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REVIEW

Global trends in nanomedicine research on triple negative breast cancer: a bibliometric analysis

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Abstract: Nanotechnology has emerged as a promising tool in the clinic to combat several difficult-to-manage diseases, such as cancer, which is the second leading cause of death worldwide. Chemotherapeutic drugs present several limitations such as undesired side effects, low specificity, resistance, and high relapse rates. Triple negative breast cancer (TNBC) is caused by cells that lack specific receptors in their membrane, such as estrogen (ER+) and progesterone (PR+) receptors, or by cells that do not express the amplification of human epidermal growth factor receptor-2 (HER-2+). This cancer type has poor prognosis, high relapse rates, and no targeted therapies. Thus, this study aimed to investigate the trends of nanotechnology research in TNBC and compare the contribution of research from different regions, institutions, and authors. A search of the studies published between 2012 and 2017, related to nanotechnology and TNBC, with different keyword combinations, was performed in the Scopus database. The keywords found in this search were grouped into four clusters, in which "breast cancer" was the most mentioned (1,133 times) and the word "MCF-7 cell line" is one of the latest hotspots that appeared in the year 2016. A total of 1,932 articles, which were cited 26,450 times, were identified. The USA accounted for 28.36% of the articles and 27.61% of the citations; however, none of its centers appeared in the list of 10 most productive ones in terms of publications. The journals *Biomaterials* and *International Journal of Nanomedicine* had the highest number of publications. The USA and China had the highest number of articles produced and cited; however, the highest average citation per article was from Singapore. The studies focused on the research of antineoplastic agents in animal models and cell culture, and these were the most used topics in research with nanotechnology and TNBC.

Keywords: oncology, breast cancer, nanotechnology, nanomedicine, bibliometric

Introduction

Cancer is a term that refers to the rapid growth and division of abnormal cells in a part of the body.[1] These cells promote alterations in primary tissue and have the ability to invade different parts of the body and spread to other organs[2] originating metastasis, which constitutes a challenge in cancer treatment.[3] There are >100 types of cancers, and different risk factors contribute to the development of cancers in different sites.[4] Cancer is the second cause of death and its main risk factor is aging. This fact is alarming, since a double of the population older than 65 years is expected to be affected in the next 20 years, increasing from 616 million to 1,157 billion worldwide.[5]

The most incident type of cancer is the non-melanoma skin for both sexes, followed by prostate cancer in men and breast cancer in women, which affects women the most worldwide.[1] Breast tumors are categorized into three main classes: those in which cells have estrogen receptor (ER+) or progesterone receptor (PR+), those in which cells have human epidermal growth factor receptor-2 (HER-2+) with or without

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ER+, and the triple negative breast cancer (TNBC) defined by the absence of these receptors.[6,7]

TNBC affects 9%–16% of the population worldwide, has a poor prognosis related to cure and survival, has high relapse rates, and has no targeted therapies.[8] Basically, breast cancer treatment constitutes surgery, chemotherapy, and radiotherapy.[9] There is an urgent need for chemotherapeutics that act selectively to inhibit neoplastic cell growth, leaving the non-tumor cells intact.[10] However, the majority of the drugs used in chemotherapy are mutagenic and cause damage to DNA from the tumor and non-tumor cells, leading to the death of rapidly dividing cells, which is associated with the collateral effects observed in patients.[11]

Aiming to improve the efficacy to decrease toxicity and increase the bioavailability of chemotherapy medication, nanotechnology has emerged as an important option.[12,13] Nanoparticles accumulate preferentially in the tumors due to the presence of well defined characteristics in tumors mass, such as the defective vasculature and poor lymphatic drainage, resulting in an increase in permeation and retention effect.[14,15] For antitumor treatment, nanoparticles may serve as carriers of compounds with higher selectivity for primary tumor and metastases, reducing the drug resistance and side effects.[16] In TNBC, gold nanoparticles conjugated with folic acid have shown significantly higher cell entry rates in both in vitro and in vivo models, indicating that folate receptors can be used as targeted therapies for TNBC.[17] This pattern was also observed with fructose-coated nanoparticles showing high selectivity (100-fold) for breast cancer cells compared to normal cells.[18–20]

This review aims to provide an update of the scientific production related to nanoparticles for breast cancer treatment, mainly for the triple negative subtype, during the period between 2012 and 2017.

Materials and methods

Literature search was performed in August 2017 in Scopus database, using the keywords (nanotechnology OR nanomedicine OR nanoparticle OR drug carrier) AND (triple negative breast cancer OR TNBC OR breast cancer), and was confined to articles published in journals related to Biotechnology, Pharmacology, Toxicology and Pharmaceutics, and Medicine areas, published in the period ranging from 2012 to 2017, and written in English language.

The results regarding authors who are publishing in the field were analyzed through tools in Scopus database. Impact factor (IF) of the journals was analyzed using InCites Journal Citation Reports from Thomson Reuters. VOSviewer version 1.6.0 software (Leiden University, Leiden, the Netherlands) was used to analyze the relationship between the most cited references and the most productive authors to generate the map and clusters visualization. STATA software and Microsoft Excel 2013 were used to calculate the cumulative volume and to predict paper trends using polynomial multiple regression models. GraphPad Prism 5 and RSudio 1.1.383 were used to create graphics.

Results

General information

The initial number of identified studies using the keyword combination was 4,676. After exclusions, the final number was 1,932, as demonstrated in the flow chart depicted in Figure 1.

In the period ranging from 2012 to 2017, 1,932 papers were published by 7,666 authors on the theme in 425 journals using 14,614 keywords (Table 1). There was a growth in the annual number of papers, from 200 in 2012 to 1,757 in 2016, with a projection of 2,256 for 2017 and 2,798 for 2018. In this period, the increase in the number of publications can be represented by the polynomial regression model: $y=21.93x^2-87{,}939.19x+88{,}163{,}841.66$, with y being the year and x being the cumulative volume of papers (Figure 2).

For the prediction model, functional specification, linear, logarithmic, polynomial, and exponential equations were tested. Hence, the choice of a second-order polynomial model for Figures 2 and 3A and B was based on the maximization of the R^2 goodness-of-fit coefficient of the available historical data, from 2012 to 2017, which served as the basis for choosing the model with the highest R^2.

Countries

The most productive country in terms of publication, using the keywords already mentioned, was the USA with 548 papers, representing 28.36% of total publications (Figure 3A). After this, China and India occupied second and third positions, respectively, with 494 (25.56%; Figure 3B) and 257 (13.30%) papers (Figure 3C). The choice of the functional specification for Figure 3A followed the same R^2 maximization logic; consequently, for the USA, the best specification was linear. This displays that India, China, and the USA show a growing trend in publications. However, the USA has a steady rate, while India and China are growing at increasing rates; thus, the expectation is that by 2018, China (which has the steepest growth rate) will exceed the USA in the number of publications. The top 10 countries that published more articles from 2012 to 2017 are shown in Figure 3D.

