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Nanomaterials as a therapeutic platform for COVID-19

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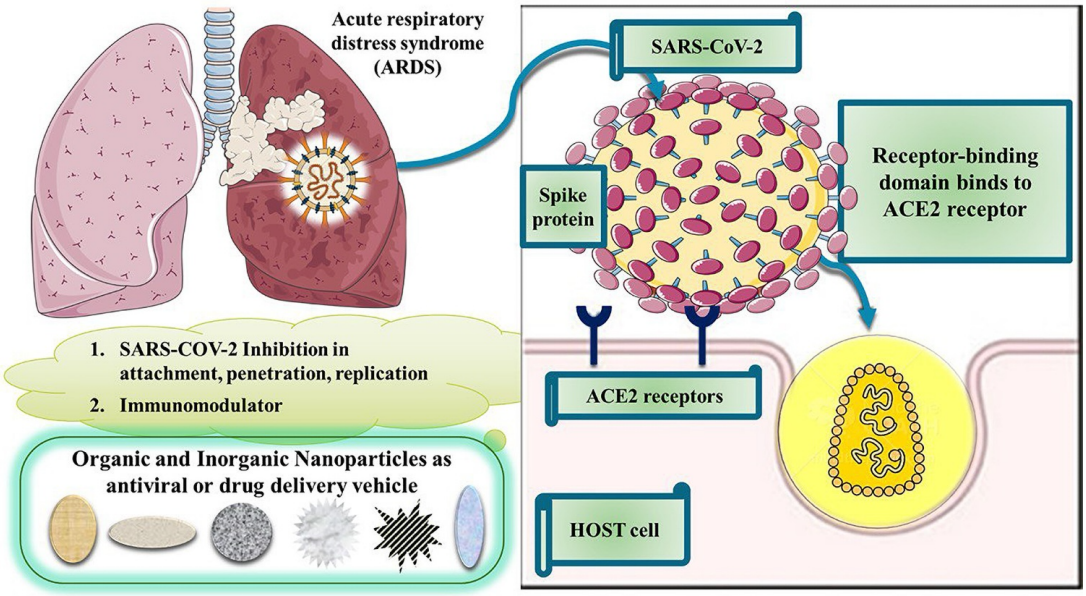
Graphical Abstract



Nanomaterials in the COVID-19 Era: A Promising Therapeutic Platform

Abstract

COVID-19 remains a major global health challenge, highlighting the urgent need for more effective treatments. Nanotechnology-based drug delivery systems provide a promising platform for overcoming the limitations of traditional antiviral, anti-inflammatory, and immunomodulatory therapies. Carefully designed nanocarriers can improve how drugs move through the body, reach target cells, and are taken up, increasing antiviral effectiveness and potentially lowering systemic toxicity. In addition to serving as carriers for approved antiviral drugs, many nanomaterials possess their own antiviral properties. Since dysregulated inflammation and cytokine storms are key factors in severe COVID-19, nanomedicine also offers ways to deliver anti-inflammatory and immunomodulatory agents directly to sites of immune activation, enabling more precise control of interleukin and cytokine release. This review covers recent developments in the design and use of nanocarriers and nanomaterials for the prevention, diagnosis, and treatment of COVID-19, and discusses future prospects for nanotechnology in the management of viral infections.

Keywords: COVID-19, SARS-CoV-2, immunopathology, nanomedicine, targeted drug delivery, repurposed nanotechnology, nanotechnology, nanoparticles

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Rationale, Purpose, and Limitations

This study explores the potential use of antiviral nanomaterials for managing COVID-19, focusing on intrinsic antiviral nanomaterials and the drug delivery of antiviral agents via nanomaterials. Nanomedicine in COVID-19 has been used mainly to improve vaccines and drug delivery, to offer novel antiviral platforms, and to enhance diagnostics, but its therapeutic use beyond vaccines remains largely experimental and faces substantial translational barriers. Its rationale lies in targeted delivery, immunomodulation, and virus-intercepting functions, while limitations include complex safety profiles, scale-up and regulatory challenges, and sparse robust clinical data for treatment indications.

