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Mini-review

A Bibliometric Study on Nanomedicines as Melanoma Therapeutics: Clinical Translation is Urgent

Wenhao Wang[1], Chao Lu[2*], Zhengwei Huang[2*], Lei Shu[2], Jianfeng Cai[3], Chuanbin Wu[2] and Xin Pan[1]

[1]*School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou, Guangdong, China;* [2]*College of Pharmacy, Jinan University, Guangzhou, Guangdong, China;* [3]*Department of Chemistry, University of South Florida, Tampa, FL, United States*

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Abstract

Melanoma has become a severe burden for human beings, with high mortality and a growing incidence. Currently, various nanomedicines integrated with novel therapeutic strategies and precision delivery have been developed to treat melanoma. Although great achievements have been made in the development of nanomedicines, clinical translation is lagging far behind. In this review, three research questions are raised to elucidate the bibliometric study on nanomedicines as melanoma therapeutics. The basic bibliometric properties are presented and analyzed. International cooperation and research foci are emphasized. Finally, future research directions for nanomedicines to promote clinical translation are raised, and several feasible suggestions are proposed. We believe that this review could serve as a guideline document for the development of nanomedicines for melanoma therapeutics.

Introduction

Cancer has become the leading cause of death globally and the most important obstruction to human health. Melanoma, a type of malignant skin cancer, has attracted tremendous attention in cancer research due to the rising incidence of cancer deaths worldwide.[1] The aggressive nature of melanoma and its resistance to existing treatments account for more than 80% of skin cancer deaths and about 95% of mortalities after the metastasis of melanoma.[2] According to the updated statistics from Global Cancer Statistics, about 324,635 new cases and 57,043 new deaths were recorded in 2020; these numbers were 2.02 times and 1.40 times greater than the incidence and mortality in 2002 when 160,177 new cases and 40,781 new deaths were reported.[3] The growth of melanoma cases has become a great crisis for human health, and it causes heavy social, medical, and economic burdens. The scientific community has made a great attempt to combat melanoma. Currently, the state-of-the-art therapies for melanoma include surgical therapy, chemotherapy, radiotherapy, and immunotherapy. Once diagnosed, the first-line therapeutic approach is surgical therapy by directly resecting the tumor lesions.[4,5] However, patients with metastatic tumors and residual tumor tissue are not suitable for surgical therapy, and immunotherapy and targeted chemotherapy through various drug-delivery techniques are alternatives.[6]

In general, nanomedicine refers to a nanosystem for diagnosis, monitoring, control, prevention, or treatment of various diseases. Numerous nanomedicines prepared from multiple materials have been reported for the treatment of cancer, including inorganic nanomedicines,[7] polymeric nanomedicines,[8] and lipid-based nanomedicines.[9] These diversified nanomedicines have been synthesized not only to deliver active pharmaceutical ingredients to tumor sites but also to play unique synergistic therapeutic effects.

Inspired by these facts, therapeutic scientists regard nanomedicines might be candidate therapeutics for melanoma. In recent decades, numerous nanomedicine studies using promising remedies to treat melanoma have been conducted.[10] According to these pioneer studies, nanomedicines have demonstrated remark-

Keywords: Melanoma; Nanomedicines; Web of Science; Bibliometric analysis; Clinical translation.

Abbreviations: AAMI, ACS Applied Materials & Interfaces; ACNB, Artificial Cells, Nanomedicine and Biotechnology; AN, ACS Nano; B, Biomaterials; B2B, Bench-to-beside; BAM, Biotechnology and Applied Microbiology; BMB, Biochemistry and Molecular Biology; C, Cancers; CAS, Chinese Academy of Sciences; Ch, Chemistry; CNR, Consiglio Nazionale delle Ricerche; CNRS, Centre National de la Recherche Scientifique; COVID-19, Corona Virus Disease-2019; CSIR, Council of Scientific Industrial Research; E, Engineering; HU, Harvard University; IJN, International Journal of Nano-medicine; JCR, Journal of Controlled Release; JNR, Journal of Nanoparticle Research; LERU, League of European Research Universities; MS, Materials Science; Nm, Nanomedicine; NNBM, Nanomedicine: Nanotechnology Biology and Medicine; Ns, Nanoscale; NU, Northeastern University; O, Oncology; P, Pharmaceutics; Ph, Physics; PP, Pharmacology and Pharmacy; PU, Peking University; R&D, Research and development; REM, Research and Experimental Medicine; RQs, Research questions; STOT, Science and Technology; SU, Sichuan University; T, Theranostics; TDM, Therapeutic drug monitoring; UNC, University of North Carolina; WIRNN, Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology; ZU, Zhejiang University.

