



Research article

Hotspots and future trends of autophagy in Traditional Chinese Medicine: A Bibliometric analysis

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ABSTRACT

Objective: To discuss the hotspots and future trends of autophagy in traditional Chinese medicine (TCM) and provide a reference for researchers in this field.

Method: Using visual analysis tools, metrological statistics and visual research on the pertinent literature in the area of autophagy use in TCM were undertaken in the core collection database of the Web of Science. By examining the authors, keywords, research circumstances, research hotspots, and trends of linked research, the use of autophagy in TCM was investigated.

Results and Conclusions: A total of 916 studies were included, among which Beijing University Chinese Medicine was the largest number of advantageous research institutions, followed by Shanghai University Traditional Chinese Medicine and Guangzhou University Chinese Medicine. The keywords of literature research primarily comprise apoptosis, activation, inhibition, pathway, mechanism, oxidative stress, proliferation, NF- κ B, cancer, mtor, etc. At present, the research on autophagy in the field of TCM is increasing on a year-to-year basis. The research has focused on the role played by TCM in malignant tumors, atherosclerosis, Alzheimer's disease through autophagy, and the regulation of autophagy signaling pathways (e.g., PI3K/AKT/mTOR signaling pathway, TLR4 signaling pathway, nrf2 signaling pathway and NF- κ B signaling pathway). In the future, the therapeutic effect of TCM on chemotherapy-resistant tumor cells through autophagy pathway, the role of TCM mediating mitophagy and activating autophagy function, and the therapeutic effect of TCM components represented by luteolin on tumors, asthma, myocardial injury and other diseases through autophagy mechanism will be the research hotspots in the future.

1. Introduction

Autophagy is a highly conserved intracellular material catabolism and material recycling process in the evolution of eukaryotes [1], recycling non-essential proteins, organelles and macromolecules in cells. Autophagy is a protective mechanism for the body to achieve self-purification by degrading damaged structures under the adverse stimulation of the internal and external environment [2]. Cell autophagy can be induced by hypoxia, lack of energy substances, as well as oxidative stress. However, insufficient autophagy or excessive autophagy will result in insufficient energy and eventually cause autophagic cell death [3]. The role played by autophagy in

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self-protection and death induction is consistent with the etiology of viscera deficiency, healthy qi deficiency and pathogenic excess in traditional Chinese medicine (TCM), involving the pathogenesis characteristics of imbalance between yin and Yang in TCM. Its role may be the micro-embodiment of the balance between yin and Yang, which lays a theoretical basis for autophagy to demonstrate the mechanism of action of TCM. Thus, the application prospect of autophagy in the study of TCM is very broad. Current studies have found that autophagy is involved in the pathogenesis of cancer, myopathy, neurodegeneration, infection and cardiovascular disease [4, 5]. TCM, a traditional medicine in China, has played an outstanding role in the exploration of new pharmacological mechanism and clinical application over the past few years. In particular, the mechanism of TCM treating diseases through autophagy has been widely concerned by scholars. For instance, pharmacological studies have suggested that the active components of *Bupelum*, *ligusticum chuanxiong*, *andrographis*, *turmeric*, and *salvia miltiorrhiza* are capable of regulating cancer, neurodegenerative diseases, and cardiovascular diseases through autophagy [6–10]. Moreover, Intervention with multiple components, multiple targets, and several ways is the material basis for TCM's effectiveness, with more complex biological function [11]. Accordingly, the research in this field has become a research hotspot.

The number of published studies on autophagy in the field of TCM has increased on a year-to-year basis, whereas there have been rare relevant bibliometric studies. Scientific knowledge mapping is a promising research direction of literature scientometrics and a visual presentation of scientific knowledge [12]. It is capable of helping scientific researchers conduct quantitative and qualitative research in the field of science more intuitively, accurately, and quickly, discover its knowledge structure and detect potential new trends. Thus, the authors, institutions, keywords, literature research status, and development process of autophagy in the field of TCM were classified in this study using the method of scientific knowledge mapping, and the research hotspots and development trends were discussed to provide a reference for the research in this field.

2. Data and methods

2.1. Data sources

The Web of Science Core Collections Database (WOS) was retrieved. Subject search (TS=(“traditional Chinese medicine” OR “Chinese herbal medicine ” OR “Chinese herbology” OR “Chinese medicine” OR “Chinese herb”)) AND TS=(autophagy), time range January 1, 1985 to Dec 31, 2022. A total of 921 studies were obtained, of which studies and review studies were retained, and 916 studies were included. The selected documents were selected as full records and cited references and exported in txt text format.

2.2. Data processing

CiteSpace 5.8.R3 was used in the study. The parameters were set as time slicing from Jan 2009 to Dec 2022 (the relevant literature on the application of autophagy in TCM research was first published in 2009); The time slicing was set as 1 year; Node types: author, institution, Keywords. Node is author: threshold (top N per slice) = 25, pruning = none; Node is institution: threshold (top N per slice) = 25, pruning = none; Node is keywords: threshold (top N per slice) = 25, pruning = pathfinder + pruning the merged network. According to the parameter setting of the respective node, visual analysis is carried out to generate the knowledge map of researchers' authors and institutions, as well as the knowledge map of keywords' co-occurrence, emergence, and clustering, and the timeline of keywords.

The literature retrieved from the WOS database was recorded as “full records and cited references” and exported as plain text format. The data were input into VOSviewer 1.6.18 software, and the calculation method was set as full calculation. The corresponding thresholds were set in accordance with different analysis items, and the visual atlas was generated for collaborative network analysis.

3. Results

3.1. Publication trend

Literature relating to the application of autophagy in TCM research was first published in 2009. Cheng CY et al. [13] examined the colon cancer cells' in vitro resistance to TCM Sanchong Kuijian Decoction (SJKJT). It was established that SJKJT could, in a time- and dose-dependent manner, up-regulate the expression of the MAP-LC3-II protein in colon 205 cells. The stimulation of autophagy is thought to be one among the biochemical mechanisms by which SJKJT prevents the proliferation of colon 205 cells. This study provides a basis for TCM to treat human diseases through autophagy. Since then, this kind of research has been published every year, and has gradually become a research hotspot. See Fig. 1 for the publishing trend. The number of relevant literature published in this field can be classified into three stages. From 2009 to 2015, relevant literature was published every year, whereas the number was small, showing a fluctuating upward trend. From 2016 to 2022, the number of published studies increased year by year, with more than 100 studies published in 2019–2021. In 2022, the number of published studies rose to more than 200 and peaked. Thus, at present, the application of autophagy in TCM has a good prospect, and there may be more literature research in the future.

