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Big impact of nanoparticles: analysis of the most cited nanopharmaceuticals and nanonutraceuticals research

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ABSTRACT

Nanopharmaceuticals and nanonutraceuticals research has been lately receiving a lot of scientific attention. We aimed to identify the top 100 most cited original articles of the scientific area, analyze their research themes, major contributors regarding authors, institutions, countries and journals. The bibliometric data was extracted from the Web of Science electronic database. Data was further processed by a bibliometric software, VOSviewer, to generate bubble maps to visualize the results. Inter-institutional and international collaboration networks were constructed to further understand the cooperation between different study centers. Results revealed that over 60% of the articles were published in the 2000s. As of November 2019, the articles were cited 576–3665 times, with 20.1–261.8 citations per year. The majority of the most prolific institutions were based in the United States. Besides the United States, China, South Korea, Canada and Germany contributed heavily to the 100 articles. Some popular themes included drug delivery, tumor, toxicity/biocompatibility and biodistribution. Regarding composition materials, gold, silver and polymeric nanoparticles were the most commonly used.

1. Introduction

According to the European Commission, nanomaterials stand for "*materials which often have specific properties due to their small particle size*" (European Commission, 2019). They can be described as products of nanotechnology with at least one dimension between 1 and 100 nm (De Jong and Borm, 2008). Our recent analysis of the biotechnology research literature identified nanotechnology and nanoparticles to be among the trending research themes (Yeung et al., 2019a). Due to their size-dependent properties, nanomaterials are being widely used in a range of applications offering several opportunities, but also posing inherent risks (Marques et al., 2019). The nanomaterials are regarded as chemical substances; hence they are regulated in Europe by the EU REACH (European Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals).

What makes nanomaterials very interesting in both pharmaceutical and food industries is the possibility to control their properties using different types of raw materials. Several pre-requisites have to be considered upon the design of nanopharmaceuticals and nanonutraceuticals (Fig. 1), which involve the use of two main categories of organic materials: polymers and lipids. Nanopolymers are polymer molecules arranged in nanoscale to offer favorable properties, such as high biodegradability and biocompatibility, easy design, preparation and scale-up in a variety of structures with interesting bio-mimetic behaviour (Larena et al., 2008; Yang et al., 2019a; Ljubimova and Holler, 2012). These nanopolymers can be surface functionalized with targeting moieties for site-specific delivery or other useful properties. For instance, the superior properties of chitosan nanopolymers have

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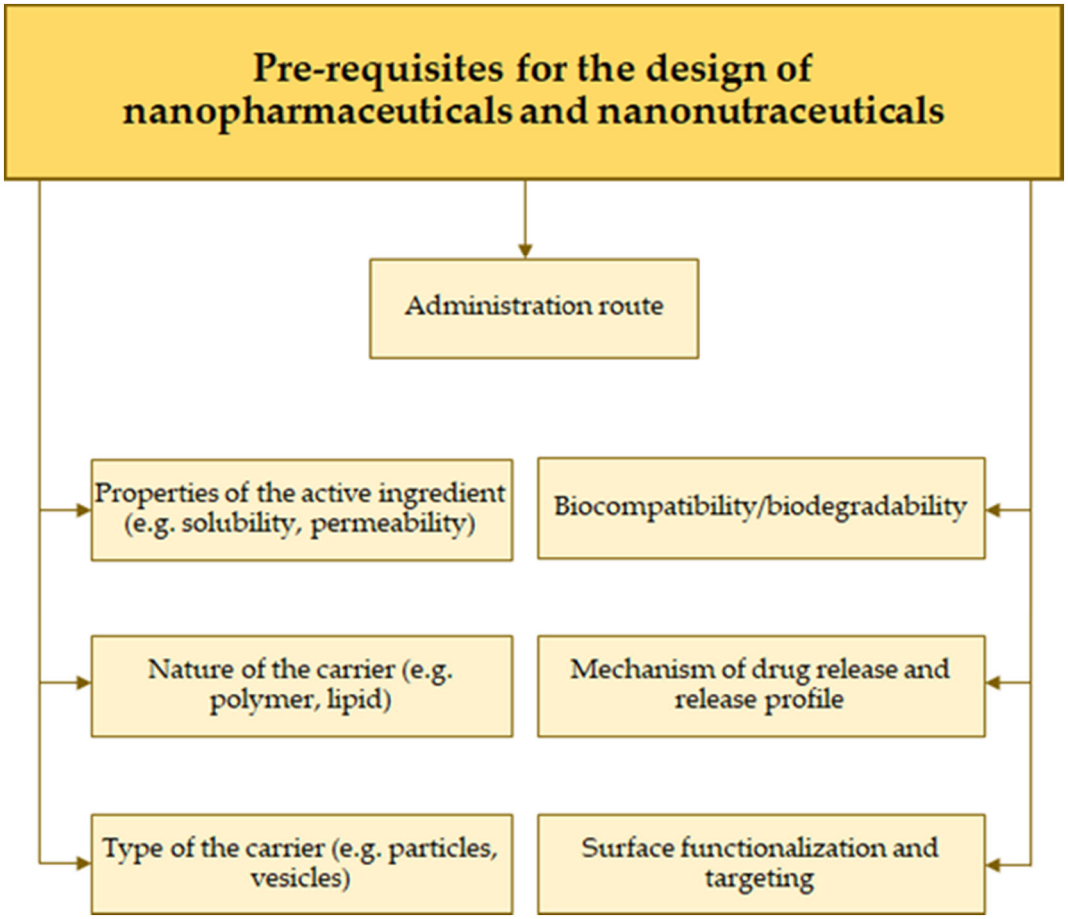

Fig. 1. Pre-requisites to consider upon the design of nanopharmaceuticals or nanonutraceuticals.

been recently reviewed in the context of serving as potential carriers for anti-cancer pharmaceuticals attributed to their biodegradability and biocompatibility (Shanmuganathan et al., 2019). Nanolipids have been put forward as an alternative carrier over polymers, particularly for lipophilic drugs, as the former use lipids existing in the human body in their composition (Souto et al., 2007), thereby reducing the risk of toxicological events (Doktorovova et al., 2016; Doktorovova et al., 2014). As lipid nanomaterials undergo similar metabolic pathways as lipids from food, they offer the opportunity to improve the bioavailability of a range of poorly soluble drugs (Muller et al., 2006; Muller et al., 2008). The nature of the compound, the lipid excipients and gastrointestinal digestion are factors to be considered in the development of these systems. Nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs) represent two major types of lipid-based nanoparticles (Souto and Doktorovova, 2009; Souto and Muller, 2010). Meanwhile, inorganic nanomaterials (e.g., gold, silver, iron) are also employed in nanomedicine, for instance in cancer therapy, imaging diagnosis, drug delivery, and also to facilitate soft tissue repair (Mody et al., 2010; Dreaden et al., 2012; Mioc et al., 2019; Arisawa, 2019; Urie et al., 2018).