***Correspondence to:** Zhengwei Huang, College of Pharmacy, Jinan University, Guangzhou, Guangdong, China. ORCID: https://orcid.org/0000-0003-2351-7347. Tel/Fax: +86-20-3994-3117, E-mail: huangzhengw@jnu.edu.cn; Chao Lu, College of Pharmacy, Jinan University, Guangzhou, Guangdong 518100, China. ORCID: https://orcid.org/0000-0002-2118-8888. Tel/Fax: +86-20-3994-3117, E-mail: chaolu@jun.edu.cn

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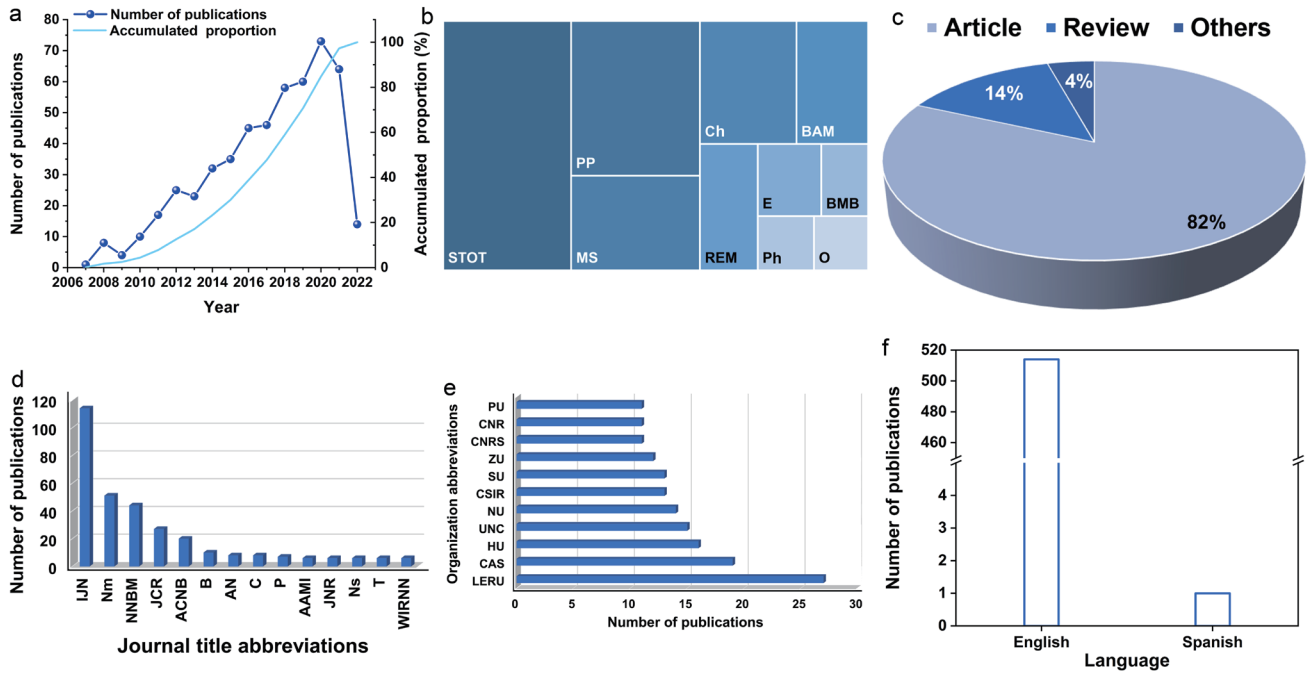