3.2. Author collaboration network and co-citation

Fig. 2 is obtained using CiteSpace to analyze the authors of the studies. The map contains 426 nodes, 578 connections, and has a network density of 0.0064. In the map, the corresponding node stands in for a single author. The connections or collaboration between

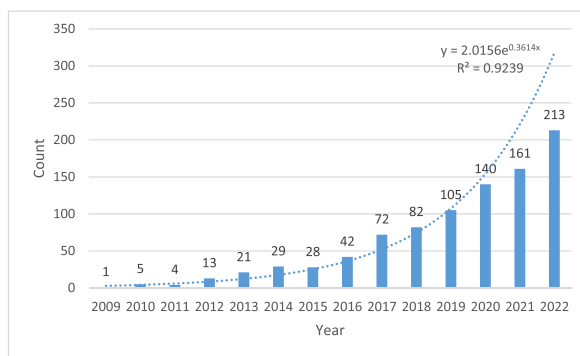


Fig. 1. Annual distribution of published studies on the application of autophagy in TCM research.

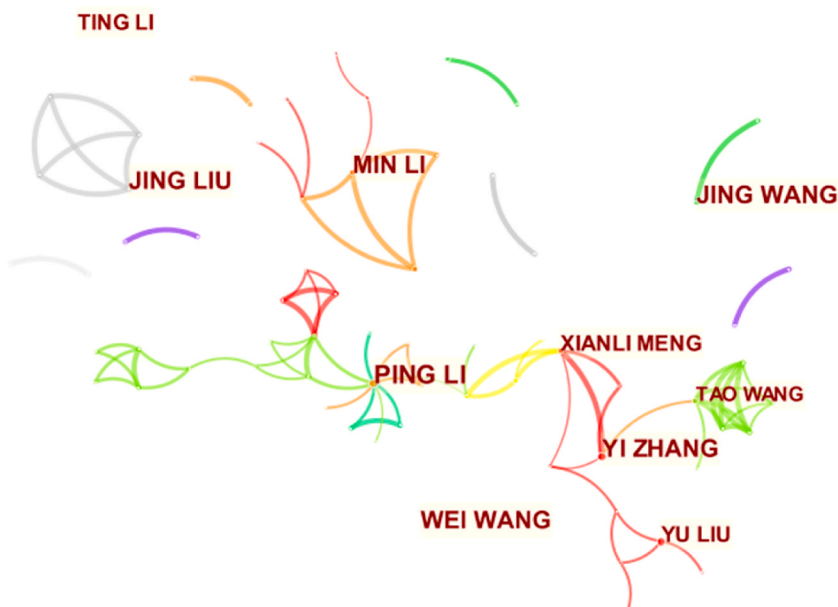


Fig. 2. Core author collaboration atlas of autophagy application in TCM research.

the writers is shown by the lines connecting the nodes. The collaboration is closer the bond is thicker [14]. The team represented by PING LI mainly studies the mechanism by which TCM improves diabetic nephropathy, Alzheimer’s disease, atherosclerosis and other diseases through the autophagy pathway. The results revealed that the main research contents of the team represented by WEI WANG are the treatment of heart failure by TCM extracts through autophagy pathway and the protective effect of TCM extracts on cardiotoxicity attributed to chemotherapy drugs through autophagy pathway. Furthermore, as revealed by the author’s cooperation network diagram, there is little cooperation among the research teams, and the cooperation network is relatively loose, probably related to the differences of research directions or diseases among the teams. Table 1 lists the top 10 authors and co-cited authors.

3.3. Analysis of institutional cooperation network

The publishing organizations in the listed studies were examined using the CiteSpace, and Fig. 3 was created. The atlas contained 282 nodes, 322 connections, and had a 0.0081 network density. A total of 282 institutions were involved, and 10 institutions published more than 24 studies (Table 2).According to the findings, Guangzhou University of Chinese Medicine (42 times), Shanghai University of Traditional Chinese Medicine (46 times), and Beijing University of Chinese Medicine (46 times) were the research institutions with the most studies (39 times). The issuing institutions primarily comprise Chinese medicine colleges, medical and pharmaceutical universities, etc. It may be related to the strong academic atmosphere of universities, and there is a certain cooperative relationship between institutions. It may be because most of the research institutions are Chinese institutions, and the cooperation is more convenient. The top three institutions have formed their own cooperation networks, whereas they have little cooperation with each

Table 1
The top 10 authors and co-cited authors.

No	Author	Count	Year	No	Source	Citations	Total link strength
1	Ping Li	9	2017	1	Mizushima,n	190	1417
2	Wei Wang	8	2017	2	Wang,y	132	2121
3	Yi Zhang	7	2021	3	Zhang,y	120	2036
4	Jing Liu	7	2011	4	Liu,j	106	1547
5	Min Li	7	2019	5	Wang,j	101	1333
6	Jing Wang	7	2015	6	Levine,b	97	841
7	Xianli Meng	6	2020	7	Klionsky,dj	96	680
8	Ting Li	6	2018	8	Li,y	94	1470
9	Yu Liu	6	2021	9	Li,j	92	1394
10	Tao Wang	5	2019	10	Zhang,l	92	1066



Fig. 3. Display of autophagy application in the cooperation network of TCM research literature institutions.

Table 2
Top 10 institutions publishing research in the field.

NO	Count	Centrality	Year	Institutions
1	46	0.15	2014	Beijing Univ Chinese Med
2	42	0.17	2012	Shanghai Univ Tradit Chinese Med
3	39	0.09	2015	Guangzhou Univ Chinese Med
4	38	0.28	2011	China Med Univ
5	31	0.2	2016	China Acad Chinese Med Sci
6	31	0.05	2014	Capital Med Univ
7	28	0.06	2019	Chengdu Univ Tradit Chinese Med
8	26	0.1	2016	Tianjin Univ Tradit Chinese Med
9	26	0.04	2017	Zhejiang Univ
10	24	0	2017	Nanjing Univ Chinese Med

other, so they can continue to strengthen cooperation among high-yielding institutions. With a value of 0.1, centrality, a measure of the relevance of a network node's location, indicates that it is important for the development of knowledge structure. The centralization results showed that China Medical University (0.28) , Shanghai University Traditional Chinese Medicine (0.17) , Beijing University Chinese Medicine (0.15) ranked the top three, thus revealing that the research importance of these institutions in this field is relatively high.

Table 3
Autophagy applied to Chinese medicine research fund.

