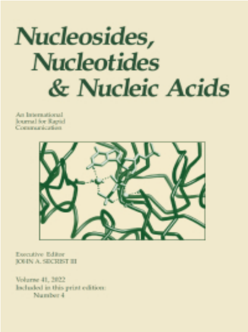

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Systematic mapping of DNAzymes research from 1995 to 2019

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ABSTRACT

DNAzymes (catalytic DNA) have gained significant diagnostic and therapeutic applications with increasing research output over the years. Functional oligonucleotides are used as molecular recognition elements within biosensors for detection of analytes and viral infections such as SARS-CoV-2. DNAzymes are also applied for silencing and regulating cancer specific genes. However, there has not been any report on systematic analysis to track research status, reveal hotspots, and map knowledge in this field. Therefore, in the present study, research articles on DNAzymes from 1995 to 2019 were extracted from Web of Science (SCI-Expanded) after which, 1037 articles were imported into Rstudio (version 3.6.2) and analysed accordingly. The highest number of articles was published in 2019 (n = 138), while the least was in 1995 (n = 1). The articles were published across 216 journals by 2344 authors with 2337 multi-author and 7 single authors. The most prolific authors were Li Y (n = 47), Liu J (n = 46), Wang L (n = 33), Willner I (n = 33) and Zhang L (n = 33). The top three most productive countries were China (n = 2018), USA (n = 447) and Canada (n = 251). The most productive institutions were Hunan University, China (n = 141), University of Illinois, USA (n = 139) and Fuzhou University, China (n = 101). Despite the increasing interest in this field, international collaborations between institutions were very low which requires immediate attention to mitigate challenges such as limited funding, access to facilities, and existing knowledge gap.

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DNAzymes; oligonucleotides; *in vitro*; chemiluminescence; bibliometrix

1. Introduction

DNAzymes are single-stranded DNA molecules with catalytic activity.[1] Deoxyribonucleic acid (DNA) was initially thought to perform only data storage function and transfer of genetic information needed for protein

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expression.[2–4] The discovery that DNA could also perform catalytic role was a major milestone in Biochemistry.[5,6] DNA based catalysts are called catalytic DNA or DNAzymes or deoxyribozymes.[7,8] Unique advantages of DNAzymes over protein enzymes such as stability during long time storage with reversible renaturation potential, easy preparation and modification, pH and thermal stability, programmability, excellent activity, low cost and flexibility in substrate recognition have promoted their various medical and biotechnological applications.[4,9–13]

There was initial doubt about the ability of DNA to catalyse meaningful reactions, because the double strands of DNA lack the flexibility that is desirous of an enzyme.[14,15] In addition, protein has twenty amino acids to use in chemical reactions, whereas DNA has just four bases. Folding of DNA into stable tertiary structures was thought to be difficult because of the fewer number of bases available for the formation of tertiary structure.[6,16,17] Furthermore, high-density negative charges in DNA and the rigid nature of the phosphate backbone do not seem to favour the formation of tertiary structure.[11,18] Also, amino acids contain different side chains ranging from polar to non-polar, acidic, neutral and basic side chain which tend to offer them unique diversity and catalytic potential when compared to DNA bases that do not possess this diversity.[2,6] Furthermore, secondary structures of protein put amino acid side chain on the outside of alpha-helices and beta-sheets which makes the amino acids to be well-positioned for tertiary contacts, whereas in DNA the unique chemical groups of the bases are largely located in the interior of base pair duplexes.[11,19,20] Breaker and Joyce[4] proposed that if RNA could catalyse reaction, single-stranded DNA (oligonucleotides) could also exhibit enzymatic activity due to their similar chemical composition with RNA.

In 1990, an *in vitro* selection known as Systematic Evolution of Ligands by Exponential Enrichment (SELEX) was introduced by researchers in several laboratories.[1,21–24] During SELEX, individual molecules were isolated from a very large population of DNA sequences, random sequence DNAs were tested to identify specific sequences that have desired catalytic activities with high efficiency.[6,25] To overcome a limited number of molecules with catalytic ability during SELEX, the few competent molecules obtained from the screening process are amplified by PCR and enriched by repeated selection and amplification process until a saturating activity is obtained i.e., when there is no further increase in activity even though the selection pressure is still on. The catalytic molecules obtained are then cloned, sequenced, and characterised.[7,26] *In vitro* selection method has been used successfully for isolating DNAzymes. Several other selection processes such as cell SELEX, *in silico* selection, next-generation sequencing, and so on have evolved over the years.[4,5,20,27,28] DNAzymes have been shown to catalyse DNA and RNA cleavage,[4,29] DNA ligation,[30] porphyrin metalation,[6,31] DNA transesterification,[32] Diels-Alder reaction,[33] phosphatase and kinase activity,[12] thymine dimer repair,[34] peroxidase activity[20,35,36] and peptide side chain and backbone modification.[12,37]

