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REVIEW PAPER

Nanomaterial-Augmented Formulation of Disinfectants and Antiseptics in Controlling SARS CoV-2

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Abstract
The worldwide COVID-19 pandemic has brought significant consideration toward innovative strategies for overcoming the viral spread. Nanotechnology will change our lives in several forms as its uses span from electronics to pharmaceutical procedures. The use of nanoparticles provides a possibility to promote new antiviral treatments with a low possibility of increasing drug resistance compared to typical chemical-based antiviral treatments. Since the long-term usage of disinfectants and antiseptics at high concentrations has deleterious impacts on well-being and the environment, this review was intended to discuss the antiviral activity of disinfectants and antiseptics required for their activity against respiratory viruses especially SARS-CoV-2. It could improve the inhibition of viral penetration into cells, solvation of the lipid bilayer envelope, and ROS production, therefore enhancing the effect of disinfectants. However, significant concerns about nanomaterial's hazardous effects on individuals and the environment are increasing as nanotechnology flourishes. In this review, we first discuss the significant and essential types of nanomaterials, especially silver and copper, that could be used as antiviral agents and their viral entry mechanisms into host cells. Further, we consider the toxicity on health, and environmental concerns of nanoparticles. Eventually, we present our outlook on the fate of nanomaterials toward viral diseases.

Keywords Nanoparticles · Disinfection · Ecological safety · Biosafety · COVID-19 · SARS-CoV-2 · Toxic nanomaterials

Introduction

Severe Acute Respiratory Syndrome-Coronavirus-2 is a novel virus with a correlated illness called COVID-19. It is spreading worldwide since late 2019, and a few months later, the World Health Organization (WHO) announced it as an epidemic (Schrank et al., 2020).

Coronaviruses are an enveloped and extensive family of viruses, transmitting between humans and animals and commonly provoke upper-respiratory-tract diseases ranging from typical cold to severe infection (Howley et al., 2020). SARS coronavirus (2002) and MERS Coronavirus (2012) are two severe and lethal members of this large family (Rai et al., 2020). SARS-CoV-2 viruses are positive-sense, single-stranded RNA viruses having a genome length of 26–32 kb (Rai et al., 2020) In comparison, SARS-CoV-2 is of special concern due to challenging control, higher reproduction numbers, longer incubation times, latent infections, and delayed symptoms (Almasi & Mohammadipanah, 2020; Schrank et al., 2020).

Since one of the most conventional interventions to inhibit the spread of this virus is adequate surface disinfection, there is an urgent requirement for disinfectants with lower toxicity (Rai et al., 2020; Saadatpour & Mohammadipanah, 2020). As the effectiveness of disinfectants depends on multiple factors, efforts to enhance their impact are inevitable in the current situation of the pandemic. Therefore, the advancement of authentic, innocuous, and eco-friendly disinfection methods is of utmost importance for the widespread continuation of their applications. Enhancement of antimicrobial effect using the natural additive to disinfectant formulation is generally regarded as safe while the emerging usage of new nanomaterial in antiseptic formulations is of health and ecological associated concern (Saadatpour & Mohammadipanah, 2021). In the first section of this review, we will focus on nanomaterials with antiviral activity. The second section will highlight several instances of their

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antiviral mechanisms. The third section will ultimately present the toxic impacts of nanomaterials on eukaryotic cells and the environment by their worldwide radically increased usage.

Nanoparticles and Nanomaterials

Nanomaterials (NMs) are materials constructed with a top-down or bottom-up nanotechnological approach. They are characterized by, at minimum, a single dimension fewer than 100 nm with a great surface area (Baroli, 2010). Depending on the composition, NMs are organized into four different groups: Based on metal, carbon, composites, and dendrimers (Kabir et al., 2018).

NMs based on carbon are concrete elements, which have been found in the form of nanoparticles (NPs), ellipsoids, sheets, and tubes that have specific and unusual physicochemical, optical, mechanical, and thermal qualities (Kabir et al., 2018). Quantum dots, silver NMs, gold NMs, and nano metallic oxides like titanium or zinc dioxide are the main metal NMs (Kabir et al., 2018). The dendrimers are symmetrical particles comprised tree-like branches in a monodispersed construction. The superficial layer may encounter variations in measure, form, and adjustability to other components (Abbasi et al., 2014). Nanocomposites have some features that could be created by referring to the requisition, selection of matrix, curing stage, and arrangement (Kabir et al., 2018).

Depending on how many dimensions fall below the 100 nm limit, NMs can also be sorted into four large families: Core–shell (zero dimension), surface films (one dimension), strands or fibers (two dimensions), and particles (three dimensions) (Baroli, 2010).

The NMs might have various shapes (e.g., spheres, rods, cups, ellipsoids, cubes) and might be coated with inorganic or organic materials to stabilize them against aggregation (Baroli, 2010). Applications of NMs include drug delivery, biosensor, reaction rate enhancement agent, magnetic separation and detection, and last but not least, as the antimicrobial agent (Li et al., 2011).

Nanomaterials with Antiviral Activity

Depending on the dimension, form, and surface charge, NMs can possess various formations and antiviral characteristics (Abd Elkodous et al., 2020). New NMs are being developed to improve their performance in treating respiratory diseases through various mechanisms (Sivasankarapillai et al., 2020).

The primary NMs reported for their inactivation effect on respiratory viruses can be subdivided into the following groups.

Polymeric NMs Their impressive qualities include adjustable features, available combinatorial protocols, and excellent biocompatibility (Sivasankarapillai et al., 2020).

Self-assembling proteins NMs They are produced by the oligomerization of monomeric proteins.

Inorganic NMs This type of NMs often has records of antiviral activities (Sivasankarapillai et al., 2020). Some of the most critical inorganic NMs include copper, silver, zinc, Titanium Dioxide (TiO_2).

