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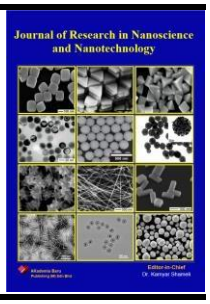

Nanogels as Drug Carrier in Cancer Treatment: A Bibliometric Overview of the Publication in Web of Science in year 2004-2021

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ABSTRACT

This is a bibliometric analysis study of nanogels in cancer treatment by studying the documents related to nanogels field. As cancer has been reported to have high amounts of cases, an efficient treatment is essential for all the tumour patients. Nanogels has the ability to transport the anticancer drug to the targeted site on the tumour microenvironment. A lot of studies have been done regarding the nanogels and nanotechnology which started to attract people in 1980s where United State initiated the lead in 2000. An analysis has been done in this paper by extracting data from WOS database and visualize through VOSviewer to study the collaboration network, topic of interest and impact of publications. Findings reveal that the collaboration work is strong between United State and China as both countries are successful in scientific knowledge technology. This study is expected to have an impact for future nanogel study in cancer treatment.

Keywords:
Nanogels, Drug carrier, Cancer treatment, Bibliometric analysis

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1. Introduction

Cancer can cause death and has been reported by World Human Organization (WHO) in 2020, nearly 10 million deaths cases cause by cancer[35]. The common cases of cancer with 2.26 million cases, 2.21 million cases, 1.93 million cases in breast cancer, lung cancer and colon and rectum cases respectively. The most common case that leads to death is lung with 1.80 million deaths reported. Cancer occurs when the abnormal cell grows uncontrollably which develop accumulation of cell due to lack of components to stop the cell from dividing. Thus, tumours are form that can damage the immune system and create additional changes which make the body unable to operate normally [16,17]. There are four main types of cancer divided

by doctors which are carcinomas, sarcomas, leukemias and lymphomas. World Cancer Research Fund [36] listed the global cancer data based on country. The cancer rate with the highest amounts of cases is Australia with 468 people per 100,000 people. Cancer treatment is essential to cure the cancer and the treatment includes radiation, chemotherapy and surgery. Chemotherapy is the major therapeutic procedure in cancer treatment through medication to destroy tumour cells [44] **.** Drug delivery system is applied to reach the tumour site and releasing drugs through drug carrier. Nanogels is the candidates for the best nanocarrier as it has high drug loading capacity and can be released to microenvironment tumour.

Nanogels is nanoparticles that composed of hydrogels that formed through physical cross-linked or chemical cross-linked. The structure of nanogels that could be protein-loaded, and the shell included carbohydrate residues that allowed for DNA complexation make it suitable as drug carriers. The unique features of nanogels are biocompatibility, excellent particle stability and variable particle size [26]. Instead of that nanogels can be designed to have an ability to response to stimuli such as pH and temperature. The responsive stimulus nanogels reacts to changes of microenvironment of tumour cells that slightly acidic compared to normal cells. The nanogels will reach the targeted site and released the loading drug through swelling and de-swelling of the nanogels network. Nanogels is chosen as an advanced drug delivery system (DDS) compared to other DDS as there are more advantages found in nanogels [6,9,33]. According to Stawicki [30], nanogels has capacity to include and distribute a wide range of medicines by immobilising them via covalent or non-covalent contacts and regulated the release of multi-drugs with the primary release mechanism being drug diffusion followed by polymeric matrix degradation. Thus, nanogels is considered as ideal drug carrier due to their high stability with good drug loading which can design in cancer treatment.

There are a lot of study of nanogels for cancer treatment and bibliometric studies are useful to examine patterns in a person's or field of study's research. Bibliometric studies can be performed on any sufficiently big publication list produced and released, for example, by a scientific institution [5]. There are two categories for bibliometric techniques which are performance analysis and science mapping. An analysis of nanomedicine by Bragazzi [2] found six centre of interest which are (i) molecular methods, (ii) molecular biology and nano-characterization, (iii) nano-diagnostics and nano-theranostics, (iiii) clinical application of nano-oncology, nano immunology and nano vaccinology, (iv) clinical application of nano-oncology and nano-infectiology and (v) nanodrugs. The nanotechnology shown a lot of interest since 1990 and shown an increment throughout the years [40].It can be seen that nanotechnology and related field is a hot topic and attract researchers from any field to develop research regarding to nanotechnology. Nanogels is one of nanotechnology branch and bibliometric investigations is applied to analyse the interest of study of the researchers from all around the world. Technological advancements have created new visual analytic tools that may be used in nanogels study to analyse research trends, emerging themes, and collaborative networks [7]**.**

By using bibliometric visualization analyses, the purpose of this paper can be achieved. This paper is to analyse and determine the collaboration network, topic of interest and impact of publications in nanogels study. To the best of our ability, there is a lack of information regarding research patterns and publication in the study of nanogels in cancer treatment. The analysis of co-authorship, co-citation and co-occurrence are conducted to determine the collaborative network and give an in-depth knowledge of the evolution of this study field.

2. Materials and Methods

This bibliometric analysis paper data used VOSviewer (version 1.6.16) to analyse and visualize the paper patterns in nanogel for cancer treatment field. The WOS collection database was examined for nanogels-related worldwide literature published between 2004 and 2021. The search keywords used to find the most closely related publication are "Nanogel" and "Anticancer" or "Nanogel" and "Cancer treatment" which was used in the topic. The WOS database provide detail information regarding to the related documents included abstract, title, publication date, the publication source title and number of citations which can be used for the analysis. Languages and documents type were not restricted throughout the retrieval procedure. The details regarding to related documents consists of publication year and citations, country, document types, research area, WOS categories, publication (source title), organizations and author were exported into CSV format. The date of retrieval was on 3rd of August 2021. The VOSviewer was used to analyse the data through visualization in term of Co-occurrence, Co-authorship, Bibliographic coupling and Co-citations.

M.M. Kessler came up with the term "bibliographic coupling" in 1963 where two publications have similar references and the strength of the bibliographic coupling increases when there are many references in common [31]. In other terms, bibliographic coupling refers to the overlap in published reference lists. Co-citation is the opposite of bibliographic coupling where two publications are cited by third publication. The visualization of bibliographic coupling document, co-citation of cited reference and cited source were determined in this paper. The summary of methodology used in this paper is visualize through **Figure 1.**

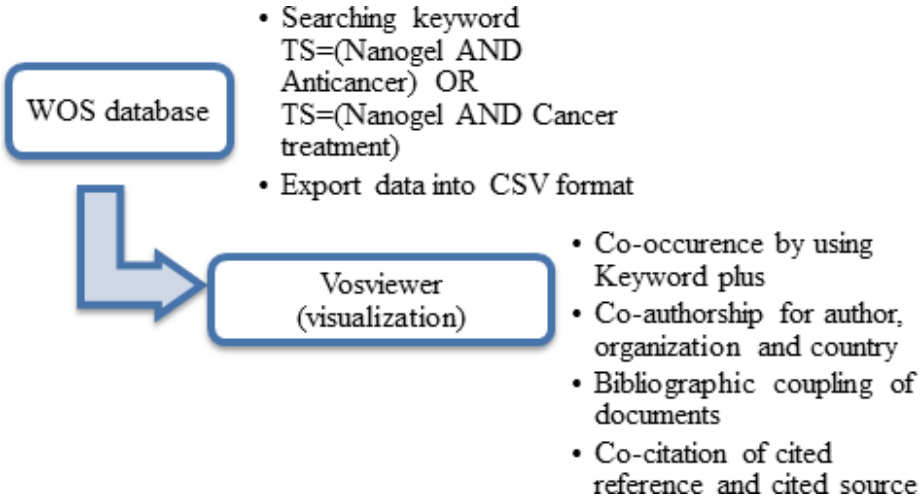


Figure 1 : Methodology summary for the data collection.

3. Results and Discussion]

3.1. Literature Publication Growth

The total of paper publication from 2004 until 2021 are 362 papers with average 21 papers were published for each year. The publication of papers in nanogel field shows an increment and upward trends. There were few studies in nanogels from 2004 until 2009 with average 2 papers per year which shows lack of interest from researchers to study the nanogels in cancer treatment. **Figure 2** shows the graph of publication and citation per year from 2004

until 2021. The line indicates the citation per year while the bar column shows the publication per year. From the graph it is clear that both publication and citation showing an upward trend throughout the year. The maximum publication was recorded in 2019, with a total of 54 (12.98 %) documents, while the lowest productivity was noticed in 2004, with a total output of 1 document (0.28%). Due to the recent rise in studies, the number of citations per document was highest for papers published in 2020 with 1,989 citations and lowest for those published in 2004 with 1 citation. In 2020 and 2021, the publications and citations decrease and this is due to pandemic Covid-19 which started at the end of 2019 that affected the academia and researchers. According to Radecki [27], more external fund is going towards COVID-19 research, and less information about what is going on with non-COVID-19 related research.