Fig. 1. (a) Number of publications each year. (b) Top-10 research areas. (c) Types of documents. (d) Top-14 journals. (e) Top-11 organizations. (f) Languages of the publications. STOT, Science and Technology, Other Topics; PP, Pharmacology and Pharmacy; MS, Materials Science; Ch, Chemistry; BAM, Biotechnology and Applied Microbiology; REM, Research and Experimental Medicine; E, Engineering; BMB, Biochemistry and Molecular Biology; Ph, Physics; O, Oncology; IJN, International Journal of Nano-medicine; Nm, Nanomedicine; NNBM, Nanomedicine, Nanotechnology Biology and Medicine; JCR, Journal of Controlled Release; ACNB, Artificial Cells, Nanomedicine and Biotechnology; B, Biomaterials; AN, ACS Nano; C, Cancers; P, Pharmaceutics; AAMI, ACS Applied Materials & Interfaces; JNR, Journal of Nanoparticle Research; Ns, Nanoscale; T, Theranostics; WIRNN, Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology; LERU, League of European Research Universities; CAS, Chinese Academy of Sciences; HU, Harvard University; UNC, University of North Carolina; NU, Northeastern University; CSIR, Council of Scientific Industrial Research; SU, Sichuan University; ZU, Zhejiang University; CNRS, Centre National de la Recherche Scientifique; CNR, Consiglio Nazionale delle Ricerche; PU, Peking University.

able therapeutic efficacies, surpassing those of conventional drugs. These nanomedicines amalgamate diverse innovative therapeutic strategies, thereby enabling more efficacious tumor ablation. Additionally, they facilitate targeted drug delivery, thereby potentially mitigating toxicity, enhancing efficiency, and enabling precision medicine. Consequently, investigating the association between melanoma and nanomedicine is essential.

Research questions (RQs)

As a large amount of literature accumulates in this field, the prerequisite of performing a bibliometric investigation with certain RQs must be fulfilled. It should be noted that raising RQs is a necessary procedure in bibliometric studies.[11] To ensure the significance of such an investigation, the following RQs were raised:

Q1: What are the basic bibliometric properties of the retrieved documents?

Q2: What is the collaboration status of this field?

Q3: What are the research foci?

To address these RQs and to scrutinize the *status quo* of the relevant research,[12] a bibliometric study was performed by using the methods stated below.

Bibliometric methods

For bibliometric analysis, a document survey was conducted using the Web of Science Core Collection (https://www.webofscience.com/wos/woscc/basic-search) on June 6, 2022, and the search set was (TS = melanoma) AND (TS = nanomedicine). Herein, 'TS' means the topic theme. As the Web of Science Core Collection is regarded as one of the most trustworthy academic databases around the world, the quality of papers retrieved could be ensured to a maximum degree. In this context, no restriction on timespan, literature type, or language was set to include as many publications as possible. It should be noted that the duplicate documents were manually excluded by the authors.

The basic bibliometric attributes were analyzed by Clarivate Analytics (associated with the Web of Science), the international cooperation network by the Bibliometric Online Analysis Platform (https://bibliometric.com/), and keywords co-occurrence by VOSviewer (version 1.6.18, Leiden University, Netherlands). The analysis paradigm was in parallel with that of previous studies.[13–15]

Bibliometric results

The literature survey returned 515 publications, and the bibliometric results are summarized in Figure 1. From 2007 to 2020, the number of publications increased (Fig. 1a). A slight drop in 2021 might be due to the interruption in experiments caused by Coronavirus Disease-2019 lockdowns.[4] After the control of the pandemic, the number of publications increased again. The research areas were predominantly in the fields of pharmaceutical, materials, and chemical sciences, while fundamental medical sciences (rather than clinical sciences) accounted for a minor frac-

