

Nanotechnology in COVID-19 Diagnosis and Treatment: A Bibliometric Analysis

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Abstract

There is an utmost urgency of having new and advanced diagnostics as well as therapeutic alternatives along with the conventional methods to treat coronavirus disease 2019 (COVID-19). For this purpose, different strategies must be explored for the advancement of testing capacity, developing effective treatments, and developing safe vaccines that provide long-term immunity. Nanotechnology has been found effective against COVID-19 in terms of diagnosis, prevention, and treatment. The diameter of SARS-CoV-2 (60–140 nm) is similar to nanoparticles. This is why, synthetic nanoparticles can precisely resemble SARS-CoV-2, and efficiently interact with the viral proteins and counter this virus. Nanotechnology offers benefits by developing efficient and cost-effective diagnosis methods and facilitating the improvement of drug properties through nano-carriers, namely liposomes, micelles, metallic nanoparticles, etc. The bibliometric analysis evaluates scholarly contributions using mathematical and statistical methodologies. In this study, the bibliometric analysis investigated the publication trends of nanoparticles and their application in COVID-19 diagnosis and treatment. We have systematically searched the different search engines and publishers (Scopus, PubMed, and Google scholar) from 2020 to 2021, and various visual maps were generated to show, the most-relevant authors, sources, countries, topics, and keywords by using a software called VOSviewer. The findings indicate the advancement of nanotechnology in the diagnosis and therapy of COVID-19. At last, the bibliometric analysis of nanoparticles for COVID-19 diagnosis and treatment provides a clear view of the future research directions and identifies the potential challenges and opportunities. This may pave the way for new researchers to find the proper subfields in nanoparticle-related research areas for combating the COVID-19.

Key words: SARS CoV-2, COVID-19, diagnosis, treatment, bibliometric analysis, nanotechnology, nanocarriers.

Introduction

Before the end of January 2020, a novel coronavirus named 2019-nCoV (2019 novel Coronavirus) was discovered in Wuhan, the People's Republic of China. Since then, the disease known as COVID-19 (Coronavirus Disease 2019) has spread outside of China to the other countries like United States, Thailand, Bangladesh, South Korea, Japan, Taiwan, Singapore, and Nepal (Harapan *et al.*, 2020). The same month, the WHO proclaimed the

coronavirus an international emergency. Several investigations indicated that the outbreak was caused by a novel beta-coronavirus called 2019 novel coronavirus (2019-nCoV), which reminded experts of the SARS-2003 pandemic which was brought on by another beta-coronavirus. People with SARS-CoV-2 infection may have symptoms (such as shortness of breath, coughing, and fever) similar to other respiratory infections or be silent bearers. A significant issue is the spreading of COVID-19 in

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communities. Physicians must have access to a quick, affordable point-of-care diagnostic test in emergency rooms, clinics and community hospitals. With the use of these diagnostics, front-line professionals can promptly screen patients and stop the infection from spreading (Udugama *et al.*, 2020). Patients with COVID-19 may need treatment once they have been diagnosed. These therapies stop the virus from spreading within the host (Huang *et al.*, 2020). Nanotechnology provides an effective and affordable way to enhance these SARS-CoV-2 detection assays. The use of nanoparticles in medicine for treatment, diagnosis, control and prevention is known as nanomedicine (Yang, 2021). Owing to its unique attributes, such as improved solubility, small size, surface adaptability and versatility, nanoparticles have been studied and used extensively over the years. This has led to the development of better and safer drugs, personalized nanomedicines, tissue-targeted treatments and early disease diagnosis and prevention. As a result, it appears that nano-based techniques will be the best option for developing the most efficient treatments for a variety of illnesses in the near future. The use of nanotechnology in the diagnosis, management and prevention of COVID-19 has the potential to be extremely useful. The nanotechnology community has the ability to significantly advance the effort to combat COVID-19. Point-of-care diagnostics, pharmaceutical carriers and vaccines have all been developed using nanomaterials (Chintagunta *et al.*, 2021). Numerous academics have published their findings about the significance of nanotechnology in COVID-19 diagnosis and therapy in prestigious, peer-reviewed journals from around the world.

