Original Article

Trends of mapping knowledge structure and themes of cancer sonodynamic therapy: a text-mining study

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Background: Sonodynamic therapy (SDT) is a non-invasive cancer treatment technique stemming from photodynamic therapy (PDT) and has garnered escalated interest among researchers in recent years. Numerous aspects of cancer SDT remain contentious, and the global research trajectory within this domain remains insufficiently explored. This study seeks to delineate the comprehensive knowledge framework, developmental trends, and pivotal research focal points concerning cancer SDT.

Methods: The study retrieved documents on cancer SDT from the Web of Science Core Collection (WoSCC) database spanning from 1 January 2000 to 7 December 2023. Bibliometric visualization was carried out through the utilization of CiteSpace 6.2 R6, VOSviewer 1.6.20, and an online analytical platform. Several bibliometric techniques including co-authorship, co-citation, co-occurrence, cluster, as well as burst analysis were used.

Results: A total of 672 publications including 603 articles and 69 reviews were included. The annual publication count exhibited a steady increase over time, notably experiencing a surge, particularly in recent years. In terms of contributors, China has maintained its prominent position with the highest outputs and the most financial support. Chinese Academy of Sciences contributed the most articles. Materials Science was the most investigated research areas. Breast cancer emerged as the most extensively studied tumor, succeeded by sarcoma, hepatocellular carcinoma, melanoma, pancreatic cancer, glioma. According to co-cited references, "harnessing nanomaterial", "sonodynamic precision tumor therapy" and "metal-organic framework" denote the current and emerging research focuses within the field. In tandem with the results from keywords co-occurrence and burst, we identified the following research topics including mechanism of induced cell death (ferroptosis, immunogenic cell death), nano-related research (nanoplatform, nanozymes, nanomaterials, nanosheets, metal-organic frameworks (MOFs), nanocomposites, nanoparticles, nanosonosensitizers, liposomes, nanocarriers), combination therapies (chemodynamic therapy, immunotherapy, radiotherapy, photothermal therapy), and tumor microenvironment (hypoxia, singlet oxygen, oxidative stress), that may remain the research hotspots and receive sustained attention in the near future.

Conclusions: For the first time, this bibliometric analysis not only presents a comprehensive portrayal of the knowledge framework, but also delineates shifts in research focal points related to cancer SDT within the last two decades. This systematic summarization offers a comprehensive and lucid comprehension of cancer SDT, providing valuable insights for further investigations in this domain.

Keywords: Cancer; sonodynamic therapy (SDT); bibliometrics; CiteSpace; VOSviewer

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Introduction

Sonodynamic therapy (SDT) is an emerging non-invasive cancer treatment technique developed based on photodynamic therapy (PDT) (1). It utilizes ultrasound waves with strong tissue penetration, particularly focused ultrasound that non-invasively concentrates sound energy into deep tissues, activating certain sonosensitive drugs/agents to produce anti-tumor effects (2,3). SDT employs sonosensitizers and oxygen under ultrasound influence to generate biotoxic reactive oxygen species (ROS), inducing the destruction of tumor cells. Most researchers support multiple mechanisms working synergistically to cause tumor cell death (4,5). Ultrasound generates cavitation phenomena and acousto-mechanical/acousto-chemical processes. The energy generated by cavitation promotes acousto-chemical reactions, which activate acoustic sensitizers through acoustic luminescence, and energy transfer, thus increasing the concentration of intracellular ROS (6-8). Singlet oxygen, as the primary ROS, effectively oxidizes surrounding substrates, inducing a series of adverse physiological responses in cells, such as mitochondrial membrane damage (9), DNA fragmentation, and cytoskeletal contraction, ultimately leading to cell death (10).

Extensive *in vitro* and *in vivo* studies have demonstrated the cytotoxicity of SDT against various cancer cells, positioning it as a potential therapeutic approach (11-13). However, there are still some unresolved issues before the actual clinical application of SDT (14). For example, some commonly used sonosensitizers, initially developed for PDT, still pose phototoxicity concerns in SDT (15-18). Moreover, the efficacy of SDT depends on the ultrasound device, and SDT requires stable and non-attenuating ultrasound to maintain energy stability during treatment (19). Furthermore, most sonosensitizers are hydrophobic molecules prone to aggregation in physiological environments, reducing their water solubility, lowering the production of ROS, and consequently weakening sonodynamic activity (20). In view of this, SDT has attracted increasing research interest and an increasing number of studies on cancer SDT have been published in recent years (21). The study of cancer SDT is advancing swiftly, posing a challenge for new researchers to swiftly gain a comprehensive understanding of the field. Therefore, it is essential to offer a comprehensive overview of research trends, key areas of focus, and notable contributions by institutions and authors in this domain. Despite numerous systematic reviews and meta-analyses published in the field of cancer SDT, a bibliometric analysis of research on cancer SDT has not been conducted (1-3).

Bibliometrics, an interdisciplinary field merging statistics and bibliography, employs quantitative analysis to scrutinize various forms of knowledge carriers (22-24). Introduced by Prichard in 1969, it has been extensively employed to evaluate and quantify publication data, encompassing researchers, countries, collaborative efforts, keyword analysis, and references (25,26). Insights derived from bibliometric studies could assist researchers in identifying prevailing research interests, guiding future research endeavors (27). Take PDT as an example, many bibliometric studies have analyzed the global research trends of PDT in skin cancer, in endodontics, as well as in head and neck

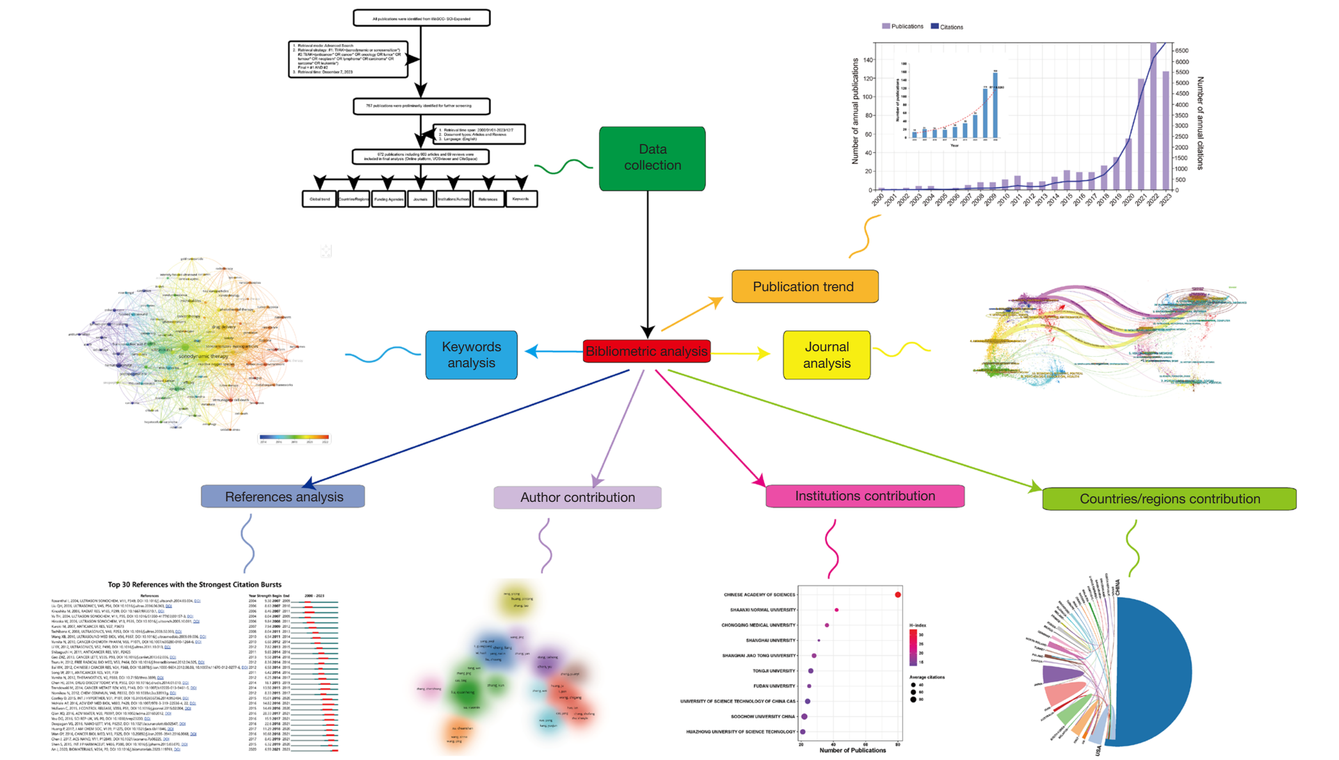

Figure 1 Graphical abstract of the study. WoSSC, Web of Science Core Collection; SCI, Science Citation Index; TI, title; AK, author keywords.

cancer (28-31). Nevertheless, few studies have analyzed the publication trend and research hotspots in the field of SDT. Hence, our study focused on utilizing bibliometric methods to analyze publications within the field of cancer SDT spanning from 2000 to 2023. Through a comprehensive analysis, we aimed to delineate the present research status and knowledge foundation, elucidating forthcoming directions and valuable insights in this field.

Methods

Data sources

Two researchers independently conducted a literature search encompassing the years 2000 to 2023. To mitigate potential biases arising from database updates, we conducted the retrieval process within a single day on December 7, 2023. Notably, to perform a comprehensive search, we opted for the Web of Science Core Collection (WoSCC), covering diverse disciplines, instead of PubMed (27,32). The former incorporates pivotal databases like the Science Citation Index (SCI), the Science Citation Index Expanded (SCIE), and so on. Additionally, the robust citation analysis functionality of WoSCC, well-suited for bibliometric analysis, contributed significantly to our choice (33). Moreover, numerous previously published bibliometric analyses have reinforced the reliability of our selection (33-35). *Figure 1* depicts the visual representation of the workflow employed in this study.

