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Exploring the global landscape of aptamer-based cancer research: Insights from keyword analysis, emerging themes, and research hotspots

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ABSTRACT

Aptamers, which are short single-stranded DNA or RNA oligonucleotides, demonstrate remarkable affinity and selectivity for molecular targets, such as cancer biomarkers. Their high stability, structural versatility, and little immunogenicity have generated significant research interest in their diagnostic, therapeutic, and nanomedical applications. We performed integrated bibliometric and thematic analysis of 2,721 research publications indexed in Scopus from 2005 to 2024 to deliver a thorough perspective of this expanding field, utilizing VOSviewer and Bibliometrix to map productivity, collaboration networks, and thematic evolution. China accounted for nearly half of all publications, while the United States led in citation impact per article. Thematic mapping revealed fundamental "basic themes" such as Systematic Evolution of Ligands by Exponential enrichment (SELEX) and nanoparticles, alongside "emerging frontiers" including aptamer-guided drug delivery, AS1411-mediated targeting, exosome-based therapies, and photothermal nanoplatforms. Temporal and citation impact analyses revealed "sleeping beauties" like exosomes and nucleolin that recently gained strong influence, contrasting with earlier "transient hotspots" such as SELEX and biosensors. Enhancing cross-regional cooperation and intercontinental alliances could improve methodological harmonization and expedite the global translation of aptamer technologies. Collectively, this study integrates bibliometric metrics with critical interpretation to provide practical insights for enhancing global collaboration and identifying promising translational pathways in aptamer-based cancer research.

1. INTRODUCTION

Aptamers are short, single-stranded DNA or RNA oligonucleotides that can adopt highly specific three-dimensional conformations, allowing them to bind with high affinity and selectivity to a diverse array of targets, including small molecules, proteins, and entire cells [1]. Synthetic nucleic acid ligands are commonly termed "chemical antibodies" because of their analogous molecular recognition capabilities; however, they present several significant advantages compared to protein-based antibodies [1,2]. Aptamers are nonimmunogenic, chemically produced, highly modifiable, and stable across many physiological settings [3]. Their diminutive size facilitates more efficient diffusion into tissues and malignancies, augmenting their utility in targeted therapeutics and diagnostic imaging. Unlike antibodies, aptamers can be rapidly generated without the need for animals or immune system activation, making

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them highly reproducible and cost-effective. Their structural flexibility and chemical diversity have prompted significant investigation into their possibilities in cancer research, where specificity and precision are required [3]. The development of aptamers is predominantly facilitated by the Systematic Evolution of Ligands by Exponential enrichment (SELEX) process. SELEX involves repeated phases of binding, selection, and amplification to identify oligonucleotides exhibiting high affinity for a certain target [4].

The SELEX process has experienced significant advancements, particularly the development of cell-SELEX, which allows the direct selection of aptamers against whole cancer cells without requiring prior knowledge of specific biomarkers [5]. These technological improvements have enhanced the ability to identify aptamers that target tumor-specific antigens, cancer-associated receptors, and secreted exosomes. These advancements offered new opportunities in both fundamental and translational cancer research [6]. Aptamers have emerged as useful tools in cancer research, with significant implications across diagnostic, therapeutic, drug delivery, and molecular imaging fields. In diagnostic applications, these nucleic acid-based ligands serve as biorecognition elements within biosensor systems (aptasensors) and microfluidic lab-on-a-chip platforms, which allow the detection of tumor biomarkers, circulating tumor cells (CTCs), and cancer-derived exosomes [7,8]. Aptamers' excellent sensitivity and specificity, often comparable to or greater than conventional antibodies, coupled with compatibility with electrochemical, optical, and microfluidic technologies, facilitate point-of-care diagnostics and real-time disease monitoring [9].

In cancer therapy, aptamers can function as direct blockers of oncogenic proteins or as precise carriers that deliver drugs, siRNAs, or nanoparticles to tumors [10,11]. Aptamer-drug conjugates have demonstrated strong efficacy in preclinical models, achieving enhanced tumor specificity with minimized systemic toxicity through *in situ* drug release [12,13]. In addition, aptamer-functionalized nanocarriers such as liposomes, graphene oxide (GO) particles, and exosome-mimetic systems, have been constructed to enable dual-action delivery of chemotherapeutic agents and diagnostic payloads [14–16].

Furthermore, in molecular imaging, aptamers conjugated with fluorescent markers, radioactive isotopes, or contrast agents enable high-resolution visualization of tumors via positron emission tomography (PET), magnetic resonance imaging (MRI), and optical imaging systems [17–19]. These advancements highlight the potential of aptamers to contribute to precision cancer therapy, nanomedicine, and advanced diagnostics, making them as promising candidates for future cancer management tools, although most applications remain at the preclinical stage [20]. Despite growing interest, several well-documented challenges slow clinical translation of aptamer platforms. Unmodified aptamers are prone to nuclease degradation and rapid kidney clearance, yielding short half-lives; chemical modifications and carrier systems help but rarely solve this fully [21]. After cellular uptake, many constructs are sequestered in endosomes, limiting target engagement [22]. Specificity can be context dependent, with off-target interactions and protein-corona effects. PEGylation can extend exposure yet may be undermined by anti-PEG antibodies [23]. Clinically, experience remains limited, for example, the nucleolin-targeting AS1411 showed minimal activity in a Phase II setting [24]. These constraints are driving work on nuclease-resistant chemistries, long-circulating and self-assembled carriers, and designs that promote endosomal escape.

Bibliometrics is the quantitative assessment of scholarly publications, using statistical methods to measure research output, impact, and trends in a field [25–28]. This method analyzes measurable features of the academic literature, such as publication and citation counts, authorship patterns, and keyword frequencies to discover a domain's structure, growth, and dynamics. Common bibliometric tools include co-authorship networks, citation mapping, and keyword co-occurrence analyses [29]. These methods identify influential researchers, main journals, collaborative networks, research hotspots, and emerging topics. Bibliometric analysis can transform massive publication data into clear visualizations and trend maps that reflect a field's academic evolution over time. In contrast to traditional narrative reviews, which often reflect interpretive subjectivity, bibliometric studies offer systematic and objective views that can be systematically reproduced [30].

In biomedical research, bibliometrics can serve as a valuable instrumental methodology. These studies offer systematic visualization of the novelty of ecosystems, monitor the distribution and impact of emerging technologies, and identify resource allocation and strategic decision-making. For example, bibliometric studies have recorded global research trends in cancer, nanotechnology, artificial intelligence in healthcare, and vaccine development. These analyses generate practical, evidence-based insights for stakeholders, including policymakers, academic institutions, and funding agencies, by mapping thematic priorities, identifying collaboration networks, and identifying the translational direction of scientific progress [31,32]. In emerging domains such as aptamer-based diagnostics and targeted cancer therapies, bibliometric tools offer a comprehensive perspective on the multidimensional character of these fields, indicating how diverse research strands meet and develop over time [33]. In addition, bibliometric methods are also valuable for highlighting under-researched areas, disparities in regional contributions, and patterns of international collaboration, thereby highlighting opportunities for encouragement of new interdisciplinary and cross-border partnerships.

Therefore, the current study aims to perform both bibliometric and thematic analytical approaches to provide a comprehensive bibliometric analysis of global research on aptamers in cancer. Specifically, the bibliometric component evaluates publishing output over the past two decades, identifying leading authors, countries, international collaboration networks, and other bibliometric indices. Simultaneously, the thematic analysis, based on author keyword clusters, qualitatively interprets thematically significant studies to contextualize emerging research themes and translational progress. Together, these complementary methodologies yield a quantitative mapping and a qualitative synthesis of the aptamer–cancer research landscape, establishing a solid foundation to lead future studies and inform strategic initiatives in biomedical innovation.

2. METHODS

2.1. Search strategy and eligibility criteria

A comprehensive literature search was performed in the **Scopus** database on May 13, 2025, covering publications from January 2005 through December 2024. **Scopus** was chosen as it is a widely used and authoritative source for bibliometric studies search strategy combined aptamer-related terms with cancer-related terms. The following search strings were used (TITLE (aptamer*)) AND TITLE-ABS-KEY ("cancer" OR "tumor*" OR "neoplasm*" OR "carcinoma*" OR "oncology") AND PUBYEAR > 2004 AND PUBYEAR < 2025 AND (LIMIT-TO (SRCTYPE, "j")) AND (LIMIT-TO (PUBSTAGE, "final")) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (LANGUAGE, "English")). This query design ensured that all publications dealing with aptamers in the context of cancer were retrieved. The search was further refined to include only **peer-reviewed journal articles** published in **English**. Specifically, the results were limited to documents categorized as articles (original research papers), thereby **excluding** review articles, conference proceedings, book chapters, editorials, and other nonprimary publications from the analysis. These eligibility criteria were applied to focus the study on original research contributions in the field of aptamers and cancer. This restriction reduces interpretive and citation bias from secondary sources, ensuring that the bibliometric mapping accurately represents genuine research productivity and emerging experimental patterns rather than combined perspectives.

2.2. Data retrieval and preparation

All bibliographic records returned by the search were downloaded in a compatible format for bibliometric analysis (specifically, as Comma Separated Values (CVS) containing full records and cited references) and checked for inconsistencies or errors in key fields [28].

2.3. Bibliometric analysis and visualization

The study employed an integrated design combining quantitative bibliometric mapping using VOSviewer and Biblioshiny with a thematic review of the most relevant primary studies based on author keyword clusters, allowing both the identification and contextual interpretation of emerging research themes.

The retrieved dataset was analyzed using specialized bibliometric software tools. We employed **VOSviewer (version 1.6.20)** and the R package **Bibliometrix** (using its Biblioshiny web interface) to perform the bibliometric analysis and generate visualizations [34,35]. These tools facilitated both performance analysis (e.g., calculating publication counts, citation counts, and *h*-index values for various entities) and science mapping of the aptamer-in-cancer research landscape. Various bibliometric networks and maps were produced to illustrate the structure of this research field. In particular, we constructed **country collaboration maps** to highlight international research partnerships. We also created **keyword co-occurrence maps** to identify prevalent research topics and their interrelations, as well as performing **citation analysis** to uncover influential publications and references in the domain. These visualizations allowed us to recognize major research clusters and collaboration networks within the aptamer-cancer field [34,35].