The current state and emerging trends in a given academic topic are evaluated using bibliometric analysis. This enables us to find prospective research gaps and areas of interest, which helps us develop ideas and future research strategies (Wang *et al.*, 2021). In order to examine research efforts across a range of themes, previous bibliometric assessments of the COVID-19 outbreak were performed. On the other hand, none were done to identify the most frequently referenced research articles on the

application of nanotechnology in COVID 19 diagnosis and treatment. A bibliometric analysis of the most frequently cited papers about the use of nanotechnology in COVID-19 diagnosis and treatment-related studies is necessary due to the rapid expansion of COVID-19-related content (Baker *et al.*, 2020b). The objective of this research was to conduct a bibliometric analysis that analyzed the components of the most referenced publications published immediately after the outbreak. It will offer a better understanding of current nanotechnology research in COVID-19 while also pointing up potential trends that could assist scientists in their scientific research (Ebrahim *et al.*, 2020).

Methodology

Data source and search strategy: A systematic search of the PubMed, Scopus and Google Scholar was performed. The global literatures regarding the use of nanotechnology in COVID-19 diagnosis and treatment published between 2020 to 2021 were scanned. The search terms applied to identify the closest matching publication were followings:

1. COVID 19, Nanotechnology, Diagnosis, Treatment
2. SARS COV-2, Nanotechnology, Diagnosis, Treatment
3. COVID 19, Nanotechnology
4. COVID 19, Nanotechnology, Vaccine
5. SARS COV-2, Nanotechnology, Therapeutic Drug
6. COVID 19, Nanoparticles, Detection

Data extraction and search result: Microsoft Excel 2019 was used to extract all COVID-19 document data. We found 375 studies through the database and manual search. 200 articles were left after eliminating those with irrelevant subject matter, ambiguous methodology and a lack of clarity in the definition of the final result. Finally, after removing all duplicate contents 122 studies were included. Title, corresponding author, affiliation, nationality, city of authorship, language, publication date, publication type, research focus and content of research were extracted directly from the publications' full text.

Bibliometric analysis: Cooccurrence analyses on terms from titles and abstracts were performed in VOSviewer (version 1.6.15) to visualize the major themes of the publications. Co-occurrence analysis indicated how frequently two terms appear together in the same text, as well as their association. Each sphere represented a term and the size was

proportional to how frequently they appear in the network (Donthu *et al.*, 2020). The thicker the line between the spheres, the stronger the link between terms (co-occurrence). Using microsoft excel, we were able to conduct time trends, geographic analyses and journal analyses.

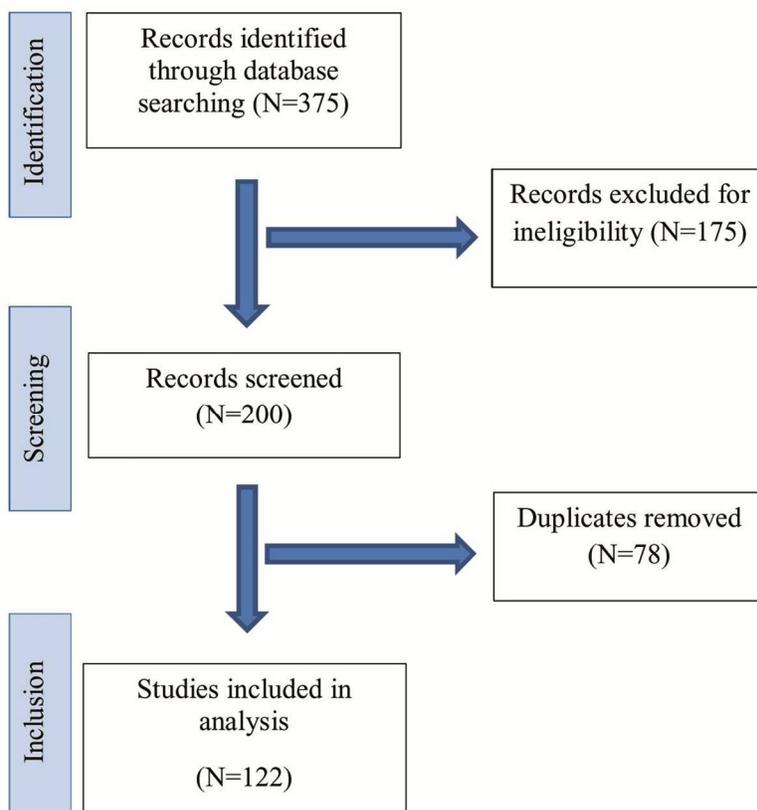


Figure 1. Diagram of the study selection process.