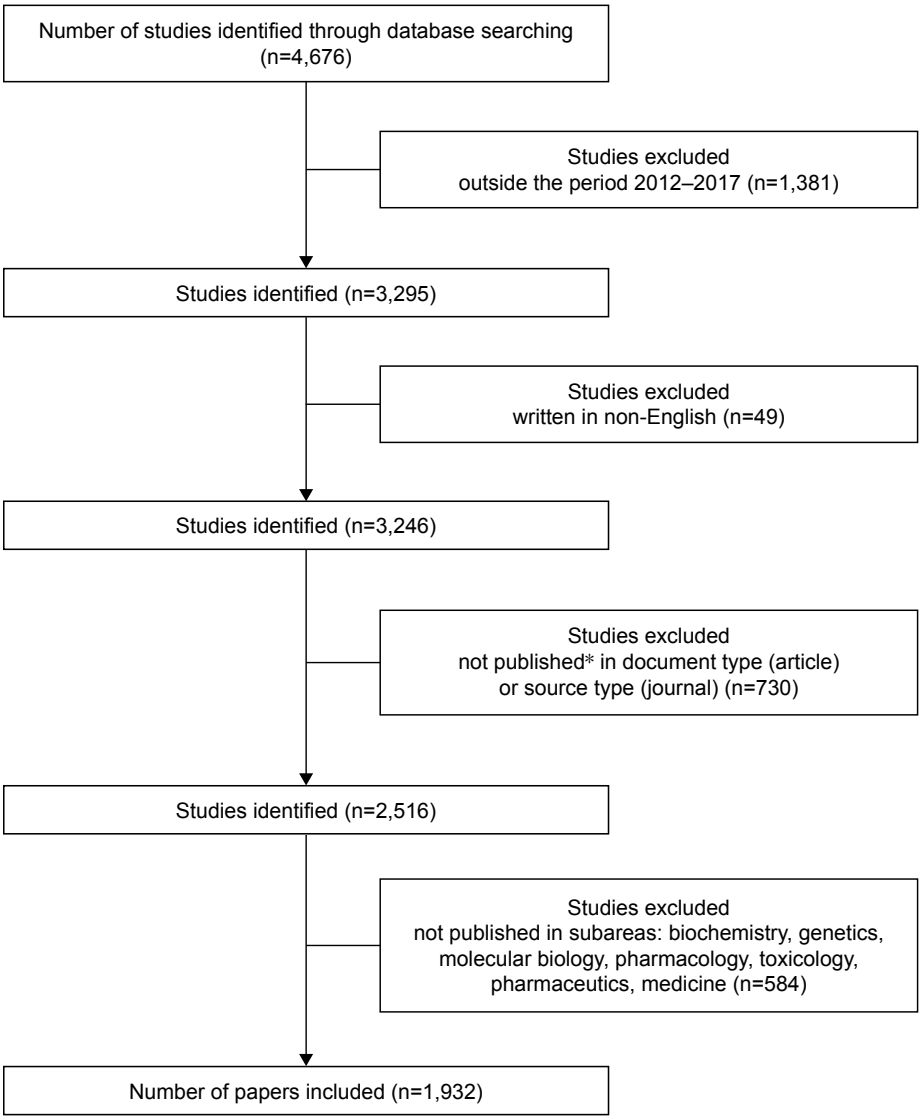

Figure 1 Flow chart of studies used in the analysis.
Notes: *Document type includes only the articles published in journals. Conference papers, short surveys, editorials, notes, letters, book chapters, and articles in press were excluded. Source type includes only journals. Conference proceedings, book series, and books were excluded from the results.

The papers were cited 26,450 times. The citation frequency was 13.69 times per paper. Singapore was the country that had the highest average of article citations (27 times). The number of citations of all papers from the USA was

Table 1 General information on articles related to nanotechnology and triple negative breast cancer published in the period from 2012 to 2017

Articles	1,932
Articles per author	0.252
Author per article	3.97
Coauthor per article	6.8
Sources (journals)	425
Keywords	3,966
Authors	7,666

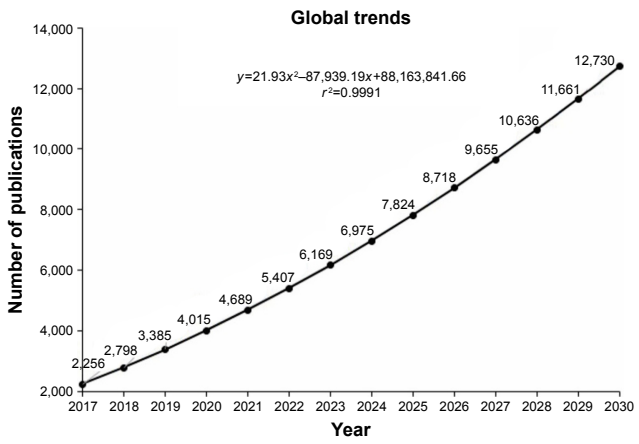

Figure 2 Cumulative volume of articles related to nanotechnology and triple negative breast cancer: global trends for 2030.

