Scientometric analysis and perspective of IgY technology study

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ABSTRACT Egg yolk immunoglobulin (**IgY**) is a class of antibody that is produced in birds against pathogens. Therefore, hyperimmunization of birds can produce a specific antibody in the egg against target antigen for a wide range of applications in diagnostic, prophylactic or treatment in human and veterinary medicine which is known today as IgY technology. Until now, the number of articles, patents and clinical studies on IgY technology has increased significantly. Hence, there is a fact that scientometric studies are needed to gain a deeper understanding of the research for the commercialization of IgY technology. Until now, no scientometric research has been directed toward IgY technology. In view of this, we conducted scientometric analysis in the WoS database. A total of 1,029 IgY-related papers were obtained including 981 journal articles and 48 reviews. The visualization of this literature showed an increasing trend in the number of IgY-related publications over the 4 decades, especially after 2008 to 2021. China, the United States, Canada, Japan, and Germany had the largest number of publications, with 220, 148, 91, 76, and 72, respectively. Among all the research institutions, Dalian University of Technology, Alberta University and Northwest Agriculture and Forestry University published the most of the articles, respectively. Among authors, Dr. Xiaoying Zhang had the highest number of publications with 21. The top most cited publications were from Dr. da Silva with 38 citations. Keywords co-occurrence network analysis showed that the correlation between different keywords is large, especially IgY, antibodies and immunoglobulin which is consistent with the rapid increase in the number of publications. Finally, through this data analysis, we hope that our result could help IgY technology to more maturity toward industrialization and commercialization.

Key words: scientometric analysis, egg yolk immunoglobulin (IgY), IgY technology, poultry

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INTRODUCTION

Egg yolk immunoglobulin (**IgY**) is a class of antibody that is produced in birds, amphibians, and reptiles to protect them against pathogens and also their embryos after transferred to egg yolk in a passive immunity manner (Schade et al., 1994; Ulmer-Franco, 2012). Therefore, it is possible to have sufficient and specific antibodies in egg yolk for the prophylactic, treatment, and diagnostic purposes by hyper immunization of avian against a specific target or pathogens for humans and animals use, which is known today as IgY technology (Baloch et al., 2015; Leiva et al., 2020). In the last 2 decades, the number of studies on the antibacterial, antiviral, antifungal, and antiparasitic actions of IgY in both in vitro and in vivo has increased significantly (Lee et al., 2021). The first study on egg yolk immunoglobulin was performed by Klemperer (1893). He observed the protective effect of yolk immunoglobulin from hens vaccinated with tetanus toxin on mice challenged with the toxin. Then in 1959, with the rise of the animal welfare debate, the importance of yolk immunoglobulin production in birds became more apparent (Russell and Burch, 1959), and in 1969 the term "IgY" was coined by Leslie and Clem. In 1996, because of animal welfare the use of IgY technology as an international standardized technology instead of mammalian IgG was recommended by the European Centre for the Validation of Alternative Method (**ECVAM**) (Schade et al., 1996). From then until now, the number of articles, patents, and clinical studies on IgY technology has increased significantly (Figure 1). IgY is known as homolog of immunoglobulin G (IgG) in mammals but has different structural and functional properties (Pereira et al., 2019). The molecular weight of IgY is

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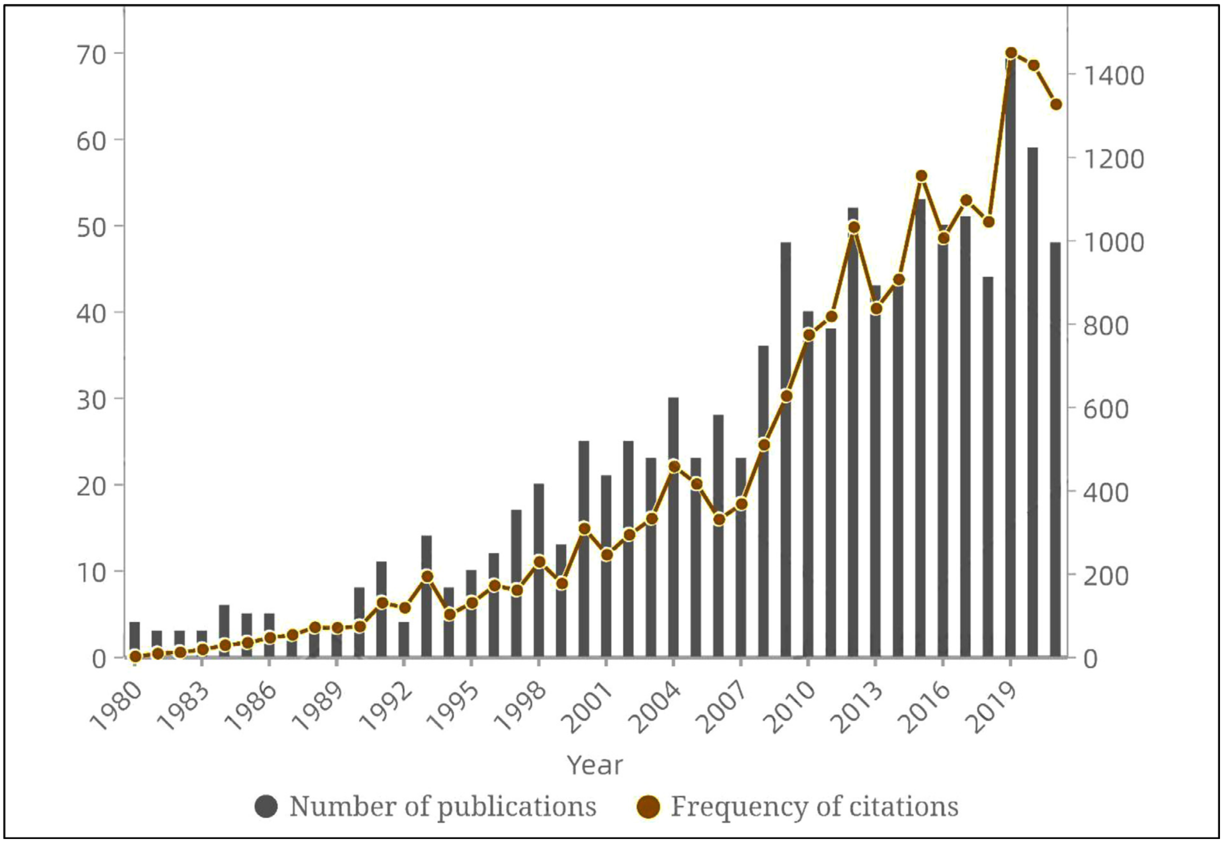

Figure 1. Number and citation frequency of IgY-related publications over 40 yr (from 1980 to 2021, data as of 25 Oct. 2021).

