Review

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Posted Date: 11 July 2023

doi: 10.20944/preprints202307.0717.v1

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Review

Research Progress of Natural Drugs for Breast Cancer in the Past 30 Years Based on Bibliometric and Knowledge Graph Analysis

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Abstract: Breast cancer is one of the most common types of malignant tumors worldwide and the leading cause of cancer-related deaths in women. According to the latest report from the World Health Organization, breast cancer has surpassed lung cancer, becoming the most diagnosed cancer globally. Herein, a systematic, quantitative, and visual analysis of the scientific achievements in natural products research and development for breast cancer over the past 30 years is presented. The study utilizes bibliometric and knowledge graph visualization techniques to analyze the trends, co-occurrence of keywords, cooperative networks, cited literature, and research hotspots in the field. The analysis shows that breast cancer natural drug development involves mutual cooperation between multiple countries, with China, the United States, and India being the most active players. Pharmacology is the discipline with the largest number of articles published in nearly 30 years. The study also reveals that the extraction of drugs from organisms and their metabolites is an important direction in the current development of anticancer drugs. The development of natural medicines for breast cancer together with the mining of genetic knowledge play an important role in treating human breast cancer. The research presented here provides insights into the current state of natural product research and development for breast cancer, and highlights the need for strengthening mutual communication and cooperation between countries and scientific research institutions to enhance the development of breast cancer treatment technologies and natural medicines.

Keywords: natural products; breast cancer; drug; bibliometric analysis; knowledge graph

1. Introduction

Breast cancer is one of the malignant tumors with the highest incidence in the world, the main type of female malignant tumors, and the first leading cause of cancer-related death in women [1]. According to the latest report released by the International Agency for Research on Cancer (IARC) of the World Health Organization, as shown in Figure 1, there was 19,290,000 new cancer cases worldwide in 2020, including 2.26 million cases of breast cancer. The top 10 cancers in terms of the number of patients were: breast cancer 2.26 million, lung cancer 2.2 million, colorectal cancer 1.93 million, prostate cancer 1.41 million, stomach cancer 1.09 million, liver cancer 910,000, cervical cancer 600,000, esophageal cancer 600,000, thyroid cancer 590,000, bladder cancer 570,000. These 10 cancers account for 63% of all new cancers. According to the analysis, the number of new cases of breast cancer in 2020 reached 2,260,000(11.7%), surpassing lung cancer for the first time 2,200,000(11.4%) to become the "No.1 cancer in the world". According to statistics [2], breast cancer kills one out of every eight women worldwide. In the face of the increasingly intractable problem of breast cancer, understanding its pathogenesis and means of prevention and treatment is of great importance to human health. Breast cancer is a disease caused by the abnormal mechanism controlling cell growth and proliferation, with biological characteristics such as abnormal cell differentiation and proliferation, invasion and metastasis [3]. Breast cancer can be further divided into invasive and non-invasive according to its location [4]. Based on the presence of progesterone receptor (PR), estrogen

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receptor (ER) and human epidermal growth factor receptor-2（HER2）, Breast cancer can also be divided into three main subtypes: (1) hormone receptor positive and HER2-negative (70%), (2) HER2-positive (15%) and (3) triple-negative (all three molecular markers negative, 15%) [5]. Among them, triple negative breast cancer (TNBC) belongs to invasive breast cancer and is the most intractable malignant tumor [6]. The treatments available for breast cancer include surgical therapy [7], radiotherapy [8], endocrine therapy [9], immunotherapy [10] and chemotherapy [11]. Among these, drug-mediated chemotherapy is the main treatment method for most breast cancer patients. However, chemotherapy has side effects, which are often accompanied by greater toxicity and adverse reactions to the human body [12]. Thus, it would be prudent to search for alternative treatments which do not negatively affect patients.

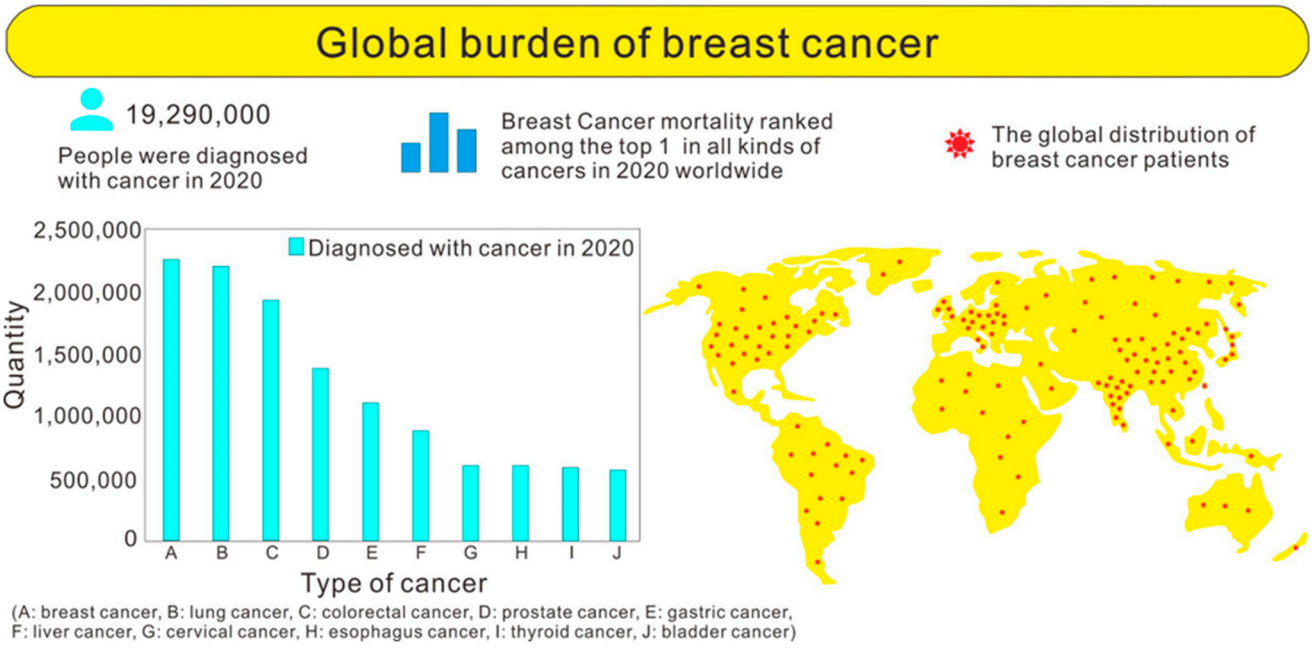

Figure 1. Global Breast Cancer Profile.

With the progress of modern science and medicine, human exploration of natural products has also developed. It has the following advantages: (1) Natural products have little or no side effects and do not produce drug resistance in human body [17]. Toxic natural products will reduce or disappear after proper processing. The toxicity of toxic natural drugs will be reduced or disappeared after proper processing. (2) Natural products do not have drug residues in the human body and do not produce side effects [18]. Because natural and biologically active components of drugs can be retained, they are more readily absorbed and utilized by the human body. Even ingredients that cannot be absorbed by the human body can be excreted efficiently. In response to the above advantages, a large number of scientific researchers seek for a less toxic regimen against natural products with antitumor activity, hoping to further solve the medical difficulty of breast tumor [19,20]. Marine organisms and their metabolites, for example, have received significant attention from drug developers in recent years. It has been demonstrated [21] that components such as sea cucumber saponins and sea cucumber polysaccharides have anti breast tumor effects. Triterpenoid saponins, the secondary metabolites of sea cucumber, also have antifungal, antipyretic, sedative, and anticancer biological activities. These substances produced by natural organisms can inhibit the proliferation of a variety of tumor cells in humans to some extent, reduce the adhesion of cancer cells, inhibit the migration of cancer cells, inhibit colony formation and tumor invasion. In addition, numerous studies have proved that natural plant products and herbal medicines also have potent effects in inhibiting tumor cell growth. For example, Angelica sinensis(Oliv.), Paeonia lactiflora Pall., Rehmannia glutinosa(Gaertn.) DC., Astragalus mongholicus Bunge, and Glycyrrhiza glabra L. may reduce the anti-cancer effect of Tamoxifen(TAM) [22]. Some other natural products including morin, silybin,

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myricetin, baicalein, curcumin, kaempferol can increase the bioavailability of TAM and its metabolites in vivo. In particular, various types of novel drugs for the treatment of breast cancer have continuously emerged in recent years, and the development of these drugs has greatly promoted the therapeutic level of breast cancer and accelerated the postoperative rehabilitation of patients [23].