Results

Co-occurrence author keywords: To illustrate the author keyword connection network, we only analyzed keywords with at least 5 co-occurrences and discovered that 13 of 525 keywords were inserted into the network and clustered into 4 groups. Among the author keywords, SARS-CoV-2 (occurrences = 81), COVID-19 (occurrences = 93), and nanoparticles (occurrences = 70) were most dominant (Figure 2).

All keywords analysis: The minimum number of times that a keyword needs to appear was set at 10.

Only 79 out of 1,921 keywords were processed. The most common author keywords were COVID-19 (with 309 occurrences), human (with 222 occurrences) and nanoparticles (with 142 occurrences). On the map, the four clusters were specified by four distinct colors: red, blue, green, and yellow. The size of the circle represented how frequently a word or phrase appears as a keyword. The correlation was determined by the distance between the two circles. There were 59, 57, 50 and 5 items in the red, green, blue, and yellow clusters respectively (Figure 3).

Analysis of sources based on number of documents: The minimum number of documents was set at 3. Only 10 sources met the threshold. The Journal of Nanomedicine was the leading source with highest number of documents (n=7), followed by ACS nano (n=6) (Figure 4).

Co-authorship country: Publications coauthored by many countries were excluded. The maximum

number of countries per publication was set at 25. The minimum number of publications per country was fixed at 5. Only 44 out of 93 countries met the criteria. Based on documents, USA was the leading country (documents =17), followed by India (documents = 23), England (documents = 11) and China (documents = 18) (Figure 5).

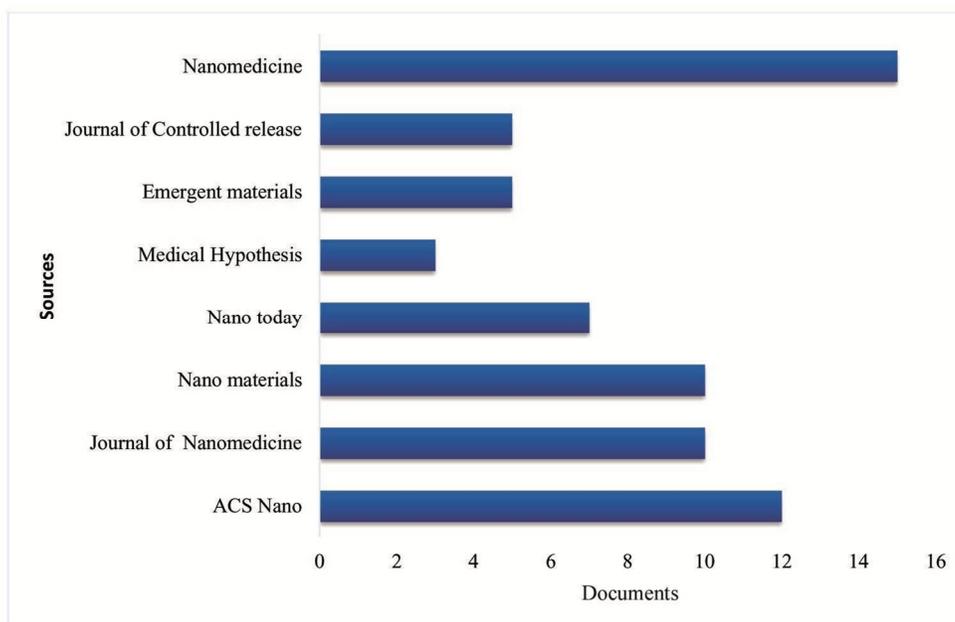


Figure 4. Analysis of sources based on number of documents.

