




# Publication Trends in Exosomes Nanoparticles for Cancer Detection

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**Background:** Exosomes are small vesicles produced by almost all cells in the body and found in all biofluids. Cancer cell-derived exosomes are known to have distinct, measurable signatures, applicable for early cancer diagnosis. Despite the present bibliometric studies on “Cancer detection” and “Nanoparticles”, no single study exists to deal with “Exosome” bibliometric study.

**Methods:** This bibliometric work investigated the publication trends of “Exosomes” nanoparticles and its application in cancer detection, for the literature from 2008 to July 2019. The data were collected from the Web of Science Core Collection. There were variant visual maps generated to show annual publication, most-relevant authors, sources, countries, topics and keywords. The network analysis of these studies was investigated to evaluate the research trends in the field of exosomes. In addition, the data were qualitatively analyzed according to 22 top-cited articles, illustrating the frequently used subjects and methods in exosomes research area.

**Results:** The results showed that the documents in this field have improved the citation rate. The top-relevant papers are mostly published in Scientific Reports journal which has lost its popularity after 2017, while today, Analytical Chemistry is leading in publishing the most articles related to exosomes. The documents containing keywords of plasma, cells, cancer, biomarkers, and vesicles as keywords plus, are more likely to be published in PLoS One journal. The clustering of the keywords network showed that the keyword theme of “extracellular vesicles” has the highest centrality rate. In global research, USA is the most corresponding country, followed by China, Korea and Australia. Based on the qualitative analysis, the published documents with at least 50 citations have used exosome release, cargo, detection, purification and secretion, as their targets and applied cell culture or isolation as their methods.

**Conclusion:** The bibliometric study on exosomes nanoparticles for cancer detection provides a clear vision of the future research direction and identifies the potential opportunities and challenges. This may lead new researchers to select the proper subfields in exosome-related research fields.

**Keywords:** exosomes, cancer detection, nanoparticles, microvesicles, bibliometrics, research productivity

## Introduction

Conventional techniques for cancer detection (eg, computed tomography, advanced imaging and tissue biopsy) are associated with many challenges, such as high cost, invasive surgical procedures, low sensitivity and high false-positive rate.<sup>1,2</sup> To address these challenges, exosome-based liquid biopsy has been introduced in the last decade for early cancer detection, given its minimally

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invasive and highly sensitive and specific performance.<sup>2</sup> The unique characteristics of cancer cell-derived exosomes make them a potential biomarker for early cancer diagnosis, detection of highly metastatic cancer cells, and assessment of cancer heterogeneity. Exosomes are also markers for tracking cancer patient's response to treatments and detection of resistance mechanisms against treatment, contributing to precise and personalized cancer treatment (Table 1).<sup>3</sup> Exosomes shed from cancer cells have shown to be highly predictive for cancer detection since they contain the biomolecules that are reflective of oncogenic signaling in cancer cells of origin.<sup>4</sup> Exosomal proteins can reliably distinguish cancer type and stage for some types of cancers.<sup>5,6</sup>

Bibliometric is defined as the application of mathematical and statistical methods to evaluate scholarly outputs.<sup>7</sup> The bibliometric research to date has focused on natural products against cancer,<sup>8</sup> nanotechnology applied in oncology,<sup>9</sup> neurotoxicity of nanoparticles,<sup>10</sup> and drug delivery and magnetic nanoparticles.<sup>11</sup> Although extensive research has been carried out on the bibliometric study of "Cancer detection" and "Nanoparticles", no single study exists to deal with "Exosome" bibliometric study. This study aims to explore the research status on "Exosome" research field in "Cancer detection" and "Nanoparticles", from the beginning to the current year (January 2020) by bibliometric approaches.

Bibliometric approach has been used to measure scientific progress in many disciplines for the systematic analysis of publications.<sup>12</sup> For research evaluation, some other indicators were needed. Citation analysis along with peer review ensured better judgment in countless cases.<sup>13</sup> Nowadays, several tools have apparently made it easier to produce a bibliometric report.<sup>14</sup> This ranges from databases such as Web of Science Core Collection (WoS), SCOPUS, and Google Scholar that have added incorporated reference-handling capabilities.<sup>14-16</sup> Google Scholar provides free access to scholarly documents of all types, which makes it questioned due to sporadic coverage.<sup>17</sup> WoS and Scopus are the most extensive databases in different scientific fields, used for searching the literature.<sup>18</sup> Therefore, in this research SCOPUS and WoS databases are compared against the coverage of "Exosome" research and the best one is selected for the study.

## Methodology

A bibliometric study was conducted to evaluate the publication trends and find the insight of publications on "Exosome". A title search of "Exosome" was carried out

on both well-known databases, SCOPUS and WoS, to select the preferred database for data collection. The number of documents on SCOPUS was 1665 which was less than the number of documents with the same search on WoS (1869 records). WoS is the most appropriate influential, extensive, and trustworthy database for literature retrieval and analysis.<sup>18,19</sup> Therefore, the data were collected from WoS database base of the title search of "Exosome". A title search of "Exosome" in WoS returned 1869 documents on 30 July 2019. The entire documents of 1869 received total citations of 64,520 and average citations per paper of 34.52. The trends in the number of publications in the "Exosome" field grow dramatically, as shown in Figure 1.

The search was refined by the topic search of "Cancer Detection\*" and "Nanoparticle\*" which therefore reached 166 documents indexed in the Science Citation Index Expanded (SCIEXPANDED), Social Sciences Citation Index (SSCI), Arts & Humanities Citation Index (A&HCI), and Emerging Sources Citation Index (ESCI) of WoS. These 166 relevant documents have received the average citations per item of 29.33, which is slightly less than "Exosome" citations. This is due to the nature of new emerging research areas, as the first related document was published in 2008. The final 166 sets of documents were analyzed by Bibliometrix-package (<http://www.bibliometrix.org/>), which is an R-Tool for science mapping.<sup>20</sup>

Table 2 shows a summary of the primary information on collected Bibliometric data. There were 135 articles, 23 review papers, and 8 editorials, meeting abstracts, and corrections. To map the present subtopics of the exosome-based research field, especially nanoparticles and cancer detection, 22 top-cited articles have been selected (from the total of 135 articles) for qualitative analysis. The quantitative and qualitative analysis of the data comes in the following sections.

## Quantitative Analysis Analysis of Publication Years

Figure 2 shows the yearly scientific production of published papers about exosomes nanoparticles and cancer detection, within the period of 2008 to 31st July 2019. Within this period, there are 166 scientific productions including 135 articles, 23 review papers, two proceedings papers and six others. The number of articles published has totally increased from the minimum one document in 2008 to 46 documents in 2018. There are two turning points during this

**Table I** Exosomal Biomarkers for Diagnosis of Different Cancers

	Type of Cancer	Exosomal Biomarkers	Approach	Body Fluid Specimen	Ref.
<b>Exosomal protein markers</b>	Ovarian cancer	HNRHPU, U2AF2 TGM2 and U2AF1 CD24	Diagnosis	Ascitic fluid	[39]
	Lung cancer	IQGAP, MUC5B, BPIFA1 and CRNN LRG1	Diagnosis	Ascitic fluid	[40]
	Hepatocellular Carcinoma	Vasorin	Diagnosis	Saliva	[41]
	Prostate cancer	PCA3	Diagnosis	Urine	[42]
	Colorectal cancer	CD147	Prognosis	Culture medium	[43]
	Pancreatic cancer	Glypican-1	Diagnosis and prognosis	Urine	[44]
	Gastric cancer	EGFR	Diagnosis and prognosis	Patient blood	[45]
	Glioma	IL13QD	Diagnosis	Patient blood	[4]
	Glioblastoma	IL-6, IL-8 and angiogenin	Diagnosis and prognosis	Culture medium	[46]
	Melanoma	HSP70, HSP90, TYRP2, VLA-4, and MET	Diagnosis and prognosis	Cerebrospinal fluid Cerebrospinal fluid	[47]
				Culture medium	[48]
				Culture medium	[49]
<b>Exosomal nucleic acid markers</b>	Ovarian cancer	miR-30a-5p	Diagnosis and prognosis	Urine	[50]
		miR-21, miR-141, miR-200a, miR200c, miR-200b, miR-203, miR-205 and miR-214	Diagnosis	Patient serum	[51]
	Lung cancer	miR-21	Diagnosis	Blood	[52]
		miR-1247-3p	Diagnosis	Patient serum	[53]
		EGFR (DNA)	Diagnosis and prognosis	Plasma and culture medium	[54]
	Prostate cancer	miR-196a-5p and miR-501-3p	Diagnosis	Urine	[55]
		miR-141 and miR375; miR-107 and miR-574-3p	Diagnosis	Serum and urine	[56]
		miR-1290 and miR-375	Prognosis	Patient plasma	[57]
		SPDEF (RNA), PCA3,ERG	Diagnosis	Urine	[58]
		PCA-3 mRNA	Diagnosis and prognosis	Patient urine	[44]
	Colorectal cancer	circ-KLDHC10	Diagnosis	Patient serum	[59]
		miR-193a	Diagnosis	Serum	[60]
	Pancreatic cancer	KRAS DNA	Diagnosis and prognosis	Patient serum	[24]
		miR-4306, miR4644, miR-3976 and miR-1246	Diagnosis	Patient serum	[38]
		miR-10b	Diagnosis and prognosis	Patient plasma	[61]
	Gastric cancer	miR-181a, miRlet7a, miR-10b, miR-21 and miR30c	Diagnosis	Patient blood	[62]
	LncRNA HOTTIP	Diagnosis and prognosis	Patient serum	[63]	
Melanoma	BRAF (DNA)	Diagnosis and prognosis	Plasma and culture medium	[54]	
			Culture medium		

(Continued)

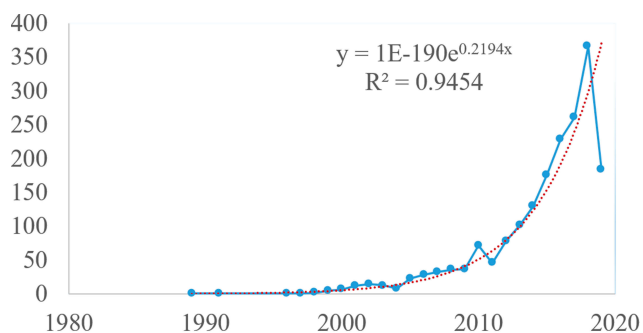
**Table 1** (Continued).

