Responsiveness of the Immune System to Nanomedicine during Coronavirus Infections: Literature Review and Bibliometric Analysis

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Abstract

Objective Nanomedicine can play an important role in the various stages of prevention, diagnosis, treatment, vaccination, and research related to coronavirus disease 2019 (COVID-19). While nanomedicine is a powerful interdisciplinary means that offers various approaches in patient treatment, a number of factors should be critically studied to find approaches and mechanisms in the prevention, diagnosis, and treatment of this disease. This bibliometric analysis was designed to explore studies on the current knowledge of the structure, its mechanism of cell binding, and the therapeutic effect of nanomedicine on COVID-19.

Materials and Methods The study data was searched from Web of Science Core Collection(WoSCC) between 2017 and 2021. Biblioshiny and VOSviewer were used to analyze and visualize patterns in scientific literature derived from WoS.

Results The three clusters of keywords resulted relating to aim. Cluster 1 looking into epidemiological and public health studies on COVID-19. Cluster 2 included terms associated with virus transition, such as receptor binding, membrane glycoprotein, membrane fusion, and viral envelope proteins. Cluster 3 involved high-frequency keywords associated with nanomedicine, such as metal nanoparticles, drug delivery system doxorubicin, immunology, immune response, inflammation, and unclassified drug. Keywords such as “nanotechnology” and “gold nanoparticles” were at the center of COVID-19 related clusters, indicating the importance of these areas during the outbreak.

Conclusions Understanding the advanced virology of coronaviruses and interfering with their spread through nanomedicine could significantly impact global health and economic stability. Continuous research is needed to accelerate the transfer of nanomedicine results into practice of treatment without risk of side effects.

Keywords
- virus transition
- nanomedicine
- metal nanoparticles
- gold nanoparticles
- advanced virology of coronaviruses

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Introduction

In recent years, nanotechnology has played an important role in advanced medicine, drug development, and delivery through the application of nanostructures and nanophases in various fields of science, thereby linking biological and physical sciences.[1–3] Thus, while nanomedicine is an emerging field in medical biology, disease prevention, and treatment, the coronavirus disease 2019 (COVID-19) outbreak has triggered multilevel collaboration between scientists and researchers from different fields, including nanomedicine. Further evidence suggests that nanomedicine can change the effectiveness of viral and arbovirus infections. They are effective against resistant new viruses, incurable viral infections, and target strain-specific viruses.[4] Small nanoparticles (NP) ranging in size from 1 to 100 nm are used for diagnosis and treatment by drug delivery.[4–6] Both organic NPs, such as polymers, liposomes, micelles, ferritin, and inorganic NPs, such as metal NPs, can be used for therapeutic purposes. Beneficial effects have been shown in preclinical and clinical studies of both these types of NPs.[7]

Nanomaterials (NM) can be built on the principle of drug loading and drug release characteristics for a better mechanism and process for the delivery of therapeutic agents.[8–10] There is extensive interaction between NPs and cellular plasma, protein, and other blood components when NPs are introduced into the bloodstream. These interactions have been studied in detail. One example of NM for drug delivery is liposomes. Studies have shown that the NM mechanism may be related to NM adsorption due to the accumulation of liposomes in the liver and spleen. Thus, various forms of NM are used as drug delivery systems.[11–13]

Furthermore, available literature suggests that nanomedicine and its components can play an important role in the various stages of prevention, diagnosis, treatment, vaccination, and research related to COVID-19.[1–3] Despite many benefits of nanomedicine, the transition of nanoproducts from the lab to the bedside remains a challenge, as there are certain barriers to its transformation into commercial products, including the costs. In addition, fundamental research is required to obtain essential information about the nanostructure of viral particles and their internal functionality and infection mechanisms. While nanomedicine is a powerful interdisciplinary means that offers various approaches in patient treatment, a number of factors should be critically studied to find approaches and mechanisms in the prevention, diagnosis, and treatment of this disease. Therefore, this bibliometric analysis was designed to explore studies on the current knowledge of the structure, its mechanism of cell binding, and the therapeutic effect of nanomedicine on COVID-19.

Methodology

The database search was conducted between January 2022 and May 2022. The study data was searched from Web of Science Core Collection (WoSCC) between 2017 and 2021. Biblioshiny and VOSviewer were used to analyze and visualize patterns in scientific literature derived from WoS. This is a Java-based application for analyzing knowledge maps consisting of nodes and links. This analysis provides a complete picture of the overall development of specific research area of interest.

Table 1 Web of Science Core Collection keyword search for articles

Date	January 2022 and May 2022
Publication dates	2017–2021
Language	English
Search string	Corona (Title) or Corona Virus (Title) or COVID-19 (Title) or SARS-CoV (Title) AND Nanomedicine (Title) and 2021 or 2020 or 2019 or 2018 or 2017 (Publication Years)

All databases were searched using Boolean operators (AND, OR, NOT) expressed in English through a combination of words in a single search (►**Table 1**).

