Medicine®

Isodon rubescens research literature based on Web of Science database for visual analysis
A review

Shaowei Xu, BD[a], Jing Wu, MS[a], Qingshan Yang, MS[a,b,*], Huqiang Fang, BD[a], Teng Xu, BD[a], Bing He, MS[a], Na Chen, PhD[c], Shihai Xing, PhD[a,d,e]

Abstract

Isodon rubescens has been used as an herbal medicine in China for a long time. The significant value of development and utilization is affirmative. Bibliometrics is used as an approach to sort out, analyze, and visualize relevant literature in a particular field. So, it can intuitively express the research trends, hot directions, significant achievements, core journals, and outstanding authors in the field. But there is no bibliometrics analysis of *I rubescens*. The relevant dataset was retrieved and exported from the Web of Science database, and the results were obtained and visualized using the R Programming Language, CiteSpace, and VOSviewer, with the creation of time zone maps also using Scimago Graphica and Gephi. There were 506 valid data retrieved and 465 analyzed data selected. The country with the most significant number of publications is China, the institution with the largest annual publication volume is China Pharmaceutical University, the publication with the most relevant literature is the *International Journal of Oncology*, and the author with the most publications is Zhou. The keyword with the greatest intensity is "matastasis," which is also an emerging keyword. The role of *I rubescens* has been continuously diversifying. It has been proven to play a role in treating major diseases such as multiple cancers, leukemia, liver and kidney function impairment, and cardiovascular and cerebrovascular diseases. This study will highlight the main research direction in this field, namely the use of *I rubescens* for the treatment of cancer.

Abbreviations: ADC = antibody-drug conjugates, Apef-1 = apoptotic protease activating factor-1, ATRA = all-trans-retinoic acid, BMP7 = bone morphogenetic protein 7, CdK1 = cyclin-dependent kinases 1, EGFR = epidermal growth factor receptor, GAS = gas anti-solvent, GC-NP = nanoparticles coated with galactosylated chitosan, HGF = hepatocyte growth factor, *I rubescens* = *Isodon rubescens*, IF = impact factor, LASP1 = LIM and SH3 protein 1, MAPK = mitogen-activated protein kinase, MCF-7 = Michigan cancer foundation-7, MRP1 = multi-drug resistance-associated protein, NLC = nanostructured lipid carriers, PCNA = proliferating cell nuclear antigen, PDLIM1 = recombinant PDZ And LIM domain protein 1, PEG-NLC = polyethylene glycol-modified nanostructured lipid carriers, P-gp = P-glycoprotein, PLA-RGD-NPs = ORI-loaded atactic poly(D,L-lactic acid) nanoparticles, PTEN = phosphatase and tensin homologue, ROS = reactive oxygen species, TC = total citations, VEGF = vascular endothelial growth factor, VPA = valproic acid, WoS = web of sience.

Keywords: bibliometrics, citespace, *Isodon rubescens*, the R programming language, VOSviwer

1. Introduction

Isodon rubescens (Hemsley) H. Hara is used as traditional Chinese medicine. Doctor of traditional Chinese medicine claims it has the effect of clearing heat and detoxification, activating blood and relieving pain, and is commonly used in sore throats, fistulas and snake bites. After years of research, *I rubescens* has been found to have a significant inhibitory effect on cancer,[1] especially digestive tract cancer. In recent years, researchers have been exploring other effects, such as anti-inflammatory,[2] antibacterial,[3] and lowering blood sugar[4] in an attempt to find more clinical applications of *I rubescens*. Primary bioactive substances contained in *I rubescens* are terpenoids,[3,5] such as oleanolic acid and ursolic acid. Most of them belong

to the ent-kaurene diterpenoid. The earliest isolated compound, named oridonin, is a component of some modern clinical cancer treatment drugs. Studies have reported that oridonin is usually synthesized in the aerial part of the plant, and the relevant expression genes are concentrated in the leaves,[6] which the content of oridonin is also similar to, including CYP796V[7] and IrUGT86A1.[8] In addition, *I rubescens* has been used as a tea beverage in China for a long time. Therefore, in some regions of China, it is cultivated as an economic crop.

Bibliometrics is a statistical method that integrates literature, which can digitize and visualize the commonalities, trends and connections of amount of literature,[9] which helps researchers quickly understand the overall occurrence process, current latest directions and hot spots in a particular field. According to research, most disciplines want a high-quality review[10] to solve the problem of reading a large amount of literature in search of a direction to explore. Traditional literature can do this, which can describe the current hot scientific research, but the connections and trends between various studies will not be concise and intuitive. This part can be expressed well by bibliometrics, using pictures such as co-existing network diagrams, surge words, time zone maps, timeline diagrams and other pictures, which can intuitively reflect the ongoing research.[11] However, there are still many limitations in bibliometrics, such as the need for manual screening and condition setting during the process, which can have a certain subjective impact on the final results.

In this article, we used bibliometrics to analyze the literature of *I rubescens*, counted the countries, institutions, journals, authors and keywords of articles published in the field, drew tables and pictures, summarized and predicted research trends in this field, and provides a reference for *I rubescens* related research.

2. Data and method

2.1. Source of data

The data was sourced from the Web of Sience (WoS) database, with a total of 781 records. After many explorations, *Rabdosia rubescens*, *I rubescens*, Oridonin and pind were used as search terms, and the search time range was set from 2000 to 2023 (as of February 28, 2023).

2.2. Data filtering

2.2.1. Filter.
Inclusion criteria: Research literature on *I rubescens* in the field of medicine.

Exclusion criteria: duplicate studies; conferences, newspapers, reports, achievements, patents, information, and revoked publications; the theme is not related to traditional Chinese medicine; literature with incomplete information such as author, keywords, journal name, and publication time.

The retrieved questions are imported into the Note Express and EndNote literature managers for aggregation, and qualified documents are identified according to the above criteria to obtain qualified documents.

2.2.2. Data visualization.
The qualified documents screened by Note Express and EndNote are saved in a recognizable format of CiteSpace (version 6.2.2)[12] and VOSviewer (version 1.6.19),[13] imported into the software for analysis, and the output file after document processing is obtained. Import it into R for secondary analysis, and visualize the results with Scimago Graphica (version 1.0.34)[14] and Gephi (version 0.10.1).[15]

CiteSpace parameter settings: time slicing is 2007 to 2023, time slicing is 1 year; G-index set the K value to 15; node type select institution, keyword; pruning chooses pathfinder and pruning sliced networks.

3. Results and analysis

3.1. Analysis of the annual distribution of literature publications

After searching and screening the WoS database, 506 valid data were obtained, excluding 6 early articles, 1 process article, 1 focus explanation article, 1 collaborative article, 1 explanatory article, 1 letter and 30 conference papers. After removing the data listed above, 465 analytical data were selected, including 448 articles and 17 review articles. In general, it can be divided into 2 periods, the first is the quiet period, which is a period when there are fewer researchers interested in this area and few articles are included. The first article was included in 2007 (Fig. 1), and there were no articles for 2 years after that. The
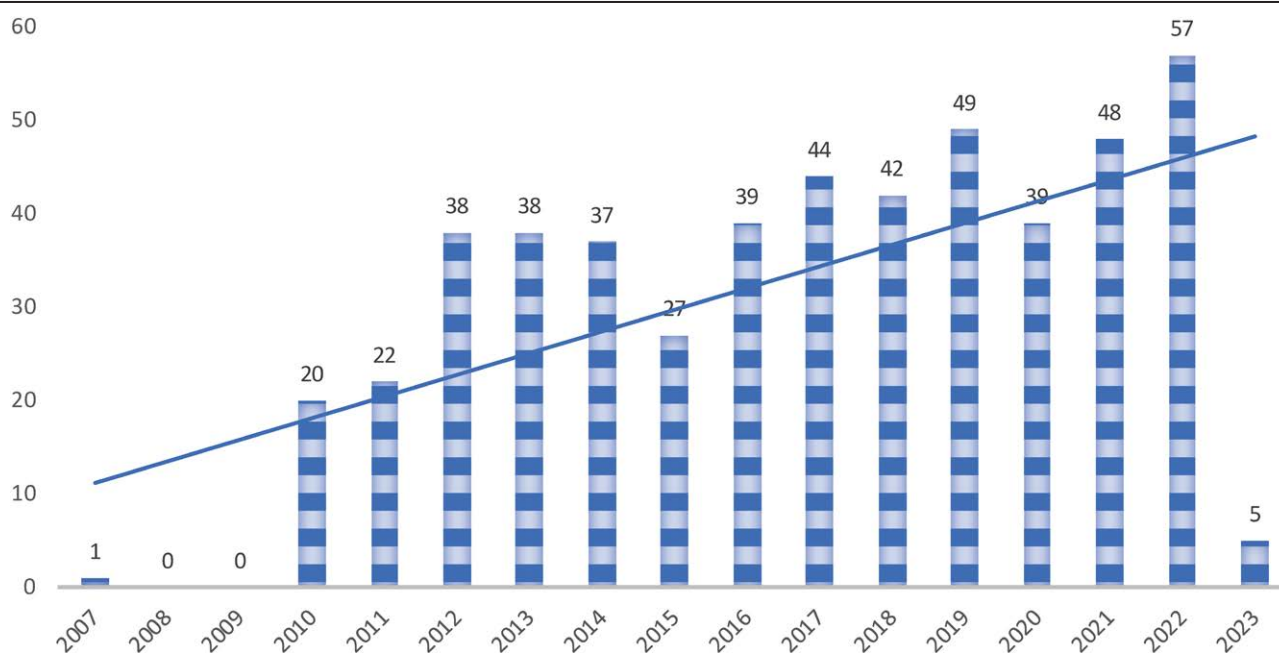

Figure 1. The number of document on *I rubescens* per years.

second stage is the period of rapid growth, that is, from 2010 to 2023. Although there are fluctuations, the number of papers published in these 10 years has been rising, reaching a peak of 57 papers in 2022. From the trend point of view, this field will continue to be watched.