Through literature analysis, we found that natural animals and plants, natural microorganisms and their metabolites have a great effect on the treatment of breast cancer, and have low self toxic side effects. Over the past few decades, numerous experiments and studies on breast cancer natural products have been carried out by many life scientists, medical and pharmaceutical specialists, but the valuable scientific achievements in this field have not been systematically summarized. Based on this, a quantitative visual analysis and discussion of the breast cancer natural products literature over the past 30 years using bibliometric analysis and knowledge graph methods is presented, to understand the research hotspot and trends in natural products research for breast cancer, provide a basis for future researchers in this field, and provide technical support and knowledge foundation for the research of various types of natural medicines.

2. Materials and Methods

2.1. Data Sources

The data were obtained from the Web of Science (WoS) Core Collection. The WoS Core Collection was chosen since it is considered the most comprehensive database, embodying the most influential and relevant journals. The WoS database is suitable for literature aggregation and analysis. For example, authors previously utilized the literature from the WoS database for a bibliometric analysis of the combined features of COVID-19 patients after cure, which quantified and discussed the post morbid symptoms occurring 12 weeks or more after diagnosis in COVID-19 patients [24]. The findings suggested that a significant proportion of patients experienced persistent fatigue or cognitive impairment after acute COVID-19. Other authors also conducted a bibliometric analysis of studies in the field of artificial intelligence in breast cancer using the WoS database to explore the current status of applications and developments of artificial intelligence technologies in breast cancer [25]. The results showed that medical images, data set analysis, and machine learning are all very important areas of research. In this study, we performed a similar bibliometric analysis and knowledge graph presentation of the literature on natural medicines for breast cancer in the WoS database. Figure 2 is an overall research framework developed by searching and analyzing the literature of the WoS database. As shown in Figure 2, this study adopted the advanced retrieval function of the WoS database to conduct the following research strategy: (1) search topics TS = (breast cancer OR breast tumor) AND TS = (natural products OR natural medicines). During the subject headings search, we did not consider English abbreviations because a large number of articles in unrelated fields would be generated if the abbreviated words were used as search topics, which would make the targeted study data inaccurate or unrepresentative. Moreover, the full form of an abbreviation can be found when it is used for the first time in an article. This indicates that the literature can still be searched even if we exclude the abbreviations from the search terms. (2) The language of the articles was set to English. (3) The article date range was set from January 1, 1993 to December 31, 2022，including literature related to natural drug development in breast cancer for nearly 30 years. A total of 3250 articles were obtained through the above search strategies. We excluded duplicates and less relevant literature by data preprocessing, and a total of 2790 valid articles were retained. The goal of this study was to present information on data materials from these 2790 academic journals, including academic literature names, authors, institutions, keywords, abstracts, and references.

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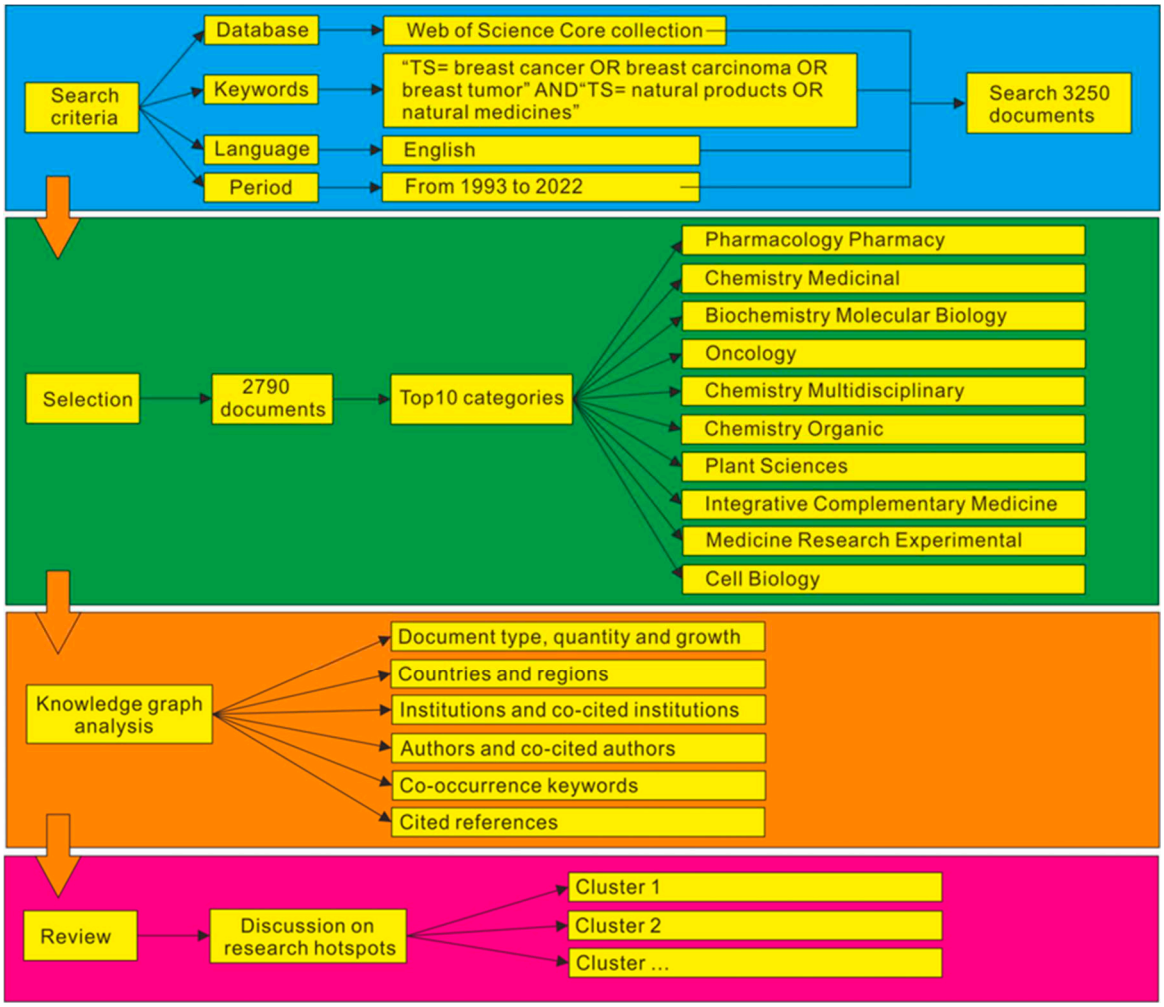

Figure 2. The Overall Research Framework.

2.2. Research Methods

2.2.1. Bibliometric Analysis

This paper presents a bibliometric and knowledge graph visualization analysis of 2790 papers in the WoS database. Bibliometric analysis [26] refers to the interdisciplinary science that employs mathematical and statistical approaches to quantitatively analyze knowledge databases. It is a comprehensive body of knowledge integrating mathematics, statistics, and literature, focusing on quantification. The most essential feature of bibliometric analysis is that its output must be volume. Bibliometric analysis can often be combined with knowledge graphing techniques to help gain a more intuitive and rapid understanding of the trends and cutting-edge technologies in the related academic fields. Knowledge graphs, known as knowledge domain visualizations or knowledge domain mapping maps in the discipline of librarian intelligence, are a series of various different graphics that display the relationship between the progress of knowledge development and their structures [27]. Knowledge graphs can use visualization technology to describe knowledge resources and their carriers, exploring, analyzing and drawing the relationship between knowledge. It combines the theories and methods of applied mathematics, graphics, information visualization technology and computer science with the methods of quantitative analysis and co-occurrence analysis, and displays the core structure, development frontier and overall knowledge structure of the discipline by using the visualized atlas image. The visualization technology of knowledge graphs can transform the original data into graphic information. In the knowledge graph, different knowledge information is represented by nodes, which represent specific key terms, such as

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countries, institutions, authors, keywords, etc. The size of the node represents the frequency. The thickness of the segment represents the tightness of the association.

2.2.2. Bibliometric Analysis Software

This paper uses CiteSpace (6.1.R3) software to assist with bibliometric analysis and knowledge graph research. CiteSpace is also called Citation Space. It is a visualization software for analyzing scientific literature knowledge. By means of visualization, it can present the structure, rule and distribution of scientific knowledge, analyze the research frontiers, knowledge base, main authors and institutions in this field, and predict future research development trends [28]. The knowledge graph drawn by CiteSpace software is marked by time, and the most influential documents are identified by the prominent features of the documents [29]. In this study, we use this software to analyze the complex data of natural drug literature of breast cancer, and discuss research hotspots and trend clustering according to keywords. With the help of CiteSpace, a bibliometric analysis tool, this paper will provide a more valuable review based on the research history of breast cancer over the past 30 years.