In order to ensure robust and meaningful mapping, we took additional steps to **unify synonyms and merge similar terms** in the data. A custom **thesaurus** approach was used (in combination with manual review) to standardize the terminology across all records. For example, plural and singular forms of keywords were merged, and alternative terms referring to the same concept were consolidated (e.g., treating *"lung cancer"* and *"hepatocellular carcinoma"* as a single keyword) [36]. To reduce fragmentation, synonymous terms were merged into a single representative word, which improved the accuracy of keyword co-occurrence maps. This standardized bibliometric dataset was then used to generate the final results and visualizations presented in our study.

3. RESULTS

3.1. Annual publication output

A total of 2,721 articles were retrieved for analysis. Over the period from 2005 to 2024, the annual publication output on aptamers in cancer showed a steady upward trend, with an approximate average annual growth of 21.0%. This sustained increase mirrors the typical developmental trajectory of emerging research fields. In particular, the field experienced pronounced surges of activity in certain years, indicating peak research interest during those periods. The bulk, including 1,425 documents or 52.4 %, were published from 2019 to 2024. Figure 1 illustrates an integrated graph depicting the yearly

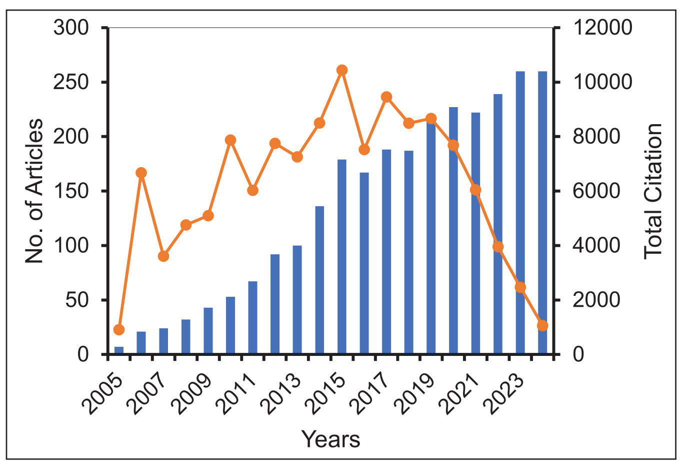

Figure 1. Annual publication and citation trends in aptamer-based cancer research (2005–2024). The bar chart represents the yearly number of publications, while the line plot illustrates cumulative citations over the same period. Data were retrieved from the Scopus database. The x-axis denotes publication year, and the dual y-axes indicate publication count (left) and total citations (right). This figure illustrates the steady increase in research activity and impact across two decades.

volume of research articles generated alongside their associated citation trends.

3.2. Leading journals

A total of 570 journals have published articles on aptamer-based cancer research with collective accumulating 124,226 citations. Table 1 highlights the top 10 journals by publication volume, with *Analytical Chemistry* leading at 135 articles (5.0%) and over 10,800 citations. Other prominent journals include *Biosensors and Bioelectronics*, *Molecular Therapy Nucleic Acids*, and *Talanta.* All these top ten journals are classified within Q1 of the Scopus percentile, reflecting their high impact and relevance. Table 2 presents the most highly cited journals, where *Proceedings of the National Academy of Sciences* stands out with just 17 publications but over 5,800 citations, indicating substantial influence per article. Similarly, *Biomaterials*, *Journal of the American Chemical Society*, and *Angewandte Chemie-International Edition* also demonstrate high citation impact despite moderate publication counts. These findings underscore that aptamer-related cancer research is not only widely disseminated across top-ranked journals but also receives significant scientific attention across disciplines such as chemistry, nanotechnology, and molecular therapy.

Table 1. Highly publishing journals.

Source	No of publication	%	Total citations	Scopus percentile (Q)
Analytical Chemistry	135	5.0	10,873	91 (Q1)
Biosensors and Bioelectronics	81	3.0	5,164	98 (Q1)
Molecular Therapy Nucleic Acids	66	2.4	2,546	95 (Q1)
Talanta	65	2.4	1,981	92 (Q1)
Plos One	55	2.0	3,991	89 (Q1)
Chemical Communications	53	1.9	1,901	87 (Q1)
ACS Applied Materials and Interfaces	52	1.9	2,335	92 (Q1)
Analyst	45	1.7	1,231	84 (Q1)
Analytica Chimica Acta	45	1.7	1,292	91(Q1)
Scientific Reports	45	1.7	1,981	92 (Q1)

3.3. Analysis of articles

Citation metrics were calculated to assess the impact of the retrieved literature. In total, the publications received 124,226 citations, averaging 45.65 citations per document. The *h*-index of the dataset was 146, indicating that 146 articles each received at least 146 citations. These bibliometric indicators (total citations, average citations, *h*-index) are standard measures of influence in scientific mapping. Table 3 lists the most-cited articles in the dataset, reflecting key foundational contributions to aptamer-based cancer research. The leading paper by Farokhzad *et al*. [37] received 1,612 citations and is noted for pioneering aptamer-guided nanoparticle delivery. In addition, Shangguan *et al*. [38] ranked highly, introducing the widely adopted cell-SELEX method. Other top-cited works, including studies by Gold *et al* (*PLos One*) [39], Bagalkot *et al*. [40] (*Nano Letters*), and McNamara *et al*. [41] (*Nature Biotechnology*), focused on aptamer sensors, targeted delivery systems, and therapeutic platforms. These articles consistently exhibited high annual and normalized citation rates, underscoring their lasting impact. Overall, the prominence of aptamer selection methods, cancer diagnostics, and nanoparticle-based delivery systems among the most-cited works highlights the core thematic pillars of the field.

3.4. Analysis of authors

The retrieved articles involved 12,112 authors, averaging 4.5 co-authors per paper. Table 4 lists the ten most prolific contributors, led by Weihong Tan (Hunan University) with 170 publications and over 18,400 citations. Most top authors are affiliated with institutions in China. Notably, 111 authors have published 10 or more articles, reflecting a strong and collaborative research network. Several authors stand out

Table 2. Top ten journals with the highest total citations in aptamer-based cancer research, showing publication count, citation impact, and Scopus ranking.

Source	No of publication	Total citations	Citation/ publication	Scopus percentile (Q)
Analytical Chemistry	135	10,873	80.5	91 (Q1)
Proceedings of the National Academy of Sciences of the United States of America	17	5,811	341.8	95 (Q1)
Biosensors and Bioelectronics	81	5,164	63.8	98 (Q1)
Biomaterials	36	4,317	119.9	99 (Q1)
Journal of the American Chemical Society	43	4,257	99.0	98 (Q1)
PLos One	55	3,991	72.6	89 (Q1)
Angewandte Chemie - International Edition	40	3,837	95.9	96 (Q1)
ACS Nano	26	3,137	120.7	99 (Q1)
Molecular Therapy Nucleic Acids	66	2,546	38.6	95 (Q1)
ACS Applied Materials And Interfaces	52	2,335	44.9	92 (Q1)

Table 3. Ranking of the top ten most highly cited articles identified through Biblioshiny analysis.

Paper	DOI	Total Citations (TC)	TC per Year	Normalized TC
Farokhzad *et al*. [37], Proc Natl Acad Sci USA	10.1073/pnas.0601755103	1612	80.60	5.07
Shangguan *et al*. [38], Proc Natl Acad Sci USA	10.1073/pnas.0602615103	1349	67.45	4.25
Gold *et al*. [39], Plos One	10.1371/journal.pone.0015004	1243	77.69	8.37
Bagalkot *et al*. [40], Nano Lett	10.1021/nl071546n	947	49.84	6.30
Mcnamara *et al*. [41], Nat Biotechnol	10.1038/nbt1223	936	46.80	2.95
Dhar *et al*. [42], Proc Natl Acad Sci USA	10.1073/pnas.0809154105	910	50.56	6.12
Sefah *et al*. [43], Nat Protoc	10.1038/nprot.2010.66	755	47.19	5.08
Fang *et al*. [44], Acc Chem Res	10.1021/ar900101s	709	44.31	4.77
Kim *et al*. [45], Acs Nano	10.1021/nn901877h	681	42.56	4.58
Guo *et al*. [46], Biomaterials	10.1016/j.biomaterials.2011.07.004	550	36.67	6.11
Bagalkot *et al*. [47], Angew Chem Int Ed	10.1002/anie.200602251	550	27.50	1.73

Table 4. Top contributing authors in aptamer-based cancer research, listed by number of publications and total citations.

Author	Documents	Citations
Tan, Weihong	170	18,433
Abnous, Khalil	76	3,420
Ramezani, Mohammad	64	3,157
Taghdisi, Seyed Mohammad	62	2,408
Wang, Kemin	49	2,440
Alibolandi, Mona	38	1,574
Shangguan, Dihua	30	5,972
He, Xiaoxiao	28	1,487
Ye, Mao	25	1,177
Sefah, Kwame	24	5,065
Zhu, Zhi	24	2,342
Zu, Youli	24	947

for high citation impact relative to output, indicating influential contributions to the field.

3.5. Active countries

The analysis revealed contributions from 66 countries, with 28 countries producing at least 10 publications. Table 5 lists the ten most productive countries in aptamer-based cancer research. China led by a significant margin, contributing 1,351 publications and over 57,800 citations, representing the dominant share of global output. The United States ranked second with 528 publications, but with a notably higher citation impact, averaging approximately 88 citations per article: highlighting its strong influence in the field. Other key contributors included Iran, South Korea, Japan, Germany, and the United Kingdom (UK). Although the last two countries (Germany and the UK) had lower publication counts, they demonstrated high average citation rates, reflecting the quality and visibility of their research. These results underscore both the global scope and regional strengths within the aptamer-oncology research landscape.