Fund-supporting organization	Quantity	Percentage
National Natural Science Foundation Of China	499	54.48%
China Postdoctoral Science Foundation	39	4.26%
National Natural Science Foundation Of Guangdong Province	32	3.49%
Beijing Natural Science Foundation	23	2.51%
Natural Science Foundation Of Zhejiang Province	23	2.51%
Fundamental Research Funds For The Central Universities	22	2.40%
Ministry Of Science And Technology Taiwan	20	2.18%
National Key R D Program Of China	18	1.97%
National Key Research And Development Program Of China	17	1.86%
Natural Science Foundation Of Jiangsu Province	16	1.75%

3.4. Fund support

Table 3 lists the top 10 funds in terms of funding frequency for the application of autophagy in TCM research. The top 10 funds all originate from China, with 709 studies funded, accounting for 77.4%. To be specific, 499 studies were funded by National Natural Science Foundation of China, accounting for over 50%, suggesting that China stresses the basic research of TCM.

3.5. Keywords analysis

3.5.1. Keywords co-occurrence analysis

Keyword is a high generalization of the theme of studies, and co-occurrence analysis is a co-occurrence map composed of nodes and lines, which is tailored with keywords as nodes. The CiteSpace was used for visual analysis of the included literatures. The atlas contained 484 nodes and 986 connections, with a network density of 0.0084. Table 4 lists the top 20 keywords. Application of Autophagy in TCM Keyword Co-occurrence Network Diagram (Fig. 4). The main research is depicted in this figure in this field. The mechanism of action comprises apoptosis, activation, inhibition, proliferation, oxidative stress, and other pathways. The signaling pathways consist of NF Kappa B, mtor, akt, and other signaling pathways. The research objects are mainly tumor cells. Visual analysis using VOSviewer generated a keyword co-occurrence network map (Fig. 5A) and a superimposed visualization map (Fig. 5B). The co-occurrence network (Fig. 5A) shows that among the 3976 keywords, 291 keywords were screened out and classified into eight clusters with the minimum occurrence 6 times that of the screening criteria. Cluster 1 (96 items) is the role of Chinese medicine autophagy in tumors. Cluster 2 (46 items) represents the role of Chinese medicine autophagy in the treatment of nervous system diseases. Cluster 3 (44 items) is the study of Chinese medicine autophagy in ischemic reperfusion of cardiovascular and cerebrovascular diseases. Cluster 4 (33 items) represents the research on autophagy-associated signaling pathways. Cluster 5 (28 items) is the research of Chinese medicine autophagy in endocrine system diseases and renal disease. Cluster 6 (20 items) represents research on the mechanism of Chinese medicine autophagy in atherosclerosis and lipid metabolism. Cluster 7 (18 items) is the study on the mechanism of autophagy and angiogenesis. Cluster 8 (6 items) represents the study on the Studies of cell death of autophagy. Keyword overlay visualization analysis adds the time factor to keywords, i.e., time is overlaid into the keyword co-occurrence network. Different colors represent the year when the keywords appear, and the time when the keywords appear changes with the color. The greener the color, the earlier it will appear (Fig. 5B).

3.5.2. Keywords cluster analysis

Carrot2 software was used to draw a keyword cluster map (Fig. 6). As depicted in this figure, the current research hotspots consist of the mechanism of action of TCM on tumor cells through autophagy pathway, the identification of mitochondrial autophagy and autophagic genes, the study on PI3K/AKT/mTOR signaling pathway, and the study of TCM on liver diseases through autophagic pathway.

Table 4
Top 20 keywords in terms of frequency.

Serial number	Frequency	Centrality	Year	Key words	Serial number	Frequency	Centrality	Year	Key words
1	630	0.03	2009	autophagy	11	91	0.01	2012	cell
2	393	0.02	2010	apoptosis	12	90	0.16	2010	death
3	144	0.09	2011	activation	13	76	0.04	2015	inflammation
4	119	0	2015	oxidative stress	14	73	0.07	2013	proliferation
5	118	0.06	2011	inhibition	15	69	0.01	2012	cancer
6	114	0.04	2012	traditional chinese medicine	16	61	0.04	2013	growth
7	112	0	2013	mechanism	17	61	0.06	2012	cancer cell
8	108	0	2013	expression	18	55	0.07	2013	nf kappa b
9	108	0.19	2010	in vitro	19	52	0.05	2012	mtor
10	97	0.04	2013	pathway	20	52	0.06	2014	signaling pathway



Fig. 4. Keywords co-occurrence network diagram based on CiteSpace.

3.5.3. Keywords emergence analysis

The term “keyword emergence” describes a sudden and considerable rise in the frequency of keywords. By paying close attention to the research during this time, it is possible to determine the research frontiers and hotspots in the subject. Fig. 7 depicts the analysis of keyword emergence of autophagy in the literature of TCM. $R = 1.0$, minimum Duration = 1, resulting in 20 emergent words (Fig. 7). As revealed by the results, the research on the application of autophagy in TCM had a late start, and more related studies were initiated in 2010. The research on diseases has primarily focused on the autophagy pathway of TCM in the treatment of hepatocellular carcinoma, pancreatic cancer, prostate cancer, as well as other tumor cells. Research hotspots suggest that the research hotspot in 2015 is the degradation pathway of autophagy. Japanese researcher Yoshinori Ohsumi received the 2016 Nobel Prize in Physiology or Medicine for his work on autophagy. In recognition of his outstanding contribution to the discovery of autophagy genes [15], autophagy research has been on the rise since then. In 2016, the research hotspots were the role of TCM in Parkinson’s disease and hepatocellular carcinoma through autophagy pathway, the regulatory effect of TCM on autophagy, and the autophagy regulation of TCM on chemotherapy resistance. In 2017–2018, the research on autophagy of matrine, the role of TCM in the treatment of pancreatic cancer, prostate cancer and other malignant tumor diseases through autophagy pathway. After 2021, the focus of scientific research has turned to the study of autophagy of luteolin and Network pharmacology research on autophagy mechanism of TCM.

The time span and association of clustering are visually analyzed by selecting “timeline” to draw the timeline atlas of literature clustering, as presented in Fig. 8. This figure indicates that cluster # 1, # 2 and # 8 have stopped evolving, while cluster # 0 (asthma), cluster # 3 (autophagy), cluster # 4 (mitophagy), cluster # 5 (network pharmacology), cluster # 6 (activation), cluster # 7 (TLR4), cluster # 9 (traditional Chinese medicine) and cluster # 10 (angiogenesis) represent a relatively long time span and continue to this day. The above are long-term research hotspots.