	Type of Cancer	Exosomal Biomarkers	Approach	Body Fluid Specimen	Ref.
	Glioblastoma	EGFRvIII (mRNA)	Diagnosis and prognosis	Patient serum	[48]
	Renal cell carcinoma	LncRNA-ARSR	Prognosis	Culture medium	[64]
	Hepatocellular carcinoma	miR-122	Prognosis	Culture medium	[65]
		LncRNA-H19	Prognosis	Culture medium	[66]
		miR-224, miR18a, miR-222, miR-10b, miR-21	Diagnosis	Patient serum	[67]
		miR-718	Diagnosis and prognosis	Patient serum	[68]

decade. In 2014 and again in 2018, the number of publications were duplicated compared to the prior year. The distribution of exosome nanoparticles and exosome cancer detection publications are split into two stages. In the first stage, from 2008 to 2013, there are only a few numbers of scientific productions. However, there is a publication growth explosion from 2014 to 2019. Although the number of published documents decreased from 28 in 2016 to 23 in 2017, more researchers focused in this area in 2018.

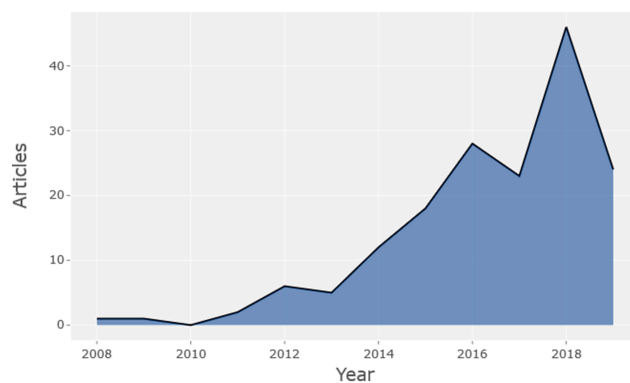
The average article citations per year from 2008 to 31st July 2019 are shown in Figure 3. According to the trend, the highest number of average citations per year, were collected by six articles published in 2012. The publications of 2017 had 15 citations on average, while the number of published papers decreased.

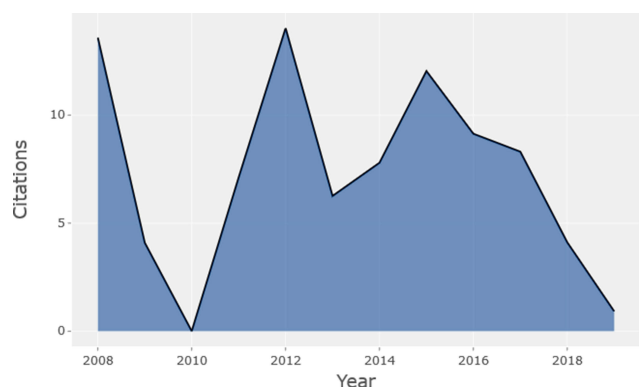
There are 166 citing documents such as articles, reviews, and conference proceedings in this bibliographic collection. Figure 4 shows the most local cited documents in the period of 2008 to 2019. Local citations measure the number of records citations received from papers involved

**Figure 1** Publication trends in Exosome research field from 1989 to 2019 (red dotted line: the prediction trends, blue line: the original trends).**Table 2** Summary of the Main Information of Collected Bibliometric Data

Description	Results
Documents	166
Sources (journals, books, etc.)	108
Keywords Plus (ID)	659
Author's keywords (DE)	330
Period	2008–2019
Average citations per document	29.33
Authors	1102
Authors of single-authored documents	5
Authors of multi-authored documents	1097
Authors per document	6.64
Collaboration index	6.81

in the analyzed set. As the figure shows, the top two highly local citations belong to the articles published in 2016. These articles gathered 15 and 11 local citations, respectively, though the leading average article citations occurred in 2012 (Figure 3).

**Figure 2** Annual scientific production of exosomes nanoparticles for cancer detection research field within 2008 to 2018 period.



**Figure 3** Average article citations per year of exosomes nanoparticles for cancer detection research field within 2008 to 2018 period.

## Analysis of Authors

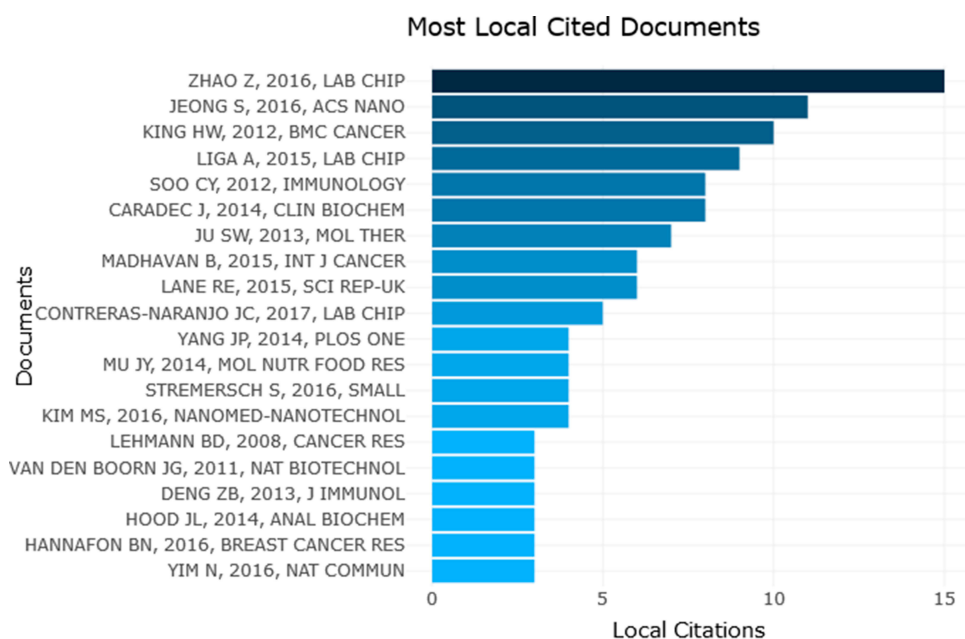
There is a total number of 1102 research works publishing their scientific accomplishments in the field of exosome nanoparticles and cancer detection from 2008 to 2019. This fact means, there are 6.64 authors and 7.55 co-authors per document in our analysis collection. [Figure 5](#) shows the most relevant authors' production over time from 2013 to 2019. The red line signifies the author's timeline. Zhang HG published six articles in the field of exosome nanoparticles or cancer detection from 2013 to 2018. The author has the most protracted timeline among other authors. The bubble size is related to the number of documents published during the years. The bubble color intensity is also related to the total

citations per year. Deng ZB, Lee J and Miller D are the authors with the highest publications in the field of exosomes, with five publications during 2013 to 2018. There are also several authors with two highly cited papers in 2013. According to the graph, more researchers are working on exosomes and getting interested in this area.

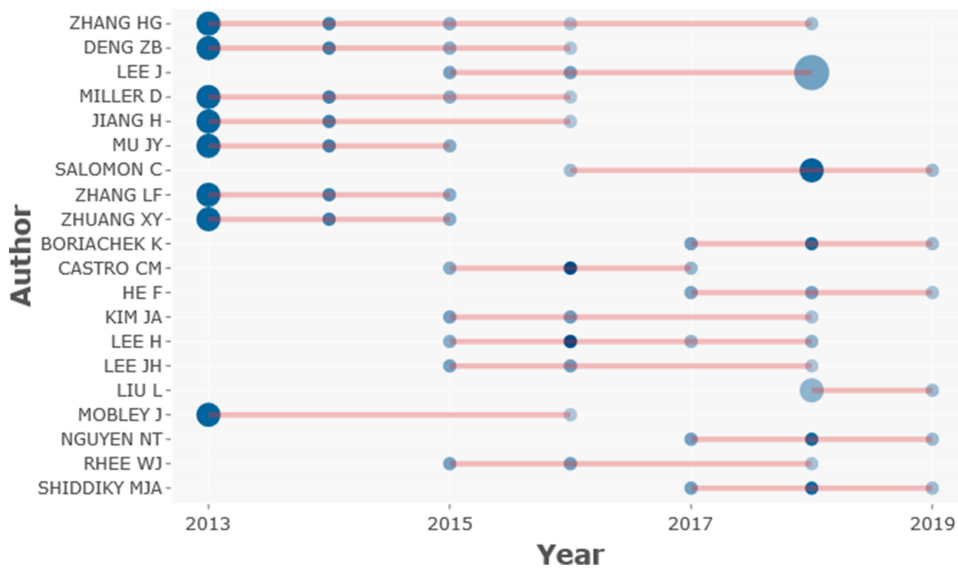
## Analysis of Sources

There are 108 sources such as journals, books, conference proceeding series and others in this bibliographic collection. [Figure 6](#) shows the most relevant sources in exosomes publications applied in the field of nanoparticles and cancer detection. Each of the sources has published one or more documents in this analyzed set. The open-access journal of Scientific Reports is the top critical journal in the field of exosomes, as it published about 11 documents from 2008 to 2019. The PLoS One journal is the second top journal with nine publication counts. The Analytical Chemistry journal has approximately five and the other journals have less than five published papers in this analysis. The three top journals in the figure are significant for researchers in the field of exosomes to consider first for submitting their articles.