Introduction

The Coronavirus Disease 2019 (COVID-19) originated in Wuhan [1] and quickly spread worldwide [2], causing acute respiratory disorders, including lung failure and pneumonia [3]. More than 700 million confirmed cases have been documented around the globe, with about 7 million confirmed deaths in 233 countries [4]. COVID-19 can cause symptoms ranging from flu-like illness to pneumonia, including fever, cough, sore throat, loss of smell or taste, and headache [5-7]. In critical cases, it could cause thrombosis [8], acute respiratory distress syndrome (ARDS) [9], septic shock, and multi-organ failure [10] before the patient died in serious situations [11].

Coronaviruses (CoVs) are classified into the positive-stranded RNA and crown-like appearance viruses with diameters of approximately 125 nm that belong to the Coronaviridae family [12-14]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new virus that can infect people, has just emerged and is currently causing the COVID-19 pandemic [15]. SARS-CoV-2 relies on the glycoprotein-spike protein (S), which is found in all CoVs [16], to enter the cell via attaching to angiotensin-converting enzyme 2 (ACE 2) [17]. ACE2 is involved in many organ functions, but it is rampant in the lungs, which are the most common site of COVID-19 infection [18-20].

Insights from Hill (2020) [21] highlight that ligand-directed nanostructures and SARS-CoV-2 converge in intracellular trafficking and signaling pathways. SARS-CoV-2 enters cells primarily through ACE2-mediated endocytosis, utilizing clathrin-coated pits and subsequently trafficking through endosomal and ER-associated compartments. These same pathways can be exploited by engineered nanostructures designed to interact with membrane receptors or specific peptide motifs. In particular, therapeutic nanostructures that incorporate cell-penetrating peptides or retrograde transport signals—such as the C-terminal KDEL motif—can be directed toward the Golgi–ER network. This is notable because SARS-CoV and SARS-CoV-2 also rely on the ER–Golgi intermediate compartment for translation, processing, and assembly of structural proteins. Co-localization of antiviral payloads with the same intracellular sites used for viral replication may therefore enhance therapeutic efficiency.

Antiviral agents can be used in the early phases, and immunomodulators can be prescribed in the end stages to restrain cytokine storms induced by host cells [22]. Despite the availability of several commercial antiviral medications, they still have limitations in protecting patients against the new coronavirus [23]. As a result, there is a worldwide need to develop new antiviral drugs or to enhance the delivery of existing therapeutic agents to manage or limit the progression of viral illnesses. To date, a few drugs, such as remdesivir, have had inconsistent effects [24]. Also, while dexamethasone [11] and tocilizumab [25] are used in the late stages of COVID-19, when inflammation arises, additional drugs and new therapeutic approaches are required to cure the disease.

Nanotechnology is a type of manipulation that can solve the challenges described above [26]. The advancement and enhancement of atomic/molecular structures with at least one dimension in the nanoscale range (1-100 nm) with changeable shape/morphology, size [27], and other features capable drug delivery to specific organs or cells without harming cells, crossing physiological barriers or deliver nanotherapeutic molecules to specific organs or cells, and interacting with biomolecules in the blood or within organs [28, 29]. Nanostructures have the potential to be used to target multiple phases of the viral life cycle, including attachment, penetration, replication, and budding [30].

One of the most critical requirements for any therapeutic agent, including nanoparticles and drug-loaded nanocarriers, is that it be delivered to the correct location at the right time and in acceptable quantities [33]. The use of nanomaterial-based drug-delivery systems in the treatment of the inflammatory stages of viral diseases can improve the selectivity of anti-inflammatory agents, such as dexamethasone, by targeting specific cells or tissues, thereby reducing off-target effects and toxicity [34]. In addition, nanomaterial-based drug-delivery systems can also be used to deliver antiviral agents directly to the site of infection, reducing the risk of off-target effects and improving drug efficacy [35]. Nanomaterials possess innate antiviral properties that enable them to interact with viral particles and disrupt their replication cycle [36]. The unique physicochemical properties of nanomaterials, such as their small size and large surface area, make them ideal candidates for developing antiviral agents [37-39].

The lessons learned from the COVID-19 pandemic can guide future research and development of nanomaterial-based drug-delivery systems for the treatment of both inflammatory and infectious stages of viral diseases. The use of nanomaterials as carriers for antiviral agents and as innate antiviral agents themselves offers significant promise for the treatment of viral diseases and improving patient outcomes. In light of the above, this review will explore the role of nanomaterials in the treatment of COVID-19 during the viral and inflammatory stages, as well as various viewpoints on this illness and the role of nanomaterials in each component.

