synthetic C-1 analogue of 7-deoxypancratistatin in human breast adenocarcinoma and neuroblastoma cells with tamoxifen	*Journal of Visualized Experiments*	Medicine; biochemistry; breast adenocarcinoma; neuroblastoma; tamoxifen; combination therapy; apoptosis; autophagy
Synthesis and in vitro antitumor activity of asperphenamate derivatives as autophagy inducer	*Bioorganic & Medicinal Chemistry Letters*	Asperphenamate; autophagy; aqueous solubility; structure-activity relationships; inducer
Differential signaling involved in Sutherlandia frutescens-*induced cell death in MCF-7 and MCF-12A cells*	*Journal of Ethnopharmacology*	*Sutherlandia frutescens*; cytotoxicity; cancer; ethnopharmacology; apoptosis; autophagy
Long term induction by pterostilbene results in autophagy and cellular differentiation in MCF-7 cells via ROS dependent pathway	*Molecular and Cellular Endocrinology*	Pterostilbene; autophagy; MCF-7 cells; ROS
A novel synthetic C-1 analogue of 7-deoxypancratistatin induces apoptosis in p53 positive and negative human colorectal cancer cells by targeting the mitochondria: Enhancement of activity by tamoxifen	*Investigational New Drugs*	Colorectal cancer; tamoxifen; combination therapy; apoptosis; autophagy
Autophagy as a target for anticancer therapy and its modulation by phytochemicals	*Journal of Food and Drug Analysis*	Autophagy; cancer; metabolism; phytochemicals
A possible cross-talk between autophagy and apoptosis in generating an immune response in melanoma	*Apoptosis*	Melanoma; ganoderic acid DM; apoptosis; autophagy; HLA class II; CD^{4+} T cells
NF-κB p65 repression by the sesquiterpene lactone, Helenalin, contributes to the induction of autophagy cell death	*BMC Complementary and Alternative Medicine*	Helenalin or hele (helenalin); autophagy; caspase; NF-κB; Atg12 and LC3-B
Involvement of ROS in curcumin-induced autophagic cell death	*Korean Journal of Physiology & Pharmacology*	Autophagy; curcumin; microtubule-associated protein 1 light chain 3; mitogen-activated protein kinase; sequestome-1; reactive oxygen species
Resveratrol-induced autophagy in human U373 glioma cells	*Oncology Letters*	Autophagy; glioma; resveratrol
Curcumin induces apoptosis-independent death in oesophageal cancer cells	*British Journal of Cancer*	Curcumin; apoptosis; mitotic catastrophe; autophagy; oesophageal cancer
Protective activity of Theobroma cacao *L. phenolic extract on AML12 and MLP29 liver cells by preventing apoptosis and inducing autophagy*	*Journal of Agricultural and Food Chemistry*	Apoptosis; autophagy; chemoprevention; cocoa roasting; liver cytotoxicity

AKT, Protein kinase B; AML12, alpha mouse liver 12; AMPK, AMP-activated protein kinase; ATG5, autophagy related 5; CPT-11-R, ; EHHM, E-[6'-(5'-hydroxypentyl)tricosyl]-4-hydroxy-3-methoxycinnamate; ERK-1/2, extracellular signal-related kinase 1/2; GLUT, glucose transporter; HCT-116, human colon cancer cell line 116; HLA, human leukocyte antigen; IGF-1, insulin-like growth factor-1; JNK, c-Jun NH_2 terminal kinase; LAMP-1, lysosomal-associated membrane protein-1; LC3-2, lung-cell 3-2; MAPK, mitogen-activated protein kinase; MCF-7, Michigan Cancer Foundation-7; miR, microRNA; mTOC, ; mTOR, NF-κB, nuclear-factor kappa B, ROS, reactive oxygen species; SIRT1, sirtuin 1; SQSTM1, sequestosome 1; STAT1, signal transducer and activator of transcription1; ULK, ; UNC-51–like kinase; VCP, valosin-containing protein; VEGFA, vascular endothelial growth factor A, VEGFR2, vascular endothelial growth factor receptor 1.

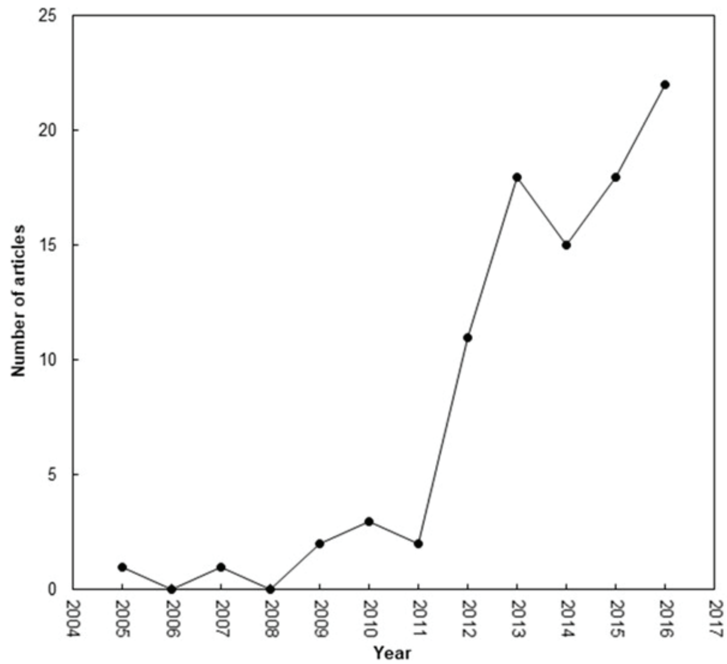

FIG. 7: Yearly publication count of articles from the subset with autophagy or autophagic in their author keywords

inhibiting autophagy.[52] Meanwhile, extracts of the African shrub *Sutherlandia frutescens* may induce autophagy that preferentially kills breast adenocarcinoma cells.[53]

IV. CONCLUSIONS

The US and Spain have published a larger number of articles with high averaged citations, whereas China has been rising in publishing articles since 2009. The 13 most-frequently cited articles with $TC_{2016} \geq 500$ mainly focused on two topics: antioxidants and genes. Apoptosis and cytotoxicity were the two most-frequently used author keywords. Cancers of the breast, prostate, and colon were the most-frequently mentioned cancers. Curcumin, flavonoids, and resveratrol were the most-frequently mentioned natural products.

ACKNOWLEDGMENT

A.G.A. acknowledges the support of Poland's KNOW (Leading National Research Centre) Scientific Consortium, Healthy Animal—Safe Food, in the division of the Ministry of Science and Higher Education (grant no. 05-1/KNOW2/2015).

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