[Figure 7](#) shows the number of sources occurrences in the time span of 2008 to 2019. The graph shows the best sources of dynamics in the field of exosomes nanoparticles and cancer detection. Yearly publications on the top



**Figure 4** Top 20 most local cited documents published on exosomes nanoparticles for cancer detection research field.

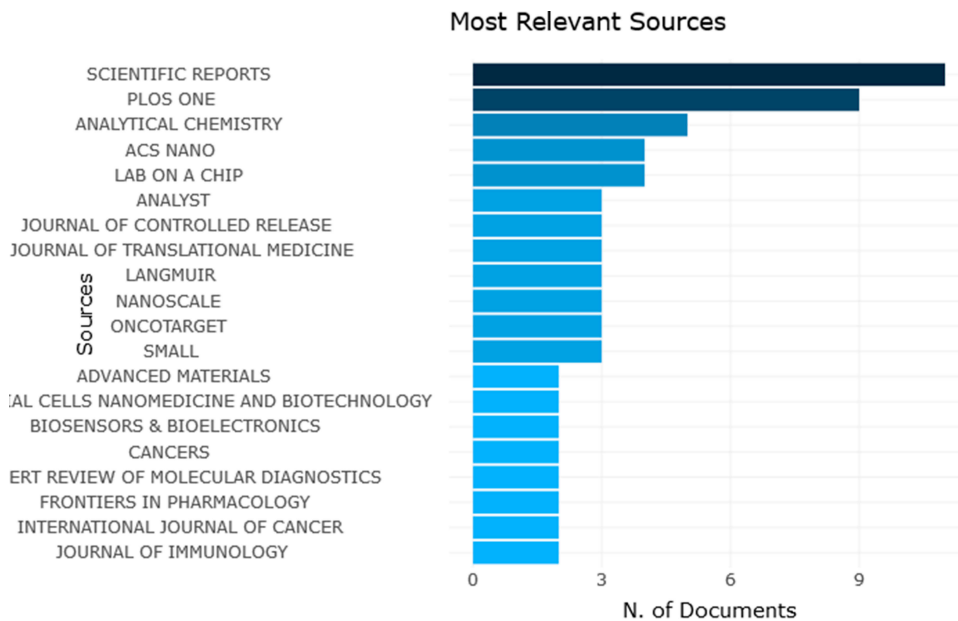


**Figure 5** Top 20 most relevant authors' production on exosomes nanoparticles for cancer detection research field from 2013 to 2019 (red line: the author's timeline, bubble size: the number of publications, bubble color intensity: total citations per year).

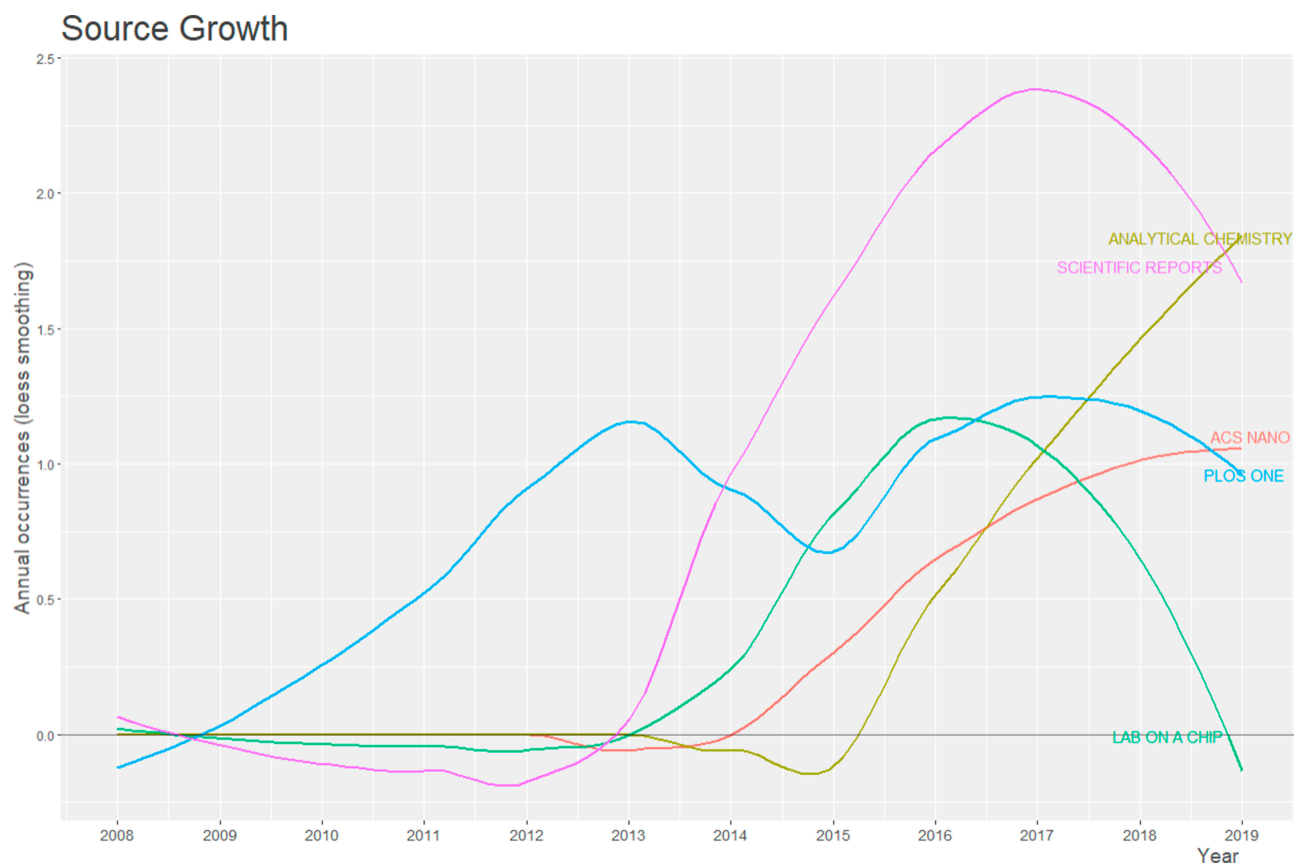
journals has increased as the time passes. Moreover, the Scientific Reports journal growth slowed down after 2017. Today, the journal of Analytical Chemistry is the leader in publishing the most relevant articles. On the other hand, Lab On a Chip journal is publishing exosome-related papers in a downward trend, since 2016. Although ASC Nano had no occurrence in 2014, its presentation has exceeded the PLoS One as the second most relevant source in exosomes in 2019.

### Analysis of Countries

There are 166 papers in the field of exosome cancer detection and nanotechnology, distributed among 43 countries. In Figure 8, top 20 countries were ranked by their count of scientific productions. The red lines demonstrate the publications rate by corresponding author's country, wherein at least one foreign co-author exists. The blue lines represent the number of publications by authors from the same country. These are called Multiple Countries publication (MCP) and



**Figure 6** Top 20 most relevant sources by the number of documents published on exosomes nanoparticles for cancer detection research.



**Figure 7** Annual occurrences of top five most relevant sources in exosomes nanoparticles for cancer detection research field within 2008 to 2018 period (method: loess smoothing).

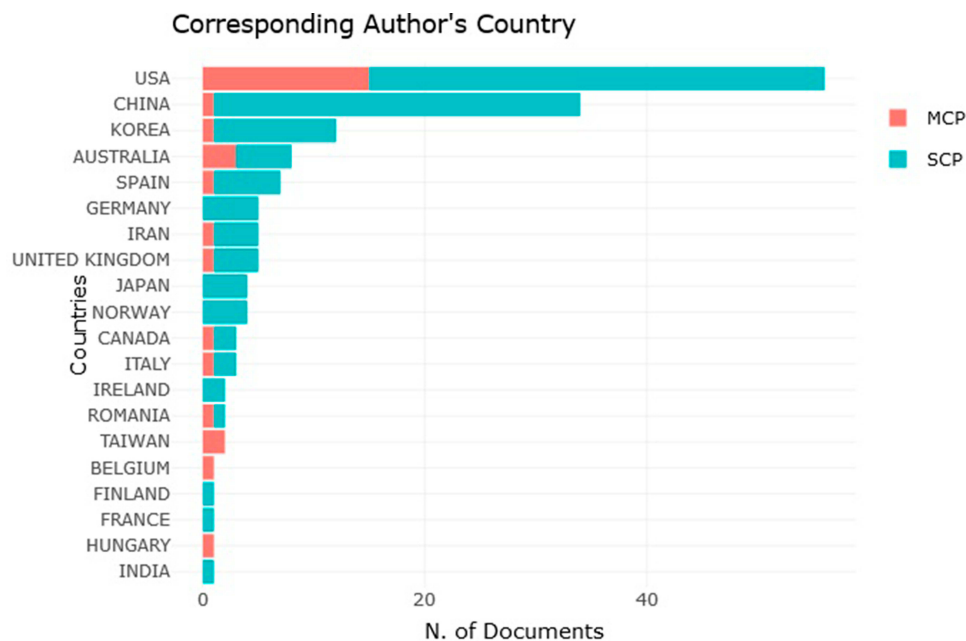
Single Country Publication (SCP), respectively. The USA with 63, China with 40, and South Korea with 14 publications are considered as the top three most relevant countries. The USA has by far the most international collaboration. Two North American countries, 11 European countries, six Asian countries and one Oceania country, are ranked as countries with highest publications in the area of exosomes.