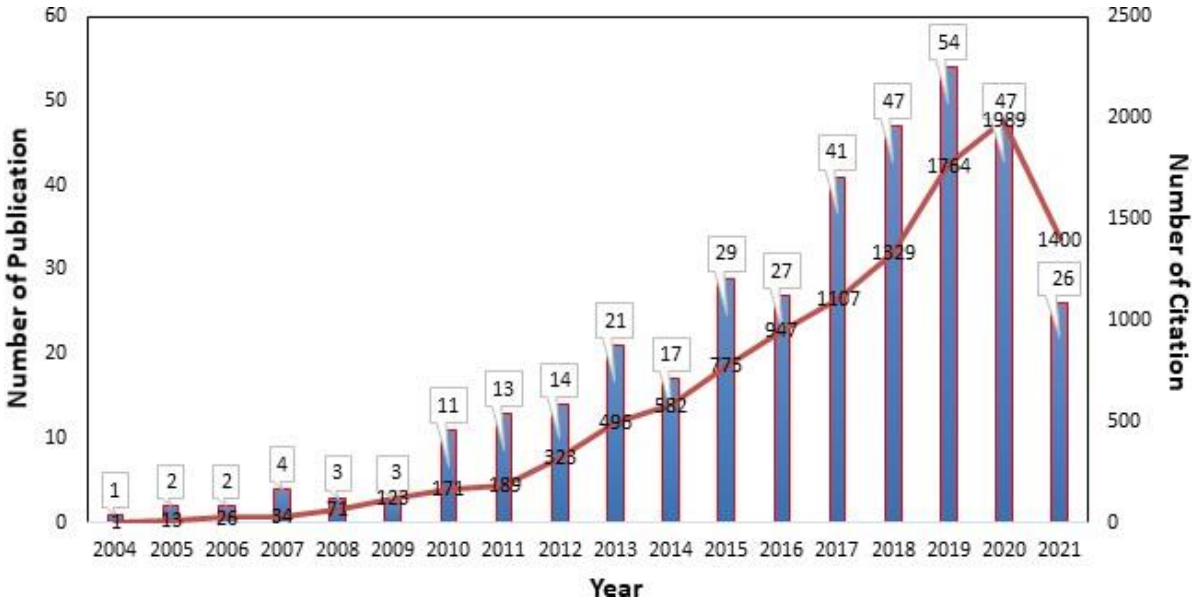


Figure 2 : Number of publication and citation per year.

Researchers from different countries contributed to the publication of documents and from all the publications, there are 41.44% ,19.06% ,11.60%, 9.67%, 7.18%,4.70%, 3.04%, and 2.76% from China, USA, Iran, India, South Korea, Japan, Germany and Italy respectively. The number of publications from China has increased dramatically in all disciplines, including nanogels. The top publications countries mostly come from Asia region as the number of researchers has expanded significantly in recent years. **Figure 3** shows the map graph and from the top 8 countries listed, there are 5 countries from Asia which are China, Iran, India, South Korea, and Japan.

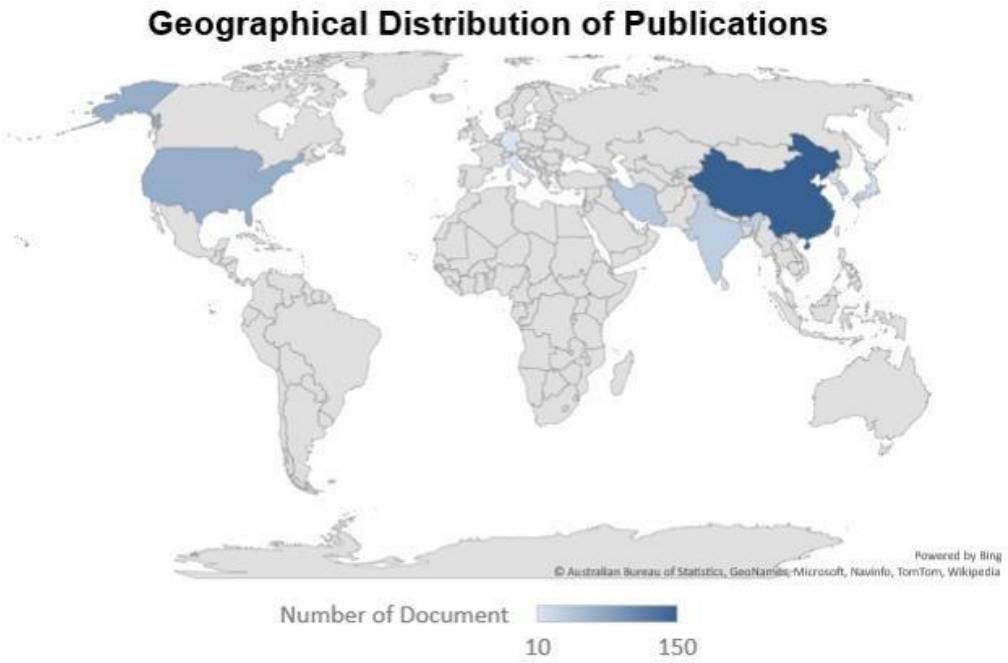


Figure 3: Publication per country.

A total of 362 documents were published, the majority of documents are in article form with 89.50%. The growth of article shows the knowledge of nanogels in cancer treatment increases and initiate new knowledge and problem solving in this field. By using the article information, the awareness of nanogels usage in cancer treatment increases in the public and can disprove any misunderstanding with proven research. Review articles were the second most prevalent form of paper, accounting for 7.74% of all documents. The details regarding to type of documents are shown in **Figure 4**. All of the documents were published 100% in English based on the data obtained from Web of Science. The documents that published in English can reach more people and the documents can be globally recognized.

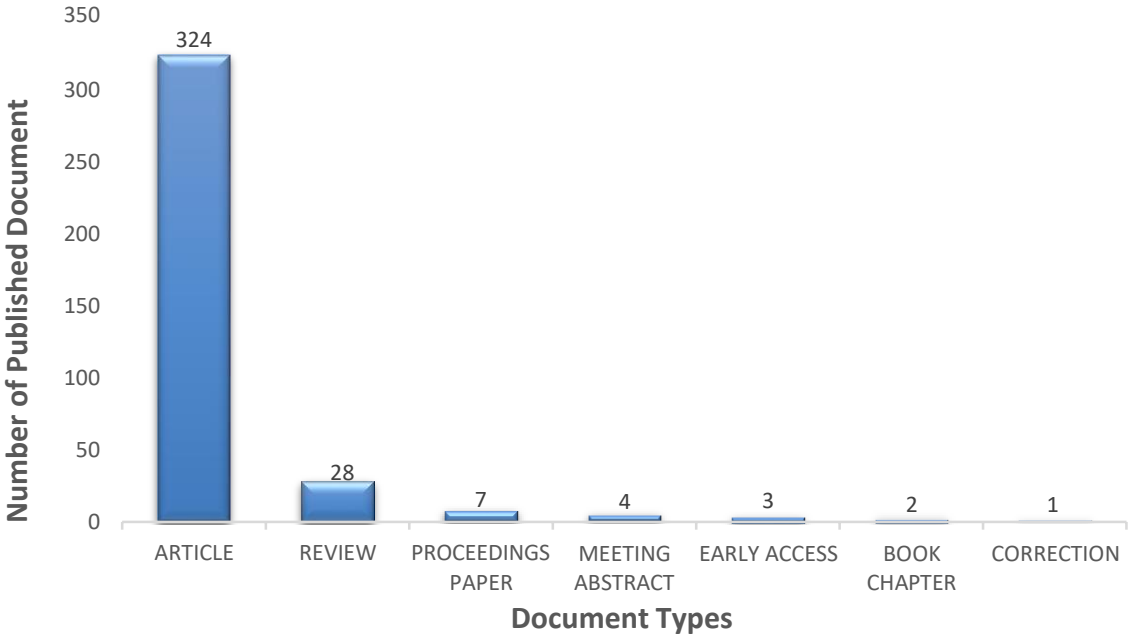


Figure 4: Number o**f** published paper based on document types.

Table 1 : Number of published paper based on funding agencies.

Funding Agencies	Country	Number of Published Paper
National Natural Science Foundation of China, NSFC	China	129
National Institutes of Health, NIH USA	United State	37
United States Department of Health Human Services	United State	37
NIH National Cancer Institute NCI	United State	24
National Basic Research Program of China	China	17
Fundamental Research Funds for The Central Universities	China	13
Ministry Of Education Culture Sports Science and Technology Japan MEXT	Japan	10
National Key Research and Development Program of China	China	10
China Postdoctoral Science Foundation	China	9
Grants In Aid for Scientific Research Kakenhi	Japan	8

According to **Table 1**, the funding agencies with the most published paper is National Natural Science Foundation of China (NSFC) from China with 129 published papers. NSFC funding agency is the largest agency in the China that involve in research and funding activities. This contributes 35.64% of 362 document of published paper in nanogel field. Out of 10 funding agencies, there are 5 funding agencies from China which leads to high number of publications from the country as the entire cost of research been supported and cover the indirect costs of research. A research study by Liu [14], shows that the annual amount of the agency is reaching more than 20 billion CNY (3 billion USD) per year and from 2014 until 2018, NSFC funded 85,726 General Program projects. United State have 3 funding agencies that top the list with total 98 published papers. Japan has 2 funding agencies with total 18 published document in the nanogels field.