3.6. Top ten cited documents and co-cited documents

The top 10 cited literatures are listed in Table 5, and the literatures cited more than 200 times are Tillhon Micol’s published in 2012 “Berberine: new perspectives for old remedies” (IF = 6.1) and Efferth, Thomas papers presented at the Cancer Biology Symposium 2017 (IF = 15.707): From ancient herbs to modern drugs: *Artemisia annua* and artemisinin for the treatment of tumors [16], the authors of the former systematically reviewed the properties and therapeutic uses of berberine, and reviewed the latest research progress of it as an anticancer lead drug. The mechanism of artemisinin acting on anti-tumor in a variety of specific ways in the past 20 years was systematically reviewed by the author of latter, in which autophagy was involved as a mode of cell death. Artemisinin and Berberine, a typical representative of TCM, plays a certain role in the mechanism of cancer treatment through autophagy pathway, which has aroused wide attention from scholars. The common feature of the top 10 cited literatures is the application of TCM in anti-tumor (e.g., colon cancer, osteosarcoma, liver cancer, and Non-Small Cell Lung Cancer) through autophagy mechanism, thus suggesting that the autophagy pathway of TCM in anti-tumor has been extensively recognized by scholars.

Subsequently, VOSviewer was adopted to analyze the co-cited literatures, and the data was extracted from the literatures with the most ten citations to generate the co-cited network of literatures (Fig. 9). The top 10 literatures with the most co-citations are listed in Table 6. The table shows that the highest total citations are published in high-level journals. The highest co-citation is “Global cancer

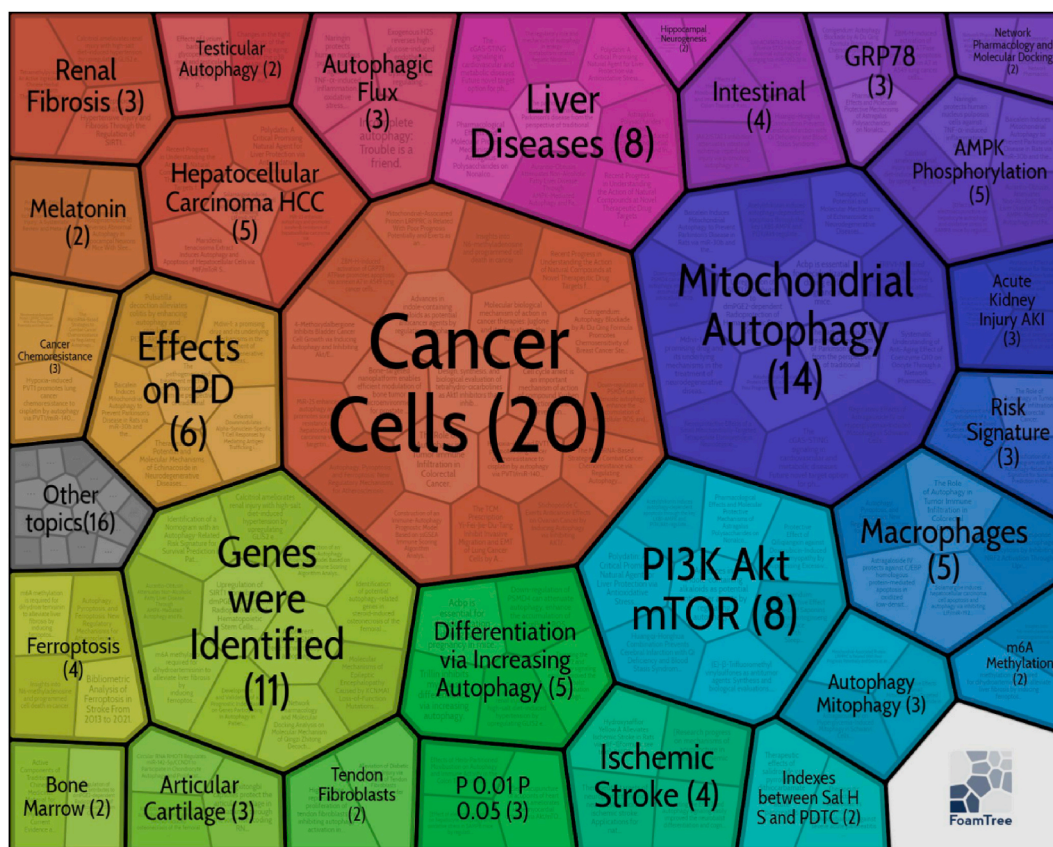


Fig. 6. Research status of autophagy in TCM Keyword analysis.

3.7. Leading journals and co-cited journals

The top 10 journals in this study are listed in Table 7, with 259 studies, accounting for 37.66% of the total. The journal with the highest number of published studies is FRONTIERS IN PHARMACOLOGY (89 studies, 9.72%), mainly reporting pharmacological studies of TCM involved in autophagy mechanism in the treatment of a wide variety of diseases. The second ranked journal is EVIDENCE BASED COMPLEMENTARY AND ALTERNATIVE MEDICINE (52 studies, 5.68%). The third ranked journal is JOURNAL OF ETHNOPHARMACOLOGY (49 studies, 5.35%), both of which focused on TCM, alternative medicine, and ethnopharmacology.

The journals that had the biggest influence on the growth of this topic were found through co-cited journal analysis. The number of citations determines a node's size, while the strength of the connection between two nodes determines a link's width. A total of 4945 journals published articles in this field, and 326 articles were selected using a minimum of 30 total citations as the threshold. The top 10 journals' citation volume and link volume are shown in Table 8. As revealed by the results, Autophagy, J ethnopharmacol, Plos one, Cell, and Nature are the most influential journals among the 326 cited journals. According to the findings of the investigation of the co-excitation sources, four significant clusters may be found (Fig. 11A). The largest cluster (red, 167 items). The most prominent journals in the cluster consisted of Autophagy, J ethnopharmacol, cell, nature, and others, mainly international first-class journals. The second largest cluster (green, 91 items) mainly comprised journals including Plos one, Biomed pharmacother, Oncotarget and others, mainly comprehensive journals. The third largest cluster (blue, 48 items) was mainly composed of Cancer Research, Cancer Cell, Cell Death&Disease, and others, mainly tumor-associated journals. The fourth largest cluster (yellow, 20 items) comprised phytotherapy research, food chem toxicol, free radical bio med, and others, mainly related to natural products. Fig. 11B presents the co-citation density chart of journals. Each point in the density visualization is supposed to have a color that represents the density of the item there, according to the keyword density visualization. The more keywords there are close to a point, the more weight those keywords will have, and the closer the point's color will be to yellow. In contrast, the weight of neighboring keywords decreases as the number of keywords close to a point increases, and the color of the point approaches blue.