The search resulted in 219 articles found available in the WOS data base. The relevant articles and publications were selected in two stages. During the first stage, the titles and abstracts of the articles were screened, and nonrelevant articles were excluded (i.e., studies that did not meet the inclusion criteria of the search) (68). In the second stage, the full text of included studies was explored. Reports and editorials, and non-English language studies were excluded (60). As a result, 91 studies were selected for the final review and assessment.

Results

A total of 91 publications were considered eligible for further assessment to explore the current knowledge of the structure, its mechanism of cell binding, and the therapeutic effect of nanomedicine on COVID-19 (►**Fig. 1**).

Occurrence Network of Keywords

For this bibliometric analysis, when searching for scientific publications, the data were reviewed by searching for keywords to access relevant information. This resulted in a number of keywords used to create a cluster of keywords. ►**Fig. 2** consists of three clusters, each representing terms related to the purpose of the study:

- Cluster 1 (blue) shows high-frequency keywords related to epidemiological and public health studies on COVID-19, such as pandemic, coronavirus, coronavirus infections, nucleotide sequence, virus genome, virus identification, and severe acute respiratory syndrome.
- Cluster 2 (green) includes terms associated with virus transition such as receptor binding, membrane glycoprotein, membrane fusion, viral envelope proteins, virus spike proteins, and Cercopithecus aethiops.

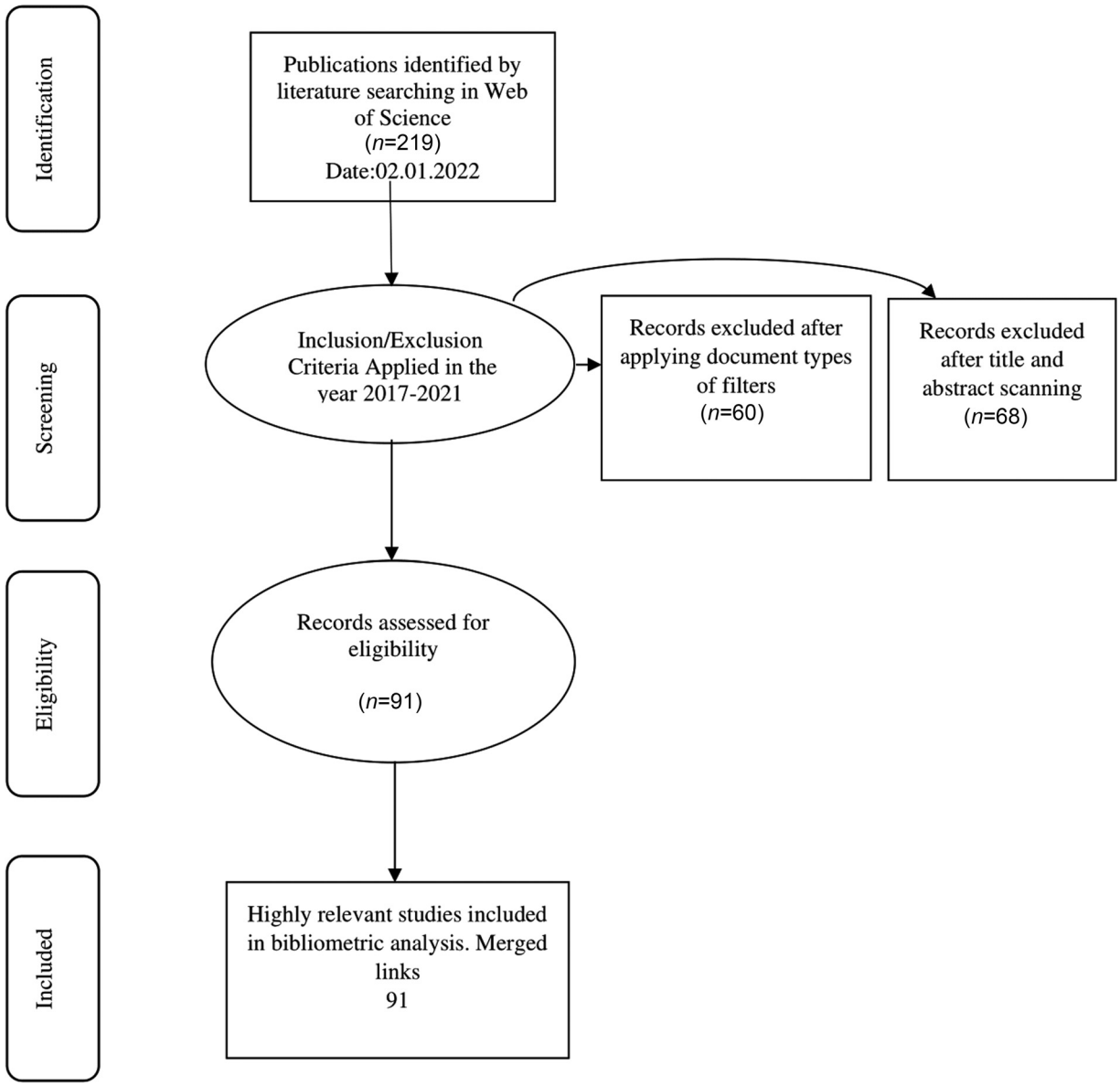

Fig. 1 Four-phase flow diagram of data extraction and filtration process of literature.