3.6. Bibliometric mapping

3.6.1. International collaboration

The global collaboration landscape in aptamer-based cancer research demonstrates a highly interconnected and dynamic network, as visualized through VOSviewer mapping (Fig. 2). In these visualizations, countries are depicted as nodes, with the size of each node corresponding to either the total number of publications (Fig. 2A) or cumulative citations (Fig. 2B). The thickness of the connecting lines between nodes reflects the intensity of co-authorship relationships across nations. The analysis shows that China and the United States are the most leading and collaborative principal points within the network, demonstrating leadership not only in research output but also in international research engagement. China shows extensive bilateral collaboration with countries such as the United States, South Korea, Iran, and Singapore. The United States also maintains strong ties with Canada, Germany, and the United Kingdom.

The map shows four distinct collaboration clusters. The green cluster, dominated by China and the United States, includes countries such as Canada, Hong Kong, Japan, the Russian Federation, Singapore, and South Korea. The red cluster represents a dense network of European and Middle Eastern countries, including Brazil, Denmark, France, Germany, Iran, Italy, Jordan, Netherlands, Poland, Portugal, Spain, Turkey, and the United Kingdom. The blue cluster comprises Australia, India, Saudi Arabia, and South Africa, while the yellow cluster is centered around Taiwan, Thailand, and Israel. Overall, the results highlight a globally interconnected research landscape, with East Asia, North America, and parts of Europe playing prominent roles in advancing aptamer-related cancer research through international cooperation.

3.6.2. Analysis of author keywords and hotspots prediction

To identify dominant research trends and expect emerging principal themes in the field of aptamers in cancer, a keyword co-occurrence analysis was performed using VOSviewer and Biblioshiny [34,35]. The analysis centered on author keywords to capture themes directly reflective of

Table 5. Top ten countries in aptamer-based cancer research, showing publication volume, total citations, share of global output, and average citations per document.

Country	Number of publications	Total citations	% of Total documents	Citation/document
China	1,351	57,880	49.7	42.8
United States	528	46,508	19.4	88.1
Iran	222	8,428	8.2	38.0
South Korea	156	10,740	5.7	68.9
Japan	92	2,945	3.4	32.0
Germany	83	3,026	3.1	36.5
Italy	83	2,734	3.1	32.9
Taiwan	81	4,539	3	56.0
Canada	78	2,554	2.9	32.7
United Kingdom	71	3,855	2.6	54.3

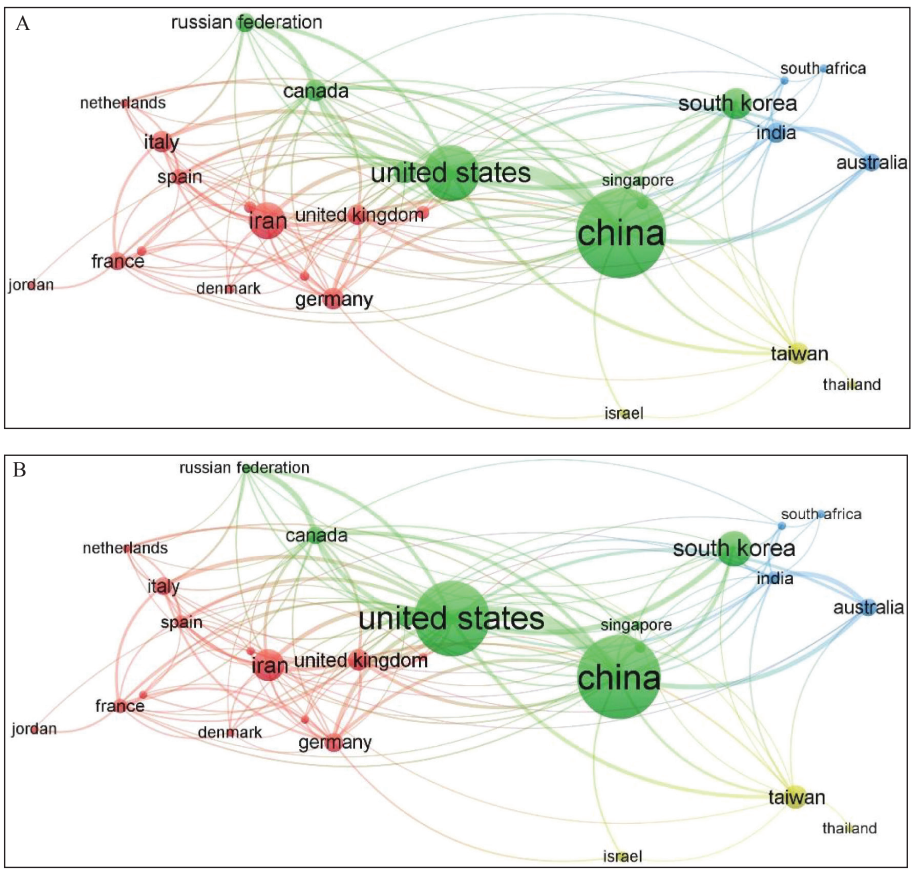

Figure 2. International collaboration network in aptamer-based cancer research. In panel (A), node size represents the number of publications per country, while in panel (B), node size indicates total citations. In both maps, the thickness of connecting lines reflects the strength of co-authorship links. Cluster colors denote groups of countries with strong collaborative ties.

scholarly emphasis. A thesaurus file was systematically applied to harmonize synonymous terms and ensure consistency in terminology throughout the dataset. Only keywords appearing at least 20 times were retained for the final analysis, thereby emphasizing the most prominent and frequently addressed topics within the literature. Although no formal cluster validation metrics were calculated, keyword clustering was performed using two independent bibliometric software platforms, VOSviewer and Biblioshiny. The resulting thematic clusters were highly consistent across both tools, supporting the stability and reproducibility of the identified structures.

The analysis identified five different clusters of keywords, each cluster represents a central research theme (Table 6 and Fig. 3). The first cluster (red) captures the foundational overlap between

Table 6. Most frequent author keywords (≥20 occurrences) in aptamer-based cancer research. Keywords are grouped into thematic clusters based on co-occurrence patterns, reflecting major research areas, and emerging trends.

Keyword	Occurrences	Cluster
Apoptosis	29	1
Aptamers	1,035	1
Breast cancer	89	1
Cancer	109	1
EGFR	21	1
Gold nanoparticles	30	1
HER2	20	1
Immunotherapy	28	1
Lung cancer	49	1
Nanoparticles	96	1
siRNA	31	1
AS1411	86	2
Colorectal cancer	30	2
Doxorubicin	77	2
Fluorescence	36	2
Glioblastoma	22	2
g-quadruplex	28	2
Nucleolin	56	2
Photodynamic therapy	22	2
Targeted drug delivery	221	2
Aptasensor	26	3
Biomarker	23	3
Biosensor	38	3
Cancer therapy	39	3
DNA aptamers	86	3
Ovarian cancer	35	3
Self-assembly	24	3
CTCs	50	4
EpCAM	20	4
Prostate cancer	46	4
RNA aptamers	45	4
SELEX	162	4
Exosomes	24	5
GO	20	5
Liposomes	22	5
PTT	20	5

aptamer science and core oncological mechanisms (Fig. 3A). It includes terms such as cancer, aptamers, breast cancer, apoptosis, Epidermal Growth Factor Receptor (EGFR) human epidermal growth factor receptor 2 (HER2) siRNA, immunotherapy, and lung cancer, in addition to nanomaterial-related keywords like gold nanoparticles, and nanoparticles.

The second cluster (green) revolves around drug delivery systems and molecular targeting approaches. Keywords include AS1411, colorectal cancer, doxorubicin, fluorescence, glioblastoma, g-quadruplex, nucleolin, photodynamic therapy, targeted drug delivery. This suggests a heavy research focus on functionalizing aptamers for therapeutic applications, particularly those involving nucleolin-targeting strategies, chemotherapeutic payloads, and photo-activated modalities. Aptamer–drug conjugates and their integration with tumor-targeting ligands are key hallmarks of this research area.

Cluster three (blue) represents the growing interest in diagnostics and biosensor technologies. It includes terms such as aptasensor, biomarker, biosensor, cancer therapy, DNA aptamers, ovarian cancer, and self-assembly.

The fourth cluster (yellow) focuses on cellular-level applications and selection techniques. It includes CTCs, EpCAM, prostate cancer, RNA aptamers, and SELEX. This group reflects the advancement of aptamer-based methods for identifying and isolating cancer-specific cells, particularly in the context of liquid biopsies.

Finally, the fifth cluster (violet) represents an emerging frontier that combines aptamers with novel nanocarrier systems and phototherapy. This group includes terms such as exosomes, GO, liposomes, and photothermal therapy (PTT). The integration of aptamers with advanced materials and therapeutic strategies reflects a shift toward multifunctional systems capable of simultaneous diagnosis and treatment (theranostics) and a deeper interest in noninvasive, targeted modalities.

To further explore the intellectual structure of these keywords, a conceptual structure map (Fig. 3B) was generated using Multiple Correspondence Analysis. This map groups keywords based on their semantic proximity and co-occurrence profiles [35,48]. The results reaffirmed the clusters found in the network visualization obtained from VOSviewer.

3.6.3. Thematic map analysis

We used Biblioshiny to build a thematic map based on author keyword co-occurrence, providing insight into the field's intellectual structure (Fig. 4). This visualization provides a two-dimensional representation of the major research themes, with the x-axis (centrality) indicating a theme's significance within the broader field, and the y-axis (density) reflecting its level of internal cohesion or developmental maturity. The resulting map categorizes themes into four distinct quadrants: motor themes, niche themes, emerging or declining themes, and basic or transversal themes. This classification facilitates a nuanced understanding of both well-established research domains and those that are newly emerging or undergoing transformation within aptamer-based cancer research [49]. The basic themes quadrant included highly central and established terms such as aptamers, SELEX, cancer, and nanoparticles, representing the foundational structure of the field. The motor themes quadrant, typically indicating well-developed and impactful domains, has minimal representation, implying a continuous evolution of primary research motivations. The niche themes quadrant contained CTCs, exosomes, biosensors, and fluorescence, indicating specialized yet thoroughly formed subjects with robust internal cohesiveness. The quadrant of emerging or declining themes highlighted apoptosis and peptide aptamer, signifying domains with diminished development and prominence that may reflect either nascent or receding research interests.