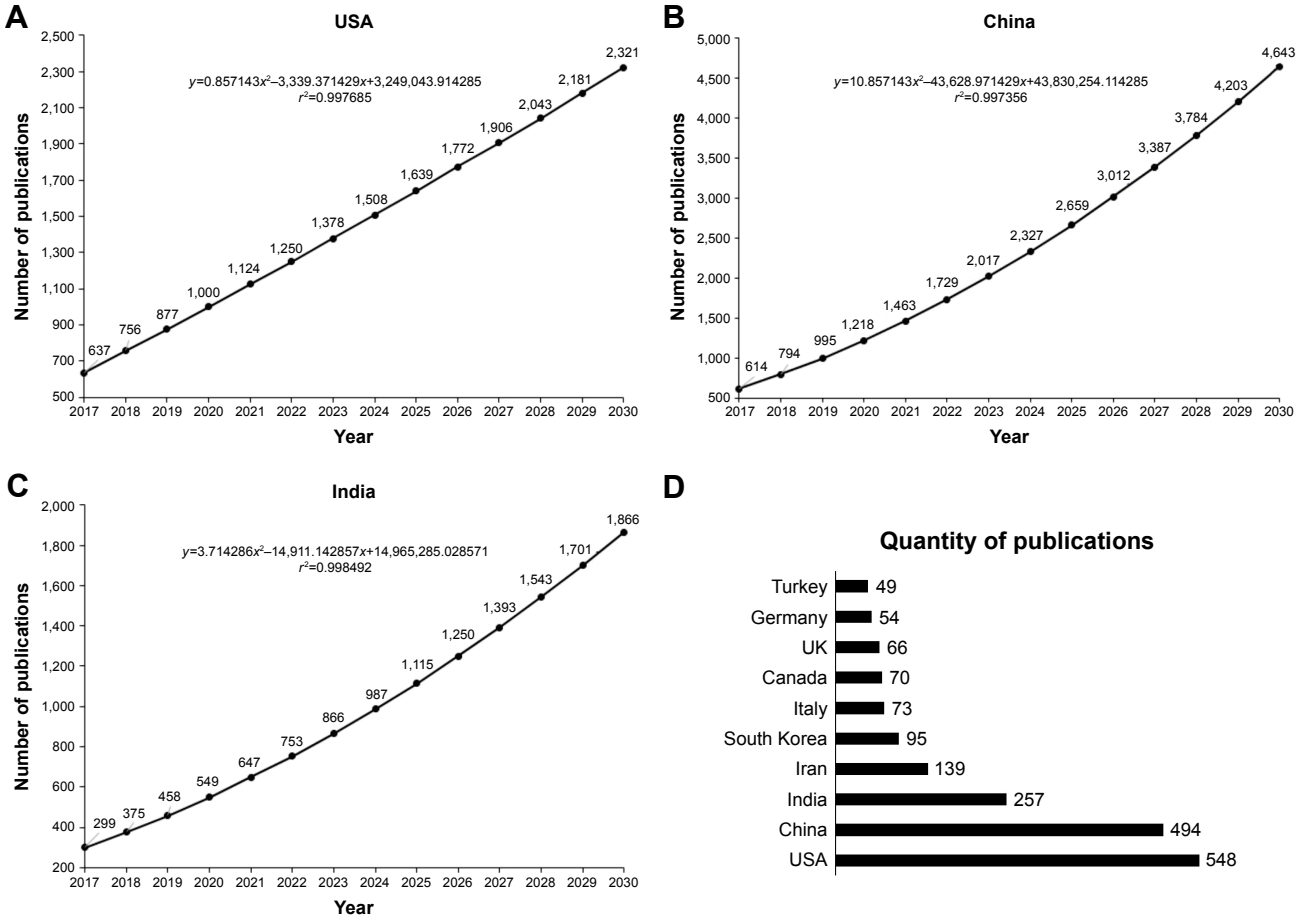

Figure 3 Prediction of the number of publications in the field of nanotechnology and triple negative breast cancer expected until 2030 from (**A**) India, (**B**) China, and (**C**) the USA. (**D**) Quantity of publications related to nanotechnology and triple negative breast cancer by country during the period 2012–2017.

7,304, comprising 27.61% of the total citations. China was in the second position with 7,126. The top 10 most cited countries are shown in Figure 4.

Institutes

The institute with the largest number of publications and citations in the area of nanotechnology and TNBC during the period was the Chinese Academy of Sciences, with 99 papers and 1,832 citations, comprising 5.12% of the total literature, and being the most cited institute. There are five other Chinese institutes in top 10 of the most cited publications and 2 are from Iran (Table 2). The USA was the country that was the most cited; however, the US institutes do not appear among the top 10 that published the most in the field. The M.D. Anderson Cancer Center from the University of Texas with 25 publications and 693 citations

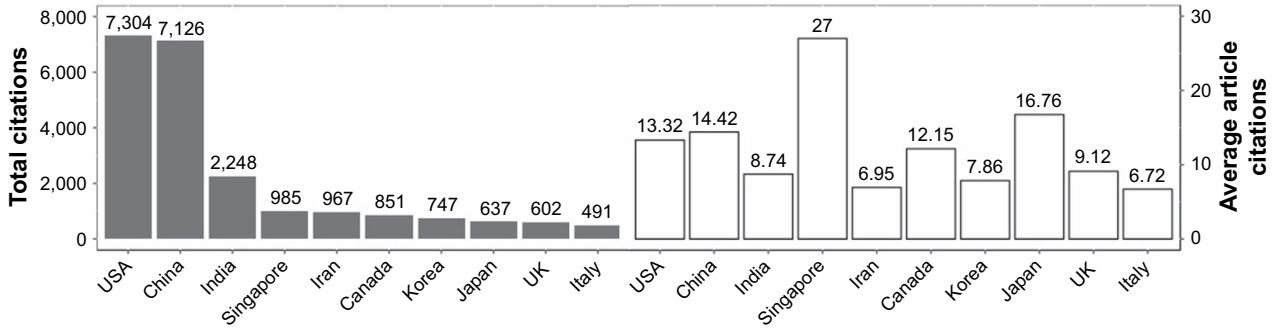

Figure 4 Total and average article citations per country of papers in the area of nanotechnology and triple negative breast cancer during the period 2012–2017.

Table 2 Main affiliations of authors publishing in the area of nanotechnology and triple negative breast cancer

Institute	Documents	Citations
Chinese Academy of Sciences	99	1,832
Tehran University of Medical Sciences	56	468
Ministry of Education China	43	460
Sichuan University	38	923
Tabriz University of Medical Sciences	36	256
University of Toronto	32	131
Perking University	29	513
National University of Singapore	28	786
Shenyang Pharmaceutical University	27	427
National Center for Nanoscience and Technology, Beijing	27	489

and the Harvard Medical School with 18 publications and 616 citations were the American institutes that published the most in the area.

Journals

The top 10 journals published 625 papers in the area of TNBC and nanotechnology, comprising 32.34% of the total. *Biomaterials* (IF 8.402; 2016) had the largest number of publications with 120 papers and was the most cited journal with 4,180 citations, followed by *International Journal of Nanomedicine* (IF 4.300; 2016) with 113 papers and 1,332 citations and *International Journal of Pharmaceutics* (IF 3.649; 2016) with 70 documents and 970 citations. The top 10 journals publishing in the area are shown in Table 3.

Authors, patents, and clinical trials

The top 10 most productive authors had a total of 160 papers, contributing to 8.3% of all publications in the field. In the period ranging from 2012 to 2017, "Li, Yaping" from Shanghai Institute of Materia Medica (China) produced most papers in the area, with 23 articles. His most cited paper is entitled "Co-delivery of doxorubicin and RNA using pH-sensitive poly (β-amino ester) nanoparticles for reversal of multidrug resistance of breast cancer" (2014) with 56 citations. "Atyabi, F" and "Yu, Hainjun" published 18 articles each. Furthermore, during the same period, >9,000 patents were filed; thus, the patents filed by the 10 authors who published the most were searched. Of these, four authors filed patents. "Ferrari, Mauro" was the most productive with 10 patents. The top 10 authors in this area are shown in Table 4, and a list of their patents is shown in Table 5.

We also performed a search on the current scenario of clinical trials in the area of TNBC and nanotechnology using the same combination of keywords described in the section "Materials and methods". The search resulted in 12 studies (Table 6). One study was excluded since it did not involve nanotechnology. Of the remaining 11 studies, 2 have their results reported. Two of them were related to the use of Abraxane® in a combined regimen with carboplatin or carboplatin and bevacizumab. Abraxane is a nanoparticle containing albumin-bound paclitaxel and bevacizumab in an anti-vascular endothelial growth factor antibody.

The results regarding the safety and tolerability for the clinical trial using Abraxane and carboplatin were not presented, according to the report provided, due to insufficient accrual for the study. However, 60% of patients (6/10) presented serious adverse effects, such as anemia, alterations in neutrophil count, gastrointestinal disorders, and allergic reactions, after treatment. All the patients (10/10) had other adverse effects such as nausea, edema, and pain. This study was terminated.

The study using Abraxane with carboplatin and bevacizumab involved 41 women with TNBC in stage IV or inoperable stage III. Results of 39 patients were provided. Of them, 18% had complete response, 69% had partial

Table 3 Top 10 journals published in the area of nanotechnology and triple negative breast cancer

Journal	Impact factor (2016)	Documents	Citations
Biomaterials	8.402	120	4,018
International Journal of Nanomedicine	4.300	113	1,332
International Journal of Pharmaceutics	3.649	70	970
Journal of Controlled Release	7.786	61	1,198
Colloids and Surfaces B Biointerfaces	3.887	61	869
Molecular Pharmaceutics	4.440	60	1,201
Nanomedicine Nanotechnology Biology and Medicine	5.720	36	550
PLoS One	2.806	36	370
Nanomedicine	4.727	34	269
Journal of Biomedical Nanotechnology	4.521	34	322

Table 4 Top 10 authors in the area of nanotechnology and triple negative breast cancer