3. Results and Discussion

3.1. Document Types and Publication Trend

It is of great significance to apply knowledge graph technology to the research of literature review in the field of pharmacy. In this paper, 2790 articles related to breast cancer natural drug research were retained after literature retrieval and data preprocessing. The 2790 papers involved are of 3 document types (Figure 3). Primary research articles (2019, 72.37%) were the most valuable, followed by the reviews (731, 26.20%), and early access articles (40, 1.43%). Some of the most common disciplines identified in the bibliometric analysis included Pharmacology pharmacy (692), Chemistry medicinal (623), Biochemistry molecular biology (579), Oncology (418), Chemistry multidisciplinary (377) Chemistry organic (193), Plant sciences (165), Integrated completion medicine (151), medical research experimental (141), and cell biology (133) (Figure 4). This shows that different disciplines have already carried out in-depth research from different angles and have made considerable achievements. Among them, pharmacology and pharmacy have produced the largest number of scientific research documents. The second is medical chemistry, which integrates medical and chemical pharmaceutical technologies. Thirdly, the discipline of molecular biology, which mainly uses molecular biology and biochemistry technology to extract drugs.

Literature research data included in the WoS database intuitively reflects the impact of this research field and also reflects the depth of knowledge accumulation of this research. Figure 5 shows the number of annual literature publications on natural products development for breast cancer over the last 30 years. The overall publications in 30 years exhibited a gradual upward trend. The number of literature publications in this field increased from 7 in 1993 to 349 in 2022. Notably, the number of articles published in this field before 2014 has grown more slowly. From 2014, the number of articles showed a rapidly increasing trend. In particular, the number of articles published in the year between 2020 and now are all above 300. This illustrates that there are an increasing number of researchers focusing on the development of natural products for breast cancer.

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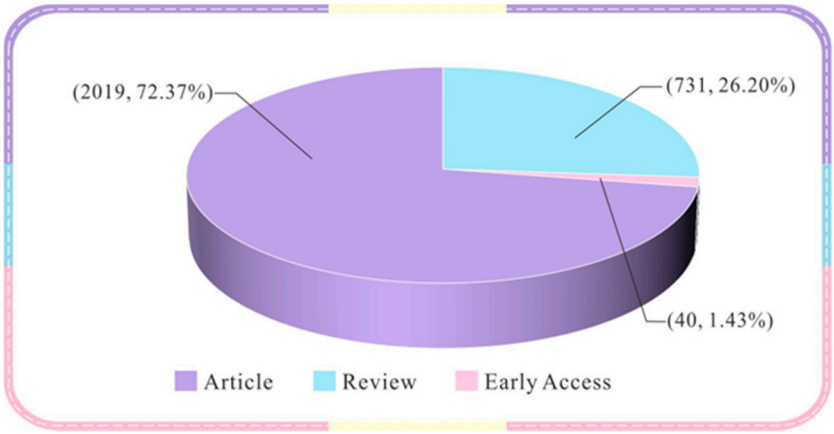

Figure 3. Literature Types.

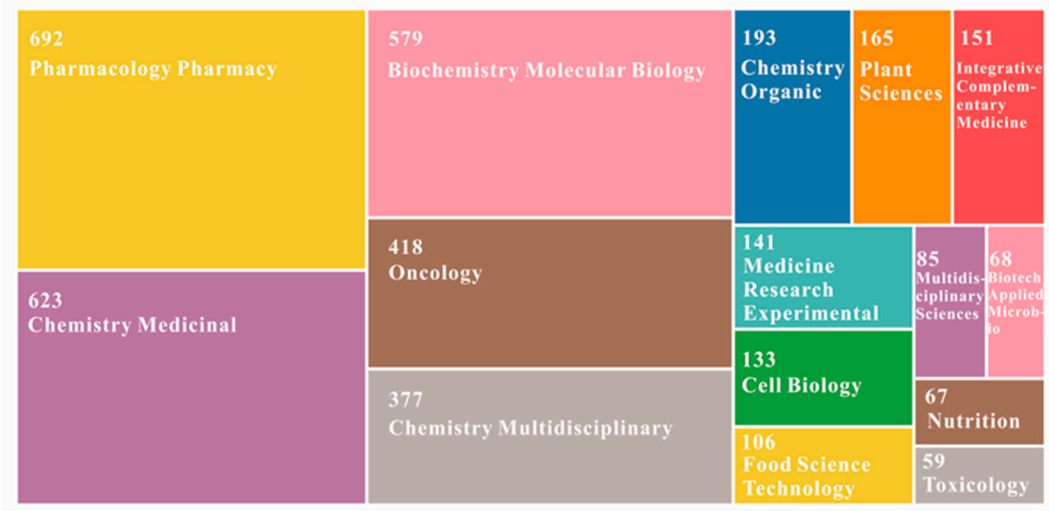

Figure 4. Types of Literature Subjects.

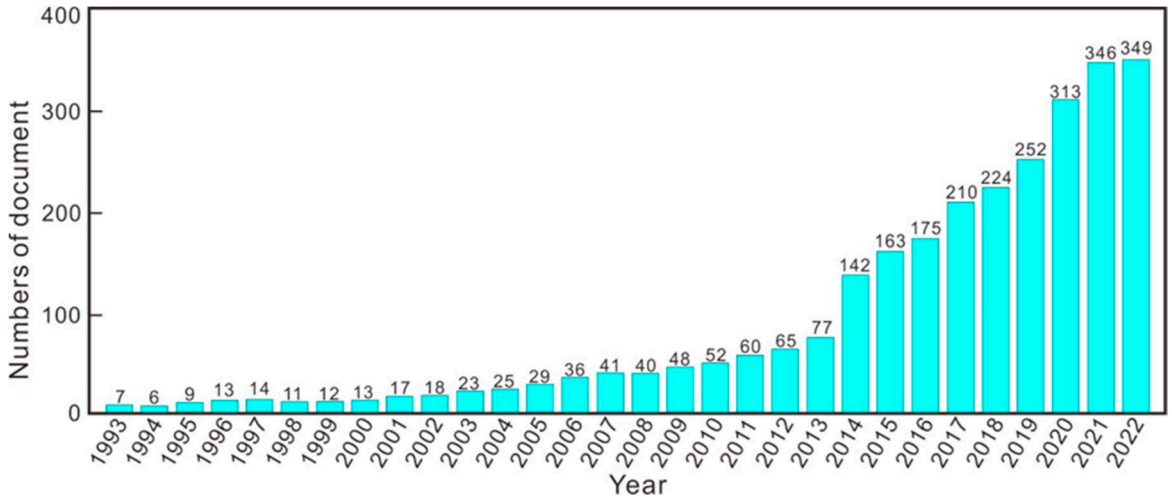

Figure 5. Annual Publication Volume of The Literature.

3.2. Analysis of Countries and Regions Publishing Papers

Experts and scientific researchers in pharmaceuticals from various countries around the world are collectively committed to the development of natural drugs for breast cancer and have made a great contribution to the field. Indeed, different geographical areas undertake different type of

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research depending on the needs of each region, and thus, results obtained are diverse. The integration of these different disciplines can promote a new breakthrough in breast cancer research. For this reason, it is important to have an awareness of the research carried out in different regions to strengthen existing ties and promote the exchange of results and knowledge in geographical areas with fewer collaborations. To this end, Figure 6 shows the volume of literature and international collaboration worldwide over the last 30 years using a knowledge graph. As shown from the graphical statistical analysis, China has the largest number of published papers (631) and the largest contribution in breast cancer natural drug development, accounting for 22.62% of the total global literature. Among them, the earliest literature in China was published in 1997. The USA ranked 2nd (604) in the number of published literatures, accounting for 21.65% of the total published articles, and the earliest literature publication in the USA was in 1993. In India the number of published articles was 330, ranking 3rd. As shown in Table 1, the other countries that ranked in the top 10 for the number of published articles were Italy (152 articles), Germany (143 articles), Saudi Arabia (138 articles), Iran (132 articles), South Korea (121 articles), Egypt (112 articles) and Brazil (102 articles), in that order. From the network of close cooperation between countries, all countries around the world are actively engaged in international cooperation. Scotland has actively partnered with Japan, Greece, and Cameroon in breast cancer drug discovery in nearly 10 years and has published a large number of scientific papers. In addition, the USA works closely with Mexico, France and Belgium. The research results from the collaboration between Italy, Spain and Switzerland were mainly published in 2000-2010. From the time of publication, the largest number of publications was in the United States between 1993 and 2012, indicating that the earliest initiation of research efforts began in the United States. Most of the research literature in China is focused on the period 2013-2022, indicating that China has actively explored, highly regarded, and conducted a large number of basic and applied studies in the past 10 years, with a goal of making breakthroughs in natural products discovery for breast cancer.