Copper Since copper NMs (CuNPs) contain a smaller size and high surface-to-volume rate, they are extensively realized antimicrobial, antifungal, and antiviral metals for use on surfaces (Imani et al., 2020; Ingle et al., 2014; Vincent et al., 2017).

Silver They have unusual physicochemical and biological features that lead to having many applications for antiviral purposes in the shape of ions, NPs (AgNPs), and hybrid coats (Gurunathan et al., 2020).

Zinc Zinc oxides are n-type semiconductor metal oxides having remarkable antiviral qualities. It has many advantages like low production costs, readiness preparation, distinctive UV filtering qualities, high catalytic and photochemical activity (Jayaseelan et al., 2012; Nisar et al., 2019).

TiO_2 TiO_2 has many technical purposes such as water treatment, air disinfection, UV absorber, food, semiconductor, and agricultural industry (Hossain et al., 2014).

*Other Inorganic Antiviral **Matters*** Other inorganic matters and NPs like gold, magnesium, transition metals, and silica have significant antiviral activities (Imani et al., 2020) (Table 1).

Peptide-based NMs Earlier research has shown that the applications of peptide restrainer and modifications of amino acids may probably act against infections, especially the ones associated with SARS-CoV (Sivasankarapillai et al., 2020). Some of the most significant NMs that have shown activity against several respiratory viruses are summarized in Table 2.

Antiviral Mechanisms of Nanomaterials

In recent years, several NMs have been suggested as an alternative material for advanced diagnostic and therapeutic uses and carriers for antiviral agents. The mechanisms of action are limited to the specific type of NMs or viruses. Some of the main mechanisms are discussed below. The antiviral activity of NMs in any form depends on the dose and the target virus (Castro-Mayorga et al., 2017; Sportelli et al., 2020).

Silver The interaction with the envelope, genome, surface proteins, replication factors, preventing cellular pathways, and viral penetration into cells are the main mechanisms (Rai et al., 2016). Silver as an antiviral interacts directly with

Table 1 Main inorganic and metal nanomaterial with antiviral activity

Nanomaterial	Virus			Virucidal Activity Level	Contact Time	Proposed Applications	Reference
	Name	Envelope	Genetic material				
Copper							
Solid state	Influenza A	Enveloped	Negative-sense ssRNA	2×10^6 decreased to 500 infected viral particles	6 h	Replacing steel instruments with copper	Noyce et al. (2007)
Copper alloys	Murine norovirus	Non-enveloped	Positive-sense ssRNA	Dependent on alloy composition Dry touch: Virus TCID50 = 0	Dry: 5–120 min	Application of copper alloys in medical and environments settings	Warnes, et al. (2015)
				Wet: Virus TCID50 = 0 or 2 – 4log reduction	Wet: within 2 h		
Cuprous oxide	Influenza A	Enveloped	Negative-sense RNA	Following exposure to 2.1 µmol, 3.7log reduction	30 min	Block new viral shapes and potential resistance to drugs to decrease transmission	Imani et al. (2020)
Silver							
Hybrid coating (ionic)	HIV-1	Enveloped	Positive-sense ssRNA	99.5% reduction	20 min	Broad-spectrum antimicrobial surface coating in hospitals	Hodek et al. (2016)
	Dengue virus	Enveloped	Positive- sense ssRNA	1.1log $TCID_{50}$ reduction	4 h		
	HSV	Enveloped	dsDNA	Virus TCID50 = 0	4 h		
	Influenza	Enveloped	Negative-sense ssRNA	0.7log $TCID_{50}$ reduction	4 h		
Silver nitrate in solution	Feline calicivirus	Non- enveloped	Positive- sense ssRNA	3log decrease in 2.1 mg/L	75 days	In effective covering and contact surfaces	Imani et al. (2020)
	Murine norovirus	Non- enveloped	Positive-sense ssRNA	1log decrease with 2.1 mg/L	75 days		
NM in solution or film	Murine norovirus	Non-enveloped	Positive-sense ssRNA	In solution: primary 3log decrease, increased to Virus TCID50 = 0 with more than 10.5 mg/L concentration As film: 0.14log reduction at 25 °C and 0.86log reduction at 37 °C	1 day	The technology offered here would provide the In adequate covering and contact surfaces	Castro-Mayorga et al. (2017)
Zinc							

Table 1 (continued)

Nanomaterial	Virus			Virucidal Activity Level	Contact Time	Proposed Applications	Reference
	Name	Envelope	Genetic material				
Rigid phase	Murine norovirus	Non-enveloped	ssRNA	1log decrease for pure zinc	2 h	The insertion of copper alloy surfaces to hinder pathogens	Warnes et al. (2015)
Zinc oxide filopodia-like structures	Herpes simplex virus type 1 (HSV)	Enveloped	dsDNA	100 µg/mL ZnO-MNSs leads to the entrance under 20%	90 min	Development as a local agent for inhibition of viral infection	Imani et al. (2020)
Ionic solution	Human rhinovirus	Non-enveloped	Positive-sense ssRNA	99% decrease in quantity of plaques with the use of zinc chloride	1 h	It developed as an antiviral agent to block the cleavage of viral protein precursors and prevent the maturation of viral RNA and capsid polypeptides	Imani et al. (2020)
TiO_2							
Solid-state coating	Influenza virus	Enveloped	Negative-sense ssRNA	3.6log decrease (UVA severity 0.1 mW/cm^2)	4 h	Adhesion into high-touch settings to decrease the contamination from spreading	Nakano et al. (2013)
	Feline calicivirus	Non-enveloped	Positive- sense ssRNA	1.7log reduction	8 h		
Ag-doped solid-state coating	Influenza A	Enveloped	Negative-sense ssRNA	≥ 4.17log reduction (15 W UVA light at a distance of 35 cm)	20 min	Disinfection of high-touch surfaces such as light switches, bed rails, door handles and disruption of organic contaminants	Moongrakset al. (2019)
Additional inorganic antiviral substances							
Modified gold NMs	Virus-like particles (VLPs), replicating human norovirus, GI.1 VLPs	Replicates non-enveloped	Replicates RNA	Virus TCID50 = 0 of VLPs at 0.37 µg/mL with the application 0.083 µM Au/CuS NMs	1 h	Recommended as an antiviral agent	Broglie et al. (2015) and Imani et al. (2020)
Multivalent gold NMs with sulfate ligands	HIV	Enveloped	Positive-sense ssRNA	Lower than twenty percent contamination rate of T-cells	30 min	Construction of a remedial anti-HIV system	Imani et al. (2020)
Silica NMs in coating	Influenza A/PR/8/34 (H1N1)	Enveloped	Negative-sense RNA	Virus TCID50 = 0 following incubation of virus suspension on surface	30 min	Usage as a microbicidal coverage	Imani et al. (2020)