Author	Affiliation	Documents (total) / Documents (5 years)	h-Index (total) / h-Index (5 years)	Most cited article (total) / Most cited article (5 years)	Citations of the most cited paper	Citations (total) by documents / Citations (5 years) by documents	References
Li, Yaping	Shanghai Institute of Materia Medica, Chine Academy of Sciences, State Key Laboratory of Drug Research and Center of Pharmaceutics, Shanghai, China	174	44	Li Y-P, et al. PEGylated PLGA nanoparticles as protein carriers: synthesis, preparation and biodistribution in rats. *J Control Release*. 2001;71(2):203–211	336	6,439 by 5,004	21
		23	15	Tang S, et al. Co-delivery of doxorubicin and RNA using pH-sensitive poly (β-amino ester) nanoparticles for reversal of multidrug resistance of breast cancer. *Biomaterials*. 2014;35(23):6047–6059	56	524 by 490	22
Atyabi, F	Tehran University of Medical Sciences, Nanotechnology Research Centre, Tehran, Iran	189	34	Dinarvand R, et al. Polylatide-co-glycolide nanoparticles for controlled delivery of anticancer agents. *Int J Nanomed*. 2011;6:877–895	154	3,862 by 3,104	23
		18	8	Taheri A, et al. The in vivo antitumor activity of LHRH targeted methotrexate-human serum albumin nanoparticles in 4T1 tumor-bearing Balb/c mice. *Int J Pharm*. 2012;431(1–2):183–189	26	155 by 142	24
Yu, Hainjun	Shanghai Institute of Materia Medica, Chinese Academy of Sciences, State Key Laboratory of Drug Research and Center of Pharmaceutics, Shanghai, China	82	24	Duan X, et al. Smart pH-sensitive and temporal-controlled polymeric micelles for effective combination therapy of doxorubicin and disulfiram. *ACS Nano*. 2013;7(7):5858–5869	156	1,949 by 1,495	25
		18	12	Tang S, et al. Co-delivery of doxorubicin and RNA using pH-sensitive poly (β-amino ester) nanoparticles for reversal of multidrug resistance of breast cancer. *Biomaterials*. 2014;35(23):6047–6059	56	437 by 374	22
Zhang, Z	Shanghai Institute of Materia Medica, Chinese Academy of Sciences, State Key Laboratory of Drug Research and Center of Pharmaceutics, Shanghai, China	116	31	He Q, et al. In vivo biodistribution and urinary excretion of mesoporous sílica nanoparticles: effects of particle size PEGylation. *Small*. 2011;7(2):271–280	262	3,624 by 2,855	26
		17	12	Tang S, et al. Co-delivery of doxorubicin and RNA using pH-sensitive poly (β-amino ester) nanoparticles for reversal of multidrug resistance of breast cancer. *Biomaterials*. 2014;35(23):6047–6059	56	431 by 368	22
Yin, Qi	Shanghai Institute of Materia Medica, Chinese Academy of Sciences, State Key Laboratory of Drug Research, Shanghai, China	69	27	Gao Y, et al. Controlled intracellular release of doxorubicin in multidrug-resistant cancer cells by tuning the shell-pore sizes of mesoporous sílica nanoparticles. *ACS Nano*. 2011;5(12):9788–9798	197	2,082 by 1,620	27
		16	10	Tang S, et al. Co-delivery of doxorubicin and RNA using pH-sensitive poly (β-amino ester) nanoparticles for reversal of multidrug resistance of breast cancer. *Biomaterials*. 2014;35(23):6047–6059	56	387 by 338	22
Akbarzadeh, Abolfazl	Tabriz University of Medical Sciences, Department of Medical Nanotechnology, Tabriz, Iran	141	25	Akbarzadeh A, et al. Liposome: classification preparation, and applications. *Nanoscale Res Lett*. 2013;8(1):1–8	295	2,202 by 1,365	28
		14	6	Ghasemali S, et al. Inhibitory effects of β-cyclodextrin-helenalin complexes on H-TERT gene expression in the T47D breast cancer cell line – results of real time quantitative PCR. *Asian Pac J Cancer Prev*. 2013;14(11):6949–6953	36	115 by 94	29

Wang, Wueqing	Peking University, Beijing Key Laboratory of Molecular Pharmaceutics and New Drug Delivery Systems, Beijing, China	118	27	Dai J, et al. pH-sensitive nanoparticles for improving the oral bioavailability of cyclosporine A. *Int J Pharm*. 2004;280(1–2):229–240	123	2,064 by 1,667	30
		14	8	Wang Z, et al. The use of a tumor metastasis targeting peptide to deliver doxorubicin-containing liposomes to highly metastatic cancer. *Biomaterials*. 2012;33(33):8451–8460	64	271 by 250	31
Zhang, Qiang	Peking University, State Key Laboratory of Natural and Biomimetic Drugs, Beijing, China	109	22	Zhang Y, et al. The eradication of breast cancer and cancer stem cells using octreotide modified paclitaxel active targeting micelles and salinomycin passive targeting micelles. *Biomaterials*. 2012;33(2):679–691	104	1,413 by 1,201	32
		14	7	Feng Q, et al. Synergistic inhibition of breast cancer by co-delivery of VEGF siRNA and paclitaxel via vapreotide-modified core-shell nanoparticles. *Biomaterials*. 2014;35(18):5028–5038	57	245 by 234	33
Dinarvand, Rassoul	Tehran University of Medical Sciences, Nanotechnology Research Center, Tehran, Iran	294	37	Ganjali MR, et al. Schiff's bases and crown ethers as supramolecular sensing materials in the construction of potentiometric membrane sensors. *Sensors*. 2008;8(3):1645–1703	169	5,580 by 4,455	34
		13	7	Taheri A, et al. The in vivo antitumor activity of LHRH targeted methotrexate-human serum albumin nanoparticles in 4T1 tumor-bearing Balb/c mice. *Int J Pharm*. 2012;431(1–2):183–189	26	129 by 123	24
Ferrari, Mauro	Methodist Hospital Houston, Department of Nanomedicine, Houston, USA	450	65	Ferrari M. Cancer nanotechnology: opportunities and challenges. *Nat Rev Cancer*. 2005;5(3):161–171	2,700	17,952 by 11,803	35
		13	10	Xu R, et al. Na injectable nanoparticle generator enhances delivery of cancer therapeutics. *Nat Biotechnol*. 2016;34(4):414–418	62	336 by 253	36

response, 8% presented stable disease, and only 5% had progressive disease. The duration of progression-free disease was 15 months; however, 53.66% and 100% of the participants had serious adverse effects and other adverse effects, respectively.

Overall, the scenario on TNBC and nanotechnology is not greatly encouraging currently. As in traditional chemotherapy, adverse effects of the regimens seem to be the main cause of concern. Notwithstanding, further research and the introduction of different nanosystems are pivotal for the improvement of therapeutic options for TNBC.

Articles

The top 10 most cited articles had 2,224 citations, representing 8.4% of the total citations. The paper entitled "Preclinical development and clinical translation of PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile" (2012) published in *Science Translational Medicine* by HrKach J et al was the most cited, with 445 citations. The top 10 most cited articles are shown in Table 7.

Hotspots

Keywords of 1,932 articles were analyzed in VOSviewer. Of 14,614 keywords, 145 were used >85 times in titles and abstracts of all papers. Keywords were classified into four clusters formed in the software VOSviewer: "Drugs", "Animal Models", "Human cell lines", and "Properties". In the cluster "Drugs", the most used keywords were "breast cancer" (1,133 times), "drug delivery system" (666 times), and "antineoplasic agent" (544 times).