- Cluster 3 (red) involves high-frequency keywords associated with nanomedicine, such as metal NP, drug delivery system doxorubicin, immunology, immune response, inflammation, and unclassified drug.

Nanomedicine and COVID-19

This was then followed by the WOS Viewer use to analyze the keyword associations between coronavirus and nanomedicine, the most frequently used in the literature. ►**Fig. 3** illustrates the combination of keywords most frequently used by the authors when studying severe acute respiratory syndrome coronavirus (SARS-CoV), COVID-19 and nanomedicine. As can be seen, keywords such as "nanotechnology" and "gold nanoparticles" have been at the center of COVID-19 related clusters, indicating the importance of these areas during the outbreak. The red and blue cluster in the figure shows the broad association of nanomedicine concerning SARS virus activity and protective immunity.

The Most Cited Articles

An analysis of the co-citation of articles on nanomedicine and coronavirus showed that 20 authors with at least five citations were leading. Research, including work done in a specific field, contains ideas, experimental or theoretical methods, or conclusions that address the relationship between nanomedicine and SARS-CoV research (►**Fig. 4**).

Discussion

To date, knowledge of the Coronaviridae family is limited to six types of human coronaviruses (HCoVs): HKU1, 229E, NL63, SARS-CoV, OC43, EMC (Erasmus Medical Center/2012, originally named human coronavirus EMC/2012 (HCoV-EMC)).[14–16] The current SARS-CoV-2 (COVID-19) pandemic has been associated with the highest rates of infection and mortality compared to other HCoV outbreaks.[14,17,18] Coronavirus research shows that HCoV causes