3.2. Analysis of documents issued by countries and institutions

According to the map obtained from the Wos literature data, the darker the color, the more posts are published. It can be seen that China and the United States are located in the darkest color, indicating a large number of articles in this field (Fig. 2A). As can be seen from Figure 2B, 26 countries have contributed to the literature in this area. China contributed the most papers (1147), accounting for 79.87% of the total publications, followed by the United States (129), South Korea (36), Japan (33) and Germany (19). The number of publications in the United States and South Korea is only equivalent to 10.61% and 2.87% of China, indicating that China paid more attention to the research and development of winter grass earlier. In Figure 2C, the annual publication volume of 5 countries is shown in different colors, China is the most prolific country, and the number is increasing year by year, and the United States publishes more than 100 articles per year.
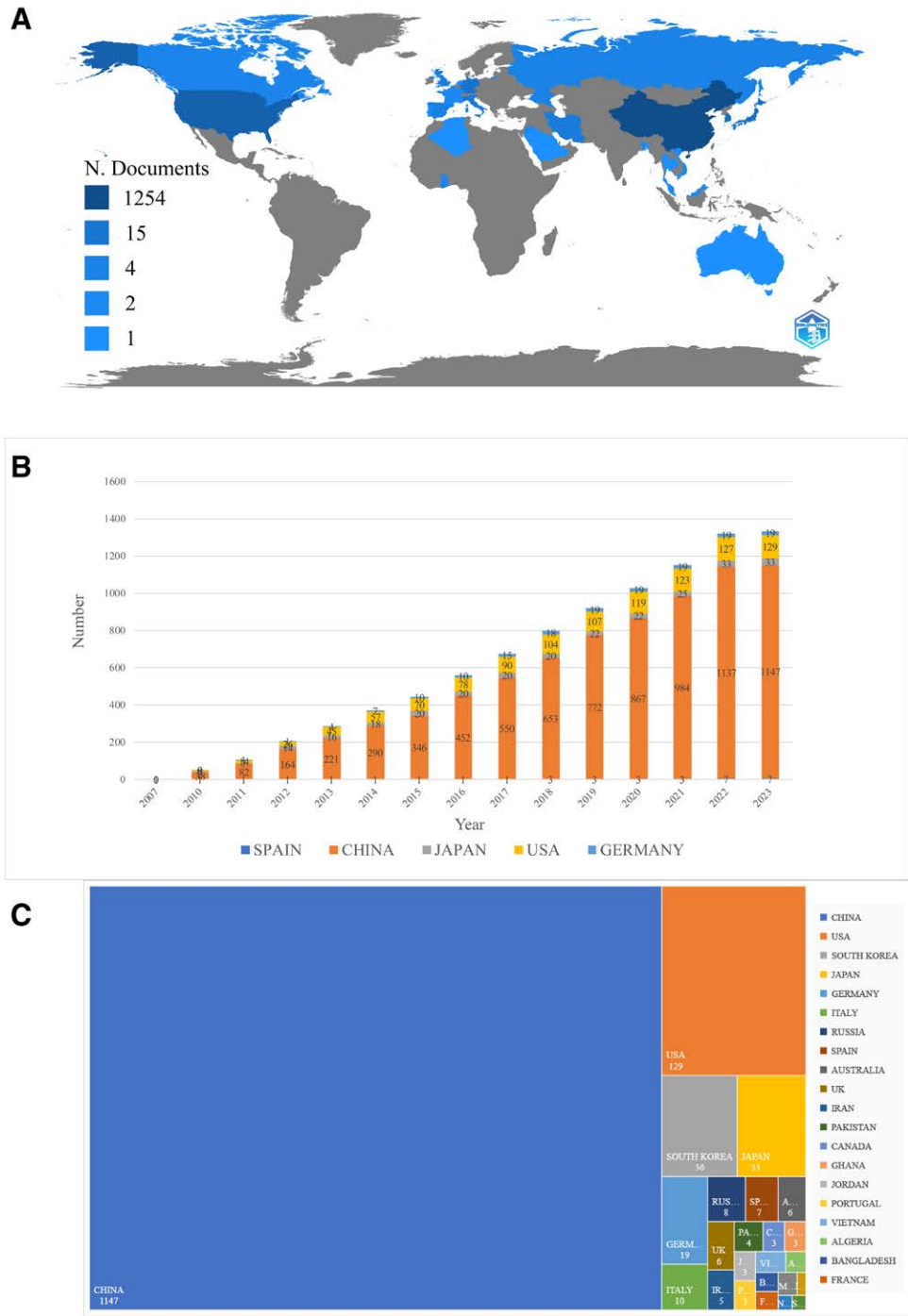

Figure 2. Analysis of country. (A) The map of county scientific production. (B) The number of publications per country per year. (C) The treemap of proportion per country's publications.

According to statistics, 472 institutions have contributed to research in this field. Figure 3A depicts the annual publication volume of the top 8 institutions, with China Pharmaceutical University (China Pharmaceut univ) being the institution with the fastest annual production growth, and Shanghai Jiao Tong University (ShangHai JiaoTong University) maintaining the highest annual publication volume until 2021, indicating that the research focus of the institution is shifting. Six of the 7 institutions in this figure belong to China, indicating that China has made an important contribution to the research of winter grass. The Figure 3B is an institutional co-discovery network diagram generated by the R language. The size of the circle reflects the number of research done by the institution, and the thicker the connection, the closer the cooperation. With Zhengzhou University, Shenyang Pharmaceutical University and Zhejiang University as the center, the institutional cooperation network diagram on the research of winter grass was constructed, indicating that these institutions attach importance to mutual exchanges and cooperation while focusing on research in this field.

3.3. Publication analysis

Bradford law, also known as the law of documentary dispersion, was proposed by Bradford in 1948 and has been continuously improved. According to this theorem, journals can be divided into core journals, related journals, and unrelated journals. The journals covered in this article also roughly follow Bradford law (1:2.5:2.52), with an approximate number of 168 articles per division (Table 1). Therefore, a total of 26 journals were selected for analysis (Table 2). The number of applications can reflect the quality of the journal, and lists the articles' total citations, citations per article and 2023 impact factor (IF) of the 26 selected journals. The largest number of publications was the International Journal of Oncology, with 13 articles, and the total number of citations also ranked first, indicating that the journal has a high acceptance rate for research related to winter grass. This is followed by International Immunopharmacology, Molecules and Oncology letters, which are also the main forums in the field. Cell Death & Disease is of high quality, as evidenced by the most cited data per article, suggesting that research on *I rubescens* is more focused on its therapeutic effects and mechanisms for cancer, and the journal with the highest IF is Cancer Research.

3.4. Author information analysis

The number of publications and citations represent the author's productivity and quality in the field, respectively. Visualize the number of articles published by authors per year (Fig. 4A), the color shade represents the citation, and the circle size indicates the number of posts. Among them, Zhou, Liu and Zhang are at the forefront of annual publications and citations. Figure 4B lists the top 10 researchers with enormous of articles, of which Zhou, J. published the most articles (24), followed by Liu, Y
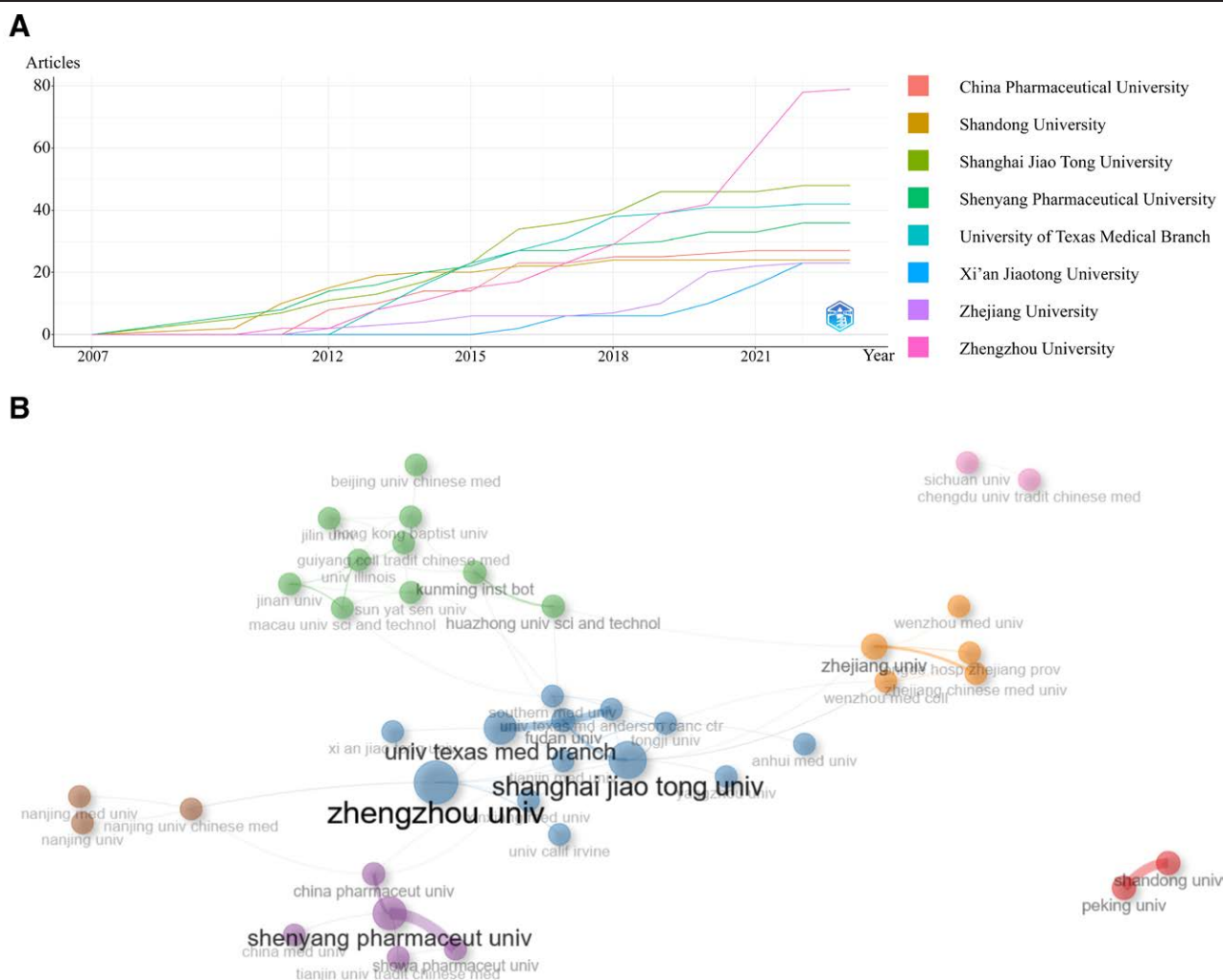

Figure 3. Analysis of affiliations. (A) The number of affiliation' production over time. (B) The collaboration network of institutions.