3.2. Paper Publication

The publication that has the highest amounts of published documents is Journal of Controlled Release (JCR) with 22 documents (6.08%). The journal produces high-quality research publications on a wide range of delivery science and technology topics such as an article published in 2008 with title "*Recent progress in tumour pH targeting nanotechnology*". Instead of that, the journal publishes studies on medication and biologically active agent control release and delivery. Thus, the number of published documents in JCR is highest as nanogels are used in drug delivery system (DDS). The second highest published record is ACS Applied Material Interfaces with 16 documents (4.42%). The details of publication (source title) with the publication records are shown in **Figure 5(a)**. According to data obtained from all the documents, the research area with the most researched is in Chemistry area with 149 documents. Chemistry has a wide range of areas and referred as the core of science as it

connects physics to other natural sciences such as geology and biology. The second highest is in material science areas with 137 documents. Material science is the core of nanotechnology and nanogels is one of nanotechnology applications. **Figure 5(b)** shows the top 10 research area of nanogels in cancer treatment or anticancer.

The classification of research area based on Web of Science categories shows that Chemistry Multidisciplinary is the highest category with 95 documents. The second highest is pharmacology pharmacy which consists of 81 documents in this area. The data regarding to Web of Science categories is illustrated in **Figure 5(c)**. The contribution of an organization with the highest published document is by Chinese Academy Science with 27 total documents. **Table 2** shows the top organizations in the study of nanogels. Based on the **Table 2**, there are 5 organizations from China and total of 9 organization from Asia. The organizations from China are Chinese Academy Science located in Beijing, Fudan University and Shanghai Jiao Tong University in Shanghai, Sichuan University in Chengdu and University of Science and Technology of China in Anhui. There are total of 70 published documents from China. The other organizations from Asia are Islamic Azad University and Payame Noor University from Iran which contributes 20 published documents in nanogels field. Catholic University Korea in Seoul, Korea and Indian Institute of Technology in Delhi, India have published 9 and 8 published documents respectively that leads to increment of publication documents in Asia regions. From the data, it is clearly shown the ability of Asia people in doing the research about nanogels. The second highest organization is University of Nebraska Medical Centre from United State with 12 published documents.

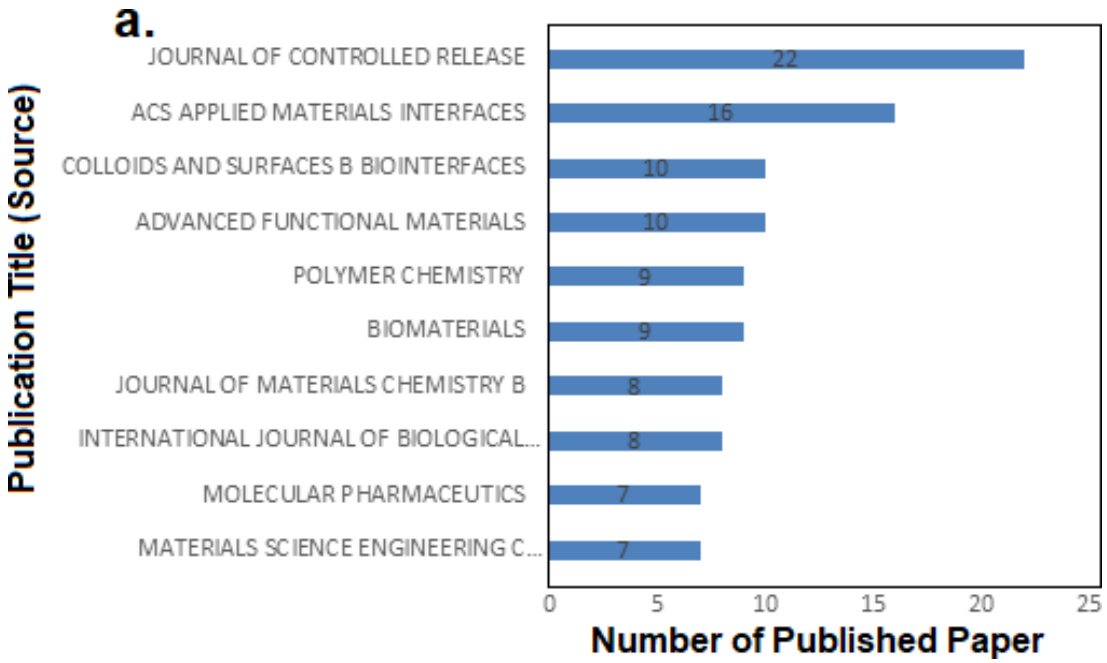


Figure 5: Number of published papers based on (a) publication (source title), (b)research area and (c) Web of Science categories

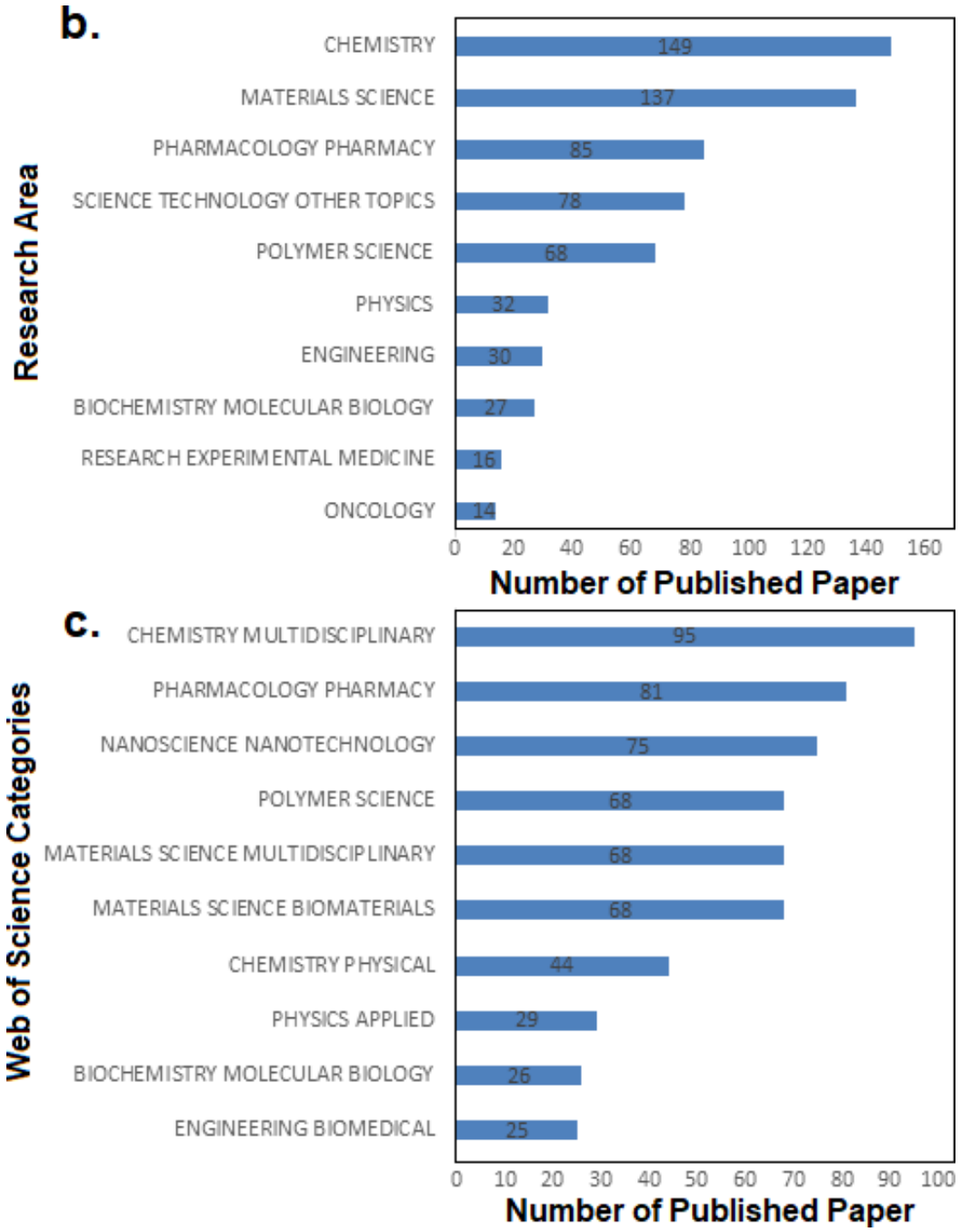


Figure 5: (*Continue*)

Table 2 : Organization with mosr number of published paper.