There are various methods for the synthesis of nanoparticles, which can be mainly classified into two large groups based on the top-down and bottom-up strategies (Fig. 2) (Souto et al., 2019; Paliwal et al., 2014; Zahin et al., 2019). The top-down approach combines the use of some processes such as milling to create structures on a nanoscale from bigger starting materials. The bottom-up strategy creates multifaceted compounds starting from smaller materials based on synthetic processes (Biswas et al., 2012). For each strategy, the operational procedure, reaction conditions and adopted protocols can be varied, and the optimal procedures in each case are selected based on the type of material taken to start production and the desired final product (Khan et al., 2019).

Due to their remarkable properties, working with nanomaterials is nowadays considered a daily challenge for researchers (Jeevanandam et al., 2018). In the last decades, many research works dealing with nanomaterials were applied in the fields of healthcare, agriculture and foodstuff, electronics, and even cosmetics (Farokhzad and Langer, 2006). Often offering breakthrough solutions, nanomaterials widen the opportunity to exploit other administration routes of (nano)pharmaceutics (Davis et al., 2008), together with the development of innovative nanotechnologies in terms of diagnosis, imaging, and therapeutics (Petros and DeSimone, 2010). This new class of products, the nanopharmaceuticals, are being applied to improved and personalized medicines, with nanoformulation-based therapies for cancer, neurodegenerative diseases, infectious diseases, pain, and others being recently developed (Shi et al., 2017; Hasanzadeh-Kiabi, 2018; Zakharova et al., 2019; Sanchez-Lopez et al., 2019; Severino et al., 2016; Andreani et al., 2017; Jose et al., 2019).

Nanopharmaceuticals can lead to a delivery of drugs with improved physical-chemical properties i.e. solubility, pharmacokinetic enhancements, and extended half-life, in order to obtain a reduction on dose and toxicity (Weissig et al., 2014; Havel, 2016; Feng et al., 2019; Öztürk-Atar et al., 2019). When a nanopharmaceutical is developed, a broad range of parameters must be attained regarding the required characteristics of safety, efficacy, improved delivery, bioavailability, and applicability on human beings. Developments in the regulatory affairs of nanopharmaceutical to legislate correctly these goods and tightly regulate them according to the requirements for the human use are still needed. Nonetheless, they have already resulted in great changes in the pharmaceutical as well as nutraceutical industries (Abenavoli et al., 2018; Daliu et al., 2018; Daliu et al., 2019; Durazzo et al., 2019; Santini et al., 2018; Santini and Novellino, 2017a; Santini and Novellino, 2017b; Santini and Novellino, 2018; Santini et al., 2017; Durazzo, 2018).

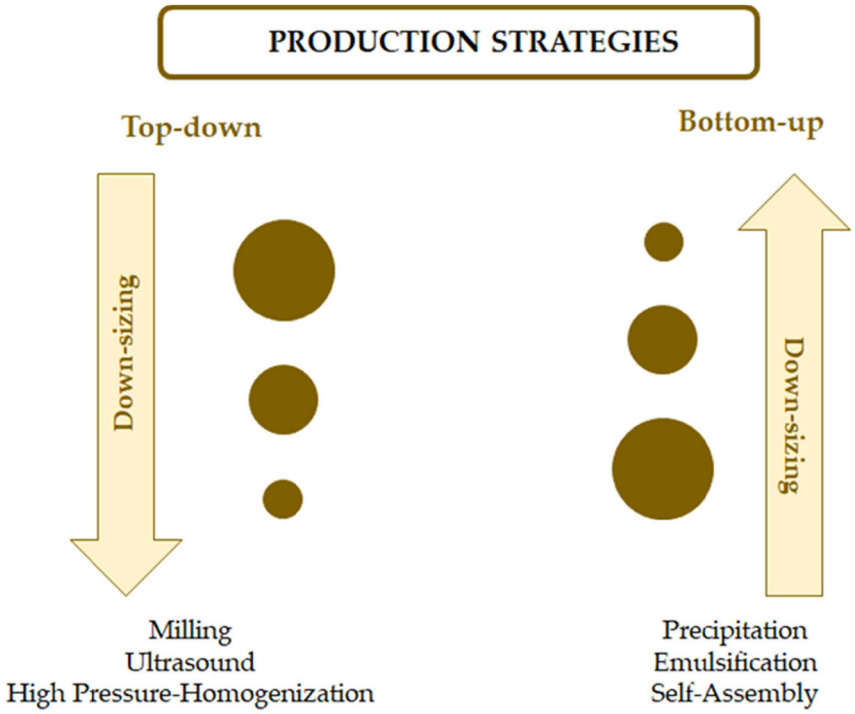

Fig. 2. Main production techniques used in the top-down and bottom-up approaches to obtain nanoparticles.

Nanotechnology applications to nutraceuticals are intensively studied in recent years, thus building up an emerging class of products: the nanonutraceuticals (Durazzo et al., 2018; Pimentel-Moral et al., 2018; Watkins et al., 2015; Pimentel-Moral et al., 2019). Nutraceuticals, a portmanteau of the words 'nutrition' and 'pharmaceutical', can be defined as "the phytocomplex if they derive from a food of vegetal origin, and as the pool of the secondary metabolites if they derive from a food of animal origin, concentrated and administered in the more suitable pharmaceutical form" (Daliu et al., 2018; Santini and Novellino, 2017b). Nutraceutical applications are also intensively investigated in numerous disease areas, including cardiovascular diseases, cancer, and diabetes, among others (Banach et al., 2018; Boots et al., 2008; Braicu et al., 2017; Rossino and Casini, 2019; Yang et al., 2019b; Yeung et al., 2018a). The nanonutraceutical formulations represent respectively a valuable strategy used in managing health conditions, particularly for patients who are not eligible for a conventional pharmacological therapy. Studies on the follow up, use, and compliance of pharmaceuticals as described by recent works (Menditto et al., 2018; Menditto et al., 2015; Iolascon et al., 2016; Putignano et al., 2017), and the studies on communication strategies and assessment (Scala et al., 2016), should be referred not only to drugs but also to nutraceuticals in view of exploiting the field applicability to different health conditions.

The nanotechnology could be applied for superior delivery of nutraceuticals with the aim to improve their bioavailability thereby increasing health benefits; examples of advantages of nanotechnology applied to the nutraceuticals are: efficient encapsulation and smart delivery and release from a nanoformulation. For instance, research on encapsulation of nutraceuticals into biodegradable, environment friendly nanocarriers, is ongoing to increase their absorption and the therapeutic potential. Nanonutraceuticals represent a promising challenge for the future. They should be properly assessed in order to estimate the maintenance of the respective nutraceutical properties at the nano-level, and to guarantee safety and efficacy. Follow-up studies to evaluate possible unwanted side effects are very important for both nanopharmaceutical and nanonutraceutical formulations (Wiwanitkit, 2012; Helal et al., 2019; Jones et al., 2019).

To gain insides on the overall high-impact research landscape of nanopharmaceuticals and nanonutraceuticals, this work identifies and analyzes the top 100 most cited original research articles of the outlined research area. Consequently, the overall aim of this report is to provide an overview of the nanopharmaceuticals and nanonutraceuticals research with a focus on the most important scientific outputs, as indicated by academic citations performance.