Intrinsic antiviral nanomaterials

Nanomaterials have been used as antiviral agents or as delivery vehicles for antiviral drugs on several occasions (Figure 1) [40]. For example, silver nanoparticles (NPs) have been shown to have antiviral activity against a range of viruses, including coronaviruses [42]. Silver nanoparticles can disrupt viral membranes, preventing virus entry into host cells, and inhibit viral replication by interfering with viral RNA synthesis [43]. Other intrinsic antiviral nanomaterials investigated for their potential in COVID-19 treatment include copper nanoparticles and graphene oxide. Copper nanoparticles have broad-spectrum antiviral activity and can inhibit coronavirus replication by binding to viral RNA. Graphene oxide has also been shown to have antiviral activity against coronaviruses by binding to the spike protein on the viral surface [44, 45]. While much research remains to fully understand the mechanisms underlying the antiviral activity of these nanomaterials and their potential for clinical use, the development of intrinsic antiviral nanomaterials could provide a promising avenue for novel treatments for COVID-19 and other viral diseases.

Figure 1. *Classification of various types of nanomaterials as antiviral agents that could have high benefits for the treatment of COVID-19.*

Chitosan

Chitosan is a naturally occurring linear polysaccharide made up of -(14)-linked deacetylated D-glucosamine units. In case of SARS-CoV-2 therapy [46], silymarin-chitosan nanoparticles as an antiviral agent against SARS-CoV-2 were investigated *in silico* and *in vitro.* Based on the binding energies with spike protein and ACE2 and IC_{50} evaluation in virucidal/replication assays, silymarin-chitosan nanoparticles have high antiviral activity against SARS-CoV-2, more than chitosan nanoparticles [47]. However, based on the data from this study, chitosan nanoparticles have effects similar to those of remdesivir. Also, β-chitosan with a degree of acetylation below 10% has been reported to exhibit higher antiviral activity than α-chitosan [48, 49]. Presumably, this results in a parallel orientation, making the intermolecular hydrogen-bond network less dense. [50].

Moreover, chitosan derivatives, such as N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride (HTCC), have attracted attention

for their antiviral, antibacterial, and anti-inflammatory properties [51]. Different HTCCs, such as HTCC-63, have been shown to exhibit antiviral activity, particularly in preventing viral replication of SARS-CoV-2 and MERS-CoV *in vitro* [52, 53]. Antiviral polymeric medicines are commonly created to block the virus's interactions with the host cell. In fact, surprisingly, HTCC does not affect virus attachment to target cells via heat shock proteins *in vitro*, but effectively blocks subsequent interaction with cellular receptors, consistent with the strong interaction between the HTCC-63 polymer and the recombinant ectodomain of the S protein NL63. For instance, an *in vitro* study using the *LLC-Mk2 and MRC-5 cell lines demonstrated a significant decrease in HCoV-NL63 and HCoV-229E viral yields in the presence of equal-volume mixtures of HTCC-62/63 or HTCC-63/77* [54, 55].

Human papillomavirus, human immunodeficiency virus (HIV)-1, vesicular stomatitis virus, and Newcastle disease virus are all susceptible to sulfated chitosan and sulfated oligochitosan with 0.82-1.55 degrees of sulfate substitution. Through attaching to viral surface glycoprotein receptors or viral capsid proteins, they limit viral entry into host cells. This binding prevents viruses from binding to target cells and prevents virus-cell fusion. Alternatively, they suppress biological pathways in the host cell, such as the PI3K/Akt/mTOR pathway, thereby preventing the autophagy required for viral entry [56-58]. N-carboxymethylchitosan N, O-sulfate with 0.18 degree of N-carboxymethyl substitution is another chitosan derivative that could exert antiviral effects by which inhibition of HIV-1 replication in human T helper cells. HIV-1's surface protein is electrostatically drawn to and bound by the highly negatively charged and ampholytic NCMCS [59].

As a result, chitosan and its derivatives are considered effective inhibitors and therapeutic candidates for the highly pathogenic SARS-CoV-2 virus.