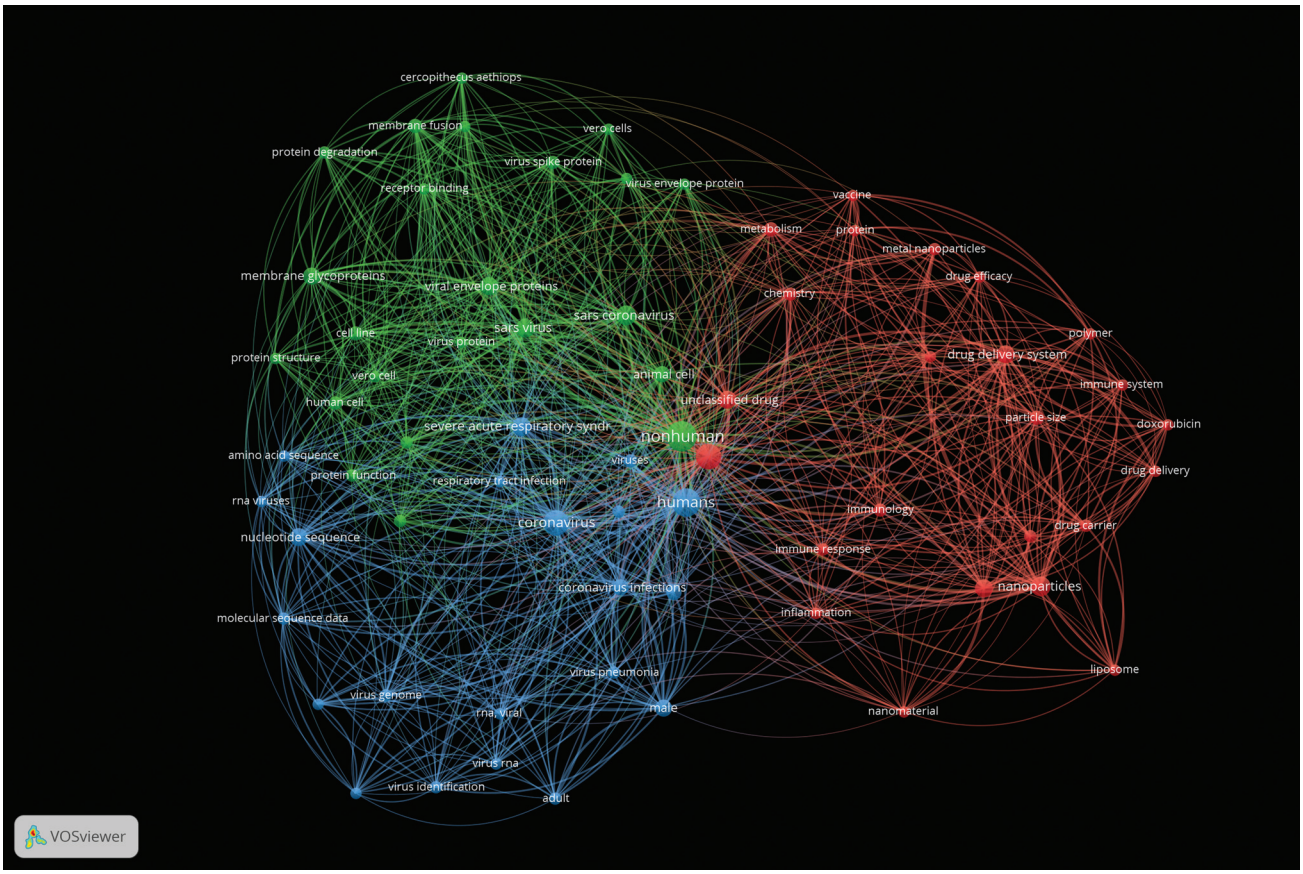

Fig. 2 Three clusters of keywords related to coronavirus disease 2019.

extensive damage to the respiratory, central nervous system, and gastrointestinal tract, endangering human health and leading to social and economic crises. Furthermore, recent years' experience confirms that coronaviruses can mutate and recombine, ultimately causing an effective change in the host range and tissue tropism.[17,18]

On the other hand, recent cutting-edge research has discussed the multitarget attack of NPs on various viruses and the subsequent development of resistance due to this multitarget attack of metals. Thus, it has already been proven that metal NPs are active antiviral agents against influenza virus, human immunodeficiency virus (HIV), and hepatitis virus, among others.[19] The cluster of keywords found in this bibliometric analysis resulted in three distinct themes.

Epidemiological and Public Health Studies on COVID-19

The first cluster resulted in high-frequency keywords related to epidemiological and public health studies on COVID-19, such as a pandemic, coronavirus, coronavirus infections, nucleotide sequence, virus genome, virus identification, and severe acute respiratory syndrome.[20,21] The COVID-19 pandemic has had a major impact on the global scientific community. Thus, in the first 3 months after the pandemic, the number of scientific papers on COVID-19 was five times higher than that of articles on swine flu H1N1.[22] In 2020, scientists published more than 100,000 papers on the coronavirus pandemic. While the number of clinical trials related to the prevention and treatment of COVID-19 has skyrocketed, it has supplanted clinical trial publication not significant by −24%. It has also been reported that people fail to read entire articles and understand the added value and limitations of many studies. As a result, some concerns about quality arise from many researchers publishing preprints to get their findings published quickly.[20,21] Future research is needed to explore the long-term structural implications of the COVID-19 crisis for biomedical research and evaluate the quality over the quantity of published papers.

Virus Transition

The second cluster of keywords included terms associated with virus transition, such as receptor binding, membrane glycoprotein, membrane fusion, viral envelope proteins, virus spike proteins, and Cercopithecus aethiops. Coronaviruses (CoV) are enveloped viruses with a positive-sense, single-stranded RNA genome that encodes four major structural proteins: spike protein (S), nucleocapsid protein (N), membrane protein (M), and envelope protein (E), all of which are necessary for the formation of a structurally complete viral particle.[23–25] The spike protein is thought to be similar to those of the HIV, influenza virus, and Ebola virus, while influenza virus hemagglutinin glycoprotein (HA) is perhaps the best studied of these proteins. HA is expressed as a single-chain precursor. The mutation of these viruses occurs very quickly; the larger the mutation, the greater the likelihood of errors in the mutation. During this mutation, the