(22) and Zhang, Q. (21). Figure 4C is the fluorescence view of the authors, Zhou, Ding, Xu, Ke, Zheng, Onodera and Satoshi. The cooperative network has an intense fluorescence brightness, indicating that these groups have made outstanding contributions to the research of winter grass. Through VOSviewer visualize the cooperation between authors, the corresponding overlay collaborative network (Fig. 4D) is drawn, the color shade represents the time, the size of the circle represents the number of authors' posts, and the connection represents the cooperation between researchers. Zhang and others have more research results, but the time has been relatively old, and the reference value may decline. Zhou, Chun and other authors have more connections between them, reflecting the importance of collaboration. Wang, Gu, Ke and other lightest colors are emerging authors in recent years, with larger circles and more connections, indicating that these researchers may continue to pay attention to the research field of winter grass.

3.5. Keyword trend analysis

Generally speaking, keywords are the center and main content of an article, so analyzing and sorting out keywords helps to grasp the overall trend and trend of field research. Using the CiteSpace algorithm to analyze the keywords, remove the keywords used in the search, and merge synonyms, the obtained data roughly conforms to Zipf law (constant is about 350). The corresponding co-occurrence network diagram (Fig. 5A) was obtained from the visual data, the higher the frequency of occurrence, the larger the square, the color represents the time, and the connection represents the simultaneous occurrence of keywords. Among all keywords, "apoptosis" appeared the most frequently, reaching 103 times, and the effect of winter grass on apoptosis was the focus of research in this area, followed by "activation" (68 times), "in vitro" (65), "expression" (62), "growth" (62), "cell" (57), It is indicated that the influence of Dongling grass on cell activity through in vitro experiments may be a hot direction in research. The keyword cluster plot shows 17 categories (Fig. 5B), which can be classified into 2 categories: the therapeutic mechanism of the disease and the innovative production of the agent, and it is possible that the research on the winter grass focuses on the mechanistic impact on cancer. CiteSpace, Gephi, and Scimago Graphics combined to make a time zone map of keywords (Fig. 5C), the legend position on the right corresponds to the location of the cluster in the figure, the size of the circle represents the frequency, and the abscissa is the year of its occurrence. "Aproptosis," "activation," and "anti-tumor" are the first batch of keywords that appear, influencing the clustering of words that appear later. "cataract" and "accuracy" are the latest to appear in 2023, due to the short time, their frequency is not high, but it may continue to appear in the future, indicating that ophthalmic medical treatment and precision drug delivery may be the research hotspot of *I rubescens* in the future. Finally, a schematic diagram of emergent words (Fig. 5D) was drawn, and a total of 13 keywords with an intensity of 3 or more were selected and sorted by the start year of emergence. "P35" is the earliest word to appear, with a strength of 3.03. The intensity of "metastasis" was the highest (4.8), indicating that there is more literature related to cell metastasis, and the metastasis of cancer cells has always attracted the attention

of medical institutions, indicating that the research of *I rubescens* is closely related to cancer.

4. Discussion

The 46 records were singled out as the basis for the analysis, and the number of publications per year showed an upward trend, suggesting that the research of *I rubescens* is likely to continue to emerge. In the world map and the number of national publications, China obviously occupies a large proportion. The United States, the second largest in number, has stabilized at more than 100 articles per year. China has the highest number of publications, which may be related to the fact that *I rubescens* is an economic crop in some regions of China. Not only as a source of traditional Chinese medicine, but also as a raw material for chemical drugs, as well as a tea beverage for daily consumption.

The research directions of the top 5 institutions published each year have their own characteristics, and the literature

Table 2

The number, reference, average citation per article and IF of journals.

Sources	Articles	TC	Average citations per articles	IF
International Journal of Oncology	13	312	24.00	5.884
International Immunopharmacology	11	173	15.73	5.714
Molecules	11	229	20.82	4.927
Oncology Letters	10	158	15.80	3.111
Molecular Medicine Reports	8	93	11.63	3.423
Acta Pharmacologica Sinica	7	165	23.57	7.169
Cancer Research	7	64	9.14	13.312
PLOS ONE	7	149	21.29	3.752
European Journal of Pharmacology	6	105	17.50	5.195
International Journal oPharmaceutics	6	219	36.50	6.510
Journal of Natural Products	6	157	26.17	4.803
Pharmaceutical Biology	6	68	11.33	3.889
Phytotherapy Research	6	37	6.17	6.388
Biochemical and Biophysical Research Communications	5	59	11.80	3.322
Biological and Pharmaceutical Bulletin	5	64	12.80	2.264
Biomedicine and Pharmacotherapy	5	129	25.80	7.419
European Journal of Medicinal Chemistry	5	222	44.40	7.088
Evidence-Based Complementary and Alternative Medicine	5	31	6.20	2.650
Frontiers in Pharmacology	5	46	9.20	5.988
International Journal of Molecular Sciences	5	91	18.20	6.208
Journal of Cellular and Molecular Medicine	5	79	15.80	5.295
Oncology Reports	5	161	32.20	4.136
Scientific Reports	5	86	17.20	4.996
Anticancer Drugs	4	56	14.00	2.389
Cell Death and Disease	4	193	48.25	9.685
Drug Development Research	4	34	8.50	5.004
Experimental and Therapeutic Medicine	4	45	11.25	2.751
Fitoterapia	4	57	14.25	3.204
International Journal of Molecular Medicine	4	91	22.75	5.314
International Journal of Nanomedicine	4	87	21.75	7.033

Abbreviations: IF = impact factor, TC = total citations.

Table 1

The analysis of journals based on Bradford law.

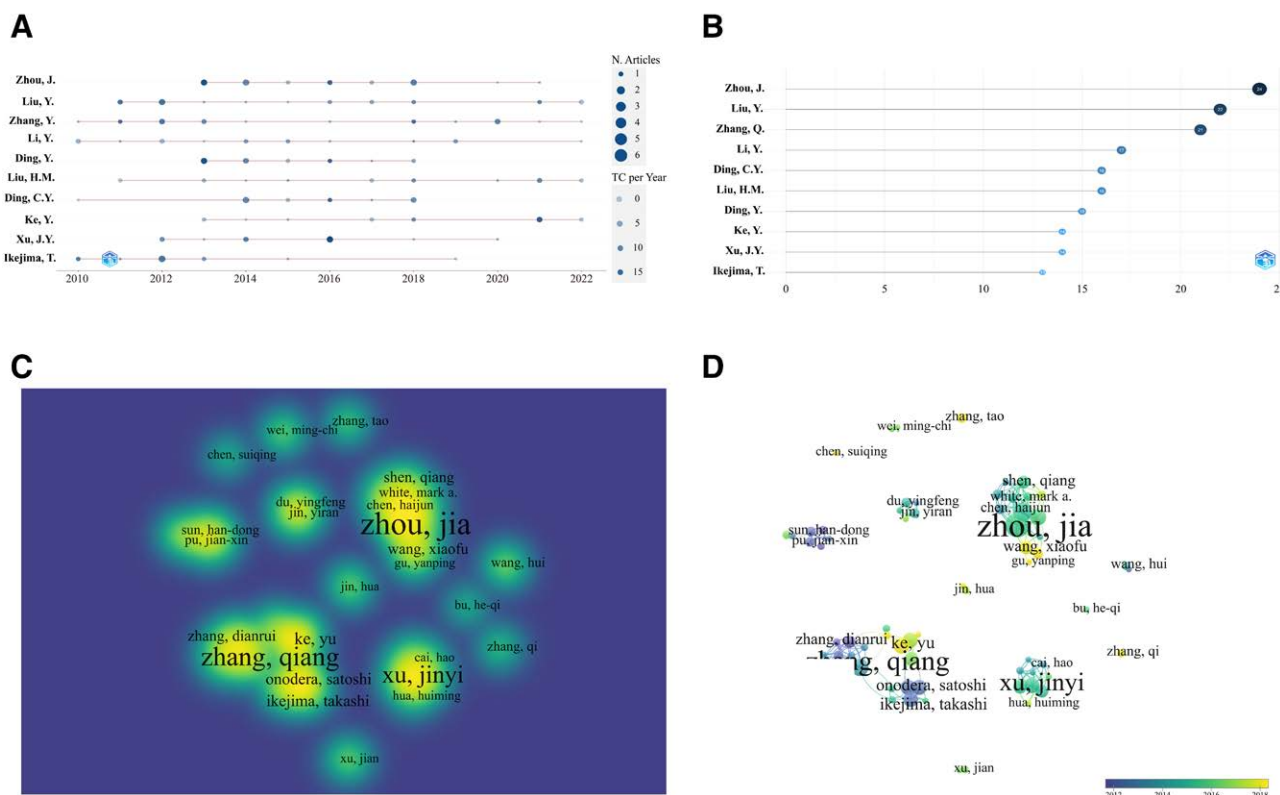| Zone	Publication	Number of journals	Number of document
First zone	>4	26	166
Second zone	2 to 4	63	168
Third zone	1 to 2	163	172