Search strategy

For this study, our focus was on retrieving publications concerning cancer SDT from the SCIE. Outlined below is the search strategy utilized: [#1: TI=(sonodynamic or sonosensitizer*) or AK=(sonodynamic or sonosensitizer*); #2: TI=(anticancer* OR cancer* OR oncology OR tumor* OR tumour* OR neoplasm* OR lymphoma* OR carcinoma* OR sarcoma* OR leukemia*) OR AK=(anticancer* OR cancer* OR oncology OR tumor* OR tumour* OR neoplasm* OR lymphoma* OR carcinoma* OR sarcoma* OR leukemia*); Final dataset: #1 AND #2]. The wildcards (*), which could substitute any other letter and permit keywords with varied ends, enable for the capture of the greatest number of data sources. For instance, "sarcoma*" would also return the words of "sarcoma" and "sarcomas".

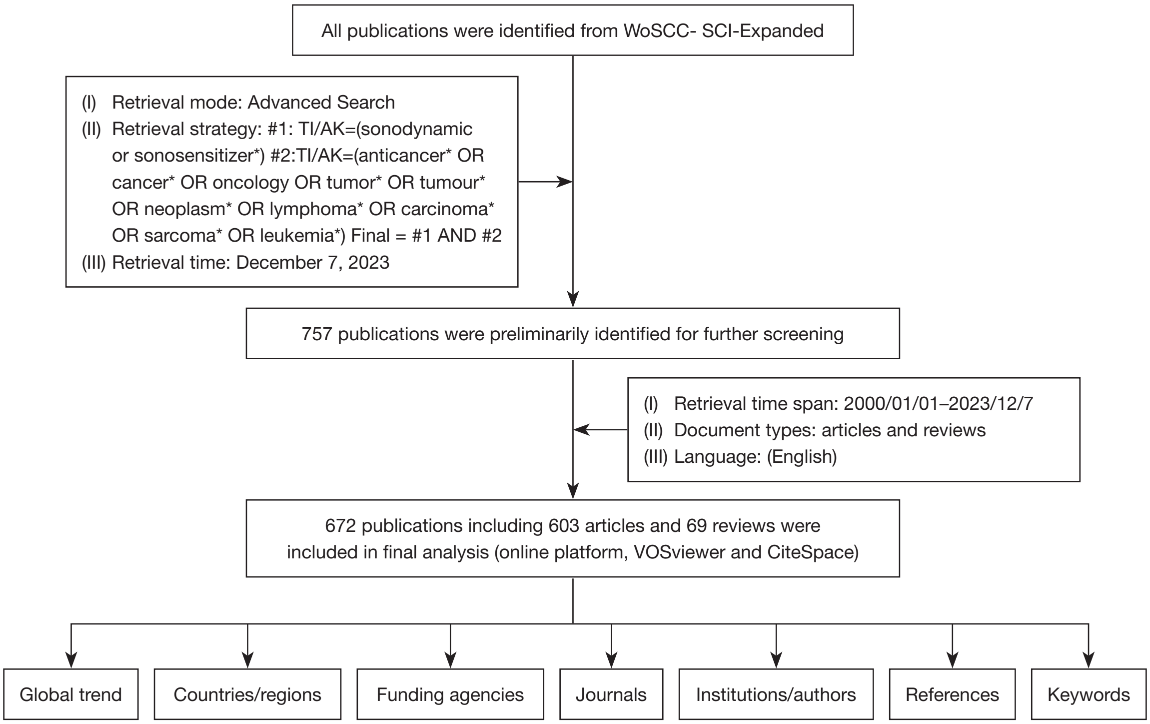

Figure 2 Data screening and collection procedures. WoSSC, Web of Science Core Collection; SCI, Science Citation Index; TI, title; AK, author keywords.

We made arrangements for the two researchers to work independently to confirm the correctness of the search and publication screening. In cases of conflict, the two researchers conversed and came to a consensus and any remaining disagreements were settled by third negotiations. The inclusion criteria for this literature were as follows: (I) the period of literatures was from January 1, 2000 to December 7, 2023; (II) only articles and reviews literatures were included; (III) the publication language was strictly restricted to English. *Figure 2* portrays the data screening and data collection process.

Data collection

Based on the search strategy, a total of 672 documents were acquired. These documents were exported in "full record and cited references", then stored in plain text format or UTF-8 encoding. The extracted data encompassed various aspects: yearly publication counts, citation numbers, geographical origin, affiliations, authors, funding sources, journals, subject classifications, highly cited articles, keywords, and references. Additionally, the "citation report" feature within WoSCC facilitated the retrieval of the Hirsch index (H-index) for authors, alongside the average citation index (ACI) for each article. The H-index defined as the number of papers (h) that have garnered at least h citations (36). Put simply, an author with a H-index of 20 has authored 20 articles, each receiving a minimum of 20 citations. This metric serves as an assessment of both the quantity and quality of scholarly output by researchers. Furthermore, the Journal Impact Factor (JIF) was sourced from the Journal Citation Report 2023 (JCR, Clarivate Analytics, Philadelphia, PA, USA, http://clarivate.com/products/web-of-science).

Data analysis

The study utilized Microsoft Excel 2019 and SPSS (IBM SPSS Statistics 21, Inc., Chicago, IL, USA) to conduct statistical analysis and visually represent the data using bar and line charts. Bibliometric visualization was carried out through the utilization of CiteSpace 6.2 R6, VOSviewer 1.6.20, and an online analytical platform (available at https://bibliometric.com/). Of them, the online analytical platform was utilized to explore collaborative networks among different countries or regions.

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VOSviewer (v.1.6.20) was employed to explore collaborative relationships across various countries/regions, institutions, and authors. It facilitated the creation of visualization maps illustrating co-cited authors, journals, references, and co-occurring keywords. VOSviewer could generate three distinct types of visual maps: network, density, or overlay maps. These knowledge maps feature nodes that symbolize various elements like countries, institutes, or authors (37). The connections between these nodes depict relationships among these elements. The lines connecting nodes signify associations, with several factors influencing an element's size, including publication count, citation frequency, or occurrences (38,39). To enhance distinction, nodes and lines are color-coded based on different clusters or their respective average appearing year (AAY) (40).

CiteSpace (v.6.2.R6) was utilized to examine journal dual-maps, keyword bursts, and the chronological evolution of keywords and references (41). The parameters were set as follows: timespan [2000–2023], one year per slice, scale factor k=25, selection criteria (top N=50), cluster labels generated through the log-likelihood ratio (LLR) algorithm, and other settings aligned with the default software configurations. Through co-occurrence, co-authorship, and co-citation analyses, high-frequency elements and their interconnections were identified. These hotspots delineated research trajectories garnering considerable attention within the academic community. The citation burst analysis highlighted references and keywords experiencing a remarkable surge in citations over a brief duration, reflecting researchers' heightened interest during those specific periods (42,43). Cluster analysis is pivotal for categorizing references and keywords, aiding in pinpointing important research domains within the realm of cancer SDT. Two key assessment measures in cluster analysis are modularity Q and mean silhouette. An Q value exceeding 0.3 implies a significant clustering arrangement, while a mean silhouette value surpassing 0.5 indicates robust clustering results (44,45). Within the map generated by CiteSpace, multiple elements are discernible. The nodes, depicted as circles, are available for analysis on the map, with their size typically denoting the quantity-larger circles indicate greater quantities. These circles comprise annual rings, where each ring's color signifies the year, and its thickness correlates with the number of nodes from that year. Thicker rings represent higher node counts for a specific year. The "Centrality" option within CiteSpace's menu refers to "betweenness centrality" (BC) (46). CiteSpace employs this metric to identify and gauge the significance of nodes, highlighting nodes with purple circles when their centrality equals or exceeds 0.1. This implies that nodes with centrality values of 0.1 or higher are the ones considered noteworthy in terms of importance (47).

Results

Quantitative analysis of publication outputs

The quantity of documents and their evolving trends within a specific field could offer insights into the developmental phase of the research domain, potentially enabling assessment and forecasting of its progress. According to the retrieval process in *Figure 2*, 672 publications on cancer SDT from 1 January 2000 to 7 December 2023 were included, of which 603 articles constitute 89.7% of the total, followed by 69 reviews. The cumulative citations for these works totaled 24,332 instances, averaging about 36.21 citations per document. *Figure 3* illustrates the annual publications and citations concerning cancer SDT. Over the past two decades, the volume of literature on cancer SDT has seen an annual increase, rising from 2 in 2000 to 158 in 2022. However, the count for 2023 appears lower, possibly due to only a partial inclusion of that year's data in the search results. According to their temporal characteristics, these publications could be categorized into three phases roughly. The initial stage, from 2000 to 2006, was an exploratory phase with relatively fewer publications. The subsequent phase, spanning 2007 to 2013, witnessed an acceleration in publishing activity. The third phase, occurring around 2014–2023, marked a rapid surge in published articles. The coefficient (R^2) for annual publications from 2014 to 2022 was determined to be 0.9283, showcasing a strong exponential growth model.

Visual analysis of popular journals and research domains

In *Figure 4A*, a dot plot illustrates the top 10 journals by publication count. In terms of publishers, three of these journals were from the USA, three from the Germany, and the others from Switzerland, New Zealand and Netherlands, respectively. Notably, *Chemical Engineering Journal* (n=27) stands out with the highest number of publications, closely trailed by *ACS Applied Materials Interfaces* (n=26) and *International Journal of Nanomedicine* (n=20). Most of these journals are situated within the Q1

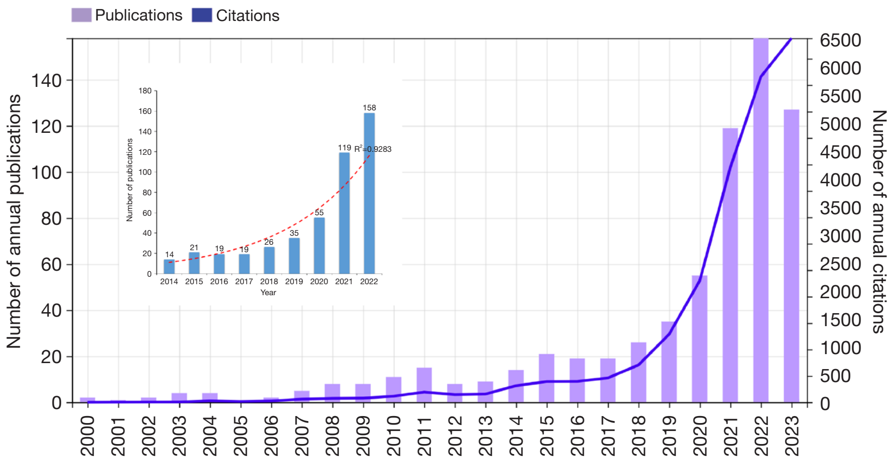

Figure 3 The annual publications and citations concerning cancer SDT. SDT, sonodynamic therapy.

