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REVIEW

Potential and risks of nanotechnology applications in COVID-19-related strategies for pandemic control

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Abstract The ongoing battle against viral infections highlighted so recently by the COVID-19 pandemic demonstrates the need to develop new approaches using nanotechnology in antiviral strategies. Nanoparticles have emerged as promising tools in the fight against viral outbreaks, offering various options for application such as biosensors, vaccine nanoparticles, disinfectants, and functionalized nanoparticles. In this comprehensive review, we evaluate the role of nanoparticles in pandemic control, exploring their potential applications, benefits, and associated risks. We first discuss the importance of nanotechnology in viral outbreak management, particularly in vaccine development. Although lipid nanoparticles play a crucial role in mRNA vaccines, there are concerns about their potential side effects. Although functionalization of protective face masks using metallic nanoparticles has emerged as a sustainable alternative to disposable masks, reducing waste production and enhancing virus filtration, improper disposal of such masks leads to environmental contamination and potential ecological harm. Second, we address the potential adverse effects associated with nanoparticle-based vaccines containing polyethylene glycol and other vaccine components, which trigger autoimmune diseases and alter menstrual cycles. To manage outbreaks effectively, we must minimize such potential risks and environmental impacts. Thus, when developing effective strategies for future pandemic control, it is crucial to understand the advantages and challenges associated with nanoparticle usage.

Keywords Antiviral strategies · COVID-19 · Health effects · Nanoparticles · Nanoparticle-associated risks · Nanotechnology · Pandemic control

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Introduction

Throughout the twentieth century, viral infections significantly impacted global health, causing millions of deaths worldwide. To combat these diseases, nanotechnology has emerged as a promising approach in the development of antiviral agents such as biosensors, nanoprobes, virus-like particles (VLPs), and functionalized nanoparticles [1–3]. The COVID-19 pandemic highlighted the importance of nanotechnology in the battle against viral infections, particularly in the development of vaccines. In turn, ongoing discoveries of new virus variants highlight the

importance of being prepared to combat potential future pandemics. Recently, for example, three new COVID-related virus variants were discovered in bats in Laos [4].

In this review, we evaluate the role of nanoparticles in pandemic control and discuss their potential applications, and also the alarms and risks associated with their use. We also draw on the insights learned from the COVID-19 outbreak regarding the use of nanoparticles in managing viral outbreaks. For instance, although antiviral face masks containing metal nanoparticles were proposed as a more sustainable alternative to disposable masks, since they reduce the amount of non-biodegradable waste material [5], their improper disposal has contributed to the release of metal nanoparticles into the environment. One recent example was their release into Colombian and Southern Brazilian waters [6, 7]. Improper disposal may also cause ecological harm [8]. A comprehensive understanding of the advantages and risks associated with nanoparticle utilization is therefore essential to their responsible and effective use.

Another significant application of nanoparticles in the fight against COVID-19 is the use of lipid nanoparticle platforms for mRNA vaccines. Although the widespread use of lipid nanoparticles containing mRNA vaccines has contributed significantly to pandemic control [9], the long-term safety and activity of the vaccine-containing nanoparticles are unclear. Neither have the logistics associated with transport — such as special equipment for storage during transport to remote areas, and the costs this involves — been addressed so far.

Below, we explore the various potentials of nanoparticles in viral outbreak management. More specifically, we discuss the use of functionalized face masks for preventing viral infections, the significance of nanoparticle-based drug delivery systems for antiviral therapeutics, and the role of nanoparticles in diagnostic platforms for rapid and accurate viral detection. We also address the concerns and risks associated with the use of nanoparticles, including their potential ecological impacts and other long-term safety considerations. We highlight the critical role of nanoparticles in tackling viral outbreaks, showcasing their potential applications and stressing the importance of their responsible and ethical use. Through proper consideration of the benefits and risks intricately linked with nanoparticle usage, we hope to ensure the development of effective strategies for future pandemic control.

Nanotechnology applications in SARS-CoV-2 transmission prevention

Functionalization of protective face masks using nanoparticles

The improper disposal of non-reusable face masks has become an environmental concern, as these masks often contain non-biodegradable materials and pathogenic particles in their filter layer. Over time, the mask weathering caused by factors such as mechanical stress, UV-light, or quartz particles causes the release of microplastics from the masks into the environment [10].

Surgical masks usually consist of three layers, with a central filter layer. To reduce waste production, this filter layer can be functionalized with metallic nanoparticles composed of silver, zinc, or copper, which interfere with viral reproductive cycles, thereby helping to improve virus filtration over that of ordinary masks [11–15]. Metallic nanoparticles can be used to functionalize face masks through the addition of substances such as photo-sensitizing nanoparticles, which produce reactive oxygen species (ROS) upon exposure to specific wavelengths of light, thereby effectively destroying pathogenic membranes, proteins, and nucleic acids after each mask use [16]. Plasma-based nanoparticles with photo-thermal efficiency, such as graphene, silver, and gold nanoparticles, are able to self-disinfect when exposed to light, and to absorb any moisture present in the mask [12, 17]. Graphene-derivatives add other properties to functionalized face masks, such as resistance to smog, mechanical and abrasion stress, and UV light [18]. Positively charged polymer nanoparticles have strong virucidal properties that reform and fluidize the lipid content of viral membranes, particularly in lipid-raft areas [19]. Similarly, biodegradable polysaccharide-based materials successfully combat COVID-19 in facial mask layers, achieving complete decomposition in soil within 4 weeks [20, 21].

Various nanotechnology applications in SARS-CoV-2 transmission prevention

As well as functionalizing protective face masks, metallic nanoparticles can be applied in mouthwash and nose rinses, offering new opportunities for combating viral infections. As silver nanoparticles (AgNPs) inhibited SARS-CoV-2 in pre-clinical studies [22, 23], they may have potential for wider application. Whereas chemical disinfectants need high concentrations of the active substance, metallic nanoparticles can be used in low concentrations, producing less harmful byproducts and being more effective than standard disinfectants [24]. Another application of nanotechnology involves spraying nano-sized electrostatic atomized water particles (NEAWPs) onto an electrode on which water molecules have first condensed. This significantly reduces the environmental virus count [25]. Such use of nanoparticles is particularly important because the excessive use of traditional disinfectants during the pandemic increased levels of quaternary ammonium compounds in water and soil, thereby posing an environmental threat [26].