Figure 4. Analysis of authors. (A) The number of author's production over time. (B) The top 10 number of author's productions. (C) The overlay visualization of author's collaborative network. (D) The density visualization of author's collaborative network.

included in China Pharmaceutical University is basically related to cancer, and the synthesis and construction of derivatives of Oridonin,[16–23] and explains the mechanism of apoptosis in cancer cells.[24,25] China Pharmaceutical University and Shandong University jointly proposed the application of fluorescent probe technology in the mechanism.[26] They found that Oridonin usually accumulates in the mitochondria of cells in large quantities, which provides a reference for subsequent research. Shandong University focuses on the construction of nanocarriers carrying Oridonin,[27–30] including nanogels,[31] nanoparticles,[27,32–34] nanosuspensions[35–38] and nanocrystals.[39] The purpose of the study is mainly for clinically targeted drug delivery, and there is usually a related collaboration with Peking University,[31,32,39,40] of course, the mechanism of ovarian cancer[41] and prostate cancer[35–37] being affected by Oridonin. The research at Shanghai Jiao Tong University can be divided into 2 directions, 1 focusing on the efficacy of *I rubescens* in leukemia,[42–45] and the other is the combination of drugs,[46] which crosses.[43,44] Other aspects of research are more complex, involving mostly the mechanism of the action of *I. rubescen* on cancer, such as the combination of certain drugs to treat tumors, which can enhance each other's efficacy.[46] Shenyang Pharmaceutical University, ranked third, focuses on the mechanism of apoptosis and phagocytosis,[47–49] and currently the pathways or components studied by the institution include JNK,[50] NO-ERK-p53,[51] NF-Kb-COX-2-IL-1B,[52] and c-Met[53] to illustrate the potential mechanism of inhibition of various cancer cells by *I. rubescen*. Among them, it is worth noting that recent research combining multi-band blending analysis, electrochemical oscillation pattern, and oxidation resistance analysis to detect the quality of the tablet named Donglingcao.[54] It may be precise and accurate, but the simplicity is also reduced, exploring the most iconic detection component of *I. rubescen* can be the key to quality control. The University of Texas Medical School differs from the previous 4 universities in that the literature focuses on the construction of derivatives[55,56] and the study of inflammatory mechanisms.[57–59] The University of Texas Medical School has developed a variety of oridonin analogs[60] and synthetic methods,[61] which have become a potential alternative to oridonin resistance,[61] targeting mainly hepatitis[62,63] and enteritis.[59] In recent years, there have been more studies on the possibility of liver fibrosis[62–65] and intestinal fibrosis[66] protected and cured by oridonin. The collaboration between China Pharmaceutical University and Shenyang Pharmaceutical University is the construction and design of derivatives,[19–22,25,67] mostly anti-inflammatory and antibacterial drug candidates. The 2 universities are closely linked and have a long cooperation time span, and further cooperation may be carried out in the direction of the construction of oridonin derivatives. Zhengzhou University, Shanghai Jiao Tong University, and the University of Texas Medical School have collaborated with each other, but they are not very closely linked, and their research focuses on their respective directions, such as the mechanism of apoptosis and phagocytosis,[68] the construction of oridonin derivatives,[69] and the possibility of treating hepatitis.[62]

Three journals were selected from the source, with the most publications, the most citations and the most IFs. The journal with the most articles is the International Journal of Oncology, in which most of the articles are related to combination drugs (38.46%), and Oridonin can enhance the effects of drugs such as arsenic trioxide,[70] NVP-BEZ235,[46] gemcitabine[71] and cecuximab.[72] Interestingly, the MAPK (mitogen-activated protein kinase) pathway has been mentioned several times in related articles,[71,73–75] suggesting that MAPK is an important pathway for Oridonin to inhibit cancer cells or induce apoptosis. The International Journal of Oncology suggests that the journal prefers the combination of drugs, which may be one of the future research directions of *I. rubescen*. Cancer research (IF = 13.312), the journal with the highest IF in the table, in which the literature on *I rubescens* deals more with derivatives
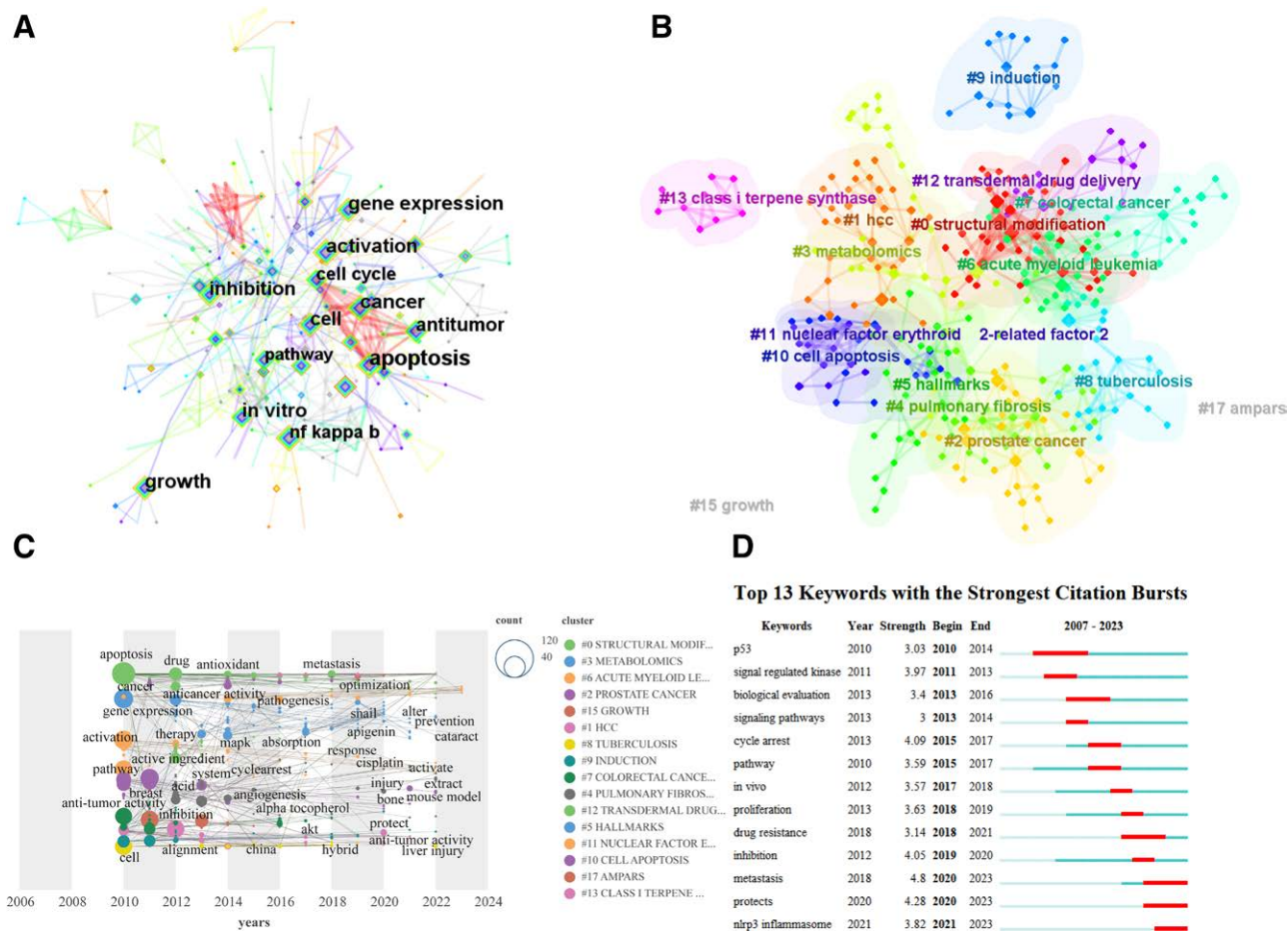
Figure 5. Analysis of keywords. (A) The co-occurrence network of keywords. (B) The cluster of keywords. (C) The time zone map of keywords. (D) Keywords with the strongest citation bursts.

and analogs for the treatment of breast cancer,[56,76–78] suggesting that the journal may be more focused on the research that can be transferred to actual production and life-impacting research. Cell death and disease (44.40 points) with the highest citation score for each article in the table, and exploring the mechanism by which *I rubescens* induces apoptosis and phagocytosis to achieve anticancer effects is the main literature category in the journal.[79,80] It is interesting to note that Oridonin is proposed as an alternative to drug resistance, and the above 3 journals have articles on,[81–83] comparing Oridonin with other drugs to form a substitute may also be a future research direction.