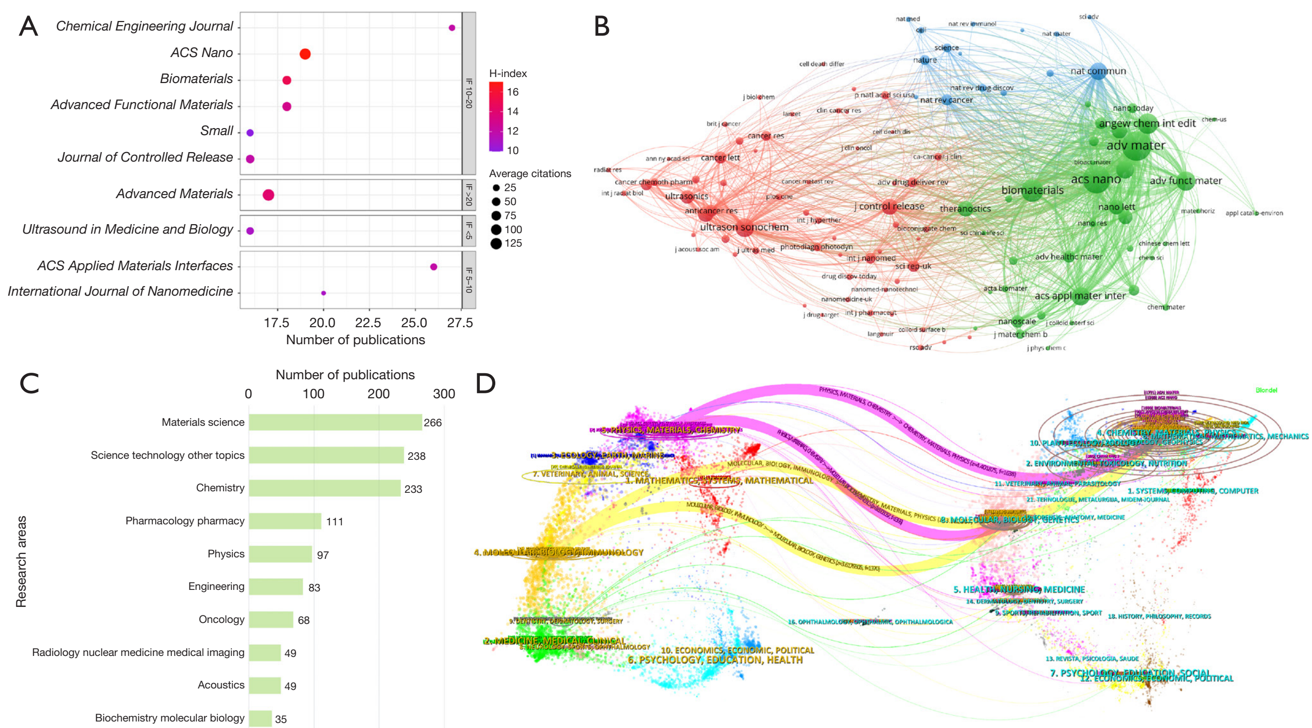

Figure 4 Visual analysis of popular journals and research domains. (A) Dot plot of the top 10 journals by publication count. (B) Network visualization map of co-cited journals in cancer SDT research. Each node corresponds to a journal, with node size proportional to citation count. The line segments denote citation relationships, with closer proximity between nodes indicating stronger correlation, categorized by similar colors. (C) Top 10 research domains categorized by their respective publication counts. (D) Dual-map overlay of journals in the field of cancer SDT. IF, impact factor; SDT, sonodynamic therapy.

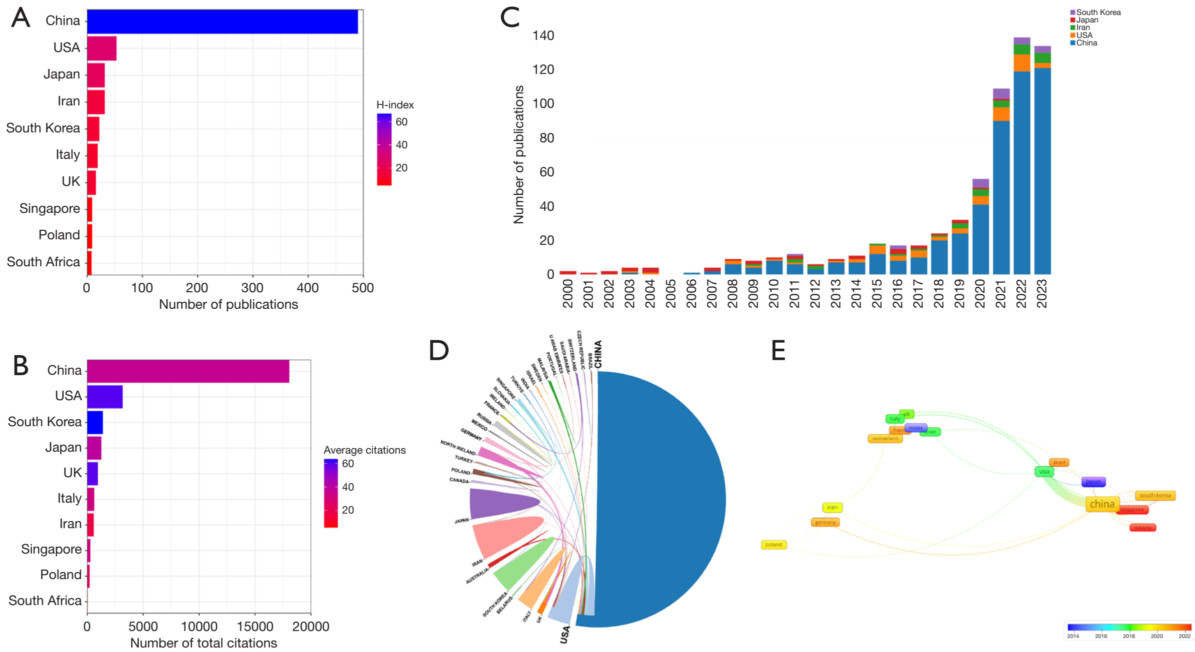

Figure 5 Contributions of countries/regions. (A) Top 10 leading countries/regions based on their publication outputs; (B) top 10 leading countries/regions based on their citations; (C) annual publication volume for the top 5 countries/regions; (D) international collaboration network among countries/regions; (E) VOSviewer analysis of country co-authorship.

categories, as indicated by the 2023 JCR Report. *Figure 4B* showcases a network visualization map portraying 115 co-cited journals, each accumulating over 50 citations. Notably, *Advanced Materials*, *ACS Nano*, and *Biomaterials* emerge as the top three journals with the most substantial Total Link Strength (TLS). Moreover, the WoSCC database could effectively categorizes these publications into distinct research areas based on their subject categories. *Figure 4C* outlines the top 10 research domains, categorized by their respective publication counts.

Figure 4D illustrates the dual-map overlay of journals on cancer SDT. The journals referenced are positioned on the right, while those doing the referencing are on the left, with colored pathways denoting their citation connections. The wider color lines were employed to illustrate the connections between citing and co-cited journals. Four prominent pathway stands out: articles in the fields of Molecular, Biology, and Immunology are mainly influenced by studies in the fields of Chemistry, Materials, and Physics, as well as Molecular, Biology, and Genetics (yellow trajectory). Moreover, articles published in Physics, Materials, and Chemistry usually cite articles published in Chemistry, Materials, and Physics, as well as Molecular, Biology.

Visual analysis of main contributors and their academic collaboration

Contributions of countries/regions

All 672 publications originated from 35 countries/regions. Notably, *Figure 5A,5B* highlights the top 10 leading contributors based on their publication outputs and citations, respectively. Among them, China notably led, contributing over two-thirds of the total publications, significantly surpassing other countries/regions, underscoring its pivotal positions in terms of published papers. Furthermore, as can be seen that China also boasted the highest total citations [18,052] and an impressive H-index of 67, surpassing all other countries. South Korea exhibited the highest average citations per document [63.73], followed by the United States [60] and UK [59.44]. *Figure 5C* depicts the annual publication volume for the top 10 countries/regions. Subsequently, *Figure 5D* illustrates the international collaboration network among countries, highlighting China's close cooperation primarily with the United States. Additionally, *Figure 5E* displays a VOSviewer analysis of country co-authorship involving 31 countries/regions. In this depiction, the nodes signify countries/regions, interconnected by lines. Node size corresponds