Top 20 Keywords with the Strongest Citation Bursts



Fig. 7. Emergent map of keywords.

3.8. Dual-map overlay

Double mapping superposition aims to reveal the overall scientific connection and contribution. The superposition of two graphs reveals the interaction between journals [36]. Publications and citations in the field may be expressed at the disciplinary level. Construction of citation biographs using CiteSpace's biograph overlay function. The left half is citing literature, while the right half is cited literature. The curve is the citation correlation line, and the cited literature is largely affected by the cited literature. This connection illustrates the knowledge flow and connection of different research fields (Fig. 12). In accordance with Z-score, the most frequently covered record domains are molecular, Biology, Immunology, which are also affected by Physics, materials, chemistry, and other fields.

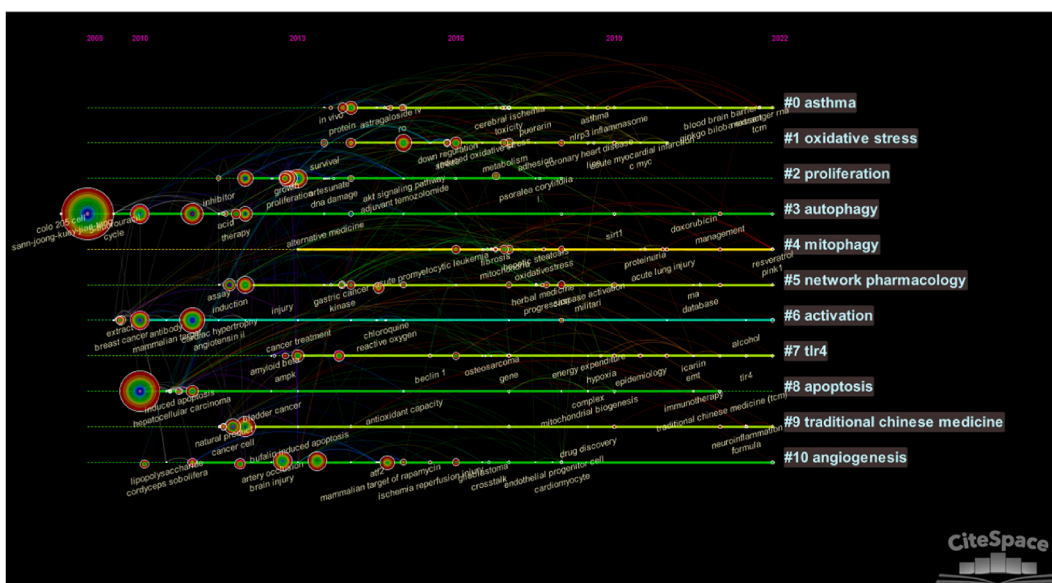


Fig. 8. Keyword timeline.

Table 5
Top 10 cited documents.

Rank	Title	First author	Publication Year	Total Citations	Average per Year
1 [16]	Berberine: New perspectives for old remedies	Tillhon, Micol	2012	296	24.67
2 [17]	From ancient herb to modern drug: Artemisia annua and artemisinin for cancer therapy	Efferth, Thomas	2017	285	40.71
3 [18]	Bufalin induces autophagy-mediated cell death in human colon cancer cells through reactive oxygen species generation and JNK activation	Xie, Chuan-Ming	2011	197	15.15
4 [19]	Pharmacological basis and new insights of quercetin action in respect to its anti-cancer effects	Tang, Si-Min	2020	196	49
5 [20]	Celastrol induces apoptosis and autophagy via the ROS/JNK signaling pathway in human osteosarcoma cells: an in vitro and in vivo study	Li, H-Y	2015	196	21.78
6 [21]	Naturally occurring anti-cancer compounds: shining from Chinese herbal medicine	Luo, Hua	2019	186	37.2
7 [22]	Arenobufagin, a natural bufadienolide from toad venom, induces apoptosis and autophagy in human hepatocellular carcinoma cells through inhibition of PI3K/Akt/mTOR pathway	Zhang, Dong-Me	2013	162	14.73
8 [23]	Toxicity of triptolide and the molecular mechanisms involved	Xi, Chen	2017	142	20.29
9 [24]	Isorhynchophylline, a natural alkaloid, promotes the degradation of alpha-synuclein in neuronal cells via inducing autophagy	Lu, Jia-Hong	2012	129	10.75
10 [25]	Polyphyllin VI Induces Caspase-1-Mediated Pyroptosis via the Induction of ROS/NF-kappa B/NLRP3/GSDMD Signal Axis in Non-Small Cell Lung Cancer	Teng, Jin-Feng	2020	118	29.5

4. Discussion

With Professor Tu Youyou winning the Nobel Prize in Medicine for her work on TCM research in 2015, TCM has aroused worldwide attention. The sudden outbreak of COVID-19 in 2019 has demonstrated the broad potential of TCM, and human beings have a deeper understanding of TCM, which has aroused increasing international attention. Yoshinori Ohsumi, who proposed the mechanism of autophagy, was awarded the Nobel Prize in Medicine in 2016, and autophagy mechanism has progressively become the focus of attention in the scientific community. The research on the combination of TCM and autophagy mechanism has attracted much attention in the scientific community. More and more researchers of TCM have done a lot of research on the autophagy pathway of TCM, and found that TCM can treat numerous diseases, especially malignant tumors via the autophagy pathway. The study's highly cited literatures mostly concentrate on the ways in which TCM promotes autophagy to treat colorectal cancer, hepatocellular carcinoma, and non-small cell lung cancer. A key mechanism of tumor treatment resistance is abnormal autophagy [37]. Tumor cells engage in a variety of autophagic processes, and these processes may contribute to the development of drug treatment resistance. In recent years, scientists have focused on the treatment of chemotherapy-resistant cancer cells, trying to study the therapeutic effect of TCM on chemotherapy-resistant cancer cells through autophagy, which has become a hot research topic in this field. In addition, atherosclerosis, Alzheimer's disease are also hot diseases in this study. An increasing body of research indicates that autophagy is crucial for