The first DNAzyme, 10–23 DNAzyme, was discovered by Breaker and Joyce in 1994 through SELEX. It was named '10–23' DNAzyme because it was obtained from the 23rd clone of the 10th round of PCR.[4,38] It is composed of a catalytic domain of 15 deoxyribonucleotides, which is flanked by two substrate recognition arms. It can bind and cleave any RNA substrate by attacking the 2′-hydroxyl group at the adjacent phosphodiester bond with a high turnover rate by using Mg^{2+} as a cofactor.[15,39] The 10–23 DNAzyme has been greatly explored for inhibiting gene expression at the mRNA level and has found vast medical applications as gene silencing agents. It is used in biosensor development and for treating cancer, cardiovascular, bacterial, and viral diseases.[29,40] Thereafter, 8–17 DNAzyme and several other DNAzymes that can cleave DNA and RNA have been selected by SELEX.

Asides cleaving DNA and RNA, DNAzymes have been shown to join DNA or RNA together. DNAzyme with ligase activity join oligonucleotides together by forming phosphodiester bonds by condensation reaction between 5′-hydroxyl group of an oligonucleotide and 3′ phosphate group of the adjacent oligonucleotide.[9,41,42] Cuenoud and Szostak[30] isolated DNAzyme with ligase activity; they used a large library random sequences that can join their own. The DNA sequence used contained biotin moiety and phosphorimidazole at 5′ and 3′ ends, respectively. DNA sequences capable of using their 5′-OH group to replace the imidazole were isolated in a streptavidin column. After about nine cycles, DNA catalytic sequence that utilised Cu^{2+} or Zn^{2+} to join two short DNA substrates was isolated.[30,43]

The formation of thymine dimers is the major defects observed when DNA is exposed to ultraviolet radiation.[44] This photo effect on DNA results in joining together of adjacent thymine residues. If this thymine crosslinking in DNA is not reversed or dealt with, it can cause genetic mutation and subsequently lead to cancer.[45,46] Photolyases (protein enzymes) repair thymine dimers by converting them back to their monomeric state [34]. Sen and co-workers used *in vitro* selection to obtain DNAzymes containing guanine in the catalytic core (Sero1C and UV1C) that can reverse thymine dimer formation without photosensitizers. Sero1C requires serotonin as a cofactor, whereas UV1C does not require a cofactor.[34,47]

Ferrochelatases are protein enzymes that catalyse the insertion of iron into porphyrin ring.[48,49] It has been reported that ferrochelatases were inhibited by N-alkylporphyrins[31]; hence, it was proposed that N-methylmesoporphyrin IX (NMM) act as a transition state analog for the metalation of mesoporphyrin IX (MPIX). Sen and co-workers isolated DNAzymes that are capable of inserting iron into empty porphyrin through *in vitro* selection.[31,50] DNA clones were isolated from a random sequence DNA library based on their binding affinity to NMM. They showed that guanine-rich sequences showed high-affinity for binding NMM.[20,31] They used guanine-rich sequences such as PS5, PS2, PS2. ST2 and PS5.ST1 to insert Cu and Zn into different porphyrins. The oligonucleotides used fulfilled properties to be regarded as enzymes as they exhibited saturation kinetics towards the substrate, utilised cofactors, and produced high rate enhancement compared to uncatalysed reaction[51,6,31] The guanine sequences folded in potassium solution to form a unique guanine quadruplex, with three guanine quartettes, four loops and one gap. They proposed that DNAzyme likely catalyses the metallation reaction by distorting the ground-state porphyrin towards the transition state form.[6,31]

Peroxidases are oxidative enzyme that catalyses one electrons transfer reaction. Sen and co-workers discovered that haemin competitively inhibits DNAzyme catalysed metallation reaction of porphyrin. Hence, they were motivated to assess the ability of the oligonucleotide-haemin complex to catalyse peroxidase reaction.[20,52] Several studies have shown that guanine-rich oligonucleotides such as PS2.M, PS5.M, Bcl-2, AGRO100, c-myc, c-kit and many others can fold into G-quartet structures through Hoogsten hydrogen bond in the presence of potassium ions.[35,53,54] These G-quartettes can assemble to form G-quadruplex structure with haemin stacking between the G-quartet and have been proven to show robust peroxidase activity in the presence of substrate like 2,2′-azinobis(3-ethylbenzthiazoline)-6-sulfonic acid (ABTS) and 3,3′,5,5′-tetramethyl benzidine (TMB).[55–57]

Bibliometric is a quantitative tool that can be used to construct an appropriate and coherent set of indicators for assessing developmental trends within a research field.[58] It can be used to track the performance of an article, the productivity of authors, countries, institutions, journals and the level of activity in a research field over time.[59] It can help to identify international collaboration, leaders in a field (key players), major themes/hotspots and knowledge gaps.[60,61] Systematic mapping of knowledge is a procedure that combines the traditional literature method with the modern text mining method.[62] The source for bibliometrics is always a database; commonly used databases for quantitative analysis include Web of Science, Scopus and google scholar. However, Web of Science (Clarivate Analytics) is the most preferred due to its wide coverage of information across various disciplines.[63–66] Despite the extensive research work and narrative reviews confirming the diagnostic and therapeutic applications of DNAzymes, there is no report on the systematic mapping of research in the field of DNAzymes. This is necessary in order to identify trends, track research status, key spots, map knowledge, identify sources of funding and potential leaders in the field.