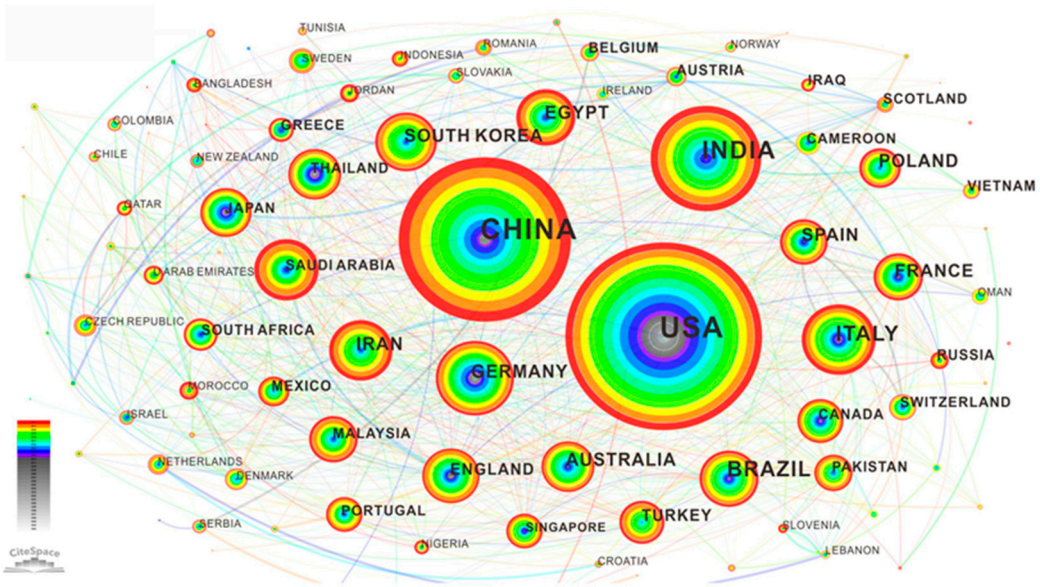

Figure 6. Knowledge Graph of Published Articles by Countries and Regions.

Table 1. Top 10 Countries.

Number	Count	Country	Number	Count	Country
1	631	China	6	138	Saudi Arabia
2	604	USA	7	132	Iran
3	330	India	8	121	South Korea
4	152	Italy	9	112	Egypt
5	143	Germany	10	102	Brazil

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3.3. Analysis of Published Articles by Institutions.

Figure 7 is the knowledge graph of research institutions. Circular nodes in the figure represent research institutions, with larger circles indicating more articles published by that institution. The line between nodes indicates communication and cooperation between institutions, and thicker lines indicate closer cooperation between institutions. Table 2 shows the institutions that ranked TOP 10 for the number of published articles. As seen in Figure 7 and Table 2, the largest number of papers in breast cancer natural products research has been published by the Chinese Academy of Sciences, which has published 65 academic papers over the past 30 years. The University of Texas in the United States follows this, with a total of 48 academic papers published. The King Saud University of Saudi Arabia ranks 3rd, which has published 46 academic papers.

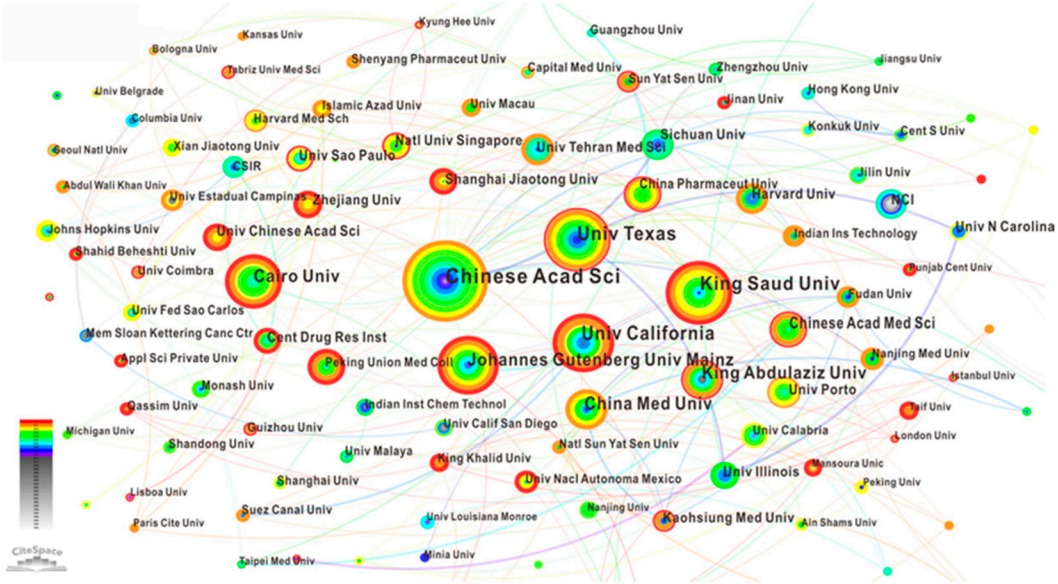

Figure 7. Institutional Knowledge Graph.

Table 2. Top 10 Institutions.

Number	Count	Institution	Number	Count	Institution
1	65	Chinese Acad Sci	6	37	Cairo Univ
2	48	Univ Texas	7	35	King Abdulazia Univ
3	46	King Saud Univ	8	32	China Med Univ
4	44	Univ California	9	30	Chinese Acad Med Sci
5	39	Johannes Gutenberg Univ Mainz	10	30	Univ Porto

3.4. Analysis of Authors of Published Articles.

Research papers included in the WoS database provide a search service for follow-up investigators. The amount of literature an author has published in a given area of research attests to his extensive research endeavors and academic influence. Through the knowledge graph, the authors' number of papers published and the cooperation between them are intuitively visible. Figure 8 is an author knowledge map of published literature related to natural drugs in breast cancer. Circular nodes in the graph represent authors, and lines between nodes represent the degree of cooperation between authors. Table 3 shows the information for the top 10 authors who have published the most articles. According to Figure 8 and Table 3, Efferth, Thomas has published the largest number of articles in the last 30 years (35). The 2nd ranked author is Kuete, Victor (17). The 3rd is Sethi, Gautam (13). They are followed by Bishayee, Anupam (12) ， EI Sayed, Khalid A (11) ， Mbaveng, Armelle T (10) ， Ahn, Kwang Seok (8) ， Khan, Haroon(8)， Wang, Wei(8)， and Kunnumakkara, Ajaikumar

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B(7). The close network of cooperation between scholars shown in the graph have all performed a lot of exploration and research on natural drug development in breast cancer and provided a knowledge base for the discipline. Efferth, Thomas, Kuete, Victor and Zeino, Maen; El Sayed, Khalid A , Foudah, Ahmed I, and AKL, Mohamed R, et al. cooperated on many scientific research articles. In addition, Chinese scholars Zhang Hongbin, Yang Xiaodong, Li Yan and Chen Wen collaborated frequently in this research area. Chen Lin, Shi Liang, Xia Tian Song, Ding Qiang, et al. formed the natural drug research team. AI Harrasi, Ahmed, Abbas, Ghulam, Csuk, Rene, Green, Ivan R, Hussain, Hidayat, Khan Husain Yar, Rehman, Najeeb Ur et al. have also worked in close collaboration on natural drug development for breast cancer. As discovered from literature analysis, Efferth, Thomas, the author who published the largest number of articles, is mainly dedicated to the research on integrating phytochemicals and phytotherapeutics into cancer precision medicine, and he demonstrated that natural products from plants are an excellent resource for the treatment of cancer [30,31].

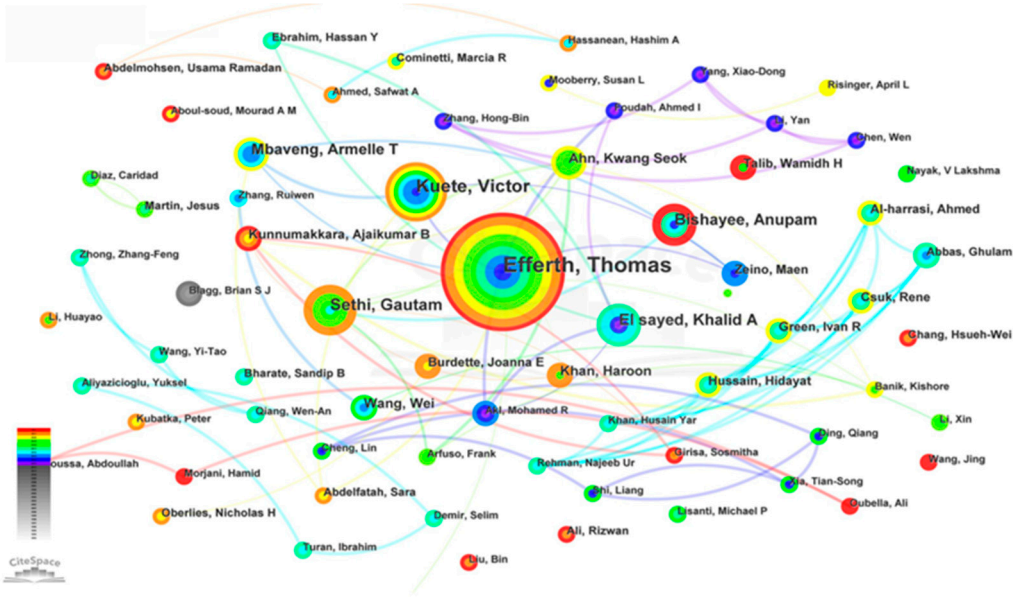

Figure 8. Author Knowledge Graph.

