RESEARCH ARTICLE

Mycomedicine research hotspots and trends in the antitumor effects of bacteriophages - based on CiteSpace and VOSviewer analysis

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Tumors are one of the diseases that seriously endanger human life and health. The existing treatments can cause side effects and drug resistance. The anti-cancer potential of medicinal mushrooms has attracted much attention due to their safety and efficacy. Understanding the research hotspots and trends in this field provides ideas and basis for Mycomedicine to treat tumors. The English literatures related to the antitumor effects of Mycomedicine were searched through Web of Science (WOS), PubMed (PM), and Elsevier ScienceDirect (SD) from January 1, 2012 to December 31, 2021. CiteSpace and VOSviewer were used to analyze and display the high frequency ranking of literatures, author collaboration view, keyword co-occurrence and clustering, and the network of issuing institutions and the number of articles issued. After screening, a total of 5,342 English literatures were included in the analysis. The most popular antitumor bacteriophages were *Ganoderma lucidum*, *Poria*, *Morus alba*, and *Cordyceps sinensis*. The high-frequency keywords were "*Ganoderma lucidum* triterpenoid", "*Ganoderma lucidum* acid", and "Biological activity". The related literature focused on the basic research of the extraction and structural properties of the active substances of edible and medicinal mushrooms and the anti-tumor mechanism of the mushroom components. Compared with traditional anticancer therapies, Mycomedicine demonstrated higher safety and multi-target pharmacological efficacy. The Mycomedicine activity analysis, reagent development, and antitumor mechanism research would become the main trend of future development in this field.

Keywords: medicinal mushrooms; keyword clustering; visualization analysis; active ingredients; *Mycomedicine*.

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Introduction

Tumors seriously threaten human health and life safety, and their morbidity and mortality rates are increasing worldwide [1, 2]. The main methods of cancer treatment are surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, among which chemotherapy is considered as one of the main means of cancer treatment. However, most chemotherapeutic drugs have problems such as short half-life and non-specific biological selectivity, which also cause serious side effects and drug resistance [3, 4]. Therefore, researchers have started to look for alternative therapies for tumors from natural products, which have higher safety and multi-target pharmacological efficacy compared to conventional therapies. The studies found that some medicinal mushrooms had low toxicity, low side effects, and a wide therapeutic range, and were receiving increasing attention due to their safety and efficacy. Mycomedicine refers to natural drugs with preventive, therapeutic, and health effects prepared by harvesting the effective extracts or specific parts of mushrooms, which includes *Ganoderma* *lamblia*, *Ganoderma lucidum*, *Morus lucidum*, *Poria*, *Cordyceps sinensis*, *etc*. [5-9]. So far, more than 980 species of medicinal mushrooms are known in China, which is the country with the largest number of mushroom species in the world [10]. Mycomedicine is a unique class of natural medicine that has been widely used in Asian countries for thousands of years. Modern Mycomedicine consists of fruiting bodies, spores, or other tissues of medicinal fungi, as well as bioactive components extracted from them including polysaccharides and triterpenoids, *etc*. Since the discovery of the famous fungal extract, penicillin, by Alexander Fleming in the late 19th century, researchers have realized the significant antibiotic and other medicinal values of fungal extracts. Additionally, these natural compounds could impede tumor angiogenesis, inhibiting cancer cell development and spread. Mycomedicine could limit cancer cell invasion by inhibiting the activity of matrix metalloproteinases which played an important role in tumor cell invasion [11-13].

Among the visual research software used for literature analysis, CiteSpace and VOSviewer are the most widely used and can comprehensively analyze the relationship and knowledge cluster progress of different structural units [14]. CiteSpace software developed by Chaomei Chen's team at Drexel University, Philadelphia, Pennsylvania, USA can perform metrological statistics and analysis of literature related to a certain research field, which can better reveal the research hotspots, trends, and development patterns in a field [15, 16]. VOSviewer is a visual bibliometric software developed by Nees Jan van Eck's team at Leiden University in Leiden, Netherlands for analyzing author networks, keyword clustering, emergence, and mapping literature knowledge, which can clearly present the degree of association of literature knowledge clusters [17]. Despite the increasing publication of literature in the field of oncology therapeutics, especially natural drug research in recent years, there is still a lack of visual analysis of Mycomedicine in the field of antitumor. This study used CiteSpace and VOSviewer to sort out, analyze, and visualize the research hotspots and trends of Mycomedicine in the field of antitumor in order to provide reference and theoretical basis for future Mycomedicine antitumor research.