Organization	Number of Published Paper	Total Citation	Average of citation
Chinese Academy Science	27	1069	39
University Nebraska Medical Centre	12	346	28
Fudan University	11	293	26
Islamic Azad University	11	283	25

Shanghai Jiao Tong University	11	159	14
Sichuan University	11	92	8
University Science and Technology of China	10	294	29
Catholic University of Korea	9	1001	111
Payame Noor University	9	73	8
Indian Institute of Technology	8	123	15

Chinese Academy Science have the highest number of published paper and total citation but with low average of citation. The highest average of citation is from Catholic University of Korea with 111 citation which showing there are high impact and good quality of article published by the organization. The lowest citation is by Payame Noor University with 73 total citations and according to Yaminfirooz [45], the citation may decrease as the number of self-citations reduces. Iran has been placed in third place in world in year 2019 with country that have high number of self-citations.

3.3. Preferred Paper

Top 10 cited documents in the field of nanogels were shown in **Table 3**. The top cited document included one review paper and nine articles. The review paper received the highest citation with title *"Recent progress in tumour pH targeting nanotechnology"* was published in 2008 and achieved 677 citations. The review paper is focusing about polymeric micelle and nanogels with pH sensitive ability to target the acidic microenvironment of solid tumour. The top cited articles included the explanation to synthesis the responsive polymeric nanogels and method to produce nanogels. The improvement of polymeric nanogels were discussed to enhanced the therapeutic efficacy as a promising drug delivery system. The top cited articles were published in journal in the field of internet. Journal of The American Chemical Society has three top cited articles in year 2014, 2010 and 2007. Instead of that, Biomaterial also has three top cited articles and all published in year 2010. Thus, it shows that both journals have a high impact as it frequently referenced throughout the academic spectrum. United State of America has the highest top cited papers with seven papers. Even though China has higher number of publications, the likelihood of citations reduced as names of the Chinese scholars are not yet recognised by the English-speaking world. The international collaboration increases the number of citations as the paper visibility increases internationally with good quality from the contributors. Based on Table 3.0, United State of America (USA) tends to collabs with Asia region especially with China, Korea and Japan. Japan is the third country with largest investor after United State and China, and funding more Research & Development (R&D) in United State [3].The study of nanogels is still get the attention of researchers and growing in the recent years. **Table .4** shows the list of recent papers published and all the papers were published in year 2021. The recent papers include eight articles and two review papers. Based on the data exported on August 3rd, the recent papers are not cited by any journal except for an article title *"X-ray-responsive polypeptide nanogel for concurrent chemoradiotherapy"* that received 7 citations and published by Journal of Controlled Release.

Table 3: The Top 10 of most cited papers.

Title	Country	Source Title	Total Citation	Summary	Reference
Recent progress in tumor pH targeting nanotechnology	USA and Korea	Journal Of Controlled Release	677	The recent progress of pH- sensitive nanotechnology development to target slightly acidic extracellular pH environment of tumour tumours	[11]
Self-Cross-Linked Polymer Nanogels: A Versatile Nanoscopic Drug Delivery Platform	USA	Journal Of The American Chemical Society	409	Doxorubicin delivery into breast cancer with different cross-linking density to determine cell-uptake efficiency and stabilization	[29]
Biodegradable nanogels prepared by atom transfer radical polymerization as potential drug delivery carriers: Synthesis, biodegradation, in vitro release, and bioconjugation	USA and Japan	Journal Of The American Chemical Society	361	Stable biodegradable nanogel prepared by inverse miniemulsion atom transfer radical polymerization (ATRP) to improve control over released of anticancer drug to suppress the growth of cancer	[19]
Nanogels for oligonucleotide delivery to the brain	USA	Bioconjugate Chemistry	274	A new method to deliver ODN to brain based on nanoscale network of cross-linked	[34]
Cocoon-Like Self-Degradable DNA Nanoclew for Anticancer Drug Delivery	USA and China	Journal Of The American Chemical Society	187	Development of anti-cancer drug delivery system consisting of deoxyribonuclease(D-Nase)-degradable DNA nanoclew(NCl)	[32]
Core-shell hybrid nanogels for integration of optical temperature-sensing, targeted tumor cell imaging, and combined chemo-photothermal treatment	USA and China	Biomaterials	176	A concept of integrating into a single nanoparticle system from functional building blocks to simultaneoulsy functioning in temperature-sensing, cancer cell targeting, fluorescence imaging and chemophothermal	[37]
Multi-responsive nanogels containing motifs of ortho ester,	China		172		[22]

oligo(ethylene glycol) and disulfide linkage as carriers of hydrophobic anti-cancer drugs		Journal Of Controlled Release		A study of thermo-responsive, acid triggering hydrolysis and reduction induced degradation of nanogels	
Sequential Intra-Intercellular Nanoparticle Delivery System for Deep Tumor Penetration	China	Angewandte Chemie-International Edition	156	A development of nanogels that able to work in reversible swelling shrinking based on the pH variation	[8]
Chitosan-based responsive hybrid nanogels for integration of optical pH-sensing, tumor cell imaging and controlled drug delivery	USA and China	Biomaterials	155	A study of hybrid nanogels that formed by non-covalent physical which can exhibit a change in term of structure and composition when exposed to physiological pH	[39]
Self-quenching polysaccharide-based nanogels of pullulan/folate-photosensitizer conjugates for photodynamic therapy	Korea	Biomaterials	143	An investigation of the potential of self-quenching polysaccharide-based nanogels in reducing their photosentizer (PS) phototoxicity	[1]

Table 4: 10 Recent published papers.

Article Title	Year	Source Title	Reference
A general prodrug nanohydrogel platform for reduction-triggered drug activation and treatment of taxane-resistant malignancies	2021	Acta Biomaterialia	[42]
Encapsulation and pH-responsive release of bortezomib by dopamine grafted hyaluronate nanogels	2021	International Journal Of Biological Macromolecules	[12]
Photodynamic therapy using self-assembled nanogels comprising chlorin e6-bearing pullulan	2021	Journal Of Materials Chemistry B	[15]
Nanomedicinary evaluation of calotropis procera me diate d silver nanoparticle on skin cancer cell line for microbes-front line analysis	2021	Journal Of Molecular Structure	[28]
Emerging Biomaterials-Based Strategies for Inhibiting Vasculature Function in Cancer Therapy	2021	Small Methods	[13]
Nucleoside transporter-guided cytarabine-conjugated liposomes for intracellular methotrexate delivery and cooperative choriocarcinoma therapy	2021	Journal Of Nanobiotechnology	[4]
Nanogels as a Versatile Drug Delivery System for Brain Cancer	2021	Gels	[30]
Self-Assembled Hybrid Nanogel as a Multifunctional Theranostic Probe for Enzyme-Regulated Ultrasound Imaging and Tumor Therapy	2021	Acs Applied Bio Materials	[38]
Antitumor Effects of pH-/Reduction-Responsive Fe3O4@Alginate Magnetic Nanoparticles Loaded with Doxorubicin on Subcutaneous Tumor Models of Hepatocellular Carcinoma Xenografts in BALB/c Nude Mice	2021	Acs Applied Nano Materials	[21]

X-ray-responsive polypeptide nanogel for concurrent chemoradiotherapy	2021	Journal Of Controlled Release	[40]

The top 10 authors were recorded and shows in **Figure 6.** Chen Xuesi and Ding Jiang Xue top the list of most record with 15 records,4.14 % of total number of publications. The top author mostly is from China, 7 out of 10 authors, which contributes to the increment of published paper from their origin country in nanogels field. The growth of China researchers was one of the study's key conclusions in number of publications. Instead of that, the rapid expansion of nanotechnology in China is due in large part to the country's constant and substantial financial support for research in the sector.

Table 5 shows the top authors with high number of citations. Zhou Shuiqin from China has the highest citation with 791 for all published paper with average 98 citations per paper. Based on average number of citations, Zhou Shuiqin has lower number of citations compared to Wu Weitai, Banerjee Probal and Shen Jing. This shows that not all the published paper from Zhou Shuiqin has high impact for the researchers references in nanogel field. From **Table 5**, most of high number of published papers has top the list which shows that the increases of published paper of an author will increase the total number of citations. According to total number of citations, the top 3 high impact authors are Zhou Shuiqin, Chen Xuesi and Ding Jianxun from China.