2. Materials and methods

2.1. Data retrieval

Ethical approval was not necessary, since the data were downloaded from the public databases and did not involve any interactions with human or animal subjects. The data explored in this present study was extracted from the Web of Science (SCI-Expanded). We used the title search strategy with the following keywords: TITLE: ((DNAzyme OR catalytic DNA OR deoxyribozyme). We obtained about 1234 documents including article (n = 1082), review (n = 19), letter (n = 5), book chapter (n = 3), meeting abstract (n = 104), correction (n = 5), news item (n = 5), editorial material (n = 3), proceedings paper (n = 22). These documents were written with two languages such as English (n = 1227) and French (n = 7). We observed that these documents were distributed in Web of Science Index (Science Citation Index Expanded (n = 1218), Index Chemicus (n = 16), Book Citation Index–Science (n = 3), Conference Proceedings Citation Index-Science (n = 78) and Emerging Sources Citation Index (n = 4)). Our interest was to monitor the research outputs on the subject and hence, we excluded other document types and focussed only on research articles. Subsequently, we removed articles written in French (n = 7) and concentrated on those written in English (n = 1227) indexed in SCI-Expanded. We further validated the data manually to remove those articles, which are not needed in the present study and arrived at 1037 articles which were further exported from WoS in a Bibtex format.

2.2. Data analysis

The extracted data were imported into Rstudio (version 3.6.2) and analysed accordingly as described by Orimoloye and Ololade (2020)[67]. The data were analysed for the annual scientific production, mean annual citation, most relevant authors, documents, institutions, countries, journals and keywords.

Table 1. Summary of information retrieved on DNAzymes from 1995 to 2019.

Description	Results
'Timespan'	1995:2019
'Sources (Journals, Books, etc)'	216
'Documents'	1037
'Average years from publication'	6.36
'Average citations per documents'	36.9
'Average citations per year per doc'	4.45
'References'	20,015
'Document types'	
'Article'	1037
'Document contents'	
'Keywords Plus (ID)'	2178
'Author's Keywords (DE)'	1577
'Authors'	
'Authors'	2344
'Author appearances'	5332
'Authors of single-authored documents'	7
'Authors of multi-authored documents'	2337
'Authors collaboration'	
'Single-authored documents'	7
'Documents per author'	0.442
'Authors per document'	2.26
'Co-authors per documents'	5.14
'Collaboration Index'	2.27

3. Results and discussion

3.1. Main information

A total of 1037 research articles (excluding review papers, letters, conference proceeding papers, books, news items, corrections, editorial materials, retracted publication, meeting abstract) were retrieved on DNAzymes from 1995 to 2019 across 216 different journals from the Web of Science. Publication of research findings is one of the major ways researchers communicate their discoveries with peers. The quantity and quality of articles are commonly used for assessing the productivity of researchers.[68] A total of 2344 authors wrote the articles, with 2337 multi-author and 7 single authors. This shows high productivity and contribution to knowledge by researchers in this field. There were 0.442 documents per author and 2.26 authors per document, there were 5.14 co-authors per document and the collaboration index was 2.27 (Table 1). The size of the research team is relatively small when compared to other fields. The collaboration index of 2.27 implies that the average research team is between 2 and 3 authors; this relatively low index shows that the level of partnership among authors is low. Research partnership can be of immense advantage as it aids knowledge transfer, improves access to funding and facilities which consequently translate to quality research output.[69,70] However, authorship size or number might not always be due to partnership and complexity in a research project, it could also be due to needs to be included in a publication in order to gain promotion in an institution.[71] The 1037

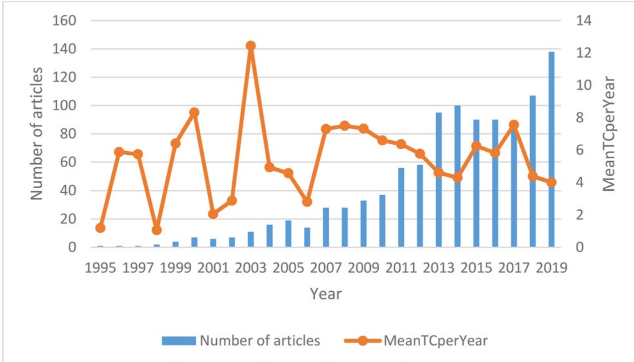

Figure 1. Annual production and mean annual citation per year on DNAzymes from 1995 to 2019.