Materials and Methods

Data resources

To analyze the research hotspots and trends in the field of antitumor in Mycomedicine in the last decade, the search period was set from January 1, 2012 to December 31, 2021. The websites of Web of Science (WOS) (http://apps.webofknowledge.com/), PubMed (PM) (https://pubmed.ncbi.nlm.nih.gov/), ScienceDirect (SD) (https://www.sciencedirect.com), and China National Knowledge Infrastructure (CNKI) (https://kns.cnki.net/) were employed for literature search. The search terms were “Antineoplastic”, “Mycelium”, “anticancer”, “Edible and medicinal fungi”. The search was conducted through a combination of free words and subject terms. The specific literature search strategy was shown in Table 1. Each resulting entry contained full record information including author, abstract, keywords, year of publication, and was saved as a plain text file. The criteria for literature inclusion and exclusion were set as follows:

(1) Inclusion criteria: relevant literature that fitted the antitumor theme of Mycomedicine; Mycomedicine sources included, but not limited to, *Ganoderma lucidum*, *Poria cocos*, *Agaricus blazei*, *Cordyceps sinensis*, *Shiitake mushroom*, *Wood ear*, *Matsutake mushroom*, *Enoki mushroom*, *Bamboo fungus*, *etc*.

(2) Exclusion criteria: The keywords, abstracts, and content of literature were unrelated to the antitumor topic of Mycomedicine; Conference papers; Scientific and technical results; Newspaper publications; Patents; Duplicate literature.

Table 1. Literature retrieval strategy.

Database	Search Type	Subject Classification	Language
WOS	TS = edible fungi (*morel, shiitake, flammulina velutipes, bamboo fungus, agaric, tremella, hericium erinaceus, pleurotus ostreatus, shiitake mushroom, matsutake, straw mushroom, truffle*, etc.) AND TS = medicinal fungi (*ganoderma lucidum, tuckahoe, polyporus, cordyceps sinensis, cordyceps militaris, leiwan, cicada flower*, etc.) AND TS = tumors (liver cancer, lung cancer, breast cancer, rectal cancer, colon cancer, stomach cancer, cervical cancer, etc.) AND TS = Antineoplastic	Chinese materia medica; molecular biology; Preventive Medicine and Hygienics; natural pharmacology; pharmacology; pharmaceutical analysis.	English
PM		Clinical medicine; basic medicine; Microbiology; Molecular Biology.	English
SD		Microbiology; Molecular Biology; Bioengineering; Structure and Function of Biomacromolecules.	English

Table 2. Analysis software and parameter setting.

Software	Applications	Purpose	Time partitioning	Time slice	Node type	Top N
CiteSpace 6.1.R3	citespace. alias	Timeline mapping construction. Keyword clustering, emergent visual analysis.	2012-2022	1	Keywords	50
VOSviewer 1.6.17	Thesaurus. terms.txt	Core author collaboration analysis. Geographic visualization. Access to high-frequency keywords (frequency ≥ 3 times)	2012-2022	-	-	-

Data analysis

The researcher independently screened and cross-validated the English-language literature with each entry containing "full record and cited references". A total of 5,342 English-language documents was screened with the caption information exported in plain text Refworks (ProQuest, Ann Arbor, Michigan, USA) format. The sieved bibliographic data were imported into Microsoft Excel 2021 (Microsoft, Redmond, WA, USA) for summary analysis. EndNote X9 (EndNote, Philadelphia, PA, USA) and NoteExpress 3.1.0 (Beijing Aegean Lezhi Technology Co, Beijing, China) were used for de-duplication and deletion of missing fields. CiteSpace 6.1.R3 (Drexel University, Philadelphia, PA, USA) and VOSviewer 1.6.17 (Centre for Science and Technology Studies of Leiden University, Leiden, Netherlands) were used for Mycomedicine hotspots and trends in antitumor research. The visualization analysis was performed by using Origin 13.0 (Malvern Panalytical Company, Amherst, MA, USA) for posting statistics and graphing. The specific parameter settings for the visualization analysis were shown in Table 2.