2. Materials and methods

2.1. Literature search

In November 2019, a search was conducted through the Web of Science (WoS) Core Collection electronic database (Clarivate Analytics, Philadelphia, USA) to identify the nanopharmaceuticals and nanonutraceuticals publications. The following search strings were used: (1) TOPIC = ("nanopharma*" OR "nanomedic*" OR "nanodrug*" OR "nano-pharma*" OR "nano-medic*" OR "nano-drug*" OR "nano pharma*" OR "nano medic*" OR "nano drug*" OR "nanonutraceutic*" OR "nano-nutraceutic*" OR "nano nutraceutic*"); (2) TOPIC = ("nanoparticle* OR "nano-particle*" OR "nano particle*") AND TOPIC = (medic* OR pharma* OR drug* OR nutraceutic*); finally, (1) OR (2). This search strategy identified publications that mentioned the relevant words or their derivatives in the title, abstract, or keywords. We limited the search to original research articles only. The final search yielded 90,248 original articles, and they were sorted by descending order of citations. The articles were independently screened for relevance by two authors (AY and AGA). A list of top 100 most cited nanopharmaceuticals and nanonutraceuticals articles was compiled. All of the top 100 articles were written in English.

2.2. Data extraction and analysis

The bibliographic data of the screened 100 most cited articles were recorded, such as the publication year, authorship, institutions, countries/regions, journal title, publication count, and citation count. The "Analyze" and "Create Citation Report" functions of the WoS platform were utilized for the basic analyses. The "full records and cited references" were exported to VOSviewer software (version 1.6.11, www.vosviewer.com) for further bibliometric analyses.

The VOSviewer software analyzes the terms used in titles and abstracts (of the top 100 most cited articles), links them to the bibliographic data, and visualizes the results by the means of a term map (Van Eck and Waltman, 2009). In a term map, the bubble size reflects how frequently a term is mentioned in the articles (multiple mentions in one article were counted once). The bubble color reflects the average citations (citations per article, CPA) of an article mentioning the term. The distance between two bubbles reflects how frequently two terms were co-mentioned among the 100 articles. Only words that appears in multiple articles (n = 2) were analyzed and visualized. The frequencies of author keywords were also analyzed by VOSviewer.

In addition, the collaboration networks of institutions and countries were analyzed by VOSviewer. Each collaboration was counted and weighed equally. The bubble size represents the number of articles. The distance between two bubbles represents how frequently the two institutions or countries collaborated. Please refer to the respective figure legends for the meaning of the bubble color.

3. Results and discussion

3.1. Overall results

The top 100 most cited nanopharmaceuticals and nanonutraceuticals articles are listed in Table 1. The oldest and latest articles were published in 1990 and 2013 respectively (Fig. 3). Over 60% of the 100 articles were published in the 2000s. The articles were cited 576–3665 times (mean = 975.8, SD = 582.3), with citations per year in the range of 20.1–261.8 (mean = 78.7, SD = 45.5). The most prolific authors of the top 100 articles were Professor Omid Cameron Farokhzad from Harvard Medical School and Professor Robert Langer from Massachusetts Institute of Technology (MIT), each with 6 contributions (Table 2).

3.2. Institutions

The majority of the most prolific institutions were based in the United States. When institutions with at least 2 articles were considered, eleven institutions formed the largest collaboration network. MIT was in the center of the network, having collaborations with local partners and international partners, such as Gwangju Institute of Science and Technology (South Korea) and University of Paris - XI (France) (Fig. 4). It should be noted that University of California Los Angeles had 5 contributions to the top 100 articles but was not in the network as it collaborated with other partners instead of the schools in the University of California system.

3.3. Countries

As expected, the United States (62%) and China (12%) were the two most prolific countries. Interestingly, in this list the articles contributed by the United States and China had similar citations per article, without the high citation bias towards the former as observed in the literature of the common nutraceuticals such as curcumin (Yeung et al., 2019b) and resveratrol (Yeung et al., 2019c). The rest of the contributing countries are all from Asia and Europe. Countries with 3 contributions included the United Kingdom, France, Ireland, Japan and Netherlands. India and Singapore each had 2 contributions. Countries with 1 contribution each included Austria, Croatia, Italy, Norway, Russia, Spain, Sweden and Switzerland. These figures showed a different distribution as observed from the top 100 articles of nutraceuticals and functional foods, in which the United States topped the list with a smaller ratio (30%), the European countries had larger contributions (e.g., United Kingdom: 11%; Belgium and Finland: 8% each) and China played a smaller role (4%) (Yeung et al., 2018b). It was also different from a nanoscience literature analysis published in 2007 that found China only accounted for 1.73% of the top 1% of highly cited papers (Guan and Ma, 2007). Perhaps these data imply that recent papers contributed by China have gained much more citations than those published in the past.

Meanwhile, for the 20 countries that contributed to the top 100 articles, 11 of them formed an international collaboration network (Fig. 5). The United States collaborated with 8 countries (Norway, Switzerland, Netherlands, China, Russia, Germany, South Korea and France), China collaborated with the United States and Germany, whereas South Korea collaborated with the United States and France. These countries tended to publish the most cited articles more recently than the United Kingdom, and were involved in collaborations between the Western and Asian countries.

3.4. Journals

The top 100 articles were published in 39 journals, with the most prolific journals having high impact factors in the range of 9.580–43.070 (Table 2). There was no single journal leading others by a large number of articles. Among the top 10 most prolific journals, 3 were dedicated to nanoparticles research, namely *ACS Nano*, *Nature Nanotechnology*, and *Nano Letters*. Others were with focus on chemistry, materials science or multidisciplinary sciences. When WoS journal categories were considered, the leading categories were *chemistry multidisciplinary* (39%), *materials science multidisciplinary* (34%), *chemistry physical* (30%), *nanoscience nanotechnology* (28%), *physics applied* (17%), *physics condensed matter* (17%), *multidisciplinary sciences* (16%), and *pharmacology pharmacy* (9%). The summation of the percentages exceeded 100% because some journals belonged to multiple categories.

3.5. Term map

The term map visualizing words appeared in the titles and abstracts of the 100 articles is shown in Fig. 6. In the lower left corner, biocidal action (n = 2, CPA = 2077.5) and antimicrobial activity (n = 3, CPA = 2060.7) are some examples of the more highly cited terms. As mentioned in the Introduction section, some of the more commonly investigated themes included drug delivery (n = 18, CPA = 910.6), and also tumor (n = 16, CPA = 984.5) and toxicity (n = 15, CPA = 829.9). Several nanomaterials were more frequently mentioned, such as gold nanoparticle (n = 14, CPA = 991.4), silver nanoparticle (n = 6, CPA = 1531.0), polymeric nanoparticle (n = 6, CPA = 780.0), silica nanoparticle (n = 3, CPA = 891.3), and iron oxide nanoparticle (n = 3, CPA = 657.0). These findings were consistent to a previous report that analyzed the nanobiotechnology literature and found that inorganic nanoparticles had more papers than polymer, carbon nanotube, and organic nanoparticles (Takeda et al., 2009). Among the top 100 articles, gold nanoparticles seemed to be most frequently investigated material, e.g., in the context of cancer cell imaging (Huang et al., 2006; Niidome et al., 2006), site-specific drug delivery (Paciotti et al., 2004), its cellular/organ uptake and removal (Chithrani and Chan, 2007; De Jong et al., 2008), and application as an x-ray contrast agent (Hainfeld et al., 2006).