HIV human immunodeficiency virus, *TCID50* median tissue culture infectious dose sulfur and phosphate groups to interrupt the cell membrane. Besides, silver ions generate ROS (Reactive Oxygen Species) inside the cells, providing significant antiviral activity (Imani et al., 2020).

Zinc The antiviral mechanisms of zinc are based on interference with the replication of the virus, such as inactivation of the free virus, suppression of viral uncoating, transcription of the viral genome, translation of viral proteins, and the process of the polyprotein (Scott A Imani et al., 2020; Read, 2019).

Copper In general, viruses are more susceptible than fungi and bacteria to copper by the lack of repair mechanisms (Borkow, 2012). The viral genome is targeted by copper, especially a gene encoding VPg (viral-genome-protein-linked, a viral protein essential for viral infectivity) leading to a gene copy number reduction (Vincent et al., 2017). Moreover, ROS formation contributes to the death of the cell via interaction with viral envelope or capsid (Imani et al., 2020).

*TiO_2***.** The antiviral mechanism of TiO_2 is based on electron/hole generation, absorption of light, and the oxidation of organic matter via ROS, which disrupts the lipid membrane and genetic materials, eventually leading to viral inactivation (Imani et al., 2020).

Since the initiation of the COVID-19 epidemic, new disinfectants and antiseptics formulations are being developed to limit disease transmission. As aforesaid, one of these changes is the use of NMs in their formulations (Abd Elkodous et al., 2020).

The action mechanism of NMs against the COVID-19 virus could be classified in distinct stages, before and after the viral entry inside the host cell (Fig. 1). Various kinds of NMs, like polymeric or virus-like NMs (Abd Elkodous et al., 2020), can inhibit the entrance of the virus inside the host cell by preventing it from attaching to the angiotensin-converting enzyme 2 (ACE2), which is the host cell receptor or the spike protein of the virus, through which the virus penetrates via the clathrin-mediated endosomal pathway (Almasi & Mohammadipanah, 2020). The spike protein NMs of virus can inhibit the viral entry or provoke the immune system to produce antibodies against it. Moreover, liposomes and nanoemulsions could break down the lipid bilayer envelope, which destroys its structure. Inorganic NMs could also produce extracellular ROS to kill viruses. Once the virus enters the host cell, Nanomaterials could provoke ROS, improve the propagation of lymphocytes, cytokines overexpression (IL-1B), and the generation of neutralizing (IL-4, IL-5, and IL-13) or opsonizing (C4b, IgE, C3b, and IgG) antibodies via Th1 or Th2 immune reactions, respectively (Abd Elkodous et al., 2020).

Approved Nanomaterial-Based Disinfectants

The antimicrobial activity of NMs depends on numerous factors, including (i) size of the NMs, since there is an optimum size that results in optimum antimicrobial activity because of the quantum size effect (Morones et al., 2005). The size difference between the NMs (10^{-9} m) and microorganisms (10^{-6} m) favors the antimicrobial action because some NMs can penetrate through the cell membrane. (ii) the shape of the NMs, since the more faceted the particle, the greater its antimicrobial efficiency due to more outstanding adhesion and contact with microorganisms (Cacciatore et al., 2020; Pal et al., 2007). (iii) surface charge, since the electrostatic interactions are favored when the NM has positive zeta potential as microorganisms present negatively charged bacterial wall. (iv) microbial sensitivity to NMs, since the organisms have different sensitivity due to their morphology (Cacciatore et al., 2020). Some of the approved disinfectants containing NMs as the main component are shown in Table 3.

Nanomaterials with Antiviral Activity Against SARS-CoV-2

As mentioned in previous sections, the main NMs with anti-coronavirus features are Quantum dots, synthetic virus-like particles, nanostructured lipid carriers, polymeric nanocapsules, carbon nanotubes, carbon dots, metal nanoparticles, nanostars, and magnetic nanoparticles (Table 4). The effect of Lipid Nanoparticles (LNP) and Virus-Like Particles (VLP) on SARS-CoV-2 have often been investigated in cell line and animal models including HEK 293 T, HeLa, Vero E6, and Freestyle CHO-S cells and animal models like transgenic hACE2 mice, C57BL/6 mice, BALB/C mice, Rhesus macaques, and Syrian golden hamsters (Geng et al., 2021; Ma et al., 2020) (Table 4).