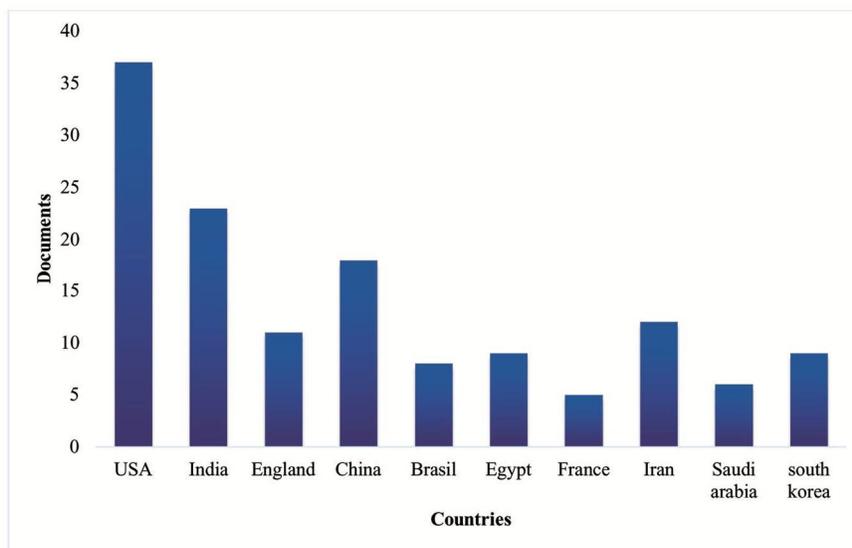


Figure 5. Co-authorship country.

Analysis of top 5 most cited articles:**Table 1. Source, citation and main theme of top 5 most cited articles.**

Author name	Article name	Source	Citation	Main theme
Keech C. (2020)	Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine	New England Journal of Medicine	878	An investigation into the safety of the rSARSCoV-2 vaccination and its ability to elicit an immune response. The study was carried out in 131 healthy participants as part of a randomized, placebo-controlled, phase 1–2 study. NVX-CoV2373 was found to be safe, and elicited immunological responses that were significantly higher than those seen with Covid-19 convalescent serum. CD4+ T-cell responses that were skewed toward the Th1 lineage were generated by the Matrix-M1 adjuvant.
Hu T.Y. (2020)	Insights from nanomedicine into chloroquine efficacy against COVID-19	Nature Nano-technology	271	In the field of nanomedicine, chloroquine has been used to study the absorption of nanoparticles in cells. As a result, the findings that have been obtained from the interactions of synthetic nanoparticles with cells in the presence of chloroquine may reveal mechanisms that are active prior to viral replication. Particularly, research on nanomedicine might illuminate the chloroquine-induced changes in SARS-CoV-2 cellular uptake that have been observed.
Moitra P. (2020)	Selective naked-eye detection of SARS-CoV-2 mediated by N-gene targeted antisense oligonucleotide capped plasmonic nanoparticles	ACS Nano	403	It would be ideal if there was a method for the selective detection of SARS-CoV-2 that could be performed "naked-eye" and evaluated without the need for complicated experimental methods. The development of a colorimetric assay utilizing gold nanoparticles (AuNPs), which, when capped with appropriately designed thiolmodified antisense oligonucleotides (ASOs), are specific for the N-gene of SARS-CoV-2, has the potential to be used to diagnose positive COVID-19 patients from isolated RNA samples within ten minutes.
Zhu X. (2020)	Multiplex reverse transcription loop-mediated isothermal amplification combined with nanoparticle-based lateral flow biosensor for the diagnosis of COVID-19	Biosensors and Bioelectronics	189	The COVID-19 mRT-LAMP-LFB test is a potential method for identifying SARS-CoV-2 infections in both public health settings and clinical laboratories, particularly in resource-limited settings. The ORF1ab (opening reading frame 1a/b) and N (nucleoprotein) genes of SARS-CoV-2 were amplified in a single-tube process using two LAMP primer sets, and the findings were easily analyzed by LFB.
Itani R. (2020)	Optimizing use of theranostic nanoparticles as a life-saving strategy for treating COVID-19 patients	Theranostics	99	Theranostic nanoparticles may be an effective way to deliver therapeutics to infection sites selectively. They also allow monitoring of infectious diseases and therapy responses. Intranasal administration was thought to be the most effective route for therapeutic agents against viral pulmonary diseases. However, NP-based delivery systems offer many advantages over intranasal medication for viral pulmonary disorders. NP-based delivery systems offer numerous benefits in overcoming the challenges of mucosal administration and ensuring that these agents achieve a concentration many times higher than expected in the targeted sites of infection while limiting side effects on normal cells.

Advancements in CoVID-19 treatment using nanotechnology: Researchers are working rapidly to develop efficient vaccinations and therapies for COVID-19 since there are an increasing number of disease determinants throughout the world without any available options for approved therapy. A limited number of COVID-19 patients may also benefit from attempts to employ medications that are currently on the market and have been approved for use in other conditions. Numerous medications with approval for other uses have been demonstrated to have some effect on SARS-CoV-2 *in vitro*, however small-scale non-randomized trials had diverse outcomes. These include chloroquine (CQ) and hydroxychloroquine (HCQ) for treating malaria, remdesivir (an experimental medicine against the Ebola virus (EBOV) discovered during the Ebola outbreak in West Africa), and lopinavir/ritonavir (LPV/r), which is used to treat AIDS (Lu *et al.*, 2020).