3.6. Keyword map

Fig. 7 shows a map of author keywords. Nanoparticles (n = 10, CPA = 957.9), biocompatibility (n = 4, CPA = 710.3), biodistribution (n = 6, CPA = 807.8) and drug delivery (n = 12, CPA = 792.5) were in the center. There were 27 keywords that were listed in at least 2 articles, 9 of which have had >800 CPA, namely nanoparticles and biodistribution as mentioned above, silver (n = 2, CPA = 1905.0), surface charge (n = 2, CPA = 1434.0), prostate cancer (n = 2, CPA = 1035.0), cellular uptake (n = 2, CPA = 916.0), fluorescence (n = 2, CPA = 826.0), nanostructures (n = 2, CPA = 826.0), and particle size (n = 3, CPA = 802.3). The remaining 18 recurring keywords were biocompatibility and drug delivery (mentioned above), toxicity, mesoporous materials, sustained release, gold nanoparticles, chemotherapy, targeting, PLGA [poly(lactic-*co*-glycolic acid)], photothermal therapy, nanoparticle, nanomedicine, nanotoxicology, silica, graphene, controlled release, vaccine, and mesoporous silica nanoparticles.

Table 1
Top 100 most cited nanopharmaceuticals and nanonutraceuticals research articles.

Rank	Article	Total citations	Citations per year
1	Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods. DOI: 10.1021/ja057254a	3665	261.8
2	In vivo cancer targeting and imaging with semiconductor quantum dots. DOI: 10.1038/nbt994	3546	221.6
3	Silver nanoparticles as antimicrobial agent: a case study on *E-coli* as a model for Gram-negative bacteria. DOI: 10.1016/j.jcis.2004.02.012	3169	198.1
4	Antimicrobial effects of silver nanoparticles. DOI: 10.1016/j.nano.2006.12.001	2424	186.5
5	Porous metal-organic-framework nanoscale carriers as a potential platform for drug delivery and imaging. DOI: 10.1038/NMAT2608	2181	218.1
6	Shell-isolated nanoparticle-enhanced Raman spectroscopy. DOI: 10.1038/nature08907	1962	196.2
7	Intrinsic peroxidase-like activity of ferromagnetic nanoparticles. DOI: 10.1038/nnano.2007.260	1930	148.5
8	The effect of particle design on cellular internalization pathways. DOI: 10.1073/pnas.0801763105	1708	142.3
9	Understanding the nanoparticle-protein corona using methods to quantify exchange rates and affinities of proteins for nanoparticles. DOI: 10.1073/pnas.0608582104	1693	130.2
10	In vivo tumor targeting and spectroscopic detection with surface-enhanced Raman nanoparticle tags. DOI: 10.1038/nbt1377	1667	138.9
11	Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. DOI: 10.1038/nature08956	1645	164.5
12	A nanoscale optical biosensor: Sensitivity and selectivity of an approach based on the localized surface plasmon resonance spectroscopy of triangular silver nanoparticles. DOI: 10.1021/ja020393x	1607	89.3
13	Shape effects of filaments versus spherical particles in flow and drug delivery. DOI: 10.1038/nnano.2007.70	1523	117.2
14	Reconstituting Organ-Level Lung Functions on a Chip. DOI: 10.1126/science.1188302	1413	141.3
15	Elucidating the mechanism of cellular uptake and removal of protein-coated gold nanoparticles of different sizes and shapes. DOI: 10.1021/nl070363y	1397	107.5
16	A mesoporous silica nanosphere-based carrier system with chemically removable CdS nanoparticle caps for stimuli-responsive controlled release of neurotransmitters and drug molecules. DOI: 10.1021/ja028650l	1351	79.5
17	Multifunctional inorganic nanoparticles for imaging, targeting, and drug delivery. DOI: 10.1021/nn800072t	1338	111.5
18	Targeted nanoparticle-aptamer bioconjugates for cancer chemotherapy in vivo. DOI: 10.1073/pnas.0601755103	1220	87.1
19	Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. DOI: 10.1200/JCO.2005.04.937	1189	79.3
20	Effects of particle size and surface charge on cellular uptake and biodistribution of polymeric nanoparticles. DOI: 10.1016/j.biomaterials.2010.01.065	1160	116.0
21	Biodegradable luminescent porous silicon nanoparticles for in vivo applications. DOI: 10.1038/NMAT2398	1158	105.3
22	Accumulation of sub-100 nm polymeric micelles in poorly permeable tumors depends on size. DOI: 10.1038/NNANO.2011.166	1156	128.4
23	Graphene Oxide: Intrinsic Peroxidase Catalytic Activity and Its Application to Glucose Detection. DOI: 10.1002/adma.200903783	1134	113.4
24	Nanocrystal targeting in vivo. DOI: 10.1073/pnas.152463399	1105	61.4
25	'Stealth' corona-core nanoparticles surface modified by polyethylene glycol (PEG): influences of the corona (PEG chain length and surface density) and of the core composition on phagocytic uptake and plasma protein adsorption. DOI: 10.1016/S0927-7765(99)00156-3	1090	54.5
26	Biocompatibility of gold nanoparticles and their endocytotic fate inside the cellular compartment: A microscopic overview. DOI: 10.1021/la0513712	1031	68.7
27	Metal oxide nanoparticles as bactericidal agents. DOI: 10.1021/la0202374	986	54.8
28	Physical-Chemical Aspects of Protein Corona: Relevance to in Vitro and in Vivo Biological Impacts of Nanoparticles. DOI: 10.1021/ja107583h	984	109.3
29	Manufactured nanomaterials (Fullerenes, C-60) induce oxidative stress in the brain of juvenile largemouth bass. DOI: 10.1289/ehp.7021	972	60.8
30	Multifunctional polymeric micelles as cancer-targeted, MRI-ultrasensitive drug delivery systems. DOI: 10.1021/nl061412u	964	68.9
31	Effects of particle size and surface coating on cellular uptake of polymeric nanoparticles for oral delivery of anticancer drugs. DOI: 10.1016/j.biomaterials.2004.07.050	909	60.6
32	Micellar nanocontainers distribute to defined cytoplasmic organelles. DOI: 10.1126/science.1078192	905	53.2
33	Titanium Dioxide Nanoparticles in Food and Personal Care Products. DOI: 10.1021/es204168d	904	113.0
34	Multifunctional Uniform Nanoparticles Composed of a Magnetite Nanocrystal Core and a Mesoporous Silica Shell for Magnetic Resonance and Fluorescence Imaging and for Drug Delivery. DOI: 10.1002/anie.200802469	881	73.4
35	Nanoparticle Size and Surface Chemistry Determine Serum Protein Adsorption and Macrophage Uptake. DOI: 10.1021/ja2084338	869	108.6
36	Mediating Tumor Targeting Efficiency of Nanoparticles Through Design. DOI: 10.1021/nl900031y	868	78.9
37	Gold nanoparticles: a new X-ray contrast agent. DOI: 10.1259/bjr/13169882	865	61.8
38	Noninvasive imaging of quantum dots in mice. DOI: 10.1021/bc034153y	864	54.0
39	Oral gene delivery with chitosan-DNA nanoparticles generates immunologic protection in a murine model of peanut allergy. DOI: 10.1038/7385	852	40.6
40	Formulation of functionalized PLGA-PEG nanoparticles for in vivo targeted drug delivery. DOI: 10.1016/j.biomaterials.2006.09.047	850	65.4
41	Particle size-dependent organ distribution of gold nanoparticles after intravenous administration. DOI: 10.1016/j.biomaterials.2007.12.037	843	70.3
42	PEG-modified gold nanorods with a stealth character for in vivo applications. DOI: 10.1016/j.jconrel.2006.06.017	837	59.8
43	Aerosol-assisted self-assembly of mesostructured spherical nanoparticles. DOI: 10.1038/18410	835	39.8
44	Transferrin-functionalized nanoparticles lose their targeting capabilities when a biomolecule corona adsorbs on the surface. DOI: 10.1038/NNANO.2012.237	825	117.9
45	In vivo photodynamic therapy using upconversion nanoparticles as remote-controlled nanotransducers. DOI: 10.1038/nm.2933	797	99.6
46	Circulation and long-term fate of functionalized, biocompatible single-walled carbon nanotubes in mice probed by Raman spectroscopy. DOI: 10.1073/pnas.0707654105	782	65.2
47	Tissue biodistribution and blood clearance rates of intravenously administered carbon nanotube radiotracers. DOI: 10.1073/pnas.0509009103	777	55.5
48	Colloidal gold: A novel nanoparticle vector for tumor directed drug delivery. DOI: 10.1080/10717540490433895	776	48.5
49	Stimuli-responsive controlled-release delivery system based on mesoporous silica nanorods capped with magnetic nanoparticles. DOI: 10.1002/anie.200501819	771	51.4
50	In vitro toxicity evaluation of graphene oxide on A549 cells. DOI: 10.1016/j.toxlet.2010.11.016	767	85.2
51	Tailor-Made Dual pH-Sensitive Polymer-Doxorubicin Nanoparticles for Efficient Anticancer Drug Delivery. DOI: 10.1021/ja207150n	759	84.3
52	In vitro cytotoxicity of nanoparticles in mammalian germline stem cells. DOI: 10.1093/toxsci/kfi256	756	50.4
53	Critical Evaluation of Nanoparticle Tracking Analysis (NTA) by NanoSight for the Measurement of Nanoparticles and Protein Aggregates. DOI: 10.1007/s11095-010-0073-2	746	74.6
54	Antibody targeting of long-circulating lipidic nanoparticles does not increase tumor localization but does increase internalization in animal models. DOI: 10.1158/0008-5472.CAN-05-4199	742	53.0
55	Superparamagnetic graphene oxide-Fe3O4 nanoparticles hybrid for controlled targeted drug carriers. DOI: 10.1039/b821416f	741	67.4
56	Oops they did it again! Carbon nanotubes hoax scientists in viability assays. DOI: 10.1021/nl060177c	740	52.9
57	Mesoporous silica nanoparticles as a delivery system for hydrophobic anticancer drugs. DOI: 10.1002/smll.200700005	738	56.8
58	Rapid *endo*-lysosomal escape of poly(DL-lactide-*co*-glycolide) nanoparticles: implications for drug and gene delivery. DOI: 10.1096/fj.02-0088com	729	40.5
59	Exchange-coupled magnetic nanoparticles for efficient heat induction. DOI: 10.1038/NNANO.2011.95	712	79.1
60	Cytotoxicity of Graphene Oxide and Graphene in Human Erythrocytes and Skin Fibroblasts. DOI: 10.1021/am200428v	706	78.4