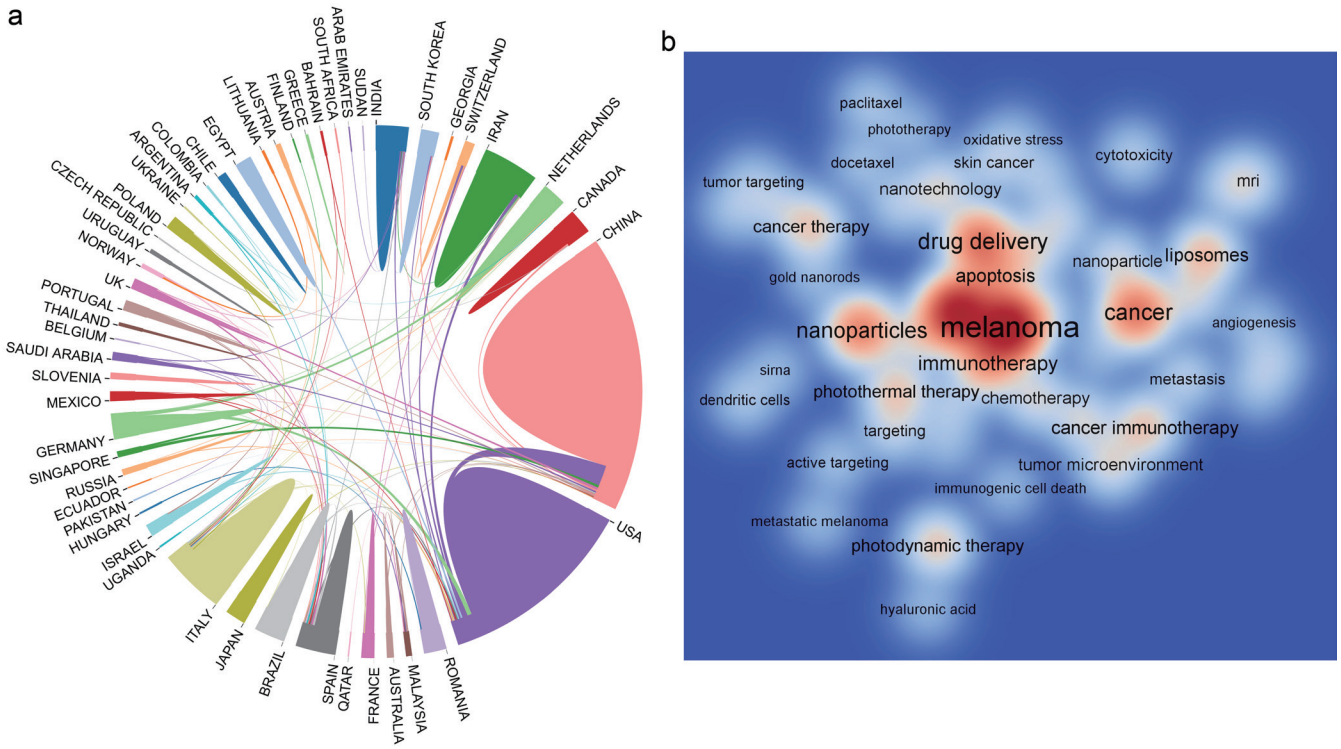

Fig. 2. (a) International cooperation chord diagram. (b) Density visualization of the co-occurrence of keywords.

tion (Fig. 1b). The proportions of article types were as follows: 82% for articles, 14% for reviews, and 4% for others (Fig. 1c), suggesting that original research was the prevailing literature category and more in-depth reviews could be expected. The top 14 publishing journals are depicted in Figure 1d. Herein, 8/14 were nanomedicine-specific journals (Nanomedicine, etc.), 3/14 were materials science journals (Biomaterials, etc.), 2/14 were pharmaceutical science journals (Pharmaceutics, etc.), and 1/14 was an oncology-specific journal (Cancers). Consistent with the research areas, the top journals focused on fundamental sciences instead of clinical sciences. Organizations in Europe (e.g., Centre National de la Recherche Scientifique), USA (e.g., Harvard University), China (e.g., Sichuan University), and India (Council of Scientific Industrial Research) accounted for the top 11 contributing organizations (Fig. 1e), indicating that these regions emphasized the related field. Emerging researchers with particular interests in this field are encouraged to join these organizations. Additionally, the predominant language was English (99.81%, Fig. 1f), which was beneficial for global interactions.

The global collaborative network is illustrated in Figure 2a. Overall, as shown by the intertwined chords in the diagram, transgeographical collaborations were active in this field. Both intercontinental (e.g., China-USA) and intracontinental cooperations (e.g., China-Japan) were established. The USA and China served as the collaboration pivots with 15 and 13 collaborators, respectively. Active international cooperation boosted the sustainable development of this field, and more high-quality cooperation is expected in the future.

Figure 2b shows the co-occurrence profile of keywords. 'Melanoma,' 'drug delivery,' 'nanoparticles,' and 'cancer' were the density centers, demonstrating their frequent occurrences. The high frequency of these keywords was necessarily determined by the search set (TS = melanoma) AND (TS = nanomedicine). 'Liposomes,' 'immunotherapy,' 'apoptosis,' 'photothermal therapy,' and 'photodynamic therapy' also presented high densities, representing that liposomes were the most-investigated nanomedicines[16] and that different therapeutic approaches were widely discussed.[17] Besides, active ingredients (like 'siRNA' and 'paclitaxel'), nanomaterials (like 'gold nanorods' and 'hyaluronic acid') and anticancer mechanisms (like 'oxidative stress' and 'immunogenic cell death') were high-density keywords. It was inferred that the design and assessment of drug-delivering nanomedicines for melanoma therapy at the laboratory level were the major topics.[18–20] On the contrary, concepts associated with dosage administration, therapeutic drug monitoring, clinical trials, and pharmacoeconomics were not included in Figure 2b. Therefore, the clinical translation of nanomedicines as melanoma therapeutics might have not become a research focus yet. In other words, the clinical aspects were still pending exploitation.