Researchers in the field of nanomedicine have been investigating the relationship between high infectivity and the capacity of various nanosystems and viral vectors to deliver genes. In order to create delivery methods that may be applied in a number of disciplines, nanomedical researchers have researched the molecular mechanisms of vectors. Since viruses and nanoparticles (NPs) operate at the same scale, developing vaccines and performing immuno engineering rely heavily on this strategy. Nanomedicine may be the ideal substitute for cutting-edge technologies for the production of vaccines since NPs are tools that may mimic the structural and functional characteristics of viruses. The current moment, in which SARS-CoV-2 is a serious threat on a global scale, is crucial from the standpoint of vaccine technology development, and nanotechnology and nanomedicine are presented as novel therapeutic tools and approaches (Tu *et al.*, 2020).

As a safe and more effective defense against viral infection and treatment, numerous studies are currently being conducted on developing a technique for delivering nanoparticles into the nasal cavity (Alshweiat *et al.*, 2019). Since SARS-CoV-2

infections start on the mucosal surface of the eye or nasal cavity, mucosal therapy is the most crucial approach for treating such infectious diseases. Due to the abundance of capillaries and the cavity's large surface area, delivery through the nasal cavity is not only quick and inexpensive but also non-invasive (Constantino *et al.*, 2007). The characteristics of the NPs, such as surface charge, size and shape, are crucial considerations to take into account while optimizing the method of delivery to the nasal cavity and play a critical role in effective and safe treatment (Tai *et al.*, 2020).

In case of theranostic nanoparticles, the tiny size, low toxicity, electrical charge and chemical plasticity of a generic medicine enable it to get past a number of obstacles that are present in different routes of administration (Kumar *et al.*, 2016). The SARS-CoV-2 entrance and life cycle can be targeted during treatment with NPs. The S protein is crucial in blocking SARS-CoV-2 entrance during the first membrane fusion process. As a result, therapeutic NPs can be created to prevent the S protein from attaching to host cells, thus pre-blocking SARS-CoV-2 entry. Since the application of nanotechnology in the treatment of common viral illnesses, numerous methods have been used to produce and market nanomedicines that have the ability to efficiently treat viruses. In particular, dexamethasone, the first SARS-CoV-2 treatment medication, was created utilizing nanotechnology a few months ago. Effective administration and therapy can be anticipated employing different nanoformulating dexamethasone. It has been claimed that SARS-CoV-2 infections can be treated using an anti-edema and anti-fibrotic mechanism (Lammers *et al.*, 2020).

Nanotechnology-based diagnosis: By combining the superior electrical and optical capabilities of nanoparticles with biological or synthetic molecules utilized as receptors, nano biosensors have the benefit of specifically detecting all sorts of analytes (Takashima *et al.*, 2011). These benefits are being used to study different SARS-CoV-2 detection techniques. The SARS-CoV-2 antibody can currently be detected in 5–15 minutes using a silicon-on-

insulator nanowire sensor built utilizing complementary metal-oxide-semiconductor compatible technology, with an expected sensitivity of 10⁻¹²–15 M.

Within 10 minutes of total RNA recovered from infected biosamples, the SARS-CoV-2 biosensor using thiol-modified antisense oligonucleotides-capped GNs may diagnose positive COVID-19 cases with the naked eye by color change. Another use for GNs is the identification of the glycan link between the S protein of SARS-CoV-2 and polymer-stabilized multivalent GNs containing sialic acid derivative utilizing a glyconanoparticle platform. By incorporating these traits, it is possible to create a low-cost detection platform that can be found in less than 30 minutes using a lateral flow diagnostic tool (Liu *et al.*, 2020).