Table 3. Top 10 Authors.

Number	Count	Author	Number	Count	Author
1	35	Efferth, Thomas	6	10	Mbaveng, Armelle T
2	17	Kuete, Victor	7	8	Ahn, Kwang Seok
3	13	Sethi, Gautam	8	8	Khan, Haroon
4	12	Bishyee, Anupam	9	8	Wang, Wei
5	11	EI sayed, Khalid A	10	7	Kunnumakkara, Ajaikumar B

3.5. Analysis of Keywords.

The key words are a high generalization of an academic paper. In analyzing hot spots and frontiers in a certain research field, keywords can provide researchers with the evolution process of the topic and predict future trends in this research field [32]. In this study, we selected high-frequency keywords from natural drug-related literature of breast cancer to construct a knowledge graph of the keyword co-occurrence network according to the keyword analysis function (Figure 9). In the map, node colors from gray to red indicate the date range from 1993 to 2022. Table 4 is the top 10 ranking for the occurrence frequency of keywords. In Figure 9 and Table 4, it is shown that the keyword graphing network was intricate and appeared frequently in relevant literatures published in 1993-2022. Among them, the most frequent keywords were breast cancer (1030 times), natural product (974

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times), in vitro (which refers to in-vitro experiments to test new potential drugs against the development of breast cancer) (463). Other keywords that appeared more frequently were apoptosis (414 times), expression (which refers to the gene expression of sequences involved in the breast cancer development) (241 times), growth (referring to tumor growth) (234 times), NF kappa B (which refers to the activation of nuclear factor-Kappa B, a proinflammatory transcription factor that facilitates the development of high-grade and late-stage breast tumor phenotype) (233 times), breast cancer cell (221 times), cell (199 times) and inhibition (174 times).

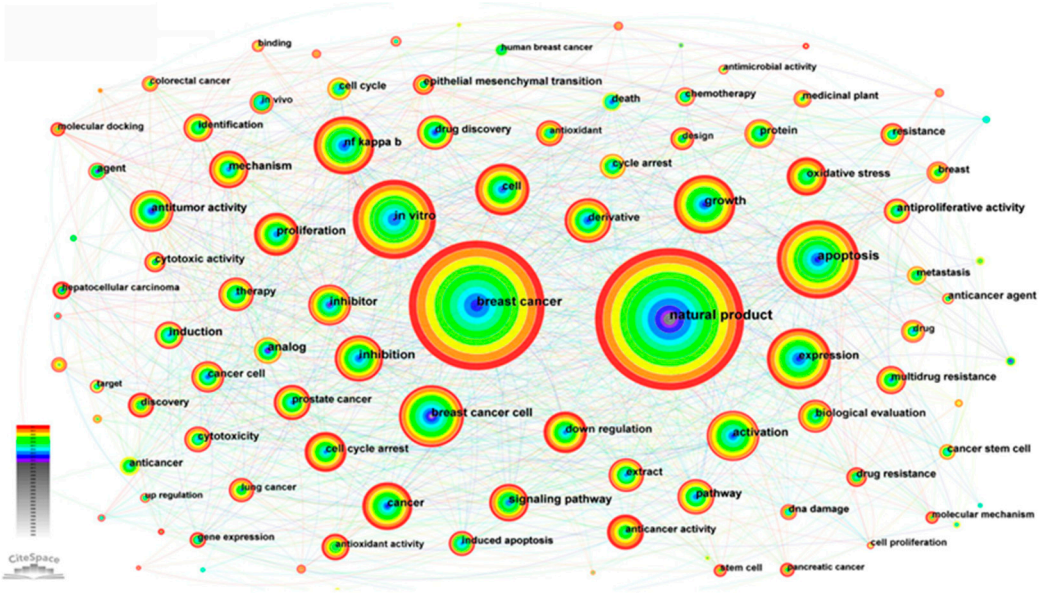

Figure 9. Keywords Knowledge Graph.

Table 4. Top 10 Keywords.

Number	Count	Keyword	Number	Count	Keyword
1	1030	Breast cancer	6	234	Growth
2	974	Natural product	7	233	Nf kappa b
3	463	In vitro	8	221	Breast cancer cell
4	414	Apoptosis	9	199	Cell
5	241	Expression	10	174	Inhibition

As shown in Figure 10, this study set the number of key word highlights for natural products research on breast cancer from 1993-2022 to 30. As can be seen from the figure, "natural product " was the key word with the highest intensity of the mutant (13.07), and appeared mostly between 2007-2013. This suggests that research on natural products received continued attention from the academic community and unfolded a range of in-depth studies during this period relative to other research topics. For example, in the literature [33], the authors analyzed resveratrol (3,4 ', 5 tri-hydroxystilbene). It was shown that resveratrol (3,4 ', 5 tri-hydroxystilbene), a natural plant polyphenol, can induce cell death in multiple types of cancer tumors. Thus, resveratrol derivatives can be novel and effective agents for the treatment of human breast cancer. Figure 10 shows that the word "death", which is closely related to cancer, was also the key word with higher intensity of mutation (11.02) and the duration was 2014-2017 [34]. In addition to that, "agent" was the keyword with the longest duration (1993-2014), which indicated that the research and development of breast cancer agents by scientific researchers has always been an important means for the treatment of breast cancer [35]. From the years that the key words of the mutants appeared, the key words of the nearly 3 year-mutants had a wide range of plant secondary metabolites "flavonoid" that existed in nature (2020-2022). Authors previously suggested that luteolin, as a natural product, is a flavonoid [36]. It has strong anticancer, antioxidant, anti-inflammatory, and antiviral activities. "Essential oil" was also

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a popular keyword between 2020-2022. In recent years, the extraction technology and products of essential oils have also greatly promoted the progress of drug discovery for breast cancer. Through breast cancer clinical experiments, it has been shown that diverse medicinal plant extracts, essential oils and natural bioactive compounds have anti-cancer activities in preclinical breast cancer models [37] In addition, the pharmacometric literature related to the key words of "drug delivery" (2020-2022), "nanoparticle" (2020-2022), "binding " (2020-2022) also generated a lot of articles, which provided research ideas for the development of novel anti breast cancer drugs [38–40].

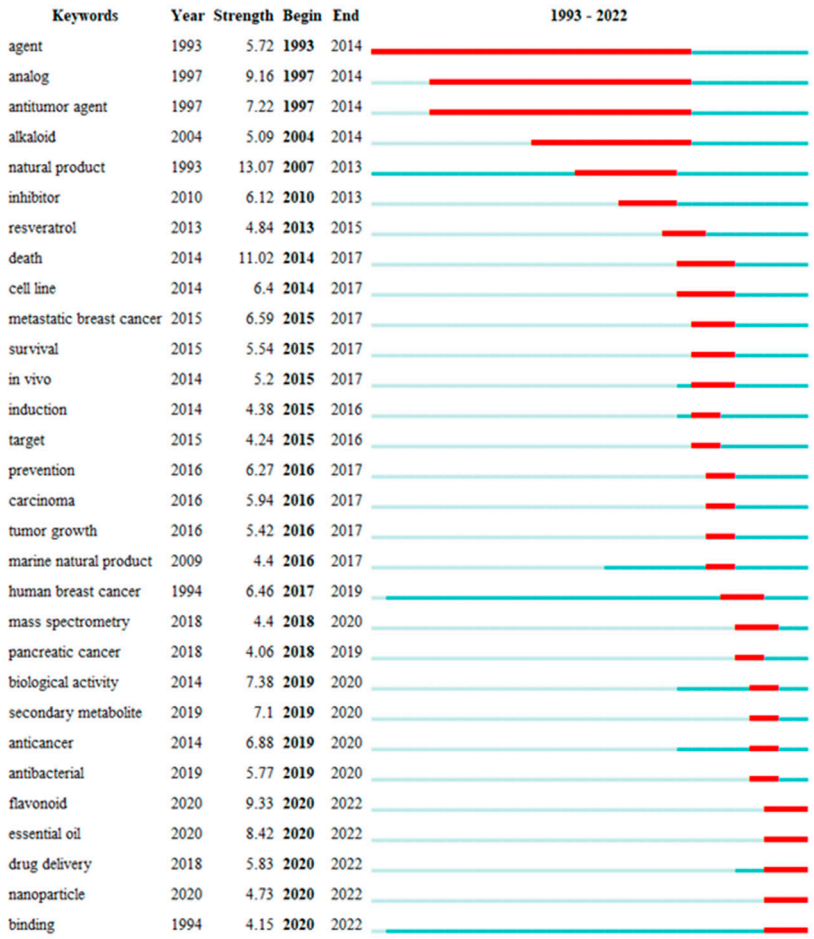

Figure 10. Top 30 Keywords with The Strongest Citation Bursts.