Nanoparticles as antiviral therapeutic agents

The main antiviral agents against SARS-CoV-2 infection, i.e., remdesivir, zanamivir, oseltamivir, and abacavir, are specific for HIV and/or influenza, but not for SARS-CoV-2 infections [27, 28]. The use of nanoparticles in COVID-19 treatment strategies is promising since the nanoparticles do combat SARS-CoV-2. For example, iron oxide nanoparticles interfere with the S1 subunit of the RBD domain [29], and amyloid-like proteins from LCB1 and LCB3 sequences of the S protein self-assemble into multivalent spherical nanoparticles, competitively blocking viral interaction with the angiotensin-converting enzyme 2 (ACE2) receptor [30]. Similarly, linear polyglycerol sulfate and its fullerene-conjugated derivative can block virus entry into host cells [31]. Biological nanovesicles from human lung spheroid cells that present ACE2, as cell-mimicking nanodecoys, are promising, since they absorb viruses and prevent their attachment to the host cells [32].

Controlled-release systems of antivirals using nanoparticles

Nanoparticles provide a controlled-release system of antivirals to reduce side effects, increase bioavailability, improve circulation time, or ameliorate delivery of the antivirals [33]. For example, polymeric nanoparticles made of poly-ε-caprolactone (PCL) or poly-lactic glycolic acid-conjugated-poly-ethylene glycol (PLGA-PEG) decorated with ACE2 ligands successfully encapsulate remdesivir, playing dual antiviral roles through competitive interference with SARS-CoV-2 in ACE2 binding, and through targeted drug delivery to lung cells [34]. The anti-COVID efficacy of the drug is enhanced by PLGA-lipid hybrid nanoparticles encapsulating fluoxetine hydrochloride [35]. Table 1 provides information on selected types of nanoparticle that are used against different coronaviruses.

Environmental challenges and urgent action

Adverse effects associated with nanoparticles in personal protective equipment

Despite some positive aspects of metal nanoparticle usage in personal protective equipment (PPEs) such as masks, potentially adverse effects of metal nanoparticles on ecosystems and their fate in the mask-washing process have not been thoroughly investigated. Their entry into the ecosystem may have unintended consequences.

Due to their high surface-to-volume ratio and reactive surface, nanoparticles are prone to interfere with biological processes. While their environmental impact, particularly that of nanoparticles originating from PPEs, has raised concerns about possible adverse effects on the ecosystem, these effects are not entirely negative. As well as aiding the removal of heavy metals and organic pollutants in wastewater treatment, metal nanoparticles can degrade microplastics and nanoplastics, and produce H_2O and CO_2 as end-products of degradation [8, 36, 37]. Nonetheless, the prolonged and continuous use of nanoparticles in PPEs leads to the accumulation of toxic levels of degradation products, posing risks to various organisms, and to the entire ecosystem [38]. In aquatic conditions, metal nanoparticles derived from PPEs can

Table 1 Nanoparticles used against different coronaviruses and their mechanism of action

Nanoparticles	Target coronavirus	Mechanism of action	Reference
Carbon quantum dots	HCoV-229E	Inhibition of viral entry and replication in the cells	[172]
Gold nanorods conjugated to peptide inhibitors	MERS-CoV	Prevention of cell membrane fusion with virus	[173]
Polyphosphate (polyP)-silica nanoparticles	SARS-CoV-2	Inhibition of S-protein interaction with ACE2	[174]
NEAWPs	SARS-CoV-2	Inhibition of virus to cell binding	[25]
Trimethyl (11-mercaptoundecyl) ammonium chloride gold nanoclusters	SARS-CoV-2	Inhibition of virus transcription and replication	[175]
Favipiravir-loaded PLGA nanoparticles	SARS-CoV-2	Sustained favipiravir release	[176]
siRNA-loaded LNPs	SARS-CoV-2	Viral gene silencing	[177]
$AgNO_3$ nanoparticles	HSV-1 and SARS-CoV-2	Induction of inflammatory cell apoptosis	[178]
Aptamer-targeted LNPs encapsulating siRNAs	SARS-CoV-2	Viral gene silencing	[179]
SNAT, Tx–[NH_2-AgNPs]	SARS-CoV-2	Viral replication inhibition	[180]
BSA-coated tellurium nanoparticles	PRRSV	Viral internalization inhibition into cells	[181]
Au@AgNRs	PEDV	Decreased internalization, caspase-3 activity, and viral replication	[182]
Ag_2S nanoclusters	PEDV	Blocked viral cycles in RNA negative-strand synthesis	[183]
Diphyllin-loaded PEG-PLGA nanoparticles	FIP	Inhibition of virus endosomal escape by blocked acidification	[184]
siRNA-loaded spray-dried PLGA nanoparticles	SARS-CoV-1	Viral gene inhibition in the lungs	[185]
Ag nanoparticles	TGEV	Virus-caused apoptosis inhibition	[186]
SinaCurcumin curcumin nanomicellar capsules	SARS-CoV-2	Decreased inflammatory cytokine levels in COVID-19 patients	[187]
DNase-I and PEG-decorated melanin-like nanoparticles	SARS-CoV-2	Excessive neutrophil clearance	[188]
DNase-I-decorated polydopamine-PEG nanoparticles	SARS-CoV-2	Excessive neutrophil clearance	[189]
HCQ and CQ-conjugated Pt nanoparticles	SARS-CoV-2	Reduction of CQ side effects	[190]
Anti-inflammatory microRNA-146a-decorated cerium oxide nanoparticles	SARS-CoV-2	Prevention of acute respiratory distress syndrome caused by bleomycin in COVID-19 patients	[191]
Niclosamide-loaded LNPs	SARS-CoV-2	Improved niclosamide solubility	[192]
PLGA nanoparticles coated with cell membrane containing ACE2 and CD147 receptors	SARS-CoV-2	SARS-CoV2 absorption	[193]
Remdesivir-loaded PEGylated dendrimers	SARS-CoV-2	Enhanced solubility	[194]
siRNA-loaded peptide dendrimer KK-46	SARS-CoV-2	Viral gene silencing	[195]
MTX-LDE	SARS-CoV-2	Enhanced cellular uptake and efficacy of methotrexate	[196]
Methotrexate-loaded nanoparticles	SARS-CoV-2	Enhanced cellular uptake and efficacy of methotrexate	[197]
Ag nanoparticles	SARS-CoV-2	Virus-caused apoptosis inhibition	[198]