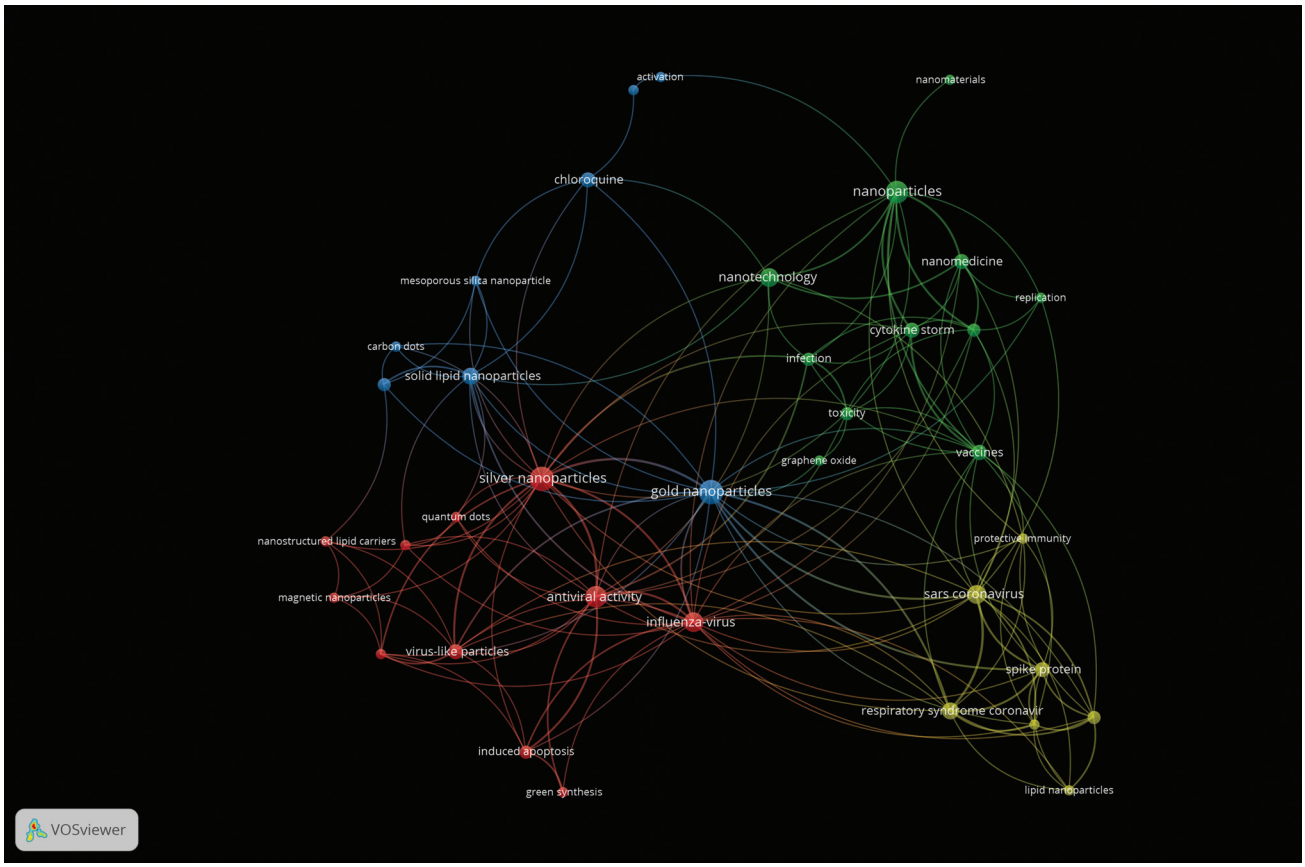

Fig. 3 Clusters of keywords related to severe acute respiratory syndrome coronavirus, coronavirus disease 2019, and nanomedicine.

