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REVIEW

Nanotechnology and COVID-19: *quo vadis?*

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Abstract The pandemic COVID-19 has worried everyone due to the high mortality rate and the high number of people hospitalized with severe acute respiratory syndrome caused by SARS-CoV-2. Given the seriousness of this disease, several companies and research institutions have sought alternative treatment and/or prevention methods for COVID-19. Due to its versatility, nanotechnology has allowed the development of protective equipment and vaccines to prevent the disease and reduce the number of severe COVID-19 cases. Thus, this article combined the main works and products developed in a nanotechnological field for COVID-19. We performed a literature search using the keywords "COVID-19," "SARS-CoV-2," "nanoparticles," "nanotechnology," and "liposomes" in the SciELO, Scifinder, PubMed, Sciencedirect, ClinicalTrials, and Nanotechnology Products databases Database. The data survey indicated 48 articles, 62 products, and 32 patents. The use of nanotechnology against COVID-19 has brought benefits in several parameters of this disease, helping develop rapid diagnostic tests that release the result in 10 min, as well as developing vaccines containing genetic material from SARS-CoV-2 (DNA, mRNA, and protein subunits). Nanotechnology is an exceptional ally against COVID-19, contributing to the most diverse areas, helping both prevent, diagnose, and treat COVID-19.

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Introduction

The world is currently facing one of humanity's greatest crises, the crisis of the new coronavirus (SARS-CoV-2). The world has recently experienced other viral epidemics, such as SARS-CoV in 2002, H1N1 in 2009, and MERS-CoV in 2012 (Munster et al. 2020). However, the respiratory disease that emerged in China in December 2019 in just a few months reached frightening global proportions. This led the World Health Organization (WHO) to declare coronavirus disease (COVID-19) as a pandemic in March 2020, and after 17 months, reached numbers such as 215,714,824 cases and 4,490,753 deaths (data obtained on August 31, 2021) (WHO. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 2019). Although some countries have been without cases of community transmission for a few months (Fig. 1), the pandemic is not over yet, and tens of thousands of people still die every day. This scenario impels worldwide scientists in an urgent search for new information about this new and unknown pathogen (Kostarelos 2020).

The virus that causes severe acute respiratory syndrome (SARS) is a virus of the *coronaviridæ* family with a long positive RNA chain, with a diameter of 60 to 100 nm, and an envelope that presents characteristic spikes of the spike protein. The entry of this pathogen into human cells is carried out through the interaction between viral membrane proteins and ECA2 and CD147 receptors of pulmonary epithelium cells and macrophages, respectively (Zhang et al. 2020a). According to one of the general characteristics of the viruses, SARS-CoV-2 mutates, quickly generating several different variant strains. Currently, about 5775 variants have already been identified (Bhat, et al. 2021). Among these variants, the Brazilian variant P1 stands out for its increased potential for transmissibility (Dejnirattisai et al. 2021).

Currently, some unknowns of the pandemic have already been solved thanks to the enormous advances caused by the joint efforts of the entire scientific community worldwide. Among these advances, the rapid sequencing of the SARS-CoV-2 genome allowed the development of better techniques for diagnosing COVID-19, and one of the most significant advances was the development of vaccines that have enabled the application of more than 750 million doses around the world (WHO. World Health Organization. Coronavirus disease 2019 (cOVID-19) situation report - 2019). However, despite these advances, there is still much to be discovered to increase the effectiveness of diagnostics, protective equipment, and new vaccines. Also, there is a great need for effective treatment since the lack of this is one of the main factors that make the fight against this disease a challenge to reduce mortality and hospitalizations (Kostarelos 2020).

In the constant search for solutions for COVID-19, nanotechnology has shown itself as a valuable and relevant choice (Chan 2020). By definition, nanotechnology is the science of manipulating structures at the nanoscale that can be used in various products, including medical, cosmetics, and food (Poole and Owens 2010; FDA 2020). Therefore, this emerging technology opens doors to endless opportunities to fight this disease. The use of nanotechnology in the health area has been observed in several applications. One application is developing drug delivery systems: nanocarriers capable of carrying and releasing drugs directly into

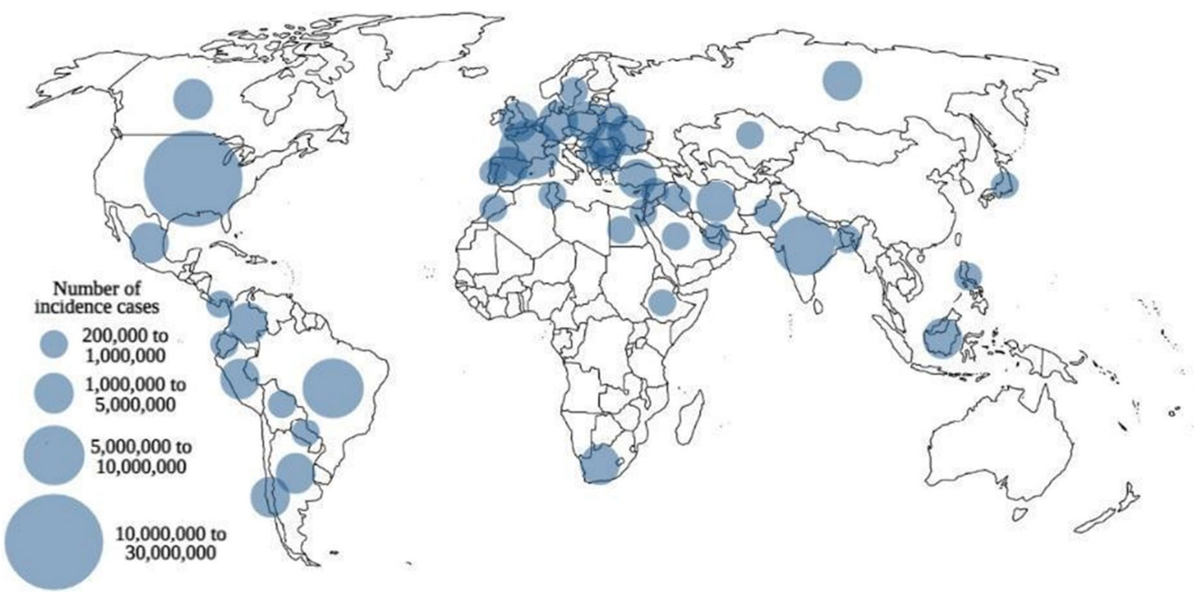

Fig. 1 Bubble diagram for the number of COVID-19 cases worldwide. Source: Adapted from (WHO. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 2019)

their respective target tissue (Vasir et al. 2005) for the treatment, diagnosis, or both.

Understanding the potential applications of nanosystems against SARS-CoV-2 is essential, as it opens up several possibilities in combating this disease. In this framework, monitoring nanotechnology innovations is mandatory, as COVID-19 remains a global health problem. In this manuscript, therefore, we summarize the latest findings on the use of nanosystems in this pandemic, looking forward to advancing (*quo vadis?*) using nanotechnology.

Therefore, we carried out this descriptive literature review based on the following databases: Scientific Electronic Library Online (SciELO), Scifinder, National Institute of Industrial Property (INPI), ClinicalTrials, US National Library of Medicine National Institutes of Health (PubMed), Sciencedirect, and Nanotechnology Products Database (NPD). The SciELO, Scifinder, PubMed, and ScienceDirect databases allowed us to survey the main articles in the health area on the subject, as well as the Scifinder and Clinical Trials allowed us to analyze clinical studies involving nanotechnology products for COVID-19, and INPI databases allowed us to survey the main published patents and the NPD platform to survey nanotechnology products proposed for COVID-19.

The research in the databases was carried out by crossing the descriptors, in English, "COVID-19," "SARS-CoV-2," "nanoparticles," "nanotechnology," and "liposomes" available in the Descriptors in Health Sciences (DeCS).