Silver nanoparticles

Silver (Ag) has long been known as an antibacterial material and has recently attracted attention as an antiviral against SARS-CoV-2 [42]. Ag NPs protect host cells from SARS-CoV-2 infection by inhibiting viral entry and pseudovirus infection through interference with viral integration (Figure 3) [42]. Although Ag NPs have been shown to interact with viral proteins on the surface of viruses to limit infection in the early stages by either inhibiting viral attachment or entry or by destroying surface proteins to compromise virion structural integrity, the actual viral-destroying mechanism of Ag NPs remains unknown. Moreover, Ag NPs have been shown to neutralize various strains of influenza and coronaviruses by physically binding to SARS-CoV-2 and inhibiting its entry into host cells. [60]. In another study, the antiviral effects of Ag NPs of polyvinylpyrrolidone, with sizes of 2-100 nm, at concentrations of 0.1 to 10 ppm in Vero cells have been evaluated. Indeed, at 10 nm Ag NPs-PVP, a larger percentage of viral replication inhibition was observed compared to other sizes and the control group (polyvinylpyrrolidone alone) [44]. Furthermore, from an inflammatory perspective, Ag NPs could reduce levels of pro-inflammatory cytokines such as IL-1, IL-6, and TNF-alpha, as well as pro-inflammatory chemokines. For example, mice treated with tannic acid-mediated Ag NPs exhibited better clinical scores and lower respiratory syncytial virus titers in vaginal tissues [44, 45].

In another approach, graphene oxide (GO) sheets containing silver nanoparticles prevented both non-enclosed and enveloped viruses from infecting cells. [61]. In fact, graphene-based nanomaterials are promising candidates for delivering antiviral medicines and exerting antiviral effects on their own due to their high surface area, high loading capacity, and exceptional mechanical strength [62]. In a recent cellular study, the antiviral activity of GO and GO-Ag was determined as the ratio of tissue culture infection dose (TCID50). The antiviral activity of graphene oxide-silver nanocomposites against enveloped viruses revealed that 0.1 mg/ml of graphene oxide-silver could prevent 24.8% of coronavirus infection [63]. It could only suppress encapsulated viruses at non-cytotoxic quantities [64]. Interestingly, compared with either GO or silver nanoparticles alone, the combination of GO and Ag NPs showed superior antiviral activity [63].

Nevertheless, it is essential to note that the development of nanomaterial-based antiviral therapies is still in its early stages, and much research remains to be done to understand their potential for clinical use fully. Nevertheless, lessons from the COVID-19 pandemic can

guide future research and development of antiviral nanomaterials for the treatment of future viral diseases. By investing in research and development, implementing effective public health measures, and exploring innovative approaches, we can improve our ability to detect, prevent, and control future viral outbreaks.

Figure 2 schematically shows graphene and graphene oxide-based nanocomposites as antiviral agents against SARS-CoV-2, an enveloped virus. Although Ag and Ag-related nanoparticles and nanomaterials have been extensively studied as antiviral agents, no clinically licensed antivirals are currently available due to the numerous and significant effects of silver particles, warranting further evaluation in subsequent laboratory and clinical studies.