(continued on next page)

Table 1 (*continued*)

Rank	Article	Total citations	Citations per year
61	Quantum dot - Aptamer conjugates for synchronous cancer imaging, therapy, and sensing of drug delivery based on Bi-fluorescence resonance energy transfer. DOI: 10.1021/nl071546n	684	52.6
62	Near-infrared optical sensors based on single-walled carbon nanotubes. DOI: 10.1038/nmat1276	683	45.5
63	Preclinical Development and Clinical Translation of a PSMA-Targeted Docetaxel Nanoparticle with a Differentiated Pharmacological Profile. DOI: 10.1126/scitranslmed.3003651	676	84.5
64	Iron oxide nanoparticles for sustained delivery of anticancer agents. DOI: 10.1021/mp0500014	672	44.8
65	The targeted delivery of multicomponent cargos to cancer cells by nanoporous particle-supported lipid bilayers. DOI: 10.1038/NMAT2992	669	74.3
66	Targeted delivery of cisplatin to prostate cancer cells by aptamer functionalized Pt(IV) prodrug-PLGA-PEG nanoparticles. DOI: 10.1073/pnas.0809154105	669	55.8
67	Mesoporous silica nanoparticles deliver DNA and chemicals into plants. DOI: 10.1038/nnano.2007.108	667	51.3
68	Ceramic-based nanoparticles entrapping water-insoluble photosensitizing anticancer drugs: A novel drug-carrier system for photodynamic therapy. DOI: 10.1021/ja0343095	667	39.2
69	PLGA nanoparticles prepared by nanoprecipitation: drug loading and release studies of a water soluble drug. DOI: 10.1016/S0168-3659(98)00116-3	661	31.5
70	Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer. DOI: 10.1158/0008-5472.CAN-04-3921	660	44.0
71	Temporal targeting of tumor cells and neovasculature with a nanoscale delivery system. DOI: 10.1038/nature03794	656	43.7
72	Residual polyvinyl alcohol associated with poly (D,L-lactide-co-glycolide) nanoparticles affects their physical properties and cellular uptake. DOI: 10.1016/S0168-3659(02)00127-X	655	36.4
73	Gastrointestinal uptake of biodegradable microparticles: Effect of particle size. DOI: 10.1023/A:1016085108889	651	27.1
74	Nanopartide-aptamer bioconjugates: A new approach for targeting prostate cancer cells. DOI: 10.1158/0008-5472.CAN-04-2550	647	40.4
75	Rapid biological synthesis of silver nanoparticles using plant leaf extracts. DOI: 10.1007/s00449-008-0224-6	641	58.3
76	Cancer siRNA therapy by tumor selective delivery with ligand-targeted sterically stabilized nanoparticle. DOI: 10.1093/nar/gnh140	641	40.1
77	Time Evolution of the Nanoparticle Protein Corona. DOI: 10.1021/nn901372t	640	64.0
78	Biocompatibility, Biodistribution, and Drug-Delivery Efficiency of Mesoporous Silica Nanoparticles for Cancer Therapy in Animals. DOI: 10.1002/smll.201000538	637	63.7
79	Controlled Release of Biologically Active Silver from Nanosilver Surfaces. DOI: 10.1021/nn102272n	621	62.1
80	Mesoporous Silica-Coated Gold Nanorods as a Light-Mediated Multifunctional Theranostic Platform for Cancer Treatment. DOI: 10.1002/adma.201104714	613	76.6
81	Antibiofouling polymer-coated gold nanoparticles as a contrast agent for in vivo x-ray computed tomography imaging. DOI: 10.1021/ja071471p	612	47.1
82	Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform. DOI: 10.1073/pnas.1106634108	611	67.9
83	Photothermally Enhanced Photodynamic Therapy Delivered by Nano-Graphene Oxide. DOI: 10.1021/nn201560b	609	67.7
84	Targeted Killing of Cancer Cells in Vivo and in Vitro with EGF-Directed Carbon Nanotube-Based Drug Delivery. DOI: 10.1021/nn800551s	609	55.4
85	Engineered Design of Mesoporous Silica Nanoparticles to Deliver Doxorubicin and P-Glycoprotein siRNA to Overcome Drug Resistance in a Cancer Cell Line. DOI: 10.1021/nn100690m	608	60.8
86	An X-ray computed tomography imaging agent based on long-circulating bismuth sulphide nanoparticles. DOI: 10.1038/nmat1571	608	43.4
87	Multimodal Imaging Guided Photothermal Therapy using Functionalized Graphene Nanosheets Anchored with Magnetic Nanoparticles. DOI: 10.1002/adma.201104964	605	75.6
88	Nanoparticle uptake by the rat gastrointestinal mucosa - quantitation and particle-size dependency. DOI: 10.1111/j.2042-7158.1990.tb07033.x	604	20.1
89	The mechanism of uptake of biodegradable microparticles in Caco-2 cells is size dependent. DOI: 10.1023/A:1012126301290	601	26.1
90	Coadministration of a Tumor-Penetrating Peptide Enhances the Efficacy of Cancer Drugs. DOI: 10.1126/science.1183057	600	60.0
91	Controlling surface morphology of electrospun polystyrene fibers: Effect of humidity and molecular weight in the electrospinning process. DOI: 10.1021/ma0351975	597	37.3
92	Interaction of Gold Nanoparticles with Common Human Blood Proteins. DOI: 10.1021/nn9011187	594	59.4
93	Mesoporous silica nanoparticles for intracellular delivery of membrane-impermeable proteins. DOI: 10.1021/ja0719780	594	45.7
94	Size Effect on Cell Uptake in Well-Suspended, Uniform Mesoporous Silica Nanoparticles. DOI: 10.1002/smll.200900005	592	53.8
95	Size-Dependent Endocytosis of Nanoparticles. DOI: 10.1002/adma.200801393	590	53.6
96	Biogenic synthesis of silver nanoparticles and their synergistic effect with antibiotics: a study against gram-positive and gram-negative bacteria. DOI: 10.1016/j.nano.2009.04.006	589	58.9
97	Biodistribution of colloidal gold nanoparticles after intravenous administration: Effect of particle size. DOI: 10.1016/j.colsurfb.2008.07.004	588	49.0
98	Iron oxide nanoparticles as a drug delivery vehicle for MRI monitored magnetic targeting of brain tumors. DOI: 10.1016/j.biomaterials.2007.08.050	587	48.9
99	Tissue-Penetrating Delivery of Compounds and Nanoparticles into Tumors. DOI: 10.1016/j.ccr.2009.10.013	580	52.7
100	Stimuli-responsive polymer nanocomposites inspired by the sea cucumber dermis. DOI: 10.1126/science.1153307	576	48.0