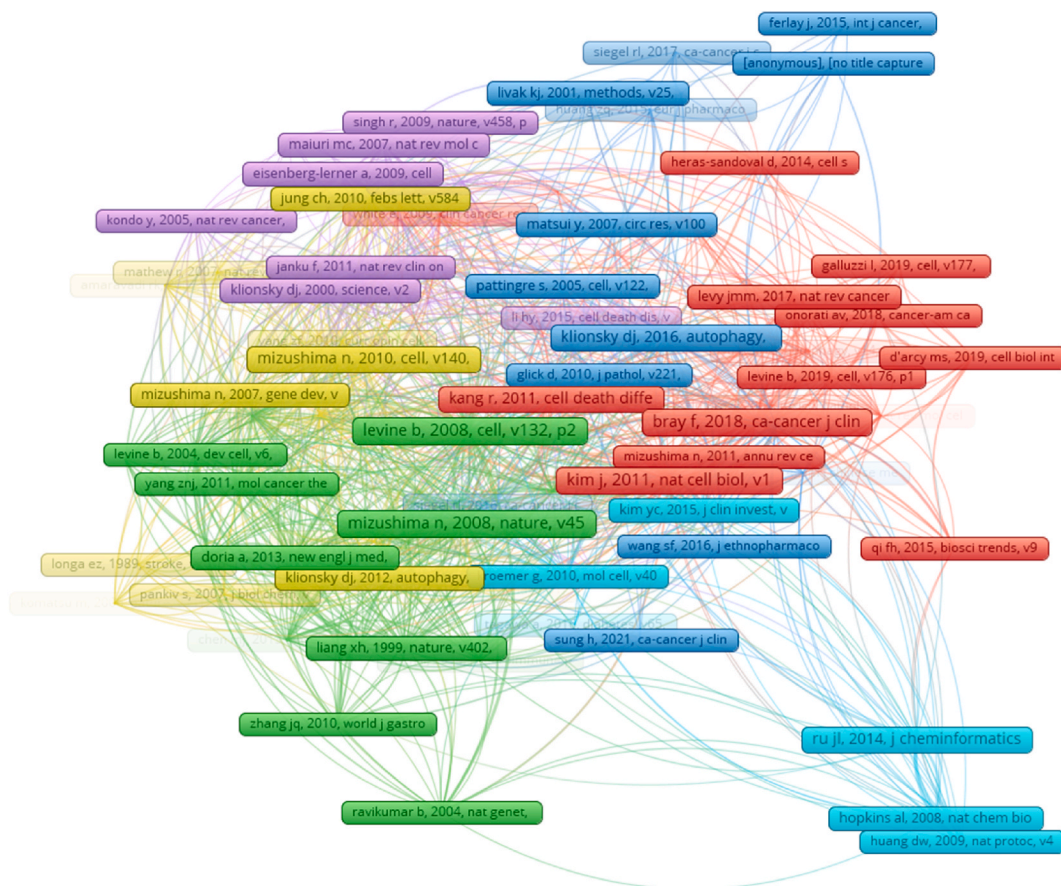


Fig. 9. Document Co-citation network.

Table 6
Top 10 co-cited references.

Rank	Title	First Author	Year	Journal	IF (2022)	Citations	Total link strength
1 [26]	Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries	Bray F	2018	CA: A Cancer Journal for Clinicians	286.13	39	80
2 [27]	Autophagy in the pathogenesis of disease	levine b	2008	Cell	66.85	38	129
3 [28]	AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1	Kim J	2011	Nature cell biology	28.213	38	100
4 [29]	Autophagy fights disease through cellular self-digestion	mizushima N	2008	Nature	69.504	36	111
5 [30]	Autophagy: renovation of cells and tissues	mizushima N	2011	Cell	66.85	32	86
6 [31]	TCMSP: a database of systems pharmacology for drug discovery from herbal medicines	Ru jl	2014	Journal Of Cheminformatics	8.489	30	48
7 [32]	LC3, a mammalian homologue of yeast App8p, is localized in autophagosome membranes after processing	Kabeya y	2000	Embo Journal	14.012	28	74
8 [33]	Guidelines for the use and interpretation of assays for monitoring autophagy	Klionsy dj	2016	autophagy	13.391	28	64
9 [34]	The Beclin 1 network regulates autophagy and apoptosis	Kang r	2011	Cell death differ	12.067	27	67
10 [35]	Methods in mammalian autophagy research	mizushima N	2010	Cell	66.85	26	58

enhancing cell efflux, promoting cholesterol efflux, and decreasing apoptosis and inflammation [38]. Induction of autophagy is likely to be a potential strategy for the treatment of atherosclerosis [39]. Finding Chinese medicine targeting autophagy may make a new breakthrough in the treatment of atherosclerosis. Several studies have suggested that autophagy defects occur in the early stages of Alzheimer’s disease (AD) [40]. Autophagy plays a critical role in the generation and metabolism of β -amyloid ($A\beta$) and the assembly of Tau, and the abnormal function of autophagy may lead to the progression of AD [41]. Several mammalian target of rapamycin (mTOR)