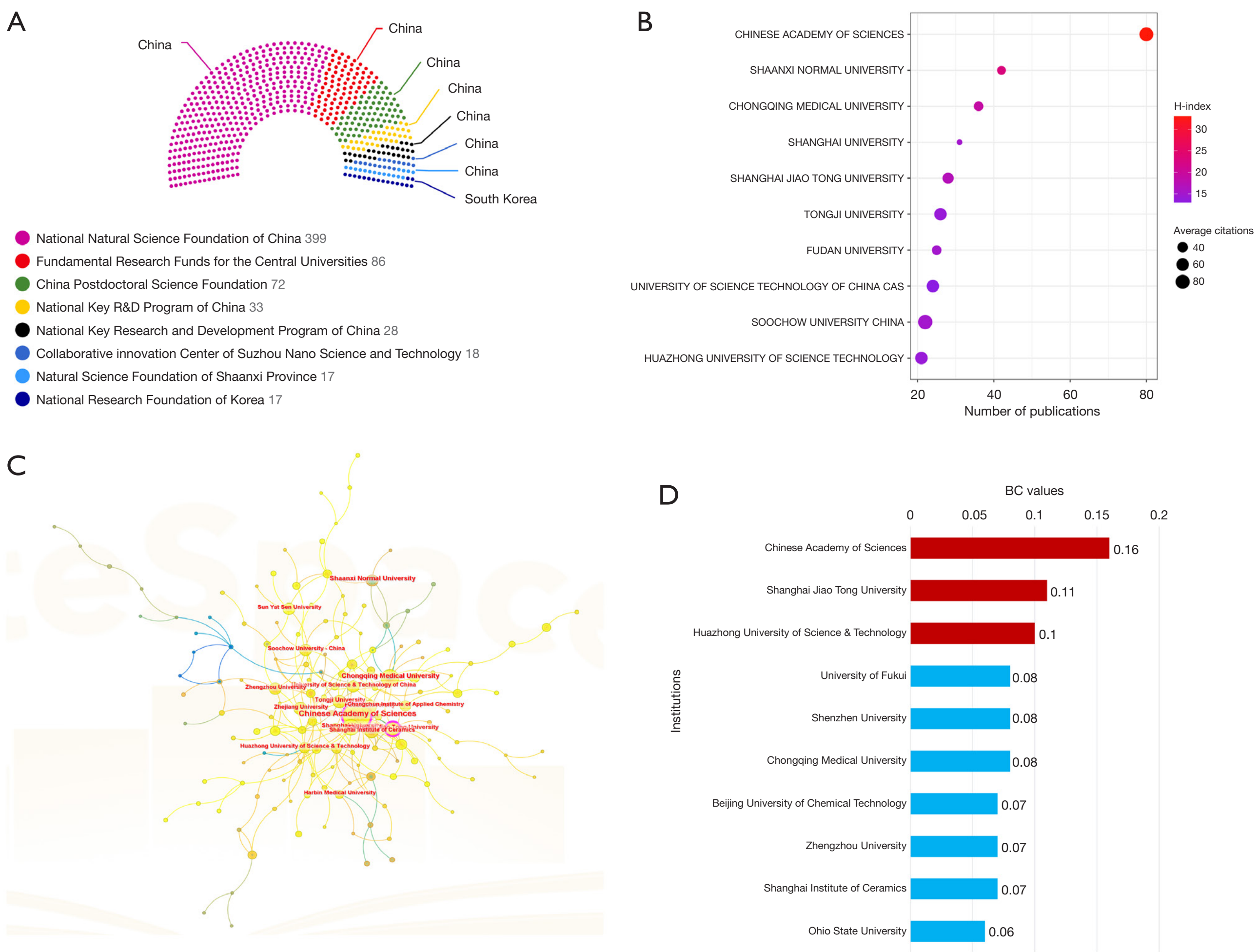

Figure 6 Contributions of funding agencies and institutions. (A) Top 8 most active funding agencies involved in this domain; (B) dot plot of the top 10 institutions based on publication count; (C) organizational collaboration analysis by using CiteSpace; (D) top 10 institutions determined by their BC values (BC >0.1, red bar; BC <0.1 blue bar). BC, betweenness centrality.

to the volume of publications, while the lines delineate collaborative ties. The thickness of these lines indicates the intensity of cooperation; denser connections denote stronger collaborative relationships. According to the color gradient at the lower right corner, countries such as Singapore, and Malaysia are denoted by a red hue, while Russia, and Japan are represented in blue.

Contributions of funding agencies and institutions

The funding agencies in the research domain play an important role in advancing studies, fostering innovation, facilitating collaborations, and driving academic output. The support from these funding agencies could significantly impact the scale and quality of research, proving critical in advancing both scientific endeavors and the academic community. Therefore, the top 8 most active funding agencies involved in this domain are summarized in *Figure 6A*, with seven of them originating from China. In terms of institution analysis, *Figure 6B* shows a dot plot summarizing the top 10 institutions based on publication count and their H-index, average citations per document. Chinese Academy of Sciences contributed the most articles (n=80) among institutions, followed by Shaanxi Normal University (n=42), Chongqing Medical University (n=36), and Shanghai University (n=31). All these active organizations were in China. It is worth noting that although Soochow University was in ninth place for total production, it had the highest average citations per

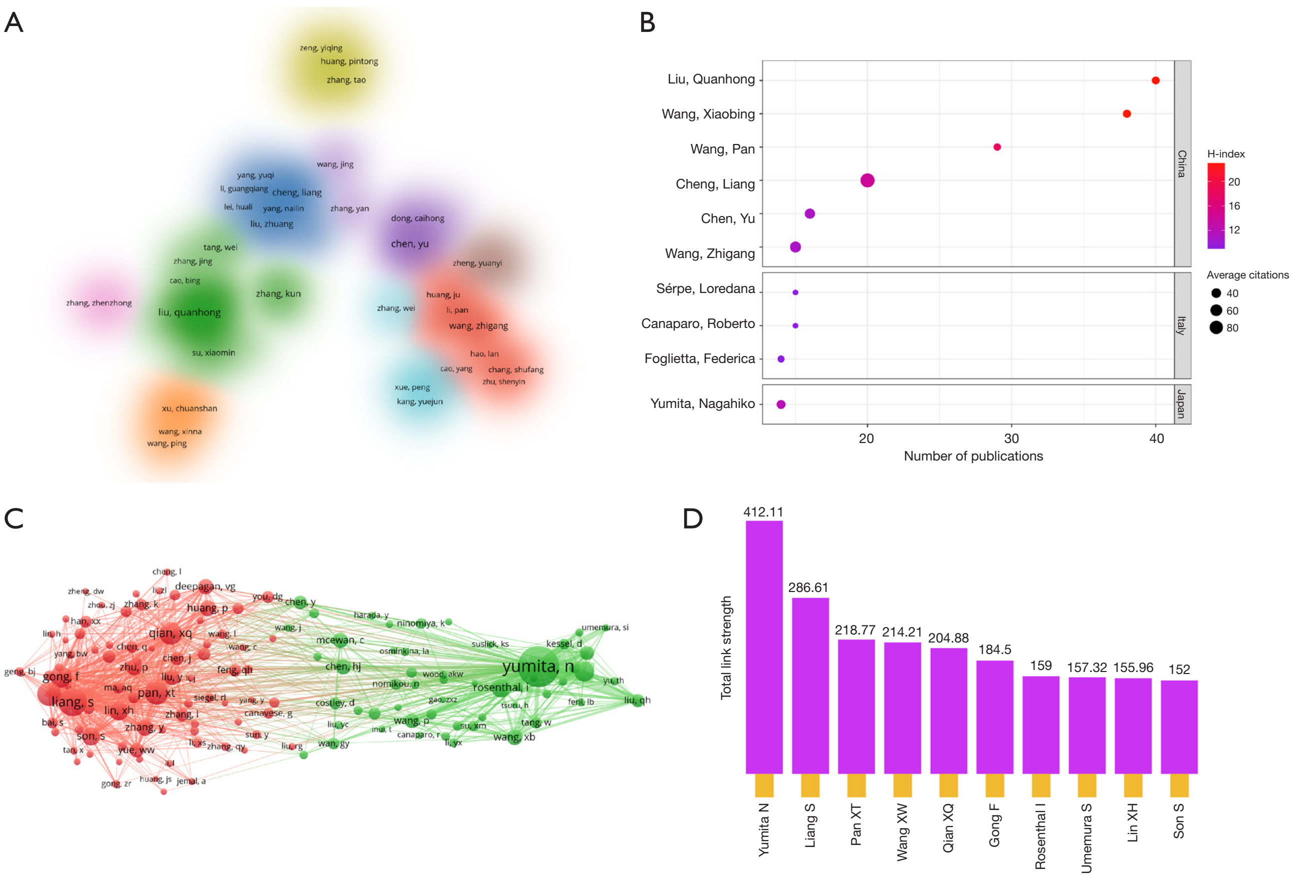

Figure 7 Contributions of authors. (A) Co-authorship cluster visualization map generated by VOSviewer; (B) dot plot of the top 10 authors by publication count; (C) network visualization map of co-cited author; (D) top 10 authors based on TLS. TLS, total link strength.

document. In addition, CiteSpace has been used to conduct an analysis of organizational collaboration. Each node represents an organization, where node size corresponded to the number of papers, while the interconnecting lines indicates collaborative connections, as depicted in *Figure 6C*. The outermost points highlight by purple circles in *Figure 6C* signify higher centrality (BC >0.1). Referring to *Figure 6D*, we present an overview of the top 10 institutions determined by their BC values. Noteworthy among these are Chinese Academy of Sciences (BC =0.16), Shanghai Jiao Tong University (BC =0.11), Huazhong University of Science & Technology (BC =0.1).

Contributions of authors

Following an initial analysis, it was found that more than 3,000 authors actively engaged in the 672 studies. To refine the co-authorship cluster visualization in *Figure 7A*, attention was directed toward authors contributing to over five publications. Authors sharing analogous color-coding in the diagram exhibit comparable co-authorship traits. These authors were segmented into nine distinct research clusters. Each of these clusters revolves around a handful of highly productive authors who publish extensively. The connections between these separate clusters seem relatively sparse, suggesting that robust collaborative relationships among research teams or laboratories involved in cancer SDT-related studies are still in the process of being fully established. Among them, the top 10 individuals exhibiting remarkable productivity in article publications could potentially serve as valuable research collaborators in the field. Illustrated in *Figure 7B*, Liu Quanhong emerged as the most prolific author, closely followed by Wang Xiaobing and Wang Pan. Among the top 10 authors, three-fifths comes from China, 3 from Italy and 1 from Japan. In terms of average citations per article, Cheng Liang ranks first with 92.4. Furthermore, *Figure 7C* illustrates the network map of