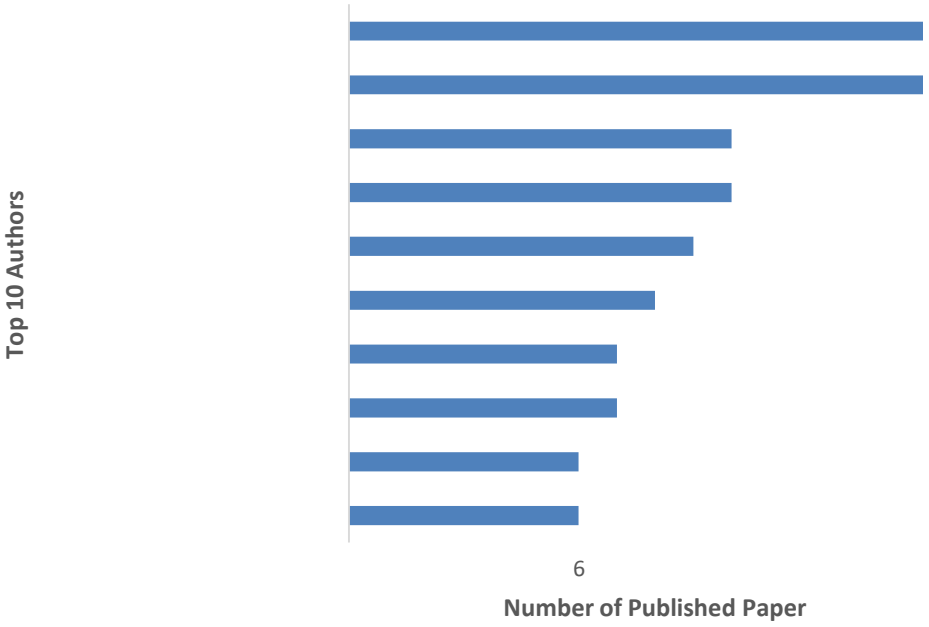


Figure 6: Top 10 Authors with most published papers.

Table 5: Top 10 Authors with most number of citations.

Author	Number of Published Paper	Citation	Average of citation
Zhou Shuiqin	8	791	98
Chen Xuesi	15	752	50
Ding Jianxun	15	734	48
Wu Weitai	6	602	100
Banerjee Probal	5	545	109

Shen Jing	5	539	107
Xu Weiguo	10	395	39
Vinogradov Serguei V.	10	334	33
Na Kun	5	303	60
Nagasaki Yukio	6	286	47

3.4.Analysis of Keywords

Keywords submitted by the paper's authors that appeared more than 10 times in the Web of Science core database were included in the final analysis. There are 114 words met threshold out of 1050 keywords. The keyword that appeared the most in the documents were "nanoparticles" (409 total link strength) with 149 occurrence and "drug delivery" (209 total link strength) with 79 occurrences. The keyword "nanoparticles" is found the most as nanogels is one of nanoparticles and instead of that it is also related to keyword "hydrogels" (13 link strength) as nanogels is composed of hydrogel. This can be explained as the nanoparticles is design to become responsive stimulus especially toward pH changes. Overall, the map of keywords has 4 clusters and can be referred to **Figure 7**. Cluster 1 is in red nodes, cluster 2 in green nodes, cluster 3 in blue nodes and cluster 4 in yellow nodes and each cluster are related to certain topics. From the analysis, cluster 1 can be named as keyword related to anticancer drug process, cluster 2 related to drug delivery system, cluster 3 related to synthesis of nanogel and cluster 4 related to polymer. The size of nodes indicates the occurrence frequency while the curve shows the co-occurrence in the same publication. The shorter the distance of two nodes shows larger number of co-occurrences between the keywords**. Table 6** shows the top 5 keyword with most occurrence and co-occurrence [45, 46]. The total link strength shows the link of the keyword with others keyword. "Drug-delivery" and "delivery" top the list as both keywords can be found in the drug delivery system of nanogel as drug carrier in delivering the antidrug to the targeted site. "Doxorubicin" keyword is one of common antidrug medicine use to treat the cancer and doxorubicin been encapsulated inside the nanogel before releasing it at tumour site. The last most co-occurrence keyword is "cancer", as the published paper are focusing on the treatment of cancer by using nanogel as drug carrier.

Table 6: Co-ocuurence of keyword.

Keyword	Occurrence	Total link strength
nanoparticles	149	409
drug-delivery	79	209
delivery	67	161
doxorubicin	48	160
cancer	56	157

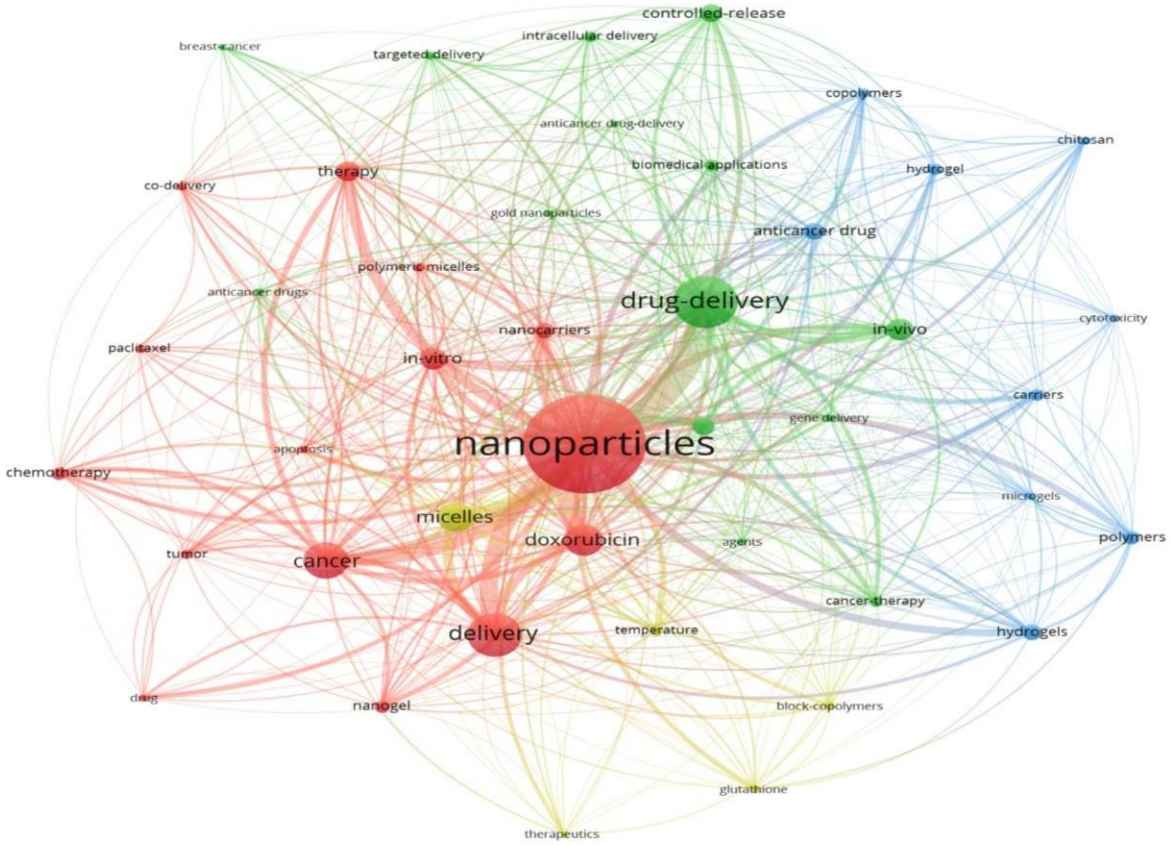


Figure 7: Co-occurrence of keyword in the publication of nanogels.