The author, Zhou, was the most prolific, participating in the completion of 24 papers, including 10 conference papers, 1 review, 13 research articles, 2 signed as first authors,[82,84] and 2 articles with the highest IFs reached 9.76 points[69] and 9.69 points[82] respectively. His earlier articles focused on the modification of the A-ring of Oridonin and the synthesis of corresponding analogues,[55,61,85,86] the enhancement of A-ring aaidatinn, its water solubility and bioavailability. His medium-term delve into the study of hepatitis and liver fibrosis.[62,63] Recent publications have dealt with D-ring modification and the synthesis of analogues,[69,87] and are more specific to breast cancer. Interestingly, the creation of a D-ring modified analogue by aziridination was first proposed by his team,[69] which is also the article with the highest IF, and another first-author high-scoring article published earlier also involved the synthesis of analogues,[82] which could be a potential alternative to kidney cancer drug resistance. The authors also led a team to study the role of Oridonin on angiogenesis,[84] hoping to find a way to reverse cancer cells and normalize blood vessels in cancer cells. Ikejima, T. has 13

research articles, all focusing on the effects of other substances on the reaction process of Oridonin in the body. Studies have shown that ROS (reactive oxygen species) promotes apoptosis in cells, while Oridonin induces its production,[49] while hydroxyl radical,[88] tyrosine[50] and NO[51] promote Oridonin apoptosis-induced effect. However, components including EGFR (epidermal growth factor receptor),[89] HGF (hepatocyte growth factor)[52] and c-Met[53] will play the opposite role. It is worth mentioning that NO has an impact by forming a positive cycle of NO-ERK-p53[51] and regulating NF-Kb-COS-2-IL-1β.[90] The article with the highest IF suggests that inhibition of EGFR can enhance the effect of Oridonin,[89] and that combining EGFR-targeted drugs with Oridonin may be a practical anticancer approach. The author with the highest H-dex score is Liu, with 22 articles, all of which are research literature. It involves diseases such as cancer, leukemia[91,92] and high-oxygen lung damage,[93] focusing on pharmaceutical agents' innovation and practical application. In order to improve the pharmacokinetics of oridonin in vivo, components including galactose,[31] MCF-7 (Michigan cancer foundation-7),[38] GAS (gas anti-solvent),[94] PEG-NLC (polyethylene glycol-Modified nanostructured lipid carriers),[40] PLA-RGD-NPs (ORI-loaded atactic poly(D,L-lactic acid) nanoparticles),[95] NLC (nanostructured lipid carriers),[29] GC-NP (nanoparticles coated with galactosylated chitosan),[32] ADC (antibody-drug conjugates)[96] and other components are used to carry oridonin to increase its retention time. Different kinds of derivatives have also been constructed,[97,98] expanding the scope of oridonin or as an alternative to drug-resistant diseases.[81,99] Liu, Y. mentioned iron death in his article with the highest impact factor (IF = 14.90),[100] which has only 3

articles in the research field of *I. rubescent*. And all of them are high-scoring works in the past 2 years, indicating that the study of the mechanism of action of oridonin inducing iron death to achieve anticancer may be one of the hot spots in the future.

Keywords are an important component that reflects the main idea of articles. Keywords can be used to understand the field of its research direction. From Figure 5B, it can be seen that keywords are divided into 2 categories: the production and innovation of drugs and the mechanism of action on diseases. The first type is the mechanism of action on diseases, most of which involve cancer, including test tube squamous cell carcinoma,[101] laryngeal cancer,[102] gastric cancer,[103] colon cancer,[84] breast cancer,[104] pancreatic cancer,[105] and lung cancer.[106] In addition, it also extensively involves major diseases such as depression,[107] enteritis,[108] cardiovascular and cerebrovascular diseases,[109–111] liver injury,[112] renal failure[113] and leukemia.[96] The above results indicate that *I rubescens* can play a certain role in various diseases, especially digestive tract diseases. However, it also indicates that *I rubescens* has not been found to significantly affect in a certain disease, so further exploration is needed. The second category is the innovation and production of medicaments. Researchers have used materials and methods, such as nano preparations[39] and liposomes[114] to carry the effective substances in *I rubescens* such as Oridonin, so that they can stay in the human body for a longer time to enhance the efficacy. In recent years, articles have focused on the combined use of drugs, allowing Oridonin to have synergistic effects with other drugs,[115] while also partially reversing the tolerance to drugs.[116]

Studies have shown that *I rubescens* has a therapeutic effect on esophageal squamous cell carcinoma by inhibiting the protein expression of LASP1 (LIM and SH3 protein 1) and PDLIM1 (recombinant PDZ And LIM domain protein 1),[101] and selectively producing cytotoxicity on p35 mutant cells.[117] Interestingly, in the concomitant drugs for this cancer, Getuximab enhances Oridonin 's induction of cell apoptosis,[118] while Oridonin can enhance the effect of cisplatin.[117] These 3 drugs may be used in combination. Oridonin inhibits Wnt/ β- Chain protein signaling pathway,[119] TGF- β The 1/ Smads PAI-1 signaling pathway,[120] colon cancer cell metastasis[121] and JAK2/STAT3 signaling pathway[84] to resist colorectal cancer. It is worth noting that Oridonin can enhance MAPK activation by upregulating BMP7 (bone morphogenetic protein 7)[122] and reduce PTEN (phosphatase and tensin homologue) phosphorylation[123] to achieve therapeutic goals, as AMPK/mTOR/ULK1 can induce apoptosis in colorectal cancer cells.[124] Interestingly, Oridonin upregulation of BMP7, p38, and P35 elements will enhance Oridonin induction effect,[75] achieving a positive cycle. The process of Oridonin treating gastric cancer involves Apaf-1 (apoptotic protease activating factor-1),[125] Caspase-3[125] cytochrome c,[125] CdK1 (cyclin-dependent kinases 1),[126] and cyclin β,[126] c-Met,[127] mitochondrial signal,[128] caspase-3,[129] VEGF (vascular endothelial growth factor),[130] integrin β,[130] PCNA (proliferating cell nuclear antigen)[130] and other pathways and elements. Oridonin promotes the apoptosis of cancer cells by enhancing the functional expression of p35,[131] activating the phosphorylated JNK/C-JUN pathway,[132] triggering the stop of the G2/M cell cycle[133] and inducing the occurrence of the iron death mechanism.[100] Studies have shown that Oridonin can reduce the levels of P-gp (P-glycoprotein), MRP1 (multi-drug resistance-associated protein), cyclin D1 and cancer inhibitor of protein phosphatase 2A in vivo, thereby reversing drug resistance.[99] Recent articles have predicted the key targets of Oridonin on gastric cancer,[103] which may be a reference direction for future research. In addition to severe gastrointestinal diseases, the number of reports related to leukemia is large, involving multiple regulatory methods. It is worth noting that different drugs are often combined in the treatment regimen.

Oridonin collaborates with ATRA (all-trans-retinoic acid) to induce differentiation of NB4 and NB4-R1,[134] inhibits LYN/ mTOR through synergistic imatinib,[135] regulates MAPK signaling through synergistic VPA (Valproic acid)[73] and downregulates Bcl-2/Bax ratio,[136] and regulates PBK/Akt/mTOR signaling through synergistic NVP-BEZ235.[46] The mechanism of Oridonin reversing drug resistance has also been explained.[81,83]

In summary, based on the keywords and research trends in the paper, it can be seen that *I rubescens* has received much attention in the application of cancer, indicating that it does have a significant effect in this area. Studying in this direction may lead to the discovery of more cancer treatment methods. However, precisely because of this, the research direction is relatively single, and other aspects such as biological control, fertilizers, environmental beautification, and food have not been reflected. Perhaps *I rubescens* still has potential application value in these aspects.

5. Limitation

There are still several limitations in the current research. First, the data in this paper are all from the Wos, while other databases are not involved. The keywords used in this data retrieval are limited, thus other related words may be omitted. Moreover, reviews, reports, and conference papers were not analyzed. Some fundamental and milestone research that performs poorly after visualization may be overlooked. Due to the limited number of articles on some emerging hot topics, they may be regarded as unimportant parts. Finally, but importantly, bibliometric research is only a superficial and systematic field investigation and cannot cover all aspects. Of course, through this method, it can provide certain references for scholars in this field.

6. Conclusion

Through bibliometric analysis, past research about *I rubescens* is integrated and organized, then visually presented by visualizing. The number of studies related to *I rubescens* is showing an increasing trend year by year, indicating that this field has great potential and that a large number of studies will emerge in the future. Most of the institutions that contribute articles are in China, but the cooperation between Chinese researchers and other countries is far away. International Immunopharmacology, Cell Death & Disease and Cancer Research are closely related to cancer. It can be predicted that cancer treatment is the leading research direction of *I rubescens*, which will involve its mechanism and the improvement of dosage. However, it cannot be denied that further validation is needed to confirm the safety and effectiveness of using *I rubescens* as a drug.

Author contributions

Conceptualization: Jing Wu.
Data curation: Shaowei Xu, Teng Xu.
Formal analysis: Qingshan Yang, Huqiang Fang.
Funding acquisition: Qingshan Yang.
Investigation: Shihai Xing.
Methodology: Shihai Xing, Shaowei Xu, Qingshan Yang, Huqiang Fang, Bing He.
Project administration: Teng Xu.
Resources: Jing Wu.
Software: Shaowei Xu.
Supervision: Bing He.
Validation: Na Chen.
Visualization: Shaowei Xu.

Writing – original draft: Shaowei Xu, Jing Wu.

Writing – review & editing: Shihai Xing, Qingshan Yang, Na Chen.

References

[1] He K, Zou J, Wang YX, et al. Rubesanolides F and G: two novel lactone-type norditerpenoids from *Isodon rubescens*. Molecules. 2021;26:3865.

[2] He H, Jiang H, Chen Y, et al. Oridonin is a covalent NLRP3 inhibitor with strong anti-inflammasome activity. Nat Commun. 2018;9:2550.

[3] Zhao CL, Zhou L, Xie WJ, et al. Bioactive isopimarane and 3,4-seco isopimarane diterpenoids from Isodon amethystoides. BMC Chem. 2022;16:96.

[4] Jintao X, Shasha Y, Jincai W, Chunyan L, Mengya Y, Yongli S. Network pharmacological screening of the active ingredients and hypoglycemic effect of Isodon rubescens in the treatment of diabetes. Planta Med. 2020;86:556–64.

[5] Huang SX, Pu JX, Xiao WL, et al. ent-Abietane diterpenoids from Isodon rubescens var. rubescens. Phytochemistry. 2007;68:616–22.

[6] Zhao FL, Sun MC, Zhang WJ, et al. Comparative transcriptome analysis of roots, stems and leaves of Isodon amethystoides reveals candidate genes involved in Wangzaozins biosynthesis. BMC Plant Biol. 2018;18:272.

[7] Sun Y, Shao J, Liu H, et al. A chromosome-level genome assembly reveals that tandem-duplicated CYP706V oxidase genes control oridonin biosynthesis in the shoot apex of Isodon rubescens. Mol Plant. 2023;16:517–32.

[8] Lian CL, Lan JX, Zhang B, et al. Molecular cloning and functional analysis of IrUGT86A1-like gene in medicinal plant Isodon rubescens (Hemsl.) hara. Life (Basel). 2022;12:1334.