In the cluster "Animal Models", the most used keywords were "unclassified drug" (685 times), "in vitro study" (584 times), and "particle size" (551 times). In the cluster "Human cell lines", the more frequently used keywords were "human" (1,481 times), "humans" (1,340 times), and "chemistry" (855 times). In the cluster "Properties", the most common keywords were "female" (1,023 times), "nonhuman" (802 times), and "animals" (793 times). Keywords and association lines are shown in Figure 5 and listed in Table S1.

Several drugs are used in TNBC treatment, and results of clinical studies demonstrated that TNBC patients have different responses to them.[47] However, the chemotherapeutic drug widely reported in nanomedicine for the treatment of TNBC was "doxorubicin" (395 times), and the most common carrier nanosystem was "liposome/liposomes" (279 times). Accordingly, during the past few years, various nanomaterials have been developed for the detection and treatment of

Table 5 Patents filed by the top 10 authors in the area of nanotechnology and triple negative breast cancer

Inventors	Patent name	Applicant	Date of filing	Patent office	Patent number
Li, Yaping (Pudong Shanghai, CN); Chen, Lingli (Pudong Shanghai, CN); Zheng, Zhaolei (Pudong Shanghai, CN); Zhang, Zhiwen (Pudong Shanghai, CN); Gu, Wangwen (Pudong Shanghai, CN)	Irinotecan hydrochloride composite phospholipid composition, preparation method and use thereof	Shanghai Institute of Materia Medica, Chinese Academy Sciences Shanghai Jingfeng Pharmaceutical CO., LTDA	March 6, 2015	United States Patent and Trademark Office Pre-Granted Publication United Kingdom Patent Application	US20170087146 GB20160016625 20150306
Gillman, Kevin W (Madison, CT); Goodrich, Jason (Wallingford, CT); Boy, Kenneth M (Durham, CT); Zhang, Yunhui (Glastonbury, CT); Mapelli, Claudio (Lawrenceville, NJ); Poss, Michael A (Lawrenceville, NJ); Sun, Li-Qiang (Glastonbury, CT); Zhao, Qian (Wallingford, CT); Mull, Eric (Guilford, CT); Gillis, Eric P (Cheshire, CT); Scola, Paul Michael (Glastonbury, CT)	Immunomodulators	Bristol-Myers Squibb Company	November 11, 2015	United States Patent and Trademark Office Pre-Granted Publication	US20160137696
Dinarvand, Rassoul (Tehran, IR); Derakhshan, Mohammad Ali (Tehran, IR); Rahbarizadeh, Fatemeh (Tehran, IR); Majidi, Reza Faridi (Tehran, IR); Borujeni, Azade Taheri (Tehran, IR); Rezayat, Seyed Mahdi (Tehran, IR)	Multi-mode cancer targeted nanoparticulate system and a method of synthesizing the same	Dinarvand; Rassoul Derakhshan; Mohammad Ali Rahbarizadeh; Fatemeh Majidi; Reza Faridi Borujeni; Azade Taheri Rezayat; Seyed Mahdi	January 11, 2012	United States Patent and Trademark Office Pre-Granted Publication	US20130178603
Mi, Yu (Houston, TX); Ferrari, Mauro (Houston, TX)	Micro/nano composite drug delivery formulations and uses thereof	The Methodist Hospital (Houston, TX, USA)	August 25, 2016	United States Patent and Trademark Office Pre-Granted Publication	US20170056327
Shen, Haifa (Houston, TX); Ferrari, Mauro (Houston, TX); Shen, Jian (Houston, TX); Zhang, Mingzhen (Houston, TX)	Polycation-functionalized nanoporous silicon carrier for systemic delivery of gene silencing agents	The Methodist Hospital (Houston, TX, USA)	December 11, 2015	United States Patent and Trademark Office Pre-Granted Publication	US20160369269
Ferrari, Mauro (Houston, TX); Tasciotti, Ennio (Houston, TX); Sakamoto, Jason (Houston, TX)	Multistage delivery of active agents	Ferrari; Mauro Tasciotti; Ennio Sakamoto; Jason	May 29, 2015	United States Patent and Trademark Office Pre-Granted Publication	US20160051481

breast cancer. These nanoparticles are made up of a variety of materials including lipids, polymers, silica, protein/peptides, oligonucleotides, and metals such as gold, silver, and iron.[48] We found in this review that the main materials used in the formulations were "macrogol" (191 times), "macrogol derivate" (177 times), and "polyethylene glycols" (265 times).

VOSviewer applied colors to keywords based on the year that they appeared in the literature. Keywords in red appeared early, followed by yellow and green colors, while keywords in blue appeared later. The average year of cluster appearance was close to each other. The cluster "Drugs" had the more recently used keyword "antineoplasic agent" (544 times cited, year of appearance 2014). The cluster "Animal models" had "Breast cancer cell lines" (231 times cited, 2015), the cluster "Human cell lines" had "MCF-7 cell lines" (165 times cited, 2016), and the cluster "Properties" had "Bagg albino mouse"

Table 6 Clinical trials in the area of nanotechnology and triple negative breast cancer

Study title	Status	Interventions	First posted	Sponsors/ collaborators	Principal investigators
Carboplatin and paclitaxel albumin-stabilized nanoparticle formulation before surgery in treating patients with locally advanced or inflammatory triple negative breast cancer	Recruiting	Drug: carboplatin Drug: paclitaxel albumin-stabilized nanoparticle formulation Other: laboratory biomarker analysis	February 3, 2012	City of Hope Medical Center National Cancer Institute	Yuan Yuan Stephen C Koehler
A trial of nanoparticle albumin-bound paclitaxel (nab-paclitaxel, abraxane®) with or without mifepristone for advanced, glucocorticoid receptor-positive, triple negative breast cancer	Recruiting	Drug: mifepristone Other: placebo Drug: nab-paclitaxel	June 2, 2016	University of Chicago	Rita Nanda Gini Fleming
Study to evaluate CORT125134 in combination with nab-paclitaxel in patients with solid tumors	Recruiting	Drug: CORT125134 with nab-paclitaxel	May 5, 2016	Corcept Therapeutics	Thaddeus S Block
Paclitaxel albumin-stabilized nanoparticle formulation and bevacizumab followed by bevacizumab and erlotinib hydrochloride in treating patients with metastatic breast cancer	Active, not recruiting	Drug: paclitaxel albumin-stabilized nanoparticle formulation Biologic: bevacizumab Drug: erlotinib hydrochloride Other: laboratory biomarker analysis	August 13, 2008	National Cancer Institute University of Washington	Jennifer Specht
Paclitaxel albumin-stabilized nanoparticle formulation in treating older patients with locally advanced or metastatic breast cancer	Active, not recruiting	Drug: paclitaxel albumin-stabilized nanoparticle formulation Other: questionnaire administration	November 1, 2011	National Cancer Institute City of Hope Medical Center	Arti Hurria
Veliparib in treating patients with malignant solid tumors that do not respond to previous therapy	Active, not recruiting	Other: laboratory biomarker analysis Other: pharmacologic study Drug: veliparib	May 4, 2009	National Cancer Institute	Shannon Puhalla
Neoadjuvant pembrolizumab(Pbr)/Nab-paclitaxel followed by pbr/epirubicin/cyclophosphamide in TNBC	Not yet recruiting	Drug: pembrolizumab Drug: nab-paclitaxel Drug: epirubicin Drug: cyclophosphamide	September 21, 2017	Merck Sharp & Dohme Corp. Celgene Corporation Institut fuer Frauengesundheit	Peter A Fasching
Phase II study with abraxane, bevacizumab and carboplatin in triple negative metastatic breast cancer	Completed*	Drug: abraxane Drug: bevacizumab Drug: carboplatin	May 28, 2007	Duke University Genentech, Inc. Celgene Corporation	Kimberly Blackwell
AZD2281 plus carboplatin to treat breast and ovarian cancer	Completed	Drug: AZ2281+carboplatin	October 3, 2011	National Cancer Institute	Jung-Min Lee
An efficacy study of trabectedin in the treatment of participants with specific subtypes of metastatic breast cancer	Completed	Drug: dexamethasone Drug: trabectedin	December 24, 2007	Johnson & Johnson Pharmaceutical Research and Development, LLC PharmaMar	Not mentioned
Study of abraxane and carboplatin as first-line treatment for triple negative metastatic breast cancer	Terminated*	Drug: abraxane Drug: carboplatin	September 22, 2010	Duke University Celgene Corporation	Kimberly L Blackwell

Note: *Studies that have results.