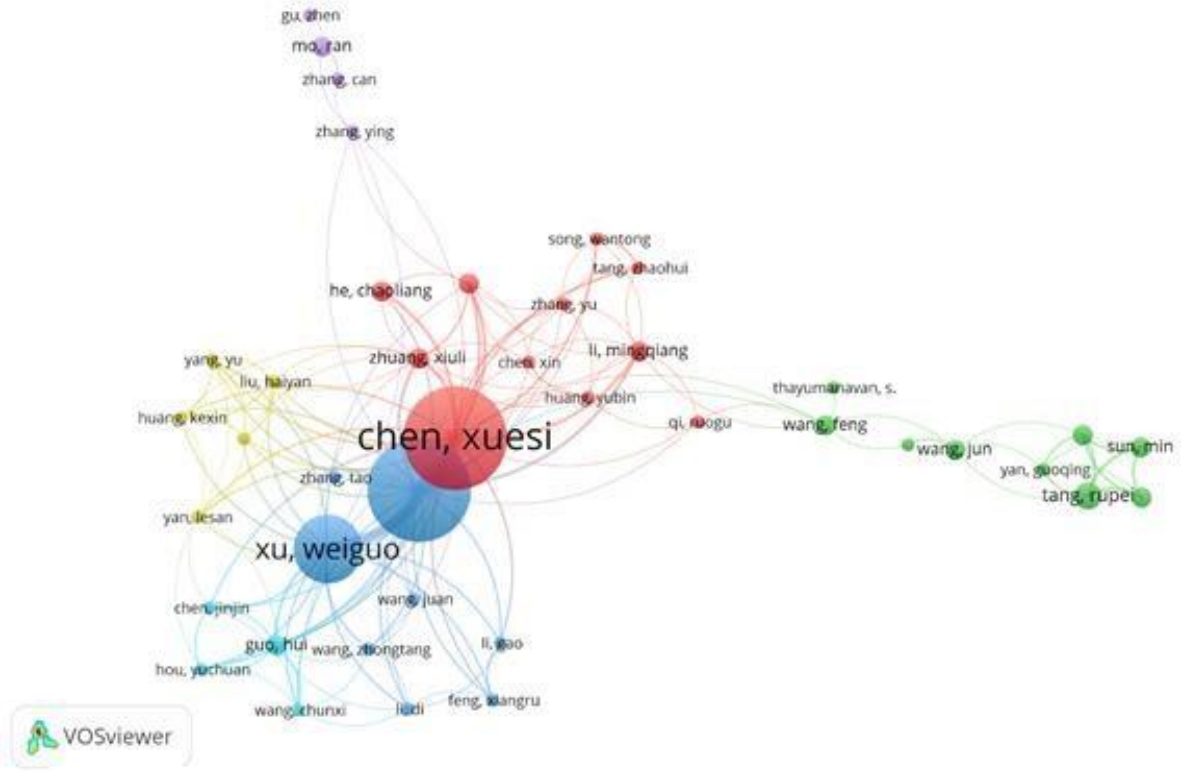
3.5. Collaboration Network

In total, 1,712 writers contributed to the publishing of the nanogels documents and with minimum 2 numbers of documents per author, there are 277 authors that met the threshold. From the result, Chen Xuesi and Ding Jianxun from University of Chinese Academy of Science has published 15 documents each. Between those authors, Ding Jianxun has the higher total link strength with 71 while Chen Xuesi is 68 total link strengths. The main collaborator of Ding Jianxun is Xu Weiguo from Changchun Institute of Applied Chemistry. The total link strength is 10. Based on **Figure 8 (a)**, it shows that the collaborations are mostly from China to produce related documents of nanogels. The map of co-authorship of author shows 6 clusters in total.

Through the global literature search, there are 402 organizations contributes in publishment of related documents regarding to nanogels and about 121 organizations have published with 2 minimum number of documents per organizations. The total clusters observed are 9 clusters. The visualization by observed 9 clusters that shown as in **Figure 8 (b)** where Chinese Academy Science in blue cluster has the biggest size of circle with 27 documents. The main partner of Chinese Academy Science is University of Science and Technology China with 4 link strengths. This is because both organizations have a direct leadership relation. From the figure, organization from China tends to collaborate with the organization from their own country.

There are 40 countries involved in publishing related documents and the analysis shows USA has the highest total link strength with 35 with 69 documents. The total number of clusters observed based on **Figure 8(c)** is 9 clusters. China has the highest number of publications with 150 documents but with lower number of total link strength compared to USA with 24. The data shows that China has emerged as a major contributor to global nanoscience research and a powerhouse of nanotechnology Research and Development (R&D). China has the strongest collaboration with USA with 15 link strengths. The number of collaborators of USA is 12 out of 40 countries while China has collaborated with 8 countries. USA shows strong connection of documents with 2 countries which are China and South Korea. This shown by the thickness of the lines between the countries. The share of Chinese overall research output including foreign collaboration has risen since 2010, reaching 24% in 2016. The level of collaboration internationally in China is lower and the rate of growth is also slower than in the United State.

a)


gu, zhen
mo, ran
zhang, can
zhang, ying
song, wentong
tang, zhaohui
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zhang, yu
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huang, kexin
qi, zhigu
wang, feng
chen, xuesi
wang, jun
sun, min
yan, guoqing
zhang, tao
tang, rupei
yan, lesan
xu, weiguo
chen, jinjin
wang, juan
guo, hui
wang, zhongtang
li, gao
hou, yuchuan
wang, zhunxi
lizdi
feng, xiangru
VOSviewer

b)


wuhan inst technol
cuny
chinese acad sci
sichuan univ
fudan univ
southern med univ
univ nebraska med ctr

c)

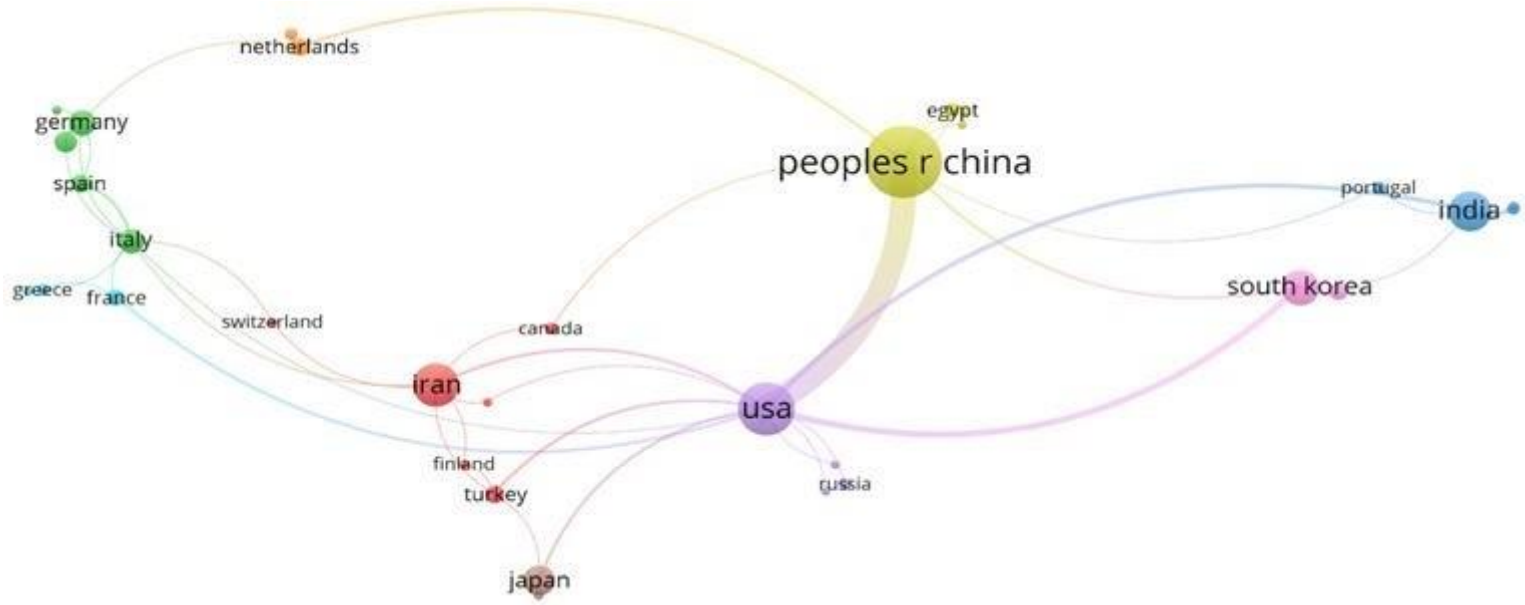


Figure 8: Bibliometric analysis of co-authorship. **a)** the co-authorship of author that cooperate in the field of nanogels. **b)** the co-authorship organizations and Chinese Academy Science has published 27 documents**. c)** the map of co-authorship countries. The collaborative link with USA is 12 with total link strength 35. Distinct colours represent different clusters, while the size of the circles represents the number of publications. The thickness of the lines indicates the nations' connection strength

Table 7 shows the top 5 authors with the most collaboration with others based on the total link strength. Zhou Shuiqin has the highest number of citation and collaborations. This shows that the collaboration with other authors can increase the visibility of the published paper. Ding Jianxun has the high number of published paper but has lower collaboration with others which reduce the link strength. Instead of that, Ding Jianxun has the lowest average citation with 48 citations per papers. The average of citation shows that Banarjee Probal has the highest average number compared to others. The paper written by Banarjee Probal shows a high quality and have high impact in the nanogels study that has been referred by the academia.

Table 7: Top 5 Author with the most collaboration network.

Author	Number of Published Paper	Citation	Average of citation	Total Link Strength
Zhou Shuiqin	8	791	98	84
Wu Weitai	6	602	100	74
Shen Jing	5	539	107	65
Banerjee Probal	5	545	109	60
Ding Jianxun	15	734	48	54

The top 5 organizations with the most collaboration network shown in **Table 8**. All the top organizations are from China. Chinese Academy Science has the highest number of citations which indicate that the organizations successfully published more high impact paper with good quality and originality of work. Instead of that Chinese Academy Science collaborates with other organization to complement each other works and evolve new solution or ideas. Thus, the creativity of the papers increases and able to produce new information of nanogels in cancer treatment.

Table 8: Top 5 Organization with the most collaboration network.

Organization	Documents	Citations	Average of citation	Total Link Strength
Chinese Academy Science	27	1069	39	30
University Chinese Academic Science	7	207	29	10
Fudan University	11	293	26	9
Shanghai Jiao Tong University	11	283	25	9
University Science & Technology China	10	294	29	9

China on top the list in term of most published paper, top author, top organization and also country with most collaboration network. China international collaboration is lower than USA but has strong link with 358. However, USA still has highest number of citations as the papers from USA has high impact and more visible due to the collaboration impact. Asia region which are China, India, Iran and South Korea has proven that Asia is leading in the research area regarding to nanogels and able to published more paper with high number of

citations. The growth of the scientific output can be due to a few roles such as investment, government policies and the economic of the country. The number of contributions from Asia will continue to rise and the quality of the articles will improve as well. **Table 9** shows the summary of top 5 country with most collaboration internationally.