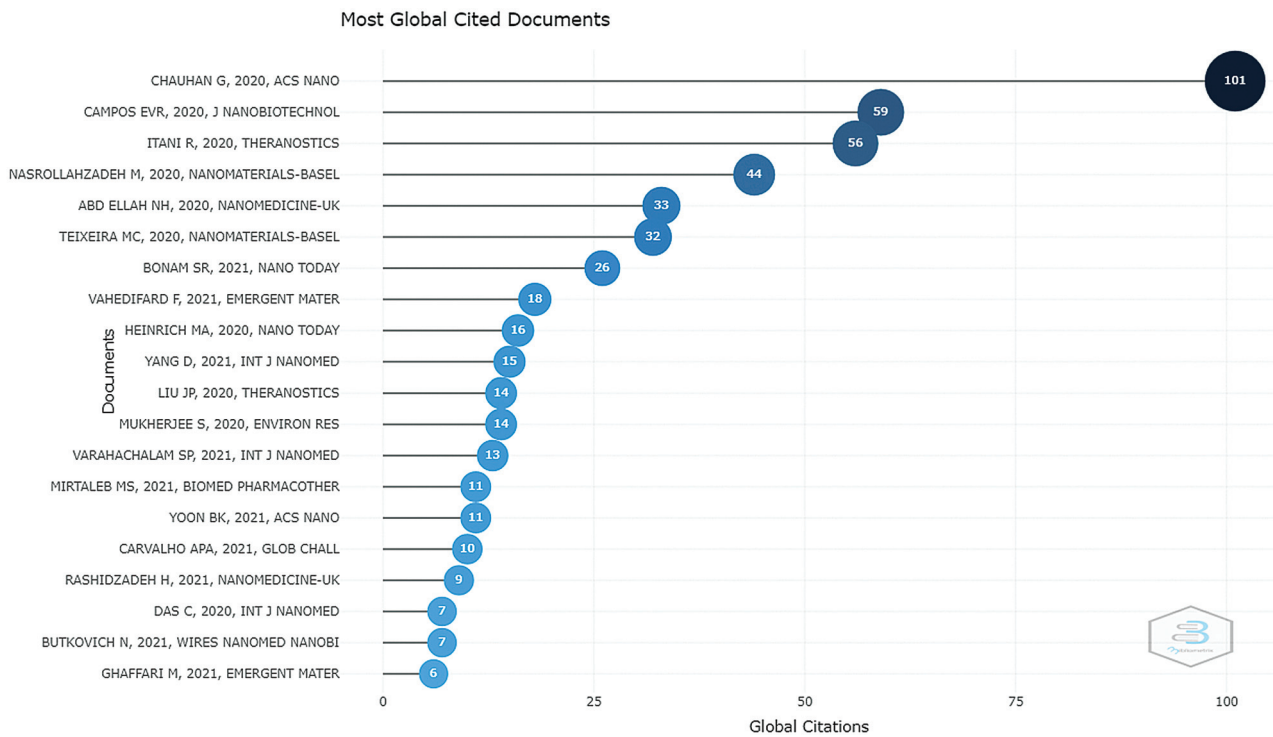

Fig. 4 Most cited authors studying the association of nanomedicine and severe acute respiratory syndrome coronavirus.

virus may be harmless or more dangerous as a new multi-stranded virus may be formed in the form of alpha and delta variants. The SARS-CoV spike (S) protein consists of two subunits; the S1 subunit contains a receptor-binding domain that interacts with the host cell's angiotensin-converting enzyme 2 receptor. The S2 subunit mediates fusion between the membranes of the virus and the host cell. The S protein is key in inducing neutralizing antibody and T-cell responses and protective immunity upon SARS-CoV infection.[23–26]

The SARS-CoV spike is processed by lysosomal proteases such as cathepsin B and cathepsin L by an endocytosis mechanism. Hence, the virus enters the host cell via endocytosis.[24,27,28] It is also clear that there are certain inhibitors, such as inhibitors of endocytosis, either against endosomal acidification or against lysosomal cysteine proteases, which block the entry of SARS-CoV. Thus, protein convertases are not responsible for splitting the SARS-CoV spike during virus packaging, and it remains intact during mature virions.[26–28] Despite this well-established research data, the results of the second cluster of keywords in this bibliometric analysis showed that virus transition and mutation continue to be a subject of ongoing research for developing new strategies for the prevention and treatment of other emerging infections caused by enveloped viruses.

Nanomedicine and Coronaviruses

The third cluster of keywords involved keywords associated with nanomedicine, such as metal NP, drug delivery system doxorubicin, immunology, immune response, inflammation, and unclassified drug. Data from studies suggest that metal NPs can interact with immune cells such as macrophages, monocytes, lymphocytes, and dendritic cells and potentially induce immune responses.[29–31] However, the challenge of metal NPs in response to the immune system depends on physicochemical properties, such as structural properties, chemisorption properties, and the medium in which the interaction occurs. In addition, the immune responses consist of adaptive and innate responses.[29–31] Therefore, unexpected interactions with the immune system and modulation of immune function by NP can be both beneficial and dangerous. Thus, elevated levels of cytokines after NP therapy have been associated with immunotoxicity and limited therapeutic efficacy, especially for pro-inflammatory cytokines.[32,33] However, nonimmunotoxin and biocompatible NP can only be synthesized after a prescient understanding of the interactions between the immune system and NP for their specific biomedical applications. Therefore, during production, special attention should be paid to the biocompatibility and immunotoxicity of NPs that will be used to modify the immune system.[29–32]

Despite controversy over nanomedicine in general and NPs in particular, research continues and expands to learn how nanomedicine can contribute to the fight against COVID-19. In this bibliometric analysis of keyword associations between coronavirus and nanomedicine, Keywords such as "nanotechnology" and "gold nanoparticles" have been at the center of COVID-19 related clusters, indicating the importance of these areas during the outbreak. Before the spread of SARS-CoV-2 (COVID-19), an earlier study by Huang et al approved a new HR1 peptide inhibitor based on gold nanorods (PIH-gold NR). According to the results of this study, PIH-gold NRs are biocompatible, biostable, and extremely potent anti-Middle East Respiratory Syndrome (MERS) agents with 10-fold greater inhibitory efficacy than a single peptide inhibitor.[34] In turn, Du et al reported in their study that glutathione-coated silver sulfide nanoclusters (5.3 nm in size) are effective against porcine epidemic diarrhea virus (PEDV), a member of the genus Alphacoronavirus in the family Coronaviridae of the order Nidovirales.[35] This study also claimed that the nanoclusters suppressed PEDV infection by increasing the synthesis of interferon-stimulating genes and proinflammatory cytokines. In addition, these nanoclusters suppressed the reproduction and budding of the virus. Mechanism studies have shown that silver sulfide NP block the production of negative strand viral RNA and virus budding.[35]