Results

Analysis of the number of articles published

After screening, 5,342 papers were included for visual analysis, and the specific annual publication volume was shown in Figure 1. Statistical analysis of the publication volume could reflect the information and changing

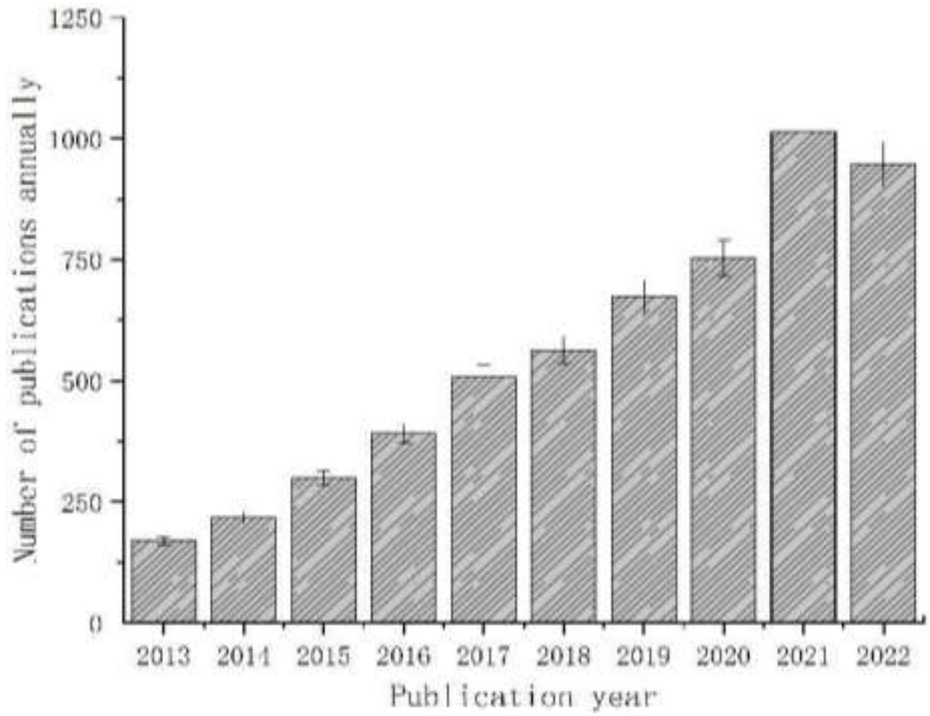

Figure 1. Periodicals published in the literature on antitumor effects of Mycomedicine.