ACE2, angiotensin-converting enzyme-2; *Au@AgNRs*, silver-coated gold nanorods; *BSA*, bovine serum albumin; *CQ*, chloroquine; *FIP*, feline infectious peritonitis; *HCoV-229E*, human coronavirus; *HCQ*, hydroxychloroquine; *MERS-CoV*, Middle East respiratory syndrome coronavirus; *MTX-LDE*, methotrexate-loaded cholesterol-rich non-protein nanoparticles; *NEAWPs*, nano-sized electrostatic atomized water particles; *PEDV*, porcine epidemic diarrhea (corona)virus; *PLGA*, poly-lactic glycolic acid; *PRRSV*, porcine reproductive and respiratory syndrome virus; *SNAT*, smart nano-enabled antiviral therapeutic; *Tx–[NH_2-AgNPs]*, taxoid-decorated amino-functionalized silver nanoparticles; *TGEV*, transmissible gastroenteritis virus

interact with other pollutants. The detrimental effects in organisms range from inflammation to cellular

damage that further exacerbate any impact on the environment [8]. A further problem is the improper disposal of PPEs in landfills, dumpsites, marine environments, or public spaces. This can cause animals to mistakenly recognize such PPE waste as food, resulting in their inadvertent and potentially harmful ingestion.

All in all, urgent action is required to address a range of significant environmental challenges. To promote proper disposal practices and prevent the dissemination of nanoparticles into the environment, specific recycling guidelines tailored to nanotechnology products should be established and enforced [19]. Before the SARS-CoV-2 pandemic, nanoparticles entered the environment mainly through household usage, industrial waste, or laboratory penetration. However, during the initial stages of the pandemic, when it was believed that the virus could be transmitted through surfaces, the use of antiseptic and disinfectant agents skyrocketed, increasing the release of nanoparticles into the environment. Now, in the post-SARS-CoV-2 period, the main source of nanoparticle pollution is the widespread uncontrolled abandonment of personal protective equipment.

Adverse effects of nanoparticles on plants and microorganisms

During the SARS-CoV-2 pandemic, the worldwide demand for masks reached over 4 billion daily, all while recycling programs for masks were inadequately planned [39]. Several countries used reusable masks containing carbon nanotubes, and/or silver (Ag), silicon dioxide (SiO_2), zinc oxide (ZnO), or nanoparticles titanium dioxide (TiO_2). Disposal of nanosilver from these masks was found to pose ecological hazards, inhibiting plant growth and photosynthesis [40]. Engineered nanoparticles commonly penetrate the roots of plants, resulting in phytotoxicity [41]. As nanoparticles generate reactive ions interacting with nutrients and inorganic compounds in plants, they cause chlorosis and wilting [42, 43]. Small-sized nanoparticles such as TiO_2 pass through protective layers like the cuticle, cell wall, and cell membrane [44], impairing the growth of seedlings crops, the uptake of minerals, and chlorophyll synthesis [45]. ZnO nanoparticles reduce chlorophyll production in bulb onions, as well as crop growth and development [46–48]. Ag nanoparticles increase the activity of antioxidant enzymes, reduce chlorophyll content, and impair photosynthesis in tomatoes [49, 50].

Similarly adverse effects of nanoparticles are observed not only in plants, but also in bacteria and aquatic animals [51]. For example, ZnO-based nanoparticles induce genetic mutations in *Caenorhabditis elegans*, resulting in offspring toxicity [52, 53]. In sea water, TiO_2 nanoparticles released from sunscreens cause severe damage to gill filaments, hampering aquatic animal reproduction [54, 55]. Overall, it is therefore clear that the adverse effects of nanoparticles eventually disrupt the food chain for higher organisms.

Adverse effects of nanoparticles on higher organisms

The generation of reactive oxygen species is a biological process. Their excessive generation causes oxidative stress, leading to inflammation, diabetes, cancer, and other degenerative diseases [56, 57]. Excessive reactive oxygen species causes free-radical production, lipid peroxidation, genotoxicity, and apoptosis [58]. Nanoparticles accumulate in various organs and have overall systemic effects [59]. Some inorganic nanoparticles such as TiO_2, SiO_2, ZnO, and Fe_2O_3 dissolve in the acidic environment of the stomach [60]. Through absorption into the skin, lungs, and liver [61], they also impair human health.

Toxicity caused by silver nanoparticles (AgNPs) in vitro depends on the surface coating and the concentration of AGNPs it contains. In vivo, AgNPs enter the bloodstream and accumulate in organs, where they cause cytotoxicity [62]. The generation of Ag^+ ions from AgNPs and oxidative stress both lead to apoptosis via translocation of mitochondrial cytochrome C into the cytosol [63], or to necrosis by reducing sulfhydryl groups [64, 65]. Table 2 provides an overview of anti-COVID-19-related cytotoxic effects caused by AgNPs and other types of nanoparticles in vitro and in vivo, and the compendial and noncompendial tests used.

Direct contact with titanium dioxide nanoparticles (TiO_2NPs) affects skin cells in various ways, for example, by impairing their viability, proliferation, and differentiation [66]. TiO_2NPs penetrate into the deep layers of the skin are known to be released in sweat [67–69]. Inhalation of TiO_2NPs poses a significant health risk: due to the lower

Table 2 Available reports on adverse effects of nanoparticles currently used in anti-COVID approaches including nanoparticle type, size, and model

Nanoparticle type	Nanoparticle size (nm)	In vivo, animal/human	In vitro, cell line	Assay(s), (C, compendial/NC, non-compendial)	Administration, dose, duration	Adverse effects	Reference
Silver-based	10	Sprague–Dawley rats		Chromosomal aberration assay (NC)	Oral, 5–100 mg/kg bw, 5 d	Genotoxicity, DNA breaks, decreased mitotic division	[211]
	30		Rat cerebellar granular cells	Alamar blue assay (NC), cell morphology (NC), HE staining (C; USP37 < 1285.1 >)	0.05–50 µg/ml	Increased caspase-3 activity	[212]
	25		Rat cerebellar granular cells	Radioactive Ca uptake (NC)	25–75 µg/ml	Overactivation of NMDA class of glutamate receptors, apoptosis induction	[213]
	18–19	Sprague–Dawley rats		Nanoparticle inhalation (C; USP37 < 5 >), TEM (NC), HE staining (C; USP37 < 1285.1 >)	Inhalation, 5 d/wk, 13 wk	Increased nanoparticle concentration in blood, liver, kidney, lungs; liver and lung inflammation	[214]
	30	C57BL/6J mice		Oral administration (NC), qPCR, western blot (NC)	Oral, 100/300 mg/kg bw, 14 d	Kupffer cell activation, liver inflammation, aggravation of non-alcoholic fatty liver disease	[215]
	60	Sprague–Dawley rats		Spectrophotometry (C; USP851), HE staining (C; USP37 < 285.1 >), micronucleus assay (NC)	Oral, 30–1000 mg/kg bw, 28 d	Liver damage	[216]
	20 (uncoated), 15 (PVP-coated)	Sprague–Dawley rats		Oral gavage (NC), spectrophotometry (C; USP851)	Oral, 90 mg/kg bw, 28 d	Nanoparticle accumulation in brain and testis	[217]
	25–80		Rat brain microvessel endothelial cells	ELISA (NC)	1.95–15.63 µg/cm2	Release of proinflammatory mediators (TNF, IL-1β, PGE_2)	[218]
	12	Wistar rats		HE staining (C; USP37 < 1285.1 >), mass spectrometry (C; USP29 < 736 >)	Oral, 6 mg/kg bw, 28 d	Effect on metabolic functions and signaling pathways in the liver	[219]