papers included in this research contain 20,015 references which might mean that the authors highly consulted and improve on the methodologies of the pioneers in this field. Referencing helps researchers to provide convincing evidence to support assertions made by authors, it also shows that an author is aware of the field he is operating in and the leading expert in that field. Accurate referencing allows readers to locate the sources of information in a research article. Collection, reading, and analysis of several references can help to improve the competence of a researcher in a chosen field.[72]

3.2. Annual publications and citations

The ability of DNA (oligonucleotide) to catalyse reaction was first reported by Joyce and Breaker in 1994, since then there has been a developmental trend in research in this field. The number of articles published increases from 1995 to 2014; however there was a slight decline in 2015 to 2017 with increase experienced again in 2018. The highest production was in 2019 (n = 138), while the least was in 1995 (n = 1). Research interest was at its infant/initiation stage from 1995 to 2003; 40 articles were published within this period, with an average annual publication of 4.44 articles. Although, there has been increasing research interest in DNAzyme over the years, the last 10 years was responsible for the significant number of productions (Fig. 1). The average citation per year fluctuates over the years, documents published in 2003 (n = 12.44) have the highest citation than documents published in any other year. A citation shows accolades a researcher gives to the shoulders of giants he/she stood on to see clearer. Giving credit to early forbearers helps researchers to display academic integrity by avoiding pitfalls of plagiarism. Citation analysis serves as

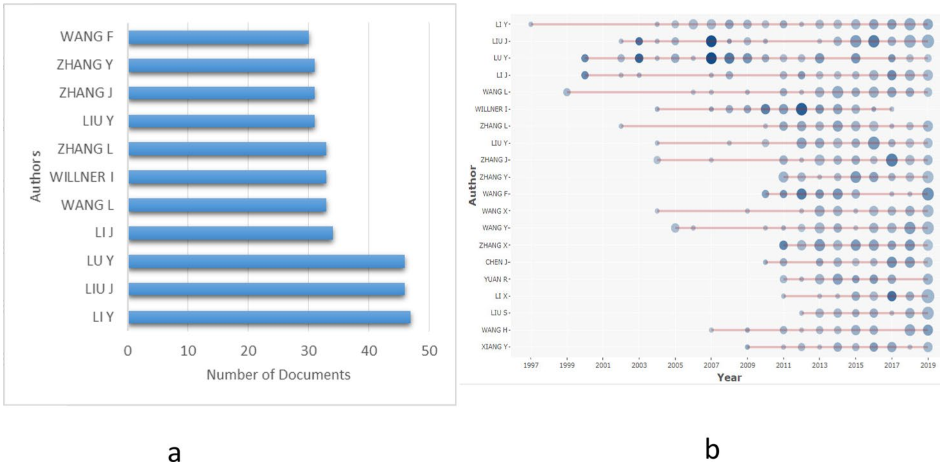

Figure 2. Productivity of authors. (a) Most relevant author and (b) Top authors production over the years on DNAzymes from 1995 to 2019.

evaluation tools in providing insight into scientific trends, impact, and quality of papers.[73] It shows historical prospect on scientific headway in a particular field, it helps to link the past efforts in a field to the present work, and it helps to put research in the right direction.[74] A proper and extensive citation shows that a researcher has valid work to back up his/her claims. Citation provides interrelated literature for articulating the intellectual structure of a research field, as a proper understanding of a specific topic is dependent on the understanding of closely related topics. The citing and cited documents reflect the research front and intellectual base, increasing citation rate indicates high research output.[75]

3.3. Most relevant authors

The most productive authors were Li Y (n = 47), Liu J (n = 46), Wang L (n = 33), Willner I (n = 33) and Zhang L (n = 33) (Fig. 2a). Production over time of the top authors helps to assess how active they have to be over the years. Among the top authors, Li Y was the first to publish an article in the field of DNAzyme. Li Y, Liu J, Liu Y, Li J, Wang L and Willner I showed consistent production over the years as shown by the presence and size of the bubbles (Fig. 2b). The author's productivity agreed with Lotka's law as only a few of the 2344 authors were highly productive (Supplementary Fig. S1). Table 2 shows that the authors with the highest impact were Lu Y (h-index = 32, g-index = 12, m index = 1.222), Willner (h-index = 29, g-index = 33, m-index = 1.706), Liu J (h-index = 23, g-index = 46, m-index = 1.643) and Li Y (h-index = 20, g-index = 35, m-index = 1.333). Assessment of quality of productivity is commonly used by funding agencies, for recruitment

Table 2. Top author's impacts on DNAzymes research (1995–2019).