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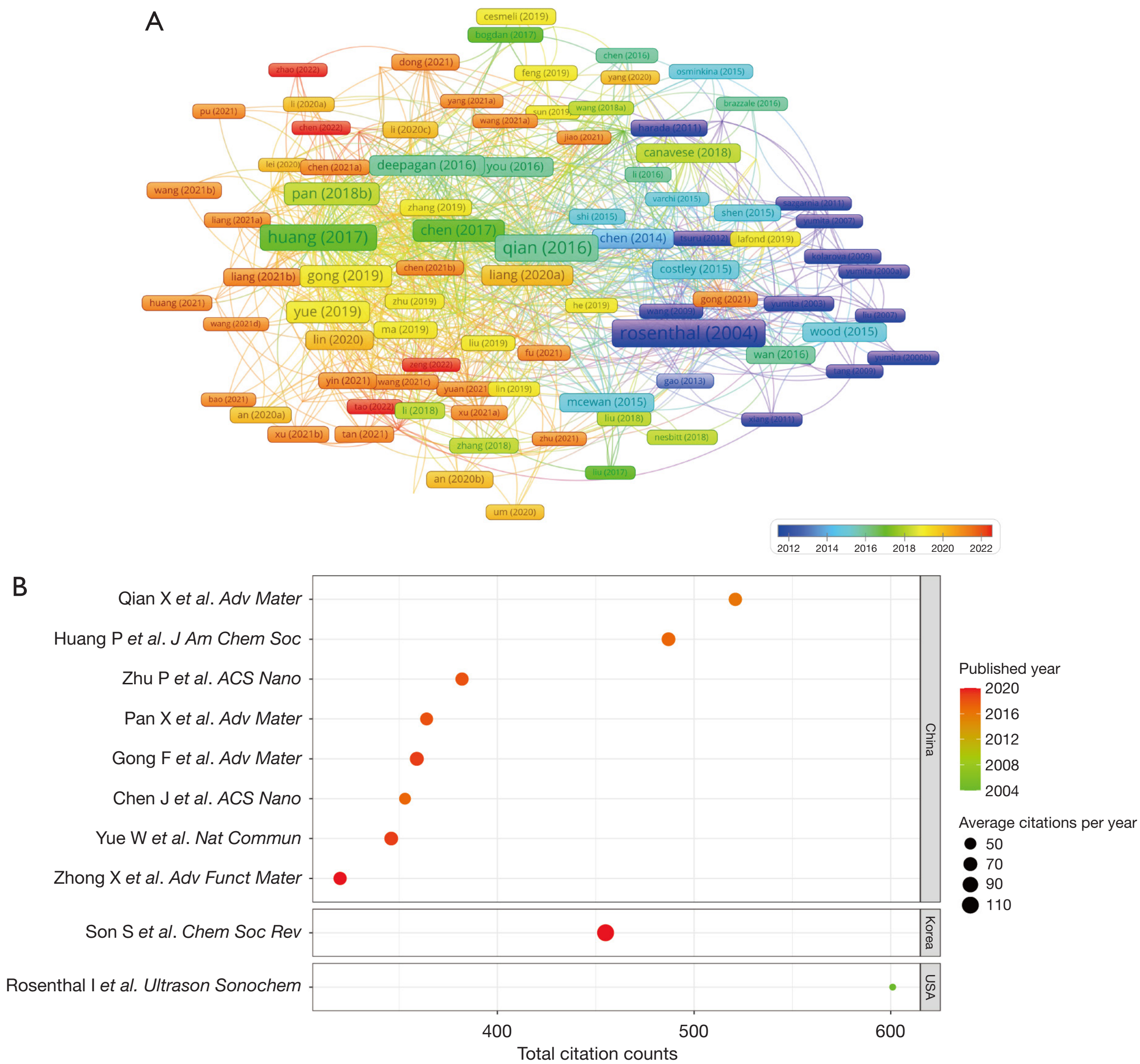

Figure 8 Visual analysis of highly cited studies. (A) Network visualization map illustrating paper citation analysis; (B) the features of the top 10 highly cited studies within the cancer SDT research domain. SDT, sonodynamic therapy.

co-cited author relationships, where each node corresponds to a cited author, sized relative to the citations received. *Figure 7D* provides a summary of the top 10 authors based on TLS, with Yumita N, Liang S, and Pan XT ranking highest.

Visual analysis of highly cited studies

Highly cited papers hold significant importance within the academic sphere. Their substantial citation rates signify widespread impact and recognition within a specific field of study. In *Figure 8A*, we depict a network visualization map illustrating paper citation analysis. Larger nodes in the diagram typically represent papers with significantly higher citation counts, indicating their substantial impact and influence within the citation network. *Figure 8B* detailed the features of the top 10 highly cited studies within the cancer SDT research domain. Of note, eight studies had a first author from China. Remarkably, most of these articles were published after 2016. Among them, two papers have accumulated over 500 citations each, and all the top 10 have been cited more than 320 times. The review authored by Rosenthal *et al.* (48) published in 2004 in *Ultrason Sonochem* claims the highest citation count, amassing an impressive

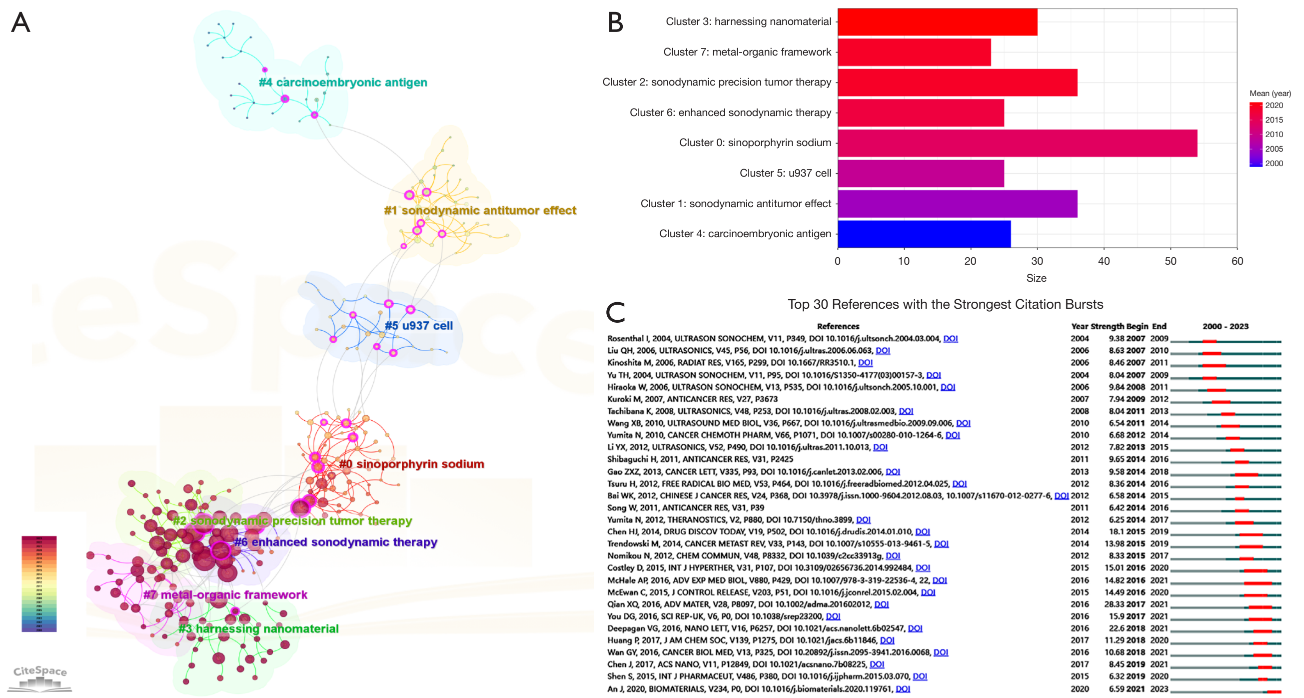

Figure 9 Visual analysis of co-cited references and reference burst. (A) CiteSpace-generated clusters of co-cited references. Each node in the representation signifies a reference, with nodes sharing the same color block indicating a cluster focused on a similar topic; (B) the size and average year of all 8 clusters; (C) CiteSpace produced the top 30 references exhibiting the most robust citation bursts. The timeline bars are depicted in blue, while the burst periods of the references are highlighted in red.

601 citations. Following in the second position is the study by Qian *et al.* (49) from 2016, with 521 citations, while in the third position stands the paper authored by Huang *et al.* (50), in 2017, having garnered 487 citations.

Visual analysis of co-cited references and reference burst

Using CiteSpace, a reference co-citation network consisting of 8 clusters was generated (*Figure 9A*). The modularity, Q, was determined as 0.7015, and the mean silhouette, S, was calculated as 0.9233. These values signify that the network clustering was notably significant and dependable. Based on the cluster size and average year, a detailed dot pot was made in *Figure 9B*. As can be seen that the largest cluster (#0) has 54 members and is labeled as "sinoporphyrin sodium". In this cluster, the major citing article is published by Liang *et al.* (51), in *Advanced Materials*, titled "Recent advances in nanomaterial-assisted combinational sonodynamic cancer therapy". In addition, by analyzing the clusters' average publication year, it could provide a rapid assessment of each cluster's evolutionary dynamics. Remarkably, "#4 carcinoembryonic antigen" and "#1 sonodynamic antitumor effect" represent early research topics. Conversely, "#3 harnessing nanomaterial", "#2 sonodynamic precision tumor therapy" and "#7 metal-organic framework" denote the current and emerging research focuses within the field. For a comprehensive understanding of the evolution of research on cancer SDT, we investigated the top 30 references that encountered significant citation bursts using CiteSpace (*Figure 9C*). The initial citation burst transpired in 2007, stemming from the publication by Rosenthal *et al.* (48) in 2004. Notably, Qian *et al.* (49) in 2016, Costley *et al.* (1) in 2015, and McHale *et al.* (6) in 2016 exhibited the highest burst strengths (28.33, 15.01, and 14.82, respectively). The most recent burst was observed in 2021.