Table 2 (continued)

Nanoparticle type	Nanoparticle size (nm)	In vivo, animal/human	In vitro, cell line	Assay(s), (C, compendial/NC, non-compendial)	Administration, dose, duration	Adverse effects	Reference
	14	CBAB6F1 mice		Polychromatic erythrocytes (NC), Romanowsky-Giemsa-May-Gruenwald staining (NC)	Oral, 0.1–500 mg/L, 2 wk	Colon cytogenic changes, lung mutagenicity	[220]
	5–20		Murine macrophages	MTS (NC), hyperspectral microscopy (NC)	20, 40, or 80 mg/L	Nanoparticle size-dependent cell toxicity	[221]
	10	Zebrafish		Leukocyte recruitment quantification (NC), immunohistochemistry (NC)	2 µg/ml, 5 min	Impaired epithelialization and blastema formation; decreased cell proliferation, amputation-induced ROS production	[222]
	27–106	Sprague–Dawley rats		In situ hybridization (NC), qPCR (NC), H2DCFDA assay (NC)	Injection, 1 ×, 5/0.0003 mg/kg bw	Increased polyploid cell numbers in the liver and kidney	[223]
	63–67	Bacteria, algae, fungi, plankton		Transcriptome sequencing (C; EP < 20,621 >)	10 µg/ml, 7 d	Hampered bacterial DNA repair, replication, metabolism	[224]
	18	Sprague–Dawley rats		Plethysmography (NC), bronchoalveolar lavage (NC)	Inhalation, 6 h/day, 90 d	Lung inflammation, dysfunction	[225]
PEGylated	Not indicated	Patients (gastrointestinal tract disease)		Not applicable		Anaphylaxis	[226]
	Not indicated	Patients (acute lymphoblastic leukemia)		Not applicable	Intramuscular (i.m.) and/or intravenous (i.v.) injection	Allergic reactions in 9% (i.m.) and 36% (i.v.)	[227]
	Not indicated	C57BL/6J mice, Rhesus monkeys		ELISA (NC), SPR (C; USP36 < 1105 >)		Inactivation of PEGylated nanoparticle activity by anti-PEG antibodies	[228]

Table 2 (continued)

Nanoparticle type	Nanoparticle size (nm)	In vivo, animal/human	In vitro, cell line	Assay(s), (C, compendial/NC, non-compendial)	Administration, dose, duration	Adverse effects	Reference
	Not indicated	Patients (acute lymphoblastic leukemia, chronic gout)		Not applicable	Injection, Krystexxa, 8 mg, 2×/wk; Oncaspar, 2500 IU/m^2, 1×/2 wk	Inactivation of PEGylated nanoparticle activity by anti-PEG antibodies, anaphylaxis, gout flare, nausea, contusion, ecchymosis	[126]
	4–5	Sprague–Dawley rats		APPT (C; EP7.8), blood coagulation analysis (NC), HE staining (C; USP37 < 1285.1 >)	Inhalation, 0.4–20 µg/m^3, 90 d	Nanoparticle accumulation in the lung and kidney	[229]
	1.3	Zebrafish (embryos)		TUNEL assay (NC), WISH assay (NC), behavioral activity (NC), qPCR (NC)	6–24 h post-fertilization, 30–50 mg/L	Effects on eye development and pigmentation, behavioral and neuronal damage	[230]
Gold-based	8.2	Mice		Mass spectrometry (C; USP29 < 736 >), TEM	Intraperitoneal injection, 7550 µg/kg bw	Nanoparticle accumulation, acute infection, inflammation, kidney damage	[92]
	< 100 nm (TiO_2/AuNPs), 200–350 nm (AuNPs)	Rats, mice, hamsters		Histopathology (NC), inflammatory markers in lung fluid (NC)	Inhalation, 90 d	Histopathological lesions, neutrophil response in the lung	[231]
	Not indicated	CD-1 (ICR) mice		Histopathology (NC), mass spectrometry (C; USP29 < 736 >), monoamine neurotransmitter assay (NC)	Nasal, 500 µg TiO2, 1×/2 d, 30 d	Nanoparticle accumulation in the cerebral cortex and striatum	[232]
	80, 155	CD-1 (ICR) mice		HE staining (C; USP37 < 1285.1 >), serum biochemical assay (NC), mass spectrometry (C; USP29 < 736 >)	Nasal, 50 µg TiO2/kg bw, 1x/2 d, 30 d	Ti accumulation in the brain, pathological changes in the kidney	[233]

Table 2 (continued)

Nanoparticle type	Nanoparticle size (nm)	In vivo, animal/human	In vitro, cell line	Assay(s), (C, compendial/NC, non-compendial)	Administration, dose, duration	Adverse effects	Reference
	10	Pregnant Wistar rats		Morris water maze (NC), immunohistochemistry (NC)	Intra-gastric, 100 mg/kg bw, 1 × /d, 20 d	Decreased offspring hippocampus cell proliferation, learning ability, and memory	[234]
	5–6	CD-1 (ICR) mice		Mass spectrometry (C; USP29 < 736 >), HE staining	Inhalation, 1–5 mg/kg bw, 1 × /d, 6 mo	Increased inflammatory and fibrogenic cytokine levels	[235]
	3.6	CD-1® (ICR) mice		HE staining	Intra-peritoneal injection, 0–2592 mg/kg bw	Repugnance, fatigue, tremor, lethargy, spleen lesion, thrombosis, necrosis, liver cell apoptosis	[236]