[9] Chen C. Searching for intellectual turning points: progressive knowledge domain visualization. Proc Natl Acad Sci U S A. 2004;101(Suppl 1):5303–10.

[10] Broadus RN. Toward a definition of "bibliometrics". Scientometrics. 1987;12:373–9.

[11] Aria M, Cuccurullo C. bibliometrix:an R-tool for comprehensive science mapping analysis. J Informetr. 2017;11:959–75.

[12] Chen CM, Ibekwe-SanJuan F, Hou JH. The structure and dynamics of cocitation clusters: a multiple-perspective cocitation analysis. J Am Soc Inf Sci Technol. 2010;61:1386–409.

[13] van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics. 2010;84:523–38.

[14] Hassan-Montero Y, De-Moya-Anegón F, Guerrero-Bote VP. SCImago Graphica: a new tool for exploring and visually communicating data. El Profesional de la información. 2022;31:5.

[15] Bastian M, Heymann S, Jacomy M. Gephi: an open source software for exploring and manipulating networks. International AAAI Conference on Weblogs and Social Media. 2009.

[16] Li DH, Wang L, Cai H, et al. Synthesis of novel furozan-based nitric oxide-releasing derivatives of 1-oxo-oridonin with anti-proliferative activity. Chin J Nat Med. 2012;10:471–6.

[17] Li DH, Wang L, Cai H, Zhang YH, Xu JY. Synthesis and biological evaluation of novel furozan-based nitric oxide-releasing derivatives of oridonin as potential anti-tumor agents. Molecules. 2012;17:7556–68.

[18] Wang L, Li DH, Xu ST, et al. The conversion of oridonin to spirolactone-type or enmein-type diterpenoid: synthesis and biological evaluation of ent-6,7-seco-oridonin derivatives as novel potential anticancer agents. Eur J Med Chem. 2012;52:242–50.

[19] Xu S, Li D, Pei L, et al. Design, synthesis and antimycobacterial activity evaluation of natural oridonin derivatives. Bioorg Med Chem Lett. 2014;24:2811–4.

[20] Xu ST, Pei LL, Li DH, et al. Synthesis and antimycobacterial evaluation of natural oridonin and its enmein-type derivatives. Fitoterapia. 2014;99:300–6.

[21] Li DH, Han T, Xu ST, et al. Antitumor and antibacterial derivatives of oridonin: a main composition of Dong-Ling-Cao. Molecules. 2016;21:575.

[22] Li DH, Hu X, Han T, et al. NO-releasing enmein-type diterpenoid derivatives with selective antiproliferative activity and effects on apoptosis-related proteins. Molecules. 2016;21:1193.

[23] Xu S, Wang G, Lin Y, et al. Novel anticancer oridonin derivatives possessing a diazen-1-ium-1,2-diolate nitric oxide donor moiety: design, synthesis, biological evaluation and nitric oxide release studies. Bioorg Med Chem Lett. 2016;26:2795–800.

[24] Li DH, Han T, Liao J, et al. Oridonin, a promising ent-kaurane diterpenoid lead compound. Int J Mol Sci. 2016;17:1395.

[25] Li HN, Sun BJ, Wang MY, et al. Bioactive enmein-type 6,7-seco-ent-kaurane diterpenoids: natural products, synthetic derivatives and apoptosis related mechanism. Arch Pharm Res. 2018;41:1051–61.

[26] Xu ST, Luo SS, Yao H, et al. Probing the anticancer action of oridonin with fluorescent analogues: visualizing subcellular localization to mitochondria. J Med Chem. 2016;59:5022–34.

[27] Li C, Zhang D, Guo H, et al. Preparation and characterization of galactosylated bovine serum albumin nanoparticles for liver-targeted delivery of oridonin. Int J Pharm. 2013;448:79–86.

[28] Guo B, Cheng Y, Li N, et al. In vitro and in vivo studies of galactose-modified liver-targeting liposomes. J Drug Target. 2013;21:257–64.

[29] Zheng DD, Dai WT, Zhang DR, et al. In vivo studies on the oridonin-loaded nanostructured lipid carriers. Drug Deliv. 2012;19:286–91.

[30] Shen J, Zhang D, Zhao Z, et al. Synthesis, characterization, in vitro and in vivo evaluation of PEGylated oridonin conjugates. Int J Pharm. 2013;456:80–6.

[31] Duan CX, Gao J, Zhang DR, et al. Galactose-decorated pH-responsive nanogels for hepatoma-targeted delivery of oridonin. Biomacromolecules. 2011;12:4335–43.

[32] Zheng DD, Duan CX, Zhang DR, et al. Galactosylated chitosan nanoparticles for hepatocyte-targeted delivery of oridonin. Int J Pharm. 2012;436:379–86.

[33] Wang Y, Liu XQ, Liu GP, et al. Novel galactosylated biodegradable nanoparticles for hepatocyte-delivery of oridonin. Int J Pharm. 2016;502:47–60.

[34] Li CY, Zhang DR, Guo YY, et al. Galactosylated bovine serum albumin nanoparticles for parenteral delivery of oridonin: tissue distribution and pharmacokinetic studies. J Microencapsul. 2014;31:573–8.

[35] Zhang Z, Zhang XM, Xue W, et al. Effects of oridonin nanosuspension on cell proliferation and apoptosis of human prostatic carcinoma PC-3 cell line. Int J Nanomedicine. 2010;5:735–42.

[36] Lou HY, Gao L, Wei XB, et al. Oridonin nanosuspension enhances anti-tumor efficacy in SMMC-7721 cells and H22 tumor bearing mice. Colloids Surf B. 2011;87:319–25.

[37] Qi X, Zhang D, Xu X, et al. Oridonin nanosuspension was more effective than free oridonin on G(2)/M cell cycle arrest and apoptosis in the human pancreatic cancer PANC-1 cell line. Int J Nanomed. 2012;7:1793–804.

[38] Feng FF, Zhang DR, Tian KL, et al. Growth inhibition and induction of apoptosis in MCF-7 breast cancer cells by oridonin nanosuspension. Drug Deliv. 2011;18:265–71.

[39] Sheng HG, Zhang YN, Nai JJ, et al. Preparation of oridonin nanocrystals and study of their endocytosis and transcytosis behaviours on MDCK polarized epithelial cells. Pharm Biol. 2020;58:518–27.

[40] Jia LJ, Shen JY, Zhang DR, et al. In vitro and in vivo evaluation of oridonin-loaded long circulating nanostructured lipid carriers. Int J Biol Macromol. 2012;50:523–9.

[41] Dong YL, Huang CP, Li J. The inhibitive effects of oridonin on cisplatin-resistant ovarian cancer cells via inducing cell apoptosis and inhibiting ADAM17. Acta Med Mediterr. 2018;34:819–25.

[42] Zhen T, Wu CF, Liu P, et al. Targeting of AML1-ETO in t(8;21) leukemia by oridonin generates a tumor suppressor-like protein. Sci Transl Med. 2012;4:127ra38.

[43] Wang Y, Zhen T, Wu C, et al. Oridonin upregulates retinoic acid receptors and shows synergistic effect when used in combination with all-trans retinoic acid in t(8:21) leukemia. Haematologica. 2013;98:691–691.

[44] Zhang W, Lu Y, Zhen T, et al. Homoharringtonine synergy with oridonin in treatment of t(8;21) acute myeloid leukemia. Front Med. 2019;13:388–97.

[45] Cao Y, Wei W, Zhang N, et al. Oridonin stabilizes retinoic acid receptor alpha through ROS-activated NF- kappa B signaling. BMC Cancer. 2015;15:248.

[46] Zhang LD, Liu Z, Liu H, et al. Oridonin enhances the anticancer activity of NVP-BEZ235 against neuroblastoma cells in vitro and in vivo through autophagy. Int J Oncol. 2016;49:657–65.

[47] Kang N, Zhang JH, Qiu F, et al. Induction of G(2)/M phase arrest and apoptosis by oridonin in human laryngeal carcinoma cells. J Nat Prod. 2010;73:1058–63.

[48] Kang N, Cao SJ, Zhou Y, et al. Inhibition of caspase-9 by oridonin, a diterpenoid isolated from Rabdosia rubescens, augments apoptosis in human laryngeal cancer cells. Int J Oncol. 2015;47:2045–56.

[49] Zhang YH, Wu YL, Tashiro S, Onodera S, Ikejima T. Reactive oxygen species contribute to oridonin-induced apoptosis and

autophagy in human cervical carcinoma HeLa cells. Acta Pharmacol Sin. 2011;32:1266–75.

[50] Yu Y, Fan SM, Ye YC, Tashiro S, Onodera S, Ikejima T. The tyrphostin AG1478 augments oridonin-induced A431 cell apoptosis by blockage of JNK MAPK and enhancement of oxidative stress. Free Radic Res. 2012;46:1393–405.

[51] Ye YC, Wang HJ, Xu L, et al. Oridonin induces apoptosis and autophagy in murine fibrosarcoma L929 cells partly via NO-ERK-p53 positive-feedback loop signaling pathway. Acta Pharmacol Sin. 2012;33:1055–61.

[52] Liu Y, Shi QF, Qi M, Tashiro SI, Onodera S, Ikejima T. Interruption of hepatocyte growth factor signaling augmented oridonin-induced death in human non-small cell lung cancer A549 cells via c-met-nuclear factor-kappa B-cyclooxygenase-2 and c-Met-Bcl-2-caspase-3 pathways. Biol Pharm Bull. 2012;35:1150–8.

[53] Liu Y, Liu JH, Chai K, Tashiro SI, Onodera S, Ikejima T. Inhibition of c-Met promoted apoptosis, autophagy and loss of the mitochondrial transmembrane potential in oridonin-induced A549 lung cancer cells. J Pharm Pharmacol. 2013;65:1622–42.