3.6. Analysis of Highly Cited Literature.

The number of times a piece of literature has been cited can reflect the article's influence on the current research field [41]. We selected 1993 to 2022 in the time span setting of the CiteSpace software parameters. Figure 11 is an important literature knowledge graph of natural medicine for breast cancer, which reflects the citation and utilization of each important article and also reflects the common citations among articles. According to Figure 11 and Table 5, Bray F's (2018) article is widely cited 168 times. Their influence in the field of natural drug discovery in breast cancer is evident from the high citation rates of classic literature by Bray F (2018) and Newman DJ (2016). Notably, Newman DJ has 3 articles in the top 10, published in 2012, 2016 and 2020. This study is followed by a brief introduction to the content of the cited literature on top 10, respectively.

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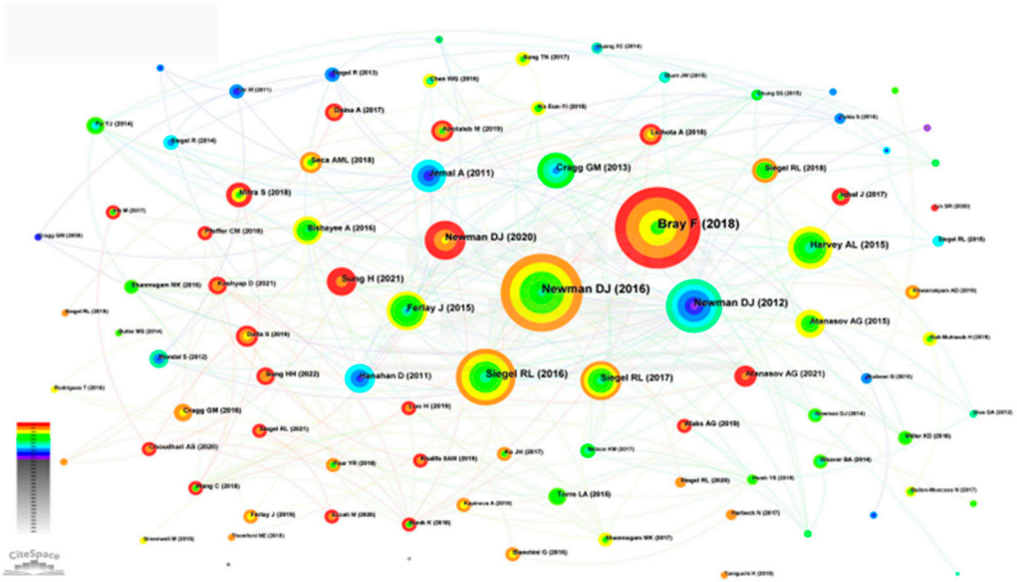

Figure 11. Knowledge Graph of Literature Cited.

Table 5. Top 10 Literature.

Number	Count	Year	Author	Cited references
1	168	2018	Bray F	Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries [42]
2	119	2016	Newman DJ	Natural products as sources of new drugs from 1981 to 2014[43]
3	68	2016	Siegel RL	Cancer statistics, 2016[44]
4	61	2012	Newman DJ	Natural products as sources of new drugs over the 30 years from 1981 to 2010[45]
5	54	2020	Newman DJ	Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019[46]
6	45	2015	Harvey AL	The re-emergence of natural products for drug discovery in the genomics era [47]
7	41	2015	Ferlay J	Cancer incidence and mortality worldwide: Sources, methods and major patterns in Globocan 2012[48]
8	39	2021	Sung H	Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries [1]
9	36	2011	Jemal A	Global cancer statistics [49]
10	36	2013	Cragg GM	Natural products: A continuing source of novel drug leads [50]

The top 10 most cited articles are mostly research reviews. The literature of [42] is the most frequently cited article. The authors statistically analyzed the incidence and mortality rates of 36 cancers worldwide in 2018. Their findings suggested that female breast cancer is the most common cancer and the reasons for its occurrence mainly depend on the degree of regional economic development and people's lifestyles. In the literature [43], the authors conducted a review study focusing on new and approved drugs for the treatment of human diseases. The results indicated that natural products and their derivatives play a critical role during the development of cancer drugs. A great number of natural products are actually produced by microbes or microbial interactions with the "host from whence it was isolated", and therefore it is considered that this area of natural product research should be expanded significantly. The authors in the literature [44] statistically analyzed cancer incidence, mortality, and survival data in the United States in 2016. The results indicated that cancer death rates have declined by 23% in the US since 1991, but that cancer death rates from breast, uterine, and other cancers are still increasing, and cancer is now the leading cause of death in America. The literature from [45,46] and [42] all belong to early research works in the [43], natural

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products and their derivatives have an important role in cancer drug development. In [47], the authors reviewed and evaluated genomic and metabolomic approaches for screening strategies in natural pharmaceuticals. The findings suggested that natural products are described for the discovery of antimicrobials and for inhibitors of protein-protein interactions, specifically as anticancer agents. The authors of [48] compiled the incidence and mortality rates of 27 major cancers worldwide in 2012 based on data from the IARC, and conducted research on data sources and cancer treatments. The results showed that the most common cancers worldwide in 2012 were lung, breast, and colorectal cancers. People need to apply appropriate interventions to reduce future cancer burden, including the development of novel medicines, smoking cessation, alcohol withdrawal, weight loss, and increasing physical activity. The results from the literature [1] showed that female breast cancer has overtaken lung cancer as the most common cancer. There will be 2,260,000 new breast cancer patients in 2020. In the literature [49], the authors counted the world cancer data from 2008. The global burden of cancer continues to increase due to an increasing aging world population and the poor lifestyle habits, such as smoking and alcohol. Breast cancer is the most common cancer, accounting for 14% of cancer deaths. To relieve the stress of cancer, implementing tobacco control, vaccination, early cancer detection and treatment, developing new medicines, and managing physical activity and dietary health should become the focus of attention. With the discovery of penicillin, drugs of microbial origin were discovered. The authors of [50] analyzed the history of natural products as medicines, concluding that many useful medicines were developed from plants. The frontier for future pharmaceuticals will be advanced by mutual cooperation between genomics, microbial natural products, and chemistry.

4. Discussions

The use of natural products has numerous strengths that make it an ideal solution to contribute to fighting global health problem of breast cancer. One advantage is the knowledge and experience of thousands of years of traditional medicines in discovering and employing bioactive natural products or their combinations. Furthermore, those treatments are also often less expensive than current pharmaceutical developments, which are often dependent on large investments. Hence, adapting and combining the natural products and remedies with modern medicine solutions can contribute not only to obtaining improved therapies with synergistic effects but also to a considerable reduction in costs. Another advantage is that current treatments such as chemo- or radio- therapies focus on treating the tumour leaving other healthy organs exposed to side effects. The use of natural products offers treatments that are less detrimental to the rest of the organs and tissues [51].

Indeed, as with all treatments, these advantages come with a series of setbacks that must be taken into account. For instance, natural products reduce but do not completely eliminate side effects; in some cases, it is their intrinsic molecular composition which induce toxicity and thus, dose has to be determined by medical professionals. In other cases, the technologies utilized to prepare medical products from natural compounds can introduce some impurities. One of the most notable examples is the chemotherapy drug Paclitaxel, originally derived from the tree Taxus brevifolia, and used in the treatment of breast, lung, and ovarian cancer, as well as Kaposi's sarcoma. In the traditional Paclitaxel formulation, the drug is dissolved in Cremophor-EL and ethanol, which are necessary solvents for delivering the drug to the affected organ but are associated with clinical toxicity and hypersensitivity reactions. In 2005, a novel formulation of Paclitaxel was approved for the treatment of breast cancer and sold under the name of Abraxane, in which insoluble Paclitaxel is bound to albumin. This provides Paclitaxel with an alternative delivery mechanism by using albumin as a carrier, and has the advantage of avoiding hypersensitivity reactions and utilizing endogenous albumin-transport mechanisms to concentrate the drug within tumor cells [52]. Similarly, traditional methods of preparing natural products for medicine are perceived as outdated, such as calcination and quenching, which are still being used for hard mineral medicines, and aqueous extraction techniques, which are preferred for herbal medicines due to their high fiber content. Modernizing these preparation technologies would imbue them with the competitive advantages of modern synthetic techniques in terms of purity, dosage, and production capacity, while also improving their

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physicochemical properties of the resulting medicines and addressing issues like low bioavailability and weak biological activity.