Figure 9 gives a complete picture of the number of authors affiliated with the country of publication. Figure 10 shows the number of joint documents published by the top countries in the field of exosomes nanoparticles and cancer detection. The blue color intensity, in both figures, is proportional to the number of affiliated authors with each country. Every blue color indicates a number of related authors ranging from the darkest blue with 223 authors in the USA, to the lightest with the minimum of one author in Sweden. The USA and China are the two central research powers in exosome nanoparticles and cancer detection research fields. South Korea, Australia and Spain are the second most highly productive countries. The red line thickness in Figure 10 is proportional to the

number of joint publications within the countries. The thickest of every red link between countries indicates a number of collaborated papers ranging from the highest thickness of six joint documents between the USA and China, to the lowest thickness of one joint document between Australia and Japan. As Figure 10 illustrates, China and USA are very collaborative in scientific productions. Interestingly, Australia and Chile have too many mutual articles in exosomes area. Overall, USA seems to be the hub country of any published document, as there are lots of scientific links between the USA and other countries.

## Analysis of Topics

To analyze the main topics of exosome publications on nanoparticles and cancer detection, keywords networks are used. Keywords networks represent the co-occurrences among bibliographic dataset. It is likely to highlight the variant themes by clustering the keywords networks. Each keyword belongs to only one theme. A thematic map is a specific plot able to represent

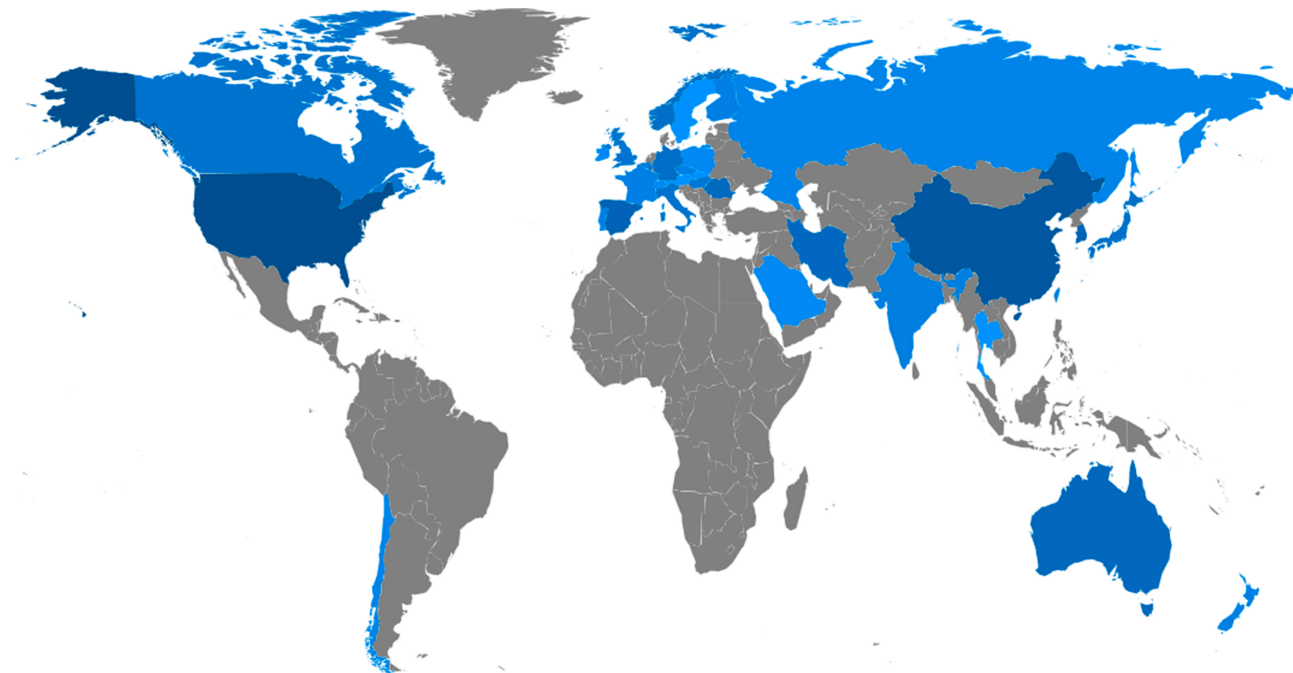


**Figure 8** Top 20 corresponding author's country (red line: Multiple Countries Publication (MCP), blue line, Single Country Publication (SCP)).

each theme. **Figure 11** shows the topics of exosome research field focused on cancer detection and nanoparticles in a thematic map. Each bubble shows one keyword network cluster. The cluster name is the word with the highest existence rate. Therefore, invitro, stem-cells, apoptosis, dendritic cells, membrane-vesicles, ovarian-

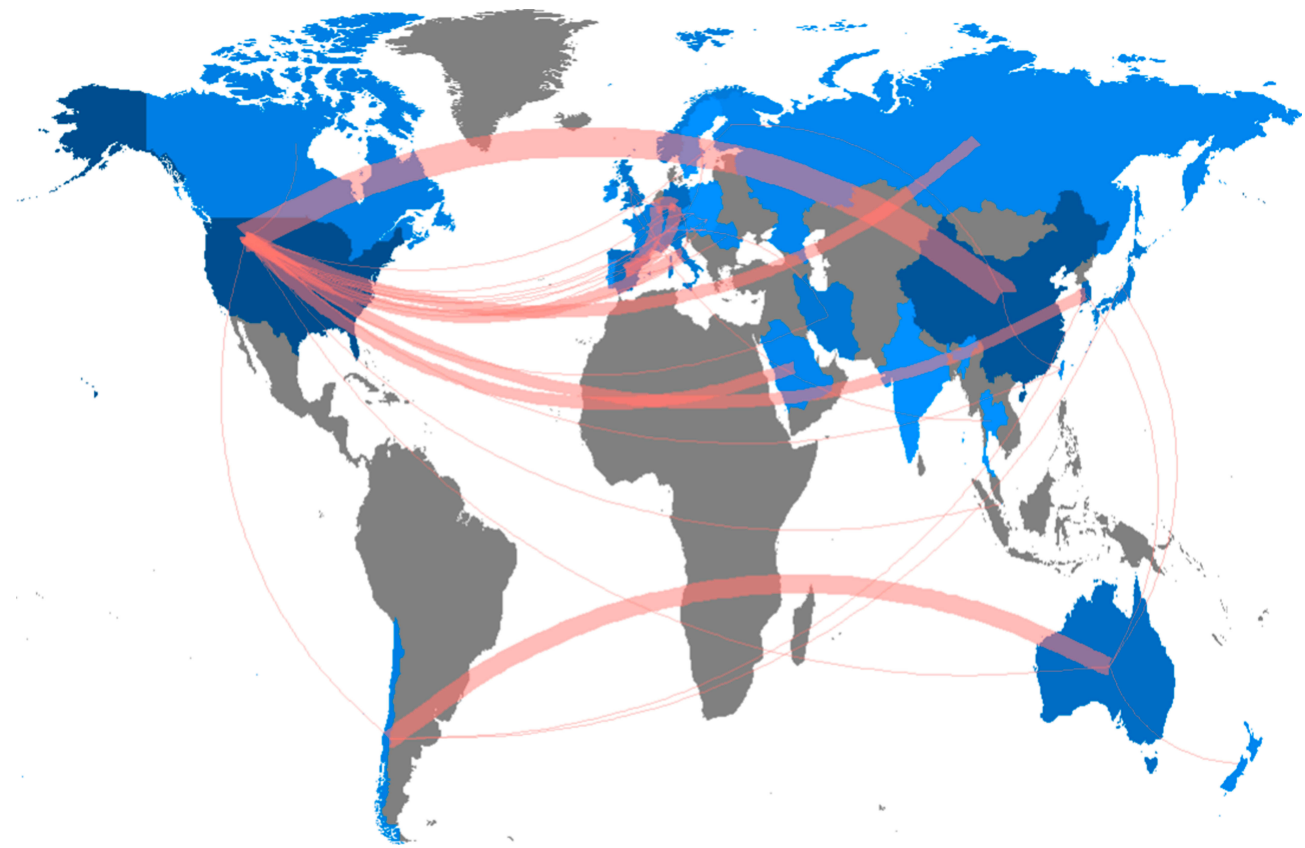
cancer, mechanism, microvesicles, biomarkers and extracellular vesicles are the most relevant theme indicators.