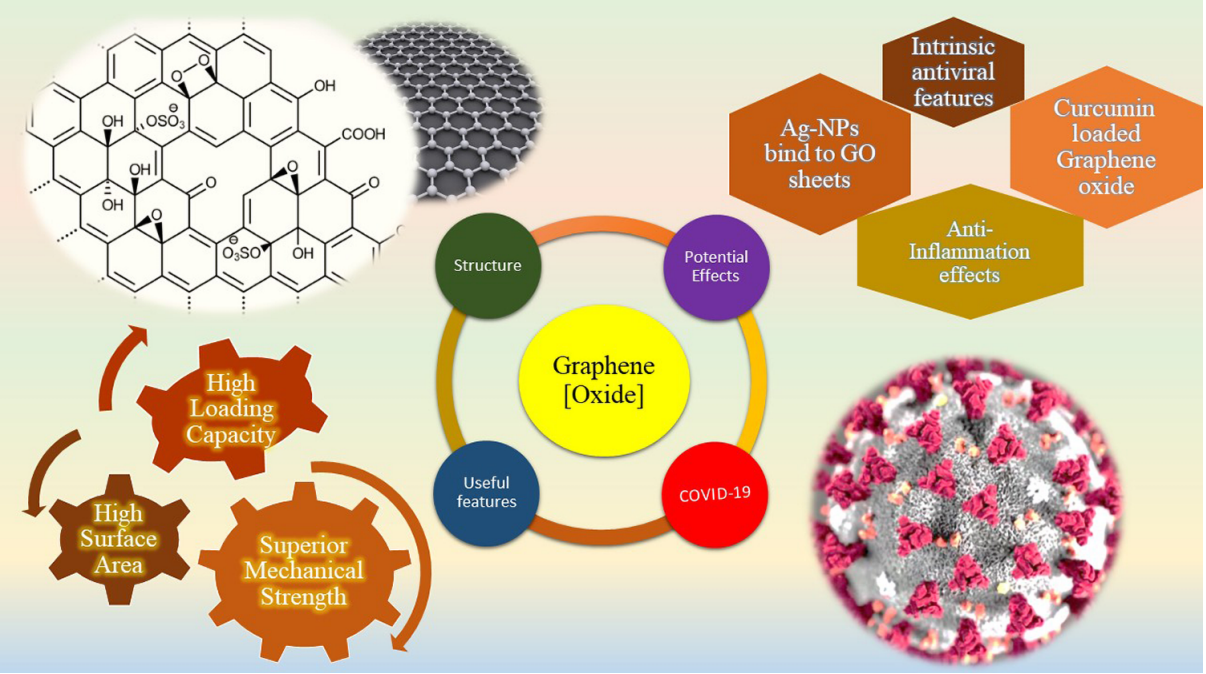

Figure 2: Graphene oxide as a carrier to fight COVID-19.

Gold nanoparticles

Gold nanoparticles (Au NPs) have attracted interest for a variety of clinical applications. Various investigations have shown that Au NPs exhibit antiviral and anticancer properties [65].

Inhibitory efficacy of functionalized gold nanoparticles (Au NPs) against SARS-CoV-2 was investigated, revealing that Au nanoparticle-conjugated peptide (Au NP-Pep) effectively inhibits the receptor-binding domain (RBD) of the virus. The study showed that Au NP-Pep reduces RBD fluctuation more than ACE2, indicating a stronger interaction [66].

Zinc oxide nanoparticles

Zinc oxide (ZnO) nanoparticles are a form of metal nanoparticle that have shown to be effective against a variety of microorganisms and viruses. ZnOTs (zinc oxide tetrapods) dramatically reduce the entry of Herpes simplex virus type 2 into target cells and thereby prevent viral spread [67, 68]. In this study, anti-influenza activity was determined by TCID50 and quantitative Real-Time Polymerase Chain Reaction (PCR) assays. Post-exposure of influenza virus with PEGylated ZnO-NPs and bare ZnO-NPs at the highest non-toxic concentrations could lead to 2.8 and 1.2 $\log_{10}$ TCID50 reduction in virus titer when compared to the virus control, respectively. In fact, PEGylated ZnO-NPs could be a novel, effective, and promising antiviral agent against H1N1 influenza virus infection.

On the other hand, from an in silico atomic docking perspective, a conceivable association between ZnO-NPs and the ACE2 receptor, a COVID-19 target, could occur [69, 70]. The obtained results propose the promising potential of the portrayed ZnO-NPs for respiratory parcel contamination flare-ups, acting either as an independent option or in combination with other pharmacologically potent agents for advanced experimentation and innovation advancement.

Of note, based on many clinical trials, zinc in its simple form, without nanoparticles, has no beneficial effects in the antiviral or inflammatory phase [71-73]. In light of ZnO-NPs' extraordinary features, they could have been used for further studies on COVID-19 treatment, in combination with zinc alone.

Iron oxide nanoparticles

Iron oxide nanoparticles (NPs), which are biocompatible and have FDA approval for the treatment of anemia, have shown antiviral activity against the Dengue virus [74, 75], influenza virus (H1N1) [76], and rotavirus [77]. Recently, **a** molecular docking study on iron oxide NPs demonstrated that both Fe_2O_3 and Fe_3O_4 nanoparticles are suitable candidates for interacting with the S1-RBD of SARS-CoV-2 and inactivating the virus (Figure 3) [78]. In fact, the structure of the chimeric S-RBD of SARS-CoV-2 was docked with Fe_2O_3 and Fe3O4. The energy minimization was calculated using "Ligand Preparation Protocol". Interestingly, although the antiviral effects of these nanoparticles can be inferred from this computer study, they were not observed against the hepatitis C virus (HCV). Indeed, the binding free energy of Fe3O4 is lower than that of Fe2O3, with values of -10.66 Kcal/mol and -8.97 Kcal/mol, respectively.