Answers to RQs

Of note, sufficient information was revealed to address the RQs.

With respect to the answer to Q1: "What are the basic bibliometric properties of retrieved documents?" in total, 515 publications were collected, with the number increasing annually. The main research categories were pharmaceutical, materials, chemical, and fundamental medical sciences. Most publications were original articles, and the prevailing language was English.

With respect to the answer to Q2: "What is the collaboration status of this field?" international cooperation was quite active, with the USA and China serving as the cooperation pivots. Most of the top-contributing organizations were located in the USA or China.

With respect to the answer to Q3: "What are the research foci?" the synthesis and evaluation of nanomedicines for melanoma therapy on the laboratory level were the major topics, and the anticancer mechanisms as well as the selection of active ingredients and nanomaterials were emphasized.

Opinions and future research directions

The bibliometric analyses demonstrated that applying nanomedicines for melanoma management was a frequently and widely discussed topic that aroused global interest and cooperation. Of note, according to the research foci revealed in Figure 2b, nanomedicines with apoptotic, immunogenic, oxidative stress-inducing, and other activities had been employed in immunotherapy, photothermal therapy, and photodynamic therapy of melanoma. Additionally, a variety of active pharmaceutical ingredients and nanomaterials had been exploited, acting as candidates for clinical application. These results elaborated on the significance of nanomedicines as melanoma therapeutics.

According to the data, most of the publications focused on fundamental research, meaning that they were laboratory investigations, such as the synthesis, *in-vitro* characterization, and animal model evaluation of nanomedicines. These studies helped to establish a firm basis for the preclinical phase. As revealed by the bibliometric results (Figs. 1 and 2), the research community did not proceed to clinical translation studies. Mainly, two kinds of bibliometric data revealed such a trend: Clinical sciences were not included in the top research areas, and no flagship clinical medicine journals ranked in the top journals. Noticeably, although some included journals (e.g., Biomaterials, Pharmaceutics, etc.) publish clinical trials and other clinic-related studies, the emphasis on clinical translation was lacking. Moreover, the papers of interest in these journals dominantly reported laboratory results. Few keywords about clinical scenarios possessed high density. Although much effort was paid to the fundamental research of nanomedicines for melanoma remedies, the bench-to-beside (B2B) translation lagged far behind, which scarcely provided available therapeutic strategies. A search within the clinical trial database (https://clinicaltrials.gov/) revealed that there were only 26 nanomedicine-related clinical trials within 3,197 studies regarding melanoma therapeutics, indicating the inadequate translation from lab to clinical trial. This conclusion was consistent with the abovementioned bibliometric results, suggesting that they are solid.

Since the emergence of nanotechnologies, the B2B translation of nanomedicines (or any other medicines) has been the goal; however, this endeavor has been impeded by various bottlenecks.[21] Primarily, the limited comprehension of the *in-vivo* fate of nanomedicines has hindered the precise prediction of their absorption, distribution, metabolism, and excretion.[22] As the nanomedicines were administrated *in vivo*, numerous nano-bio interactions would significantly change their transportation process, which might compromise their therapeutical efficiency and cause an unforeseen systemic distribution. In addition, the absence of clear definitions and regulatory guidance might confuse the research and development department.[23] Furthermore, the criteria or guidelines in different regions (like the US, EU, and China) were not consistent and clear enough, obstructing the research interest of the global corporation. The third bottleneck was the uncontrollable synthetic process and the irreproducible large-scale production.[24] Some reported nanomedicines were synthesized in complicated ways with multiple materials, which were uncontrollable and hard to scale up. The current manufacturing and controls and good manufacturing practice manufacturing units might not meet the scalable requirements of these complicated nanomedicines. Therefore, versatile production techniques are needed to solve these critical issues.

For the development of the field of pharmaceutical sciences, several feasible suggestions have been proposed to facilitate the B2B transformation of nanomedicines for melanoma treatment and are described below.