higher than IgG (180 kDa vs. 150 kDa), it is more hydrophobic and more resistant to proteases (Chalghoumi et al., 2009). It is stable and active for 6 mo at room temperature and 5 yr at 4°C (Abbas et al., 2019). Due to the phylogenetic distance, IgY is unable to bind or activate the mammalian complement system, Fc gamma receptors (**FcγRs**), and rheumatoid factors (Lee et al., 2017). Therefore, its use for oral/topical administration in mammals does not induce reactogenic effects and cannot activate the antibody-dependent enhancement (**ADE**), especially for viral dieses (O'Donnell et al., 2019). In addition, for diagnostic or immunoassays, IgY may result in less background noise, fewer false positives, and decreased aggregation of antibodies than IgG (Lee et al., 2021; Da Silva and Tambourgi, 2010). IgY production, in addition to being a noninvasive method in terms of animal welfare, also has a lower cost in large-scale production (Pereira et al., 2019). Given that there are about 100 mg of IgY in each egg yolk, then one hen can produce about 325 eggs with about 32 g of IgY annually (Da Silva and Tambourgi, 2010). This is 5 times higher in specific pathogen free birds (500 mg vs. 100 mg) (Lee et al., 2021). Therefore, due to the properties of IgY, it can have a wide range of applications in prophylaxis and treatment in human and veterinary medicine (Leiva et al., 2020), for examples, periodontitis, gingivitis, dental caries, gastric ulcer, enteric infectious diseases, dysbiosis, toxins, nutritional and metabolic diseases, chronic diseases, and neoplasms in human medicine and also calf diarrhea, bovine mastitis, infectious and respiratory diseases of birds, shrimp white spot virus and diarrhea of pets in the veterinary field (Kumaran and Citarasu, 2016; Amro et al., 2018; Budama-Kilinc et al., 2018; Lanzarini et al., 2018; Criste et al., 2019; Constantin et al., 2020; Leiva et al., 2020; Hakalehto et al., 2021; Shen et al., 2021). From 2010 to 2021, more than 400 patents have been registered, 56% of which are related to therapeutic use, 33% to diagnostic and 11% to IgY purification methods (Patentscope). The first clinical trial on IgY (Identifier: NCT01455675) began in 2011 to study the prevention of *Pseudomonas aeruginosa* infections in patients with cystic fibrosis. To date, about 14 clinical trials have been recorded in FDA (www.ClinicalTrials.gov), and one in particular has been commercialized (IgY Max, Identifier: NCT02972463). Also, with the outbreak of coronavirus, clinical trial on IgY as anti-SARS-CoV-2 drug (Identifier: NCT04567810) is in phase I study (www.ClinicalTrials.gov). There are at least 9 IgY veterinary drugs licensed by Chinese veterinary drug authority (http://www.ivdc.org.cn/), and one IgY human drug in clinical trial according to the disclosure of Sino FDA (http://www.chictr.org.cn/). In the research area (primary or secondary antibodies and diagnostic kits), more than 40 companies have produced IgY products, but their share of the total market of antibodies is about 0.24% (www.benchsci.com). The current number of commercial IgY products in the market is low, but observations show that this technology is being development (Leiva et al., 2020; Zhang et al., 2021a). So, it is now a right time to analysis the technology retrospectively and prospectively. Hence, there is a fact that scientometric studies are needed to gain a deeper understanding of the research and studies process for the commercialization of IgY technology. Scientometric analysis can be used in quantitative evaluation and analysis on all aspects of the literature in different development stages by computational approaches (Mooghali et al., 2012). In particular, measurement and analyze of the citation data, research community, technology, and innovation, understanding of scientific citations and mapping scientific fields can facilitate the exploration of the field at issue (Rajendran et al., 2011; Mooghali et al., 2012). Until now, no scientometric research has been directed toward IgY technology. In view of this, we conducted a scientometric analysis of studies on IgY technology research published from 1980 to 2021. The aims of this study were to identify the major players and their cooperation networks, including countries, academic groups, and individuals; to analyze research status and hotspots, especially the key study findings in this field; to summarize the main research themes and clusters, discuss the potentially valuable research directions, including drug delivery systems (Lee et al., 2021; Zhang et al., 2021a) and the broad prospect of clinical application (Leiva et al., 2020).

MATERIALS AND METHODS

Data Collection and Search Strategy

Web of Science (**WoS**, Clarivate Analytics) is the authoritative database for bibliometric research owning to the existence of the Journal Citation Reports (**JCR**) and the large amount of citation data. CiteSpace software is developed based on the WoS database, which ensures that the use of WoS data will be better adapted to the diverse functions of the CiteSpace (Boyack et al., 2005; Leeuwen, 2006). Web of Science Core Collection (**WoSCC**), as the premier resource on the WoS database, was used to collect information on IgY-related literature and the searched time span 1980-2021 (Data as of 25 Oct. 2021). Combining all keywords related to the topic (including synonyms and alternative terms) with Boolean operators before starting the search for documents is an effective search strategy (Timmins and McCabe, 2005). The search terms and retrieval strategies were developed as follows: TI (Tittle) = (IgY OR Immunoglobulin Y OR egg yolk antibodies) OR AK (Author Keywords) = (IgY OR Immunoglobulin Y OR egg yolk antibodies); the language type = English; and the document type = articles or reviews or book or book chapter. All data obtained were saved in text format, named "download_xx.txt", and imported into software for analysis.

Statistical Analysis

Microsoft Office Excel (v.2016) was conducted for literature quantity analysis, and the CiteSpace 5.8. R1 was used for scientometric analysis, including country, institution, author, journal, literature co-citation and keyword analysis. The software parameters were set as follows: the time partition was 1980-2021, the time slice (year per slice) was "1", and term sources were selected as "title", "abstract", "author keywords" and "keywords plus"; node types included country, author, institution, keyword and reference; Top N value was set to 50, and the overall graph was simplified by using pathfinder, pruning sliced network and pruning the merged network. The size of nodes and their font in the graph indicated their occurrence times, and the thickness of the connecting line between 2 nodes represented their closeness of connection; the thickness of the node chronology was proportional to the frequency of literature occurrence, and the cold tone of blue to the warm tone of red in the outer circle indicated the change of time from early to recent (Chen, 2006).

RESULTS

Quantity Analysis and Global Distribution of the Literature

A total of 1029 IgY-related papers were obtained on the database Web of Science, including 981 journal articles and 48 reviews. The visualization of this literature showed an increasing trend in the number of IgY-related publications over the 4 decades from 1980 to 2021, with a corresponding increase in the frequency of citations per year. The number of publications and citation frequencies were low for more than 20 yr before 2007, but from 2008 onward, the relevant literature and citation frequencies spiked, eventually maintaining a high level that fluctuated up and down. Moreover, the highest number of publications and frequency of citations was in 2019 with 70 and 1,450, followed by 59 and 1,420 in 2020, and both indicators may be the same in 2021 as in 2020 (Figure 1). In terms of global distribution, research on IgY has been concentrated in Asia, the Americas (including North and South America) and Europe. In terms of population proportion, African countries contribute the least to IgY research, mainly from Egypt and South Africa (Figure 2). Regarding to IgY related books and chapters, from 2000 to 2021, the results show that the number of books published on IgY was low, but the number of book chapters in relation to IgY was relatively higher (Table 1). In 2001, the world's first IgY laboratory manual was published in Germany which standardized the laboratory practices of IgY technology (Schade et al., 2001). In 2011, a first IgY monograph in Chinese was published (Xiaoying Zhang 2011). Then, in 2021, the second IgY monograph published by Dr. Zhang et al in springer which is now known as the latest and most complete reference (Zhang et al., 2021a). Most IgY chapters have been published in different books