Table 7 Top 10 cited papers in the area of nanotechnology and triple negative breast cancer

Authors and journal	Article	Main results	Total citations	Average citations per year	References
Hrkach J, et al. *Science Translational Medicine*. 2012;4(128):128ra39	Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile	Docetaxel encapsulated in polymeric nanoparticle exhibited enhanced tumor accumulation and prolonged tumor growth suppression in low doses also, compared to that typically used in the clinic	445	88.2	37
Ohno S-I, et al. *Molecular Therapy*. 2013;21(1):185–191	Systemically injected exosomes targeted to EGFR deliver antitumor microRNA to breast cancer cells	Exosomes can efficiently deliver miRNA to EGFR-expressing breast cancer cells, also can be used therapeutically to target EGFR-expressing cancerous tissues with acid drugs	291	70.5	38
Danhier F, Breton AL, Préat V. *Molecular Pharmaceutics*. 2012;9(11):2961–2973	RGD-based strategies to target alpha(v) beta (3) integrin in cancer therapy and diagnosis	This review aims to highlight the position of RGD-based nanoparticles in cancer therapy and imaging	283	55.4	39
Ge J, et al. *Nature Communications*. 2014;5:4596	A graphene quantum dot photodynamic therapy agent with high singlet oxygen generation	Graphene quantum dots can be used as photodynamic agents allowing imaging and providing a highly efficient cancer therapy	219	71.7	40
Yuan H, Fales AM, Vo-Dinh T. *Journal of the American Chemical Society*. 2012;134(28):11358–11361	TAT peptide-functionalized gild nanostars: enhanced intracellular delivery and efficient NIR photo-thermal therapy using ultralow irradiance	The entrance of TAT-peptide-functionalized gold nanostars in the cells is increased after photothermolysis, enhancing its intracellular delivery and action	212	41.4	41
Cheng L, et al. *Biomaterials*. 2012;33(7):2215–2222	Multifunctional nanoparticles for upconversion luminescence/MR multimodal imaging and magnetically targeted photothermal therapy	Multifunctional nanoparticles under application of near-infrared laser irradiation promotes photothermal therapeutic efficacy with 100% tumor elimination in in vivo model	208	41.4	42
King HW, Michael MZ, Gleadle JM. *BMC Cancer*. 2012;12:421	Hypoxic enhancement of exosome release by breast cancer cells	Hypoxia promotes the release of exosomes by breast cancer cells mediated by HIF-1α	166	32.4	43
Amoozgar Z, Yeo T. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*. 2012;4(2):219–233	Recent advances in stealth coating of nanoparticle drug delivery systems	This review aims to disseminate strategies to improve the action of nanoparticles using different synthesis methods and to present general characteristics about it	156	31.0	44
Pecot CV, et al. *Nature Communications*. 2013;4:2427	Tumour angiogenesis regulation by the miR-200 family	miR-200 inhibits angiogenesis in several cancer types through direct and indirect mechanisms by targeting interleukin-8 and CXCl1 secreted by tumor endothelial and cancer cells	126	31.2	45
She W, et al. *Biomaterials*. 2013;34(9):2252–2264	Dendronized heparin-doxorubicin conjugate-based nanoparticle as pH-responsive drug delivery system for cancer therapy	The nanoparticles were shown to effectively kill cancer cells in vitro, showed strong antitumor activity, showed high antiangiogenesis effects, and induced apoptosis in vivo	118	29.0	46

Abbreviation: HIF, hypoxia-inducible factor.

(193 times cited, 2015) as the more recently used keywords (Figure 6). The density map shows the citation concentration areas for keywords (Figure 7).

Conclusion

Nanotechnology cancer field has the potential for improving therapeutic efficacy, creating methods for detection, and targeting different cancer stages. Development of various nanomaterials and nanotechnology had allowed the improvement of cancer biomarkers area with high precision and sensibility that was not the case some years ago. In this study, the global scientific production from the period ranging from 2012 to 2017 related to the nanotechnology applied to TNBC research was analyzed quantitatively and qualitatively. Results showed an increase in the cumulative volume of papers worldwide and a tendency to continue growing in terms of publication numbers. Research has focused on the search for drug carrier systems for the treatment of breast cancer in in vitro studies using the MCF-7 cell line and animal models, specifically Bagg albino mouse. Thus, through the study of the quantitative aspects of the production and dissemination of the

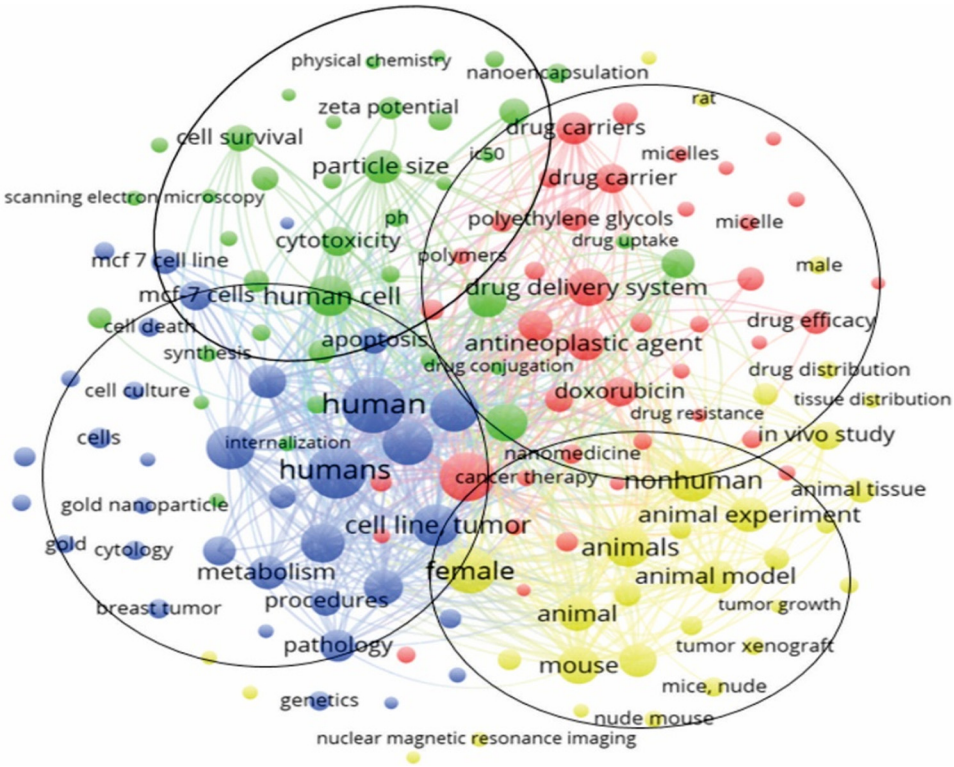

Figure 5 Association line of keywords from papers in the area of nanotechnology and triple negative breast cancer.