This data indicates greater stability for the Fe3O4 S1-RBD complex. Therefore, the FDA-approved iron oxide NPs may warrant further studies as a treatment for COVID-19.

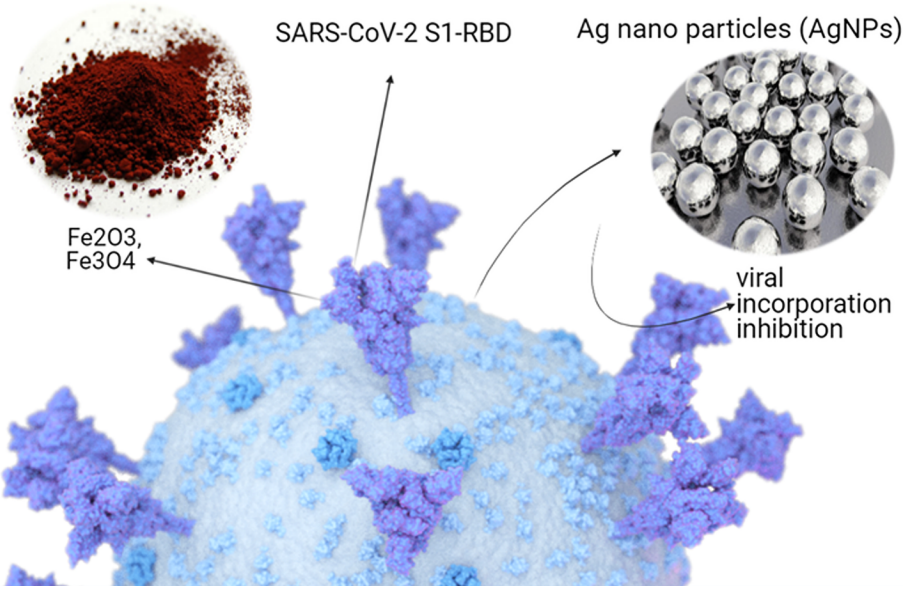

Figure 3: Ag NPs and iron oxides as good antiviral nanomaterial options to combat COVID-19.

Drug delivery of antiviral agents using nanomaterials

Nanosystems are 10-1000 nm in size. [79, 80]. The main goals of the nanoparticle drug-delivery system preparation include controlling the drug size and surface properties, and drug release at the site of action with desirable speed and dose [81]. Drug-delivery nanosystems can enhance drug kinetics and improve drug biodistribution in the target tissue, thereby increasing the drug's therapeutic index [82, 83]. Moreover, drug side effects are reduced by targeted delivery to the site of action and lower concentrations in healthy tissues. Many nanocarriers can increase the solubility of hydrophobic drugs in aqueous media, enabling intravenous administration. Drug-delivery systems can enhance the stability of many therapeutic agents, including small hydrophobic molecules, peptides, and oligonucleotides [84, 85]. Different therapeutic antiviral agents are presented in Figure 4. In the following, the use of nanodelivery systems for some antiviral agents is discussed and summarized in Table 1.

Hydroxychloroquine

Hydroxychloroquine is a medicine previously used as an antimalarial medication and for the treatment of some autoimmune diseases [86]. The medicine has shown inhibitory activity against SARS-CoV-1 and SARS-CoV-2 *in vitro* [87]. After the Coronavirus outbreak,

studies focused more on the delivery of antiviral drugs using nanomaterials to treat this new disease. Hydroxychloroquine could have antiviral impacts both pre- and post-infection.

Besides, this drug can also inhibit cytokine storm by reducing CD154 expression in T cells. Although the preventive dose of this drug prescribed for patients with COVID-19 has few positive effects, this may be due to low drug concentration in the lungs, which reduces its antiviral effects. However, an increased oral dose of this drug could result in side effects such as cardiac complications. Tai & Wu designed an inhalable liposomal formulation of hydroxychloroquine and examined it in vivo, revealing that it could achieve higher lung drug concentrations and reduce heart distribution and systemic exposure. The results of this preclinical study indicate that inhalable liposomal hydroxychloroquine could have antiviral effects at lower, safer doses [88].