After the initial research, the inclusion and exclusion criteria were applied. Inclusion criteria were research articles published in 2020–2021, available electronically, full text, and written in English. Also, it included data from companies and clinical studies developing and testing nanotechnological products to treat or prevent COVID-19. The exclusion criteria used were duplicate articles in the databases, review articles, abstracts of congresses, naps, editorials, monographs, dissertations, short communications, and theses. Also, was excluded articles that, although addressed on COVID-19, did not correlate with nanotechnology, products that dealt with nanotechnology but have no application for COVID-19, and clinical studies that do not focus on the implementation in pharmaceutical nanotechnology for the diagnosis, treatment, and prevention of COVID-19. After this, the final sample of articles was tabulated and plotted using Microsoft Excel software and GraphPad Prism 8.

Overview of nanotechnology products for COVID-19

An initial sample of 593 manuscripts was searched. A total of 48 articles were considered after applying the inclusion and exclusion criteria. In parallel, 62 nanotechnology-based products were selected from the Nanotechnology Products Database (NPD) platform. In Fig. 2, is observed a significant increase in the R&D and commercialization of nanotechnology-based products after the COVID-19 pandemic. The impact of the pandemic on the investment in nanotechnology with marketed healthcare products was impressive.

It is noteworthy from 2020 to 2021, an increase of more than 50% of nanotechnology-based products was verified, with 62 products placed on the market for the prevention, diagnosis, treatment, and protection against COVID-19, compared to that occurred in the last thirty years (< 1993 to 2019), with the launch of only 53 nanotechnology-based products, aimed at the diagnosis and treatment of diseases.

After data tabulation, graphs that allow a clear interpretation were plotted. Using the date of product registration published on the NPD platform, we observed the profile of monthly disclosure of

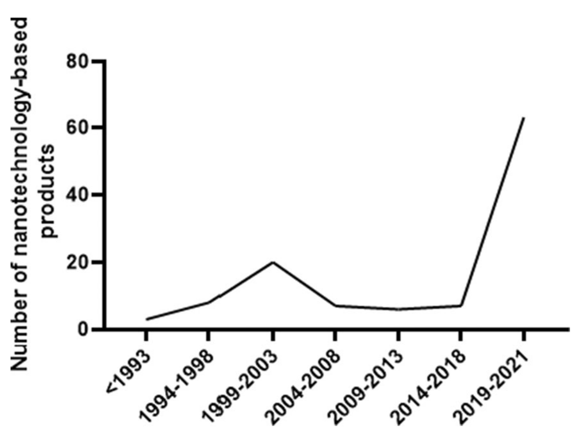

Fig. 2 Growth of nanotechnology products after the COVID-19 pandemic. Source: (Anselmo and Mitragotri 2019; Bobo et al. 2016; Caster et al. 2016; Farjadian et al. 2019; Nanotechnology Products Database 2020)

products based on nanotechnology proposed for COVID-19 during the year 2020 (Fig. 3). The development of nanotechnology-based products started to appear in March, representing 11.29%. In April, there was a considerable increase in product registration, representing 37.09% of all products, reflecting the relevance of the nanotechnology field for COVID-19.

A comparison was established between the number of articles, considering the acceptance data, for each month of the years 2020–2021 (Fig. 3). It is worth mentioning that the date of article acceptance was chosen due to the considerable delay in the publication. A large discrepancy between the date of acceptance and publication of articles could result in an erroneous interpretation of the frequency of articles available. As the first COVID-19 nanotechnology-based product appeared in March, the first publication on the subject also rose in March 2020 (6.25% publications) (Fig. 4). Most of the nanosystems publications concerning COVID-19 were in July 2020 and February 2021, accounting for 12.50% of publications for both months, followed by October and December 2020 with 10.42% of publications.

Figure 5 shows a great diversity of nanosystems being used in different ways to obtain medicines, vaccines, personal protective equipment (PPEs), and other efficient products against the SARS-CoV-2 virus. However, it is notable that despite the great diversity of systems, nanoparticles are highly prevalent and have been used in more than 50% of the selected articles. We highlight the metallic nanoparticles present in 32% of the developed products. Mainly products aimed at the diagnosis and development of PPEs and, in second place, the polymeric nanoparticles present in 12% of the designed products, their use focused more on products aimed at the treatment

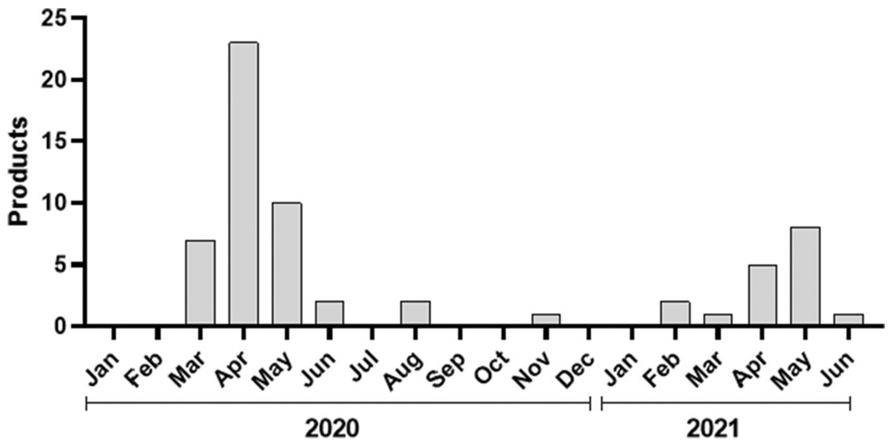

Fig. 3 The number of nanotechnology-based products registered for use in COVID-19 according to the month of their registration. Source: (Nanotechnology Products Database 2020)

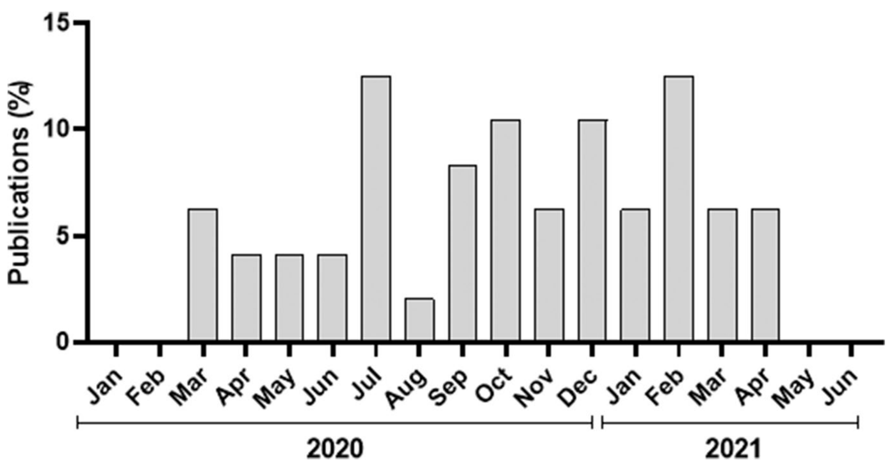

Fig. 4 Publication profile of nanotechnology and COVID-19 according to the month of acceptance date. Source: Research data

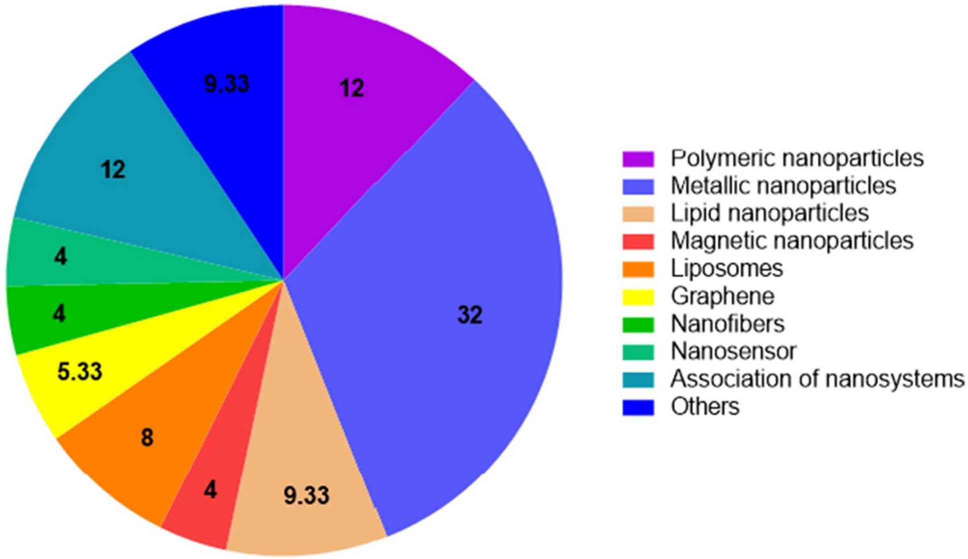

Fig. 5 Percentage of nano-based products used against COVID-19. Source: Research data

and/or prevention of COVID-19. Due to the large number of publications concerning nanoparticles than other nanocarriers, a greater focus on this nanosystem was done.