Visual analysis of keywords co-occurrence and keywords burst

Keywords form the essence of a paper, and analyzing the trending high-frequency keywords can unveil leading-edge knowledge within specific fields. Therefore, keyword

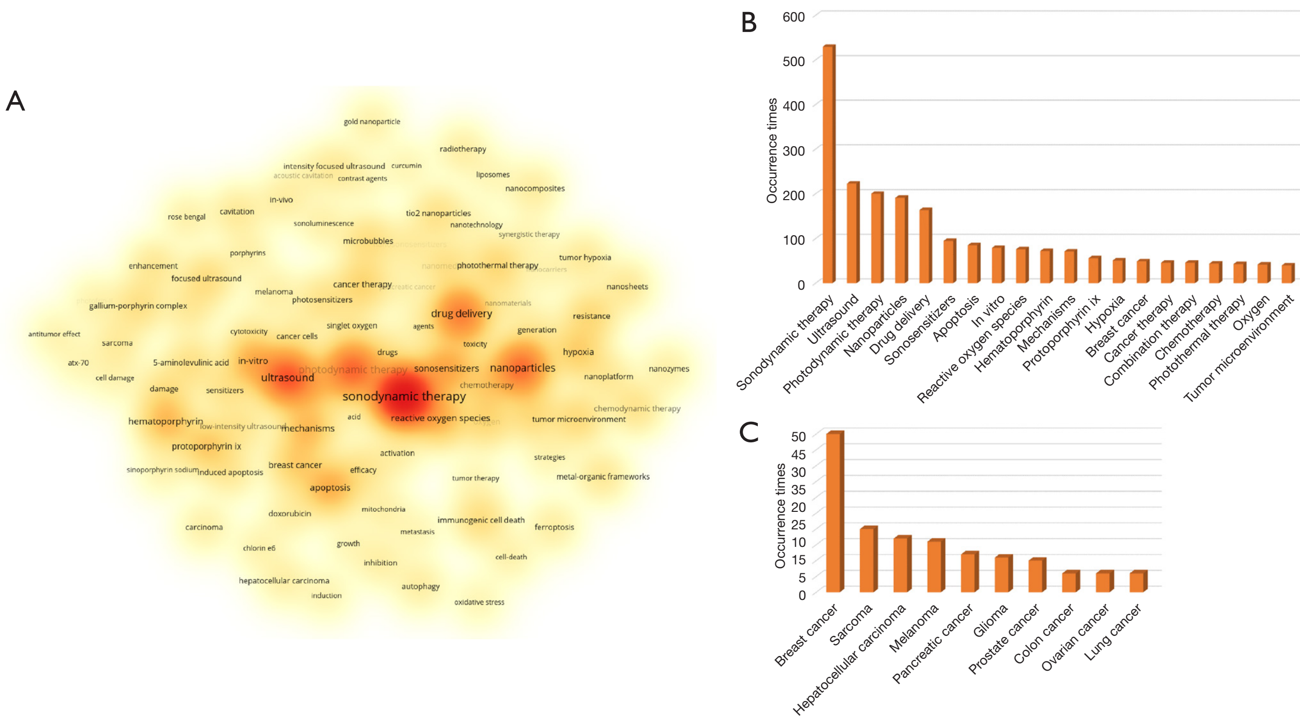

Figure 10 Keyword frequency analysis. (A) The density visualization map illustrates the analysis of keyword co-occurrence. This heat map represents keyword frequency through a spectrum of color gradients. Darker red hues denote active research areas with a higher frequency of keyword co-occurrence, while lighter yellow hues indicate less active areas with a lower frequency of keyword co-occurrence; (B) top 20 highest-frequency keywords; (C) top 10 tumors investigated in the realm of cancer SDT. SDT, sonodynamic therapy.

analysis is imperative. This study utilized VOSviewer to construct a visual map depicting keyword density (*Figure 10A*). After excluding nonsensical keywords and amalgamating synonymous terms, a total of 93 keywords with a minimum of 10 occurrences were identified. The occurrence frequency of the top 20 highest-frequency keywords is presented in *Figure 10B*, highlighting "sonodynamic therapy", "ultrasound", "photodynamic therapy", "nanoparticles" and "drug delivery" as the five most frequently employed keywords. Furthermore, we compiled a summary of the top 10 tumors investigated in the realm of cancer SDT. As illustrated in *Figure 10C*, breast cancer emerged as the most extensively studied tumor, succeeded by sarcoma, hepatocellular carcinoma, melanoma, pancreatic cancer, glioma, and so on. Additionally, in accordance to the color gradient in the bottom right corner, *Figure 11A* presents an overlay visualization map of these keywords, categorized by their AAY, with earlier appearing keywords marked in blue and more recent ones in red. In *Figure 11B*, the top 20 keywords with the highest AAY. The following keywords such as "ferroptosis", "nanoplatform", "immunogenic cell death", "nanozymes", "chemodynamic therapy", "tumor microenvironment", etc., seemed to represent the current research frontiers. As many current focus keywords are related to nanomaterials and nanotechnology. We also summarized the publication trend of nano-related studies in the field of cancer SDT in *Figure 11C*, and an exponential increase was observed. Moreover, CiteSpace was also employed to identify emerging keywords, and *Figure 11D* showcases the top 20 keywords exhibiting the most robust citation bursts.

Discussion

In the era of big data, the surge in the volume of research publications presents a myriad of challenges to researchers. The exponential growth in academic literature could lead to information overload, posing difficulties in effectively sifting through and utilizing the vast amount of information available (52). As a method of big data analysis, bibliometric analysis distinguishes itself from review and meta-analysis by offering distinct advantages (53). It

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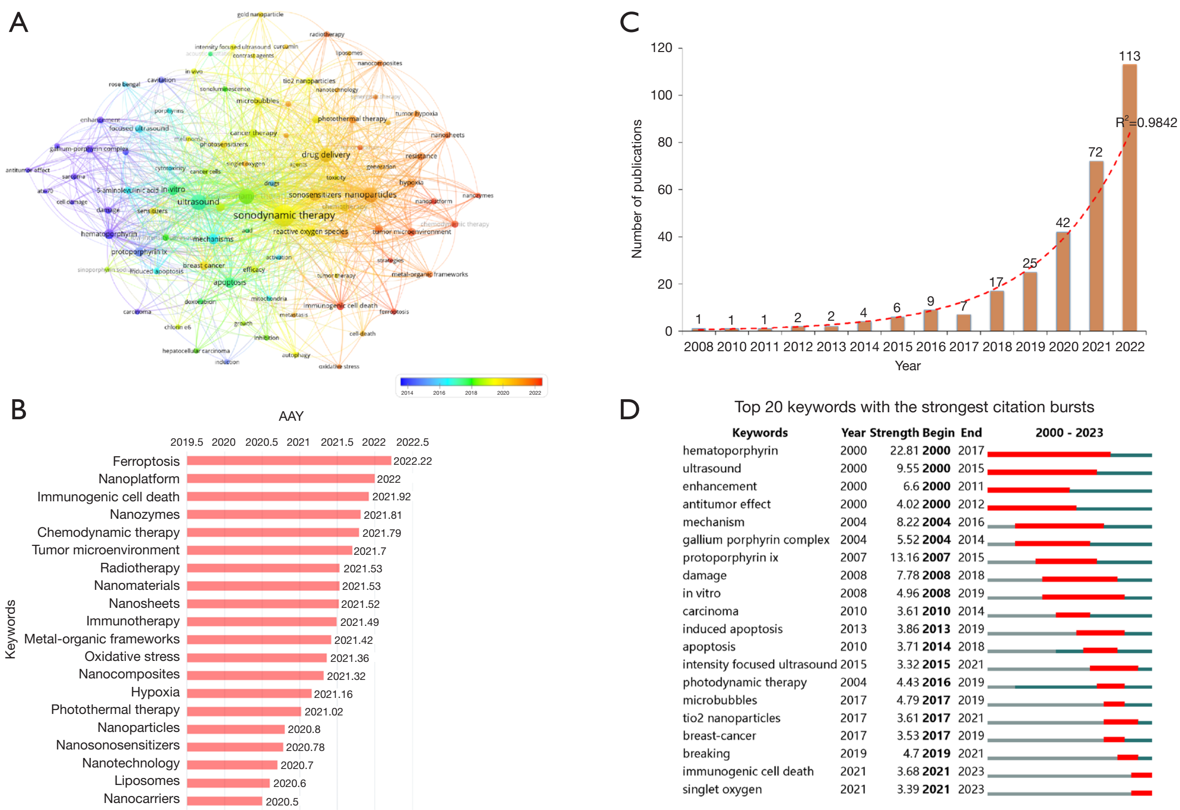

Figure 11 Trend analysis of keyword changes. (A) Overlay visualization map of keywords co-occurrence analysis. Each node symbolized a keyword, with the node's size proportional to its frequency of occurrence. The node color corresponds to the respective AAY, as indicated by the color gradient in the lower right corner. Nodes shaded in blue signify keywords with earlier appearances, while those in red denote current research focuses. (B) Top 20 keywords with the highest AAY; (C) publication trend of nano-related studies in the field of cancer SDT; (D) top 20 keywords exhibiting the most robust citation bursts. AAY, average appearing year; SDT, sonodynamic therapy.

quantitatively evaluates and exhibits the developmental trends and research hotspots in literature while revealing relationships among authors, institutions, and journals (54). In contrast, reviews and meta-analyses focus on comprehensive interpretation and synthesis of literature, emphasizing the organization and synthesis of existing research outcomes (55,56). The significance of bibliometric analysis within the scientific community lies in its provision of an objective, data-driven approach to comprehend and assess the developmental status of academic research (57). It serves as crucial reference material for decision-makers and academic stakeholders, fostering scientific collaboration and advancement. SDT represents a novel approach extensively utilized to address bacterial resistance to antibiotic therapy and tissue penetration limitations associated with near-infrared light in PDT (58,59). Simultaneously, as a burgeoning method for tumor inhibition, it has garnered significant interest in cancer treatment in recent years (60,61). This study conducts the primary bibliometric analysis spanning from 2000 to 2023, employing CiteSpace and VOSviewer, to outline the current research panorama and anticipate future focal areas concerning the application of SDT in cancer therapy.

The volume of papers published is an important indicator used to measure whether a theme is widely attracting the attention of scholars. Summarizing the annual publication count provides insights into the field's activity level and developmental trajectory (62). In accordance with the findings in *Figure 3*, the quantity of literature pertaining to cancer SDT has consistently risen over the past two decades. This trend was similar to other bibliometric study that identified the publication trend on cancer PDT between 2000 and 2021 (28). Broadly, this progression could be categorized into three phases. The initial stage, from 2000 to 2006, was an exploratory phase with relatively fewer publications. During this period, cancer SDT was still in its early research and proof-of-concept stage. As an emerging technology, it required a significant investment of time and effort in basic research to explore its therapeutic mechanisms, optimize treatment parameters, and evaluate its effectiveness and safety in cancer treatment (48,63). Consequently, the scientific findings and data were still insufficient, limiting the production of extensive literature. Additionally, technical and equipment limitations were significant factors. Between 2000 and 2006, the development of the ultrasound equipment and sonosensitizers required for SDT was not yet mature.