Finally, social perception remains a significant obstacle to the widespread acceptance and distribution of natural products for the treatment of breast cancer [53]. Modern research of the use of natural products and their combination and treatment with modern techniques may contribute to bridging the knowledge gap between different medical theoretical systems. From our study, through the visual analysis of the knowledge map of such scientific achievements in natural products modern research and development in breast cancer over the past 30 years, research trends in this field are mainly divided into the following five clusters (Figure 12). Next we describe such clusters in detail.

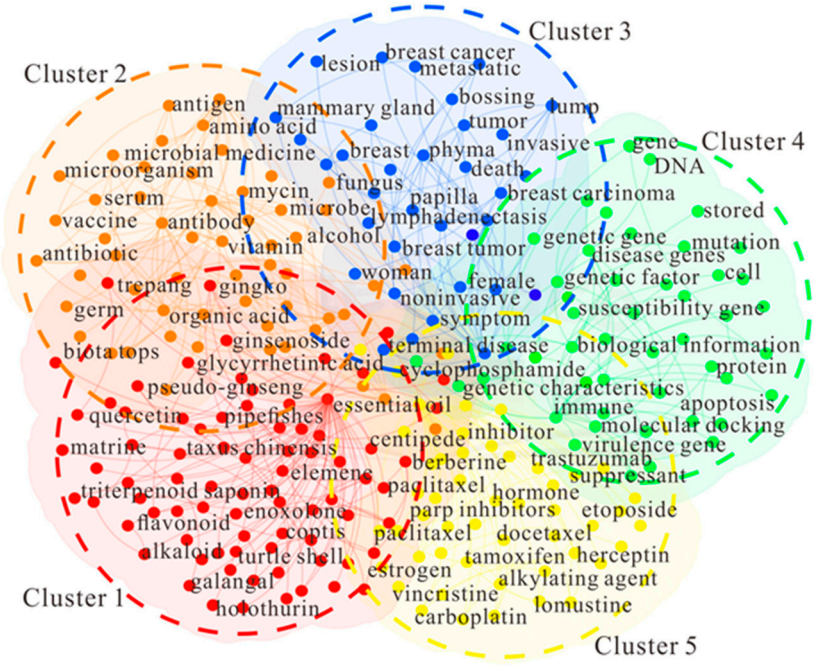

Figure 12. Clustering Knowledge Graph of Research Trends.

4.1. Animal and Plant Natural Products.

Cluster 1 is plant and animal natural products. The main keywords include alkaloid, matrine, flavonoid, quercetin, berberine, coptis, pseudo-ginseng, gingko, ginsenoside, paclitaxel, taxus chinensis, organic acid, glycyrrhetinic acid, enoxolone, elemene, essential oil, holothuria, turtle shell, centipede etc. Extraction of highly effective and nontoxic anticancer drugs from natural animals and plants has become one of the research hotspots in recent years. The anticancer components of animal and plant natural drugs mainly include the following categories:

(1) Alkaloid based natural drugs. Matrine, for example, is an active component of plant herbs such as the legumes matrine and bitter bean. Clinical experiments have shown that matrine can effectively inhibit tumor cell proliferation, and can also be combined with chemotherapy drugs to treat middle and advanced malignant tumors. Matrine can improve the patient's body immunity and alleviate the intestinal reaction caused by chemotherapy [54]. Berberine, used in traditional medicine, is an important natural alkaloid drug isolated and extracted from the herb Coptis chinensis, and it has efficacy such as anti microbial, anti protozoal, anti diarrheal activities. It can interact with DNA and has promising anticancer effects [55].

(2) Flavonoids natural medicines. Quercetin is a natural flavonoid widely distributed in the floral parts of angiosperms. Panax notoginseng, Ginkgo biloba, galangal, and Phellodendron leaves, and many other herbs have quercetin components. Quercetin has an inhibitory effect on tumor cells by inhibiting proliferation and is also a potent free radical trap and antioxidant [56].

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(3) Glycosides. Ginsenosides are important components of ginseng and have strong anticancer activity. Ginsenosides can inhibit cell proliferation and prevent cancer cell metastasis, in addition to increasing immunity in humans.

(4) Terpene. Paclitaxel is recognized as the most active and widely used modern anticancer drug. It was first a diterpenoid extracted from the leaves of Taxus. Paclitaxel can induce cancer cell death and relatively improve patient survival. But paclitaxel is almost water insoluble. Oral administration cannot be achieved, and so it can only be administered intravenously. Improving the water solubility of paclitaxel and increasing its specificity is currently difficult [57].

(5) Organic acids. Glycyrrhetinic acid is an organic acid compound extracted from licorice, which is a potent anticancer drug. Glycyrrhetinic acid can prevent cancer cell growth and differentiation, cancer cell mutation, and can also regulate the immune system [58].

(6) Essential oil. Elemene is an anticancer component of volatile oils extracted from natural plants. It can induce tumor cell death and anti-tumor metastasis, and prevent tumor cell differentiation. Elemene can also enhance body immunity and increase the lifespan of cancer patients [59].

(7) Animal extracts. Centipede is a kind of medicinal herb commonly used in medicine, and the extract of centipede has anti-tumor, anti inflammatory, analgesic and other properties, which can improve the symptoms of patients. In addition, soft shelling, honey, reptile extracts, etc. also have more potent anti-cancer effects and can enhance human immunity [60,61].

4.2. Microbial Natural Products.

Cluster 2 is microbial natural products. The key words included were mainly microorganism, microbial products, germ, microbe, antibiotic, bacteriocin, vaccine, fungus, vaccinum, serum, mycin, antigen, antibody, amino acid, vitamin, organic acid, alcohol. Microbial natural medicine is a type of medicine made using microorganisms. These can be divided into three categories by their origins:

(1) Drugs derived from microbial whole or partial entities. For example, vaccines, sera, mycin, antigens, antitoxins, antisera and antibodies for therapeutic use. They have many advantages such as high efficacy, immunity and benefit in anti-tumor therapy, and have a promising market worldwide [62].

(2) Drugs derived from microbial primary metabolites. These include amino acids, vitamins that make up the macromolecular backbone of the microbial organism, and organic acids or alcohols involved in substance metabolism. Microbial primary metabolites play a crucial role in maintaining human health and treating diseases [63].

(3) Drugs derived from microbial secondary metabolites. Antibiotics, the most important class of pharmaceuticals derived from microbial secondary metabolites, have played an important role in the treatment of cancer, control of infections, and so on. In addition, physiologically active substances are also derived from microbial secondary metabolites, including enzyme inhibitors, inducers, immunomodulators, modulators of cell function, receptor agonists, etc. [64]. Drugs with microbial secondary metabolites will help to provide new avenues for cancer treatment and are a research hotspot for future therapeutic cancer drug development.

4.3. Breast Cancer.

Cluster 3 is breast cancer. The key words included were mainly breast cancer, breast carcinoma, lesion, mammary gland, metastatic, breast, invasive, bossing, phyma, tumor, lump, lymphadenectasis, death, papilla, proliferation, woman, noninvasive, female, terminal disease, symptom, etc. Breast cancer is a phenomenon in which breast epithelial cells undergo uncontrolled proliferation in response to multiple oncogenic factors. Early symptoms of breast cancer usually include breast masses, nipple discharge, axillary lymphadenopathy, and so on. The late stages of breast cancer due to the occurrence of metastasis in cancer cells will develop multi-organ lesions, which directly threaten the life of patients [65]. The incidence of breast cancer ranks at the top of malignant tumors in women, while breast cancer in men is relatively rare. The types of breast cancer can be divided into two main categories.

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(1) Noninvasive carcinoma, which may also be referred to as carcinoma in situ. It refers to cancer lesions confined to the primary site without metastasis and can be classified as lobular carcinoma in situ, ductal carcinoma in situ, and papillary eczema like breast cancer. Noninvasive cancers generally have a better prognosis [66].