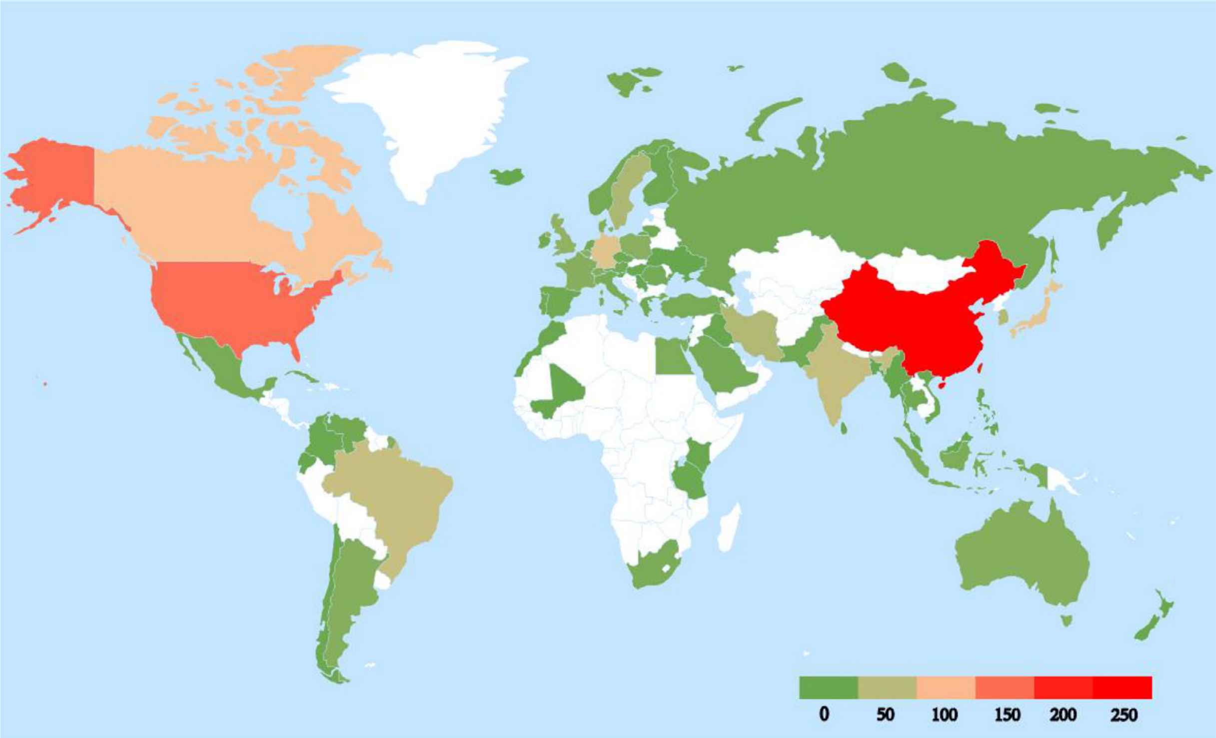

Figure 2. Global distribution of IgY-related studies.

related to egg properties include nutritional or functional foods and bioactive compounds.

Country Analysis

In total, 69 countries have done studies on IgY, establishing 197 links between each other (i.e., connecting lines between 2 nodes). Among these 69 countries, China (including Taiwan and Hong Kong, 220), the United States (148), Canada (91), Japan (76), and Germany (72) had the highest number of publications, accounting for 21.38%, 14.38%, 8.84%, 7.39% and 7.00%, respectively. However, in terms of research importance, the top 5 countries were the

Table 1. IgY-related books and chapters publication.

IgY Books

	Book title	Publisher	Authors (Year)	ISBN
1	IgY-Technology: production and application of egg yolk antibodies	Springer	XY. Zhang et al. (2021)	9783030-726867
2	Egg Yolk antibody technology Note: (in Chinese)	China Science Press	XY. Zhang et al. (2011)	9787030-309020
3	Chicken egg yolk antibodies, production and application: IgY-technology	Springer	R. Schade et al. (2001)	9783662-044902

IgY chapters

	Book title (Chapter number)	Publisher	Authors (Year)	ISBN
1	Functional foods and biotechnology (14)	CRC Press	R. Chakrabart (2020)	9781003-003793
2	Eggs as functional foods and nutraceuticals for human health (16)	J. Wu	J. Wu (2019)	9781788-013833
3	Current laboratory Techniques in rabies diagnosis, research and prevention, Vol 2 (24)	Academic Press	C. Rupprecht et al. (2015)	9780128019191
4	Avian immunology (6)	Academic Press	F. Davison et al. (2013)	9780123-969651
5	Improving the safety and quality of eggs and egg products (17)	Wood-head	M. Bain et al. (2011)	9780857-090720
6	Therapeutic monoclonal antibodies: from bench to clinic (28)	Wiley	ZQ. An (2009)	9780470-117910
7	Bioactive egg compounds (5)	Springer	R. Huopalahti et al. (2007)	9783540-378839
8	Egg bioscience and biotechnology (5)	WILEY	Y. Mine (2007)	9780470-039984
9	Egg nutrition and biotechnology (part V; 22 to 28)	CABI	J.S. Sim et al. (1999)	9780851-993300
10	Hen eggs: their basic and applied science (11)	CRC Press	T. Yamamoto (1997)	9780203-752081

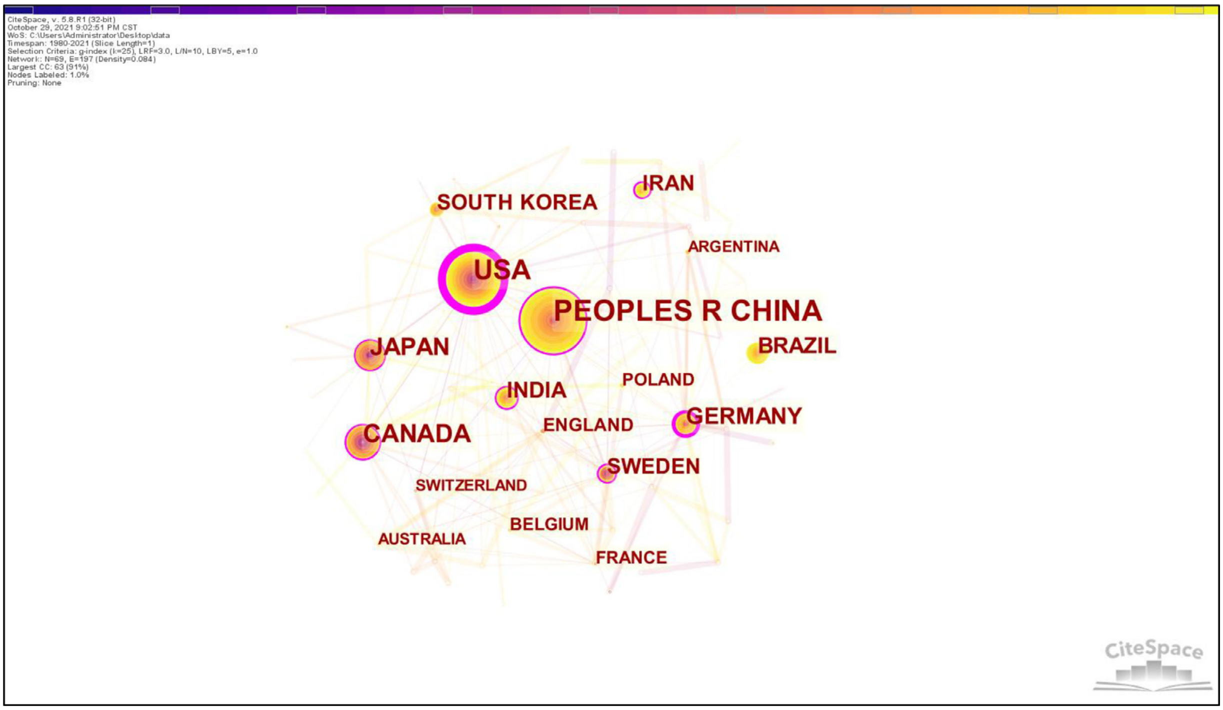

Figure 3. Collaborating countries for IgY-related research. Nodes in the network represent countries. Node size: the amount of publications of the country; node color: the time of publication of the literature, from the center of the node to all around, color from green to yellow, time from 1980 to 2021; purple circle: institutional centrality (intermediary centrality of the node where the purple circle appears ≥ 0.1); line: the diameter represents the degree of international cooperation, color from purple to yellow represents the time from 1980 to 2021.