The subsequent phase, spanning 2007 to 2013, witnessed an acceleration in publishing activity. The third phase, occurring around 2014–2023, witnessing a significant surge in articles, notably exceeding 100 publications in 2021, possibly linked to advancements in nanomaterials. SDT presents unique advantages as a potential alternative to traditional treatments. Its efficacy requires a combination of sonosensitizers and ultrasound stimulation to produce cytotoxic ROS, effectively targeting and treating affected cells. In contrast to conventional therapies such as surgery, radiotherapy, and chemotherapy, SDT has the advantages of non-invasive, small side effects, and low systemic toxicity (64). In addition, despite a strong potential of SDT for clinical applications, developing highly active sonosensitizers is a key step to achieve highly efficient SDT (65). While conventional organic sonosensitizers have been extensively researched, their poor tissue accumulation, low bioavailability, and stability limitations impede further clinical translation (66,67). The development of biomaterials and nanotechnology holds potential in overcoming these challenges by enhancing SDT's efficiency, potentially addressing its drawbacks and paving the way for more efficient and safer treatment strategies (51,68,69). However, despite the significant benefits derived from these advancements, SDT based on biological nanomaterials remains in its early stages, with the mechanisms behind its high therapeutic efficacy not yet fully elucidated (14,70). To prove this, we have summarized the publication trend of nano-related studies in the field of cancer SDT in *Figure 11C*, and an exponential increase was observed. It is clearly seen that literature in the third phase were mainly from the nano-related studies. In addition, we also conducted fitting analysis on the data in the third stage. The results show that the number of published articles has increased exponentially in recent years. These observations imply sustained interest from researchers in this domain, highlighting its potential as a research hotspot. Consequently, we speculate that this area will likely continue its rapid expansion.

With the continuous advancement and refinement of technologies related to SDT, clinical translation is a crucial step in SDT research and key to achieving breakthroughs in cancer treatment. Consequently, in the future, there will be an increasing number of clinical studies on SDT across various fields of cancer treatment. To our knowledge, SDT has been applied in the clinical treatment of glioblastoma (71), breast cancer (72) and lung cancer (73). For example, Zha *et al.* (71) have conducted a phase I clinical trial of SDT combined with temozolomide in the treatment of recurrent glioblastoma (rGBM). Nine patients with rGBM, who had exhausted standard treatments, received magnetic resonance imaging (MRI)-localized porphyrin drug injections followed by intermittent low-frequency ultrasound for 5 days. Post-treatment results showed one patient with stable disease and eight patients with disease progression, with a median progression-free survival of 84 days and median overall survival of 202.5 days. No adverse effects related to SDT were observed in any of the patients. Their results suggested that SDT was shown to be safe and tolerable in patients with rGBM. To our knowledge, this research team has published a second clinical trial of SDT combined with chemoradiotherapy to treat patients with brainstem glioma and is recruiting volunteers in China. Moreover, Inui *et al.* (72,73) implemented SDT for two individuals diagnosed with breast cancer and lung adenocarcinoma, respectively, achieving a notable extension in patient survival while avoiding significant toxicity and adverse effects. Based on the findings of these current studies, clinical research on SDT is hindered by the limited number of enrolled patients and short follow-up periods. However, as fundamental research advances, the mechanisms and efficacy of SDT have been increasingly substantiated. These foundational studies provide a robust theoretical basis and technical support for its clinical application. We propose that future clinical investigations should further evaluate the efficacy of SDT across various tumor types, thereby broadening its therapeutic scope. Given the distinct biological characteristics of each tumor type, it is essential to tailor treatment protocols accordingly. Large-scale clinical trials are crucial to systematically assess the safety and efficacy of SDT, determining the optimal therapeutic dosage and regimen to ensure its clinical reliability and feasibility. Moreover, future clinical

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research should explore the synergistic potential of SDT in combination with other treatment modalities such as radiotherapy, chemotherapy, and immunotherapy (74). This multimodal approach aims to enhance overall therapeutic outcomes while reducing the risks of tumor recurrence and metastasis. Through extensive future clinical studies, SDT is anticipated to become a standard cancer treatment modality, offering patients a safer and more effective therapeutic option.

In terms of the major contributors in this field, there is no doubt that China has occupied the dominant position, accounting for more than two-thirds of all publications. In addition, according to the statistics, China also ranked first in terms of H-index and total citations, which further reflect the important scholarly influence of China. Potential explanations for this phenomenon are intricately tied to substantial governmental investments. Among the top 8 most active funding agencies within this field, seven of them originating from China. In addition, China has emerged as a prominent global force in the field of Materials Science, leading the world in both cutting-edge research innovations, including patents, and the sheer volume of scholarly publications (75,76). Furthermore, on May 26, 2023, the Chinese Academy of Sciences and the National Natural Science Foundation jointly released the "Chinese Nanoscience 2035 Development Strategy". This strategy explicitly identifies nano-biomedicine, particularly in cancer diagnosis and treatment, as well as infectious disease prevention and control, as focal areas for future development. In addition, although China ranked first in terms of the number of articles, it ranked only fifth in terms of ACI value. This result can be explained by the change in the number of publications per year in the top ten countries in *Figure 5C*. It can be seen that a large number of publications in China come from the last three years, and most articles do not have enough time to accumulate citations. Regarding collaborative networks involving countries, institutions, and authors, a consistent challenge persists in the enduring asymmetry of academic resources between developed and developing nations (77). For instance, while Iran represents developing countries and ranks third globally in publication volume, their impact on other countries within this field appears limited. This limitation is evident in the average citation rates of this country, which rank second lowest among the top 10 countries in terms of publication volume.

In addition to financial and policy-related supports, top-tier research institutions and scientists play a pivotal role in driving the advancement of a field. Top-tier research institutions often gather top experts and scientists from various fields, enabling interdisciplinary collaborations that foster the cross-fertilization of the field of cancer SDT (78). Moreover, these institutions possess state-of-the-art technological equipment and research infrastructure, which drive innovation in SDT techniques (79). Continuously exploring novel acoustical tools, treatment modalities, and medical devices allows them to lead advancements in this field, offering new approaches for tumor treatment. Based on our results, Chinese Academy of Sciences contributed the most articles among institutions, followed by Shaanxi Normal University, Chongqing Medical University, and Shanghai University. All these top 10 active organizations were in China. Meanwhile, among the top 10 highly cited studies within the cancer SDT research domain, 8 studies had a first author from scientific research institutions in China (48-50,80-86). Of them, three high-quality reviews have summarized the mechanism of SDT, especially the effect of ultrasound induced free radicals, the advance of micro/nanoparticle-augmented SDT including organic and inorganic sonosensitizers, as well as multifunctional sonosensitizers and the combination of SDT with other modalities (48,49,85). These reviews could be important reference for young scholars in this field. As for authors, among the top 10 authors, three-fifths comes from China, 3 from Italy and 1 from Japan. The leading authors, with a significant body of work, are established experts of the highest standing and are expected to continue propelling advancements in cancer SDT. Moreover, the collaboration analysis depicted in *Figure 7A* illustrates that collaborations among authors from the same country occur frequently, emphasizing the necessity for enhanced international academic connectivity and communication. Illustrated in *Figure 7C*, Yumita *et al.* (87), Liang *et al.* (51), and Pan *et al.* (82) emerge as prominent authors with the highest frequency of co-citation, showcasing the international recognition and esteem these researchers have gained in this field.

Apart from the analysis of contributors, we conducted an analysis of the journals linked to these publications, and the results are presented in *Figure 4*. Noteworthy, the journals *Chemical Engineering Journal* emerged as the most productive publishers, closely trailed by *ACS Applied Materials Interfaces* and *International Journal of Nanomedicine*. These top 10 active journals identified are anticipated to be the favored choices for submissions among researchers in the domain of cancer SDT. Keeping track of these journals is recommended to access the latest advancements in this field. Regarding impact factor (IF) and H-index, *Advanced Materials* boasts the highest IF at 29.4 and highest average citations per article at 132.76, while *ACS Nano* leads with the highest H-index of 17. And most of these journals are situated within the Q1 categories. It is conceivable that, considering both quantity and quality, the top 10 journals listed are positioned as significant channels for upcoming high-quality research. In addition, most of the journals in *Figure 4A* are material-science- and chemistry-related journals. The results are consistent with the top 10 research domains in this field. Of them, Materials Science research dominates, contributing to 39.6% of the publications, closely followed by *Science Technology* and *Chemistry*, which accounts for 35.4% and 34.7%, respectively. In addition, a co-citation analysis based on journals was performed to assess the impact of publications, quantifying the overall citation count. *Figure 4B* illustrates that *Advanced Materials*, *ACS Nano*, and *Biomaterials* emerge as the top three journals with high influence. The dual-map analysis also reflects the research focal points in Chemistry, Materials, and Physics.