3.6.4. Temporal trends and citation impact of author keywords

To further understand the development and research momentum of aptamer-related cancer topics, we used two complementary bibliometric approaches. The first method involved generating an overlay visualization map using VOSviewer, which displays the average publication year of author keywords (Fig. 5A). In this visualization, each term is color-coded along a gradient from blue to yellow, with yellow tones representing the most recently emerging topics. Core

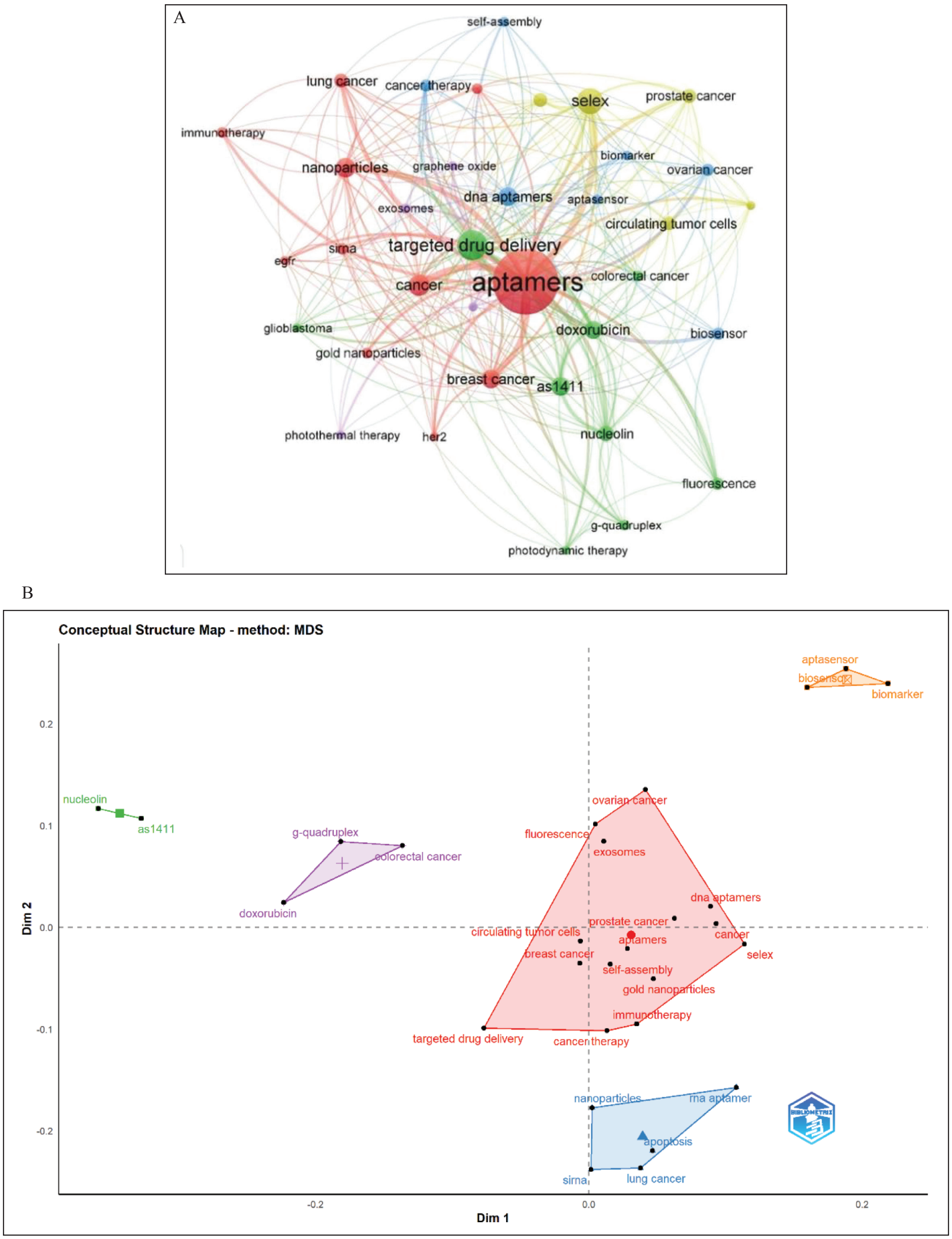

Figure 3. Most frequently occurring author keywords (≥20 occurrences) in aptamer-based cancer research. (A) Network visualization map created using VOSviewer. (B) Conceptual structure map generated with Biblioshiny.

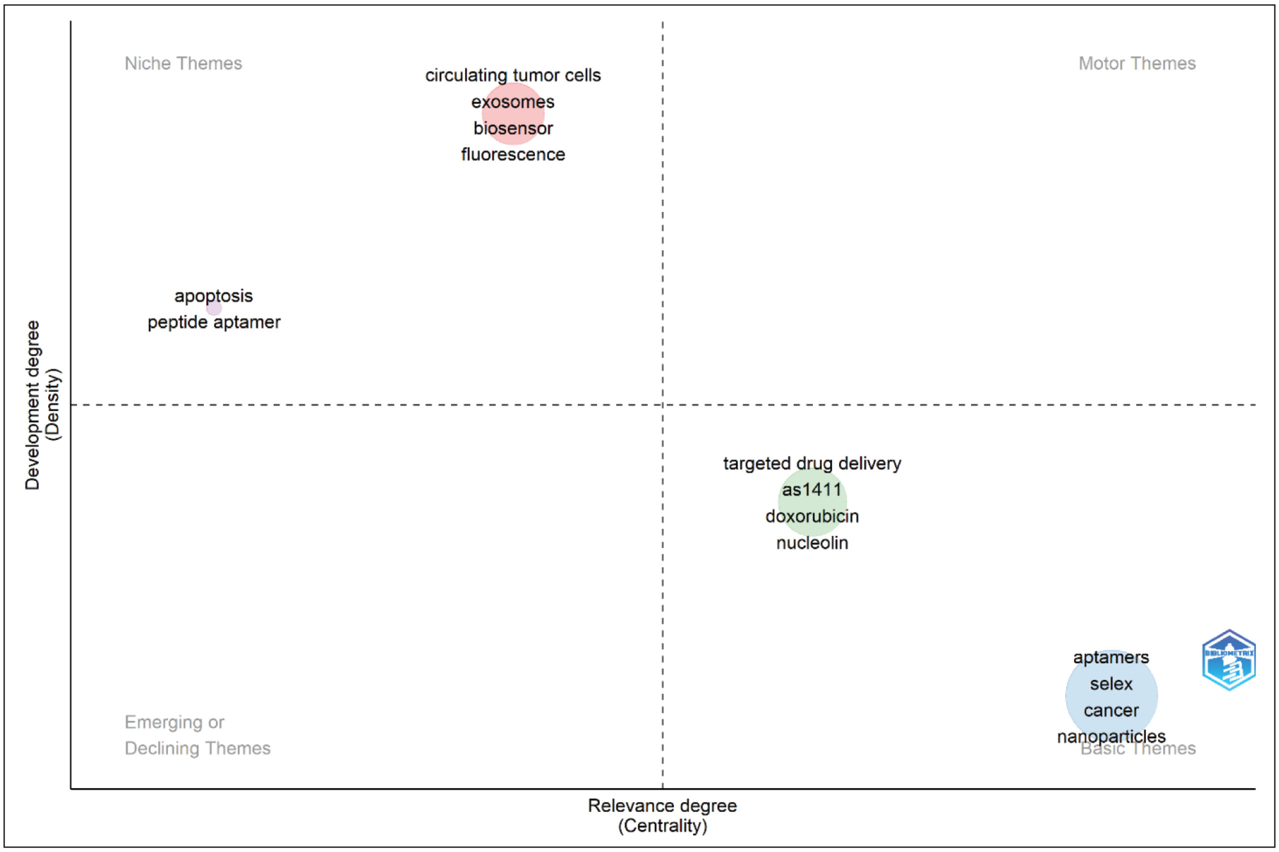

Figure 4. Thematic map of author keywords in aptamer-based cancer research, constructed using Biblioshiny based on keyword co-occurrence. The x-axis (centrality) represents a theme's relevance to the broader field, and the y-axis (density) indicates its internal cohesion or development level. Quadrants are motor themes (developed and important), niche themes (specialized), basic themes, and emerging or declining themes. Bubble size reflects keyword frequency.

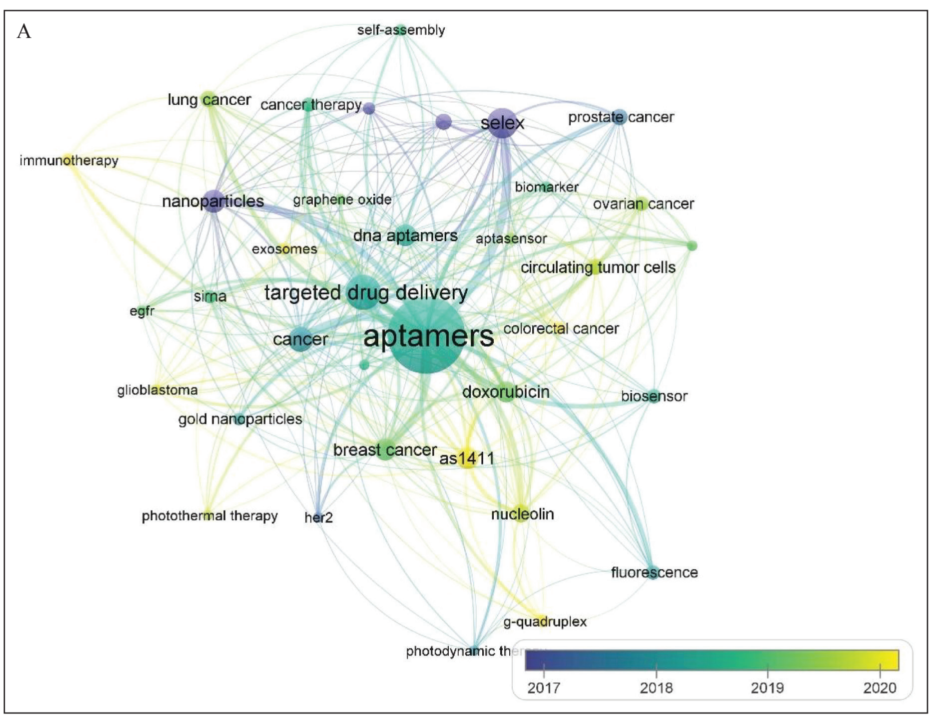

Figure 5. (***Continued***)