We also searched patent filings associated with nanotechnological products for the application against COVID-19. It is worth noting that China is responsible for the largest number of patents filed, representing 81.25%. Gold nanoparticles and liposomes are the most studied regarding nanosystems, each representing 18.75% of patents. Regarding the proposed products, 46.88% of the patents are for vaccines containing antibodies against SARS-CoV-2 coupled to nanoparticles or mRNA encapsulated in liposomes for inducing antibodies against SARS-CoV-2 (Table 1).

Diagnosis and treatment of COVID-19

Testing for COVID-19 is of crucial importance. It allows for a quick diagnosis of the disease and provides isolation on the part of the infected patient to prevent contamination of more people. Even more importantly, testing provides the number of infected daily, vital information for the control and monitoring the disease by health organizations (Udugama et al. 2020).

Several different methods have been developed to achieve diagnosis by different routes. Among these techniques, it is possible to observe molecular, clinical, imaging, and immunological diagnosis.

Although there is a wide range of different methods, some are used more. One of the most important tests is the *reverse transcription-polymerase chain reaction* (RT-PCR). This test is based on detecting SARS-CoV-2 genetic material in the patient's sample, so it is extremely specific and is considered the gold standard for diagnosing COVID-19. This technique involves the reverse transcription of the viral RNA in a complementary DNA (cDNA) strand, followed by amplifying specific regions of that strand. During the amplification stage, fluorescent markers are added to each replicated sequence. These markers allow identifying and quantifying these sequences using computers and light sensors (Udugama et al. 2020; Shih et al. 2020).

Several kits used to diagnose COVID-19 are based on RT-PCR, being possible after sequencing the genome of SARS-CoV-2. Some targeted genes include the E gene (encodes the envelope protein), which is used in the initial screening, the RdRP gene (encodes the RNA-dependent RNA polymerase) used in disease confirmation, and the N gene (encodes the N protein) have been used for an additional confirmatory trial (Gupta et al. 2020). Some genomes used to identify SARS-CoV-2 variations

Table 1 Patented products that propose nanotechnology for prevention, diagnosis, and/or treatment of COVID-19

Products	Nanocarriers	Application	Country	Patent number
Optical fiber sensor	Gold/silver nanoparticles-aptamer	To detect SARS-CoV-2 with high specificity, high sensitivity, and fast detection	China	CN 112,730,340
Vaccine	Gold nanoparticles	Gold nanoparticles for vaccine development against SARS-CoV-2	Romania	RO 134,811
Vaccine	Nanoparticles	Coronavirus Spike (S) proteins and nanoparticles suitable for use in vaccines	USA	US 10,953,089
Vaccine	Nanoparticles	Vaccines based on the S antigen protein of SARS-CoV-2	China	CN 112,480,217
Immunochromatographic test	Colloidal gold	For detecting of neutralizing antibodies after vaccination against COVID-19	China	CN 112,485,436
Nano-antibody	Magnetic nanoparticles	Nano-antibody with high neutralization activity against SARS-CoV-2	China	CN 112,500,480
Alveolar macrophage-like multifunctional nanoparticles	Polymeric nanoparticles	Receptors-modified surface nanoparticles for adsorption of SARS-CoV-2 and cytokines	China	CN 112,438,960
Nucleic acid detection method	Gold magnetic particles	Gold magnetic nanoparticles are used to rapidly detect free or bound nucleic acids	China	CN 112,375,812
SARS-CoV-2 affinity polypeptide	Gold nanoparticles	System used for detection of SARS-CoV-2	China	CN 112,375,754
Anti-SARS-CoV-2 nucleocapsid protein Ig	Magnetic nanoparticles	Kit for the detection of SARS-CoV-2 using anti-SARS-CoV-2 antibodies	China	CN 112,239,501
Vaccine	Self-assembling nanoparticles	Stabilized coronavirus Spike (S) protein immunogens for vaccine development	USA	US 20,200,407,402 US 10,906,944 US 20,210,139,543 CN 112,300,253 CN 112,538,105
gRNA targeting SARS-CoV-2	Nanoparticles	gRNA for medicine development to treat COVID-19	China	CN 112,143,731
Test kit	Magnetic nanoparticles	Test for detection of SARS-CoV-2 antibodies	China	CN 112,079,906
Vaccine	Self-assembly nanoparticles	Vaccine used against the SARS-CoV-2 virus to prevent COVID-19	China	CN 111,991,556
Vaccine	Aluminum nanoparticles	Vaccine against COVID-19 inducing immune response with SARS-CoV-2 antigen and cytotoxic T cells production	China	CN 111,939,253
Vaccine	Aluminum nanoparticles	Indicated against COVID-19 significantly increasing antibodies specific to the SARS-CoV-2 antigen and cytotoxic T cells	China	CN 111,920,946
Nano plasma resonance	Gold nanoparticles	Quantitative detection method for SARS-CoV-2 particles	China	CN 111,812,321
mRNA antigen adjuvant	Lipid nanoparticles	Adjuvant mRNA antigen for the prevention of COVID-19	Korea	KR 2,020,118,386

Table 1 (continued)

Products	Nanocarriers	Application	Country	Patent number
Nanovaccine	Nanoparticles	Nanovaccine containing the SARS-CoV-2 receptor binding domain and protein F epitope fused with Helicobacter pylori ferritin used for the prevention of COVID-19	China	CN 111,607,002
Nanovaccine	Coronavirus subunit nanoparticles	Nanovaccine can activate humoral and cellular immunity and can be used to prevent and treat COVID-19	China	CN 111,603,556
Detection device	Oleic acid-modified zinc sulfide nanoparticles	The device can be used to the joint detection of influenza virus and SARM-CoV-2 antibody IgM, presenting high sensitivity, strong specificity, and great practicality	China	CN 111,579,792
Nanosilver spray	Silver nanoparticles	Antiviral activity that can be used to prevent the spread of SARS-CoV-2	China	CN 111,466,407
Silver-complexed therapeutic neutralizing antibody	Silver nanoparticles	Neutralizing antibodies for the treatment of COVID-19	China	CN 111,471,105
Nanovaccine	Nanoparticles	Nanovaccine used for the prevention of COVID-19	China	CN 111,217,918
Vaccine	Nanoparticles	Prevention of SARS-CoV-2 infection	China	CN 111,218,458
Test kit	Gold nanoparticles	Kit for the detection of respiratory pathogens	China	CN 105,018,644
Vaccine	Liposomes	Bacterial biofilm vesicle for vaccine development	China	CN 112,662,695
Anti SARS-CoV-2 drugs	Liposomes	COVID-19 treatment	China	CN 112,472,791
Vaccine	Liposomes	Prevention and treatment of SARS-CoV-2 infection	China	CN 112,300,251
Topical application of povidone-iodine on mucous membranes	Liposomes	Prevention of highly pathogenic respiratory virus infection	Australia	WO 2,020,232,515 US 20,200,384,016 AU 2,020,102,610
Vaccine	Liposomes	Development of vaccines for the prevention of COVID-19	India	IN 202,021,024,459
Vaccine	Liposomes	mRNA vaccines for the prevention of COVID-19	China	CN 111,218,458
Vaccine	Recombinant Peptide Subunit	Vaccine for the prevention of COVID-19	Brazil	BR 1,020,210,008,431

Source: Research data.

include the L, S, O, V, and G clade with the GH and GR subclade (Yang 2021).