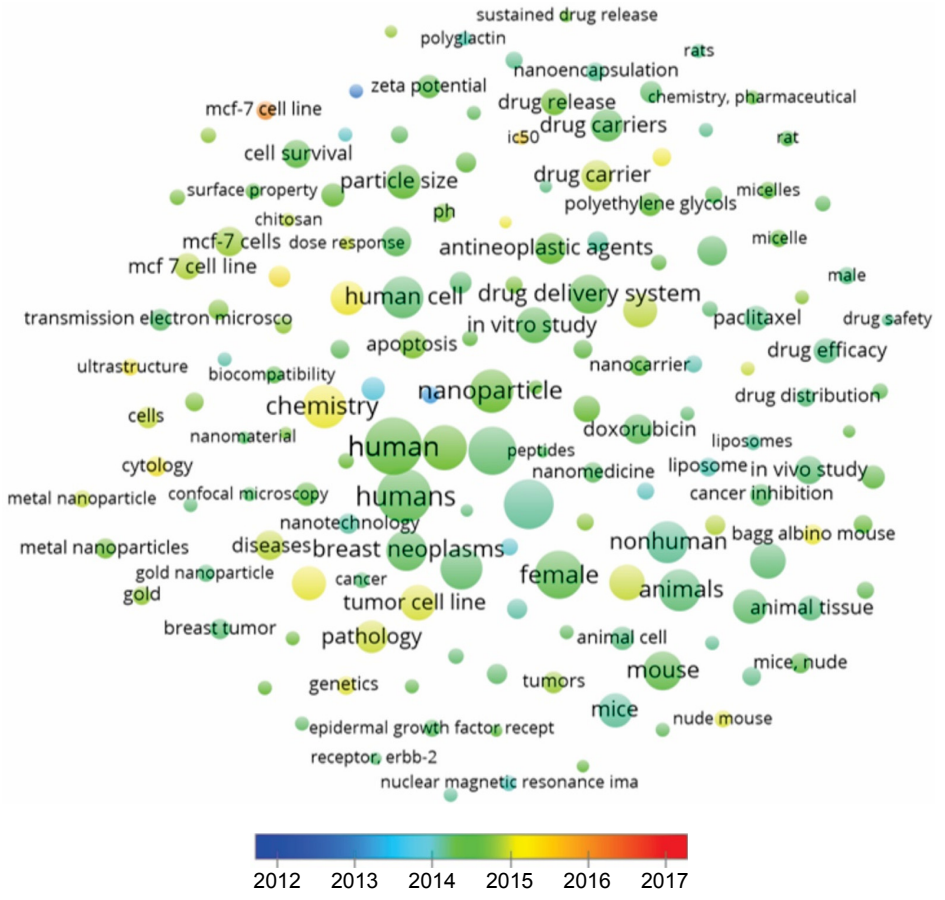

Figure 6 Average year map of keywords.

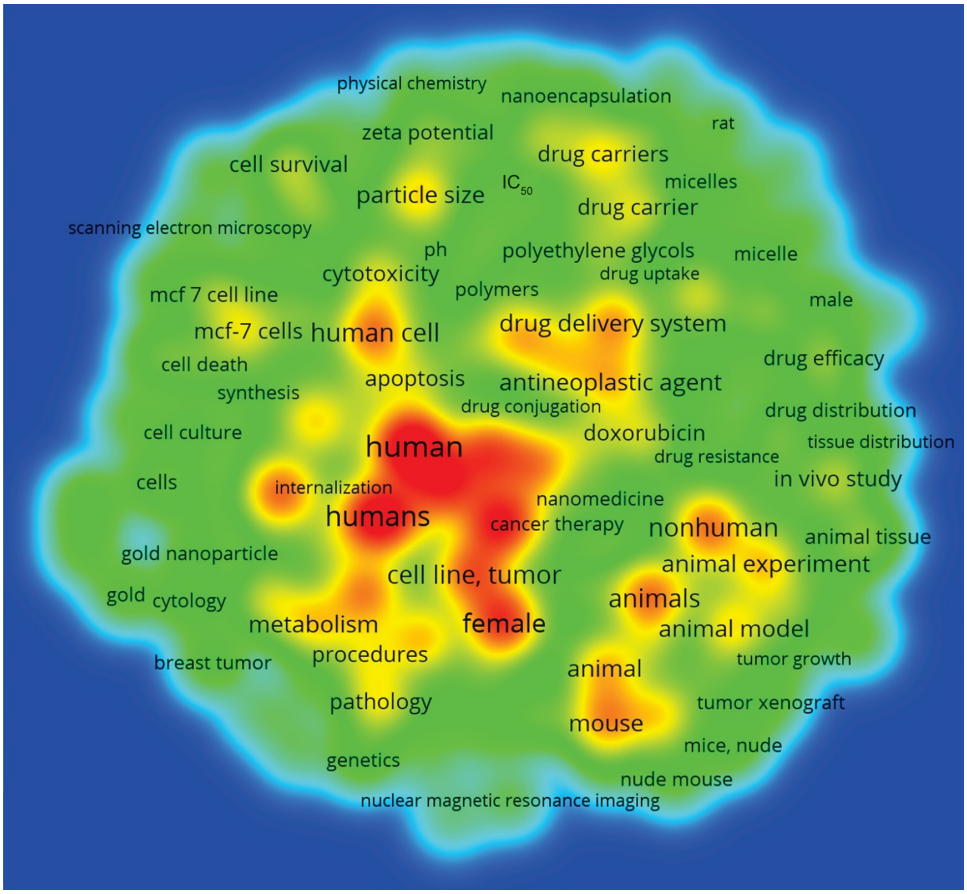

Figure 7 Density map of keywords.

knowledge generated in the time interval observed through bibliometric analysis, it was possible to trace the research profiles of different countries, centers, and researchers, offering an important analysis of the scientific production, behavior, and development in this field of research.

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Author contributions

All three authors have made substantial contributions to the acquisition, analysis and interpretation of the data in this study. All authors also critically revised the manuscript. The authors agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 List of keywords generated by VOSviewer