The recent evidence of the promise of nanomedicine for the treatment of COVID-19 was the use of lipid NPs to deliver an mRNA vaccine. The researchers also studied using silver NPs to reduce virus transmission in personal protective equipment. The SARS-CoV-2 titer dropped to zero when a composite coating of silver-silica nanoclusters was applied to the FFP3 face mask.[36] The mechanism of coronavirus and its relationship with nanomedicine can be discussed in the following points. First, coronaviruses interact with a receptor on the host cell surface through its S1 subunit after fusion with the virus and host membranes through its S2 subunit. Domains in the S1 subunit recognize and locate host receptors through which viral attachment occurs.[35–37] The spike protein exists in two well-defined structural conformations: prefusion and postfusion. A change in the conformation of the spike protein from prefusion to postfusion can be initiated, resulting in membrane fusion. The use of nanomedicine, such as PIH-gold NR, can completely inhibit cell fusion. These PIH-gold NRs are biocompatible, biostable, and extremely effective anti-MERS agents. It was further suggested that drugs based on the PIH-gold NRs could be taken orally via inhalers or in specially designed micelles for specific delivery to slow the activity and spread of the virus, and at the same time, the immune system can respond to these drugs 35-37.

The co-citation of articles on nanomedicine and coronavirus research showed that authors mostly explored ideas, experimental or theoretical methods, or conclusions regarding the relationship between nanomedicine and SARS-CoV research. The most co-cited article was by Chauhan et al, Nanotechnology for COVID-19: Therapeutics and Vaccine Research, providing systematic information on nanomedicine strategies.[38] The authors concluded that while nanotechnology tools could play a key role in developing COVID-19 treatments and a vaccine, data regarding the structural morphology of the SARS-CoV-2 virus, pathophysiology, and associated immunological response are vital to nanotechnology scientists. The authors further looked into the potential offered by nanocarriers to enhance the success of the COVID-19 vaccine efficacy and safety. Some of these possibilities include efficient/targeted nanocarrier-based delivery, better

antigen presentation, and induction of an additional immunomodulatory effect.[38]

Understanding the advanced virology of coronaviruses and interfering with their spread through nanomedicine could significantly impact global health and economic stability. On the other hand, although NMs have shown great potential in treating several diseases, NMs also carry a real risk, such as nanotoxicology.[35–37] Thus, one of the most common toxicities associated with NMs is a response to oxidative stress caused by the formation of reactive oxygen species, which can further cause pathophysiological effects such as genotoxicity, inflammation, fibrosis. Therefore, continuous research is required to accelerate the transfer of nanomedicine results into real practice and treatment without the risk of side effects.[35–37]

Conclusion

It is evident that using nanomedicine like PIH-gold NRs can completely inhibit cell fusion. These medicines can be taken orally or as targeted drug delivery to slow down the activity and diffusion of the virus. While the immune system can be responsive against these viruses, some side effects, like nanotoxicity, are also in the way of further improvement for nanomedicines. At the same time, nanomedicine can be applied in studying the side effects of COVID-19 vaccines.

Competing Interests
The authors have no competing interests to declare that are relevant to the content of this article.

Consent for Publication
Not applicable.

Ethics Approval and Consent to Participate
Not applicable.

Availability of Data and Material
All data generated or analyzed during this study are included in this published article.

Authors' Contributions
T.U.R. helped in conceptualization, methodology, and software. A.W. was involved in data curation, visualization, writing—reviewing and editing. M.R. contributed to writing—original draft preparation, visualization, and investigation; M.Z. was involved in supervision, methodology, software, and validation.

Compliance with Ethical Principles
Not applicable.

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Conflict of Interest
None declared.

References

1 Patra JK, Das G, Fraceto LF, et al. Nano based drug delivery systems: recent developments and future prospects. J Nanobiotechnology 2018;16(01):71
2 Ruiz-Hitzky E, Darder M, Wicklein B, et al. Nanotechnology responses to COVID-19. Adv Healthc Mater 2020;9(19):e2000979
3 Sharma S. The role of nanomedicine in COVID-19 therapeutics. Nanomedicine (Lond) 2022;17(03):133–136
4 Aderibigbe BA. Metal-based nanoparticles for the treatment of infectious diseases. Molecules 2017;22(08):1370
5 Joob B, Wiwanitkit V. Nanotechnology for health: a new useful technology in medicine. Med J Dr. DY Patil Uni 2017;10(05): 401
6 Prasad M, Lambe UP, Brar B, et al. Nanotherapeutics: an insight into healthcare and multi-dimensional applications in medical sector of the modern world. Biomed Pharmacother 2018; 97:1521–1537
7 Anselmo AC, Mitragotri S. Nanoparticles in the clinic: an update. Bioeng Transl Med 2019;4(03):e10143
8 Pitt CG, Gratzl MM, Kimmel GL, Surles J, Schindler A. Aliphatic polyesters II. The degradation of poly (DL-lactide), poly (epsilon-caprolactone), and their copolymers in vivo. Biomaterials 1981;2 (04):215–220
9 Barratt GM. Therapeutic applications of colloidal drug carriers. Pharm Sci Technol Today 2000;3(05):163–171
10 Bertholon I, Ponchel G, Labarre D, Couvreur P, Vauthier C. Bioadhesive properties of poly(alkylcyanoacrylate) nanoparticles coated with polysaccharide. J Nanosci Nanotechnol 2006;6(9-10):3102–3109
11 Moghimi SM, Hunter AC, Murray JC. Long-circulating and target-specific nanoparticles: theory to practice. Pharmacol Rev 2001;53 (02):283–318
12 Panyam J, Labhasetwar V. Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Adv Drug Deliv Rev 2003;55 (03):329–347
13 Panyam J, Sahoo SK, Prabha S, Bargar T, Labhasetwar V. Fluorescence and electron microscopy probes for cellular and tissue uptake of poly(D,L-lactide-co-glycolide) nanoparticles. Int J Pharm 2003;262(1-2):1–11
14 Chan JF, Lau SK, Woo PC. The emerging novel Middle East respiratory syndrome coronavirus: the "knowns" and "unknowns". J Formosan Med Assoc 2013;112(07):372–381
15 Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012;367(19):1814–1820
16 Al-Ahdal MN, Al-Qahtani AA, Rubino S. Coronavirus respiratory illness in Saudi Arabia. J Infect Dev Ctries 2012;6(10):692–694
17 van der Hoek L, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. Nat Med 2004;10(04):368–373
18 Fouchier RA, Hartwig NG, Bestebroer TM, et al. A previously undescribed coronavirus associated with respiratory disease in humans. Proc Natl Acad Sci U S A 2004;101(16):6212–6216
19 Osterhaus AD, Fouchier RA, Kuiken T. The aetiology of SARS: Koch's postulates fulfilled. Philos Trans R Soc Lond B Biol Sci 2004; 359(1447):1081–1082
20 Else H. How a torrent of COVID science changed research publishing - in seven charts. Nature 2020;588(7839):553