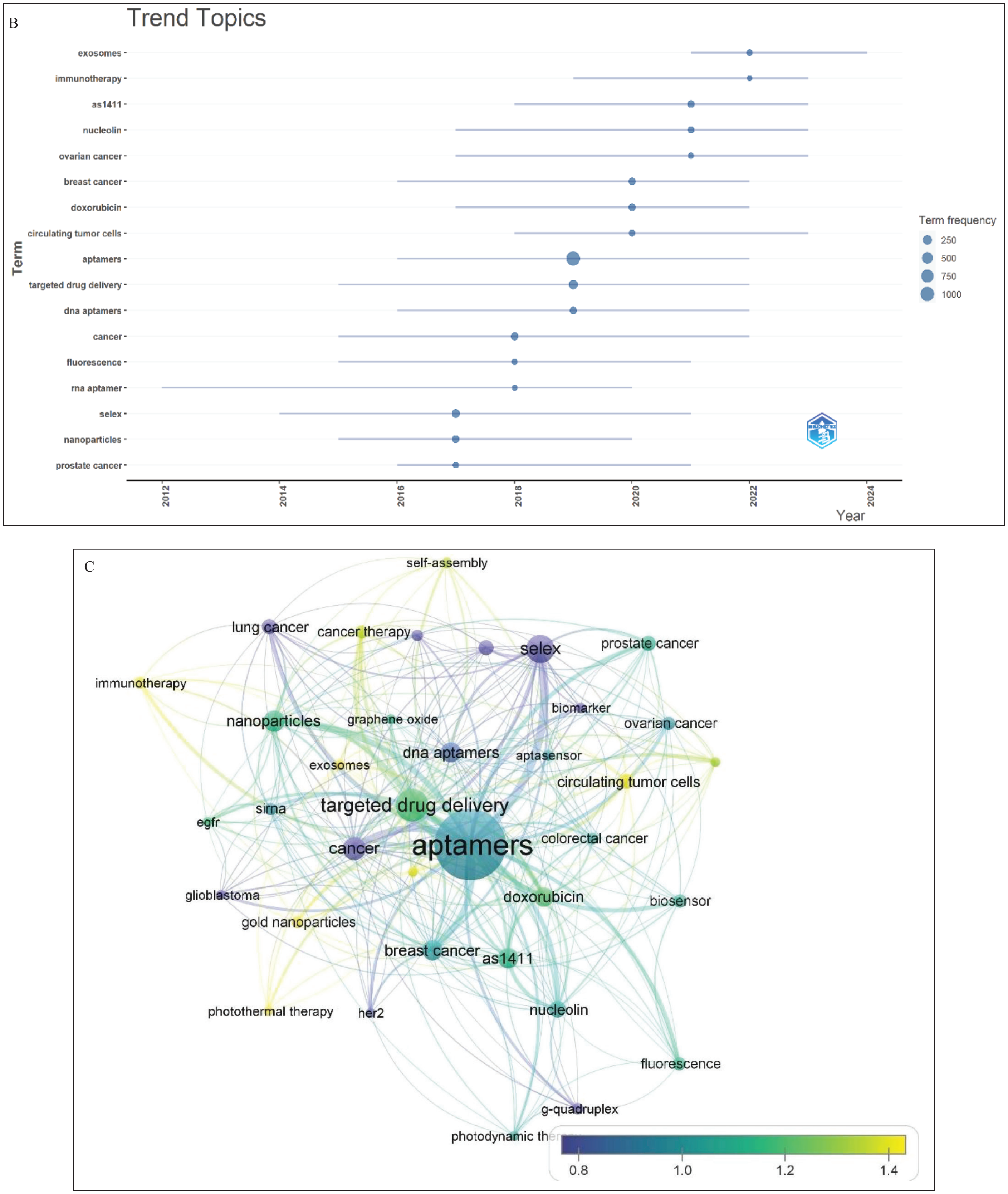

Figure 5. Temporal and citation-based visualization of author keyword evolution. (A) Overlay visualization map: Node size corresponds to keyword frequency, and color gradient (blue → yellow) indicates the average publication year, revealing the chronological progression of research themes. (B) Trend topic timeline: Displays the lifespan of major author keywords over 2005–2024, with bar length representing the duration of active research focus and color intensity denoting the peak activity period. (C) Normalized citation overlay map: Adjusted for publication year to compare citation impact across time. Node size represents normalized citation count, and the color scale (dark blue → bright yellow) indicates relative influence.

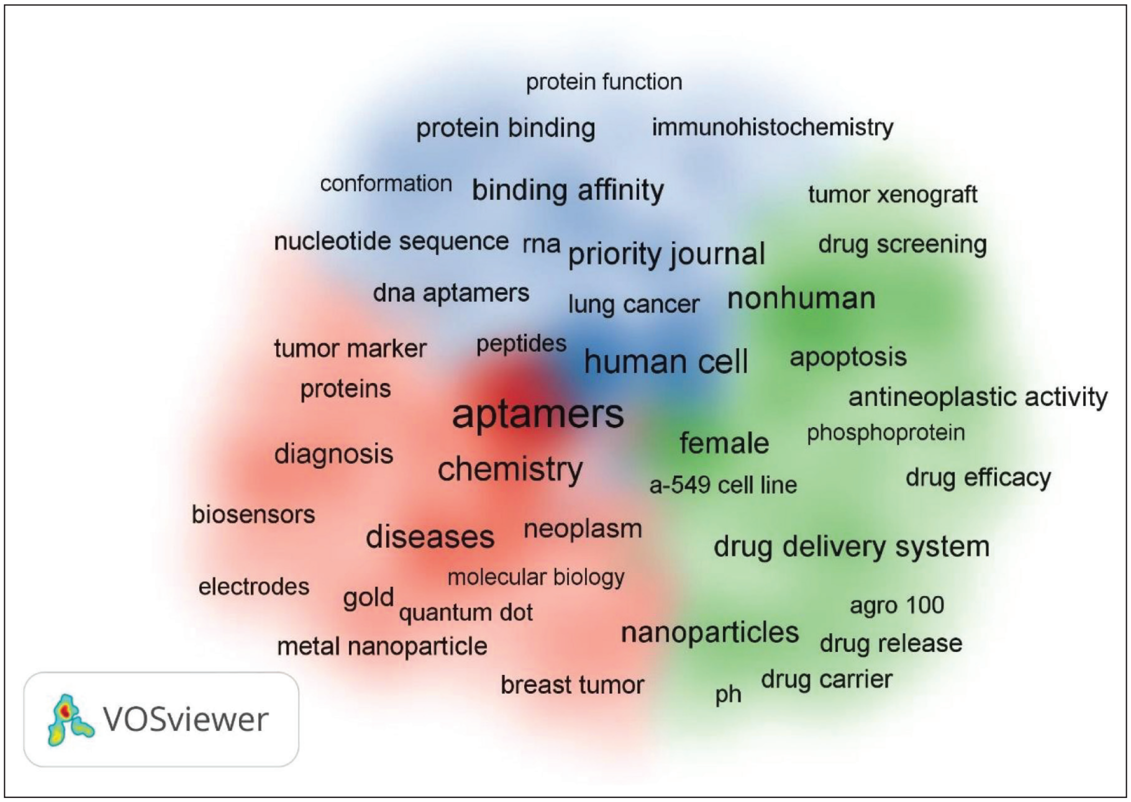

Figure 6. Cluster density visualization of all keywords derived from titles and abstracts. The map groups frequently co-occurring terms into color-coded clusters. Red indicates chemistry and diagnostic applications, green emphasizes drug delivery and therapeutic evaluation, while blue represents molecular interactions and cell-based models. Node size reflects term frequency, while spatial proximity and color reflect thematic relationships.

terms such as "aptamers," "cancer," and "SELEX" appear in darker hues, reflecting their long-standing prominence in the literature. In contrast, emerging topics like "exosomes," "immunotherapy," "AS1411," and "nucleolin" are highlighted in yellow, suggesting their increasing relevance in recent years. This temporal distribution provides insights into the research field's chronological development and indicates which areas are currently gaining traction.

Another method was applied using the Biblioshiny interface of the Bibliometrix package to investigate the trend topic timeline (Fig. 5B). This trend map visually represents the lifespan and intensity of key author keywords based on their frequency and year of occurrence. Foundational terms such as "aptamers," "cancer," and "targeted drug delivery" show consistent presence across the timeline, indicating their centrality and continuity in the field. Meanwhile, more recent interest has shifted toward "exosomes," "immunotherapy," "AS1411," and "CTCs," reflecting a broadening of research focus toward molecular diagnostics, delivery systems, and therapeutic targeting. Notably, "fluorescence" and "biosensors" have also emerged as sustained areas of interest, especially in the context of detection and monitoring platforms. The clear progression of terms from niche to mainstream reflects the field's dynamic nature and the gradual adoption of new biomedical innovations.

3.6.5. Analysis of all keywords

A cluster density map was generated using VOSviewer to visualize the distribution and thematic relationships of all keywords extracted from titles and abstracts (Fig. 6). Applying a minimum occurrence threshold of 50 allowed for the inclusion of 314 terms out of 16,728 analyzed. The map shows a color gradient where warmer tones (red and orange) signify higher frequency and research intensity, while cooler tones (green and blue) indicate lower density. Three major thematic regions emerged: one densely populated cluster centers on core concepts such as "aptamers," "chemistry," "diseases," and "diagnosis," reflecting sustained focus on aptamer development and diagnostic utility. A second cluster is anchored around "drug delivery system," "nanoparticles," "apoptosis," and related therapeutic terms, highlighting the integration of aptamers in drug delivery and cancer treatment. The third area groups molecular and cellular biology themes, including "binding affinity," "human cell," and "protein expression," emphasizing mechanistic and translational research. This mapping illustrates the multidimensional landscape of aptamer-based cancer research, capturing both established and evolving focal points across disciplines (Fig. 6).