Author	h-index	g-index	m-index	TC	NP	PY_start
LI Y	20	35	1,333	1343	47	2006
LIU J	23	46	1,643	2646	46	2007
LU Y	32	46	1,524	6614	46	2000
LI J	19	34	0,905	2356	34	2000
WANG L	19	32	0,864	1069	33	1999
WILLNER I	29	33	1,706	3387	33	2004
ZHANG L	18	30	0,947	922	32	2002
LIU Y	15	27	0,882	763	31	2004
ZHANG J	16	24	0,941	636	31	2004
ZHANG Y	17	26	1,7	710	31	2011
WANG F	20	30	1,818	2005	30	2010
WANG X	13	18	1,083	357	26	2009
WANG Y	9	18	0,818	351	24	2010
ZHANG X	14	22	1,556	504	26	2012
CHEN J	14	25	1,273	848	25	2010
YUAN R	19	25	1,9	904	25	2011
LI X	10	20	1	408	23	2011
LIU S	12	20	1,333	411	23	2012
WANG H	14	21	1,167	622	21	2009
XIANG Y	14	22	1,167	847	22	2009

and promotion purposes. H-index and other metrics are commonly used indicators ranking authors for their contribution in a particular field.[76] Knowing the most influential researchers can help to facilitate partnership.[77] Citation counts have its own demerits, as authors tend to cite the work of renowned authors and people in their research group.[78] Hence, the use of the author's metric index is commonly used to overcome this. Local citation deals with citations of authors in the same collection. Zhang Y, Zhang X and Zhang J have the largest and most central collaboration network. The major collaborators of Zhang Y were Zhang I, Zhang X, Wang I, Wang Y, Yang X, Yang I and Li H. Zhang X major partners were Zhang Y, Yang I, Li J, Chen Y, Wang S, Liu X and Liu S. Zhang J had the highest number of network; he collaborated with Chen J, Zhao Y, Li C, Lu, Y, Tang Y, Zhao, Y, Liu H, Li X Wang S, Yuan Y and Yuan R. The network between Willner I and Wang F is very strong as shown by the thickness and closeness of the line joining them together. The same is applicable to the network between Yuan R, Yuan Y, Xiang Y and Chai Y. (Fig. 3). The stronger the network, the likelihood the number of articles they must have co-authored and the easier it is for knowledge diffusion.[79] The author's collaboration network can help to reveal the level of partnership between authors; this can consequently help to identify the influential groups and possibly help to establish collaborations.[61,66]

3.4. Most global cited documents

Authors with the most globally cited documents were Liu JW, 2003, Journal of America Chemical Society (n = 1070); Li J, 2000, Journal of America Chemical Society (n = 521) and LI J, 2000, Nucleic Acids Research (n = 479)

Figure 3. Authors' collaboration network on DNAzyme research (1995–2019).

(Table 3). Liu JW, 2003, Journal of America Chemical Society also top in terms of the highest total citation per year (n = 59.444), followed by Liu J, 2007, J Am Chem Soc (n = 34) and Liu J, 2007, Angew Chem -Int Edit (n = 32.571). The global citation refers to citations the authors received both within and outside the articles collected in this study.[80] Total citation is the sum of all the citation counts the document/article received since publication, while the total citation per year is the sum of the citation count the document received divided by the number of citeable years. Total citation per year gives a better reflection of the impact of the document because documents that were published several years ago will tend to have more citation count that documents published a few years ago. Therefore, using the average citation will give a true picture of things.[81] A high citation shows landmark and how relevant a document is because authors tend to cite articles who have contributed significantly to knowledge.[77] Articles describing ground-breaking methodology/protocol usually record extremely high citation rate, for instance, Lowry et al.[82] which described measurement of protein concentration has recorded about 300,000 citations since publication. Accessibility of an article can also affect its citation count as authors from institutions without a subscription to some journals often cite papers from open access journals.[83] Citation count can also be influenced by the number of people working in a

Table 3. Most globally cited documents on DNAzyme from 1995 to 2019.

Paper	Total citations	Tc per year
Liu JW, 2003, J Am Chem Soc	1070	59,444
Li J, 2000, J Am Chem Soc	521	24,81
Li J, 2000, Nucleic Acids Res	479	22,81
Liu J, 2007, J Am Chem Soc	476	34
Liu J, 2007, Angew Chem -Int Edit	456	32,571
Stojanovic Mn, 2003, Nat Biotechnol	423	23,5
Xiao Y, 2007, J Am Chem Soc	358	25,571
Wang Z, 2008, Adv Mater	339	26,077
Lee Jh, 2008, J Am Chem Soc	330	25,385
Li Di Ld, 2007, J Am Chem Soc	294	21
Elbaz J, 2010, Nat Nanotechnol	293	26,636
Zhao Xh, 2011, Anal Chem	292	29,2
Xiang Y, 2009, J Am Chem Soc	279	23,25
Li T, 2010, Anal Chem	278	25,273
Tian Y, 2005, Angew Chem -Int Edit	277	17,312
Travascio P, 1999, Chem Biol	274	12,455
Niazov T, 2004, Nano Lett	258	15,176
Hollenstein M, 2008, Angew Chem-Int Edit	253	19,462
Wang F, 2011, J Am Chem Soc	244	24,4
Shimron S, 2012, Anal Chem	237	26,333

field;[84] this is also applicable to this study as DNAzyme has several sub-divisions based on the intended use. Critical review papers oftentimes receive more citations than research articles as they tend to summarise results of several articles, hence researchers tend to consult them to get the trend in a particular subject, this often leads to citation.[85] However, this is not applicable in this study as only research articles indexed in the Web of Science were used.