APPT, activated partial thromboplastin time; *bw*, body weight; *d*, day; *EP*, European pharmacopeia; *H2DCFDA*, dichlorofluorescin diacetate; *HE*, hematoxylin/eosin; *i.m.*, intramuscular; *IL-1β*, interleukin 1β; *i.v.*, intravenous; *min*, minute; *mo*, month; *MTS*, 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazoium); *NMD*, N-methyl-d-aspartate; *NP*, nanoparticle; PGE_2, prostaglandin E_2; *PVP*, polyvinylpyrrolidone; *ROS*, reactive oxygen species; *SPR*, surface plasmon resonance; *TEM*, transmission electron microscopy; TiO_2, titanium dioxide; *TMAT*, N,N,N-trimethylammonium ethanethiol; *TNF*, tumor necrosis factor; *TUNEL*, terminal deoxynucleotidyl transferase dUTP nick end labeling; *USP*, United States pharmacompeia; *wk*, week; *WISH*, whole-mount in situ hybridization

protection provided by the olfactory bulb than by the blood–brain barrier, nano-sized materials can penetrate the brain faster through the olfactory nerve than through systemic injection [70, 71].

Being in direct contact with the skin and the air we breathe, protective masks containing Ag and TiO_2 nanoparticles are potentially harmful. The presence of these nanoparticles has been shown to significantly inhibit the growth rate of human osteoblasts, indicating that the adverse effects of the masks are not limited to the skin, inhalation, or brain [72].

The leaching of Ag^+ or Cu^{2+} ions from metal-impregnated masks has also been linked to potential health risks for humans [73]. Exposure to these nanoparticles through ingestion, inhalation, or dermal penetration can cause toxicity [74]. Ingestion is followed by exposure to the complex and harsh condition of the gastrointestinal tract, i.e., pH variations, gastric salts, ions, and enzymes. These interactions modify the composition of nanoparticles, leading to biomolecule adsorption and aggregation [75–77].

Although nanoparticles have toxic effects on the immune system and are involved in oxidative stress-related disorders, many people attribute these disorders to factors such as air pollution. This has led to proposals for public education on proper disposal of personal protective equipment in government-provided trash containers. Long-term monitoring of coastal waste and citizen initiatives for litter collection in populated areas have also been suggested [78–80], as has the recycling of carbon powders from masks for use in batteries [81] or renewable fuels [82], and the promotion of reusable alternatives and cellulose-fiber textiles. Potential disposal methods also include incineration and optimized pyrolysis [82, 83].

The toxicity of metal nanoparticles varies according to the size, surficial coating, and shape of the nanoparticles [84]. The solubility of AgNPs is inversely proportional to the size of the nanoparticle. Due to increased dissolution and cell penetration efficacy, small nanoparticles exhibit high toxicity, with a strong attachment to DNA also causing DNA damage. Use AgNPs sized more than 20 nm shows less genotoxicity [85, 86]. As metal nanoparticles sized less than 100 nm cause increased toxicity in vivo, the recommended ranges lie between 100 and 150 nm [87, 88].

Toxicity is also influenced by the type of nanoparticle coating. Coating AgNPs with polyvinylpyrrolidone (PVP) has been found to have a greater toxicity and tissue uptake than citrate coatings, while positively charged polymers such as chitosan enhance the toxicity of AgNPs more than citrate-stabilized particles do. A bovine serum albumin (BSA) coating of gold nanoparticles (AuNPs) also leads to greater toxicity and poorer renal clearance than a glutathione (GSH) coating. On the other hand, coating AuNPs with PEG reduces nanoparticle toxicity and appears to be a suitable coating option [85, 89–92].

Nanoparticles in vaccines and risk assessment

The WHO defines vaccines as pharmaceutical formulations that activate the immune system in order to produce specific antibodies, thereby generating protective immunity against a disease caused by a pathogen [93]. The conventional vaccines developed since the late eighteenth century rely on the discovery of antibodies in patients who have recovered from infections. To elicit an immune response, these use attenuated or inactivated pathogens and purified pathogen fragments [94]. Second-generation vaccines are produced using recombinant DNA technology in bacteria or in cell cultures [95].

Recently, a third generation of vaccines has emerged, which introduces the gene encoding the protective antigen into a host cell. By improving antigen processing and its presentation to antigen-presenting cells (APCs), this enhances the activation of $CD4^+$ and $CD8^+$ cells. This recent advance in vaccine technology holds promise for eliciting protective immune responses against the virus [96].

To overcome the limitations of conventional vaccines, i.e., attenuated or inactivated viruses, alternative options such as RNA- or DNA-based vaccines have also been sought recently. These new RNA- or DNA-based vaccine production technologies aim both to improve reactivity and efficacy and to reduce the cost of vaccines. They can also be used to effectively treat other diseases, such as cancer. But whereas vaccines need to be delivered to the right places in the body in a suitable form so as to prepare the immune system to combat an invading pathogen effectively, most vaccine molecules are prone to degradation. Due to limited accessibility and poor cell permeation

[97], they may not be recognized efficiently by the immune system. A crucial role in enhancing the effectiveness of vaccines is played by delivery systems based on nanoformulations. By tailoring nanoencapsulation, vaccines can be delivered with precision and stability [96].

These delivery systems contribute to the in vivo behavior of vaccines in various ways: they protect vaccines from enzymatic degradation, improve their pharmacokinetic properties through surface engineering techniques such as PEGylation, enable active targeting to specific organs or cell types, and engineer controlled release of vaccines [93, 98, 99].

Lipid nanoparticles, self-assembling protein nanoparticles, virus-like particles, liposomes, and cationic nanoemulsion vaccines have been designed against SARS-CoV-2 [100]. The most prominent vaccines against SARS-CoV-2 are lipid-based nanoparticles (LNPs), which have been designed as drug nanocarriers for nucleic acid delivery [101]. By protecting fragile and unstable nucleic acids from degradation by nucleases, LNPs can increase the half-life of nucleic acids in the blood circulation. Charge-reversible LNPs contain ionizable lipids, either positively or negatively charged, that allow the LNPs to remain neutrally charged in the bloodstream, effective encapsulation of nucleic acids in the LNPs, and a high degree of endosomal escape of LNPs (Fig. 1) [102].