4. DISCUSSION

Aptamers have emerged as valuable and promising molecular tools in cancer research due to their high specificity, minimal immunogenicity, and can be easily chemically modified. These single-stranded oligonucleotides can adopt distinct three-dimensional conformations that enable selective binding to diverse targets, including proteins, small molecules, and whole cells. Their promise encompasses diagnostics, therapies, targeted drug delivery, and biosensor technologies, rendering them progressively appealing options or complements to antibodies in oncology [2,3]. Aptamers like AS1411 and their conjugated delivery systems have demonstrated significant efficacy in preclinical and translational models, highlighting their importance in precision oncology [50]. This study integrates a quantitative bibliometric mapping of the global aptamer–cancer research landscape with a thematic review derived from author keyword clusters, providing both empirical evidence of research trends and interpretive insights into emerging thematic directions.

Bibliometric analysis functions as an effective method to quantitatively map scientific advancement, pinpoint significant themes, and uncover global trends within a study domain. In rapidly advancing fields such as cancer therapies and molecular diagnostics, bibliometric analyses facilitate the synthesis of extensive literature into practical insights by emphasizing publishing patterns, significant contributions, collaboration networks, and upcoming frontiers [36,48,49]. Considering the interdisciplinary and rapidly evolving landscape of aptamer-based cancer research, a systematic bibliometric analysis is both timely and essential to evaluate the intellectual progress and strategic trajectory of the discipline. We examined the global output on aptamers in cancer research utilizing the Scopus database. This database was chosen because of its strict indexing criteria, comprehensive coverage of peer-reviewed journals, and effective citation tracking. The inclusion of high-impact journals and comprehensive information in Scopus facilitated precise mapping of authorship, institutional productivity, and keyword trends. This analysis offers a detailed examination of research productivity, international collaborations, and topic development, facilitating future planning and strategic investment in aptamer-based cancer innovation.

The bibliometric analysis from 2005 to 2024 indicates substantial expansion in aptamer research, characterized by a steady increase in annual publication volume. Most studies were published after 2017, aligning with the increased utilization of aptamers in drug delivery, biosensing, and nanomedicine. The significant citation count and elevated *h-index* of pivotal papers indicate the scientific and clinical importance of this field. Leading journals in this field, all classified in the Q1 rank (e.g., *Analytical Chemistry*, *Biosensors, and Bioelectronics*), underscore the field's significant influence and methodological consistency.

China stands out as the leading contributor, producing nearly half of all publications in the field, followed by the United States, Iran, and South Korea. While China leads in volume, the United States demonstrates a higher citation-per-document rate, suggesting a concentration of high-impact contributions. Strong international collaborations, particularly between China and the United States, have accelerated the global dissemination of aptamer research. Bibliometric mapping revealed distinct regional clusters reflecting shared scientific priorities and complementary research strengths, which are crucial for sustaining innovation and advancing clinical translation of aptamer-based technologies. While intra-regional collaborations within Asia, Europe, and North America enhance specialization and coordination, limited cross-regional integration may constrain the exchange of expertise and hinder the development of unified research standards. Enhancing inter-continental collaborations could facilitate methodological standardization, encourage diversity in research methodologies, and expedite global advancements in aptamer-based cancer therapies.

The thematic map analysis (Fig. 4) provides a structured overview of the conceptual organization and maturity of research themes within the field of aptamer-based cancer studies. In the **basic themes** quadrant, we observe core foundational topics such as **"aptamers," "SELEX," "cancer,"** and **"nanoparticles."** These themes form the conceptual backbone of the field and represent the essential components in aptamer technology and its integration into cancer. Their location in this quadrant suggests that while these topics are central and frequently referenced, their internal structure may still be under expansion, indicating significant room for methodological refinement and broader interdisciplinary applications [6]. The **motor themes** quadrant, typically represents mature and influential areas. However, in this map, no themes are currently positioned within this quadrant, implying a potential opportunity for growth rather than saturation. Themes such as targeted therapy and advanced diagnostic tools might evolve into this quadrant as more translational and clinical research develops [2,20]. The **niche themes** quadrant highlights specialized and well-developed topics that are relatively isolated from the core field. This includes keywords such as **"CTCs," "biosensor," "fluorescence,"** and **"exosomes."** These themes are technically advanced and have well-established methodologies, especially in diagnostic and imaging applications. However, their limited integration with broader research clusters may reflect their specialization or the early-stage nature of cross-disciplinary adoption [51,52]. In contrast, the emerging or declining themes quadrant includes topics such as "apoptosis" and "peptide aptamer." These themes have low centrality and density, which in bibliometric terms indicate limited current representation rather than reduced scientific significance. While apoptosis continues to be a crucial mechanism in cancer treatment, its diminished prominence in research likely indicates a transition toward broader, application-oriented fields such as targeted delivery systems, immunotherapy, and nanomedicine, where apoptosis is examined as a secondary effect rather than a central theme. This bibliometric positioning signifies an advancement in research focus rather than a diminishment in significance. Similarly, the restricted prevalence of "peptide aptamer" may reflect the increasing preference towards nucleic acid-based aptamers, which provide enhanced structural flexibility and synthetic accessibility [53]. Notably, the "targeted drug delivery" cluster, alongside keywords such as "AS1411," "doxorubicin (DOX)," and "nucleolin" appear in a transitional zone, bordering between basic and motor themes. This placement highlights its growing significance and increasing coherence, positioning it as a rising research front. The prominence of AS1411 and doxorubicin in the literature underscores the ongoing interest in aptamer-based chemotherapeutic delivery systems, particularly those designed to target cell surface proteins such as nucleolin across various tumor models [12]. Collectively, the thematic map illustrates a dynamic and growing research landscape. While some areas remain in early stages of development, others most remarkably those related to drug delivery and diagnostic applications, are characterized with significant growth. These findings suggest valuable opportunities for aligning between specialized diagnostic approaches and more comprehensive therapeutic frameworks, highlighting a promising direction for the advancement of aptamer-based technologies in cancer research.

The temporal trend and citation impact analyses (Fig. 5) provide significant insights into the chronological development and scientific effect of research themes in aptamer-based cancer investigations. These visualizations highlight not only when specific topics emerged but also how their relative importance and impact have shifted over time. The normalized citation overlay map (Fig. 5C) was created to adjust citation counts relative to the year of publication. Which allows a fair comparison of impact across different periods. In this visualization, node size represents normalized citation count, while the color gradient—from dark blue to bright yellow—reflects citation intensity. Keywords such as "AS1411," "nucleolin," "targeted drug delivery," and "exosomes" exhibit high normalized citation values, demonstrating their influence in the literature regardless of their relatively recent emergence. Foundational terms such as *SELEX*, *nanoparticles*, and *biosensors* display moderate normalized citation density, reflecting their established yet plateaued influence. These can be viewed as "transient hotspots," representing themes that were once central to aptamer research but now show slower citation growth. In contrast, *AS1411*, *nucleolin*, and *exosomes* can be regarded as "sleeping beauties," having initially limited visibility but later achieving significant citation momentum, underscoring their growing translational relevance in drug delivery and biomarker discovery. Collectively, these findings indicate a thematic transition in aptamer research from methodological development toward application-oriented innovation. The chronological evolution reveals a shift from foundational platform establishment to integration with advanced therapeutic systems such as exosome-based delivery, fluorescence-guided imaging, and immune-targeting constructs. Together, these emerging directions highlight the field's movement toward precision and personalized cancer treatment strategies. Within this broader transition, "exosomes" have emerged as a particularly promising theme, as evidenced by their rapid rise in keyword frequency and normalized citation impact. Their inherent role as biocompatible nanocarriers and their integration with aptamer technology for targeted delivery and liquid biopsy applications suggest that exosome-related research will likely define the next phase of aptamer-based cancer innovation. Moreover, their frequent co-occurrence with established terms such as "targeted drug delivery" in the clustering and citation overlay maps highlights how exosome research is evolving from an emerging niche into a central component of the broader aptamer-based therapeutic landscape. This growing integration parallels recent progress in systemic cancer therapy, where biomarker-guided and response-predictive strategies have become increasingly important in optimizing treatment outcomes [54–56]. Aptamer-based systems naturally align with this shift, offering dual diagnostic and therapeutic potential. Current studies demonstrate Aptamer-conjugated Poly(lactic-co-glycolic) acid (PLGA) nanoparticles for delivery, molecular imaging, and immunotherapy modulation of cancer therapeutic drugs [57], while exosome-integrated aptamer platforms are being explored for precision diagnostics and real-time monitoring [52]. Collectively, these trends highlight the translational potential of aptamers as adaptable tools that bridge targeted treatment and predictive oncology.

4.1. Research trends and hotspots

VOSviewer and Biblioshiny were employed to identify hotspots by analyzing the frequency of author keywords in the collected literature (≥20 occurrences). Consequently, five intersecting conceptual clusters comprising 36 principal author keywords were found. These clusters represent the domains of interest and emphasis of the recovered documents for their investigation. Figures 3–5 and Table 5 illustrate how these clusters represent interrelated themes, mirroring contemporary priorities and nascent issues in the domain of aptamer-associated cancer research. The subsequent hotspots were deduced from the five identified clusters derived from both VOSviewer and Biblioshiny.

4.1.1. Cluster 1

It includes terms such as cancer, aptamers, breast cancer, apoptosis, EGFR, HER2, siRNA, immunotherapy, lung cancer, gold nanoparticles, and nanoparticles.