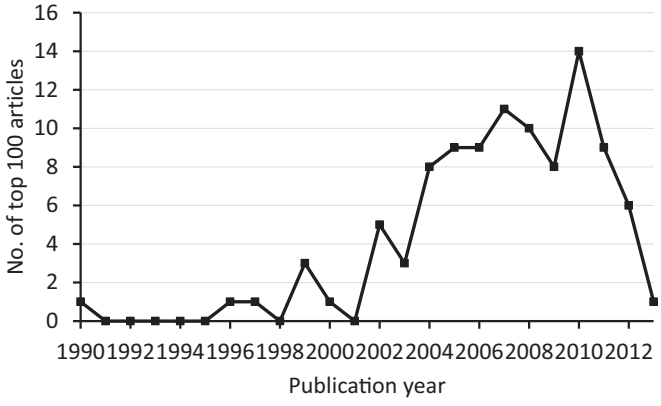

Fig. 3. Distribution of the top 100 articles in term of their publication years.

3.7. Lack of clinical trials in the top 100 list

As mentioned in the Introduction section, application of nanoparticles to cancer or tumor therapy and site-specific drug delivery have been important topics. The current results supported these notions. In particular, the top 2 articles were dealing with cancer imaging, targeting and photothermal therapy (Huang et al., 2006; Gao et al., 2004). Meanwhile, the articles concerning drug delivery in the top 20 of the list were dealing with the effects of shape, size and structures of nanoparticles on biodistribution and drug delivery (Chithrani and Chan, 2007; Geng et al., 2007; Horcajada et al., 2010; Liong et al., 2008). However, readers should be aware that there was only a single human clinical trial among the top 100 articles, namely the one conducted by Gradishar et al. (Gradishar et al., 2005) that showed a greater efficacy in slowing down tumor progression in patients with metastatic breast cancer and showed favorable safety profile of albumin-bound paclitaxel synthesized in nanoparticle size, relative to the standard size. The number of nanomedicine clinical trials is very small compared to non-nanomedicine, it

Table 2
Most prolific authors, institutions, countries, and journals of the top 100 articles.

	No. of articles	Citations per article
Authors with ≥ 4 articles		
Farokhzad, Omid Cameron	6	819.5
Langer, Robert	6	819.5
Labhasetwar, Vinod	5	690.0
Chan, Warren C.W.	4	1091.0
Lin, Victor S.Y.	4	865.3
Liong, Monty	4	844.3
Ruoslahti, Erkki	4	891.5
Trewyn, Brian G.	4	865.3
Zink, Jeffrey I.	4	844.3
Institutions with ≥ 4 articles		
University of California System	13	1109.8
Massachusetts Institute of Technology	10	849.0
Harvard University	9	906.8
Brigham Women's Hospital	7	869.9
Chinese Academy of Sciences	5	1071.8
Georgia Institute of Technology	5	2356.6
United States Department of Energy	5	723.2
Gwangju Institute of Science and Technology (South Korea)	4	818.3
Sanford Burnham Prebys Medical Discovery Institute	4	891.5
University of Michigan	4	651.3
Countries with ≥ 4 articles		
United States of America	62	991.0
China	11	1019.5
South Korea	9	1141.0
Canada	4	1031.3
Germany	4	934.8
Journals with ≥ 4 articles (Impact Factor)		
Journal of the American Chemical Society (14.695)	9	1256.2
Proceedings of the National Academy of Sciences of the United States of America (9.580)	8	1104.5
ACS Nano (13.903)	7	727.9
Nature Nanotechnology (33.407)	6	1091.9
Biomaterials (10.273)	5	890.6
Nano Letters (12.279)	5	953.0
Nature Materials (38.887)	5	1074.6
Advanced Materials (25.809)	4	749.5
Nature (43.070)	4	1314.8
Science (41.063)	4	898.8

was estimated that there were 1430 nanomedicine trials published from 2005 to 2014, equivalent to approximately 0.8% of the number for non-nanomedicine (Woodson and Rodriguez, 2019). Among the nanomedicine trials, cancer was most prevalent (19.3%), particularly breast cancer (6.9%), whereas other diseases seemed to be much less prevalent (Woodson and Rodriguez, 2019). The comparably small number of clinical trials concerning nanoparticles is consistent to the situation for a popular nutraceutical - curcumin, for which 3.8% of the relevant literature were clinical trials (Yeung et al., 2019b); and also for the ethnopharmacology literature, in which 1.3% were clinical studies (Yeung et al., 2019d). We hope that more clinical trials for nanopharmaceuticals and nanonutraceuticals will be conducted in the near future, and they will gain high citations as a recognition of the efforts.