The bubble size is relative to the cluster word occurrences, and its position depends on the cluster centrality and density. Centrality and density show the theme

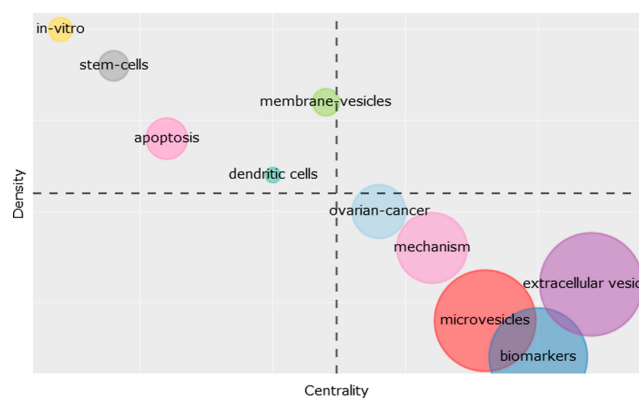


**Figure 9** Country's scientific production world map of exosomes nanoparticles for cancer detection research field (blue color intensity: the number of authors affiliated with each country, grey color: non-related country).





**Figure 10** Country collaboration world map of exosomes nanoparticles for cancer detection research field (blue color intensity: the number of authors affiliated with each country, grey color: non-related country, red line thickness: the number of joint publications).



**Figure 11** Thematic map of keywords network clusters in exosomes nanoparticles for cancer detection research field (bubble size: the clusters word occurrences).

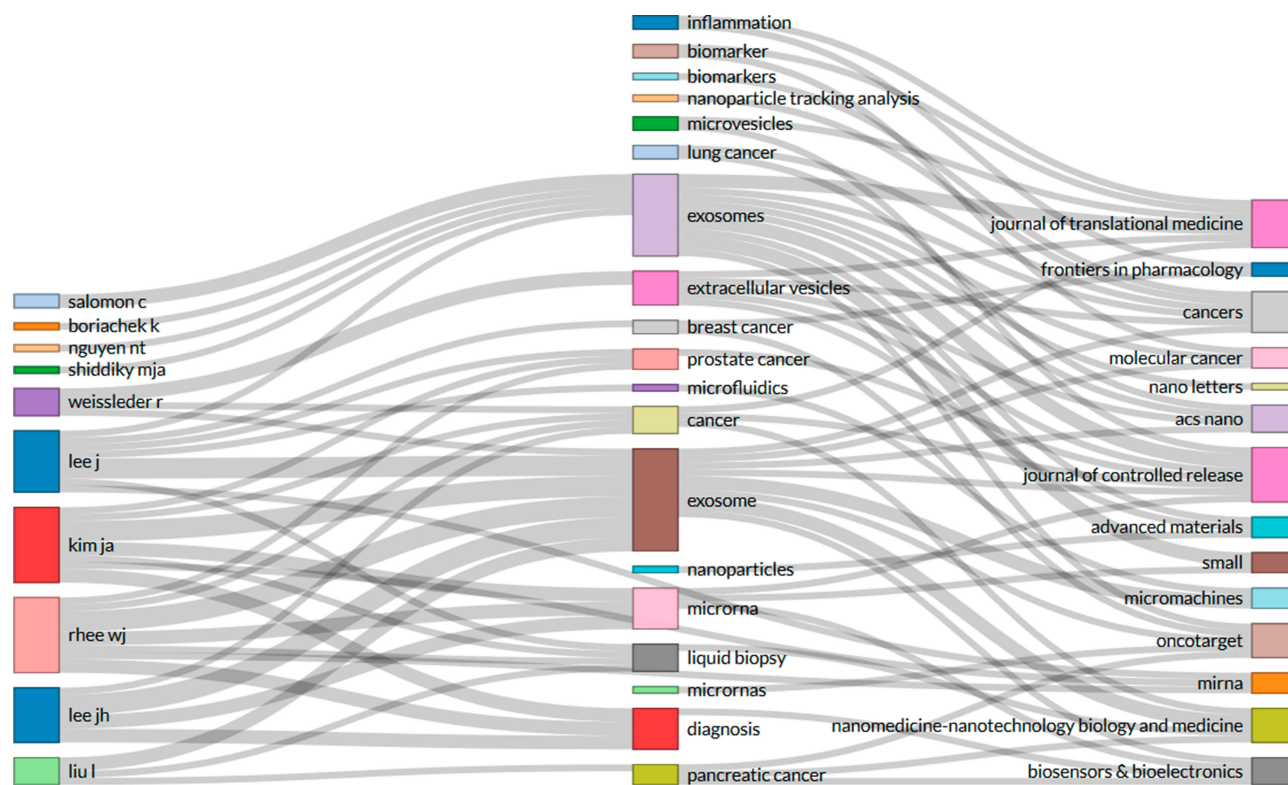
importance and theme improvement in the exosomes research area, respectively. Therefore, highly developed and isolated themes are on the top left, motor themes are on the top right, emerging or declining themes are on the bottom left, and primary and transversal themes are on the bottom right of the thematic topic map. Keywords such as in-vitro, stem-cells, apoptosis, membrane vesicles and dendritic cells, are the five cluster representatives with

a few numbers of occurrences. They are called as highly developed and isolated themes for their low level of importance and high level of improvement.

On the other side, keywords such as ovarian cancer, mechanism, microvesicles, biomarkers and extracellular vesicles, are the five cluster representatives called basic and transversal themes. Extracellular vesicles' keywords theme is the most important theme with the highest centrality, among others. Microvesicles, extracellular vesicles and biomarkers are the top mostly occurred keywords theme and more likely to be used in future exosomes research.

## Analysis of Keywords

Three-field plots are created to give a general view of the articles' keywords referring to the application of nanoparticles and cancer detection in exosomes. Figures 12 and 13 show the three-field plots, which mostly focus on the top keywords. Figure 12 is formed by selecting the three main metadata fields, keywords as the middle field, authors as the left field and sources as the right field. It shows the relationship among top keywords, top authors and top



**Figure 12** Three-fields plot for the relationship among top keywords (the middle field), top authors (the left field) and top journals (the right field) in exosomes nanoparticles for cancer detection publications.

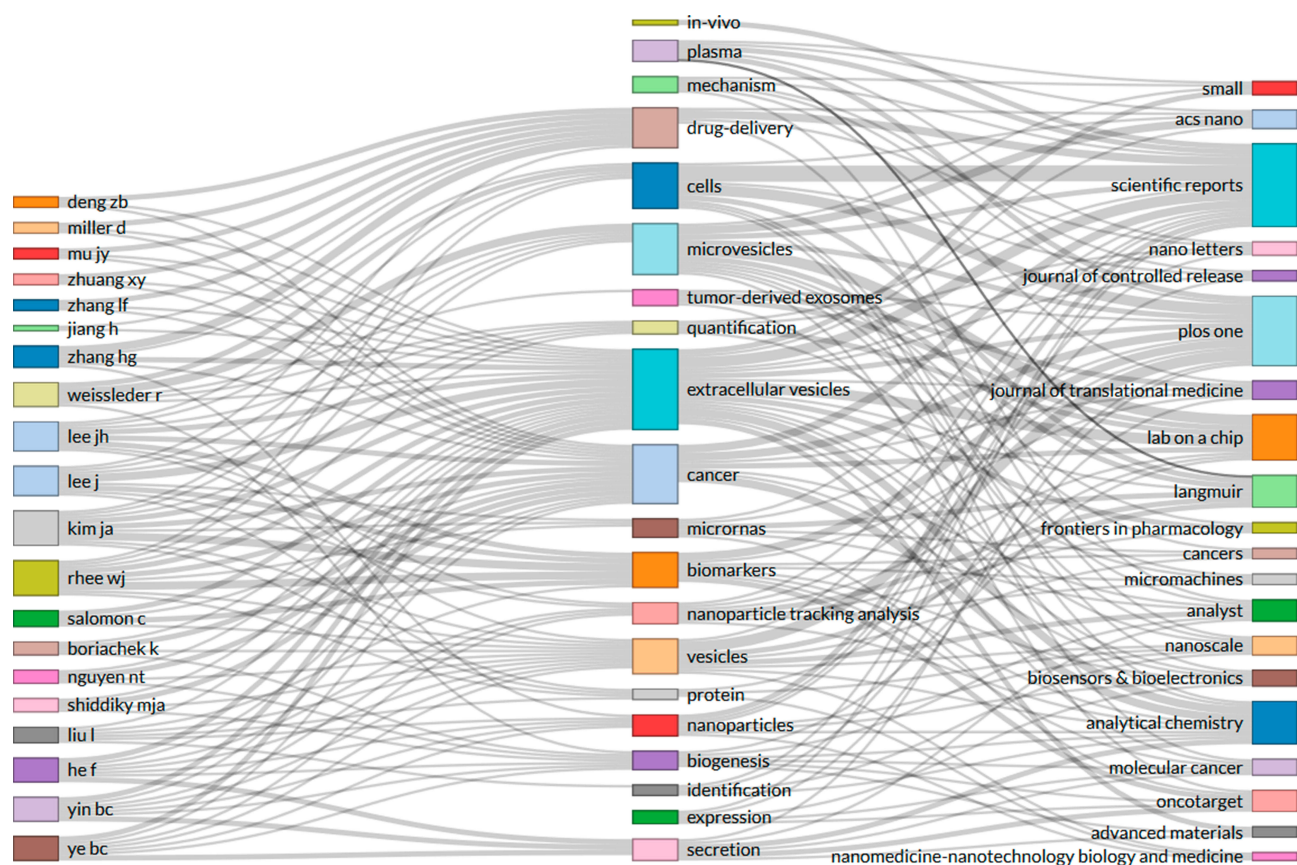
journals. As it is shown in [Figure 12](#), Salomon C, Boriachek K, Nguyen NT, Shiddiky MJA, Weissleder R, Kim JA, Rhee WJ, Lee JH, Lee J and Liu L, have used almost every top keyword in their publications.