Table 9: Top 5 Country with the most collaboration network.

Country	Documents	Citations	Average of citation	Total Link Strength
China	150	4244	28	358
United State of America	69	4713	68	272
India	35	766	21	203
Iran	42	517	12	117
South Korea	26	1389	53	76

3.6. Bibliohraphic Coupling and Co-Citation

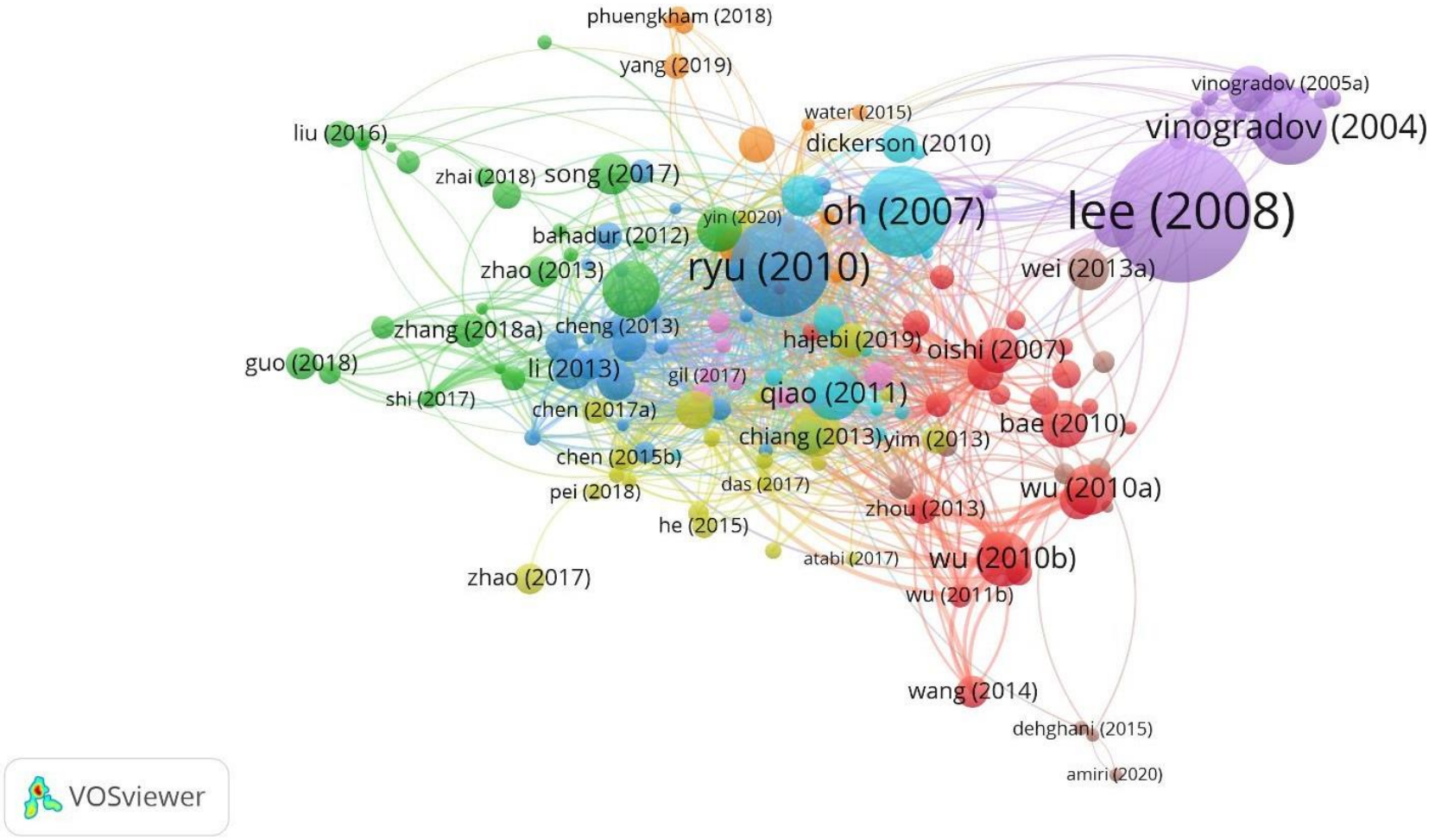
Bibliographic coupling is when two publications been cited by third publications while co-citation is pairs of publications that are cited together in the source articles are tracked. The bibliographic documents are shown in **Figure 9(a)** and co-citation of cited author in **Figure 9(b)**. Nine clusters are obtained in bibliographic coupling and153 documents met the threshold with 20 minimum number of citations per document. Cluster 1 shown in red includes 24 items and the research are regarding with smart stimulus response. Cluster 9 that shown in light purple consisted of 8 items and the research area is focus on development of nanogels in drug combination therapies. **Table 10** shows the description of each cluster and the number of documents related within the cluster.

Table 10: Research topic based on cluster.

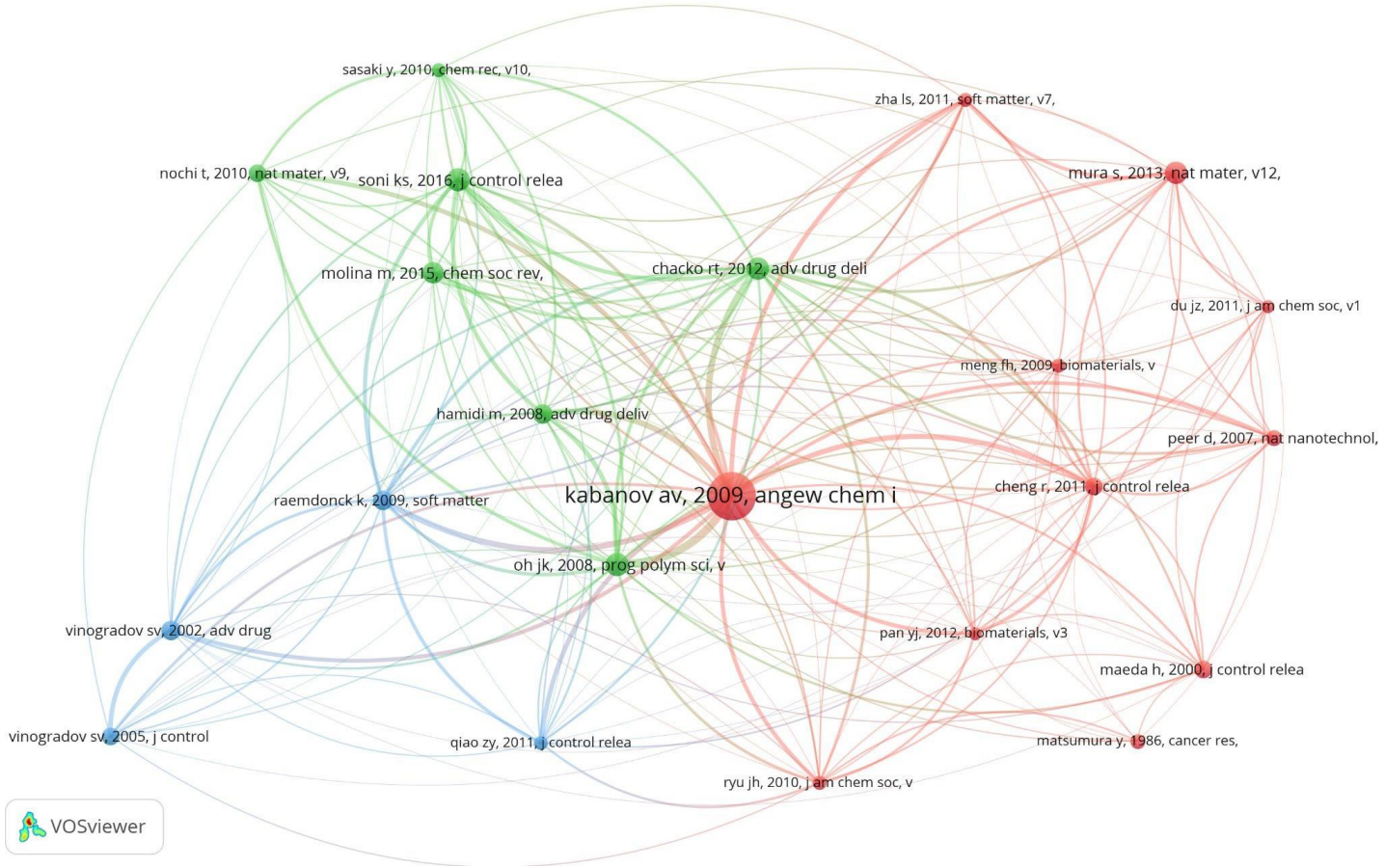
Cluster	Number of Item per Cluster	Topic
1	24	Research regarding smart stimulus response nanogels.
2	23	Improvement of polypeptide nanogels to response toward stimuli responsive from tumour microenvironment by designing good anticancer drug release during chemotherapy.
3	23	A potential system for controlled drug delivery by pH and dual responsive nanogel to prevent from drug toxicity
4	21	Research related to pH responsive nanogels
5	18	Research of modification of nanogels
6	14	Research of multi-responsive nanogels
7	11	Research regarding self-assembly nanogels
8	11	Research of the development of nanogels
9	8	Research on development of nanogels in drug combination therapies