United States, Germany, Canada, China, and India. In addition, compared with European and American countries, the research on IgY in China, India and Brazil was mainly concentrated in the past 10 yr (Figure 3, Table 2).

Journal and Discipline Analysis

A total of 457 journals published articles or reviews in this field. The top 10 journals by publication volume published nearly 20% (123 articles) of the articles in the top 10 journals. Among the top 10 journals, *Poultry Science* (impact factor or IF 2020, 3.352), *Journal of Immunological Methods* (IF 2020, 2.303) and *Food and Agricultural Immunology* (IF 2020, 3.101) contributed considerably to the number of publications, with 37, 35 and 18 publications, respectively. As of October 2021, the total number of publications corresponding to the 3 journals was 79,878, 4,998, and 2,432, respectively (Table 3). On the other hand, a total of 915 cited journals were present in IgY study and these journals formed 4531 connections. The top ten journals were cited more

Table 2. Top 10 countries in terms of number of publications.

Ranking	Country	Publications	Centrality※	Percentage (%)
1	China	220	0.13	21.38
2	USA	148	0.72	14.38
3	Canada	91	0.15	8.84
4	Japan	76	0.11	7.39
5	Germany	72	0.39	7.00
6	Brazil	57	0	5.54
7	India	56	0.11	5.44
8	South Korea	46	0.06	4.47
9	Iran	44	0.11	4.28
10	Sweden	41	0.1	3.98

Notes: ※Centrality is an indicator of the importance of a node in the network, and a larger centrality value means that the node is more important in the whole network.

Table 3. Top 10 journals in terms of number of publications.

Ranking	Journals	IgY-related publications	Percentage$^{\Delta}$(%)	Total publications	Publication year
1	Poultry Science	37	3.60	79,878	1921
2	Journal of Immunological Methods	35	3.40	4,998	1971
3	Food and Agricultural Immunology	18	1.75	2,432	1989
4	Journal of Agricultural and Food Chemistry	16	1.55	103,707	1953
5	Avian Diseases	14	1.36	5,200	1957
6	Developmental and Comparative Immunology	14	1.36	10,980	1977
7	Veterinary Immunology and Immunopathology	14	1.36	4,085	1979
8	Toxicon	13	1.26	15,060	1962
9	Journal of Food Science	12	1.17	29,951	1961
10	Vaccine	12	1.17	40,599	1983

Notes: $^{\Delta}$ indicates the percentage of IgY-related articles in the journal to the total IgY publications (1029).

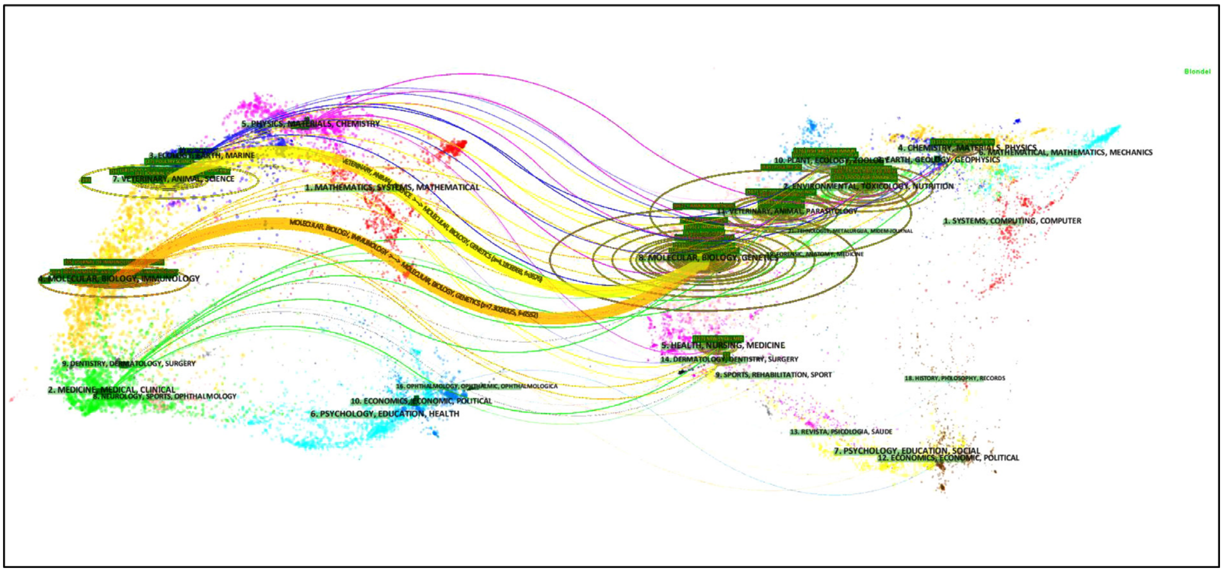

Figure 4. The dual map overlay of journals. Each point in the graph represents a journal, with different colors to symbolize different disciplines. This map can be divided into 2 parts, the left side shows the citing journals in this field and the right side shows the cited journals in this field. The wavy links to both sides mean that publications in journals on the left cite publications in journals on the other side.

than 200 times. Among these ten journals, *Nature* had the highest impact factor (IF 2020, 49.962) and the *Journal of Immunological Methods* had the highest number of citations (458), followed by *Poultry Science* (374), and *Journal of Immunology* (263) (Table 4). In addition, the dual map overlay of journals showed that the most contributed journals were from molecular, biology, and immunology fields and veterinary, animal, and science fields, and these journals mostly cited journals from molecular, biology, and genetics fields (Figure 4).

Institution Analysis

A total of 639 institutions have participated in IgY research, with 501 collaborations established. Among all the research institutions, Dalian University of Technology, Alberta University, Northwest Agriculture and Forestry University, China Agricultural University and Huazhong Agricultural University published the most articles, with 23, 20, 16, 13 and 12, respectively. In terms of research time, Alberta University's related research was concentrated around 1998, while more Chinese institutions were after 2000, such as Dalian University of Technology in 2005, China Agricultural University in 2009, and especially Northwest A&F University in 2014. In additional, inter-institutional cooperation is mainly dominated by Chinese research institutions, with Dalian University of Technology working closely with Dalian Medical University and the University of Manitoba, and Northwestern A&F University working closely with the Free University of Berlin, together forming a large network of research cooperation (Figure 5, Table 5).

Table 4. Top 10 active core journals on IgY study.

Ranking	Cited journals	Count	Year
1	Journal of Immunological Methods	458	1980
2	Poultry Science	374	1986
3	Journal of Immunology	263	1980
4	Veterinary Immunology and Immunopathology	260	1996
5	Journal of Biological Chemistry	251	1980
6	Infection and Immunity	250	1984
7	Journal of Food Science	243	1988
8	Nature	238	1980
9	Vaccine	232	1996
10	Proceedings of the National Academy of Sciences of the United States of America	224	1980

Author Analysis

A total of 987 researchers are involved in IgY research, forming a collaborative network with 1,323 collaborations. Among them, Dr. Xiaoying Zhang had the highest number of publications with 21, followed by A Larsson (12), Xiaoyu Li (11), Yongping Xu (11), and Atsushi Mural (10). In addition, the teams with the most and closest collaborators are represented by Xiaoyu Li, Yongping Xu and Agnieszka Lupickaslowik (Figure 6, Table 5).