Id	Cluster	Links	Total link strength	Ocurrences	Avg. pub. year
Antibiotics, antineoplasic	1	142	2,748	91	2014.32
Antineoplasic agent	1	145	15,216	544	2014.86
Antineoplastic agents	1	145	12,789	466	2014.52
Antineoplastic agents, phytogenic	1	144	3,049	110	2014.37
Breast cancer	1	145	25,473	1,133	2014.20
Cancer	1	145	2,299	111	2014.31
Cancer chemotherapy	1	145	3,622	135	2014.11
Cancer therapy	1	145	3,606	150	2014.02
Chemistry, pharmaceutical	1	140	2,597	89	2014.53
Chemotherapy	1	145	3,395	132	2014.67
Docetaxel	1	142	3,174	128	2014.39
Doxorubicin	1	145	10,337	395	2014.38
Drug carrier	1	145	12,086	427	2014.87
Drug carriers	1	145	13,199	478	2014.49
Drug delivery	1	145	5,533	226	2014.32
Drug delivery system	1	145	17,825	666	2014.43
Drug delivery systems	1	145	8,691	318	2014.51
Drug efficacy	1	145	8,873	299	2014.26
Drug formulation	1	145	6,652	237	2014.35
Drug resistance	1	145	2,946	93	2014.90
Drug resistance, neoplasm	1	145	3,199	110	2014.90
Drug safety	1	137	2,056	85	2014.24
Drug targeting	1	145	3,707	137	2014.07
Encapsulation	1	142	2,966	104	2014.22
Epidermal growth receptor 2	1	145	2,759	129	2014.37
Liposome	1	145	3,933	165	2014.10
Liposomes	1	144	2,916	114	2014.18
Macrogol	1	145	5,495	191	2014.18
Macrogol derivate	1	144	5,737	177	2015.06
Micelle	1	145	4,475	149	2014.53
Micelles	1	144	4,104	137	2014.53
Molecularly targeted therapy	1	145	2,453	86	2014.37
Multigrud resistance	1	144	2,708	93	2014.69
Nanocarrier	1	145	5,136	179	2014.50
Nanomedicine	1	145	4,366	179	2014.36
Nanotechnology	1	145	3,660	200	2014.15
Neoplasms	1	145	4,503	198	2014.15
Paclitaxel	1	145	6,411	277	2014.26
Polyethylene glycols	1	145	7,772	265	2014.51
Polymer	1	145	4,412	163	2014.44
Polymers	1	145	4,078	149	2014.62
Antineoplastic activity	2	145	12,103	411	2014.35
Biocompatibility	2	145	3,250	129	2014.44
Breast cancer cell line	2	144	6,465	231	2015.23
Cancer cell	2	145	6,297	267	2013.88
Cancer cell culture	2	143	3,361	150	2013.12
Cell strain MCF-7	2	141	1,972	90	2012.83
Cell survival	2	145	9,525	352	2014.43
Cell viability	2	145	7,251	267	2014.50
Chitosan	2	144	2,019	91	2014.87
Concentration response	2	145	2,310	86	2014.05
Confocal microscopy	2	144	2,658	99	2014.35

(*Continued*)

Table S1 (*Continued*)

Id	Cluster	Links	Total link strength	Ocurrences	Avg. pub. year
Cytotoxicity	2	145	10,253	406	2014.37
Drug conjugation	2	145	3,059	103	2014.53
Drug cytotoxicity	2	145	5,914	204	2014.47
Drug release	2	145	9,809	338	2014.57
Drug stability	2	145	3,688	135	2014.22
Drug synthesis	2	145	3,459	132	2014.37
Drug uptake	2	145	3,290	109	2014.45
Endocytosis	2	145	3,664	125	2014.46
Flow cytometry	2	145	4,128	158	2914.37
Fluorescence microscopy	2	145	2,217	89	2014.13
Human cell	2	145	20,170	787	2014.32
Hydrogen ion concentration	2	145	2,670	89	2014.37
IC_{50}	2	143	3,263	103	2015.41
In vitro study	2	145	16,554	584	2014.39
Infrared spectroscopy	2	143	2,917	122	2014.70
Internalization	2	145	3,244	112	2014.53
Nanoencapsulation	2	145	5,072	175	2014.21
Particle size	2	145	14,569	551	2014.48
pH	2	145	4,373	154	2014.63
Physical chemistry	2	145	2,814	103	2014.48
Polyglactin	2	145	2,349	87	2014.11
Scanning electron microscopy	2	144	2,429	111	2014.59
Surface property	2	145	2,998	113	2014.47
Synthesis	2	145	3,766	138	2014.72
Transmission electron microscopy	2	145	5,382	227	2014.34
Unclassified drug	2	145	16,929	685	2014.13
Zeta potential	2	145	6,990	253	2014.44
Apoptosis	3	145	9,513	354	2014.65
Breast cancer cells	3	145	2,200	105	2014.30
Breast neoplasms	3	145	18,161	729	2014.37
Breast tumor	3	145	4,316	182	2014.31
Cell culture	3	145	3,973	169	2014.63
Cell death	3	145	5,057	193	2014.63
Cell line, tumor	3	145	21,152	814	2014.33
Cell proliferation	3	145	6,910	263	2014.48
Cells	3	145	5,212	226	2914.90
Chemistry	3	145	22,331	855	2015.02
Cytology	3	145	4,356	187	2015.14
Diseases	3	145	9,406	400	2014.87
Dose response	3	145	2,356	87	2014.91
Drug effects	3	145	15,154	527	2015.11
Gene expression	3	142	2,240	96	2014.54
Genetics	3	145	4,557	178	2014.98
Gold	3	143	3,108	161	2014.73
Gold nanoparticle	3	144	2,840	148	2014.28
Human	3	145	33,652	1,481	2014.47
Humans	3	145	31,754	1,340	2014.39
MCF-7 cell line	3	145	8,507	308	2014.82
MCF-7 cell lines	3	143	4,219	165	2016.04
MCF-7 cells	3	145	10,907	419	2014.75
Metabolism	3	145	13,700	530	2014.99
Metal nanoparticle	3	144	2,822	146	2014.90
Metal nanoparticles	3	143	3,623	191	2014.61
Nanoparticle	3	145	20,739	856	2014.54
Nanoparticles	3	145	21,557	918	2014.55
Pathology	3	145	12,505	474	2014.92

(*Continued*)

Table S1 (*Continued*)

Id	Cluster	Links	Total link strength	Ocurrences	Avg. pub. year
Procedures	3	145	9,188	368	2015.16
Protein expression	3	145	5,090	200	2014.33
RNA, small interfering	3	143	2,303	86	2014.43
Small interfering RNA	3	145	2,952	120	2014.33
Tumor cell line	3	145	16,200	584	2014.95
Ultrastructure	3	144	3,356	129	2015.16
Animal	4	145	16,923	563	2014.90
Animal cell	4	145	7,522	262	2014.27
Animal experimente	4	145	17,049	571	2014.31
Animal model	4	145	15,890	524	2014.33
Animal tissue	4	145	8,724	293	2014.27
Animals	4	145	22,161	793	2014.29
Bagg albino mouse	4	145	6,713	193	2015.00
Cancer inhibition	4	145	7,263	231	2014.35
Drug distribuition	4	145	5,077	157	2014.28
Drug screening	4	145	5,716	180	2014.83
Female	4	145	25,711	1,023	2014.41
In vivo study	4	145	11,108	360	2014.31
Magnetic resonance imaging	4	142	2,176	87	
Magnetite nanoparticle	4	144	2,027	90	2014.50
Magnetite nanoparticles	4	142	2,119	95	2014.35
Male	4	145	4,262	151	2014.26
Mice	4	145	14,860	517	2014.18
Mice, inbred balb c	4	145	8,385	256	2014.44
Mice, nude	4	145	6,470	194	2014.43
Mouse	4	145	19,679	679	2014.42
Nonhuman	4	145	21,738	802	2014.20
Nuclear magnetic resonance imaging	4	144	2,582	113	
Nude mouse	4	145	5,420	149	2014.97
Rat	4	145	3,456	124	2014.43
Rats	4	143	2,374	91	2014.24
Tissue distribuition	4	145	3,387	114	2014.39
Treatment outcome	4	144	2,351	91	2014.37
Tumor growth	4	145	2,848	93	2014.22
Tumor volume	4	145	4,774	153	2014.52
Tumor xenograft	4	145	4,757	154	2014.24
Tumors	4	145	5,707	218	2014.76
Xenograft model antitumor assays	4	145	4,978	150	2014.41