The top relevant keywords such as exosomes, extracellular vesicles, microRNA, prostate cancer, cancer, exosome, diagnosis, liquid biopsy, breast cancer, microfluidics and pancreatic cancer are the most frequently used keywords. While, microvesicles, exosomes, biomarkers, extracellular vesicles, nanoparticles, lung cancer, biomarkers, nanoparticle tracking analysis, inflammation, breast cancer, microfluidics, pancreatic cancer and microRNAs are mostly the top journal articles' keywords. Sources such as Nano Letters, Small, Journal of Controlled Release, Journal of Translational Medicine, Advanced Materials, Molecular Cancer, ACS Nano, Cancers, Biosensors & Bioelectronics, Nanomedicine-Nanotechnology Biology and Medicine, miRNA, Oncotarget, Micromachines and Frontiers in Pharmacology are the top journals publishing articles about exosomes.

[Figure 13](#) is created by selecting another three metadata fields, keywords plus as the middle field, authors as the left field and sources as the right field. It shows the

relationship among top keywords plus, top authors and top journals. Keywords plus are words or phrases that frequently appear in the article references titles and generated automatically by computer. In [Figure 13](#), compared to [Figure 12](#), there are more authors mentioned with more keywords. Analyzing top keywords plus represents hot research topics in exosomes field of research and helps the reader to find research frontiers.

As it is shown in [Figure 13](#), articles related to in-vivo, are only published in the Scientific Reports journal. This journal also has a high number of publications in plasma, drug delivery, cells, extracellular vesicles, cancer and nanoparticles. Keywords plus such as plasma, cells, cancer, biomarkers and vesicles are more likely to be published in PLoS One journal. There is a spectacular reception of extracellular vesicles, as every top author has used it in their articles with a vast number of available publishers. 80% of top authors in exosomes have been working on cancer, where their publications are mainly published in Scientific Reports, PLoS One and Analytical Chemistry journals. Authors as Weissleder R has published articles on microvesicles in the journals of ACS Nano and Lab on a Chip.



**Figure 13** Three-fields plot for the relationship among top keywords plus (the middle field), top authors (the left field) and top journals (the right field) in exosomes nanoparticles for cancer detection publications.

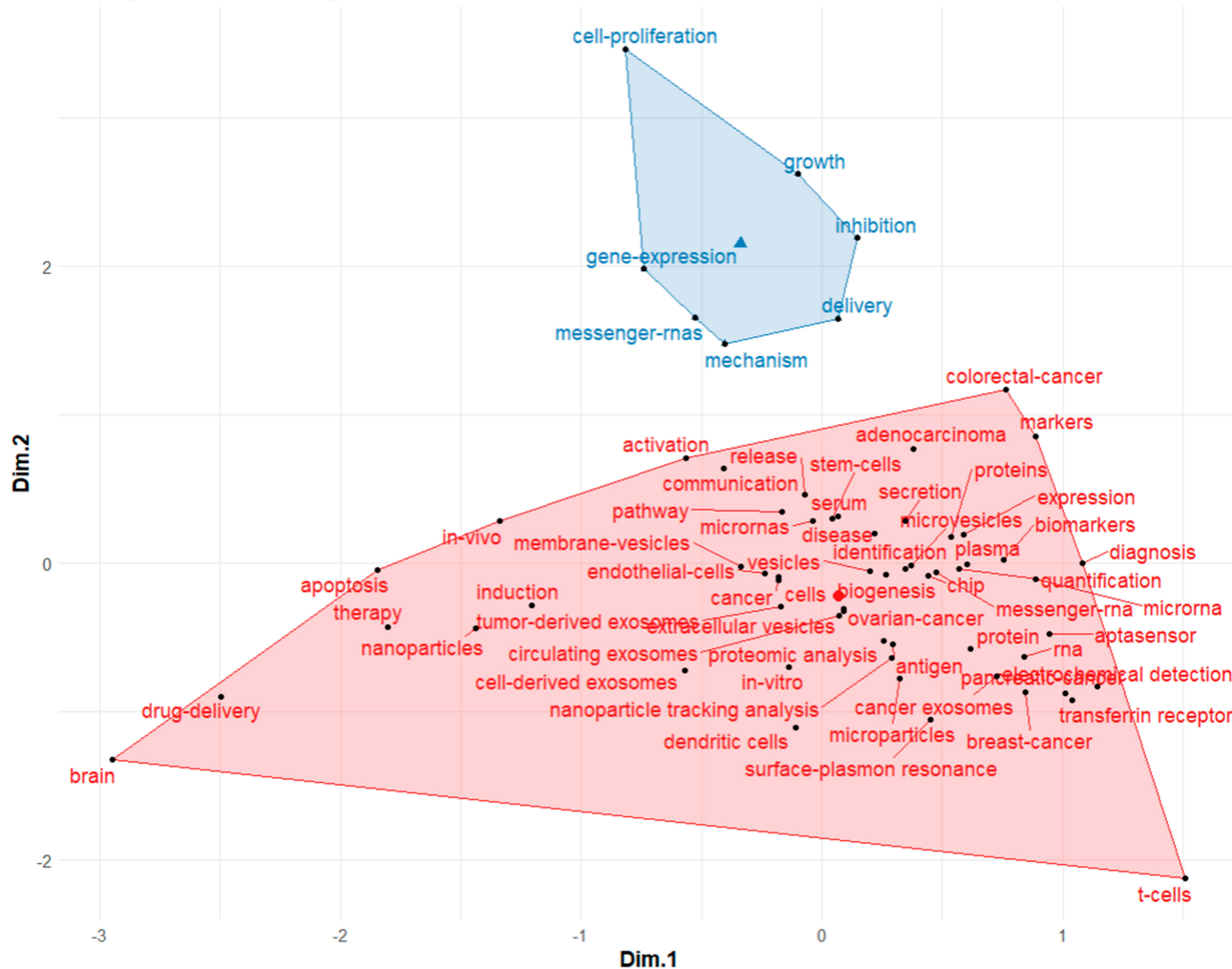
Therefore, [Figure 13](#) is very suitable in finding the subjects and topics of the articles published in the top journals, in order to provide guidance to submit a paper to a specific journal.

[Figure 14](#) shows the relationship among keywords of the publication set by designing a conceptual structure map. The two dimensions of the map represents the average position of the articles included in each keyword, and the midpoint of the map represents the center of the exosomes nanoparticles for cancer detection research field.<sup>21</sup> In a conceptual structure map, every document's words are linked via one network. This co-word network structure helps the readers to understand research fields' covered topics and find the research fronts (top new highlighted matters). Data reduction techniques (factorial analysis) can detect subfields, separately from the network analysis. Correspondence analysis (CA), as a dimensionality reduction technique, is chosen in the creation of the conceptual structure map. Factorial approaches aim to reduce data dimensionality and represent it in a low-dimensionality space.

As [Figure 14](#) illustrates, each color represents a cluster of words which is known by classified clustering. Therefore, keywords are divided into two clusters. The blue cluster consists of seven keywords and shows cell-proliferation, gene-expression, messenger RNAs, mechanism, delivery, inhibition, and growth due to its color. Approximately all keywords in this cluster are far from each other. On the other hand, the red cluster contains 55 keywords and is more prominent than the blue cluster. Keyword sets such as stem-cells and serum, cancer and cells, ovarian-cancer and extracellular vesicles, identification and microvesicles, chip and messenger-RNA, plasma and quantification, proteomic analysis and antigen, proteins and expression, and pancreatic-cancer and transferrin receptor are close to each other.

[Figure 15](#) shows another type of conceptual structure graph of keywords called dendrogram. This figure contains the same information as in [Figure 14](#), with a different view. Similarly, the conceptual structure dendrogram shows two clusters of keywords. The height measures the distance among words or clusters of words. Every dendrogram describes a partition, while split in a right place.

## Conceptual Structure Map - method: CA



**Figure 14** Conceptual structure map of keywords in exosomes nanoparticles for cancer detection publications (Dim.1 and Dim.2: the average position of the articles included in each keyword).

Distant words are keywords with different topics, which are not usually included in the same articles.

Sometimes the reader needs to quickly perceive the most prominent terms in his/her research area. Word cloud is a visual illustration of keywords metadata which instantly remarks the top words. Top keywords plus, top author's keywords, top title words and top abstract words are represented in Figures 16–19, respectively. Keywords plus are extracted by article reference titles. These words are capable of reaching the article's in-depth content. Author's keywords are a list of words that suites the article from authors' point of view. There is total of 659 keywords plus and 330 author's keywords produced for this analysis. Although keywords plus and author's keywords have the same effect in exploring knowledge from the bibliometric analysis, author's keywords are more

inclusive in providing subjects. The top title and abstract words are driven from abstracts or titles cleaned of any punctuation or trivial terms, like paper, study, work, data etc. Figure 16 visualizes the keywords plus in the field of exosomes from 2008 to 2019. The font size or color of these single words shows their importance. The keywords plus occurrences ranging from 58 to four are mentioned in Figure 16. Microvesicles, cells, cancer and biomarkers are the top ranked terms indicated in the picture and the best keywords plus in our research area.