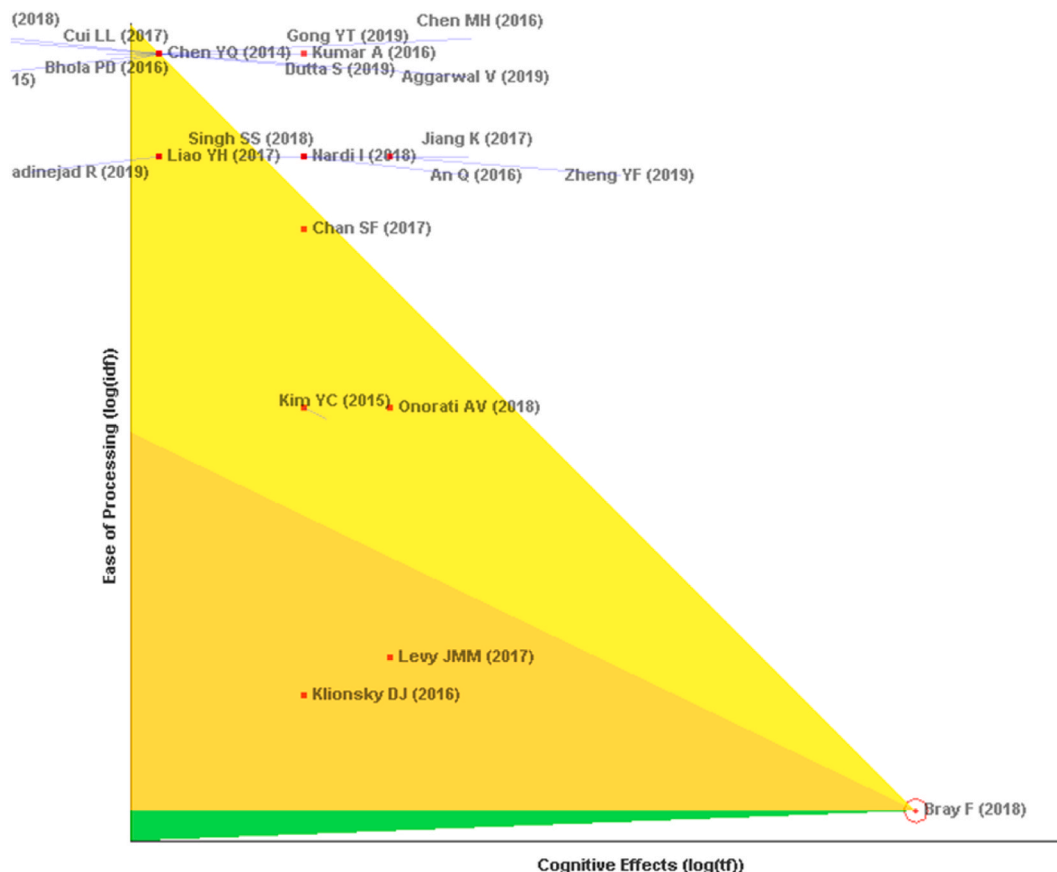


Fig. 10. Diagrams of the highest co-cited literature pennants.

Table 7
The top 10 journals.

Rank	Journals	Count	%	IF2022 (JCR)
1	Frontiers In Pharmacology	89	9.72%	5.988 (Q1)
2	Evidence-based Complementary And Alternative Medicine	52	5.68%	2.650 (Q3)
3	Journal Of Ethnopharmacology	49	5.35%	5.195 (Q1)
4	Biomedicine & Pharmacotherapy	46	5.02%	7.419 (Q1)
5	Phytomedicine	29	3.17%	6.656 (Q1)
6	Molecular Medicine Reports	20	2.18%	3.423 (Q3)
7	Oxidative Medicine And Cellular Longevity	16	1.75%	7.310 (Q2)
8	American Journal Of Chinese Medicine	15	1.64%	5.928 (Q1)
9	Experimental And Therapeutic Medicine	15	1.64%	2.751 (Q4)
10	International Journal Of Molecular Sciences	14	1.53%	6.208 (Q1)

Table 8
Top 10 cited journals.

Rank	Source	Citations	Total link strength
1	Journal Of Ethnopharmacology	1020	66580
2	Antophagy	928	39955
3	Plos one	827	70778
4	Biomed pharmacother	652	60452
5	International Journal Of Molecular Sciences	614	51573
6	Frontiers in Pharmacology	595	41201
7	Cell	588	33390
8	Evidence-based Complementary And Alternative Medicine	570	38173
9	Nature	561	33961
10	Scientific Reports	545	43498

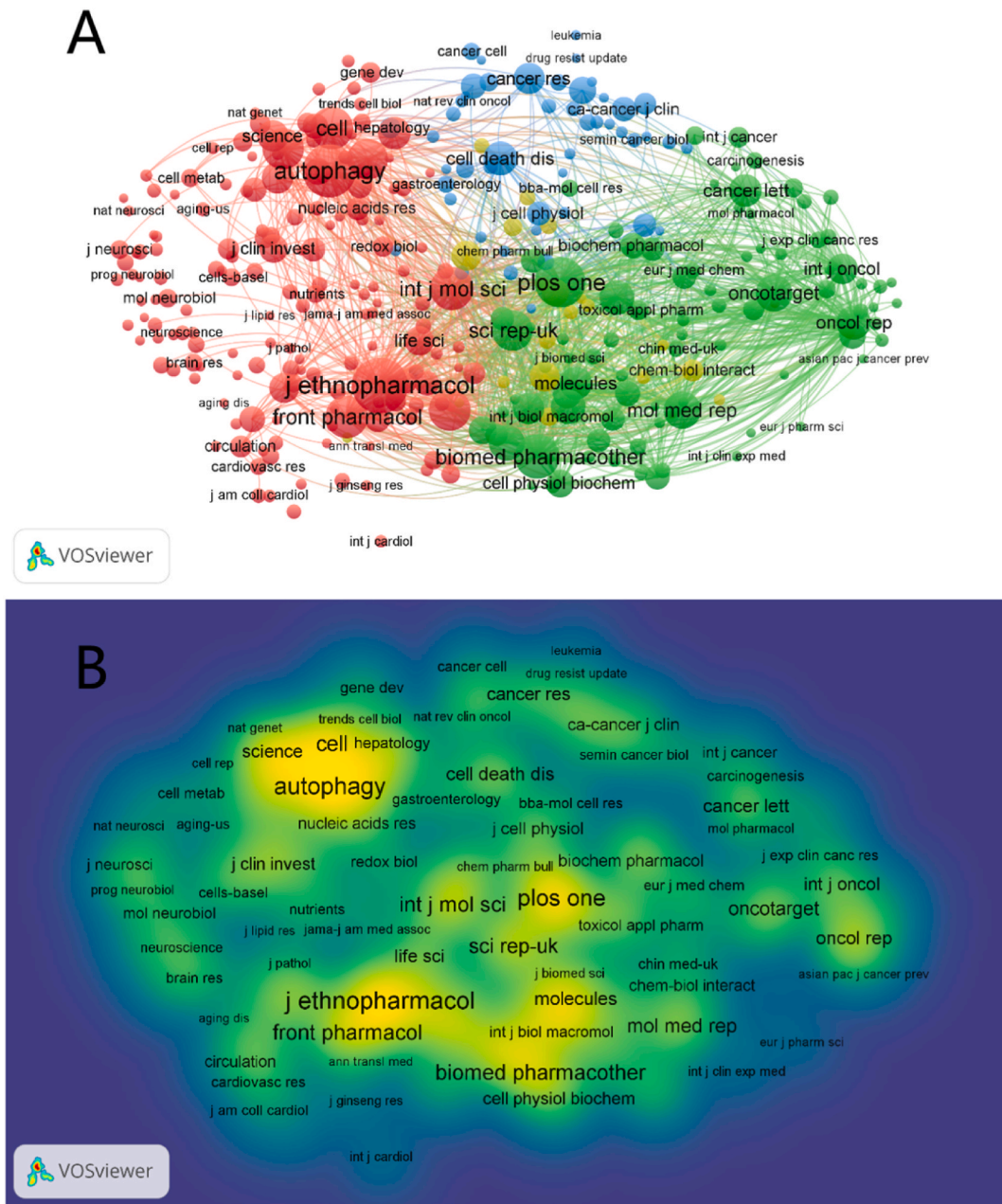


Fig. 11. (A) Co-citation network diagram of journals, (B) Co-citation density of journal.