(2) Invasive carcinoma. It refers to the occurrence of cancer cells infiltrating, and widely invading the surrounding tissue. This kind of breast cancer is the most threatening to the human body, and usually treatment is relatively difficult. Invasive breast cancers include invasive ductal carcinoma, invasive lobular carcinoma, scirrhous carcinoma, simple carcinoma, papillary carcinoma, apocrine carcinoma, squamous cell carcinoma, medullary carcinoma, and mucinous adenocarcinoma. Studies have shown that alcohol is a risk factor for breast cancer, and people who drink regularly have a higher risk of invasive breast cancer than those who drink occasionally [67].

4.4. Inherited Gene.

Cluster 4 is inherited genes. The keywords include gene, DNA, genetic gene, mutation, duplication, genetic factor, stored, susceptibility gene, genetic characteristics, cell, biological information, virulence gene, disease genes, apoptosis, immune, protein, molecular docking etc. The occurrence of cancer has been attributed to genetic or expression legacy factors. Therefore, there are significant implications for breast cancer management through expression genetics studies and screening for biomarkers [68]. Genetic factors are chemicals that determine biogenetic characteristics and have a complex structure. They are also capable of transmitting genetic information and replicating the primary material basis of the cell. Genes have two characteristics: one is to duplicate themselves to maintain the basic characteristics of organisms. Another feature is carcinogenesis initiated by genetic mutations. When looking at breast cancer treatments and therapeutics, it is important to look at mutated genes. In recent years, many medical researchers have carried out a lot of research on human genes, and have made some contributions to the pathogenic genes of breast cancer. For example, [69] utilized bioinformatics approaches to identify key pathogenic genes unique to different breast cancer subtypes, identifying a total of 1114 differentially expressed genes, of which 500 were common to subtypes. After statistically scoring the information of breast cancer genes as new key pathogenic genes, these genes were recommended as potential targets for clinical therapy. The authors of [70] also conducted a study to identify gene correlations between two groups of breast cancer patients and to derive potential prognostic gene pairs for breast cancer.

4.5. Inhibitor.

Cluster 5 is inhibitors. The keywords include inhibitor, suppressant, parp inhibitors, trastuzumab, paclitaxel, docetaxel, estrogen, tamoxifen, vincristine, etoposide, alkylating agent, hormone, carboplatin, cyclophosphamide, palbociclib, herceptin, targeted therapy, lomustine, fluorouracil and Mitomycin. Breast cancer cells are characterized by unlimited proliferation. Without effective treatment, cancer cells are more likely to spread via metastasis. Antitumor therapies are therefore needed to inhibit the activity of cancer cells. Studies have been launched on how to inhibit the spread of cancer cells. For example, in the literature [71], the authors found that Cyclin dependent kinase 4/6 inhibitors (CDK4/6i)) are innovative small target molecules that can be combined with the endocrine method to achieve the inhibition of cancer cell proliferation and metastasis. It is known from literature analysis that drugs which can control and inhibit cancer cell growth generally include the following 5 classes.

(1) Phytochemical antitumor drugs. For example, paclitaxel, docetaxel, vincristine, etoposide, carboplatin and other drugs, all play a significant role in inhibiting tumor growth [72].

(2) Cytotoxic classes of antitumor drugs. Drugs in this class can exert cytotoxic effects on tumor cells. However, it lacks sufficient selectivity, and so it causes various degrees of damage to normal tissue cells while also killing tumor cells [73]. Common cytotoxic antineoplastic agents are cyclophosphamide, lomustine, semustine, and others. This class of drugs possesses alkylating groups which react with intracellular DNA or protein molecules, leading to cell death, which can inhibit

 doi:10.20944/preprints202307.0717.v1

tumor growth. In addition, drugs such as fluorouracil, methotrexate, doxorubicin, and mitomycin can also infect nucleic acids or inhibit cellular DNA, RNA, and protein synthesis through metabolic substances, which in turn can inhibit tumor cell growth.

(3) Hormonal antineoplastic agents. Such drugs mainly include estrogen, androgen, tamoxifen, megestrol, dexamethasone, etc. Hormonal antitumor drugs control tumor growth by regulating hormone levels [74].

(4) Targeted agents. Representative drugs are imatinib, gefitinib, lapatinib, Tarceva, et al. Targeted agents can inhibit tumor growth by binding specific molecular targets associated with malignancy and intervening in tumor cell signaling regulatory pathways [75].

(5) Immunotherapy drugs. Interleukin-2, yercoy, nivolumab, atezolizumab) are the main drugs in this class. Immunotherapy drugs can inhibit tumor growth by provoking the body's antitumor immune system, killing tumor cells [76].

5. Conclusions

In this paper, we systematically, quantitatively, and visually analyzed the scientific achievements within the WoS database on the research and development of natural products for breast cancer treatment over the past 30 years by bibliometric analysis and knowledge graph visualization. The analysis concluded that factors related to breast cancer natural products ranged from macroscopic factors, such as natural plants, natural animals and patients' bodies, to microscopic factors, such as microbial products, heritage genes, and cancer cell molecules, and they have all been intensively studied by academia. Breast cancer is a serious problem worldwide. It is necessary to further strengthen the mutual communication and cooperation between countries and scientific research institutions to enhance the development of breast cancer treatment technologies and natural medicines. Therefore, extraction of effective and nontoxic anti-cancer drugs from animals, plants, and microorganisms with no toxic side effects is still an important direction of current research. Through the review, this paper concludes that:

(1) In terms of the volume of literature published on natural products on breast cancer treatment per year and the type of discipline, the number of articles published in each year worldwide shows an increasing trend from year to year. From 2020 to present, the number of articles published by researchers has grown rapidly. The number of articles published per year remains above 300, and the type of articles is mainly primary research articles. In addition, different disciplines conduct research on breast cancer natural medicine from different perspectives, among which pharmacology has published the largest number of articles in nearly 30 years.

(2) In terms of cooperative networks, breast cancer natural drug development involves mutual cooperation between multiple countries. China was the country with the highest number of published articles in this field (631, 22.62%). The United States ranked 2 (604, 21.65%), and India ranked 3 (330, 11.83%). The China Academy of Sciences, the University of Texas, King Saud University and other institutions collaborate extensively and are the most active units in natural medicine R&D. Of all scientific research institutions worldwide, the Chinese Academy of Sciences publishes the highest number of articles, resulting in 65 papers. The authors who have published the most articles have Efferth, Thomas, Kuete, Victor, andSethi, Gautam. As shown from the above data analysis, China and the United States have the most profound impact on breast cancer natural drug discovery in recent years.

(3) From the key words co-occurrence analysis, the most frequently occurring key words were breast cancer (1030 times), followed by natural product (974 times), which were the search subject terms in the field. The two keywords "in vitro" (463 times), "apoptosis" (414 times) also had a high search frequency. "Natural product" was the key word with the highest intensity of occurrence (13.07), followed by "death" which was ranked 2nd (11.02). The 5 keywords "flavonoid", "essential oil", "drug delivery", "nanoparticle", and "binding" showed the strongest level of emergence within the past 3 years (2020-2022). This indicates that extraction of drugs from organisms and their metabolites is an important direction in the current development of anticancer drugs.

(4) From the cited literature, the articles by Bray F (2018) and Newman DJ (2016), which are key papers in the field of natural medicine for breast cancer, were cited a total of 168 times and 119 times respectively. In addition, the top 10 cited papers were mostly reviews, which included an analysis of the global burden of breast cancer, anticancer natural drug discovery, the role of the genome in drug discovery, cancer mitigation approaches, microbial drug discovery, and so on.

(5) From the research hot spot cluster knowledge map, key problems identified in this research field include 5 main cluster maps including animal and plant natural products, microbial drugs, breast cancer, genes, and inhibitors. Life science and pharmaceutical researchers not only focus on how to extract anticancer drugs from natural animals and plants, microbes, and their derivatives, but also pay much attention to the intrinsic genetic factors of the human body and their influence on cancer cells. The development of natural medicines for breast cancer together with the mining of genetic knowledge play an important role in treating human breast cancer.

Author Contributions: Conceptualization, L.G.; methodology, L.G. and T.Y.; software, Z.X.; validation, L.G., T.Y. and C.C.; formal analysis, L.G.; investigation, T.Y.; resources, L.G.; data curation, B.L.; writing—original draft preparation, L.G.; writing—review and editing, T.Y.; visualization, L.G. and Z.X.; supervision, L.G.; project administration, L.G.; funding acquisition, L.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Teaching Reform Project of Guangdong Provincial Department of Education(Nos. GDJX2020009).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Supplementary material for this article is available on Web of Science(December 31, 2022). https://www.webofknowledge.com

Conflicts of Interest: The authors declare no conflict of interest.

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