Toxic Effects of Nanomaterials on Health

Nanotoxicity concerns are primarily raised by tiny dimensions of nanotechnological NMs and are secondly correlated to type and duration of exposure, NM penetration depth, preferential localization, and local delivery and/or systemic translocation (Baroli, 2010). Studies have shown that NMs may provoke the fragmentation of chromosomes, DNA strand breakage, point mutations, and modifications in gene expression (Singh et al., 2009). The toxicological studies of NMs so far have shown that the entry of NMs through inhalation, ingestion, and skin is of utmost importance, respectively (Laux et al., 2018). Repeated application of

Table 2 Effective nanomaterial (NMs) on facing respiratory viruses

Nanomaterial	Measure (nm)	Antiviral activity	References
Polymeric NMs			
Poly(lacticcoglycolic acid) (PLGA)	225.4	Bovine parainfluenza type 3 virus (BPI3V)	Dhakal et al. (2017)
		Swine influenza virus (H1N2)	
Poly-γ-glutamic acid (γ- PGA)	100–200	Influenza (H1N1)	Sivasankarapillai et al. (2020)
	300–350	Influenza (H1N1)	
Chitosan	300–350	Influenza (H1N1)	Sivasankarapillai et al. (2020)
	571.7	Swine influenza virus (H1N2)	
N-(2-hydroxypropyl) methacrylamide/ N-isopropylacrylamide (HPMA/NIPAM)	12–25	Respiratory syncytial virus (RSV)	Francica et al. (2016) and Sivasankarapillai et al. (2020)
Self-assembling NMs based on peptide and proteins			
N nucleocapside protein of RSV	15	RSV	Sivasankarapillai et al. (2020)
Ferritin	12.5	Influenza (H1N1)	
Inorganic NMs			
Gold	12	Influenza	Sivasankarapillai et al. (2020)
Other NMs			
VLP	80–120	Influenza (H3N2, H5N1, H1N1)	Sivasankarapillai et al. (2020)
	80–120	Respiratory syncytial virus (RSV)	
Dilauroyl phosphatidyl choline (DLPC liposomes)	30–100	Influenza (H1N1)	

antiseptics can bring along the penetration of NMs through inhalation and skin. The entrance of NMs into the cells are demonstrated in Fig. 2.

Before any toxicological trial, a comprehensive and precise characterization of the contents of the nano-based antiseptics/disinfectants is essential. Duke et al. has proposed a three-stage solution for determining the properties of NMs, which includes (I) appearance properties of the composition like size, morphology, and surface area (II) dispersion properties including aggregation or agglomeration, and (III) interface of nano-bio (Laux et al., 2018).

Skin Adsorption

The skin is the most extensive (~ 10%) body part, which has a pivotal protective function (Crosera et al., 2009). The epidermis has a complicated structure consisting of composite physical and chemical systems and barriers at the nano- and micro-scale that, all together, form what is generally referred to as the defensive barrier.

Based on physicochemical features and integrity of barrier, NMs can enter the skin in four ways, including intracellular, extracellular, and two transappendageal via follicles of hair and sweat glands (Crosera et al., 2009). Sometimes skin exposure to NMs is intentional, such as dispersion of a liquid or creamy fluid (sunscreens having titanium or zinc oxides) or textiles (antimicrobial gauzes containing AgNPs) (Baroli, 2010) even though, allergic reactions also occur due to this penetration. Studies with macroscopically non-compromised skin showed that nanotechnological NMs mainly accumulate in SC (stratum corneum) and HF (hair follicle) infundibulum (Table 5). Even small permeation of agents inside the superficial strata of SC may lead to fatal reactions (Baroli, 2010). Figure 3 has been shown that NMs could induce cytotoxicity,genotoxicity, endothelial activation, and impairment of NOS signaling.

Epigenetic Effect

Inappropriate regulation of cellular epigenetic mechanisms can be deleterious to health making it a necessity to analyze the effect of NM exposure on epigenetic pathways. The mechanisms are methylation and hydroxymethylation of DNA, posttranslational adjustment of histones tails, remodeling of chromatin, methylation of RNA, and noncoding RNA. Epigenetic modifications, which can change in response to specific cellular and environmental status, could be permanent or even passed on to later generations (Table 6). Since these modifications play crucial roles in regulating various cellular activities like gene expression, DNA replication, and recombination, they could affect exposed people and their next generation (Sierra et al., 2016; Stoccoro et al., 2013) [52].

Cell Accumulation

NMs are being used due to their novel features, while nanotoxicological studies are relatively neglected. NMs could