LNPs contain two other main components: cholesterol, a neutral phospholipid, and PEG-lipid, which protects LNPs from phagocytosis and aggregation in the blood circulation and also during manufacturing and storage. In vaccine formulations, the PEG-lipid also ensures that the LNP maintains the desired diameter (200 nm) [103]. A factor that is crucial to efficient nucleic acid delivery is the complete escape of nucleic acids from the endosomal compartment after LNP internalization. By increasing the diffusibility of PEG-lipids, the addition of distearoylphosphatidylcholine (DSPC) and dioleoylphosphatidylethanolamine (DOPE) lipids to nanoparticles enhances endosomal escape [104].

To produce viral proteins, leading anti-COVID vaccine developers such as Moderna, Pfizer/BioNTech, CureVac, Walvax, Sanofi, Pasteur, and Entos Pharmaceuticals all use cationic LNPs to deliver mRNA or DNA encapsulated into host cells. Although mRNA vaccines are more prone to instability and functional defects than DNA vaccines, they are preferred due to their higher immunogenicity, their direct translation in the cytosol, and their higher loading potential into LNPs [106–108]. To achieve the same level of efficiency, self-amplifying mRNA-LNP vaccines such as those developed by Imperial College London and Arcturus/Duke-NUS require ten times less mRNA than mRNA vaccines. However, they have less flexibility in nucleotide modification than their mRNA counterparts [102, 109].

Most LNP-derived vaccines currently available induce immune responses against the Spike protein (S protein). Interestingly, the receptor binding (RBD) and N-terminal (NTD) domains of the S protein are targeted by the most potent of the 61 monoclonal

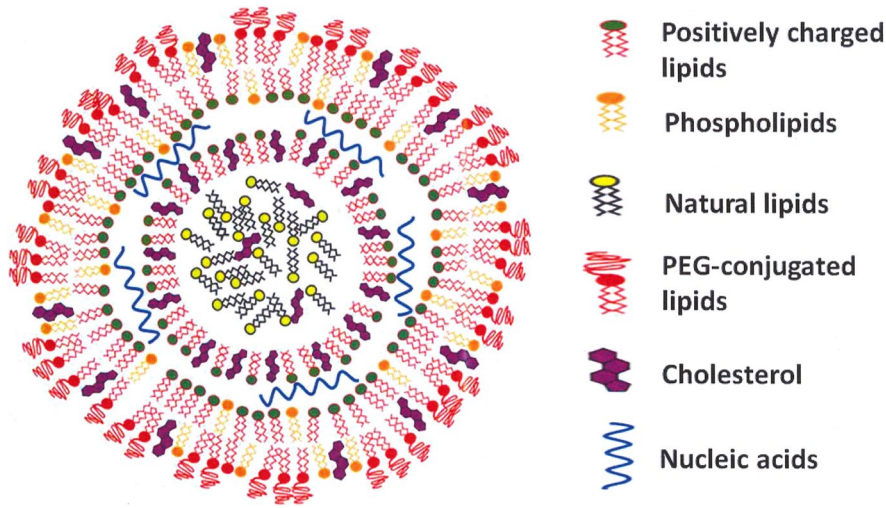

Fig. 1 Schematic illustration of an mRNA-based SARS-CoV-2 lipid nanoparticle vaccine. Different components of the vaccine are visualized, i.e., positively charged lipids, phospholipids, natural lipids, PEGylated lipids, cholesterol, and nucleic acids. This figure is modified from those published in [105]. PEG, polyethylene glycol

antibodies isolated from infected patients [110]. As anti-NTD antibodies inhibit and anti-RBD antibodies neutralize viral infections [111], the presentation of one of the virus protein domains is preferred above presentation of the whole protein for optimal immunity against new COVID-19 variants.

Due to the need for expensive low-temperature storage required by the SARS-CoV-2 vaccines currently available, their distribution poses challenges in developing countries. As the mechanical stresses caused by shaking might lead to aggregation and mRNA degradation in LNPs, vaccines also need to be administered promptly after preparation [112–114]. By enhancing the long-term stability of mRNA-LNPs, freeze-drying offers a solution to both these problems. However, if freeze-drying is to be successful, vaccine structure should not be affected by the lyoprotectants and by temperature stress. A new generation of the Pfizer/BioNTech vaccine is currently being prepared in lyophilized (freeze-dried) form [115].

Adverse effects associated with SARS-CoV-2 nanoparticle vaccines

Mild to moderate side effects are experienced after vaccinations. Compared to conventional vaccines, Pfizer and Moderna vaccines have been shown to cause more serious allergic reactions, including anaphylaxis. While side effects such as flushing and transient dyspnea were also observed in some of these mRNA vaccines, they were not considered to be allergic reactions [116]. Similar side effects were reported in earlier clinical safety studies of mRNA vaccines against influenza [116].

Although the rate of allergic reactions for LNP vaccines containing mRNA cargo is generally around 1.31 (95% CI, 0.90–1.84) per million doses, the number of severe immune reactions may be higher with booster doses [117]. LNPs induce inflammation, especially in non-adherent cells, due to the higher availability of cell surface receptors than in adherent cells [118, 119]. The main suspect for anaphylactic reactions in mRNA vaccines is the coating polymer, PEG, which alters the water solubility of the vaccine-containing nanoparticles [120]. Although PEG is widely used in cosmetics, food, medication, and pharmaceutical agents, its use in vaccine technology is rare [121].

Initially, PEG molecules were thought to be safe and biologically inert, but nowadays PEG and PEG-like polymers are not considered to be as safe as initially thought [122]. An immune response mediated by anti-PEG IgG antibodies may develop in allergic individuals, particularly females [123]. These antibodies can target the PEG backbone or specifically bind to PEG terminal functional groups [124]. In the presence of reactive oxygen species, anti-PEG antibodies detrimentally affect the respiratory chain and signal transduction pathways, and also disrupt cell membranes [125]. In vivo, oxidation of PEG, especially of the PEG low-molecular polymer chains, produces toxic molecules, i.e., glycolic acid and hydroxy acid metabolites [126]. PEGylated nanoparticles cause pseudoallergic reactions such as complement-activation-related pseudo allergy (CARPA) [127] and toxic or immunogenic responses, particularly with booster doses. Anaphylactic responses to PEG occur in 2–8 cases per year worldwide, which has led the clinical use of two PEGylated pharmaceuticals to be abandoned [128–130]. The concentration of PEG in mRNA vaccines is much lower than in PEGylated drugs, and intramuscular administration induces less inflammation [131]. While anaphylactic reactions are caused not only by PEG, allergic reactions are also caused by vaccine components such as polysorbate 80 in the vaccines developed by AstraZeneca and Johnson [132]. On the other hand, polysorbate 80 is considered to be safer than PEG [128]. Figure 2 provides a schematic illustration of the various SARS-CoV-2 vaccines, and Table 3 a summary of the side effects associated with them.