[54] Shen TY, Gong DD, Xu ST, Wang JH, Sun GX, Guo P. Multi wavelengths fusion profiling for quality evaluation of donglingcao tablets combined with electrochemical oscillation fingerprints and antioxidant activity analysis. Electroanalysis. 2022;34:1507–18.

[55] Ding C, Zhang Y, Chen H, et al. Overcoming synthetic challenges of oridonin A-ring structural diversification: regio- and stereoselective installation of azides and 1,2,3-triazoles at the C-1, C-2, or C-3 position. Org Lett. 2013;15:3718–21.

[56] Zhang YS, Ding CY, Yang ZD, et al. Discovery of potent oridonin derivatives for the treatment of breast cancer. Cancer Res. 2013;73:5573–5573.

[57] Bohanon FJ, Wang XF, Herndon DN, et al. Oridonin inhibits burn injury-induced activation and inflammatory signaling of hepatic stellate cells. J Am Coll Surg. 2014;219:S41–2.

[58] Wang X, Lopez ON, Bohanon FJ, et al. Oridonin prevents endotoxin-induced inflammatory response in human endothelial cells in vitro. Shock. 2016;45:117–117.

[59] Cummins C, Wang XF, Gu YP, Fang X, Radhakrishnan R. Protective effects of oridonin on intestinal epithelial cells by suppressing TNF alpha-Induced inflammation and epithelial-mesenchymal transition. J Am Coll Surg. 2019;229:e239–40.

[60] Ding Y, Ding CY, Ye N, et al. Discovery and development of natural product oridonin-inspired anticancer agents. Eur J Med Chem. 2016;122:102–17.

[61] Ding CY, Wang LL, Chen HJ, et al. ent-Kaurane-based regio- and stereoselective inverse electron demand hetero-Diels-Alder reactions: synthesis of dihydropyran-fused diterpenoids. Org Biomol Chem. 2014;12:8442–52.

[62] Cummins CB, Wang XF, Sommerhalder C, et al. Natural compound oridonin inhibits endotoxin-induced inflammatory response of activated hepatic stellate cells. Biomed Res Int. 2018;2018:6137420.

[63] Bohanon FJ, Wang XF, Graham BM, et al. Enhanced anti-fibrogenic effects of novel oridonin derivative CYD0692 in hepatic stellate cells. Mol Cell Biochem. 2015;410:293–300.

[64] Bohanon FJ, Wang XF, Ding CY, et al. Oridonin inhibits hepatic stellate cell proliferation and fibrogenesis. J Surg Res. 2014;190:55–63.

[65] Wang XF, Bohanon F, Kandathiparampil A, et al. Suppressive effects of novel oridonin derivative CYD0625 on activated hepatic stellate cells. FASEB J. 2015;29:1.

[66] Wang XF, Cummins C, Gu YP, Song JQ, Zhou J, Radhakrishnan R. Therapeutic effect of oridonin against inflammatory bowel disease involves inhibition of intestinal fibrosis via NF-kappa B pathway. FASEB J. 2020;34:1–1.

[67] Li H, Mu J, Sun J, et al. Hydrogen sulfide releasing oridonin derivatives induce apoptosis through extrinsic and intrinsic pathways. Eur J Med Chem. 2020;187:111976.

[68] Zhu HQ, Zhang C, Guo ZY, et al. Oridonin induces Mdm2-p60 to promote p53-mediated apoptosis and cell cycle arrest in neuroblastoma. Cancer Med. 2019;8:5313–26.

[69] Li DF, Wang H, Ding Y, et al. Targeting the NRF-2/RHOA/ROCK signaling pathway with a novel aziridonin, YD0514, to suppress breast cancer progression and lung metastasis. Cancer Lett. 2018;424:97–108.

[70] Chen G, Wang K, Yang BY, Tang B, Chen JX, Hua ZC. Synergistic antitumor activity of oridonin and arsenic trioxide on hepatocellular carcinoma cells. Int J Oncol. 2012;40:139–47.

[71] Bu HQ, Luo J, Chen H, et al. Oridonin enhances antitumor activity of gemcitabine in pancreatic cancer through MAPK-p38 signaling pathway. Int J Oncol. 2012;41:949–58.

[72] Cao SJ, Xia MJ, Mao YW, et al. Combined oridonin with cetuximab treatment shows synergistic anticancer effects on laryngeal squamous cell carcinoma: involvement of inhibition of EGFR and activation of reactive oxygen species-mediated JNK pathway. Int J Oncol. 2016;49:2075–87.

[73] Shi MY, Ren X, Wang XD, et al. A novel combination of oridonin and valproic acid in enhancement of apoptosis induction of HL-60 leukemia cells. Int J Oncol. 2016;48:734–46.

[74] Oh HN, Seo JH, Lee MH, et al. Oridonin induces apoptosis in oral squamous cell carcinoma probably through the generation of reactive oxygen species and the p38/JNK MAPK pathway. Int J Oncol. 2018;52:1749–59.

[75] Liu RX, Ma Y, Hu XL, et al. Anticancer effects of oridonin on colon cancer are mediated via BMP7/p38 MAPK/p53 signaling. Int J Oncol. 2018;53:2091–101.

[76] Li DF, Zhang ZW, Ding Y, et al. Discovery of novel oridonin-derivatives for the treatment of metastatic breast cancer. Cancer Res. 2018;78:P3–06.

[77] Ke Y, Liu ZB, Liu HM, Zi XL. Novel acetal and halogen oridonin analogues potently induce apoptosis in prostate cancer cell lines via induction of p53/p73 and PUMA expression. Cancer Res. 2014;74:1254–1254.

[78] Ding Y, Li DF, Ding CY, et al. Regio- and stereospecific synthesis of oridonin D-ring aziridinated analogues for the treatment of triple-negative breast cancer via mediated irreversible covalent warheads. Cancer Res. 2018;78:2668–2668.

[79] Yao Z, Xie FH, Li M, et al. Oridonin induces autophagy via inhibition of glucose metabolism in p53-mutated colorectal cancer cells. Cell Death Dis. 2017;8:e2633.

[80] Xu M, Wan CX, Huang SH, et al. Oridonin protects against cardiac hypertrophy by promoting P21-related autophagy. Cell Death Dis. 2019;10:403.

[81] Xiao XL, He ZW, Cao W, et al. Oridonin inhibits gefitinib-resistant lung cancer cells by suppressing EGFR/ERK/MMP-12 and CIP2A/Akt signaling pathways. Int J Oncol. 2016;48:2608–18.

[82] Zhou JC, Yun EJ, Chen W, et al. Targeting 3-phosphoinositide-dependent protein kinase 1 associated with drug-resistant renal cell carcinoma using new oridonin analogs. Cell Death Dis. 2017;8:e2701.

[83] Weng HY, Huang HL, Dong BW, Zhao PP, Zhou H, Qu LH. Inhibition of miR-17 and miR-20a by oridonin triggers apoptosis and reverses chemoresistance by derepressing BIM-S. Cancer Res. 2014;74:4409–19.

[84] Zhou J, Li Y, Shi X, et al. Oridonin inhibits tumor angiogenesis and induces vessel normalization in experimental colon cancer. J Cancer. 2021;12:3257–64.

[85] Ding C, Zhang Y, Chen H, et al. Novel nitrogen-enriched oridonin analogues with thiazole-fused a-ring: protecting group-free synthesis, enhanced anticancer profile, and improved aqueous solubility. J Med Chem. 2013;56:5048–58.

[86] Ding C, Zhang Y, Chen H, et al. Oridonin ring A-based diverse constructions of enone functionality: identification of novel dienone analogues effective for highly aggressive breast cancer by inducing apoptosis. J Med Chem. 2013;56:8814–25.

[87] Ding Y, Li DF, Ding CY, et al. Regio- and stereospecific synthesis of oridonin d-ring aziridinated analogues for the treatment of triple-negative breast cancer via mediated irreversible covalent warheads. J Med Chem. 2018;61:2737–52.

[88] Yu Y, Fan SM, Song JK, Tashiro S, Onodera S, Ikejima T. Hydroxyl radical (center dot OH) played a pivotal role in oridonin-induced apoptosis and autophagy in human epidermoid carcinoma A431 cells. Biol Pharm Bull. 2012;35:2148–59.

[89] Kang N, Zhang JH, Qiu F, Tashiro S, Onodera S, Ikejima T. Inhibition of EGFR signaling augments oridonin-induced apoptosis in human laryngeal cancer cells via enhancing oxidative stress coincident with activation of both the intrinsic and extrinsic apoptotic pathways. Cancer Lett. 2010;294:147–58.

[90] Zang LH, He H, Ye YC, et al. Nitric oxide augments oridonin- induced eff erocytosis by human histocytic lymphoma U937 cells via autophagy and the NF-kappa B-COX-2-IL-1 beta pathway. Free Radic Res. 2012;46:1207–19.

[91] Li FH, Gao CY, Li XM, et al. Jiyuan oridonin A induces differentiation of acute myeloid leukemia cells including leukemic stem-like cells. Front Pharmacol. 2022;13:1001552.

[92] Qu M, Duan Y, Zhao M, et al. Jiyuan oridonin A overcomes differentiation blockade in acute myeloid leukemia cells with MLL rearrangements via multiple signaling pathways. Front Oncol. 2021;11:659720.

[93] Liu Y, Zhang PX, Han CH, et al. Oridonin protects the lung against hyperoxia-induced injury in a mouse model. Undersea Hyperb Med. 2017;44:33–8.

[94] Li SM, Liu Y, Liu T, Zhao L, Zhao JH, Feng NP. Development and in-vivo assessment of the bioavailability of oridonin solid dispersions by the gas anti-solvent technique. Int J Pharm. 2011;411:172–7.

[95] Xu J, Zhao JH, Liu Y, Feng NP, Zhang YT. RGD-modified poly(D,L-lactic acid) nanoparticles enhance tumor targeting of oridonin. Int J Nanomedicine. 2012;7:211–9.