Another widely used method is the immunological, which does not detect the presence of the virus but detects the presence of antibodies produced by the patient's immune system after contact with the virus. This test is not recommended at the onset of symptoms because antibody production has not yet peaked. More specifically, this test detects IgM and IgG antibodies in the patients' blood samples. An advantage is that it can be performed using several techniques, including enzyme-linked immunosorbent assay (ELISA), immunochromatographic assay, and chemiluminescent immunoassay. In addition, this method is widely used due to its low financial cost and quick result (Udugama et al. 2020; Shih et al. 2020).

As can be observed, the scope of diagnosis for COVID-19 is already relatively consistent. Unfortunately, this is not the case when it comes to treatment for this disease. After more than a year of pandemic, there is still no treatment with proven efficacy and safety for SARS-CoV-2. This is one of the most significant impasses to significantly reduce the number of deaths from this virus (Kostarelos 2020). The simplest and quickest way to establish a drug for the treatment of COVID-19 is from drug repurposing, which consists of giving new uses to drugs already approved for other diseases (Kabir et al. 2021).

From this strategy, several molecules already approved are being tested for possible treatment against COVID-19, including chloroquine, hydroxychloroquine, lopinavir, ritonavir, ivermectin, remdesivir, and favipiravir (Shih et al. 2020). Among these, some drugs stand out. Chloroquine and hydroxychloroquine are anti-malarial drugs that, despite being studied for the treatment of COVID-19, have a predisposition for the development of cardiotoxicity (Mehra et al. 2020). Since remdesivir is an antiviral previously indicated for treating the Ebola virus, this drug has shown some promising results in clinical tests, but it has not yet been approved for SARS-CoV-2 (Shih et al. 2020).

In addition to these drugs, several others are being tested using in silico tools, which allow the testing of thousands of molecules quickly and financially acceptable (Zhang et al. 2021a). However, despite all these efforts, there is still no drug for the treatment of COVID-19 that the WHO approves.

Application of nanotechnology in the diagnosis of COVID-19

Although the field of COVID-19 testing is solidified, nanotechnology can allow the development of new techniques or improve existing ones. Thus, the focus of researchers in this area is to decrease the time of diagnosis, increase reliability, sensitivity, and other analytical characteristics. Table 2 shows some products developed with nanotechnology to assist in diagnosing COVID-19.

Aiming at such objectives, Hashemi et al. (Hashemi et al. 2021) developed a detection kit based on a nanobiosensor complex (Fig. 6B) that mixes, among other compounds, graphene oxide, and gold nanostars. This nanosystem can identify a different range of pathogens from any aqueous biological sample from the patient due to the interaction with active functional groups of glycoproteins specific to each virus. In addition, this method can detect SARS-CoV-2 in just 1 min and has, compared to the gold standard RT-PCR, sensitivity and error rate of 95% and 5%, respectively. Graphene has gained prominence for presenting as a unique property a large surface area, easy functionalization, chemical stability, high electronic conductivity, and among other properties, which call attention to the development of sensors to detect biological and non-biological species (Cheng and Ou 2019). Graphene associated with gold nanoparticles allows fast and ultra-sensitive detection (Hashemi et al. 2021). The device developed by Hashemi et al. (Hashemi et al. 2021) is based on electrochemical detection through a confined surface mechanism through an adsorption process which allows the detection of pathogens in aquatic biological media.

Another approach was taken by Liu et al. (Liu et al. 2020a), who developed a rapid test role based on chemiluminescent nanozymes. The material core comprises Co–Fe@hemin-peroxidase nanozyme (Fig. 6A), which catalyzes and amplifies the reaction signal on the outside of the paper with the Spike protein antigen SARS-CoV-2. This role has specificity for the COVID-19 virus and can deliver results in just 16 min. The nanozyme is a nanomaterial that has an intrinsic enzyme mimicking activity. Therefore, the Co–Fe@hemin-peroxidase nanozyme viral detection mechanism is based on the chromogenic reaction catalyzed by the Co–Fe@hemin-peroxidase nanozyme, thus acting as enzymatic biosensors. Thus, the nanozyme developed by Liu et al. (Liu et al. 2020a) combined the chemiluminescence of the nanozyme with the high sensitivity of chemiluminescence and high specificity of the immunoassay in developing a rapid antigen detection test for early screening for SARS-CoV-2 infections.

Huang et al. (Huang et al. 2021) developed a low-cost method that detects and quantifies the new coronavirus in just a 15-min step. This new technique is based on a nanoplasmonic sensor chip coupled with titration plates' microwells. Thus, the antigen–antibody connection between the virus and the chip can be read through spectroscopy. Therefore, this method may be suitable for diagnosing COVID-19 due to its low cost, rapid diagnosis, high specificity, and sensitivity. The nanoplasmonic sensor chip proved advantageous for detecting the entire SARS-CoV-2 virus in a time < 15 min and low cost.

Another application widely used by large industries in diagnosing COVID-19 is the use of gold nanoparticles (AuNP). This nanosystem allows the test's sensitivity to increasing and the response time to decrease, based on the connection between the nanoparticle and biological compounds (Draz and Shafiee 2018). For this reason, Canadian researchers have proposed a rapid lateral flow detection kit that can give the result in 5 to 15 min due to its composition of gold nanoparticles. Similarly, UK researchers have developed another type of rapid detection kit using AuNP that detects IgG and IgM antibodies. This test can present the diagnosis in just 10 min and has an accuracy of 97.8% (IgM) and 99.6% (IgG) (Nanotechnology Products Database 2020).

The development of several Point of Care devices for diagnosing COVID-19 allows evaluating the transmission of SARS-CoV-2 in the community, even in asymptomatic cases, through fast, cheap, and reliable methods. Nanotechnology-based devices have provided these characteristics to COVID-19 rapid diagnostic tests. One of the advantages of nanotechnological products is that the devices are highly selective, not requiring sample treatment for RNA isolation, which is the case for the use of aptamers, for example, that can be used in different technologies. The conjugation of aptamer and AuNP makes the virus protein bind to the formed complex, thus allowing the diagnosis of COVID-19 (Rao 2021).

Table 2 Nanocarriers are used in products for the diagnosis of COVID-19

Product	Nanocarrier	Applications	Manufacturer	Country
ROS detector	Carbon nanotube	Software that includes an electrochemical ROS/H2O2 system, providing a flexible and direct way, quickly and accurately as an in vitro diagnostic device	Nano Hesgar Sazan Salamat Arya	Iran
Detection kit	Gold nanoparticles	Reagents with gold nanoparticles with the ability to maximize the sensitivity and reliability of COVID-19 rapid tests	NanoComposix	USA
Detection kit	Gold nanoparticles	Test for primary and secondary diagnosis of COVID-19, with an IgM detection accuracy of 97.8% and an IgG detection of 99.6% with results within 10 min	SureScreen Diagnostics Ltd	UK
Detection kit	Gold nanoparticles	Easy to use tests can be used at home, in the community, or at the clinic to detect the virus in 10 min	Mologic Ltd	UK
Sample kit	-	Medical sample collection device facilitates more accessible testing for viral infections such as COVID-19	Lucence Diagnostics Pte Ltd	Singapore
Detection kit	Gold nanoparticles	Test based on RT-LAMP with results similar to those presented by the RT-PCR test and with a time of about 30 min. RT-LAMP has sensitivity and specificity	Sri Lanka Institute of Nanotechnology (SLINTEC)	Sri Lanka

Source: (Nanotechnology Products Database 2020).