Figure 17, shows the author's keywords, ranging from the total number of 41 to the minimum of two occurrences, with exosomes, exosome, biomarker, microRNA and extracellular vesicles on top of them. Figure 18 shows the words that appeared in titles, where exosome, cancer, cells, detection, exosome-like and nanoparticles are the

Topic Dendrogram

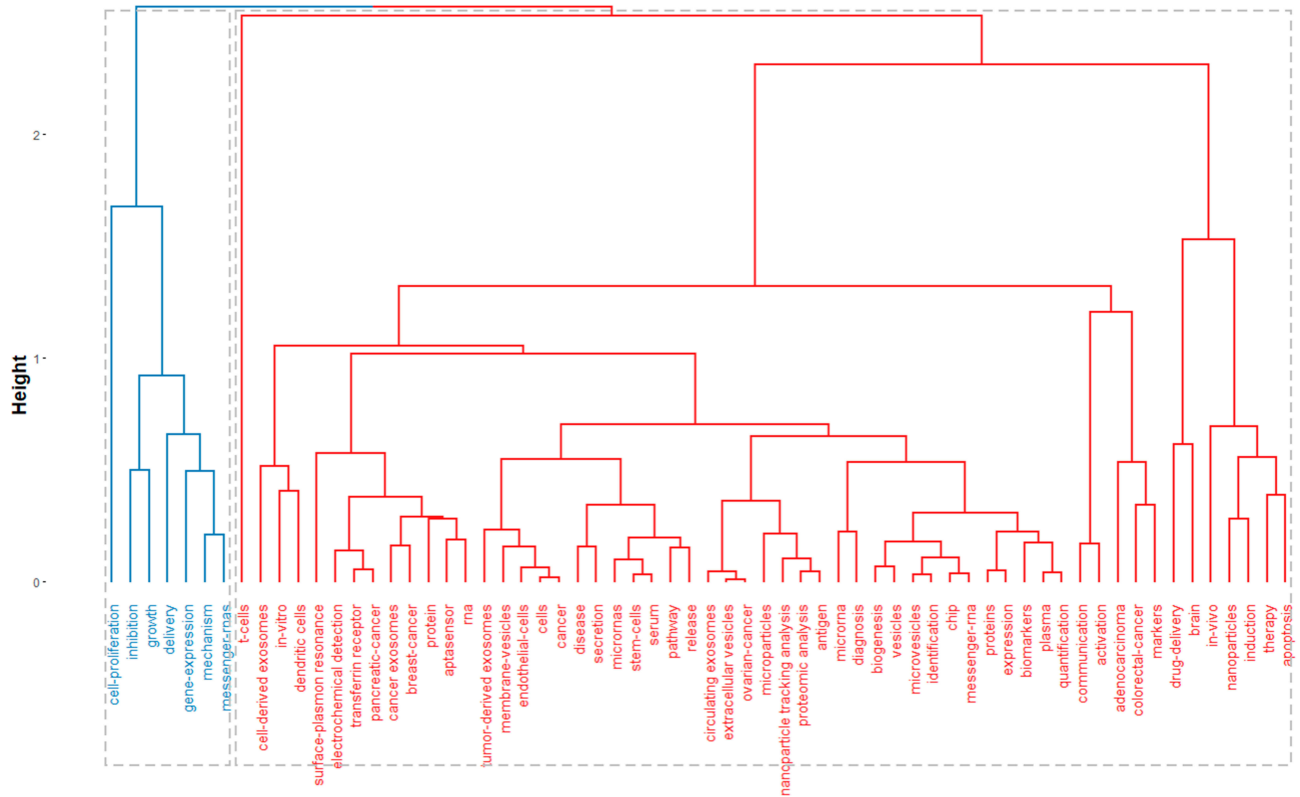


Figure 15 Conceptual structure dendrogram of keywords in exosomes nanoparticles for cancer detection publications (height: the distance among clusters of words).

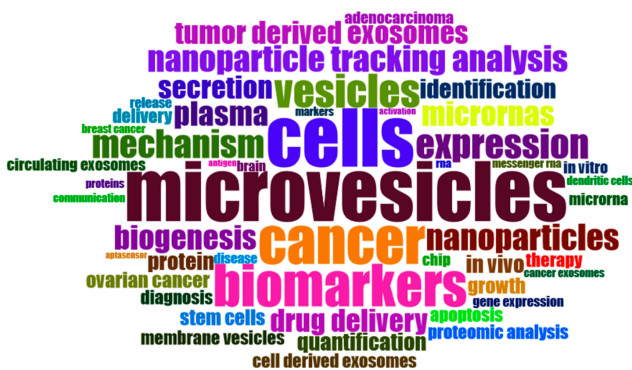


Figure 16 Word cloud of top keywords plus in exosomes nanoparticles for cancer detection publications (font size: word occurrences).

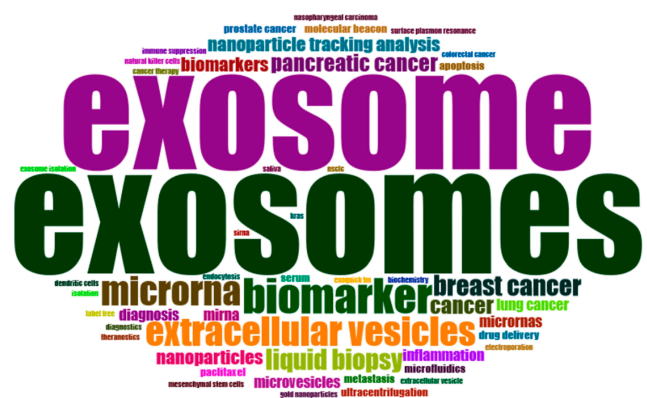
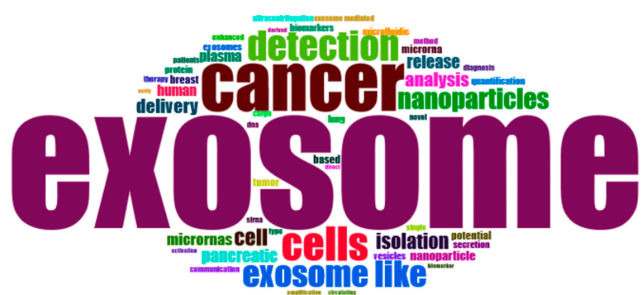


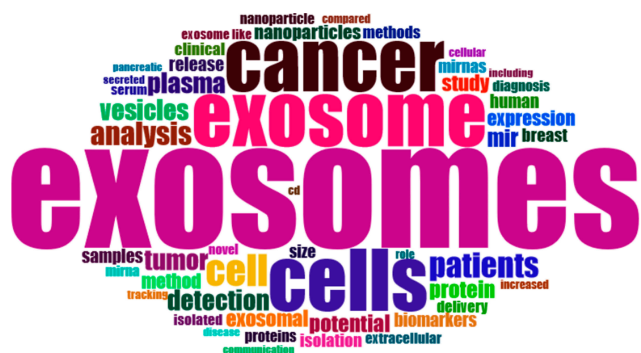
Figure 17 Word cloud of top author's keywords in exosomes nanoparticles for cancer detection publications (font size: word occurrences).

most relevant keywords. The title word occurrence is ranged from as high as 111 to as low as four times. Figure 19 shows the words appeared in abstracts, most frequently exosomes, exosome, cells, cancer, cell and patients. The top abstract words are frequently (from the word exosomes with 549 to pancreatic with 40) appeared in Exosome-related publications. It is interesting to know that the top two or three results in figures, come straight

from the terms used for collecting the data and are very bold and massive. In conclusion of these word clouds, surprisingly, word clouds of author's, title or abstract keywords are not following the pattern in keywords plus word cloud. Therefore, authors should attend to use more relevant words, as illustrated in the word cloud of keywords plus (such as microvesicles), in the title, abstract or as keywords of the publications.



**Figure 18** Word cloud of top title words in exosomes nanoparticles for cancer detection publications (font size: word occurrences).



**Figure 19** Word cloud of top abstract words in exosomes nanoparticles for cancer detection publications (font size: word occurrences).

Figure 20 shows the number of top keywords in exosome-based cancer detection or nanotechnology in the time span of 2008 to 31st July 2019. Extracellular vesicles as a research topic is overgrowing since 2013, reaching 15 occurrences in 2019. Keywords such as cells, cancer, biomarkers, expression and nanoparticles, are getting more visible in recent publications. Nanoparticle tracking analysis and microvesicles have lost their popularity since 2016 and 2017. Most commonly used keywords are increasing yearly, and research on these topics is also enlarging. Due to the dramatic rise in frequency from 2008 to 2019, a vast amount of research work is predicted on these topics in the exosomes research field.