Here, we would also like to draw readers' attention to the KeyWords Plus feature of WoS, which are "words or phrases that frequently appear in the titles of an article's references, but do not appear in the title of the article itself… based upon a special algorithm" (https://support.clarivate.com/ScientificandAcademicResearch/s/article/KeyWords-Plus-generation-creation-and-changes?language=en_US). In other words, KeyWords Plus are additional keywords added by WoS to the indexed articles. In the top 100 list, 3 articles had keywords related to clinical trials listed in the KeyWords Plus, namely "clinical-trial" for (Cabral et al., 2011), which was an in vivo study; "phase-I" for (Nasongkla et al., 2006), which was an in vitro study; and both "phase-I" and "clinical-trial" for (Paciotti et al., 2004), which was in vivo study. Meanwhile, the phase III trial mentioned above was tagged with "in-vivo" in the KeyWords Plus. These findings show that KeyWords Plus data should be used with caution for bibliometric purposes. Meanwhile, readers should be aware of some other limitations of this study. For example, some papers may not be indexed by Web of Science and thus not identified in this study. Since different databases count the number of citations differently, it was not possible to use multiple databases. Besides, citation count is dynamic, meaning that the top 100 list will be composed of different papers in the future.

4. Conclusion

This bibliometric study identified the top 100 most cited original articles about nanopharmaceuticals and nanonutraceuticals research. Over 60% of the 100 articles were published in the 2000s. The articles were cited 576–3665 times, with 20.1–261.8 citations per year. The majority of the most prolific institutions were based in the United States. Besides

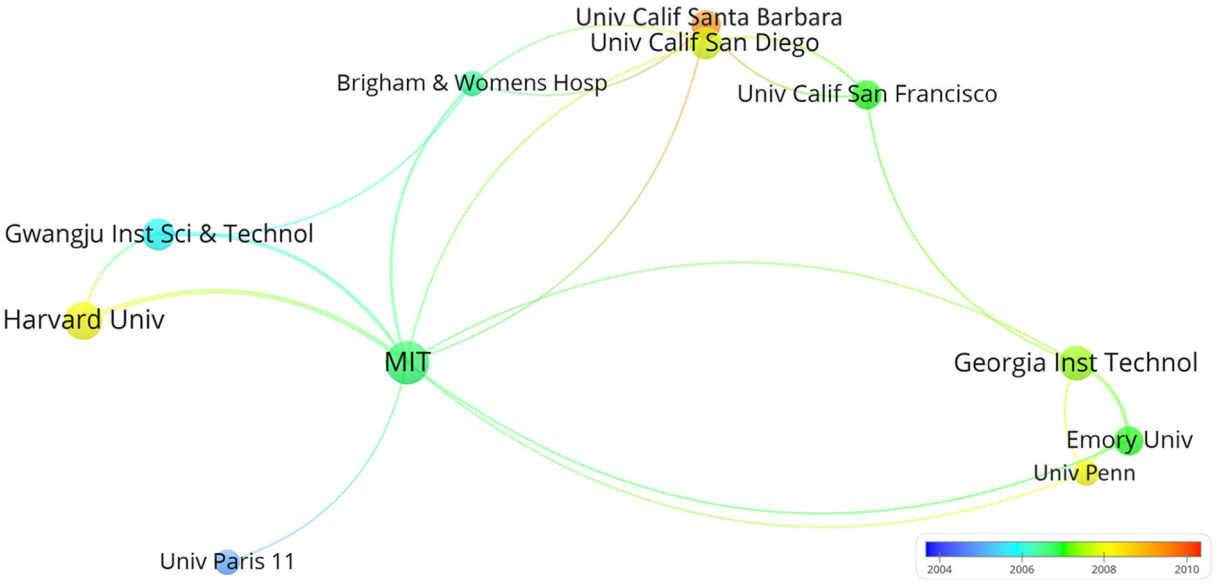

Fig. 4. The largest collaboration network between institutions with at least 2 articles. The bubble size represents the number of articles. Bubble position is based on how frequently the institutions collaborated with each other. Bubble color indicates the average publication year of the articles.

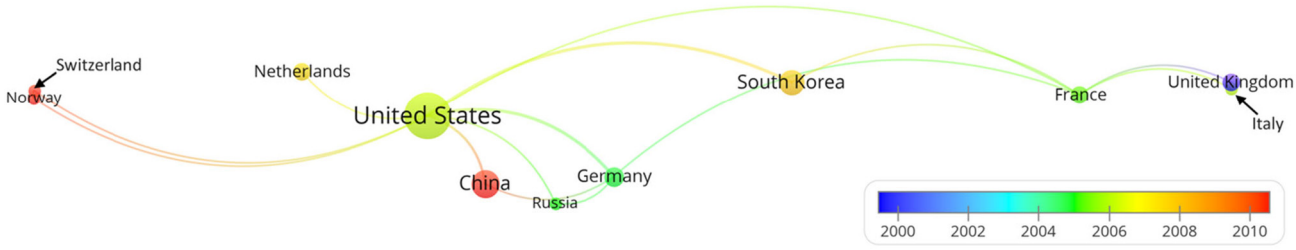

Fig. 5. International collaboration network between countries. The bubble size represents the number of articles. Bubble position is based on how frequently the countries collaborated with each other. Bubble color indicates the average publication year of the articles.

the United States, China, South Korea, Canada and Germany also contributed heavily to the 100 articles. Some popular themes included drug delivery, tumor, toxicity/biocompatibility and biodistribution. Regarding materials, gold, silver and polymeric nanoparticles were the most commonly used.

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Andy Wai Kan Yeung: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Funding acquisition.**Eliana B. Souto:**Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Funding acquisition.**Alessandra Durazzo:**Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Funding acquisition.**Massimo Lucarini:**Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Funding acquisition.**Ettore Novellino:**Conceptualization, Methodology, Validation,