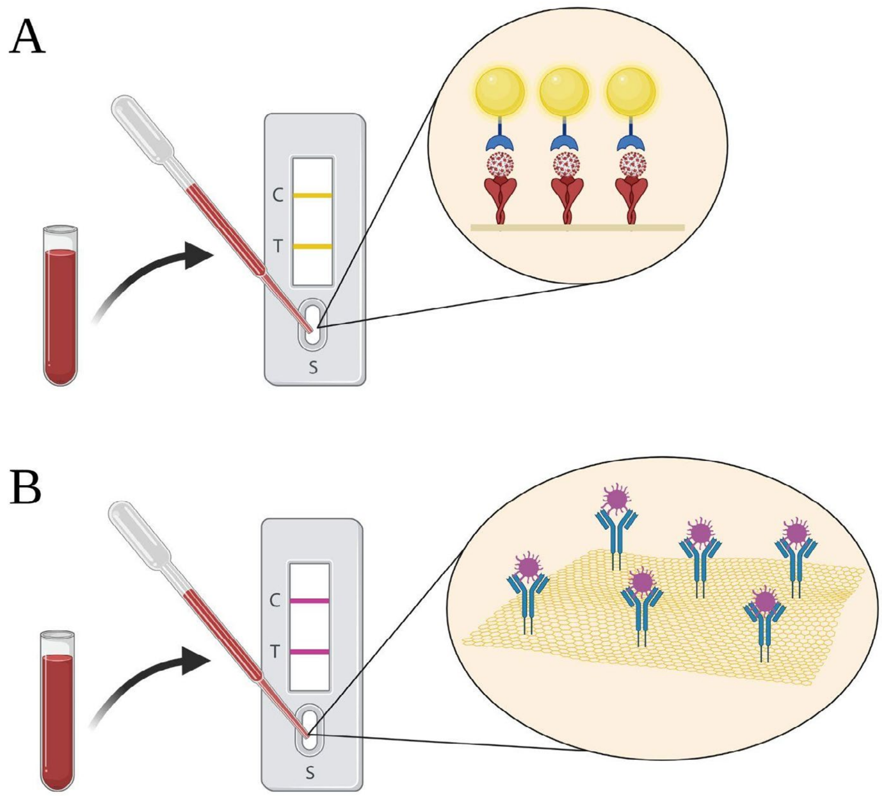

Fig. 6 Nanosystems are used to increase the sensitivity of biosensors. (**A**) Co–Fe@ hemin-peroxidase nanozyme; (**B**) Nanobiosensor composed of graphene oxide and gold nanostars. Source: Created with BioRender.com

Still, researchers from the USA manufactured a rapid detection kit that uses a BioReady gold reagent composed of gold nanoparticles in the same segment. This test allows the result in 10 to 15 min after applying a drop of patient blood and 2 to 3 drops of the reagent (Nanotechnology Products Database 2020).

Vaccine production in the prevention of COVID-19: contribution of nanotechnology

As a consequence of COVID-19 increasing the number of cases, the world has turned to the development of vaccines, which is hoped to prevent and reduce cases and deaths by COVID-19 (The Lancet Microbe 2021; Wise xxxx). The urgency for advanced therapeutic choices has led several laboratories and industries to invest in research that focused on developing and releasing an effective vaccine for the most diverse mutations of the SARS-CoV-2 virus (Wise 2021; Forni and Mantovani 2021; Liu et al. 2020b; Yan et al. 2021).

The introduction of nanotechnology has enabled innovative vaccines that carry genetic material from the virus (Cavalcanti and Nogueira 2020). The identification of targets to interrupt the pathogenesis of COVID-19 has gained prominence. From the discovery of the viral protease (3CLpro and PLpro), the protease produced by the host cells (TMPRSS2), the RNA polymerase (RdRp), and the interaction site of viral protein S with the host cell ACE2 receptor has been significant target for vaccine development (Liu et al. 2020b; Choudhary et al. 2021; Uzunian 2020). The most common strategy for most vaccine candidates is related to the induction of neutralizing antibodies against viral S protein, thereby avoiding ACE2-mediated host uptake (Cavalcanti and Nogueira 2020; Chauhan et al. 2020; Dai and Gao 2021; Kyriakidis et al. 2021; Mehta et al. 2020).

The main advantage of using nanotechnology for the development of vaccines against COVID-19 is the possibility of carrying the nanosystems to a wide range of antigenic fractions, protecting the native structure of the antigen, and improving the delivery and presentation of the antigens to the presenting cells of antigen (Yang 2021; Pati et al.

2224; Shin et al. 2020). Additionally, nanosystems are well tolerated in biological systems and can be administered orally, intranasally, subcutaneously, and intramuscular injections. Depending on the administration choice, nanosystems can overcome tissue barriers and direct to target sites (Cavalcanti and Nogueira 2020; Chauhan et al. 2020; Cavalcanti et al. 2020; Germain et al. 2020).

Another advantage of vaccines produced with nanotechnology is the immune response produced. According to the study by Walls et al. (Walls et al. 2020), nanoparticle vaccines exhibit 60 SARS-CoV-2 spike receptor-binding domains (RBD), in addition to being highly immunogenic and inducing the production of 10 times more neutralizing anti-corpora than pre-fusion stabilized spike. Also, antibodies produced by nanoparticle vaccines target multiple distinct epitopes. This makes them not easily susceptible to mutations, exhibiting a lower neutralizing bond than convalescent human sera, thereby reducing the risk of disease's increased respiratory rate associated with the vaccine. Furthermore, the coexposure of several antigens on the same nanoparticles can improve the amplitude of the immune responses induced by the vaccine. Table 3 shows some vaccines that are being developed using nanotechnology.

The approval of two mRNA-based vaccines developed using lipid nanoparticles (LNPs) emerges as a milestone in history, as the first vaccines with these technologies have received authorization for the clinical therapy of COVID-19 by the US FDA (Germain et al. 2020; Khurana et al. 2021). The role of nanotechnology was important, as it accelerated the development of vaccines invented by Moderna and Pfizer/BioNTech, which are currently in phase 4 (Table 1). The primary data for Moderna and Pfizer/BioNTech vaccines revealed an efficacy of 94.5% and 95%, respectively, against SARS-CoV-2, showing a high efficacy of both vaccines. The difference between the two is related to the genetic material: Moderna (mRNA-1273) uses stabilized mRNA from viral spike protein, while BNT162b2 from Pfizer/BioNTech uses nucleoside-modified RNA (modRNA) from SARS-CoV-2 (Dai and Gao 2021; Polack et al. 2020; Walsh et al. 2020a, 2020b; Zhang et al. 2020b).

Still showing the effectiveness of BNT162b1, Sahin et al. (Sahin et al. 2020) published a study proving that the Pfizer/BioNTech vaccine can induce the production of human antibodies and TH1 cell responses. The authors show that in the two doses of 1–50 μg of BNT162b1 in healthy adults (18 to 55 years), CD4 + and CD8 + T cells and strong antibody responses were produced concentrations of IgG binding to the RBD of the SARS-CoV-2 virus spike protein. These results are essential, as they show that these mRNA vaccines can both produce an antibody response and CD4 + T cells and produce CD8 + T cells that play a key role in eradicating the virus (Shin et al. 2020; Han et al. 2021). Figure 7 shows the mechanism of action of these vaccines produced with mRNA.

Vaccines using the SARS-CoV-2 protein subunit have also been gaining prominence for enabling the initiation of the protective immune response when administered with molecular adjuvants for increased immunogenicity (Shin et al. 2020; Kanno et al. 2021). The SARS-CoV-2 subunits used in vaccine production are full-length protein S formulations or S1/S2 subunits with adjuvants. Novavax is one of the protein subunit vaccines in phase 3, using Novavax recombinant nanoparticles and the Matrix-MTM adjuvant. NVX-CoV2373 presented a phase 3 study with an efficiency of 89.3% (Shin et al. 2020; Han et al. 2021; Callaway and Mallapaty 2021). Also, Keech et al. (Keech et al. 2020) evidenced in their study that Novavax's NVX-CoV2373 was safe when administered to healthy adults aged 18 to 59 years, using a two-dose regimen of 5 μg and 25 μg of the vaccine plus the adjuvant Matrix-MTM. The results showed that the vaccine could induce high immune responses in the production of neutralizing antibody levels that are closely correlated with the anti-spike IgG antibody.