## Qualitative Analysis

There are 166 papers in the field of exosomes which are related to cancer detection and nanoparticles, published from 2008 to July 2019. It is considered that 16.8% of the total scientific productions have equal to or more than 50 citations. This number points the high-quality papers within our bibliographic dataset. Therefore, there are 50 articles with at least 50 citations published in 2008–2019. In this section, the data is qualitatively analyzed according

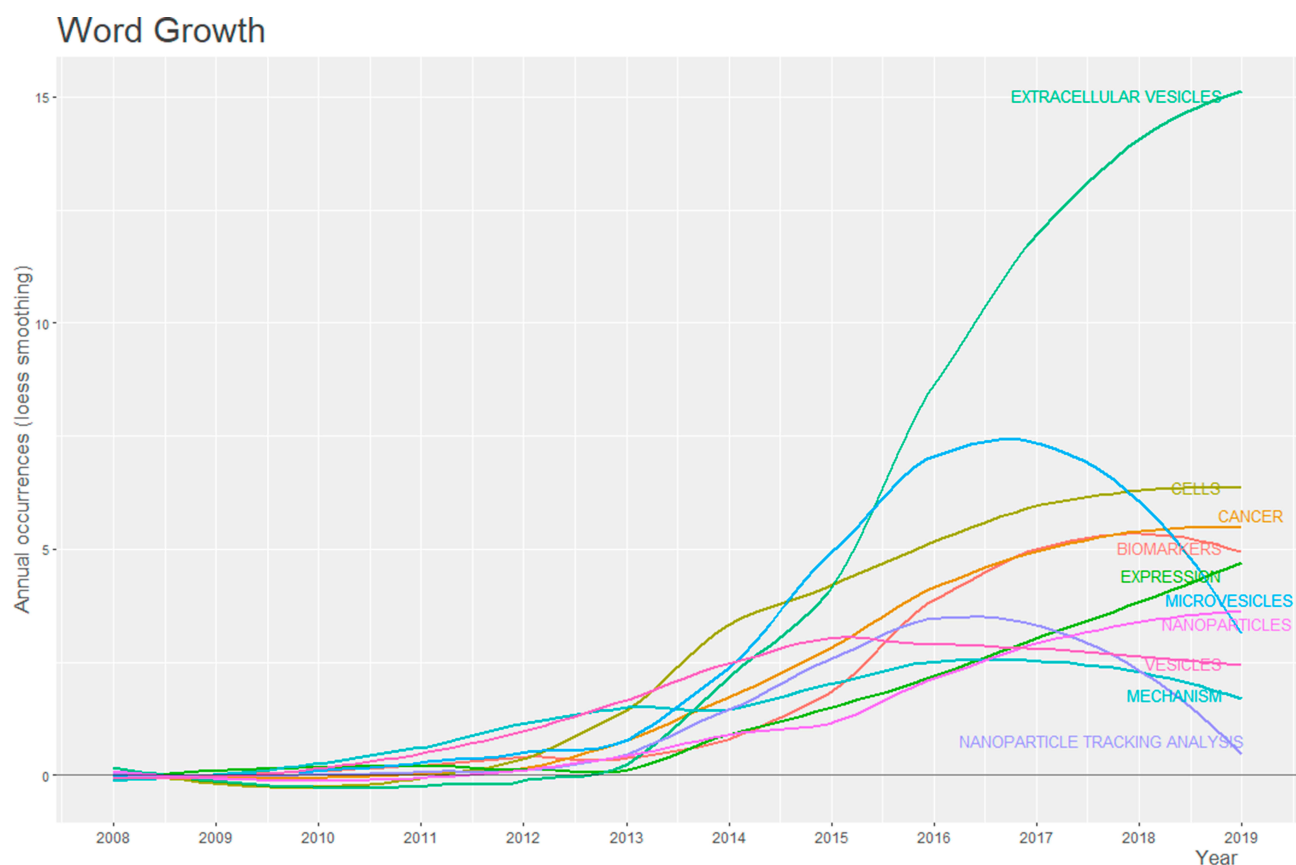
to 22 top-cited articles. [Supplementary Table](#) shows the most/least studied subjects and methods in exosomes research field.

## Subjects

The frequently used subjects in top-cited exosome articles include exosomes, cancer/experimental cells, targeting and protective mechanism. The most relevant article topics followed by their subtopics are mentioned in [Supplementary Table](#). Every top article has discussed or somehow used exosomal protein in its case study. About 68.1% of the authors in this analysis has focused on exosomal membrane and exosomal markers as their articles' subjects. Although microRNA is a typical author's keyword and previously was seen in the top keywords' graph, it has been occurred in half of the top-cited articles.

Research subjects such as tumor-derived exosomes, serum-derived exosomes, liposomes (synthetic lipid vesicles), exosome-like vesicles (ELVs), exosome-like nanoparticles and extracellular vesicles (EVs) have also attracted almost half the authors of most cited documents. There are only limited papers that use all exosomal protein, microRNA, tumor-derived exosomes, exosomal membrane, serum-derived exosomes, microvesicles, liposomes, and exosome-like vesicles (ELVs) subject keywords together.<sup>22,23</sup> Microvesicles, as the most critical term in the total articles' keywords plus, seems to have a moderately rare usage here. Multivesicular endosomes and exosome-derived DNA are quite rare headings in this collection set, as just a few titles are focusing on them.<sup>22,24,25</sup>

Human cancer cells were regularly observed by authors. Breast cancer cells, prostate cancer cells, and lung cancer cells are the extremely examined cells in these highly cited papers. [Supplementary Table](#) illustrates that almost every top cited article experimenting on cancer cells uses tumor-derived exosomes. Scientific documents with the minimum number of 50 citations target exosome release, exosome cargo, exosome detection, exosome purification, and exosome secretion. 77.2% of the articles aimed to purify exosomes, 68.1% of them considered released exosomes, and only 45.4% of them detect the exosomes. Interestingly, exosome cargo comes with exosome release in every article's purpose. There are a few targeting titles in our top collection in exosome secretion which has been applied by five articles.<sup>22,23,26-28</sup> Serum exosome protein, exosome-based drug delivery, and nanoparticle-mediated protein delivery concluded to be the best



**Figure 20** Annual occurrences of top keywords in exosomes nanoparticles for cancer detection research field within 2008 to 2018 period (method: loess smoothing).

protective mechanisms in highly cited papers. Nearly every article with a protective exosome-based drug delivery works with exosome-like nanoparticles, which makes them very related.<sup>25,29-31</sup>

## Methods

The analysis of exosomes based methods are divided into two groups, characterization and quantification of exosomes and statistical analysis. As [Supplementary Table](#) shows, only a few numbers of articles misses cell culture or exosome isolation methods. The reason refers to frequently usage of cell cultivation in articles with a running experiment. Most cited papers characterized the isolated exosomes by nanoparticle tracking analysis (NTA), Western blot analysis (WB), staining, electron microscopy, quantitative analysis, and fluorescence detection methods. These are exosomes characterization and qualification methods utilized by more than half of the analyzed set. Among these, the exosomes preparation method of electron microscopy has attracted 19 (out of 22) top-cited articles' authors. Meanwhile, confocal microscopy, used for micrometre ranged cells, has rarely been found in the top five papers.<sup>25,29,30,32,33</sup>

Other representation methods such as plasma collection, RNA extraction, flow cytometry, dynamic light scattering, and real-time PCR have been applied to 45.4% of the total papers with higher than 50 citations. It is notable that, articles monitoring the PCR reaction in real-time have often used RNA extraction preparation techniques for exosomes.<sup>27,33-37</sup> As it is shown in [Supplementary Table](#), statistical analyses were mostly carried out using ANOVA statistical analysis and Student's *T*-test. Microarray statistical analysis, Tukey HSD statistical analysis, and Mann–Whitney test were captured in 45.4% of the top articles' statistical analysis. Two related authors were interested in using parametric analysis as their statistical analysis.<sup>23,38</sup> Nearly every top-cited article in the field of exosomes nanoparticles and cancer detection, has displayed the error bars as the standard error of the mean (SEM).

In this final section, 22 exosome based articles with the highest WoS times cited count were reviewed. Exosomal protein has been accounted for the most popular material in exosomes research. Most of the analyzed references have nominated breast and prostate cancer cells as their

experimental cells. There is a huge percent of research studies that applied exosome isolation. Cell culture and electron microscopy are the other focused characterization methods in top-cited articles. Finally, the related authors ran the student's T-test as the statistical analysis and plotted the standard error of the mean as a result in every top article.

## Conclusion

Bibliometric analysis uses mathematical and statistical methods to evaluate scholarly outputs. Although extensive research has been carried out on the bibliometric study of "Cancer detection" and "Nanoparticles", there is no study dealing with "Exosome" bibliometric analysis. This work focuses on the bibliometric analysis of exosomes research literature from the year 2008 to 2019 with WoS data source. The results show that exosomes and applications of exosome-based detection are progressing in recent years. Annual publication in exosomes nanoparticles and cancer detection research field continue to increase due to turning points in 2014 and 2018. Researchers from USA, China, Korea, Australia and Spain contributed the most to the publications. The USA and China were ranked first and second in quantity of paper outputs. Scientific Reports, PLoS One, and Analytical Chemistry were identified as the most relevant journals in exosomes research field. The basic and transversal themes in our bibliographic set are representative keywords such as ovarian-cancer, mechanisms, microvesicles, biomarkers and extracellular vesicles. Keywords like cancer and biomarkers are improving their visibility and microvesicles are losing their occurrence in recent years. Furthermore, the qualitative analysis nominated breast and prostate cancer cells as the top experimental cells and exosome isolation as the most frequent research method. It is expected that the outcomes from this work provide a better vision on the future research direction and identify the potential opportunities for translation of the exosome research into clinical applications.

## Disclosure

The authors report no conflicts of interest in this work.

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