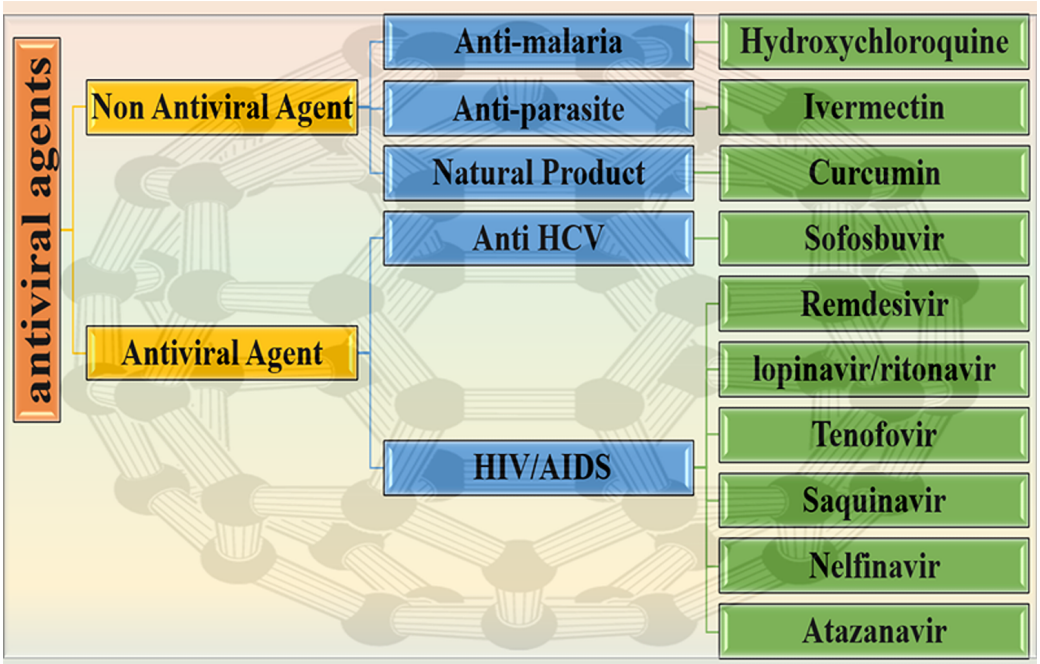

Figure 4. Classification of antiviral agents that use nanomaterials could have more positive effects on the treatment of COVID-19.

Ivermectin

Ivermectin has various therapeutic effects, including antiviral, antiparasitic, antimicrobial, and anticancer. Recent studies indicate that this drug has antiviral effects against a range of viruses, including the Zika virus, influenza A virus, tick-borne encephalitis virus, and SARS-CoV-2. Hence, the hope for finding a suitable treatment for COVID-19 was raised [89, 90]. Although preliminary clinical trials of this drug yielded promising results, it has many pharmacokinetic issues, including low water solubility [91]. It has been observed that ivermectin is associated with improved survival and somewhat lower mortality in hospitalized patients with COVID-19 [92]. Also, in other studies, ivermectin has been shown to inhibit SARS-CoV-2 *in vitro*; at a concentration of 5 µM, it reduces viral RNA by 5000-fold after 48 hours [93]. Of course, the objection to this study concerns that the plasma concentration of ivermectin will not reach the IC50 reported in the study, even if ivermectin were prescribed at 10 times the usual dose, or if it were prescribed again [94]. As a result, a novel drug-delivery strategy can address the challenge of delivering drugs to target tissues and overcome limitations, such as ivermectin's undesirable water solubility. So, nanocarriers can be a good option for optimizing ivermectin's bioavailability [95]. Polymeric nanoparticles are emerging as a means of controlled, sustained drug delivery, even in the face of environmental changes such as temperature and pH. Poly (lactic-co-glycolic acid) (PLGA) has been used to encapsulate ivermectin for the treatment of Brugian filariasis. *In vitro* studies show that it exhibits an initial burst release followed by a single stage of sustained release

[96]. The use of poly(lactide-co-glycolide)-b-poly (ethylene glycol) (PLGA-b-PEG) core-shell nanoparticles enables the complete entrapment of low-water-soluble ivermectin, leading to the prolongation of ivermectin's half-life and circulation time. This orally administrable nanoformulation of ivermectin exhibited sustained-release properties and improved ivermectin's therapeutic index for Zika virus [97].