Like Novavax, the Walter Reed Army Institute of Research has been developing liposomes containing SARS-CoV-2 subunit proteins called SpFN, which is in phase 1. The technology is based on the use of spike ferritin nanoparticles, which allows the repetitive and orderly presentation of the spike protein to the immune system, thereby inducing highly potent and broad neutralizing antibody responses against SARS-CoV-2 (Yan et al. 2021; Powell et al. 2020; Nel and Miller 2021). According to the study by Powell et al. (Powell et al. 2020), spike-functionalized ferritin nanoparticles trigger neutralizing

Table 3 Vaccine candidates for the treatment of COVID-19 using nanotechnology

Platform	Nanotechnology	Developer	Vaccine name	Clinical status	Trial registration No
Protein subunit	Nanoparticles	Novavax	NVX-CoV2373	Phase 3	Phase 1/2: NCT04368988 Phase 2: NCT04533399 Phase 3: NCT04611802 EUCTR2020-004,123–16-GB NCT04583995
Protein subunit	Ferritin nanoparticle	Walter Reed Army Institute of Research (WRAIR)	SpFN	Phase 1	Phase 1: NCT04784767
mRNA	Lipid nanoparticles	Moderna	mRNA-1273 mRNA-1283	Phase 4	Phase 1: NCT04283461 NCT04813796 Phase 1/2: NCT04677660 NCT04712110 Phase 2: NCT04405076 NCT04761822 Phase 2/3: NCT04649151 NCT04796896 Phase 3: NCT04470427 NCT04811664 NCT04805125 NCT04806113 Phase 4: NCT04760132 NCT04792567
mRNA	Lipid nanoparticles	Pfizer/BioNTech + Fosun Pharma	BNT162b2	Phase 4	Phase 1: NCT04523571 ChiCTR2000034825 NCT04816643 Phase 1/2: NCT04588480 NCT04380701 NCT04537949 EUCTR2020-003,267–26-DE Phase 2: NCT04649021 NCT04761822 Phase 2/3: NCT04754594 Phase 3: NCT04368728 NCT04713553 NCT04800133 NCT04805125 NCT04816669 Phase 4: NCT04760132 EUCTR2021-000,412–28-BE EUCTR2021-000,412–28-BE NCT04780659 NCT04775069
mRNA	Lipid nanoparticles	Imperial College London	LNP-nCoVsaRNA	Phase 1	Phase 1: ISRCTN17072692
RNA	Lipid nanoparticles	Academy of Military Science (AMS), Walvax Biotechnology and Suzhou Abogen Biosciences	ARCoV	Phase 2	Phase 1: ChiCTR2000034112 ChiCTR2000039212 Phase 2: ChiCTR2100041855
Virus like particle	-	Medicago Inc	Coronavirus-like particle COVID-19 (CoVLP)	Phase 2/3	Phase 1: NCT04450004 Phase 2: NCT04662697 Phase 2/3: NCT04636697

Table 3 (continued)

Platform	Nanotechnology	Developer	Vaccine name	Clinical status	Trial registration No
DNA	Proteo-lipid vehicle	Entos Pharmaceuticals Inc	Covigenix VAX-001	Phase 1	Phase 1: NCT04591184
mRNA	Lipid nanoparticles	GlaxoSmithKline	CoV2 SAM (LNP)	Phase 1	Phase 1: NCT04758962
mRNA	Lipid nanoparticles	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	mRNA-1273.351	Phase 1	Phase 1: NCT04785144
Virus-like particle	-	The Scientific and Technological Research Council of Turkey	SARS-CoV-2 VLP	Phase 1	Phase 1: NCT04818281

Source: (Yan et al. 2021).

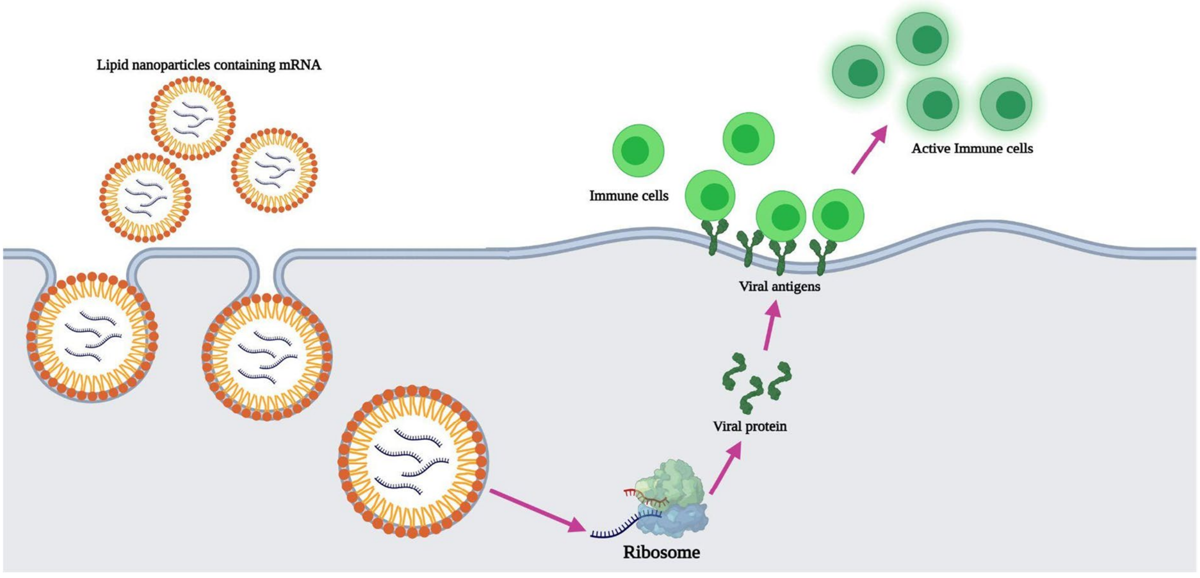

Fig. 7 Mechanism of action of vaccines containing mRNA encapsulated into lipid nanoparticles. Source: Created with BioRender.com

antibody responses against SARS-CoV-2 with only a single immunization in their research with mice compared to immunization with the spike RBD monomer.

Saunders et al. (Saunders et al. 2021) developed a vaccine for COVID-19 using self-assembling protein nanoparticles of 24 *Helicobacter pylori* ferritin subunits expressing RBD of SARS-CoV-2. The vaccine is administered using the 3 M-052/Alum adjuvant. The authors observed that this vaccine induces a cross-neutralizing antibody response against batCoVs, SARS-CoV-1, SARS-CoV-2, and variants B.1.1.7, P.1, and B.1.351 of the SARS-CoV-2 virus.

Subunit vaccines also allow them to take the form of protein nanoparticles or virus-like particles (VLPs) (Nooraei et al. 2021). The vaccine in production by Medicago Inc. is produced from VLPs, featuring a recombinant spike glycoprotein expressed as SARS-CoV-2-like particles and is administered together with an adjuvant produced by GlaxoSmithKline (GSK). Currently, the vaccine is in phase 2/3 (Forni and Mantovani 2021; Kyriakidis et al. 2021; Galdiero et al. 2021; Kumar et al. 2021). The Scientific and Technological Research Council of Turkey is also developing VLP vaccines. However, it is in phase 1 (Yan et al. 2021).

Nanocarriers in the treatment of COVID-19

As already discussed, one of the biggest challenges in overcoming the COVID-19 crisis is the lack of drugs to treat the disease. Moreover, in response to this problem, the repurposing of already known drugs is being studied. Thus, the association of these drugs with nanocarriers can be an essential strategy for success in this area.

Nanocarriers are a system at the nanoscale into which materials are encapsulated. These nanosystems allow a controlled release of encapsulated drugs, increased bioavailability, and targeted specific cells, among other particularities (Reinholz et al. 2018).

Aiming at these advantages, Pindiprolu et al. (Pindiprolu et al. 2020) proposed using Salinomycin lipid nanoparticles to treat COVID-19 by the pulmonary route. Salinomycin has antibacterial, antifungal, antiparasitic, antitumor, and antiviral properties, but it has very low water solubility (Zhang et al. 2012). For this reason, its encapsulation into lipid nanoparticles allows an increase in solubility for faster and more efficient absorption and, consequently, enables the inhibition of SARS-CoV-2 entry and replication in cells (Pindiprolu et al. 2020).

In addition, the pulmonary route (Fig. 8), which is a non-invasive route, has been widely used by scientists in recent years and can provide enormous advantages in treating COVID-19. This route allows the targeting of drugs directly to the target cells located in the respiratory system, decreasing the first-pass metabolism and, thus, reducing side effects and increasing the bioavailability of the molecule (Douafer et al. 2020).