The side effects of PEGylated vaccines and polysorbate-containing vaccines include urticaria, dizziness, diarrhea, wheezing, and tachycardia [133]. Dermal side effects, such as erythema or swelling, are slightly more common with mRNA vaccines than with adenoviral vaccines (10–15% versus 5–7% of the patients) [134–136]. Rare side effects of viral vector vaccines include thrombosis and thrombocytopenia. When there is cross-reactivity between PEG and polysorbates, immediate hypersensitivity reactions occur [137, 138]. For approximately 6 months, mRNA and adenoviral vaccines can both cause changes in menstrual cycles, such as dysmenorrhea, alterations in frequency, volume, or cessation of bleeding. Women with pre-existing platelet disorders [139], those

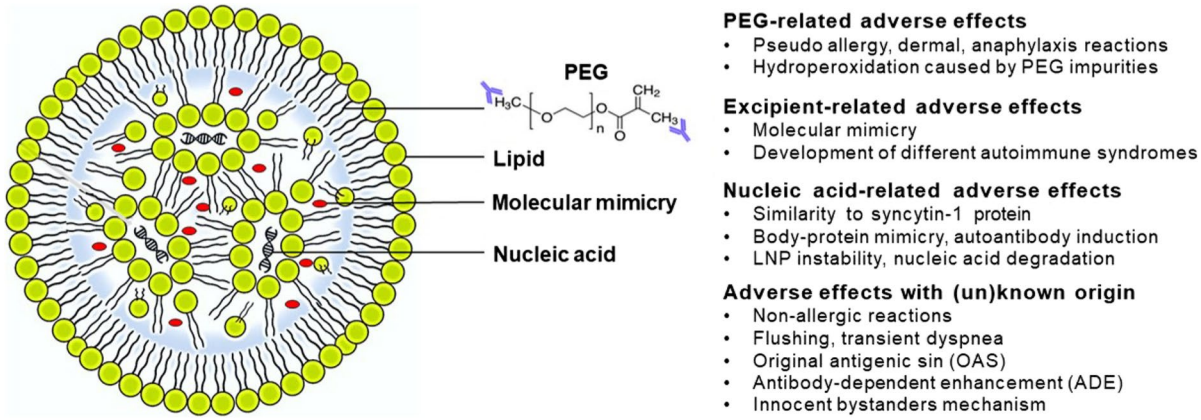

Fig. 2 Categorized adverse effects associated with different components of nucleic acid-based lipid nanoparticle vaccines. PEG, excipient, or nucleic-acid-related adverse effects, and adverse effects of known and unknown origin are indicated. Formation of anti-PEG backbone auto-antibodies (blue). PEG, polyethylene glycol

Table 3 Side effects of SARS-CoV-2 vaccines

Vaccine(s)	Side effects	Reference(s)
BTN162b2	Bullous pemphigoid	[199]
CoronaVac, Janssen, Ad26, CoV2-S, BTN162b2	Lichen planus	[200–202]
mRNA-1273	Chilblains, pityriasis lichenoides chronica	[203]
mRNA-1273	Severe thrombocytopenia	[204]
mRNA-1273, BTN162b2	Papulovesicular rashes, bullous pemphigoid-like, pernio toes, urticaria, neutrophilic dermatosis, leukocytoclastic vasculitis	[205]
mRNA-1273	Morbilliform rashes, delayed large local reactions, erythromelalgia, erythema multiforme, granuloma annulare, sarcoid tattoo reaction, psoriasis onset	[205, 206]
BTN162b2	Pityriasis rosea	[207]
mRNA-1273, BTN162b2	COVID arm symptom	[208]
mRNA-1273, BTN162b2	Orofacial edema	[209]
BTN162b2	Herpes zoster reactivation	[210]

taking estrogen-based contraceptives [140], and those with thrombocytopenia [141] are all at a higher risk for such changes in their menstrual cycle. Messenger RNA- and viral vaccines affect the menstrual cycle, but the strongest changes are observed with mRNA-LNP vaccines [142, 143].

A major concern with the use of nanoparticle vaccines is that they trigger autoimmune diseases. SARS-CoV-2 mRNA-NPs vaccines trigger autoimmune liver diseases, Guillain-Barré syndrome, IgA nephropathy, myocarditis, optical neuromyelitis, autoimmune polyarthritis, Graves' disease, type 1 diabetes mellitus, and systemic lupus erythematosus [144–149]. A second concern is the possibility of reverse transcription of mRNA vaccines in liver cells, which has been observed in vitro [150], although genotoxicity in vivo remains debatable [151]. A third concern is the phenomenon of original antigenic sin (OAS), which occurs when antibodies from previous infections or vaccinations hinder the neutralization of newly mutated antigens, particularly the omicron antigen variant [152]. A fourth concern is the concept of antibody-dependent enhancement (ADE), where low antibody titers bind to virus particles without

neutralizing them, thereby facilitating virus entry into macrophages and enhancing respiratory disease responses. ADE has been linked to SARS-CoV-2 mRNA-NP vaccines [153].

A fifth concern has also arisen regarding the cross-reaction of vaccine-induced antibodies against syncytin-1, a placental protein similar to the SARS-CoV-2 spike protein, which activates the immune system and impacts female pregnancy [154]. Another significant consequence that can arise, mainly in young men, after a second dose of mRNA-based vaccines is myocarditis; this has an incidence of 12.6 cases per million. Sex hormones can contribute to the development of myocarditis [155], which is not only related to molecular mimicry of S protein, self-antigens, or the formation of autoantibodies, but may also be caused by vaccine adjuvants, activation of "innocent bystanders," or induction of autoantibodies [149].