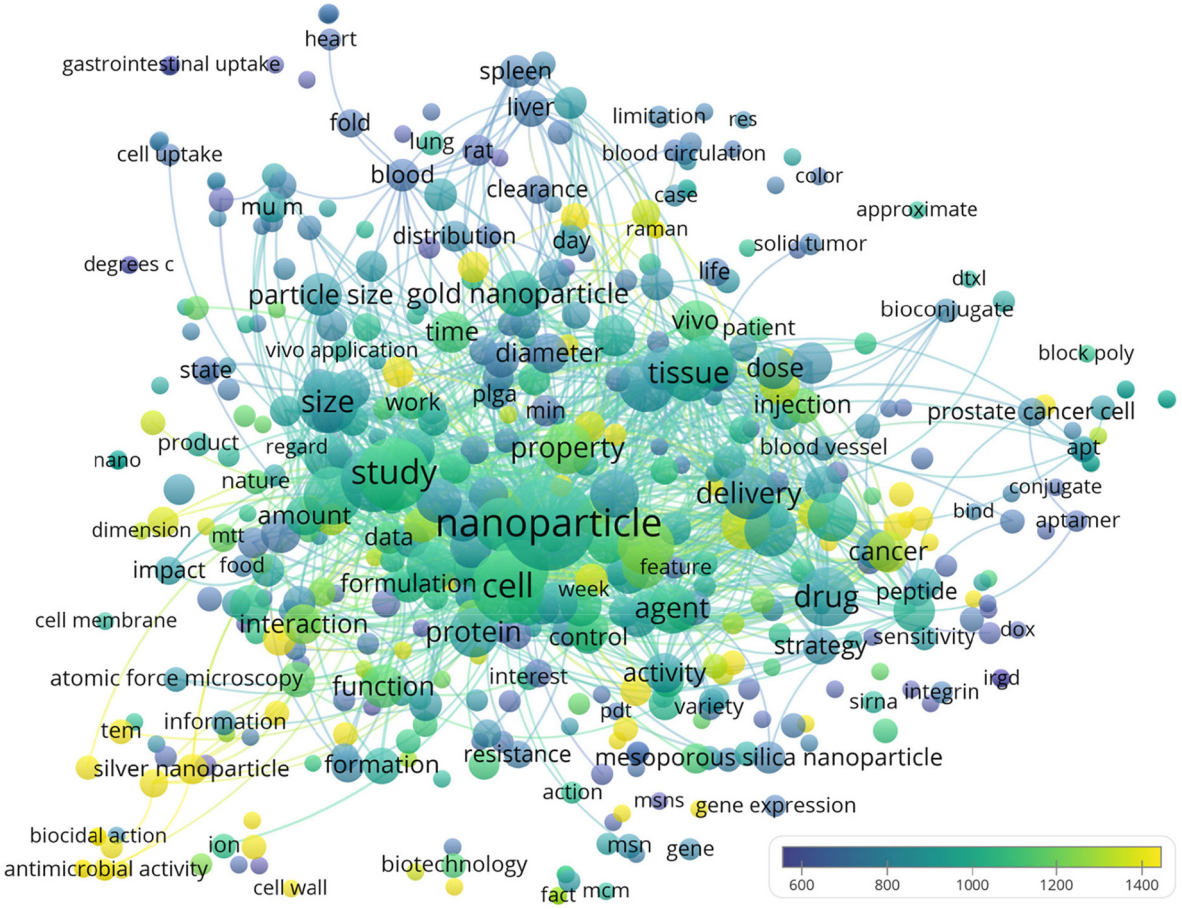

Fig. 6. Term map showing words appeared in at least 2 of the 100 articles. Bubble size reflects how frequently a term is mentioned in the articles (multiple mentions in one article were counted once). The bubble color reflects the average citations (citations per article, CPA) of an article mentioning the term. The distance between two bubbles reflects how frequently two terms were co-mentioned among the 100 articles. The lines illustrate the 1000 most commonly co-mentioned term pairs.

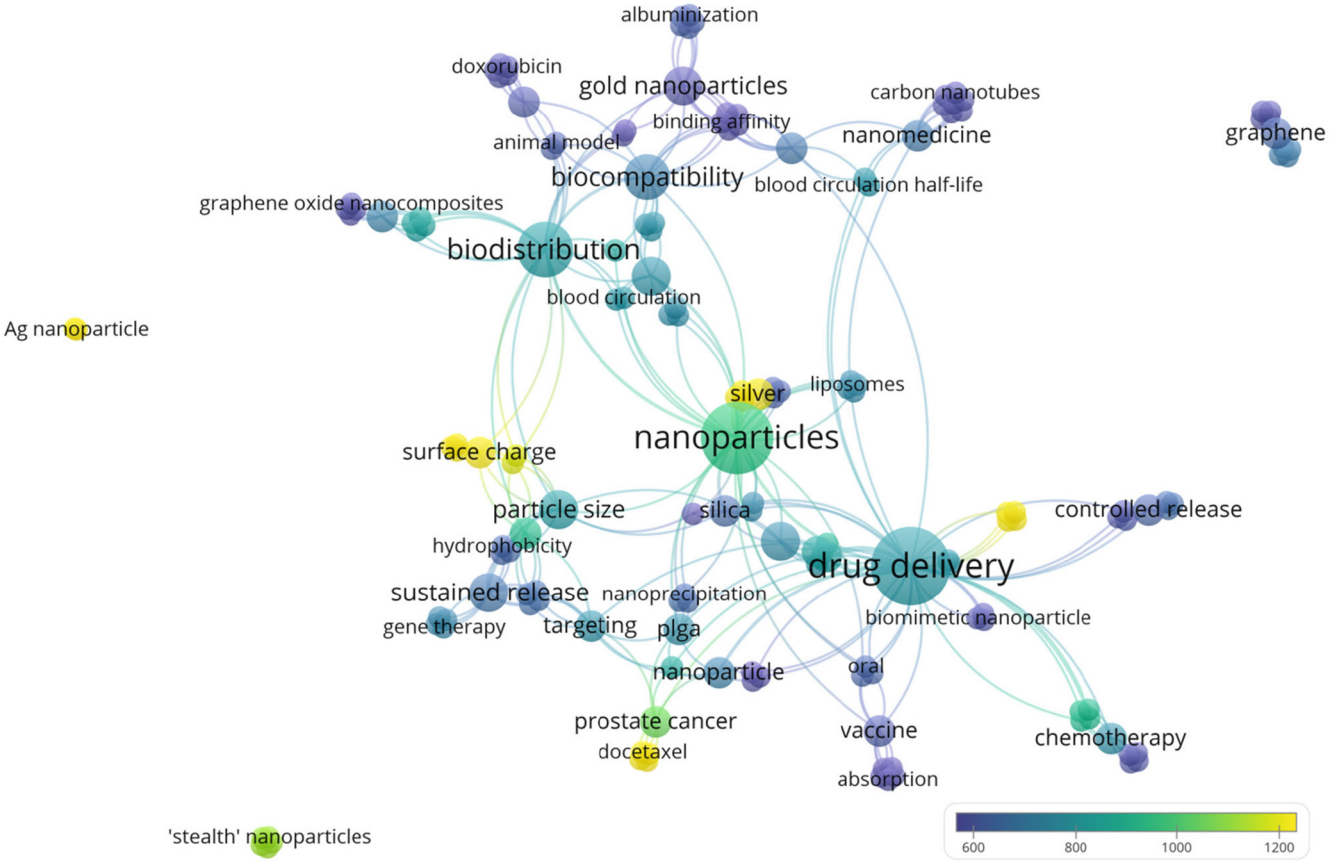

Fig. 7. Keyword map showing all author keywords that appeared in the 100 articles. Bubble size reflects how frequently a keyword is mentioned in the articles. The bubble color reflects the average citations (citations per article, CPA) of an article mentioning the keyword. The distance between two bubbles reflects how frequently two keywords were co-mentioned among the 100 articles. The lines illustrate the 1000 most commonly co-mentioned keyword pairs.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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