Using the same route of administration, researchers from Cyprus developed a chitosan nanoparticle for application in aerosol called Novochizol. This nanosystem allows the encapsulation of different drugs for the respiratory system to allow an efficient treatment for patients with COVID-19. In addition to the benefits of using this route, these nanoparticles have the property of controlled drug release, maintaining a plasma concentration with therapeutic action within 3 h after Novochizol administration (Nanotechnology Products Database 2020; Novochizol. 2020).

Another nanocarrier that uses this same route of administration was developed by researchers in the USA named NanoBio® Protect. This product is an antiseptic solution for intranasal use consisting of nanodroplets containing benzalkonium chloride (BZK). These nanoparticles are attracted to electrokinetic germs and present BZK, causing the death of microorganisms by contact. Thus, this product allows further infection prevention by the SARS-CoV-2 virus (Nanotechnology Products Database 2020; Available. 2020).

In search of a more innovative treatment, Refaat et al. (Refaat et al. 2021) developed a liposomal formulation to increase the antiviral property of propolis. Propolis is a resin produced by bees from the sap

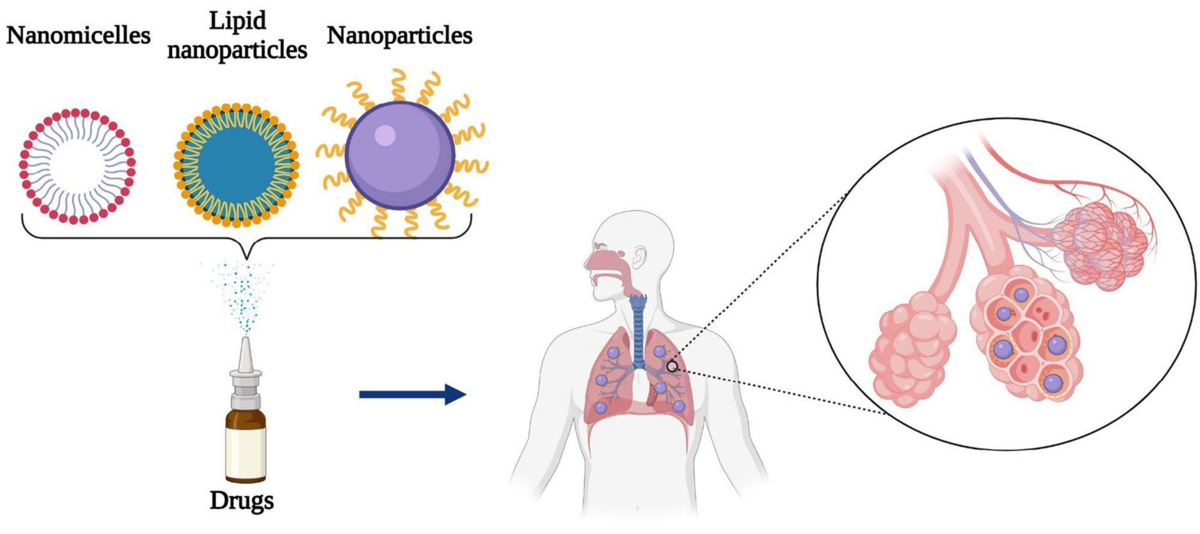

Fig. 8 Nanocarriers are administered via the pulmonary route to deliver drugs directly to the lung. Source: Created with BioRender.com

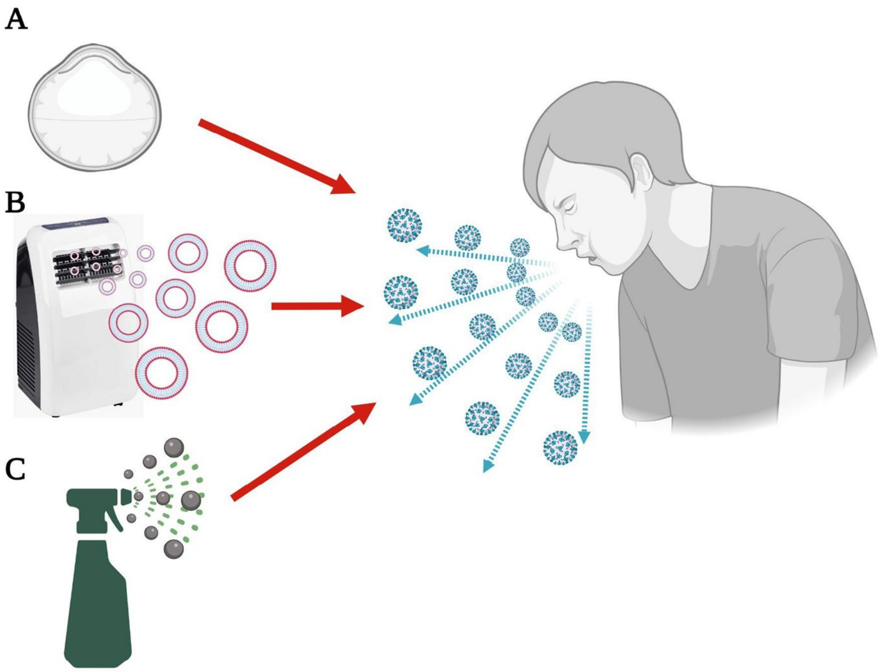

Fig. 9 Nanoparticles inserted in individual and collective protection equipment against COVID-19. (**A**) Graphene in protective masks; (**B**) Air conditioning containing nanotechnology for cleaning the environment; (**C**) Solution for surface cleaning containing nanoparticles. Source: Created with BioRender.com

of trees, rich in numerous compounds with various pharmacological activities, including antibacterial, immunomodulatory, anti-inflammatory, and antiviral (Refaat et al. 2021; Simone-Finstrom and Spivak 2010). Given this, these encapsulated propolis liposomes have shown encouraging results and viral inhibition parameters similar to potent antivirals such as Remdesivir (Refaat et al. 2021).

Similarly, Valizadeh et al. (Valizadeh et al. 2020) developed nanomicelles, encapsulating curcumin to evaluate the effects of this nanosystem on modulation or suppression of cytokines. The over-activation of the inflammatory system caused by SARS-CoV-2 is the leading cause of lung tissue damage and, consequently, of the deaths caused by COVID-19. In contrast, curcumin is the active substance in *Curcuma longa* and is widely used due to its medicinal properties as an antioxidant, anti-tumor, and anti-inflammatory. Therefore, the association of curcumin in nanomicelles allowed the delivery of this molecule efficiently, and it was possible to observe an attenuating decrease in the expression of IL1β and IL-6.

US researchers have developed NanoBio® Protect, which is based on the inclusion of the antiseptic benzalkonium chloride (BZK) on the surface of nanodrops. These nanoparticles are attracted to the microorganisms by electrokinetic charge, and the presence of BZK causes the microorganism to be killed after contact. These nanodrops persist in the hair for 4 h or more, showing long-lasting effectiveness. In addition, these nanodrops also significantly moisturize the skin, thereby preventing dryness and cracking after application to the skin around the nose (Nanotechnology Products Database 2020).

Personal and collective protective equipment against COVID-19

Another crucial aspect for controlling COVID-19 is the protection provided by personal protective equipment (PPE) and collective protection equipment (CPE). Implementing nanosystems in these devices enables antiviral properties and increases particle filtration capacity (Palmieri et al. 2021). Figure 9 shows some protective equipment that is being developed using nanotechnology.