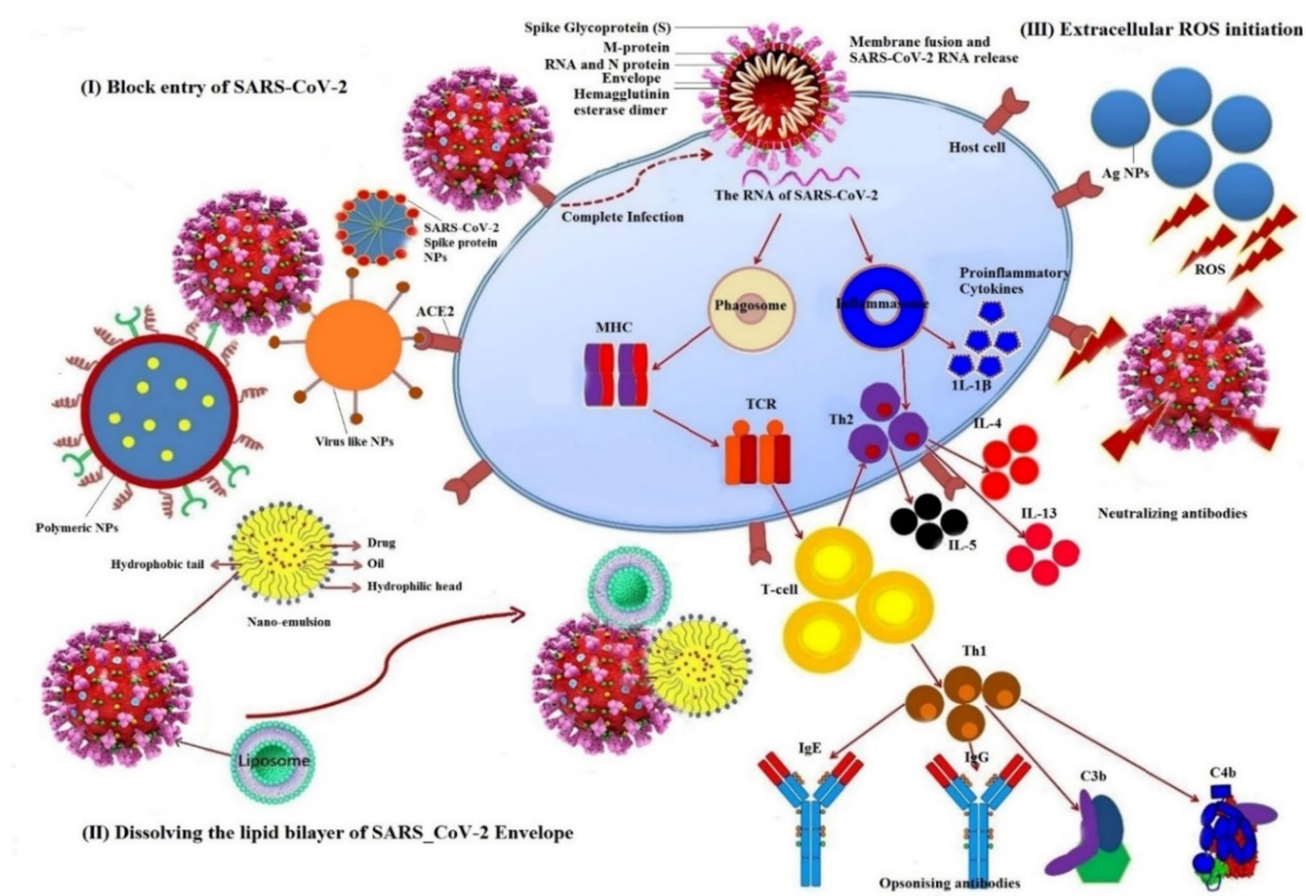

Fig. 1 Molecular targets of SARS-CoV-2 which could be inactivated by NMs. Mechanism of action outside the host cell includes (I) inhibiting the viral entry inside the cell, (II) solvation of the lipid bilayer envelope of it, and (III) production of ROS via inorganic NMs. Mechanisms of action inside of the cell are overexpression of cytokines, polyprotein processing, transcription of the viral genome, blockage of viral uncoating, translation of the viral protein, and the most common mechanisms are activation of transcription agents through receptor signaling as a response of viral RNA, and the production of (IL-1B), and activation of the Th2 route, which leads to the production of neutralizing antibodies, or Th1 route, leading to the production of opsonizing antibodies, which are shown above (Abd Elkodous et al., 2020)

enter the mucosal membrane by inhalation, and NMs lighter than 10 µm could rapidly penetrate the respiratory system. The extent of cellular destruction depends on the size of NMs, which means the smaller the NMs, the stronger their damage (Rai et al., 2020).

These NMs can accumulate in alveoli and cause inflammation in the lungs. Also, repeated exposure to them induces alveolar cell injuries, penetrates the blood vessels, and could be transmitted to other organs by systemic circulation (Rai et al., 2020).

Because there is no mechanism in the body to exclude the majority of NMs, NMs with low-solubility that have accumulated in the tissues and cells can remain for a longer duration. Metal NMs also reduce the viability of the cells and induce ROS, which leads to oxidative stress and cellular irreversible damages. The accumulated ROS inside the cell communicates with the cellular protein machinery and consequently can modify whole cellular processes, destroying mitochondria and nuclear DNA, leading to apoptosis (Cioffi & Rai, 2012; Rai, Ashok, et al., 2020; Rai, Bonde, et al., 2020).

Biological Accumulation

Detrimental effects of NMs on biology, particularly their toxic effects on plants, are among the most frequent study cases. NMs like carbon could even repress the plant nutrients absorption; others could restrain the content of plant protein, carotenoids, and chlorophyll. NMs can also be transferred from roots to leaves, entering the food chain. Generally, bioaccumulation factor (BAF) is a chemical mass per kg biomass in an organism to that in water (Hou, et al., 2013). As an example, Ag negatively affects the remediation process of the plant, ZnO, even at low concentration has a toxic effect

Table 3 The commercial NM-based products approved for surface or skin disinfection (https://statnano.com/)

Commercial name	Usage	Type of NMs	Company
NPS 100 & NPS-200	All types of fabrics, Shoes, Air/Water Purification Filters	Silver NMs	NANOBIZ.PL Ltd
Copper Dispersion Antibacterial Coating	Hospitals, Personal protective equipment, Surface Coatings	Copper NMs	Nanoshel LLC
Klenz Shoes Sanitizer	Shoes sanitizer	Silver NMs	Maha Corporation
Gel antiseptic nanoparticulate silver	Hand sanitizer	Silver NMs	M9 Ltd
Soap antibacterial facial and body treatments with NMs of silver	Skin sanitizer	Silver NMs	M9 Ltd
Nanover Dishwashing detergent	Dishwashing detergent	Silver NMs	Nanogist Co., Ltd
Nanover Disinfectant Spray	Surface disinfectant/household goods sanitizer	Silver NMs	Nanogist Co., Ltd
Nanover Laundry detergent	Laundry detergent	Silver NMs	Nanogist Co., Ltd
Nanover Mouth wash	Mouth wash	Silver NMs	Nanogist Co., Ltd
Sanitizer (hand carry)	Hand sanitizer	Essential oils nanoemulsion	Shepros SDN. BHD
Defenser Series-Respirator masks	Mask disinfectant	Silver and copper NMs	Nexera Medical-Canada
MVX Nano Mask	Mask disinfectant	Titanium and silver zeolite NMs	MVX Prime Ltd

Table 4 Nanomaterials with anti-coronavirus activity (Carvalho & Conte-Junior, 2021)