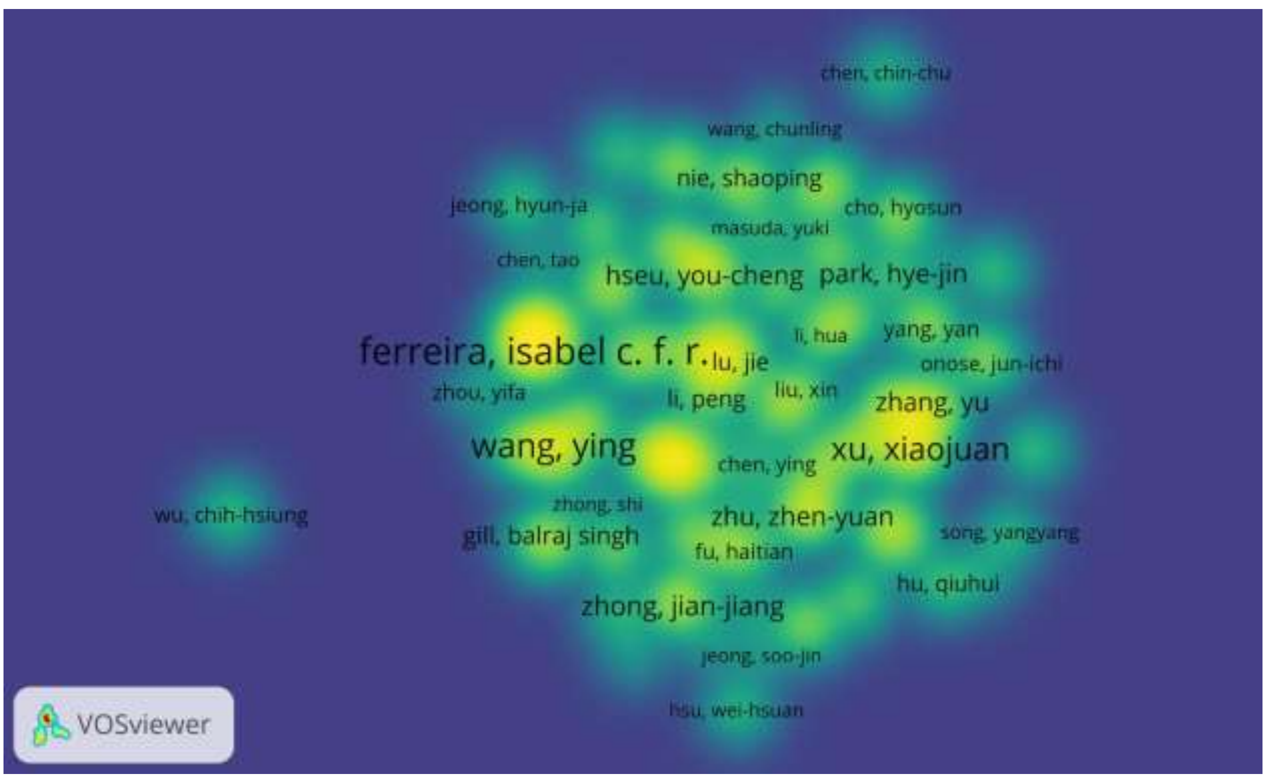

Figure 2. Core author density view of Mycomedicine antitumor effect literature from 2013 to 2022. (**Note:** The larger the author visualization area, the greater the volume of articles posted, and the greater the density in the yellow area, the closer the author collaboration)

Figure 3. Cooperation network of major countries.

trends of the research team in the field of Mycomedicine antitumor [18]. The overall publication volume in this field had been increasing year by year in the last decade with the largest increase of 1,014 articles in 2021, which was presumably due to the fact that, with the broaden of global research workers' interest and in depth studies in *Ganoderma lucidum*, *Cordyceps*, and other medicinal mushrooms, as well as the optimization of international journals' policies, researchers over the world preferred to submit more articles to English journal societies. In general, Mycomedicine antitumor field research has always received continuous attention from the academic community.

Author collaboration mapping analysis

The density view of core authors including first author or corresponding author can, to a certain extent, reflect the social relationship among authors in the field, and has important reference value for academic resource sharing, scientific and technological achievement assessment, and talent introduction [19, 20]. The core author density view was constructed by the Author function in VOSviewer 1.6.17, and the results were shown in Figure 2, which demonstrated the authors with ≥ 7 publications. The results showed that 5,342 English literatures involved 12,632 authors. Among which, 926 were core authors, and the global research in this field formed a research team represented by Ferreira, Isabel c.f.r., Wang Ying, Xu Xiaojuan, Hye-jin, and so on. The core authors mostly adopt the "integration-sharing" model, *i.e.*, regional cooperation across regions in the same research area, and the integration and sharing of resources by relying on the advantages of senior research teams, which also enabled the team to study in the field in depth and produce more high-quality research results while maintaining scientific vitality, forming a virtuous cycle. The team would be able to maintain its research vitality and produce more quality research results, forming a virtuous cycle.

Geographical visualization analysis of literature

The geographic visualization of publication volume was constructed by using VOSviewer to analyze the publication volume of countries/regions (Figure 3). A total of 70 countries/regions had made outstanding contributions to Mycomedicine antitumor field research, among which China had the most publications with 786 articles. The top five countries in terms of publication volume were