Reference Co-Cited Analysis

The total 1,029 IgY publications have 1,345 co-citations, resulting in 3,462 links. The 6 most cited articles were all review, focusing on the use of IgY antibodies in immunoassays, veterinary medicine, and human medicine. The most cited study was published by Vega et al. (2011) in *Veterinary Immunology and Immunopathology*, entitled "Egg yolk IgY: protection against rotavirus-induced diarrhea and modulation of systemic and mucosal antibody responses in newborn calves". In addition to the above 6 review articles, the top ten cited papers are Abbas AT (2019), Pauly (2009), Zhen YH

Figure 5. Collaborating institutions for IgY-related research. Nodes in the network represent institutions. Font size: the amount of publications of the institution; line: the diameter represents the degree of inter-institutional cooperation, color from purple to yellow represents the time from 1980 to 2021.

(2008), with 19, 17, 17 times respectively (Figure 7). On the other hand, the top 20 cited articles were mainly published after 2007, with 16 articles, accounting for 80% (Table 6). Cluster analysis revealed that these literatures were clustered into 187 categories, with the largest category being venom neutralization with 125 literatures and a silhouette of 0.935. In this category, Middle East Respiratory Syndrome Coronavirus (**MERS-CoV**) and Coronavirus Disease 2019 (COVID-19) were presented as 2 candidate terms. The subsequent categories were norovirus and avidin-biotinylated IgY with 117 and 79 publications, respectively, with silhouette values of 0.904 and 0.944 (Table 7). Figure 8 showed the timeline of significant cited references under different clusters. Influenza a, neuropeptides and bothrops alternatus were previously studied based on IgY antibodies, but after 2000, there was no literature on this subject and attention decreased. In contrast, the main topics being studied in recent years are venom neutralization (#0), norovirus (#1), quail (#3), teleost (#6) and ELISA (#12), and accordingly, the references under these clusters are mainly published in the last decade (Figure 8).

Table 5. Top 10 institutions and authors in terms of number of publications.

R	I	P1	Y1	A	P2	Y2
1	Dalian Univ Technol	23	2005	Xiaoying Zhang	21	2012
2	Univ Alberta	20	1998	A Larsson	12	1990
3	Northwest A&F Univ	16	2014	Xiaoyu Li	11	2008
4	China Agr Univ	13	2009	Yongping Xu	11	2008
5	Huazhong Agr Univ	12	2009	Atsushi Murai	10	2008
6	Dalian Med Univ	10	2008	H Hatta	10	1990
7	Nagoya Univ	10	2008	Liji Jin	8	2008
8	Univ Guelph	10	1998	Yuhong Zhen	8	2008
9	Natl Taiwan Univ	9	1999	Ruediger Schade	8	2011
10	Chinese Acad Sci	9	2001	Naiyana Gujral	8	2012

Notes: R, ranking; I, Institutions; P1, institutional publications; Y1, average year of publication for the institutions; A, authors; P2, author publications; Y2, average year of publication for the authors.

Keyword Study

A total of 793 keywords were extracted from the titles, abstracts, and author keywords of 1,029 papers, and 1,862 links were created. Visualizations network map of keyword co-occurrence showed that the most frequently occurring keywords in articles published between 1980 and 2021 were IgY (365), antibody (219), immunoglobulin (182), chicken (163), purification (154), and egg yolk (148), which are highly correlated and are all related to the IgY antibody's own properties. In addition to the above, keywords related to IgY applications also appear many times, such as infection (109), ELISA (106), passive immunization (78), and *Escherichia coli* (75) (Figure 9, Table 8). Based on the keyword co-occurrence mapping, the Burstness label was adjusted by setting the parameters $\gamma = 0.5$ and minimum duration = 2, and 112 burst items were generated. Of the 112 keywords or phrases with the strongest citation bursts, the earliest and longest-lasting occurrence was antigen, followed by immunized hen and dental caries (Figure 10). A total of 18 keywords have been highlighted in the last few years and

Figure 6. Inter-author collaboration in IgY-related research. Nodes in the network represent Authors. Font size: number of publications; node color: average time to publication, color from purple to yellow, time from 1980 to 2021; line: the diameter represents the degree of inter-author cooperation, color from purple to yellow represents the time from 1980 to 2021.

continue to be highlighted until now. The top 5 keywords with the highest intensity are IgY antibody, immunotherapy, chicken IgY, immunoglobulin IgY and therapy, which are consistent with a significant increase in the number of articles published from 2017 onwards. In addition, circulating antigen, biofilm and nanoparticle have seen a significant increase in attention in IgY-related studies in the last 2 yr (Figure 10).

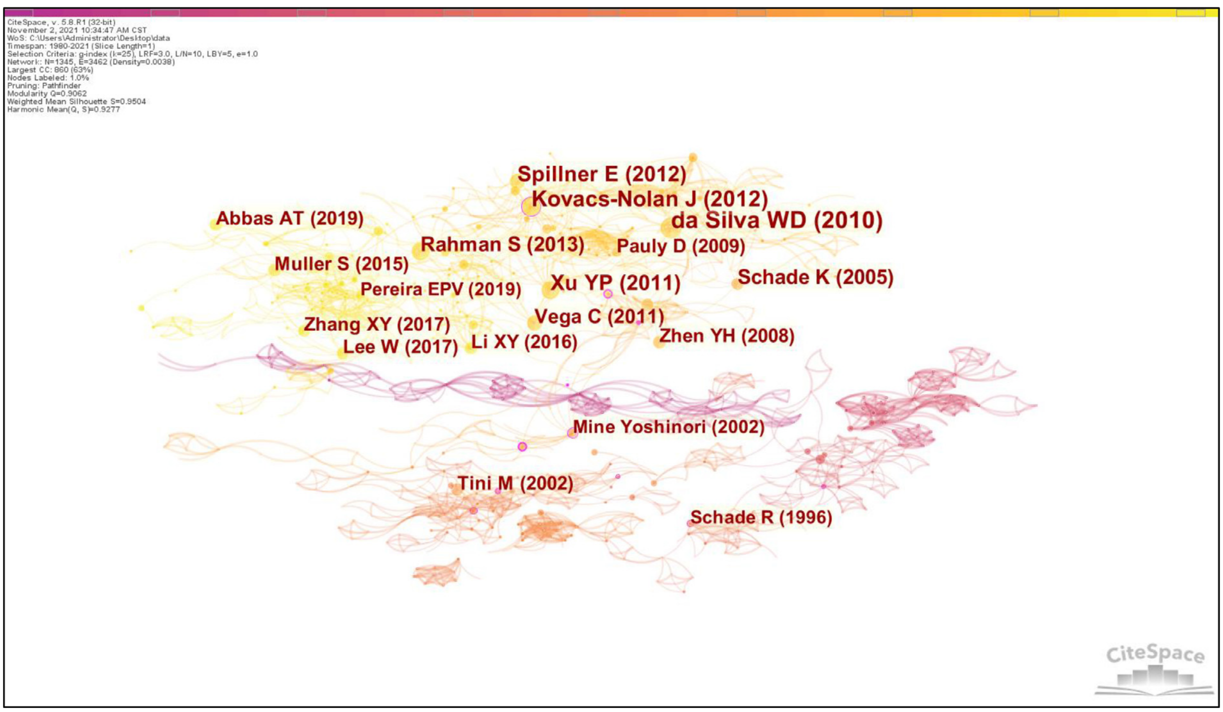

Figure 7. Co-citation references for IgY-related research. Nodes in the network represent Co-citation references. Node size: number of citations; line diameter: literature association strength; line and node colors: node color: the time of publication of the literature, color from purple to yellow, time from 1980 to 2021.

Table 6. The top 20 co-cited references.