Co-citation refers to the concurrent citation of two documents within a single publication. The co-cited references map assesses the scientific significance of publications by analyzing their frequent co-citation in other papers (88). Additionally, employing co-citation clustering allows for the elucidation of the knowledge foundation and disciplinary framework within associated research. Utilizing the CiteSpace software, *Figure 9A* illustrates a visual network map presenting co-cited references. These 8 research clusters spanning the last 24 years were arranged based on the size and average year of co-cited references in *Figure 9B*. As outlined that, the largest clusters were "sinoporphyrin sodium" (#0) (51), succeeded by "sonodynamic antitumor effect" (#1) (89) and "sonodynamic precision tumor therapy" (#2) (90). Moreover, the timeline chart aids in clustering references while incorporating a temporal aspect, facilitating an understanding of the timeline of a specific subject and tracking the evolution within this field. Evaluating the mean years within these clusters reveals a shift in research focus towards "#3 harnessing nanomaterial", "#2 sonodynamic precision tumor therapy" and "#7 metal-organic framework". Take metal-organic frameworks (MOFs) as an example, MOFs represent a novel class of porous coordination compounds (91). They exhibit a unique capability wherein their organic linkers absorb ultrasound, inducing a sonoluminescence effect, and harness this energy to transfer electrons, thereby generating ROS (92). Furthermore, the porous structure of these materials significantly facilitates the diffusion of oxygen and ROS within tumor cells (93-95). Multiple studies have revealed that MOFs nanoparticles possess the capacity to load substantial amounts of sonosensitizers or other agents, allowing easy modification and enabling their combined application with chemotherapy, radiotherapy, or photothermal therapy, thus opening new avenues for cancer treatment (96). Furthermore, *in vitro* and *in vivo* experiments have demonstrated the effective enhancement of SDT by MOFs nanoparticles, augmenting their accumulation at tumor sites and improving prognoses for cancer patients (97-99). However, for clinical translation of MOFs-mediated SDT, substantial practical support and validation remain imperative.

In addition to cluster analysis, burst references represent a crucial indicator for monitoring and identifying research focal points and emerging trends across time (44,45). These references denote works that have received substantial citations from other studies over a specific timeframe, suggesting heightened attention during that period. Top 30 references with the strongest citation bursts were listed in *Figure 9C*. Of them, the reference exhibited the highest burst strength starting from 2017, and was study published by Qian *et al.* in 2016 (49). This is also one of the highly cited papers. Moreover, references with the strongest citation bursts were first appeared in 2007 due to 4 papers published in 2004 or 2006 (48,100-102). For example, an experimental study analyzed the cytotoxic effect of protoporphyrin IX disodium salt (PPIX) on isolated sarcoma 180 cells induced by ultrasound (101). They confirmed the increased rate of ultrasonically induced cell damage with 40–160 μM PPIX. It is worth highlighting that one references published in 2020 continue to exhibit an ongoing burst, indicating it has received substantial attention within the academic community recently (103). In this study, the authors have designed an efficient ROS-generating platform with abilities including mitochondrial-targeted, pH-responsive drug release and enzyme-like catalytic function. The researchers validated the exceptional biosafety of this nanoplatform, demonstrating its ability to accumulate at the tumor site and be eliminated from the body within 24 hours. And *in vitro* and *in vivo* experiments further demonstrated its remarkable enhanced therapeutic effect of combined chemotherapy and SDT to eliminate tumors (103). Therefore, how to efficiently generate ROS is currently the key to improving the effect of SDT.

It is well-established that the generation of ROS constitutes a crucial step in SDT. These ROS, such as hydroxyl radicals, superoxide radicals, and singlet oxygen, elicit various cellular responses, inducing oxidative stress within cells, ultimately leading to cellular damage and apoptosis (104,105). However, researchers have noted that the efficacy of ROS in the treatment of cancer cells through SDT is not optimal. Primarily, ROS generation relies heavily on oxygen molecules at the tumor site. However, most solid tumors experience limited oxygen diffusion or unstable tumor microvasculature, resulting in a hypoxic state that is unfavorable for ROS generation (106). Furthermore, the fleeting lifespan of ROS restricts its diffusion distance, often leading to premature clearance before exerting its effects. Additionally, conventional ROS generation depends on ultrasound excitation, but ultrasound penetration depth and transmission efficiency are constrained by tissue structures. To surmount these challenges, investigators have examined diverse platforms designed to generate ROS for cancer SDT (107). The unique properties of nanomaterials position them as an ideal choice for ROS therapies (108). For instance, the high surface area-to-volume ratio and tunable surface characteristics of nanoparticles could offer increased reactive sites, thereby facilitating ROS generation (109-111). Certain nanocarriers have been employed for the direct transportation of ROS-generating agents to the mitochondria, which are susceptible to ROS, through the modification of surface molecules targeting mitochondria (112,113). Additionally, nanoscale structures could be functionalized, enabling precise targeting of tumor cells, thereby enhancing therapeutic efficacy and minimizing damage to surrounding tissues (114). Overall, the application of nanomaterials in generating ROS offers new avenues for ROS-based therapeutic approaches and holds promise for delivering more effective treatment modalities in areas such as cancer therapy. Future research will be dedicated to optimizing the biocompatibility and safety of nanomaterials and developing intelligent and responsive nanoplatforms to further enhance the application potential of SDT in cancer treatment. At the same time, nanoplatforms could also be combined with multiple treatment methods such as chemotherapy to provide comprehensive treatment options.

Keyword co-occurrence analysis in bibliometric studies represents a pivotal methodology, unveiling interconnections and research trends within a scholarly domain by identifying simultaneously appearing keywords in publications (115). This analytical approach holds several pivotal roles: firstly, through scrutinizing co-occurrence patterns among keywords, it unveils the current hotspots and leading directions within the research sphere (40). Keywords frequently co-occurring potentially signify focal points of researchers, aiding in discerning themes or domains garnering broader attention. Subsequently, by analyzing present co-occurrence patterns, it enables extrapolation of potential future research trajectories and emerging topics (116,117). This aids researchers, institutions, or policymakers in better preparing for forthcoming research focal points. Furthermore, keyword co-occurrence analysis could uncover associations between distinct fields or concepts, facilitating the exploration of new research directions or potential crossroads (38,39). This, in turn, fosters interdisciplinary research and innovation. By amalgamating findings from co-occurrence and keyword bursting analyses, several prospective research domains emerge. These encompass mechanism of induced cell death (ferroptosis, immunogenic cell death), nano-related research (nanoplatform, nanozymes, nanomaterials, nanosheets, MOFs, nanocomposites, nanoparticles, nanosonosensitizers, liposomes, nanocarriers), combination therapies (chemodynamic therapy, immunotherapy, radiotherapy, photothermal therapy), tumor microenvironment (hypoxia, singlet oxygen, oxidative stress). Certainly, numerous exemplary review articles extensively explore the involvement of immunogenic cell death, oxidative stress or hypoxia in SDT-mediated cell death, as well as the therapeutic roles played by SDT across various tumor types (118,119). Interested readers are strongly urged to reference these comprehensive reviews for deeper insights into the mechanisms behind cancer SDT.

Take ferroptosis as an example, it represents a distinct form of cell demise propelled by iron-dependent pathways and lipid peroxidation (120,121). The pivotal events in ferroptosis involve the excessive interaction of ROS with polyunsaturated fatty acids and their derivatives, leading to substantial lipid peroxidation and subsequent cell membrane damage. The distinctive mechanism of ferroptosis paves the way for the promising prospects of developing a synergistic therapeutic approach by combining SDT with ferroptosis in the field of oncology (122). Scholars have devised a manganese porphyrin-based MOF as a nano-sensitizer, employing a self-oxygenating mechanism to alleviate tumor hypoxia, thereby fostering the generation of ROS, reducing glutathione (GSH) and GPX4 levels (123,124). This strategy concurrently enhances the efficacy of SDT while inducing iron-mediated cell death in tumor cells. Zhou *et al.* (123) engineered a liposomal nanoplatform co-

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loading the sonosensitizer protoporphyrin and clinically approved drug nano-iron oxide. Under ultrasound exposure, this platform not only induces SDT with protoporphyrin, leading to tumor-suppressive apoptosis, but also enhances the sensitivity of nano-iron oxide-induced ferroptosis. Therefore, exploring the amalgamation of cell death pathways induced by SDT, such as ferroptosis and immunogenic cell death, with other therapeutic modalities to enhance SDT efficacy, and investigating novel photosensitizers guiding diverse cellular demise pathways, represents a crucial future direction in SDT research. Delving into this direction aids in a deeper comprehension of combined SDT therapies, potentially broadening the scope of SDT applications in oncological treatments.

Limitation

Recognizing the constraints within this study is crucial. Initially, our search strategy aimed to encompass a wide array of textwords associated with cancer SDT. Nevertheless, there is a possibility that certain pertinent publications, lacking these specific terms, might have been omitted. Additionally, our search was confined to the WoSCC database, potentially excluding papers from other databases such as Scopus and Google Scholar (116,117). Secondly, filtering based on citation counts and refraining from excluding self-citations might inadvertently incorporate contentious works, potentially impacting the neutrality of the analysis (125). Thirdly, due to the limitation of the search deadline, the research data in 2023 were not completely included. Therefore, some research results in 2023 may be omitted. Finally, it is plausible that the latest, high-quality papers might not have accrued ample citations, potentially causing a disparity between the insights from the bibliometric analysis and ongoing real-world advancements (126). Consequently, we advise researchers to stay attentive to the most recent publications, especially those in languages other than English, to maintain a comprehensive and current grasp of the field.

Conclusions

This research conducted the first bibliometric analysis of cancer SDT using tools like CiteSpace, VOSviewer, and an online bibliometric platform. This study systematically delineated global trends, aiding researchers in identifying influential authors, institutions, and journals within this field. Over the last two decades, there has been a noticeable surge in interest in this domain. Notably, China has maintained its prominent position with the highest outputs and the most financial support. Chinese Academy of Sciences contributed the most articles, followed by Shaanxi Normal University, Chongqing Medical University, and Shanghai University. Materials Science was the most investigated research areas. Breast cancer emerged as the most extensively studied tumor, succeeded by sarcoma, hepatocellular carcinoma, melanoma, pancreatic cancer, glioma. Recent research has focused on "harnessing nanomaterial", "sonodynamic precision tumor therapy" and "metal-organic framework". We also identified the following research topics including mechanism of induced cell death (ferroptosis, immunogenic cell death), nano-related research (nanoplatform, nanozymes, nanomaterials, nanosheets, MOFs, nanocomposites, nanoparticles, nanosonosensitizers, liposomes, nanocarriers), combination therapies (chemodynamic therapy, immunotherapy, radiotherapy, photothermal therapy), and tumor microenvironment (hypoxia, singlet oxygen, oxidative stress), that may remain the research hotspots and receive sustained attention in the near future. All in all, this study provides a comprehensive overview of the current global research landscape on cancer SDT, offering a reference for future investigations.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-128/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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