NMs	Size	Shape	Effective dose	Application
Ag	Colloids: 10 nm Nanoparticles: < 20 nm	Spherical	3.125–12.5 (μg/mL)	Antiviral therapy
Tellurium nanostars	57 nm	Triangular star shape	15 (μg/mL)	Antiviral agents
TiO2 Nanoparticles	Not Reported	Predominantly spherical	300 (mg/mL)	Self-cleaning surfaces
Gold nanoparticles	Not Reported	Peptide-functionalized gold nanoparticles	Not Reported	Antiviral agents
Nano-sized formazans	23.75 ± 7.16 nm	Formazan analogs by dithizone and α-haloketones reaction	Not Reported	Antiviral agents
Carboxyl quantum dots	20 nm	Spherical	Not Reported	Antiviral agent
L-PLGA	Not Reported	Not reported	Not Reported	Antiviral therapy
Silica-copper nanoparticles	Not Reported	Spherical	Not Reported	Superhydrophobic self-cleaning surfaces
Polymeric nanoparticles	Not Reported	Not reported	Not Reported	Antiviral drug
ZnS-NPs	3.8 nm	Spherical	0.1 mM	Antiviral drugs
Silver-sulfide nanoclusters	5.3 nm	Spherical	Not Reported	Antiviral drugs

on Hydrilla verticillata and Phragmites, and Ag, CeO2, Co, and Ni influence Ocimum basilicum L's fresh weight (Zhu et al., 2019).

Environmental Impact of the NM Containing Wastes

Despite the progress mentioned earlier in NM technology, data on the potential impacts of NMs on personal health is insufficient. The remediation process of NMs is essential because they are not detectable and may have long-term destructive effects on the environment by their persistent presence in the environment. Although some approaches such as green nanoscience have been introduced to decrease the detrimental outcomes of NMs on health and the ecosystem, their environmental discharge must be avoided (Iavicoli et al., 2014; Kabir et al., 2018).

NMs with various shapes as free NMs, functionalized NMs, aggregates, or embedded in a matrix can be found in the ecosystem (Nowack & Bucheli, 2007). The fate of NMs in environmental conditions is related to their interactions with different contaminants and their physicochemical features (Kabir et al., 2018; Maiti et al., 2016). According to their type, they may be discharged into the air and persisted in aerosols and the soil, sediment, and surface water for a long time or absorbed by organic molecules or biological systems. Therefore, their accumulation can cause an

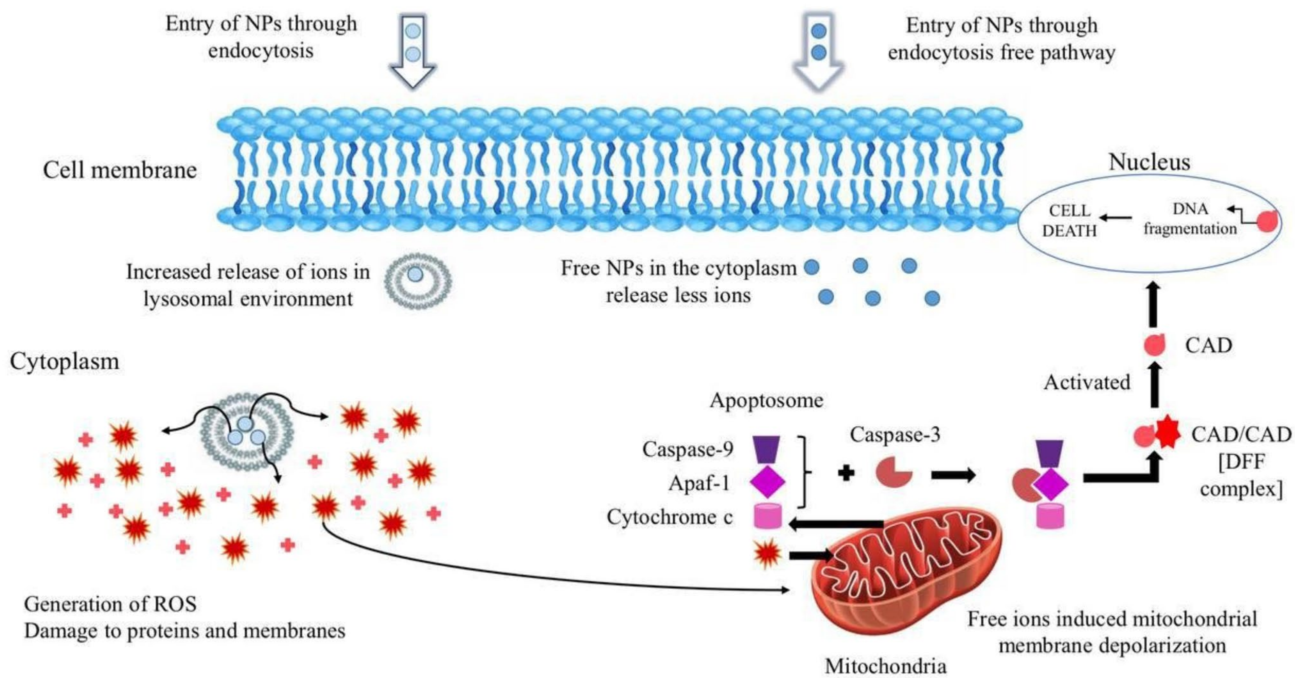

Fig. 2 NMs enter into the cells through endocytosis and endocytosis-free pathway. The endocytosis pathway can provoke intensive harm to the cell in contrast with the other one. The acidic environment of the lysosome leads to the burst discharge of NMs that interact with the proteins of cytosol and other molecules producing ROS, which mediate oxidative stress into the mitochondria, so cytochrome c is discharged. Discharged cytochrome c connects to Apaf-1, which stimulates the caspase cascade reaching to caspase-dependent apoptosis, leading to cell death and DNA fragmentation (Zielińska et al., 2020)

ecotoxicological risk, biodegradation, or bioaccumulation in the food chain. In this part, we present the destiny of NMs in various environmental matrices.