3.5. Distribution of countries and institutions

Table 4 shows that China was the most productive country, it accounted for 2018 of published articles on DNAzyme followed by the USA (n = 447) and Canada (n = 251). Publications from these three top countries accounted for over 70% of the production in the field of DNAzyme. High-income countries are the main forces in DNAzyme research. China (n = 16,877), USA (n = 10,573), Israel (n = 3888) and Canada (n = 3451) were the most significantly cited country. Israel had the most average citation per article (n = 102.32), followed by USA (n = 85.96) and Germany (n = 53.25) (Supplementary Table S1). China (n = 621), USA (n = 123), Canada (n = 83), Israel (n = 38) and Korea (n = 26) were the top five nations of the corresponding authors. Among the top five countries, Israel (0.211) ranked first in terms of multi-country production ratio, followed by Canada (0.181) and USA (0.122) (Supplementary Table S2). Corresponding authors are important as they show a crucial leadership position during the design of research, writing, and submission of articles to journal editors. The

Table 4. Top 20 countries and institutions contribution to DNAzyme research (1995–2019).

Rank	Country	Frequency	Institution	Articles
1	China	2018	Hunan Univ	141
2	USA	447	Univ Illinois	139
3	Canada	251	Fuzhou Univ	101
4	South Korea	93	Mcmaster Univ	97
5	Australia	89	Nanjing Univ	91
6	Germany	86	Hebrew Univ Jerusalem	83
7	Israel	83	Southwest Univ	81
8	Japan	79	Univ Waterloo	69
9	Iran	49	Cent S Univ	66
10	India	31	Changchun Inst Appl Chem	52
11	Russia	27	Nankai Univ	52
12	Poland	25	Chongqing Med Univ	46
13	Taiwan	24	Tsinghua Univ	41
14	UK	22	Jilin Univ	38
15	Belgium	16	Wuhan Univ	38
16	France	16	Simon Fraser Univ	37
17	Spain	15	Qingdao Univ Sci And Technol	34
18	Singapore	13	Guangxi Normal Univ	32
19	Argentina	8	Sun Yat Sen Univ	32
20	Italy	8	Sichuan Univ	30

country's collaboration was also extremely weak; China had the biggest collaboration followed by the USA and Germany. China formed an alliance with the USA, United Kingdom, Japan, Canada, Singapore, France, Russia and Australia (Fig. 4a). This shows that the most developed countries with highly skilled researchers and resources are the ones partnering in this field. This has implication of limiting the funds received by developing countries with potential of widening the knowledge gap in medical technology between the developed nations and countries with limited resources. China formed the strongest network with USA and Canada as shown by the size of the node, the thickness of the line joining them together, and the distance between the countries in the map. It is highly essential to prioritise intra and international collaboration of research in order to overcome challenges like limited funding, access to facilities, and knowledge gap.[86] The top five institutions in terms of production number of publications were Hunan University, China (n = 141), University of Illinois, USA (n = 139), Fuzhou University, China (n = 101), McMaster University, Canada (n = 97) and Nanjing University, China (n = 91). China accounted for three of the top five universities in the field of DNAzyme (Table 4). The research collaboration between institutions in the field of DNAzyme was extremely low as many institutions were isolated from the network. Hunan University, Nanjing University and Changhum Institute of Applied Chemistry all based in China have the strongest collaboration network, this can possibly help in judicious use of limited resources, access to facilities that may not be available in some of the institutions and skill transfer. Nanjing University has the highest collaboration network, this