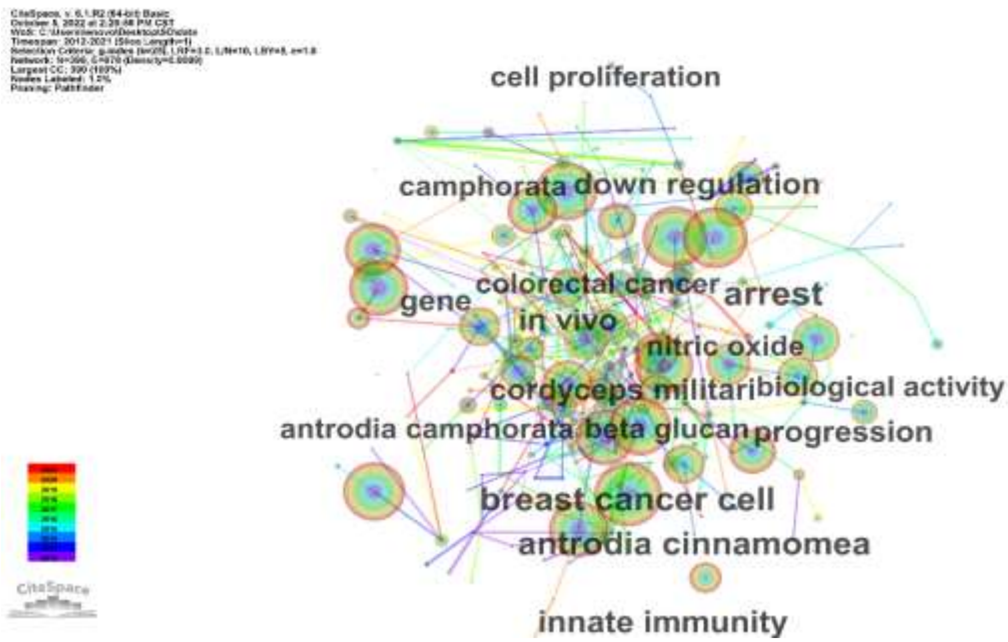

Figure 4. Keyword co-occurrence network of Mycomedicine antineoplastic literatures from 2013 to 2022.

China, USA, Japan, Germany, and India. The main reasons for more publications in China were (1) long history that Chinese mushrooms have a history of more than 2,000 years; (2) diverse species that China has identified more than 960 species of edible and medicinal mushrooms, which is the largest number of species in the world; (3) in-depth research that Chinese researcher, Chen Meipeng, and others were the first to use dung grass culture to develop strains in the 1950s, while China was the first to domesticate edible mushrooms such as silver fungus and monkey head mushroom in the international arena; (4) medicinal and food that the mushrooms for food and medicine are closely related to the Chinese food culture and medicine culture. As shown in Figure 3, there was transnational cooperation between countries with a large number of publications such as close cooperation between China Medical University and the University of Tokyo and Seoul National University in 2014, and closer scientific cooperation and exchange between Zhejiang University and the University of Belgrade and Waseda University in 2020. The academic cooperation and close communication between countries are conducive to the depth of research topics and the output and transformation of research results in this field.

Keywords analysis

The keyword co-occurrence network was shown in Figure 4. A total of 7,269 keywords were involved in the English literature, and the ones that appeared more frequently were cell proliferation, camphorata down regulation, gene, colorectal cancer, active ingredient, *Ganoderma lucidum* polysaccharide, *Ganoderma lucidum* triterpene, *cordyceps militari*, breast cancer cell, beta glucan, innate immunity. The clustering analysis of keywords in Chinese and English literatures was performed by likelihood (LLR) algorithm in CiteSpace, and the structure was shown in Figure 5. In which "#" indicated key clustering words, the more nodes represented the higher research hotness in this direction, and the larger shear words represented the higher key degree. Modularity Q was 0.5863, which was greater than 0.3, indicating significant keyword clustering. The English literature mean Sihouette was 0.7582, which was greater than 0.5, indicating that the mapping results were reasonable. The 14 keywords of English literature were clustered with the tag #0 *poria cocos*, #1

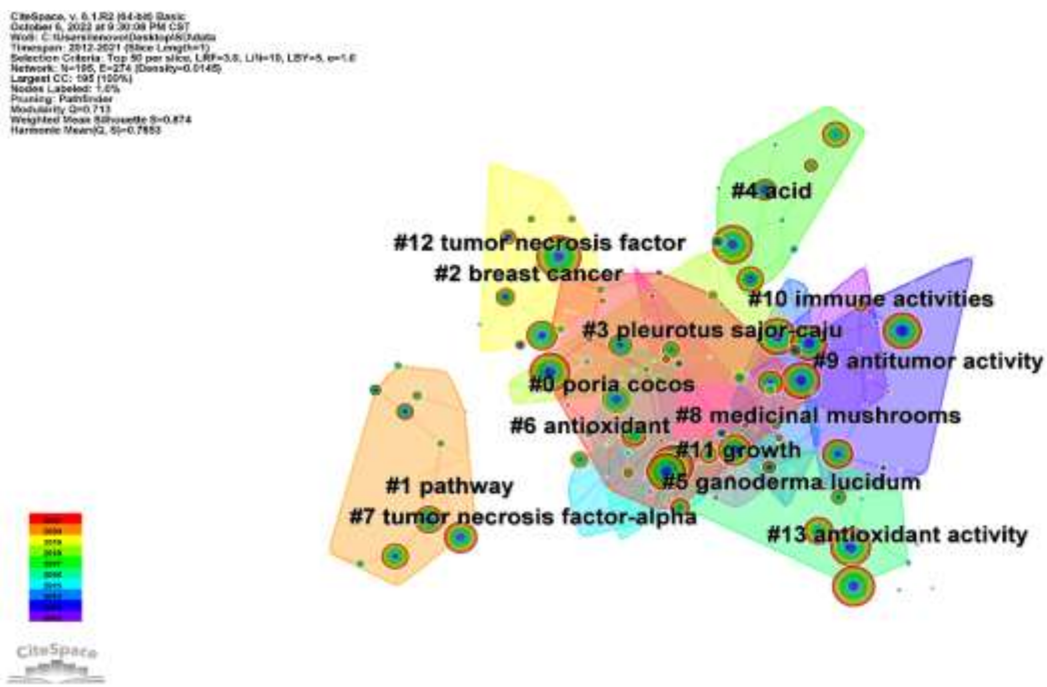

Figure 5. Keyword clustering mapping of Mycomedicine antitumor literatures in English from 2013 to 2022.