Ranking	Counts	Centrality	Cited documents
1	38	0.01	da Silva WD, 2010, DOI 10.1016/j.vetimm.2009.12.011
2	31	0.15	Kovacs-Nolan J, 2012, DOI 10.1146/annurev-food-022811-101137
3	26	0.01	Spillner E, 2012, DOI 10.1016/j.biologicals.2012.05.003
4	26	0.28	Xu YP, 2011, DOI 10.1016/j.biotechadv.2011.07.003
5	25	0.08	Rahman S, 2013, DOI 10.4161/hv.23383
6	23	0	Schade K, 2005, DOI 10.1177/026119290503300208
7	22	0.25	Vega C, 2011, DOI 10.1016/j.vetimm.2011.05.003
8	19	0.01	Abbas AT, 2019, DOI 10.1080/21645515.2018.1514224
9	17	0.08	Pauly D, 2009, DOI 10.3382/ps.2008-00323
10	17	0	Zhen YH, 2008, DOI 10.1016/j.vetmic.2007.12.014
11	17	0	Tini M, 2002, DOI 10.1016/S1095-6433(01)00508-6
12	16	0	Lee W, 2017, DOI 10.1016/j.jim.2017.05.001
13	16	0	Zhang XY, 2017, DOI 10.1111/brv.12325
14	16	0.04	Li XY, 2016, DOI 10.1016/j.fsi.2015.11.024
15	16	0.04	Muller S, 2015, DOI 10.1186/s12937-015-0067-3
16	15	0	Pereira EPV, 2019, DOI 10.1016/j.intimp.2019.05.015
17	15	0.01	Mine Yoshinori, 2002, DOI 10.1089/10966200260398198
18	15	0.04	Schade R, 1996
19	14	0.01	Thomsen K, 2016, DOI 10.1080/21645515.2016.1145848
20	14	0.03	Li XY, 2015, DOI 10.1186/s40104-015-0038-8

DISCUSSION

In the last 2 decades, numerous studies on IgY technology for the purposes of diagnosis, prophylactic or treatment have been published (Figure 1). Therefore, a deeper understanding of the research and studies process on IgY is needed. We conducted an in-depth scientometric analysis of literature on IgY using a computational tool to explore the trends in publications on IgY technology. To our knowledge, this is the first scientometric study on IgY technology to assess research efforts related to the process on the quantity of articles published in this field. We examined the IgY technology from multiple perspectives including analysis of the literature quantity, country, institution, author, co-citation references and keywords co-occurrence network (Mooghali et al., 2012; Rajendran et al., 2011). Based on the WoS database, and the analysis of 1029 IgY-related articles since 1980 and IgY related books or chapters, we found that research on IgY technology had been increased significantly especially after 2007 and mainly focused on the following 2 sections: firstly, technical development, include the understanding of IgY molecule, production, extraction and purification; and secondly, drug development, include clinical application of IgY products, companies, regulations and product approval (Lee et al., 2021). In 1996, with the discussion of animal welfare by the ECVAM and the production of antibodies in mammals as an invasive method, the production of IgY in egg as a noninvasive method, with a lower cost in large-scale production became very prominent (Schade et al., 1996). Since then, the number of articles, books or chapters published on the production of IgY in chicken has increased. At the same time, the number of articles on methods of extraction and purifying IgY from eggs expanded (Nilsson et al., 2012; Bizanov, 2017). The number of articles, patents and companies working on diagnostic products also increased (Lee et al., 2021). IgY technology attracted an increasing number of researchers owning to IgY's unique properties, including lack of binding and activation of the Fc gamma receptors (FcγRs), no reactogenicity and greater phylogenetic distance which has led to an increase in the number of publications in the prophylactic or treatment of some animal and human diseases

Table 7. Clustering results of cited documents.

Cluster ID	Cluster name	Size	Silhouette	Mean(Year)	Label (LLR)
0	Venom neutralization	125	0.935	2016	Venom neutralization; burn; mers-cov; pseudomonas aeruginosa; covid-19
1	Norovirus	117	0.904	2010	Norovirus; rotavirus; egg yolk antibody (igy); passive immunization; egg yolk antibody
2	Avidin-biotinylated IgY	79	0.944	1999	Avidin-biotinylated IgY; helicobacter pylori; immunization; pig igg; antibody library
3	Quail	74	0.972	2008	Quail; evolution; fc receptors; igy transport; antibody evolution
4	Escherichia coli o78:k80	74	0.919	2004	Escherichia coli o78:k80; pla; egg yolk immunoglobulin (igy); feed additive; venom
5	Soluble proteins	58	0.93	1990	Soluble proteins; ethanol precipitation; pig; comparison; postweaning diarrhea
6	Teleost	53	0.966	2014	Teleost; vibrio parahaemolyticus; vibrio harveyi; anti-igy; immunoglobulin y
7	Influenza a	51	0.996	1982	Influenza a; bothrops alternatus; immunoglobulin y (igy); chicken antibodies (igy); immunoassay
8	Neuropeptide	48	0.981	1988	Neuropeptide; von willebrand factor; yolk immunoglobulins; alternative method; flow cytometry
9	Chicken egg yolk antibodies	34	0.981	1996	Chicken egg yolk antibodies; lipopeptide; adjuvant; freunds adjuvant; immunoglobulin y (igy)
10	Isolation	27	0.933	1999	Isolation; stability; avian; pathogens; monoclonal antibody
11	Bothrops alternatus	20	1	1978	bothrops alternatus; influenza a; immunoglobulin y; chicken antibodies (igy); immunoassay
12	ELISA	18	0.975	2013	ELISA; rhein; western blotting; toxoplasma; lateral flow immunoassay

Notes: LLR, Log-likelihood ratio (an algorithm in the CiteSpace software that gives the best results in terms of uniqueness and coverage).