Air There is not enough information concerning the environmental destiny of NMs, particularly after releasing into the atmosphere. In all phases of the life cycle of NMs (e.g. generation, transportation, storage, and usage), it might swift release into the ambient atmosphere (Kabir et al., 2018).

Soil Soil is a multilayer matrix and complicated interface among several materials and organisms. Since NMs have a large surface area, NMs can adhere to the particles of the soil. Moreover, large aggregates of NMs through precipitation and purification could be immobilized in small holes. Plants could absorb and transport NMs from the soil, thereby affecting the germination and plant growth (Hong et al., 2014; Khodakovskaya et al., 2009).

Water NMs could immediately enter the aquatic ecosystems through industrial discharge, dumping of wastewater, and surface runoff from soils (Batley et al., 2011; Kabir et al., 2018). Several factors such as aggregation, distribution, reactions among different elements, organic matter, and aerobic, anaerobic, and abiotic degradation may influence the concentration of NMs in aquatic ecosystems. Exposure of NMs to aquatic organisms poses many detrimental consequences, such as DNA fragmentation,, oxidative pressure, and growth reduction (Kabir et al., 2018).

Concluding Remarks

Numerous reports are available demonstrating remarkable bioactivities of NMs, including antiviral activity against RNA viruses, due to their unique physicochemical properties. Due to its potent antiviral nature, specific NMs have been used to prepare various nano-based disinfectants and antiseptics.

In this report, the latest advancement in studying NMs and disinfectants are discussed from three perspectives: positive impacts, toxicity, and their mechanisms of action. The type of nanomaterial that has been studied for augmentation of antiseptics and disinfectants included polymeric, self-assembling proteins, inorganic and peptide-based among which inorganic nanomaterial are more frequently studied and applied for these purposes.

Despite this remarkable antiviral effect at low concentration, there is a serious consequence in the long-term application of nanomaterial in the antiseptic formulation which has been underestimated. Although NMs have molecular targets

Table 5 The skin absorption studies of NMs

Composite (Size nm)	Module of the study		Outcome	Reference
	In vitro	In vivo		
Polystyrene NMs (20–200)	Vertical diffusion cells by whole-width the skin of ear of porcine	Not Reported	The aggregation of NMs in follicular openings	Alvarez-Román et al. (2004)
Titanium Dioxide	Human volunteers—tape stripping	Diffusion cells by human epidermis plus cultivated skin	Microfine titanium dioxide entered through the follicles of hair	Bennat and Müller-Goymann (2000)
Titanium Dioxide (20)	Human volunteers— tape stripping	Static diffusion cells with human skin	Titanium dioxide could not infiltrate into the viable skin layers	Mavon et al. (2006)
Zinc Oxide (15 to 40)	Not Reported	Franz diffusion cells with human epidermis	There were no NMs in the deeper layer of corneum or epiderm	Cross et al. (2007)
Silver (25)	Not Reported	Full-thickness human epidermis with Franz diffusion cells	Penetration may occur via damaged skin	Larese et al. (2009)
4 various formulations comprising Titanium Dioxide	The biopsies of pig skin	Not Reported	Penetration of NMs within granulosum layer through intercellular area	Menzel et al. (2004)
Ellipsoid (4.6) and Spherical QD (12×6)	Not Reported	Porcine skin within flow-through cells	Quantum Dots of various forms and surface coatings may enter intact skin in an appropriate dosage (62.5 pmol per cm^2)	Ryman-Rasmussen et al. (2006)
Gold (15, 102, and 198)	Not Reported	Franz cells with ratepidermis	The permeability and diffusion coefficient decrease with the increase in the size of gold NMs	Sonavane et al. (2008)