First, the formulation of nanomedicines should be simplified. Currently, the design of nanomedicines is increasingly sophisticated. Although this could improve the targetability and efficacy of developed systems,[25] biosafety might become quite challenging. The increase in the materials and structures of sophisticated nanomedicines could enhance the unpredictability of the absorption, distribution, metabolism, and excretion process. Furthermore, the potential aggregation state and protein corona formation could make the *in-vivo* transportation uncontrollable. Up to now, no well-established guidelines focusing on nanotoxicity have been released by drug regulatory agencies.[26] Various byproducts of synthetic nanomaterials might provoke unpredictable adverse effects.[16] Worse still, large-scale production might be hampered if the nanostructure is too complicated. Simplifying the design could mitigate these difficulties in B2B transformation.

Second, nanomedicines for macromolecular drug delivery need to be developed. Antibodies, peptide drugs, and siRNA with anti-melanoma activities have been comprehensively studied over the years.[27] Especially for immunotherapy and other novel therapies, the application of macromolecules represents the next-generation alternative for metastatic or malignant melanoma. However, one of the critical shortcomings of these macromolecules is their low physicochemical stability. Conventional drug delivery systems like tablets and injections can hardly surmount the instability problem due to the lack of studies on stabilization mechanisms. Many types of nanomedicines have been successfully employed for the delivery of macromolecules. By self-assembling into nanomedicines and encapsulating into polymeric nanocarriers, serval bioactive peptides have been efficiently delivered for the treatment of melanoma.[28,29] In addition, it has been documented that many kinds of nanomedicines can stabilize macromolecules by steric barrier mechanisms;[30] thus, nanomedicines exhibit superiority in the delivery of macromolecular drugs. This delivery superiority is promising to be transformed into clinical superiority.

Third, drug repurposing using nanomedicines should be carried out. Several old drugs approved by the US Food and Drug Administration have been constructed into nanomedicines for new therapeutic outcomes. Disulfiram, artemisinin, chloroquine, metformin, and aspirin are typical representatives.[26] By combining with other drugs and novel materials, these old drugs could be repurposed for cancer therapy. Equipped with high biosafety, the repurposing of an old drug is an attractive strategy for accelerating the clinical translation of melanoma treatment.[31] However, it is worth noting that although the *in-vivo* biosafety of these old drugs has been investigated, the *in-vivo* behavior of the constructed nanomedicine should also be systematically evaluated.

Fourth, lab-clinic interactive teamwork should be implemented. Scientists of pharmaceutical and materials science have emphasized the development of new therapeutics; however, they do not have a sufficient understanding of the clinical demand and practice. Without the participation of pharmaceutical scientists in the research and development process, some plausible nanomedicine systems may not satisfy the actual clinical needs. It is recommended to collect suggestions and feedback from clinicians in the

research and development process in order to avoid impractical directions and focus on real-world applications.[32]

For future directions, we appeal to experts and investigators in this field to consider these above recommendations. To be specific, attempts should be made to simplify the formulation of nanomedicines, develop nanomedicines for macromolecular drug delivery, achieve drug repurposing using nanomedicines, implement lab-clinic interactive teamwork, and then succeed in developing new nanomedicine-based therapeutics for melanoma.

Conclusion

In summary, the advantages of nanomedicines should be used to develop potent therapeutics for melanoma. By bibliometric approaches, the *status quo* of nanomedicines intended for melanoma management was scrutinized, and the basic bibliometric properties, cooperative state, and research hotspots were revealed. Although this topic has gained increasing attention worldwide, it was showcased that the major emphasis has been laid on laboratory investigations, and the B2B transformation process has lagged far behind compared with fundamental studies. The reasons for this might include a lack of understanding of absorption, distribution, metabolism, and excretion as well as imperfect regulatory guidance and difficulties in quality control. It is anticipated that therapeutic scientists will simplify the formulation of nanomedicines, develop nanomedicines for macromolecular drug delivery, achieve drug repurposing using nanomedicines, and implement lab-clinic interactive teamwork in order to accelerate the B2B transformation process in the near future.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study concept and design (W.W., Z.H.), acquisition of data (Z.H., C.L.), analysis and interpretation of data (W.W., Z.H., L.S.), drafting of the manuscript (W.W., Z.H.), critical revision of the manuscript (C.L., J.C., C.W., X.P.), and study supervision (J.C., C.W., X.P.). All authors have made a significant contribution to this study and have approved the final manuscript.

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