These terms define a cohesive thematic domain within aptamer-focused cancer research, emphasizing the application of aptamers for targeted therapy, diagnostics, and molecular delivery in significant malignancies, including breast and lung cancer. Aptamers, due to their exceptional specificity, are increasingly recognized for targeting critical oncogenic drivers like EGFR and HER2 in cancers where these receptors are overexpressed. In EGFR-mutant nonsmall cell lung cancer (NSCLC), anti-EGFR aptamers preferentially diminish tumor cell viability by causing S-phase arrest and activating caspase-mediated apoptosis [58,59]. This indicates the increasing recognition of aptamers as both targeting agents and catalysts for intracellular responses that result in programmed cell death. Aptamers have been designed to inhibit HER2 signaling and deliver therapeutic agents in breast cancer, particularly in HER2-positive subtypes [60]. A modular aptamer chimera targeting HER2 and HER3, while concurrently delivering an EGFR-siRNA, effectively reduced tumor growth *in vivo* and triggered death by comprehensive receptor blockage [61,62]. These examples demonstrate the dual function of aptamers in this cluster, serving as molecular antagonists and as targeted carriers for gene-silencing agents.

Nanotechnology is an essential element that further enhances the utility of aptamers in this cluster. Aptamer–nanoparticle conjugates, particularly those involving gold nanoparticles, are frequently employed to improve drug delivery specificity and enable photothermal or diagnostic applications [63]. Gold nanoparticles offer excellent surface chemistry and biocompatibility, allowing for conjugation with aptamers to form multifunctional complexes [36]. These platforms have been applied in targeted PTT, where nanoparticle-induced heat under irradiation selectively eliminates tumor cells bound by aptamers [64]. Furthermore, in diagnostics, HER2-specific aptamer–gold nanoparticle conjugates have been developed for colorimetric detection of the HER2 protein. These conjugates produce visible color shifts that can be detected by the eye [65–68]. The convergence of aptamers and nanomaterials in this context allows for dual diagnostic and therapeutic (theranostic) functionality, a concept that has rapidly gained traction in personalized oncology [64].

This integration of aptamers with nanomaterials not only enhances sensitivity but also enables theranostic applications, where a single platform combines diagnostic precision with therapeutic potential, which offers significant value in personalized oncology research [61]. Beyond gold, other nanocarriers such as liposomes, PEGylated polymers, and hybrid nanoparticles are also used to deliver aptamers and associated therapeutics to tumors in a site-specific manner [69–72].

A crucial element of this cluster is the incorporation of aptamers with small interfering RNA (siRNA) technology. Aptamer–siRNA chimeras facilitate the precise delivery of gene-silencing agents directly into cancer cells, circumventing the constraints of nonspecific systemic delivery. Aptamer-functionalized liposomes were used to deliver Notch 1 siRNA into triple-negative breast cancer cells. These liposomes demonstrated improved cellular uptake and markedly higher antiproliferative effect relative to unfunctionalized control liposomes. This indicates a valuable potential in therapeutic strategy for triple-negative breast cancer [73,74]. In breast cancer models, HER2-specific aptamers have been conjugated with siRNAs that target BCL2, an anti-apoptotic protein. These chimeras successfully inhibited BCL2 expression and increased the susceptibility of tumor cells to anticancer agents [75]. In lung cancer, aptamers directed at EGFR have been utilized to deliver siRNAs that inhibit EGFR expression, leading to apoptotic cell death [61]. These methods highlight the importance of aptamers as delivery systems that activate apoptotic mechanisms through RNA interference, emphasizing the significance of both “siRNA” and “apoptosis” as prevalent themes in this cluster. Aptamers’ capacity to direct therapeutic RNAs to specific receptors and facilitate cellular internalization offers a potent method for selectively downregulating oncogenes and enhancing tumor sensitivity to current treatments [76]. The appearance of immunotherapy-related terms within this cluster highlights a growing interest in integrating aptamer-based targeting with immune-modulatory strategies. Notably, aptamers have been investigated in lung cancer models against immune checkpoints such as PD-L1, and they could enhance T-cell-mediated tumor cell killing [77]. Apta35, an aptamer, could reverse immune suppression and induce apoptosis in NSCLC cells by inhibiting the PD-L1/PD-1 axis [78]. Furthermore, DNA aptamers have been engineered to target CTLA-4 and PD-1, with preliminary preclinical findings indicating improved T-cell activation and tumor suppression [79]. While the application of aptamers in immunotherapy is still an evolving domain, these investigations indicate encouraging prospects for aptamers in both direct tumor targeting and immune modulation, especially in cancers such as NSCLC and HER2-positive breast cancer, where immune evasion mechanisms are well-defined. Apart from therapeutic functions, aptamers in this category have shown significant promise in diagnostic and imaging applications [20]. EGFR- and HER2-targeted aptamers have been incorporated into biosensors and imaging probes for noninvasive tumor identification [80,81]. Radiolabeled aptamers have been investigated for PET imaging, whereas aptamer-conjugated fluorescence probes provide real-time observation of malignancies at the cellular level [18,82]. Aptamers employed in diagnostic lateral-flow assays or electrochemical sensors provide remarkable specificity and sensitivity for biomarker detection in clinical specimens. These diagnostic discoveries enhance therapeutic advancements by providing instruments for early diagnosis and assessment of treatment effectiveness [2].

4.1.2. Cluster 2

This cluster includes the following terms: AS1411, colorectal cancer, doxorubicin, fluorescence, glioblastoma, g-quadruplex, nucleolin, photodynamic therapy, and targeted drug delivery.

The theme of this cluster focuses on AS1411, a guanine-rich DNA aptamer that forms a stable G-quadruplex structure and specifically binds to nucleolin, a protein overexpressed on the surface of various cancer cells [83]. This unique structure not only offers notable nuclease resistance but also enables selective uptake by malignant cells and not saving normal tissues. AS1411’s high specificity and biostability have made it one of the most clinically advanced aptamers. It reached Phase II trials for leukemia and renal carcinoma and was used as a novel platform for both therapeutic and diagnostic applications [84]. AS1411 has a significant therapeutic use in targeted **drug** delivery, especially for colorectal cancer. Functionalizing exosomes with AS1411 and loading them with DOX has facilitated selective targeting of nucleolin-overexpressing colorectal cancer cells, resulting in effective intracellular delivery, pronounced cytotoxicity, and substantial tumor growth inhibition *in vivo* [50,85]. Comparable methodologies employing AS1411 to direct multifunctional nucleic acid constructs, integrating DOX with miR-143—have augmented antiproliferative efficacy, illustrating AS1411’s capacity to transport both chemotherapeutics and gene silencers directly into cancer cells [86]. These efforts demonstrate how AS1411-based constructions enhance therapeutic precision and diminish systemic toxicity.

This targeted delivery capability applies to glioblastoma, a particularly aggressive brain tumor characterized by increased nucleolin expression [87]. AS1411-decorated DNA, protein nanospheres encapsulating DOX have demonstrated superior tumor infiltration and increased drug retention, surpassing traditional EPR-based delivery methods. AS1411-functionalized DNA–protein nanospheres encapsulating doxorubicin have shown superior tumor penetration and prolonged drug retention compared with conventional EPR-based delivery. Aptamer-mediated targeting markedly improved therapeutic outcomes in 3D tumor spheroids and animal models, suggesting that AS1411 can overcome major barriers such as the blood–brain barrier and insufficient drug accumulation in brain tumors [88]. AS1411 has also been utilized in photodynamic treatment. Researchers have created constructs by conjugating photosensitizers, such as indium (III) phthalocyanine conjugates or porphyrins, to AS1411, which can generate reactive oxygen species (ROS) upon light activation, selectively eliminating nucleolin-positive cancer cells [89,90]. Advanced platforms co-load cytotoxic drugs and photosensitizers onto aptamer-guided liposomes or micelles, resulting in synergistic chemo-photodynamic therapy effects [91,92]. These technologies facilitate localized ROS formation, optimizing tumor destruction while reducing impact on healthy tissue.

Furthermore, AS1411 facilitates diagnostic imaging and biosensing. Its capacity to bind nucleolin with great affinity makes it an optimal probe for fluorescence-based detection of cancer cells. AS1411-conjugated fluorophores have facilitated real-time visualization of aptamer uptake, while polymer-linked AS1411 structures have accomplished super-resolution imaging of cell-surface nucleolin. In addition, tailored derivatives such as AS1411-N6 show fluorescence amplification upon binding, functioning as "turn-on" sensors for nucleolin-abundant cancer cells [57,93–95]. At the core of these applications is AS1411's G-quadruplex structure, which improves binding affinity and serum stability while providing a framework for drug loading. Numerous planar medicines intercalate directly within G-quartets, and the inherent affinity of nucleolin for G-quadruplexes enhances the interaction between the aptamer and its target. Rational modifications of AS1411 have demonstrated the ability to optimize its structure and minimize polymorphism and maintain biological function. Such improvements can improve both delivery efficiency and therapeutic efficacy [96,97].

4.1.3. Cluster 3

It encompasses keywords such as **aptasensor, biosensor, biomarker, cancer therapy, DNA aptamers, ovarian cancer,** and **self-assembly,** reflecting a strong focus on diagnostic innovation and DNA aptamer-based therapeutic strategies.

Aptamers are essential to cancer biosensing platforms because of their exceptional selectivity, chemical stability, and simplicity of modification. When immobilized on sensor surfaces, they establish the foundation for aptasensors that may detect tumor biomarkers with great sensitivity [81]. Electrochemical and colorimetric aptasensors may identify targets such as MUC1 and HER2 with femtomolar sensitivity, while fluorescent aptamer arrays provide multiplex detection across different cancer types [68]. These platforms provide swift, economical, and portable solutions for point-of-care cancer diagnostics. Aptasensors have been utilized for liquid biopsy targets, including exosomes and CTCs [8]. Advanced platforms involve fluorescent hydrogels, magnetic beads, and sandwich-type aptasensor structure to selectively capture and quantify tumor bimarkers [98,99]. The incorporation of nanomaterials and signal amplification methods, such as isothermal hybridization, significantly improves sensitivity, advancing early cancer detection initiatives [100].

Furthermore, DNA aptamers function as precise medicinal agents. Aptamers such as AS1411, which specifically target nucleolin, have been employed to transport therapeutics (e.g., doxorubicin) and gene regulators (e.g., miRNA and siRNA) directly to tumor cells, particularly in ovarian cancer, where chemoresistance and inadequate early detection persist as clinical obstacles [12,101]. Many types of aptamer-nanostructures, including DNA strips and biomimetic nanoparticles, have been produced to deliver both cytotoxic and gene-silencing drugs, which facilitate tumor-targeted therapy and reduce off-target toxicity [3].