A question we are currently unable to answer is whether the S protein should be replaced by other viral proteins as the immunogenic target to develop vaccines. New generations of vaccines such as spike-trimers and spike-ferritin in liposomes will continue to be based on spike proteins [156, 157]. To address and mitigate the side effects of nanoparticle-based vaccines, certain modifications might be considered. PEG chain length and topological configuration affect immunogenicity. Pre-treatment with small amounts of high-molecular-weight PEG reduces anti-PEG reactions, and in animal models, short and hyperbranched PEG polymers, such as poly(oligo-ethylene glycol) methacrylate, exhibit decreased interaction with anti-PEG IgG and IgM antibodies [158]. To prevent inflammation and side effects, glyceryl monostearate (GMS) should not be included in LNPs [118]. Promising alternatives for PEG are polyglycerol polyricinoleate, polysarcosine, polyhydroxypropylmethacrylamide, polysulfobetaine, and polycarboxybetaine polymers [159]. Replacing PEG with polysulfobetaine coating results in higher biological activity of insulin; in nude mice, a dextran coating eliminated toxicity and liver stress of iron oxide nanoparticles [160, 161]. Polyesters like polycarbonates and polyphosphoesters might also be viable alternatives to PEG, since they degrade in vivo into non-toxic fragments, and can be easily produced using ring-opening polymerization (ROP) [162].

More preclinical studies are needed to evaluate vaccines. As two-dimensional in vitro studies may not always completely capture the complex immune environment, and as the phenotype and expression of receptors on cells may be influenced by culture conditions [163], the prediction of vaccine performance systems might be improved by three-dimensional cell culture systems [164] and/or standardized in vitro culture systems [164]. And as small rodents are anatomically different from humans, non-human primates might be more reliable for in vivo studies [165].

When evaluating nucleic acid vaccines, it is essential to assess not only the quantitative distribution of DNA or mRNA cargo, but also protein expression. This will help to monitor the distribution, retention, and release pattern of the delivered DNA or mRNA, providing a predictive tool for vaccine safety. In addition, valuable insight into the tissue localization of delivered nanoparticles is provided by information on vaccine distribution in lymph nodes, organs, and APCs [100]. Although a skin-sensitization test is recommended before vaccination with PEG and polysorbate [121, 128, 166, 167], the number of positive cases in skin tests is considerably lower than the number of sensitive cases after vaccine administration [168]. Protocols for graded dosing of vaccines have been developed for hypersensitive individuals, such as those with basophil disorders and uncontrolled asthma. Allergic individuals are advised to receive a second dose of a different vaccine, or, in some cases, heterologous prime-boost vaccines are recommended [169–171]. Finally, in Fig. 3, we propose several solutions that will minimize the disadvantages associated with nanoparticle use.

Conclusions

The use of nanoparticles in combatting viral infections has proved to represent a promising and valuable approach in the realm of global health. The COVID-19 pandemic underscored the significance of nanotechnology in vaccine development, infection prevention, and therapeutic strategies. By offering innovative solutions — including functionalized face masks, antiviral therapeutics, and diagnostic platforms — nanoparticles have already showcased their potential in pandemic control. However, the potential risks and challenges associated with their use still require attention, particularly in vaccine development.

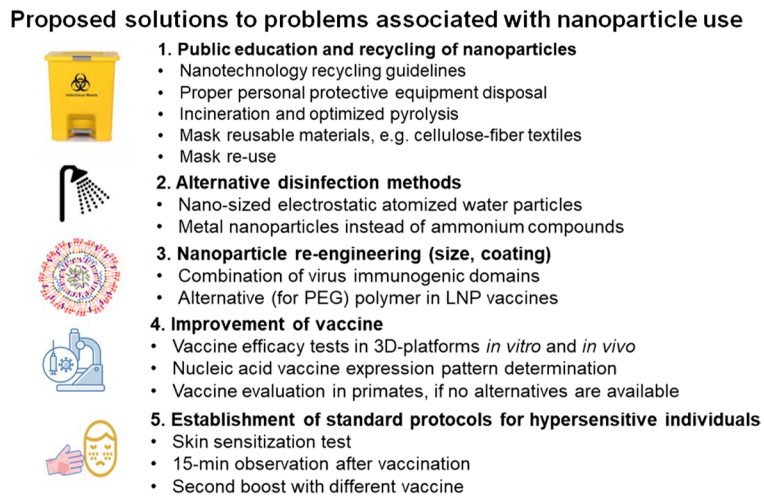

Fig. 3 Proposed solutions for minimizing the disadvantages associated with nanoparticle usage

Existing LNP formulations have played a crucial role in the rapid development of SARS-CoV-2 vaccines. Unfortunately, vaccine-induced immunity against SARS-CoV-2 is of limited duration, and, to enhance vaccine safety, adverse effects such as anaphylaxis and autoimmune reactions call for modifications in nanoparticle design such as after receiving primary doses, individuals with a history of COVID-19 vaccine anaphylaxis should not receive booster doses of the same vaccine.

The development of long-lasting and immunogenic nanoparticle formulations against SARS-CoV-2 is crucial. To prevent nanoparticle aggregation, surface modification of LNPs is also vital. It is also possible that alternative coating materials, such as shorter-length PEG polymers or other synthetic or natural polymers, may help to minimize side effects and enhance vaccine safety.

Whatever their promise in combating viral infections, the main concerns raised by metal nanoparticles involve their entry into the ecosystem. However, they can also aid in wastewater treatment, microplastic degradation, and environmentally friendly H_2O and CO_2 production. If responsible nanoparticle use is to be ensured, it is imperative to achieve better control of their toxicity through modifications of nanoparticle size, surface coating, and shape, and also to stimulate public education and proper disposal practices for nanoparticle-based personal protective equipment. Although multiple factors determine whether nanoparticles are toxic, very little information is available on their toxicity, which is sometimes related to the specific drug delivery, and/or to the physical characteristics of the nanoparticles (i.e., their size, surface area, charge, shape, and composition). The adverse effects associated with the use of nanoparticles such as LNPs containing PEG (PEGylated LNPs; Fig. 2) limit the use of LNPs in clinical applications. PEG is an FDA-approved compound that is used in pharmacochemical and personal care products. A solution to problems involving its toxicity in clinical uses may be provided by LNP modification, such as by replacing PEG with natural polymers.

The lessons learned from the COVID-19 pandemic have shed light on the importance of responsible and ethical nanoparticle use. In the pursuit of future pandemic control and global health protection, it is essential to continue harnessing the potential of nanotechnology while simultaneously remaining cautious and well-informed. By prioritizing the safety of nanoparticle-based products and vaccines, we will be able to ensure that nanotechnology remains a valuable tool in our fight against viral outbreaks, with minimized risks and enhanced benefits for both human health and the environment.

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Author contribution B. Zandieh-Doulabi had the idea for the article. F. Araste performed the literature search and data

analysis. F. Araste and B. Zandieh-Doulabi drafted the work, and all authors critically revised it.

Declarations

Conflict of interest The authors declare no competing interests.

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