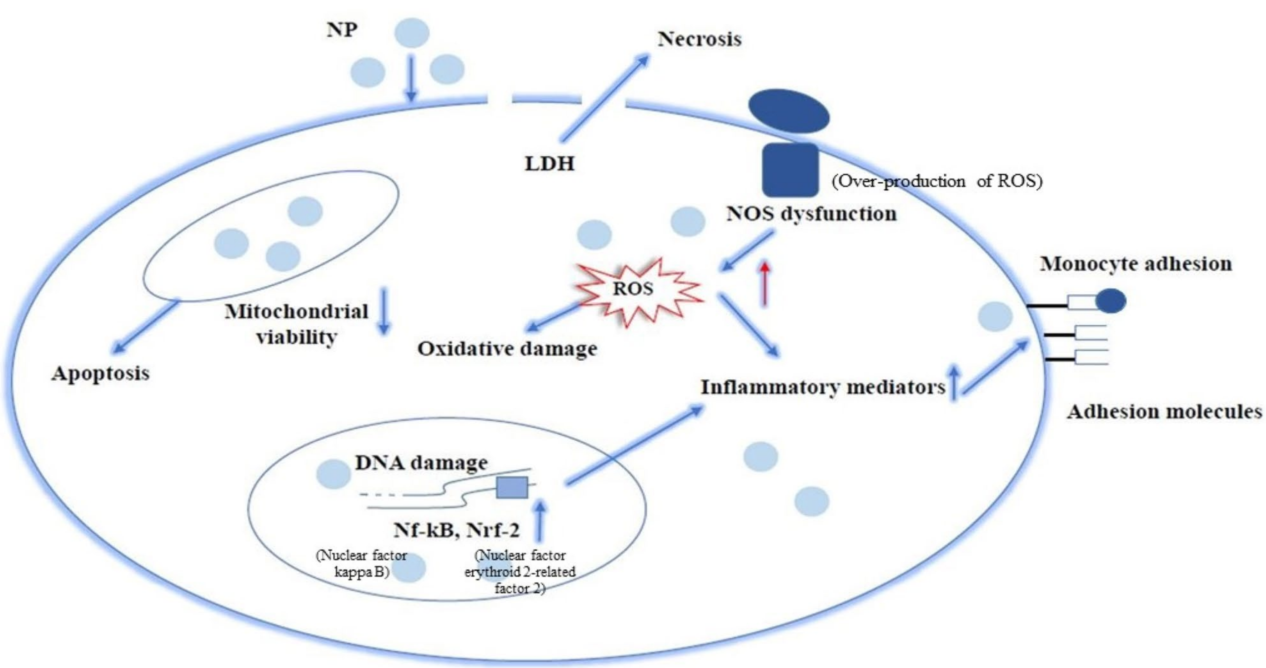

Fig. 3 Schematic illustration of toxic effects of NMs on endothelial cells. NMs could provoke cytotoxicity (necrosis, apoptosis), genotoxicity (DNA destruction), the activation of endothelial (adhesion molecules, the adhesion of monocyte), and NOS dysfunction (overproduction of ROS) in endothelial cells. *LDH* Lactate dehydrogenase, *NOS* Endothelial nitric oxide synthase (Zielińska et al., 2020)

Table 6 Epigenetic effects of some NMs and their current applications

NMs	Common applications	Epigenetic effect	NM properties			Reference
			Form	Size (nm)	Charge	
Silver	Antimicrobial agent to prevent wound infection and formation of dental plaque biofilms	Reduced histone methylation (H3K4me3 and H3K79me1)	Spherical	25–30	Negative	Qian et al. (2015)
	Ultrasensitive recognition of biomarkers	Modified DNA methylation	ND	3–20	− 28 mV	Mytych et al. (2017)
	Food covering for longer shelf life Anti-caking matter in powder goods like salt	mi-RNA expression changes	ND	< 100	ND	Eom et al. (2014)
	Bactericidal textiles like socks and towels	Modified HDAC activity	Spherical	10, 25–30, and 80	ND	Braydich-Stolle et al. (2010)
Gold	Transfer carriers in biomedicine	The changes of expression on mi-RNA	Spherical	40, 100	ND	Balansky et al. (2013)
	Contrast factors in imaging techniques	Condensation and reconstitution of chromatin and expression changes of mi-RNA	ND	20	ND	Ng et al. (2011)
Quantum dots	Imaging based on Fluorescence	Deacetylation of Histone	ND	ND	ND	Choi et al. (2008)
	Anticancer purpose applying photodynamic UV or photothermal therapy	Modifications of Histone	ND	3.4	Negative	Conroy et al. (2008)
Silica	Lighter, more durable, and powerful than concrete, steel, stick, and crystal	Global genomic hypomethylation and reduced methyltransferase machinery	ND	15	ND	Gong et al. (2010)
	Nanosensors could be used to detect conversions caused via external agents	Hypermethylation and inactivity of poly ADP-ribose polymerase 1 (PARP-1) promoter	ND	15	ND	Gong et al. (2012)
Titanium dioxide	Sunscreen and cosmetics lotions	PARP-1 promoter hypermethylation	Spherical	22	− 29.8 mV	Choi et al. (2008)
	Bleaching agents applied in soaps, several kinds of toothpaste, and wet wipes	Changed the methylation machinery expression levels and long interspersed nuclear elements 1 (LINE1) and ALU* expression levels	Spherical	21.0	Negative	Lu et al. (2016)
	Remediation (elimination of organic contaminants of soil and water)	Dysfunction of methylation cycle	ND	10–100	ND	Tucci et al. (2013)
Copper oxide	Doping substances in semiconductors	Global DNA and transposable elements methylation changes	Spherical	58.7	Negative	Lu (2016)
	Chemical sensors	Hypermethylation of Alu	Spherical	58.7	Negative	Lu et al. (2016)

ND not defined, *HDAC* histone deacetylase, *ALU, *Arthrobacter luteus.*

and remarkable antiviral activity to inactivate several viral pathogens, these compounds have toxic effects on social health and the ecosystem due to the accumulation of their wastes in the environment and the inability to eliminate or detoxify them from the ecological cycles.

Some investigations have shown that these nanoparticles can produce critical impairment in respiratory sites and toxic effects on the skin, and even could weaken lung function. The oxidative stress, inflammation, fibrosis, and genotoxicity are among pathological consequences of the repeated exposure of human cell lines to nanomaterial (Imani et al., 2020).

As a result, the prevalent commercialization and usage of NM-based disinfectants during this pandemic can have long-lasting detrimental effects on human health and other animals, environmental microorganisms and plants in the ecosystem (Hossain et al., 2014; Imani et al., 2020; Zhu et al., 2019). According to multiple studies, these formations are influencing the environment by several mechanisms, e.g. (i) by raising the non-decomposable contamination level of air, soil, and water, (ii) through environmental accumulation, and (iii) via changing the life-cycle of living systems in the ecosystem (Kabir et al., 2018).

Future Perspective

The effect of NMs exposure is starting to be analyzed, and to reveal the full impact of such disclosure on human physiology, a great deal of effort needs to be made. However, precise prediction can calculate the toxicity potential of nanomaterial-based antivirals and decrease their long-term side effects. This prediction can be also achieved by a machine learning approach like the other lines of applications for control of SARS-CoV-2 (Sadeq et al., 2021).

Besides, the principal focus of later studies is to expand biocompatible and biodegradable NMs without any cytotoxicity, developing new techniques for nanotoxicology analysis, defining the level of exposure and level of discharge for different nanoparticles, understanding the biological effects of NMs in the environment.

Considering the ecological destiny and the possible consequence of NM on ecotoxicity, it appears essential to recognize the modifications of NMs during their diverse life cycle steps since they are capable of changing the toxic properties of substances in different conditions.

Moreover, NMs are extremely reactive constructions; they may interact with different contaminants and make more/less virulent forms. So investigations should also be included in the forthcoming analysis.

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Data Availability There is no experimental data for this paper and the inferred data from the cited references are included in the text of the paper.

Declarations

Conflict of interest There are no conflicts to declare.

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