Nanotechnology-based vaccine development: It is necessary for subunit vaccine candidates to successfully increase immunogenicity by inducing an immune response when co-administered with molecular adjuvants employing particular structural elements of SARS-CoV-2. Therefore, it is of utmost importance to create a vaccine that specifically targets the SARS-CoV-2 S protein subunit (Jiang *et al.*, 2012). This is due to the S protein's inclusion of membrane fusion and receptor-binding sites. Antibodies that are activated by vaccines based on the S protein block viral infection by preventing viral binding and subsequent membrane fusion (Coleman *et al.*, 2014). The SARS-CoV-2 S protein, which interacts with ACE2, is a noteworthy candidate suitable for the creation of both a vaccine and a treatment (Zhang *et al.*, 2020). Additionally, using the exclusive recombinant nanoparticle vaccine technology of Novavax®, NPs identical to immunogenic viruses have been created and produced.

A novel SARS-CoV-2 subunit vaccine is also being developed by the University of Queensland in Brisbane, Australia, employing a "molecular clamp" technique that prevents viral proteins from adhering in the first place. As an alternative, work is being done to create subunit vaccines employing NPs such

protein NPs and VLPs. It has been discovered that RBD in SARS-CoV-2 has a greater binding affinity for ACE2 than RBD in SARS-CoV. Thus, the RBD-based SARS-CoV vaccine can aid in the prevention of SARS-CoV-2 infection and is crucial for the development of the SARS-CoV-2 vaccine (Baker *et al.*, 2020a).

Discussion

Scientific research played a vital role in pandemic/epidemic control and prevention, and deserves to be completely mobilized, implemented and strengthened to update our understanding of the relationship between disease, humanity and history (Naveen *et al.*, 2021). Furthermore, scientific and technological methodologies and methods should be prioritized in our ongoing battle against viruses and in making us completely prepared for epidemic prevention and control. Many scientific studies have been conducted for COVID-19 treatment and prevention, providing a foundation for virus identification, vaccine development, prevention, and control measure formulation, and therapeutic R&D (Ebrahim *et al.*, 2020). In this regard, this review highlights the scientific research papers following the epidemic outbreak and seeks to provide a reference and thought for the future path of COVID-19 scientific study. The scientific community showed a prompt response to this pandemic and this is reflected in the citations received from our identified articles in the last four months.

The open-access policy of various journals eases the path of knowledge sharing and rapid dissemination of new findings regarding COVID-19 and nanotechnology as well. (Wang and Tian, 2021).

This study focuses on the bibliometric analysis of nanoparticle research literature from 2020 to 2021 using Scopus, PubMed, and Google Scholar as data sources. The findings indicate that nanotechnology and the use of nanotechnology in COVID-19 diagnosis and therapy are advancing. Our findings will help the researchers identifying significant subjects, the nature and characteristics of the study, and research shortcomings in the literature by

highlighting the characteristics of the top-cited articles. The origin of the majority of the papers was from the USA, the UK, India, China, Iran and Korea. In terms of paper output, the United States and India were placed first and second, respectively. The most relevant journals on the subject of nanotechnology research were Nanomedicine, ACS Nano and International Journal of Nanomedicine. Representative terms in our bibliographic database include metal nanoparticles, nanocarriers, spike glycoproteins, nanomaterials and so on. The analysis of the most frequently used terms in the COVID-19 literature highlighted specific areas of concentration over the study period.

Conclusion

The COVID-19 pandemic has affected the whole world in every possible way in terms of mortality, mental health or economic crisis. The study portrays the present state of SARS-CoV-2, with a focus on the research agenda for combating COVID-19. The review also focuses on potential particulate delivery methods and the research agenda to prevent this disease. Nanotechnology is an area in which scientists from a wide range of backgrounds have collaborated to solve complex issues. Currently nanotechnology is much needed to create new foundations for countering the present public health crisis, preparing for potential new threats, such as contagious diseases, and imagining a more imperishable future based on science. And so, nanotechnology is a versatile multidisciplinary weapon that may be used to develop a variety of tactics and strategies to aid in the promotion of research initiatives around the world to combat this devastating infectious coronavirus disease.

The bibliometric analysis evaluates scholarly contributions using mathematical and statistical methodologies. Although substantial research has been conducted on the bibliometric study of "COVID-19" there is no study dealing with the bibliometric analysis of "Nanotechnology in COVID-19 diagnosis and treatment. Our findings suggest that the research community seems to be very rigorous

and proactive in authoring "use of nanotechnology in COVID-19" related articles, as indicated by the massive citation count the top most articles obtained in less than a year after the disease's inception. The majority of these works have been published in the world's most prestigious journals. The findings of this study are expected to provide a better perspective for future research and identify new opportunities for turning nanoparticle research into clinical applications.

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