[96] Feng H, Liu Y, Zhang MY, et al. De Novo design of a humanized antiCD33 antibody-oridonin conjugate for acute myeloid leukemia therapy. Biochem Biophys Res Commun. 2022;629:152–8.

[97] Ke Y, Liang JJ, Hou RJ, et al. Synthesis and biological evaluation of novel Jiyuan Oridonin A-1,2,3-triazole-azole derivatives as antiproliferative agents. Eur J Med Chem. 2018;157:1249–63.

[98] Ke Y, Wang W, Zhao LF, et al. Design, synthesis and biological mechanisms research on 1,2,3-triazole derivatives of Jiyuan Oridonin A. Bioorg Med Chem. 2018;26:4761–73.

[99] He ZW, Xiao XL, Li S, et al. Oridonin induces apoptosis and reverses drug resistance in cisplatin resistant human gastric cancer cells. Oncol Lett. 2017;14:2499–504.

[100] Liu Y, Song Z, Liu YJ, et al. Identification of ferroptosis as a novel mechanism for antitumor activity of natural product derivative a2 in gastric cancer. Acta Pharm Sin B. 2021;11:1513–25.

[101] Zhang XJ, Xing MT, Ma YC, et al. Oridonin induces apoptosis in esophageal squamous cell carcinoma by inhibiting cytoskeletal protein LASP1 and PDLIM1. Molecules. 2023;28:805.

[102] Kou B, Yang Y, Bai YE, et al. Oridonin induces apoptosis of laryngeal carcinoma via endoplasmic reticulum stress. Cancer Manag Res. 2020;12:8387–96.

[103] Hu Y, Cui Q, Ma D, et al. Key targets and molecular mechanisms of active volatile components of rabdosia rubescens in gastric cancer cells. Curr Comput Aided Drug Des. 2022;18:493–505.

[104] Zhao Y, Xiao WW, Peng WQ, et al. Oridonin-loaded nanoparticles inhibit breast cancer progression through regulation of ROS-Related Nrf2 signaling pathway. Front Bioeng Biotechnol. 2021;9:600579.

[105] Cui WQ, Zhang JW, Wu DQ, et al. Ponicidin suppresses pancreatic cancer growth by inducing ferroptosis: insight gained by mass spectrometry-based metabolomics. Phytomedicine. 2022;98:153943.

[106] Xu L, Bi Y, Xu Y, et al. Oridonin inhibits the migration and epithelial-to-mesenchymal transition of small cell lung cancer cells by suppressing FAK-ERK1/2 signalling pathway. J Cell Mol Med. 2020;24:4480–93.

[107] Liang L, Wang H, Hu Y, Bian HT, Xiao L, Wang GH. Oridonin relieves depressive-like behaviors by inhibiting neuroinflammation and autophagy impairment in rats subjected to chronic unpredictable mild stress. Phytother Res. 2022;36:3335–51.

[108] Wang M, Xu B, Liu L, et al. Oridonin attenuates dextran sulfate sodium-induced ulcerative colitis in mice via the Sirt1/NF-kappa B/ p53 pathway. Mol Med Rep. 2022;26:312.

[109] Lin S, Dai SS, Lin JH, et al. Oridonin relieves angiotensin II-induced cardiac remodeling via inhibiting GSDMD-mediated inflammation. Cardiovasc Ther. 2022;2022:3167959.

[110] Zhao XJ, Zhu HY, Wang XL, et al. Oridonin ameliorates traumatic brain injury-induced neurological damage by improving mitochondrial function and antioxidant capacity and suppressing neuroinflammation through the Nrf2 pathway. J Neurotrauma. 2022;39:530–43.

[111] Chen ZP, Liu HQ, Zhao XQ, et al. Oridonin attenuates low shear stress-induced endothelial cell dysfunction and oxidative stress by activating the nuclear factor erythroid 2-related factor 2 pathway. BMC Complement Med Ther. 2022;22:180.

[112] Zhan ZK, Zhang T, Dai FH, et al. Effect of oridonin on oxylipins in the livers of mice with acute liver injury induced by D-galactosamine and lipopolysaccharide. Int Immunopharmacol. 2022;102:108387.

[113] Gu H, Gwon MG, Kim JH, Leem J, Lee SJ. Oridonin attenuates cisplatin-induced acute kidney injury via inhibiting oxidative stress, apoptosis, and inflammation in mice. Biomed Res Int. 2022;2022:3002962.

[114] Lin FE, Zhang XY, Zhang YP, Wang J. Preparation, characterization, and pharmacokinetics of oridonin-loaded liposomes. Biomed Chromatogr. 2023;37:e5603.

[115] Kazantseva L, Becerra J, Santos-Ruiz L. Oridonin enhances antitumor effects of doxorubicin in human osteosarcoma cells. Pharmacol Rep. 2022;74:248–56.

[116] Li X, Chen W, Liu K, et al. Oridonin sensitizes hepatocellular carcinoma to the anticancer effect of sorafenib by targeting the Akt pathway. Cancer Manag Res. 2020;12:8081–91.

[117] Yang HY, Wang J, Khan S, et al. Selective synergistic anticancer effects of cisplatin and oridonin against human p53-mutant esophageal squamous carcinoma cells. Anticancer Drugs. 2022;33:e444–52.

[118] Kang N, Cao SJ, Jiang BK, et al. Cetuximab enhances oridonin-induced apoptosis through mitochondrial pathway and endoplasmic reticulum stress in laryngeal squamous cell carcinoma cells. Toxicol In Vitro. 2020;67:104885.

[119] Bu HQ, Liu DL, Cui JH, Cai K, Shen F. Wnt/beta-catenin signaling pathway is involved in induction of apoptosis by oridonin in colon cancer COLO205 cells. Transl Cancer Res. 2019;8:1782–94.

[120] Bu HQ, Shen F, Cui J. The inhibitory effect of oridonin on colon cancer was mediated by deactivation of TGF-beta 1/Smads-PAI-1 signaling pathway in vitro and vivo. Oncotargets Ther. 2019;12:7467–76.

[121] Yang YS, Wen D, Zhao XF. Preventive and therapeutic effect of intraportal oridonin on BALb/c nude mice hemispleen model of colon cancer liver metastasis. Transl Cancer Res. 2021;10:1324–35.

[122] Ren CM, Li Y, Chen QZ, et al. Oridonin inhibits the proliferation of human colon cancer cells by upregulating BMP7 to activate p38 MAPK. Oncol Rep. 2016;35:2691–8.

[123] Wu QX, Yuan SX, Ren CM, et al. Oridonin upregulates PTEN through activating p38 MAPK and inhibits proliferation in human colon cancer cells. Oncol Rep. 2016;35:3341–8.

[124] Bu H, Liu D, Zhang G, Chen L, Song Z. AMPK/mTOR/ULK1 axis-mediated pathway participates in apoptosis and autophagy induction by oridonin in colon cancer DLD-1 cells. Oncotargets Ther. 2020;13:8533–45.

[125] Sun KW, Ma YY, Guan TP, et al. Oridonin induces apoptosis in gastric cancer through Apaf-1, cytochrome c and caspase-3 signaling pathway. World J Gastroenterol. 2012;18:7166–74.

[126] Gao SY, Li J, Qu XY, Zhu N, Ji YB. Downregulation of Cdk1 and CyclinB1 expression contributes to oridonin-induced cell cycle arrest at G(2)/M phase and growth inhibition in SGC-7901 gastric cancer cells. Asian Pac J Cancer Prev. 2014;15:6437–41.

[127] Liu H, Qian CL, Shen ZY. Anti-tumor activity of oridonin on SNU-5 subcutaneous xenograft model via regulation of c-Met pathway. Tumour Biol. 2014;35:9139–46.

[128] Gao SY, Tan HX, Zhu N, et al. Oridonin induces apoptosis through the mitochondrial pathway in human gastric cancer SGC-7901 cells. Int J Oncol. 2016;48:2453–60.

[129] Shi M, Lu XJ, Zhang J, et al. Oridonin, a novel lysine acetyltransferases inhibitor, inhibits proliferation and induces apoptosis in gastric cancer cells through p53-and caspase-3-mediated mechanisms. Oncotarget. 2016;7:22623–31.

[130] Yang Q, Ma WD, Yu K, et al. Oridonin suppresses human gastric cancer growth in vitro and in vivo via inhibition of VEGF, integrin beta 3, and PCNA. Biol Pharm Bull. 2020;43:1035–45.

[131] Bi EX, Liu DQ, Li YX, Mao XY, Wang AH, Wang JT. Oridonin induces growth inhibition and apoptosis in human gastric carcinoma cells by enhancement of p53 expression and function. Braz J Med Biol Res. 2018;51:e7599.

[132] Ren DL, Ghoorun RA, Wu XH, Chen HL, Zhou Q, Wu XB. Oridonin induces apoptosis in HGC-27 cells by activating the JNK signaling pathway. Oncol Lett. 2020;19:255–60.

[133] Zhu D, Tian X, Yin X, Yan H, Li W. Oridonin triggers G2/M cell cycle arrest, cellular apoptosis and autophagy in human gastric cancer cells. J BUON. 2020;25:2308–14.

[134] Gao F, Tang Q, Yang P, Fang Y, Li W, Wu Y. Apoptosis inducing and differentiation enhancement effect of oridonin on the all-trans-retinoic acid-sensitive and -resistant acute promyelocytic leukemia cells. Int J Lab Hematol. 2010;32:e114–22.

[135] Guo Y, Shan QQ, Gong YP, Lin J, Yang X, Zhou RQ. Oridonin in combination with imatinib exerts synergetic anti-leukemia effects in Ph+ acute lymphoblastic leukemia cells in vitro by inhibiting activation of LYN/mTOR signaling pathway. Cancer Biol Ther. 2012;13:1244–54.

[136] Li W, Ma LE. Synergistic antitumor activity of oridonin and valproic acid on HL-60 leukemia cells. J Cell Biochem. 2019;120:5620–7.