Several companies have invested in developing products using nanotechnology as a basis for the supply of hygiene products that have more extended durability in action against pathogens and the development of self-cleaning masks and purifiers that can purify work environments and make them free of pathogens. Table 4 shows the most diverse products

Table 4 Individual and collective protective equipment based on nanotechnology for COVID-19

Product	Nanocarrier	Applications	Manufacturer	Country
Respiratory mask	Silver nanoparticles	Mask used to protect against infection by COVID-19, with antiviral efficacy of up to 90%	SEN WORLD	Czech Republic
Respiratory mask	Nanofibers	Mask used to protect against infection by COVID-19, presents ≥ 99.9% of the capture of particles in the membrane	Pardam Nano4fibers	Czech Republic
Respiratory mask	Silver nanoparticles	Respiratory protection has a 99.9% action capacity against bacteria after 60 washes	Dony Garment Company Limited	Vietnam
Respiratory mask	Silver nanoparticles and graphene	Respiratory protection manages to destroy 99.9% of the SARS-CoV-2 virus	NM Material	India
Respiratory mask	Graphene	Respiratory protection can kill particles of the SARS-CoV-2 virus, in addition to other infectious diseases, capable of killing 99% of viruses and germs	Medicevo Corporation	USA
Respiratory mask	Copper yarn and nanofabric spandex	Elastic and durable masks with action against COVID-19	Gian Ferrente	Thailand
Respiratory mask	Graphene	Washable masks with graphene antiviral filter, providing respiratory protection to the user	Flextrapower Inc	USA
Respiratory mask	Graphene	Masks that have the ability to stop 99% of particles over 0.3 microns and 80% of particles less than 0.3 microns	LIGC Applications Ltd	USA
Respiratory mask	Graphene	Respiratory protection in the prevention of COVID-19	Directa Plus PLC	UK
Respiratory mask	Copper nanoparticles	Respiratory protection in the prevention of COVID-19	Promethean Particles Ltd	UK
Respiratory mask	Nanofibers	Respiratory protection in the prevention of COVID-19	Kim Ii-Doo Research Institute	South Korea
Respiratory mask	Molecular nanocoat	Self-cleaning and sanitizing surgical mask that kills 99.9% of all viruses and bacteria	MVX Prime Ltd	UK
Respiratory mask	Nano Biotech	Respiratory protection against SARS-CoV-2 with a complete inactivation effect of up to 99%	Wakamono	Vietnam
Respiratory mask	Hydrophobic coating	Respiratory protection against SARS-CoV-2	Integricote Inc	USA

Table 4 (continued)

Product	Nanocarrier	Applications	Manufacturer	Country
Disinfection chamber	-	Portable ultraviolet light disinfectant to sanitize all types of surfaces, acting against bacteria and viruses	Log 9 Materials Pvt. Ltd	India
Liquid screen protector	Silver and titanium dioxide nanoparticles	Protection of cell phones, making the cell phone screen scratch-resistant, germ-free and water-repellent	Nanofixit Inc	Philippines
Coating	-	Indicated for all types of fabrics that transmit superhydrophobicity, non-toxicity, and breathability, forming a protective barrier under the fabric surface	Curran Biotech	USA
Disinfecting spray	-	Eradicates bacteria from surfaces and purifies the air	Sri Lanka Institute of Nanotechnology (SLINTEC)	Sri Lanka
Air purifier	ShortWaveLight Emitter	Through ultraviolet light with germicidal action, this purifier neutralizes coronavirus and other pathogens on surfaces and in the air	NS Nanotech, Inc	USA
Screen protector	Copper nanoparticles	Screen saver that eradicates viruses and bacteria in minutes, due to the antiviral and antibacterial properties of copper	Nanoveu Inc	Australia
Disinfectant	Photocatalytic nanotechnology	Protects high-touch surfaces against bacteria, viruses, fungi, among others	EnvisionSQ	Canada
Antiviral ink	Silver nanoparticles and graphene	Used to manufacture PPE's against COVID-19	ZEN Graphene Solutions Ltd	Canada
Disinfectant	Mineral nanocrystals	It provides self-cleaning surfaces with the possibility of using the product on the door handles, elevator buttons, and on the back of the phone	Nanotouch Materials, LLC	USA
Hand sanitizer	Silver nanoparticles	Broad-spectrum hand sanitizer against microorganisms, without the need for water or towels	Shepros SDN. BHD	Malaysia
Air-conditioning cleaner	-	Clean air filtration system against SARS-CoV-2 virus, mold and mildew, animal hair	Mark Antonoff HVAC	USA
Air purifier	-	Captures 99.5% of viruses and bacteria, with 6–12 air changes per hour	Turn-Key Environmental Consultants	USA

Table 4 (continued)

Product	Nanocarrier	Applications	Manufacturer	Country
Air purifier	-	Efficiently removes chemicals, pollutants, viruses, bacteria, and allergens from the air	AAVI Technologies Co	Finland
Air purifier	-	Prevents airborne infections, as is the case with COVID-19	TEQOYA	France
Air purifier	-	It works by improving the performance of central ventilation as an additional purification system, providing constant nanoscale contamination control	Genano Ltd	Finland

Source: (Nanotechnology Products Database 2020).

indicated in the prevention and protection against SARS.CoV-2.

Zhang et al. (Zhang et al. 2021b) developed an exciting method to increase the time of use and useful life of surgical masks using triboelectric nanogenerator technology (TENG). This generator can transform external mechanical energy into electrical energy based on static electricity and triboelectric effect (Fan et al. 2012; Wu et al. 2018). The method developed by Zhang et al. (Zhang et al. 2021b) consists of the discharge of this generated energy using an electrode in the surgical mask, already used and decontaminated. This process allows re-energizing the layers of electrostatic filtering tissues, which generally dissipate this energy in a few hours (Lee and Kim 2020). The authors demonstrated that even after 10 cycles of this method, the filtering efficiency of the masks remained above 95%. Therefore, usage time and useful life can be increased by at least 10 times (Zhang et al. 2021b).

Using the same concepts, Leung and Sun (Leung and Sun 2020) developed and produced 4 new electrostatically charged nanofiber fabrics for filtering particles up to 100 nm suspended in the air. These tissues were made using polyvinylidene fluoride in electrospinning and were charged electrostatically from a process called corona discharge. Still, in the tissue segment, Almeida et al. (Almeida et al. 2020) produced a biodegradable fabric composed of nanofibers from the cellulose acetate polymer and the surfactant cetylpyridinium bromide, also using the electrospinning technique. This tissue proved to be efficient in the filtration of particles with diameters smaller than 300 nm. Therefore, it could be used for the filtration of SARS-CoV-2.

Different nanoparticles in fabrics used in masks to protect against COVID-19 are being studied and carried out by the medical industry. Among these, silver nanoparticles (AgNP) were considered the most useful disinfectant metal to fight bacteria and viruses due to the release of silver ions by oxidation (Wang et al. 2019). Therefore, researchers in India produced the first graphene mask with silver nanoparticles. This product was developed from the coating of graphene and AgNP on the fibers of polyester fabric, so this technology neutralizes and filters viruses and bacteria with extremely high efficiency. For SARS-CoV-2, the filtration efficiency reached 99.9%, so this mask has exceptionally high protection in preventing COVID-19 (Nanotechnology Products Database 2020; Nanomatrix materials. 2021). Vietnamese researchers developed another product produced using AgNP. The Dony Mask is a 3-layer mask containing AgNP, allowing efficient filtration of viruses and bacteria even after 60 wash cycles (Nanotechnology Products Database 2020).

Still concerning the production of masks, Chinese researchers developed masks that use diamond nanoparticles (ND). These surgical masks contain 3 layers: a hydrophobic outer layer containing ND, an intermediate layer that performs the filtration, and a non-allergenic inner layer for skin contact.

According to manufacturers, ND allows killing some bacteria and viruses with 99% and 97.75% efficiency in up to 1 min (Nanotechnology Products Database 2020; Patented anti-microbial NanoDiamonds (ND) mask. 2020;).

In addition to this personal protective equipment, several air purifiers and filters are being produced for collective protection. US researchers have developed the ShortWaveLight Purifier, a portable air purifier that emits UVC radiation to neutralize various pathogens, including SARS-CoV-2. Another purifier designed in the USA is the HealthPro Compact Air Purifier, capturing 99.5% of viruses and bacteria in the environment. EnvisionSQ has developed an air purifier based on photocatalysis. It uses light energy to accelerate chemical reactions with the filtered particles (Nanotechnology Products Database 2020).

Conclusion

Since the emergence of the SARS-CoV-2 virus, COVID-19, has infected and killed millions of people worldwide and has been regarded as the world's worst public health problem since the Spanish flu in the twentieth century. After a century, technology has advanced exponentially and can be used to save countless lives. In this sense, nanotechnology and nanomedicine play a crucial role against numerous diseases, including COVID-19.

We note the importance of nanotechnology for the treatment, prevention, and protection against SARS-CoV-2. However, despite all significant advances reported in this article, much investment and research are still needed to overcome the pandemic definitively.

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Declarations

Conflict of interest The authors declare no competing interests.

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