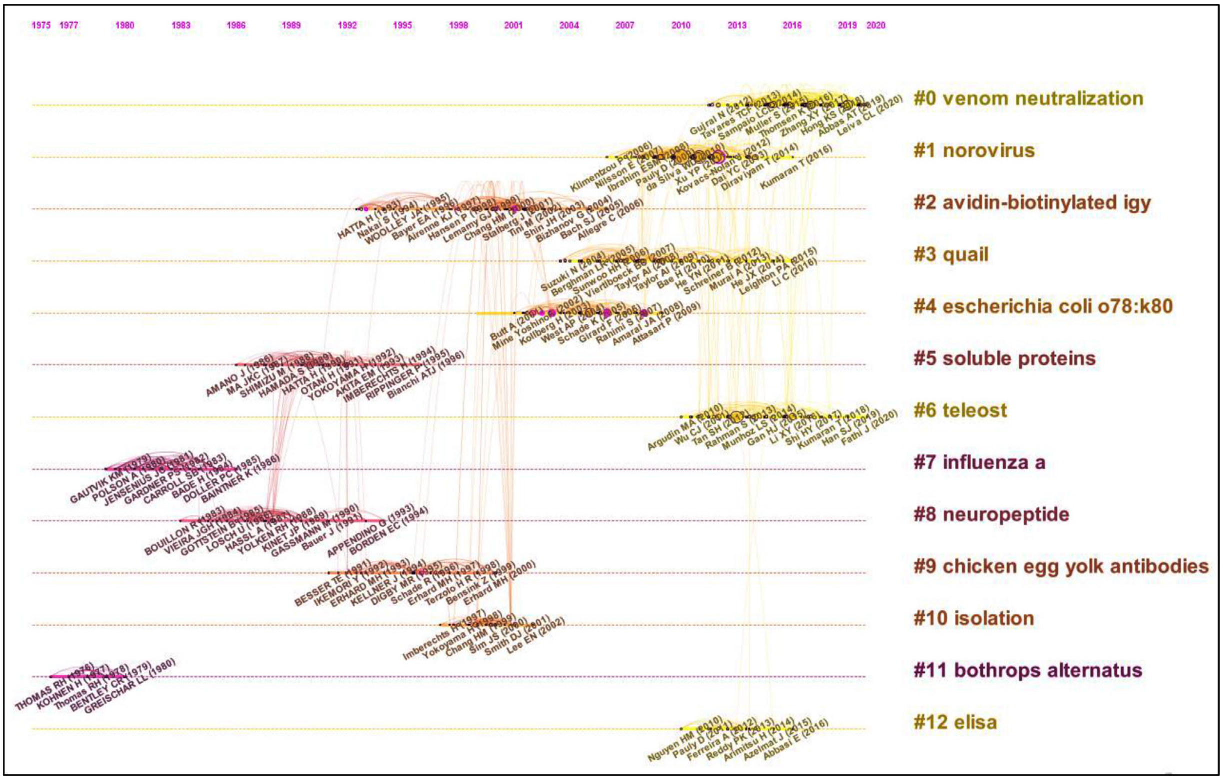

Figure 8. The timeline of significant cited references under different clusters. There are 13 clusters of references in total. In each cluster, the position of each node shows the time of publication of the literature, the size of the node shows the number of citations of this article, and the line between the nodes shows the co-citation relationship between 2 pieces of literature.

(Pizarro et al., 2017; Sudjarwo et al., 2017). Increased publications in the diagnostic or immunoassays branch can be described as less background noise or false positives and decreased aggregation of IgY than mammalian IgG (Lee et al., 2021). On the other hand, a significant increase in publications over time especially from 2007 onwards may be attributed to growing of the scientific journals for article publishing, growing funding volume

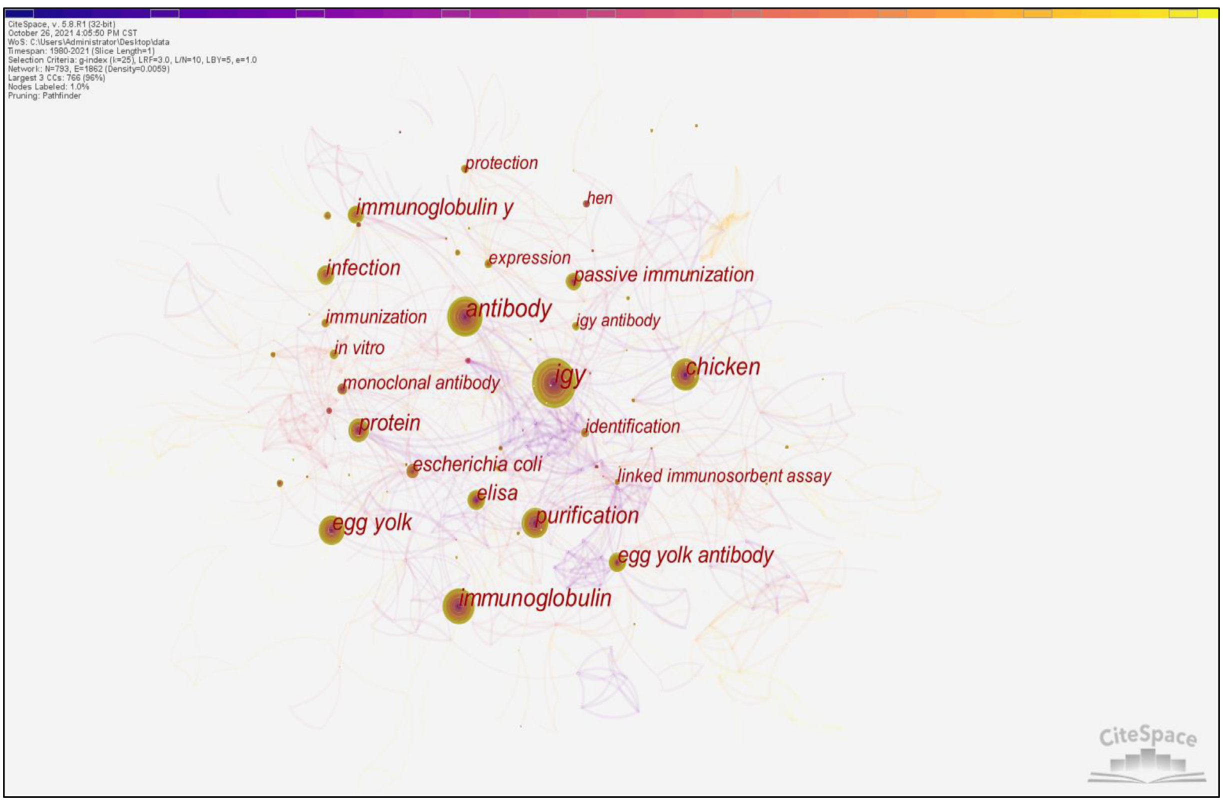

Figure 9. Visualizations network map of keyword co-occurrence. Nodes and font size represent the number of keyword occurrences.

Table 8. The top 20 keywords ranked by centrality and number of counts in IgY study.

Ranking	Counts	Centrality	Mean (year)	Keywords
1	365	0.08	1991	IgY
2	219	0.03	1990	Antibody
3	182	0.03	1991	Immunoglobulin
4	163	0.06	1991	Chicken
5	154	0.06	1991	Purification
6	148	0.03	1993	Egg yolk
7	130	0.04	1990	Protein
8	118	0.06	1993	Immunoglobulin Y
9	117	0.08	1991	Egg yolk antibody
10	109	0.02	1993	Infection
11	106	0.05	1991	ELISA
12	78	0.04	1997	Passive immunization
13	75	0.1	1993	Escherichia coli
14	57	0.11	1991	Monoclonal antibody
15	55	0.18	1992	Identification
16	55	0.01	2004	In vitro
17	54	0.04	1996	Immunization
18	50	0.08	1998	Expression
19	49	0.07	1993	Protection
20	46	0.12	1991	Linked immunosorbent assay

or companies' attention to IgY technology. As shown in Figure 1, after 2007, the number of publications increased significantly. Accordingly, the number of citations significantly increased, which indicates the quality index of articles also increased. The peak of this index was from 2014 and this trend has continued until 2021. The results showed that attention to IgY technology was increasing, and this trend was expected to continue in the future. The results of journal analysis showed that about 20% of IgY articles have been published in high-impact journals (from the JCR indicator), in which, researchers have been more interested in publishing articles in specialized journals, for example *Poultry Science* or *Journal of Immunological Methods.* IgY publications in more specialized journals indicates the greater accuracy of published articles related to this technology. In addition, the dual map overlay of these journals showed that IgY study was concentrated in the fields of molecular biology, immunology and veterinary medicine, and that advances in theory and technology in these disciplines could, to some extent, contribute to the development of IgY technology.