pathway, #2 breast cancer, #3 *pleurotus sajor-caju*, #4 *Ganoderma lucidum* acid, #5 *Ganoderma lucidum*, #6 antioxidant, #7 tumor necrosis factor-alpha, #8 medicinal mushrooms, #9 antitumor activity, #10 immune activities, #11 growth, #12 tumor necrosis factor, and #13 antioxidant activity. Among them, #0, #3, #5, and #8 discussed the research objects, #6 and #13 discussed the antioxidant activity of the bacteriophage, #1 and #10 discussed the research method and research direction, and #7 and #12 discussed the main research factors. The keyword emergence and timeline analysis are important references for sorting out the development trend and research pulse in the field of Mycomedicine antitumor, and the keyword emergence and timeline mapping were constructed by Burstness in CiteSpace in order to explore the latest research dynamics in this field. The burst threshold was 0.5, the time span was 1, and the maximum number of citations per time zone was set to 50. The results of keyword burst analysis were shown in Table 3, and the timeline results were shown in Figure 6.

Mycomedicine antitumor English literature research hotspots during 2012 to 2016 were that (1) the research objects were mycelium and dendritic cells of edible and medicinal mushrooms with the representative mushrooms of shiitake, morel, and white mushrooms; (2) the malignant tumor cell were small cell osteosarcoma, primitive neuroectodermal tumor (PNET), and Ewing's sarcoma; (3) the main factors studied were tumor necrosis factor-α (TNFα); (4) the research methods were *in vitro* animal models and mycological interventions; (5) the anticancer mechanism of action studied were the production of cytotoxicity, inhibition of tumor-induced angiogenesis. During the years of 2017 to 2021, the research hotspots were that (1) research objects were new mycological active ingredients such as *Ganoderma lucidum* polysaccharides, *Ganoderma lucidum* triterpenes, *Poria* polysaccharides, Shiitake active protein, *etc*.; (2) the content of new intestinal flora and melanoma cell specificity, *etc*.; (3) the new research methods such as RT-PCR, cell migration, cell value-added, and protein

Table 3. List of English literature analysis highlights.

Keywords	Strength	Initial year	Plunge year	2013-2022
Edible mushroom	4.27	2013	2014	
Dendritic cell	3.17	2013	2014	
Mycelia	4.2	2013	2015	
Tumor cell	4.32	2014	2016	
Tumor necrosis factor	4.42	2015	2016	
Inflammatory bowel disease	3.67	2016	2018	
Signaling pathway	3.55	2016	2018	
Arrest cell cycle	3.48	2016	2017	
Anticancer	4.95	2017	2019	
Carcinoma	4.66	2017	2019	
Cell migration	3.88	2017	2019	
Trirerpenoid	3.47	2017	2022	
Nano carrier	3.64	2019	2022	
Lingzhi	3.43	2019	2022	