21 Riccaboni M, Verginer L. The impact of the COVID-19 pandemic on scientific research in the life sciences. PLoS One 2022;17(02): e0263001
22 Di Girolamo N, Meursinge Reynders R. Characteristics of scientific articles on COVID-19 published during the initial 3 months of the pandemic. Scientometrics 2020;125(01):795–812
23 Mortola E, Roy P. Efficient assembly and release of SARS coronavirus-like particles by a heterologous expression system. FEBS Lett 2004;576(1-2):174–178
24 Masters PS. The molecular biology of coronaviruses. Adv Virus Res 2006;66:193–292
25 Schoeman D, Fielding BC. Coronavirus envelope protein: current knowledge. Virol J 2019;16(01):69
26 Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of SARS-CoV–a target for vaccine and therapeutic development. Nat Rev Microbiol 2009;7(03):226–236
27 Xiao X, Chakraborti S, Dimitrov AS, Gramatikoff K, Dimitrov DS. The SARS-CoV S glycoprotein: expression and functional characterization. Biochem Biophys Res Commun 2003;312(04):1159–1164
28 Simmons G, Gosalia DN, Rennekamp AJ, Reeves JD, Diamond SL, Bates P. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. Proc Natl Acad Sci U S A 2005;102 (33):11876–11881
29 Look M, Bandyopadhyay A, Blum JS, Fahmy TM. Application of nanotechnologies for improved immune response against infectious diseases in the developing world. Adv Drug Deliv Rev 2010; 62(4-5):378–393
30 Kononenko V, Narat M, Drobne D. Nanoparticle interaction with the immune system. Arh Hig Rada Toksikol 2015;66(02): 97–108
31 Pandey RK, Prajapati VK. Molecular and immunological toxic effects of nanoparticles. Int J Biol Macromol 2018;107(Pt A): 1278–1293
32 Dobrovolskaia MA, McNeil SE. Immunological properties of engineered nanomaterials. Nat Nanotechnol 2007;2(08): 469–478
33 Elsabahy M, Wooley KL. Cytokines as biomarkers of nanoparticle immunotoxicity. Chem Soc Rev 2013;42(12):5552–5576
34 Huang X, Li M, Xu Y, et al. Novel gold nanorod-based HR1 peptide inhibitor for Middle East Respiratory syndrome coronavirus. ACS Appl Mater Interfaces 2019;11(22):19799–19807
35 Du T, Liang J, Dong N, et al. Glutathione-capped Ag_2S nanoclusters inhibit coronavirus proliferation through blockage of viral RNA synthesis and budding. ACS Appl Mater Interfaces 2018;10(05): 4369–4378
36 Balagna C, Perero S, Percivalle E, Nepita EV, Ferraris M. Virucidal effect against coronavirus SARS-CoV-2 of a silver nanocluster/ silica composite sputtered coating. Open Ceramics 2020;1; 100006
37 Singh R, Lillard JW Jr. Nanoparticle-based targeted drug delivery. Exp Mol Pathol 2009;86(03):215–223
38 Chauhan G, Madou MJ, Kalra S, Chopra V, Ghosh D, Martinez-Chapa SO. Nanotechnology for COVID-19: therapeutics and Vaccine Research. ACS Nano 2020;14(07):7760–7782