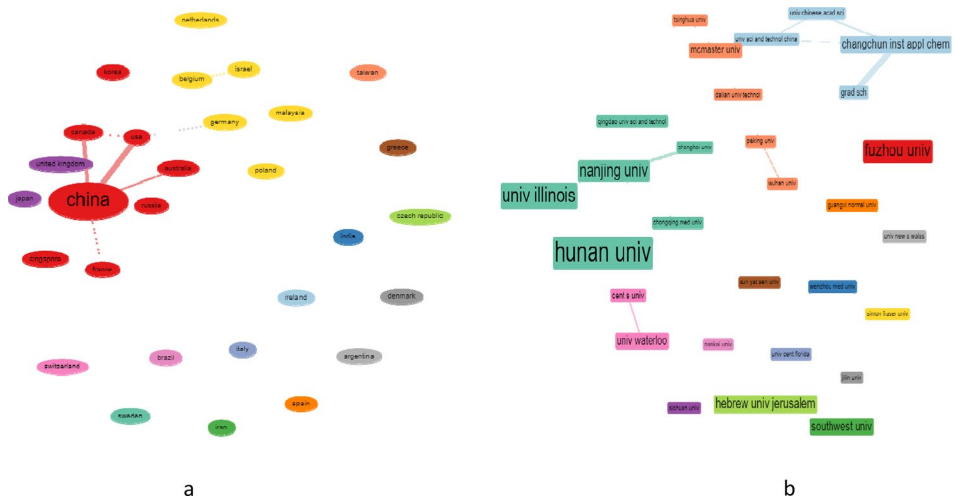

Figure 4. Collaboration network on DNAzymes from 1995 to 2019. (a) Institutional collaboration and (b) Country's' collaboration.

can enhance visibility and citation counts of researchers from this institution. Nanjing University collaborated with University of Illinois, Qingdao University of Science and Technology, Shanghai University, Chongqing Medical University and Hunan University, however Shanghai University formed the strongest network with Nanjing University among the partners as shown by the proximity and the thickness of the line joining them together (Fig. 4b).

3.6. Distribution of journals

Based on the number of articles published, the top three most relevant sources of the 216 journals that have published in the field of DNAzymes were Biosensors & Bioelectronics (n = 101), Chemical Communications (n = 85) and Analytical Chemistry (n = 66) (Supplementary Fig. 2a). It is not surprising that Biosensors & Bioelectronics came top among the relevant sources because DNAzymes are commonly applied in biosensors development; the specialty of the journal might have influenced researcher's choice on where to publish their work. Journal of America Chemical Society (n = 4143), Analytical Chemistry (n = 3806), Chemical Communications (n = 1994) and Biosensors & Bioelectronics (n = 1939), respectively are the most cited sources (Supplementary Fig. 2b). This might be due to the visibility and accessibility of articles from these journals. Citation counts are important as they are often used to calculate impact factors of journals which in turn is used to rate the relevance and influence of journals.[75] Authors usually consider the impact factors of journals

Table 5. Impacts of relevant sources on DNAzymes research (1995–2019).

Source	h_index	g_index	m_index	TC	NP	PY_start
Biosensors & Bioelectronics	38	52	2.235294118	3637	101	2004
Chemical Communications	39	63	2.6	4205	85	2006
Analytical Chemistry	41	66	2.277777778	5084	66	2003
Analyst	20	29	1.333333333	958	51	2006
Sensors and Actuators B-Chemical	15	18	1.875	476	44	2013
Journal of the American Chemical Society	32	37	1.523809524	6551	37	2000
Analytica Chimica Acta	17	26	1.416666667	736	36	2009
Microchimica Acta	13	17	1.181818182	354	35	2010
Nucleic Acids Research	18	26	0.857142857	1366	26	2000
Talanta	10	18	0.625	354	24	2005
Angewandte Chemie-International Edition	20	23	1.25	2263	23	2005
Chembiochem	13	22	0.866666667	578	22	2006
RSC Advances	9	13	1.125	201	22	2013
Analytical Methods	9	12	1	182	20	2012
Biochemistry	14	19	0.583333333	755	19	1997
Chemistry-A European Journal	12	16	0.923076923	680	16	2008
Acs Applied Materials \& Interfaces	11	15	1.375	486	15	2013
Chemical Science	9	12	1.125	316	12	2013
Journal of Molecular Biology	11	12	0.47826087	382	12	1998
Analytical Biochemistry	6	9	0.285714286	177	9	2000

when deciding where to submit their prospective articles.[87] However, citation counts and impact factors have their limitations. Analytical Chemistry (h-index = 41, m-index = 66, g-index = 2.27), Chemical Communications (h-index = 39, m-index = 63, g-index = 2.6) and Biosensors & Bioelectronics (h-index = 38, m-index = 52, g-index = 2.24) were the highest on the list (Table 5). The trends in the metrics might be due to the quality of research output from these sources. Sensors and Actuators B-Chemical have the highest source growth, it experienced sharp and unprecedented growth from 2011 to 2019. Biosensors & Bioelectronics, Analytical Chemistry and Chemical Communications experienced significant growth; however, their growth peaked and experienced a decline. The analyst experienced steady growth from 2005 to 2019 (Supplementary Fig. S3).