-dependent and independent modulators of autophagy have been shown to play a positive role in the treatment of AD [42]. Autophagy may be a novel target for AD drug development.

The results of this study also showed that the PI3K/AKT/mTOR signaling pathway, the nrf2 signaling pathway, the TLR4 signaling pathway, and the NF- κ B signaling pathway are the hot research pathways in this area, and TCM may mediate autophagy via the channels mentioned above. Rapamycin, protein kinase B (AKT), and phosphoinositide 3-kinase (PI3K) (mTOR) Mammalian target proteins are important regulators of autophagy and have been found to be involved in the beginning and promotion of a number of pathological illnesses, including all types of malignancies. Signaling pathway has been identified as the traditional pathway of autophagy [43]. There is growing evidence that numerous natural products target PI3K/AKT/mTOR-mediated autophagy to inhibit tumor growth [44,45]. Studying the role of TCM in tumorigenesis, progression and drug resistance through PI3K/AKT/mTOR-mediated autophagy may be beneficial to design better therapeutic strategies for various tumors. TLR4 (toll like receptor 4) signaling pathway is also the focus of this study. According to pertinent studies, PDE5A-AKT and TLR4-NOX4 pathways are responsible for the active components of TCM formula's ability to reduce autophagy and apoptosis in an isoproterenol (ISO)-induced heart failure

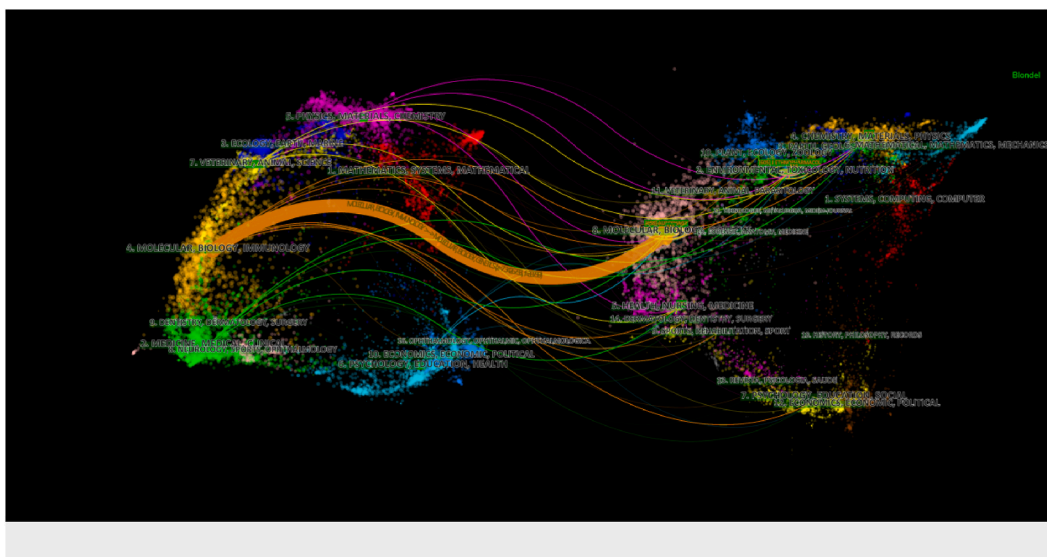


Fig. 12. Overlay of double spectra of literatures.

model [46]. The Nrf2/Kelch-like ECH-associated protein 1 (Keap1) pathway is the primary antioxidant stress route, and Nrf2 is a crucial protective transcription factor and a sensor of intracellular redox state. Existing research suggests that Nrf2 plays a protective role in malignant tumors, and is associated with chemotherapy resistance [47]. Based on the above pathway, the effect of TCM mediated autophagy on chemotherapy resistant tumor cells may be the current research focus in this field. NF- κ B serves as a critical nuclear transcription factor, which is significantly correlated with inflammation, apoptosis, and other processes [48,49]. Moreover, research has indicated a connection between the NF- κ B pathway's activation and the suppression of autophagy [50]. A group of proteins from the autophagy associated gene (ATG) family play a significant role in the autophagy process through the AMPK-mTOR signaling pathway [51]. TCM can play a role in the treatment of diseases by up-regulating or down-regulating autophagy via AMPK-mTOR pathway [52,53].

This study had some limitations. The WoS database was the only data source used in this analysis; data from other relevant search engines (including Embase, Medline, and Scopus) were excluded. Nonetheless, because it is one of the largest and most organized databases in the world, the caliber of its research has been acknowledged. VOSviewer and CiteSpace can analyze the data from the database bibliometrically with ease.

5. Conclusion

The approaches and techniques used by TCM to cure diseases have tremendous medical significance and involve a variety of components, targets, and pathways. It has been established that autophagy process contributes in some way to the onset and progression of numerous diseases. The control of autophagy has evolved into a research focus for the clinical management of several disorders. By fusing the two current hot topics of TCM and autophagy, this study sought to analyze the research hotspots and future trends of autophagy mechanism in the study and application of TCM. The role that TCM plays in autophagy-related malignant tumors, atherosclerosis, and Alzheimer's disease has become a focus of research in this area. The regulation of autophagy signaling pathways by TCM (PI3K/AKT/mTOR signaling pathway, TLR4 signaling pathway, Nrf2 signaling pathway as well as NF- κ B signaling pathway) has become a research hotspot in this field. In the future, the therapeutic effect of TCM on chemotherapy-resistant tumor cells through autophagy pathway, the role of TCM mediating mitophagy and activating autophagy function, and the therapeutic effect of TCM components represented by luteolin on tumors, asthma, myocardial injury and other diseases through autophagy mechanism will be the research hotspots in the future. It is expected that this study can provide researchers with more research ideas in this field and promote its clinical application by further exploring the mechanism of action of TCM regulating autophagy in the future to lay a solid basis for in-depth treatment of human diseases.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Author contributions

Jun Zhao and Cheng Tao conceived and designed the work; Jun Zhao, Guang-wei Liu collected the data and performed the analysis; Jun Zhao wrote the original draft. All authors read and approved the manuscript and all data were generated in-house and that no paper mill was used.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2023.e20142>.

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