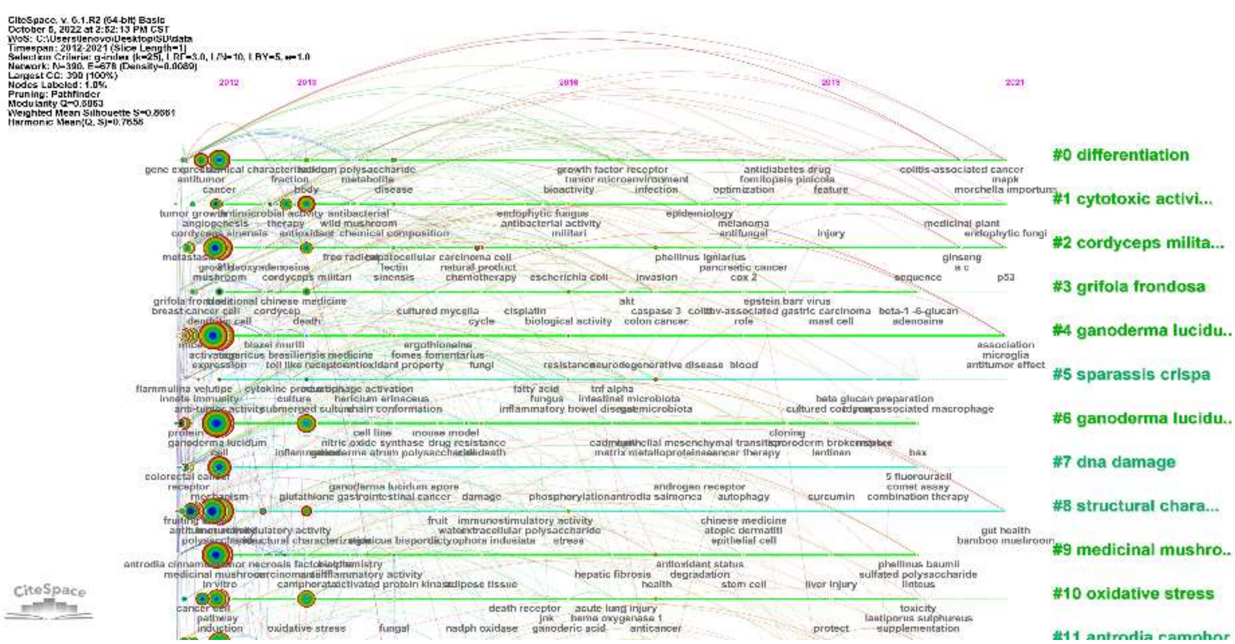

Figure 6. Timeline of keywords in English literatures on antitumor of fungicides from 2013 to 2022 (**Note:** nodes indicated high-frequency keywords, the larger the node indicated the higher the frequency of occurrence, and the chart from left to right indicated the time from near to far)

blotting, *etc*.; (4) Mycomedicine regulation of ERK, PI3K/Akt, JAK/STAT5, and other signaling pathways; (5) TNF-α.

Discussion

Based on keyword clustering, co-occurrence, and timeline spectrogram analysis, the results showed that the research hotspots in the field of Mycomedicine antitumor were mainly focused on the following two aspects.

The first aspect was Mycomedicine bioactivity studies such as extraction, identification, and structural analysis of chemical components including steroids, triterpenoids, glycoproteins, lectins, mannans, flavonoids, alkaloids, polysaccharides, lipids, and peptides in *Ganoderma lucidum* and *Agaricus blazei* by ultra performance liquid chromatography (UPLC) with single markers. Previous studies had confirmed the significant inhibitory effects of triterpenoids in *Ganoderma lucidum* spore powder on human gastric cancer SGC-7901, lung cancer A549, and lymphoma Ramos cells by UPLC and single marker quantitative analysis [21-23]. Lin, *et al*. found that *Ganoderma lucidum* extract (13.5% *Ganoderma lucidum* polysaccharides, 6% *Ganoderma lucidum* triterpenes) could increase the rates of lymphocyte transformation and macrophage phagocytosis in lung cancer mice with the same effects on hepatic arterial duct cancer cells, breast cancer MCF7, and cervical cancer Hela cells [24]. Wang, *et al*. analyzed the extraction, purification, structural characteristics, and antitumor activity of the polysaccharide of Chinese *Magnolia vine* fruit, which could increase the cytotoxicity of nature killer (NK) cells and lymphokine-activated killer (LAK) cells against targeted K562 malignancies by synergistically enhancing the immune response [25]. It was also shown that Chinese *Magnolia vine* fruit polysaccharide increased the cytotoxicity of K562 malignancies by activating macrophages and releasing a large number of cytokines such as interferon to indirectly inhibit or kill tumor cells [26]. Pandya, *et al*. demonstrated that shiitake mushroom polysaccharide, *Ganoderma lucidum* polysaccharide, and mushroom glycopeptide complexes could inhibit the proliferation of malignant tumor cells [27]. Chen, *et al*. analyzed the regulation of *Ganoderma lucidum* extract on A594 protein expression in non-small cell lung cancer by Western blot, calculated the tumor suppression rate and organ coefficient in animal models, and confirmed that *Ganoderma lucidum* extract induced apoptosis in lung cancer cells by downregulating Bcl-2 and activating Caspase-3 [28]. Hsu, *et al*. extracted cordycepin from *Cordyceps sinensis* and confirmed its ability to reduce interleukin-6, nitric oxide synthase (NOS) expression, and metastatic density of lung cancer cells [29]. Patients who received 4 mg daily of shiitake mushroom polysaccharide chemo-immunotherapy for 12 weeks showed increased proliferation of cytotoxic T cells and CD56+, CD3+, and NKT cells along with increased levels of TNF-α, IFN-γ, and IL-12 [30]. The search for new antitumor agents from mushrooms and the assessment of their therapeutic value has become a matter of intensive research [31].