Based on the comparative scientometric analysis among these 69 countries, China, the United States, Canada, Japan and Germany were the main countries involved in IgY research, accounted for 59% of the publications. A special phenomenon also emerged, with China having a high number of total publications but less impact due to the short period of research (as shown in Table 2, the centrality values for China are smaller to that of the US and Germany). As for institutions analysis, more than 600 institutions have participated in IgY research from 1980 to 2021. As can be seen in Figure 5, the 6 institutions were the most prolific in the field of IgY technology, the greatest number of which existed in Asia, especially in China. The international connection of these institutions has been less than their internal communication, except for the 5 institutes from China, which had good international connections. Nevertheless, these data showed that there was very weak cooperation between institutions. Therefore, to help the better growth of this technology, it may be necessary to strengthen international exchanges or form an international community of IgY technology. The author's

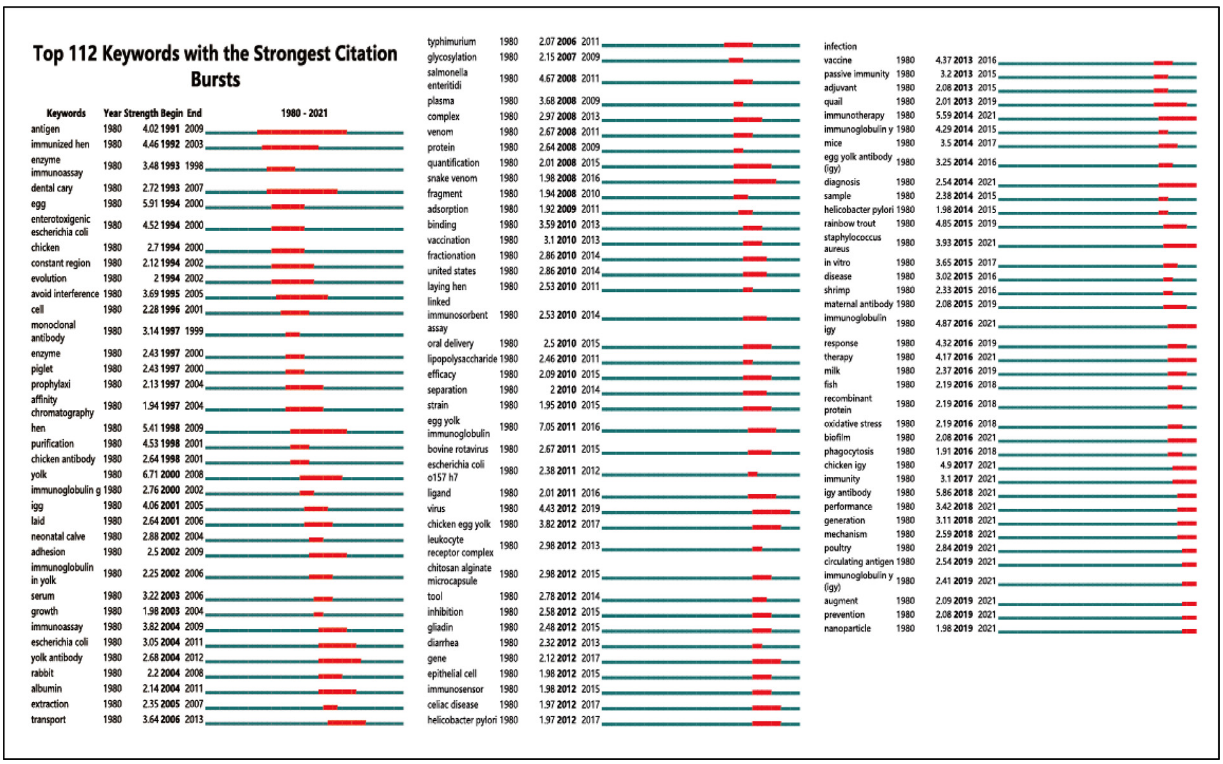

Figure 10. The top 112 keywords with the strongest citation bursts.

analysis in co-citation network map using CiteSpace indicated that more than 987 authors contributed to the IgY publications and had cooperate with 2 or more core authors. This data can provide information on influential research groups and collaboration between individual authors and/or institutions. Dr. Xiaoying Zhang was located at a central position of the author coauthorship network map as "core strength" in this field, with broad research focuses cover IgY molecule and evolution, IgY extraction and purification, IgY based immunoassay and therapy, perspective and popularization of IgY technology, and IgY book and standard editing, etc. Apart from these 6 authors mentioned in the results section, most authors had limited publications and networking, indicating that collaboration between authors, particularly between different research groups in this area has not been very common. Therefore, more attention should be paid to improving and increasing communications between authors and research teams. Citation counts are one of the most significant indicators of scientometric analysis and estimate the scientific relevance of the publications to quantify the relative impact of papers (Mooghali et al., 2012; Rajendran et al., 2011). Looking at the results of this section, as shown in Figure 7 and Table 6, out of 10 articles that had the most citations that were 7 review and 3 research articles. The main topics of the review articles were immunodiagnostic or immunotherapeutic, while the research articles were on the extraction and purification of IgY. Also, the highest rate of citation was in the period of 2010-2013. But high-quality articles have been published recently that have less citations. The reason could be that the citation rate in this section has been more influenced by the year since published than the quality of the article (Lee et al., 2021). The clustering results of the cited documents showed that "venom neutralization" and "norovirus" were the 2 largest clusters, which are closely associated with coronavirus and passive immunity (Table 7; Figure 8), indicating the great potential value of IgY antibodies in the context of a global pandemic of COVID-19 (Constantin et al., 2020). Keyword co-occurrence network analysis showed that IgY, antibody and immunoglobulin were the most frequent keywords (Figure 9), which indicates that these words are the core terms in IgY research, and our search strategy is comprehensive and credible. Keywords burstness reflected the dynamics of research priorities and hotspots during the IgY development (Figure 10). Antigen, immunized hen, and dental caries were the key phrases that researchers focused on the earliest and longest, indicating the importance of basic research for IgY technology and the fact that dental caries may be one of the first IgY applications to receive attention (Otake et al., 1991). In recent years, IgY research has focused on disease prevention and immunotherapy, both in veterinary and human medicine. Studies have shown that IgY antibodies can be used to treat disease by inhibiting the growth of bacterial biofilms that are responsible for certain diseases, such as *Porphyromonas gingivalis* and *Pseudomonas aeruginosa*, which cause periodontitis and cystic fibrosis, respectively (Li et al., 2020; Thomsen et al., 2021). Examples include biofilm and nanoparticles, indicating that this technology is well on its way to conducting clinical trials to commercial products (Pereira et al., 2019). In conclusion, scientometric analyzes have shown that research on IgY has evolved from the initial discovery and purification methods of antibodies to more extensive research on applications for disease control and health promotion, with commercial applications perhaps in the near future. On the other hand, some welcome change and development tendency in hen egg industry have been emerged in the recent years, including increasing comprehensive utilization of hen egg along with the development of comprehensive extraction and purification techniques, application of bioactive egg compounds in nonfood sectors (Zhang et al., 2021b), such tendency also promotes the application of IgY antibody.

CiteSpace is a Java-based application for detecting and visualizing possible trends and fundamental changes in scientific disciplines over time and is an effective and comprehensive tool for bibliometric analysis (Chen, 2006; Cobo et al., 2011). As far as IgY technology is concerned, the CiteSpace software-based scientometric analysis has helped to identify the development history and status of IgY studies, influential research individuals and groups, research frontiers and hot spots. However, this software may still have some limitations, the analyzed literatures are largely limited by the search source and the composite query used (Chen, 2017); it can only perform a co-citation analysis based on the referenced literature and cannot present the total number of citations of each literature. To better overcome such limitations, multiple databases and combined visualization techniques, such as citation context analysis and VantagePoint software, could be applied for a more in-depth analysis of a specialty area like IgY technology.

CONCLUSION

In summary, IgY technology has made significant progress in the last 2 decades and has proven that it can be applied for diagnostic, prophylactic, or treatment purposes. In this study, for the first time, the structure and the evolution trend of this knowledge over the time were performed using scientometric analyzes. As showed in the results, the ascending trend in the number of publications or citations indicates that this technology has attracted a great deal of interest from researchers, especially in the last 10 yr. Also, the number of research institutions in different countries and the scientific connections between them has increased. In addition, the development of laboratory methods and applying the other technologies to this field has led to more maturity of IgY technology toward commercialization.

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Notes: The article contains no dealings with human or animal subjects for any analysis.

DISCLOSURES

The authors declare that they have no competing interests.

SUPPLEMENTARY MATERIALS

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