3.7. Keywords analyses

There were 1577 author keywords and 2178 keyword plus (Table 1). The most relevant author's keywords were DNAzyme (n = 264), G-quadruplex (n = 35), biosensor (n = 34), DNA (n = 34) and fluorescence (n = 32) (Supplementary Table S3). Author's keywords represent words that are frequently used, they represent the main content and focus of an article.[88] They are core words included as part of the abstract of a research paper to capture the essence of an article.[58] Keywords provide information on how researches are conceptualised, it also helps to monitor development in a field.[89] The most prominent keyword plus were DNA (n = 307), biosensor (n = 136), nanoparticle (n = 122), amplification (n = 121) and *in vitro* selection (n = 121) (Supplementary Table S3). Keywords plus provide additional keywords beyond the ones provided by the author in the abstract of an article, it explores important words in the entire article. It can help researchers to access more articles that may not appear during a search based on changes in the scientific keywords over time.[90] Both DNA and biosensor occurred in the author's keywords and keywords plus. DNA (oligonucleotide sequence) is commonly used for preparing DNAzyme, while DNAzymes are commonly used in biosensors development. G-quadruplex is a type of structure form when guanine-rich oligonucleotides fold into G-quartet structures through Hoogsten hydrogen bond in the presence of metal ions.

DNAzymes co-occurred significantly with the biosensor, signal amplification, chemiluscence, colorimetry, haemin, g-quadruplex, sensor, aptamer, lead ion (Supplementary Fig. S3). Co-words show the interconnection between words or terms that are frequently used in the title, abstract, or entire article.[91] It reveals hotspot, main theme and knowledge in a particular field.[92,93] Haemin is iron (III) protoporphyrin, which acts as cofactors of many oxidase enzymes. When haemin is complex with G-quadruplex structures, a synthetic enzyme with peroxidase mimetic activity is obtained. Fluorescence, chemiluminescence and colorimetry are the most common analytical techniques for monitoring DNAzyme research. A sensor is an analytical device that brings together an immobilised sensing material and a transducer to produce an electronic signal that is proportional to the concentration of the target chemical substance.[94] DNAzyme is commonly used for detecting metal ions; of particular interest is lead ion due to health risk it poses when present in water. Aptamers are molecules that are capable of binding to specific substrates or proteins.[20] They are usually produced using *in vitro* selection (SELEX) and can be used in developing biosensors.[95] Nanoparticles are substances less than 100 nm.[96] They have gained increasing use as a catalyst, they can also enhance catalytic activity and stability of DNAzymes when complexed to it.[97,98] Nanoparticles have also gained increasing use in DNAzyme based biosensor as they help to improve shuttling of electrons and sensitivity of such sensors.[99] They have also gained application for the delivery of DNAzymes into cells for gene silencing and other therapeutic uses due to their small size, site-specific and non-cytotoxic nature.[100] The trends topic (Supplementary Fig. S4) in this study also supports the emerging use of nanoparticles in the field of DNAzyme with high frequency from 2016 to date.[63] Aptamer serves as the recognition element while the DNAzyme generates an analytical signal. Aptasensors are sensitive tools for detecting molecules like adenosine monophosphate (AMP), cocaine, and proteins.[101]

4. Conclusions

This study carried out the first systematic mapping of DNAzymes research. The study revealed that there is an increasing interest in research in the field of DNAzyme as shown by the rising trend in the number of publications over the years. From the early work on potentials of DNAzymes to cleave RNA and DNA, research interest in this field has grown to more practicable applications such as in biosensors development for rapid, cheap and highly sensitive detection of analytes and wide range of diseases. There is increasing shift from *in vitro* to *in vivo* applications of DNAzyme in silencing and regulation of cancer genes with many formulations currently in the clnical trials. New applications for DNAzyme will emerge in the future due to excellent programmability, stable nature and ease of synthesis of this versatile system. Bibliometrix was used to describe the characteristics, global status, key players, and trends in DNAzyme research. The highest number of articles was published in 2019 ($n = 138$). China ($n = 2018$) was the most influential country in this field in terms of the number of articles published, while Yingfu Li ($n = 47$) of Mc Master University, Canada was the most prolific author. This study was able to identify research gaps as research involving DNAzyme was conducted by high-income countries and there was little collaboration between institutions from different countries. The discovery from this study will help researchers to find potential collaborators and provide leads to hot research themes in the field of DNAzyme. It will also help to provide directions for future research on DNAzymes.

4.1. Limitations

The data explored for this present study were retrieved from Web of Science database without considering other databases and this information does not represent the holistic research on DNAzymes as research articles on the subject in other databases were not included. However, WoSCC is often used for bibliometric analysis due to its wide coverage of high-quality research and it is highly reproducible in nature. Furthermore, we only included articles written in English in our analysis, and excluded French Langauge. This is not a serious concern as most articles on research on DNAzyme were written in the English language.

Author contribution statement

Adeoye Raphael and Okaiyeto Kunle conceptualised the study; Okaiyeto Kunle carried out the data collection and analysis; Adeoye Raphael wrote the first draft of the manuscript. Oguntibeju OO supervised the study; Okaiyeto Kunle, Igunnu Adedoyin and Oguntibeju OO proofread the manuscript and all authors approved the manuscript for submission.

Competing interest statement

The authors declare no conflict of interest.

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