A key novelty within this cluster is aptamer-mediated self-assembly [102]. DNA aptamers have been integrated into nanostructures such as micelles, origami sheets, and responsive hydrogels to provide multifunctional therapeutic platforms [73]. These devices can encapsulate pharmaceuticals, react to tumor-specific cues, and deliver payloads accurately at the disease location [103]. Micelles modified with AS1411 facilitated efficient photodynamic therapy by selectively delivering a photosensitizer to tumor cells [90]. Likewise, DNA origami boxes and aptamer-crosslinked hydrogels have exhibited regulated drug release in response to cancer biomarkers [104,105]. Recent advancements indicate an increasing translational potential for these technologies. Aptamer-based biosensors are approaching clinical application for fast screening, and DNA aptamer drug conjugates are under investigation in clinical trials [106]. Despite challenges such as nuclease degradation and rapid clearance, recent investigations, including chemical modifications and protective carriers, have significantly improved the *in vivo* stability and efficacy of aptamers. Recent FDA approval of RNA aptamer therapies, along with the initiation of clinical studies exploring aptamer-directed cancer treatments, suggests a gradual movement toward potential clinical application [107,108].

4.1.4. Cluster 4

This cluster centers on keywords such as CTCs, EpCAM, prostate cancer, RNA aptamers, and SELEX, highlighting a strong focus on diagnostic and therapeutic applications of RNA aptamers, particularly in prostate cancer. RNA aptamers, which were selected via SELEX, have been used to target prostate-specific markers like PSMA for both therapy and imaging [109,110]. For instance, PSMA-targeted RNA aptamers have been linked to siRNAs or chemotherapeutic agents to suppress tumor growth. Dual-functional platforms, such as ^{99m}Tc-labeled aptamer–siRNA chimeras, have further demonstrated the ability to combine tumor imaging with therapeutic delivery *in vivo* [111]. In addition, PET and fluorescence probes decorated with PSMA aptamers have shown high specificity for prostate cancer lesions [18].

This cluster also reflects improvements in (circulating tumor cells) CTC detection. Aptamer-functionalized microfluidic and nanosensor platforms, such as those using the EpCAM-binding SYL3C aptamer, have shown efficient capture of CTCs from blood samples [112–114]. Dual-aptamer strategies have been designed to improve detection by simultaneously targeting epithelial and mesenchymal markers (such as EpCAM and N-cadherin), thereby exploring the heterogeneity of CTCs [115–117]. SELEX remains the cornerstone technique for aptamer production, but these conventional methods are often labor-intensive and time-consuming. Recent innovations, such as microfluidic SELEX and cell-SELEX, have introduced greater efficiency, improving both speed and target selectivity [8]. Computational modeling is progressively employed to refine aptamer design, improving target binding by forecasting EpCAM dimer interactions [8,117].

4.1.5. Cluster 5

This cluster comprises keywords such as exosomes, GO, liposomes, and PTT, reflecting a strong focus on aptamer-functionalized nanocarriers for targeted cancer treatment and diagnosis.

Aptamers are increasingly being integrated into delivery platforms such as liposomes to enhance therapeutic precision. Aptamer–liposome conjugates offer improved cellular uptake and greater tumor accumulation by targeting overexpressed antigens like MUC1 and EpCAM. This approach, in turn, boosts chemotherapeutic efficacy while reducing off-target toxicity. For example, MUC1-specific aptamer–liposomes have been shown to selectively deliver doxorubicin to MUC1-positive breast cancer cells, bypassing antigen-negative cells and thereby improving treatment specificity and safety [76,117]. Exosome-based systems are further enhanced by aptamer guidance, offering exceptional selectivity and biocompatibility in cancer targeting [52]. Researchers have accomplished tumor-specific drug delivery with high biocompatibility by engineering exosome surfaces with aptamers like AS1411, which targets nucleolin [118]. Exosomes decorated with AS1411 and loaded with doxorubicin demonstrated enhanced tumor accumulation and superior therapeutic efficacy in colon cancer models [85]. Aptamers improve exosome-based diagnostics; for example, aptamer-mediated detection of PD-L1 on circulating exosomes exhibited superior sensitivity and accuracy, surpassing traditional assays and facilitating noninvasive cancer monitoring [52,119,120]. Furthermore, the bibliometric clustering indicated that "exosomes" are becoming increasingly associated with established research subjects like "targeted drug delivery." Their recurrent co-occurrence and spatial closeness in the keyword and citation overlay maps (Figs. 3–5) underscore this theme integration, indicating that exosomes are transitioning from a separate research focus to a connecting platform for aptamer-mediated targeting and nanocarrier delivery. This convergence signifies a translational shift towards hybrid bio-nanoplatforms that integrate the targeting accuracy of aptamers with the physiological compatibility of exosomes, hence enhancing the development of multifunctional, precision-guided cancer therapies.

Similarly, GO offers another promising platform due to its large surface area and easily chemically modified. These systems demonstrate high drug loading and selective delivery. In one study, a breast cancer-targeting aptamer (HB5) was conjugated to GO co-loaded with doxorubicin and silibinin, resulting in high encapsulation efficiency and potent, tumor-specific cytotoxicity [121]. GO-based hybrids have also been explored for different models of cancer therapy. For instance, a GO–gold nanoparticle platform functionalized with aptamers and loaded with doxorubicin enabled laser-triggered drug release in combination with photothermal ablation. Under near-infrared (NIR) irradiation, this system induced significant cancer cell death, demonstrating the synergistic potential of chemo–photothermal approaches [64,121,122].

Aptamer conjugation further enhances PTT, as nanomaterials such as gold nanostars and GO composites selectively bind tumor cells and convert NIR light into heat for targeted ablation [123]. These constructs often integrate chemotherapy, as demonstrated by AS1411–GO complexes co-loaded with cytotoxic agents, which achieved dual-mode killing of lung cancer cells under NIR exposure [124,125]. More recently, aptamer-guided PTT platforms have been adapted for theranostic applications, combining tumor imaging and treatment in preclinical models [126,127].

While the frequency of keywords and citation counts in each cluster reflects areas of strong and continuous research interest, these metrics should not be interpreted as direct indicators of translational readiness or clinical success. Instead, they highlight the scientific fields where efforts and resources are currently focused. Many of the aptamer-based strategies identified, although showing promising preclinical results, remain in early progress stages and require further investigations and validation before their use in clinical applications.

5. LIMITATION

This study presents a thorough bibliometric analysis of aptamer-based cancer research; nonetheless, some limitations should be recognized. The exclusive use of the Scopus database, the largest abstract and citation repository with robust multidisciplinary coverage that also includes PubMed and a substantial portion of Web of Science records, may introduce source bias by excluding studies indexed solely in other databases. This approach is common in bibliometric research to ensure dataset consistency and tool compatibility; however, future studies could integrate multiple databases to enable sensitivity testing and cross-validation of results.

The restriction to English-language publications may make a potential linguistic bias, as relevant studies published in other languages may have been overlooked. Furthermore, the analyses include original research articles only, thereby excluding conference proceedings, reviews, editorials, and book chapters, which could provide valuable insights. In addition, keyword analysis utilized a custom thesaurus to amalgamate synonyms, a requisite yet subjective procedure that may have impacted clustering results and keyword correlations. The establishment of inclusion thresholds, such as requiring keywords to have a minimum of 20 occurrences, although essential for clarity and manageability, may have unintentionally excluded emerging terms and nuanced research topics that are still evolving in the field. Notwithstanding these constraints, the study offers significant and empirical insights into the structure, dynamics, and global collaboration patterns of aptamer-related cancer research. This study focuses on thematic mapping and hotspot identification rather than detailed keyword lifespan or burst analysis. While trend maps and thematic evolution provide an indirect view of temporal dynamics, in-depth burst detection and rise/decline rate analysis were beyond the current scope and could be addressed in future research.

6. CONCLUSION AND FUTURE PERSPECTIVES

This bibliometric and thematic analysis provides a comprehensive overview of the global research landscape on aptamers in cancer research, highlighting important contributors, theme clusters, and promising research trajectories. The findings indicate a significant transition towards the incorporation of aptamer-based approaches in diagnostics, therapeutics, and nanotechnology. Aptamers have transitioned from specialized molecular tools to multifunctional platforms for targeted drug delivery, biosensing, and imaging. Prominent themes such AS1411, SELEX, targeted treatment, and exosome-based delivery systems highlight the translational potential of the field. Among the rising research themes, "exosomes" emerge as a significant keyword likely to influence the direction of aptamer–cancer research in the next years, as indicated by their swift increase in frequency and normalized citation impact. The absence of well-defined motor themes indicates a continual disparity between experimental progress and clinical application. Funding agencies should prioritize multidisciplinary programs that connect aptamers with exosome-based delivery, immunotherapy, and biosensing, therefore translating these promising fields into clinically applicable discoveries.

Future studies should continue addressing major challenges affecting clinical translation, including aptamer instability, off-target interactions, and pharmacokinetic constraints. Enhancing collaboration among molecular biologists, materials scientists, and physicians is essential for progressing aptamer–nanocarrier systems from preclinical assessment to clinical use. Expanding clinical pipelines and promoting international collaboration and data exchange will further advance innovation and standardization. This study combines quantitative bibliometric mapping with thematic analysis to establish a solid, evidence-based framework for directing future research priorities and expediting the implementation of aptamer-based cancer therapies.

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8. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

9. CONFLICTS OF INTEREST

The authors declare that they have no financial or personal relationships with any individuals or organizations that could inappropriately influence their work. There are no professional or personal interests of any nature in any product, service, or company that could be construed as influencing the content or conclusions of this manuscript.

10. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

11. DATA AVAILABILITY

All data generated and analyzed are included in this research article.

12. PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

13. DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

QuillBot and ChatGPT were used to refine the language and improve readability. The authors thoroughly reviewed and edited all content and take full responsibility for its accuracy and integrity. No figures or images were generated or modified using AI tools.

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