The co-citation of cited reference consists of 3 clusters from the analysis with 15 minimum citations of a cited reference. The 3 clusters represent three different research field that shown in the colour of green, red and blue. The biggest clusters of cited references include 11 items and the representative is from Angewandte Chemie in 2009 written by Kabanov AV. The two biggest cited source clusters consist of 50 and 47 items, respectively. The representative journals are Journal of Control Release and Journal of the American Chemical Society as shown in **Figure 9(c)**. Journal of Control Release has the highest citation with 891 citations and strong total link strength with 44,542. This journal shows a high impact as the number of citations is highest and linked with 132 other sources. According to a website, the current impact factor (IF) for this journal is 8.66 in year 2020 which leads to one of influential journal in drug delivery field [23]. Journal of American Chemical Society has high impact factor in year 2020 with 14.33[24]. Even though Journal of American Chemical Society has higher impact factor but Journal of Controlled Released still has the highest citation and total link strength in nanogels field. Instead of that Journal of Controlled Released focus on technologies related to Pharmaceutical Science while Journal of American Chemical Society focus to technologies in Biochemistry. Cluster 3 consists of 36 items and the most cited source in this cluster is Biomacromolecules with 431 citations and 26,782 total link strengths. The impact factor for Biomacromolecules journal is 6.46 in year 2020 and shows an increment compared to year 2019 [25].

a)


phuengkham (2018)
yang (2019)
vinogradov (2005a)
water (2015)
vinogradov (2004)
liu (2016)
dickerson (2010)
zhai (2018)
song (2017)
oh (2007)
lee (2008)
yin (2020)
bahadur (2012)
ryu (2010)
zhao (2013)
wei (2013a)
zhang (2018a)
cheng (2013)
hajebi (2019)
oishi (2007)
guo (2018)
li (2013)
gil (2017)
qiao (2011)
shi (2017)
chen (2017a)
bae (2010)
chiang (2013)
yim (2013)
chen (2015b)
wu (2010a)
pei (2018)
das (2017)
zhou (2013)
he (2015)
atabi (2017)
wu (2010b)
zhao (2017)
wu (2011b)
wang (2014)
dehghani (2015)
amiri (2020)
VOSviewer

b)


sasaki y, 2010, chem rec, v10,
zha ls, 2011, soft matter, v7,
nochi t, 2010, nat mater, v9,
soni ks, 2016, j control relea
mura s, 2013, nat mater, v12,
molina m, 2015, chem soc rev,
chacko rt, 2012, adv drug deli
du jz, 2011, j am chem soc, v1
meng fh, 2009, biomaterials, v
hamidi m, 2008, adv drug deliv
peer d, 2007, nat nanotechnol,
raemdonck k, 2009, soft matter
kabanov av, 2009, angew chem i
cheng r, 2011, j control relea
oh jk, 2008, prog polym sci, v
vinogradov sv, 2002, adv drug
pan yj, 2012, biomaterials, v3
maeda h, 2000, j control relea
vinogradov sv, 2005, j control
qiao zy, 2011, j control relea
matsumura y, 1986, cancer res,
ryu jh, 2010, j am chem soc, v
VOSviewer

c)

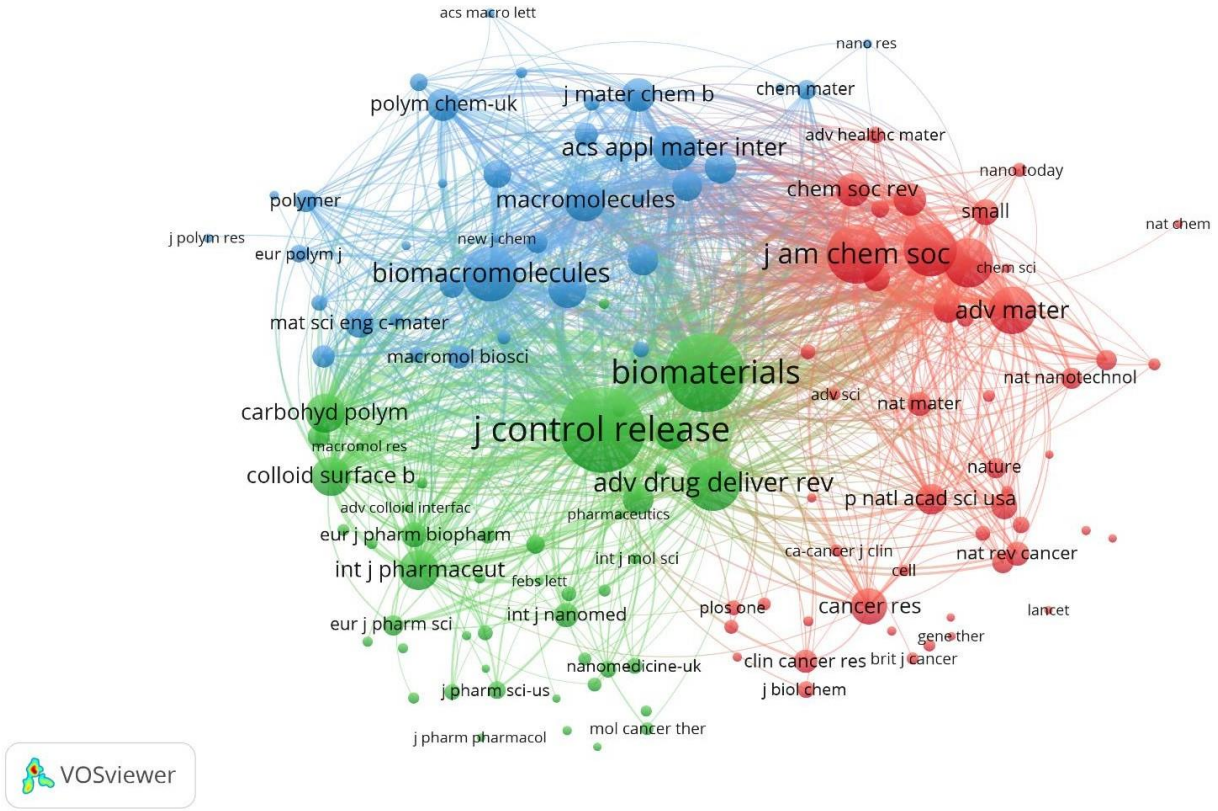


Figure 9: Bibliometric analysis of bibliographic coupling and co-citation. **a)** Bibliographic of documents. **b)** Co-citation of cited reference. **c)** co-citation of source. Different colours represent different study topics. The size of the circles corresponds to the number of co-citations. The distance between the two circles denotes their relationship.

4. Conclusions

The bibliometric analysis of nanogel in cancer treatment were discussed by the data extracted from WOS database and visualization of VOSviewer. This study demonstrated the pattern of nanogel field throughout the year from 2004 until 2021to better understand this field globally. The study is one of the few that integrate co-occurrence, co-authorship, and co-citation analyses to better understand the evolution of nanogels in cancer treatment from many points of view. The growth of publication shows good increment where the study of nanogels is apply through the application in cancer treatment as nanocarrier to encapsulated the drugs. The Covid-19 pandemic affect the researchers and academia in handling new research. Thus, the number of publications decreases starting from 2020 until 2021. This study able to display the visualization of nanogels field and analyse the result obtained. China is the highest publication in nanogels field with 150 documents which successfully put their authors in the top 10 globally. Most of the papers are from Asia which shows the increase of researchers in this region including South Korea, Japan and Iran. However, the most cited papers are from United State of America (USA) which indicate that the papers have high impact in nanogel field. The finding through VOS viewer can shows the collaboration that occur between author and country. The strong collaboration is between USA and China as in the contemporary knowledge economy, the both countries are undoubtedly the top two global superpowers, as both nations are at the forefront of scientific knowledge creation [10]. Thus, high impact paper can be published in the nanogel or nanotechnology field. China also is one of the biggest contributors in nanotechnology research to keep up with international pace of progress. It is also shown where most the author in nanogel field from China able to produce more papers and listed in the top 10 authors. In the bibliographic coupling and co-citation, the research area for each cluster can be observed. Most of the article tends to study nanogels with stimulus response towards the microenvironment. From this analysis, the objectives to analyse and determine the collaboration network, topic of interest and impact of publications in nanogels study are achieved. The future research can develop new study of nanogels in cancer treatment through this analysis. The method for the analysis and study are available to be tested with other nanotechnology field. There is still limitation where there is effort to generalize the research area for each cluster as there are 362 documents collected in WOS database. Nevertheless, this study can be useful for the bibliometric path of the future study.

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