The second aspect was the studies on the mechanisms of anticancer action of Mycomedicine, which included (1) the regulation of immune response. Smina, *et al*. found that *Ganoderma lucidum* triterpenes could alter the expression levels of D1, Bcl-xl, Caspase-9, and other cell cycle proteins in breast cancer cells by studying the regulation mechanism of Mycomedicine on the expression of apoptotic proteins [32]. Zhang, *et al*. determined the ratio of effector T cells to regulatory T cells in a liver cancer mouse and found that Mycomedicine could exert antihepatocellular carcinogenic activity by upregulating the expression of micro RNA-125b; (2) the cytotoxic to tumor cells. The studies found that *Ganoderma lucidum* acids N, E, and A isolated from *Ganoderma lucidum* substrates could be toxic to Hep-G2 and p-388 tumor cells, and could reduce cancer cell migration, decrease their survival rate, and significantly inhibit the release of IL-6, IL-8, and MMP2 in cancer cells [33, 34]; (3) inhibit tumor cell-induced angiogenesis. The research found that Mycomedicine could inhibit angiogenesis induced by stromal gel, vascular endothelial growth factor, and heparin. It was confirmed that Mycomedicine could inhibit subcutaneous tumor growth in SMMC-7721 nude mouse liver cancer model [35]. It had been hypothesized that the antitumor activity of Mycomedicine might be related to its inhibition of angiogenesis [36, 37]. Liu, *et al*. combined Mycomedicine with gefitinib and oxaliplatin and confirmed the significant Mycomedicine inhibitory effects on vascular endothelial growth factor receptor gene and protein expression when constructing an A549 tumor cell bearing nude mouse model [38]; (4) blocking cell cycle and inducing apoptosis. Mycomedicine could activate apoptotic factors Caspases-3 and Caspases-9 and inhibit the value-added of cancer cells from G_1 to DNA synthesis phase (S phase) period [39]. Qu, *et al*. demonstrated that *Ganoderma lucidum* triterpenes could decrease the expression of anti-apoptotic proteins and increase the expression level of pro-apoptotic proteins by inhibiting the expression of matrix metalloproteinases, which inhibited the growth of prostate cancer cells as well as their migration and invasion while inducing apoptosis [40]. Kong, *et al*. found that *Ganoderma lucidum* polysaccharides could activate Caspase-3 expression and inhibit cyclooxygenase-2 expression to accelerate tumor cell apoptosis by establishing a mouse model of cervical cancer [41]. The triterpenoids in Mycomedicine accelerated tumor cell apoptosis by blocking G_0 phase to pre-DNA synthesis (G_1 phase) of the hepatocellular carcinoma cell cycle, causing cell cycle arrest and inhibiting the growth of hepatocellular carcinoma cells [42]; (5) regulation of signaling pathway. PI3K/Akt signaling pathway is an important pathway that regulates the biological process of tumor cells. Activated PI3K can bind to its downstream molecule Akt, which will lead to its phosphorylation and then continue to activate downstream apoptosis-related proteins [43]. Mycomedicine inhibited PI3K and Akt phosphorylation. The inhibitory effect was proportional to the extract concentration. Through the regulation of PI3K/Akt signaling pathway, Mycomedicine could inhibit the proliferation and migration of SK-HEP-1 and Huh-7. Mycomedicine also played a role in inducing G_1 phase cell cycle arrest and apoptosis [44].

Conclusion

Based on the above findings, this study made the following outlooks on the field of Mycomedicine antitumor: (1) research in this field is currently focused on single bacteriophages, and in the future, the research themes of compound Mycomedicine development and drug combination use can be increased, and its mechanisms of action in various tumor diseases can be explored in depth to provide new ideas for Mycomedicine applications; (2) global authors have a central role in the field of Mycomedicine antitumor, and there are more collaborative exchanges within the team. In the future, academic cooperation and exchanges between institutions and teams can be increased, and resources can be integrated and shared to produce more high-quality results; (3) international academic exchanges and scientific cooperation should be strengthened to promote the application and promotion of Mycomedicine.

Acknowledgements

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