Nanostructured lipid carriers (NLCs) have also been used to deliver ivermectin for the treatment of hydatidosis. NLCs comprise a solid lipid matrix containing a liquid lipid, offering advantages such as controlled and sustained release [98]. Mucoadhesive nano-suspension of ivermectin intranasal spray in patients with COVID-19 showed that local use of ivermectin in this formulation was safe and effective in patients suffering mildly from COVID-19. Also, it will lead to viral clearance and improvement in patients' respiratory symptoms [99].

Curcumin

Curcumin is a hydrophobic natural compound that has shown beneficial effects against many viruses, including influenza and syncytial virus. It has also been reported that adjuvant curcumin treatment is effective against SARS-CoV-2 [100]. According to numerous studies, curcumin is safe and well-tolerated in both healthy individuals and patients [101]. The use of a curcumin nanoformulation will increase stability, reduce cellular efflux, enhance solubility, enhance absorption, and improve targeted drug delivery [102]. A study showed that an oral soft-gel capsule containing curcumin nanomicelles (Sinacurcumin®) can reduce the time to resolution of COVID-19, reduce symptoms, improve oxygenation, and shorten hospitalization duration compared to the control group [103].

Remdesivir

Remdesivir is a broad-spectrum antiviral agent against RNA viruses. This drug has shown antiviral effects on SARS-CoV-2. Remdesivir is a prodrug that is converted to its active form in the body and inhibits viral RNA polymerase, as well as preventing viral exonuclease correction [104]. Remdesivir is the first FDA-approved treatment for COVID-19. However, remdesivir does not show a highly effective therapeutic effect in the lungs due to low drug levels after intravenous injection and low expression of enzymes required for remdesivir activation.

Another problem is that remdesivir has very low solubility. Therefore, a study investigated the preparation and evaluation of a liposomal remdesivir inhalation solution, which showed that liposomal remdesivir significantly increases the concentration of the remdesivir-active metabolite, nucleotide triphosphate (NTP), and enhances drug accumulation in the lungs. Also, it proposes a better safety profile [105].

Lopinavir/Ritonavir

Lopinavir/ritonavir combination therapy has been used safely to treat HIV. Lopinavir/ritonavir also proposed promising effects in animal and clinical studies against SARS-CoV and MERS-CoV. The viral load was significantly lower in this group than in the control group. Lopinavir/ritonavir showed significant inhibitory effects on SARS-CoV-2 at normal plasma concentrations *in vitro*. Lopinavir shows low oral bioavailability. The main contributors to the low oral bioavailability are P-glycoprotein (P-gp) efflux transport and high first-pass metabolism by CYP450 3A enzymes. In most drugs available on the market, lopinavir is prescribed because it inhibits the CYP3A enzyme in combination with a sub-therapeutic dose of ritonavir. However, this may lead to ritonavir side effects such as hyperlipidemia, glucose intolerance, gastrointestinal intolerance, and perioral paresthesia. Therefore, there is a need for a ritonavir-free strategy to improve lopinavir's oral bioavailability. A study showed that lopinavir solid lipid nanoparticles (SLNs) could improve their oral bioavailability [106]. Also, a study investigated the preparation and evaluation of encapsulated lopinavir and ritonavir using in situ self-assembled nanoparticles for long-acting subcutaneous injection, demonstrating sustained release *in vitro* and in vivo. Therefore, this formulation has a high potential for injectable nanoformulations of lopinavir and ritonavir, with a constant dose and long-acting effects [107].

Lessons learned from the COVID-19 pandemic can inform future research and development of nanomaterial-based carriers for antiviral drugs. By investing in research and development, implementing effective public health measures, and exploring innovative approaches, we can improve our ability to detect, prevent, and control future viral outbreaks. The

use of nanomaterials as carriers for antiviral drugs has the potential to revolutionize the treatment of viral diseases and improve patient outcomes.

Tenofovir

Tenofovir is a nucleotide analogue used for several decades in combination with emtricitabine for the treatment of HIV and hepatitis B virus, as well as the prevention of HIV. Tenofovir exerts its effect through the RNA-dependent RNA polymerase (RdRp), which is a necessary enzyme for SARS-CoV-2 [108]. Studies show that using tenofovir rather than hydroxychloroquine reduces hospitalization duration, mechanical ventilation, and mortality [109]. It has been claimed that tenofovir nanoemulsions can lead to an evolution in HIV treatment following an increase in drug diffusion and reduction of administration frequency. Also, in an animal study, tenofovir nanoemulsions exhibited the same toxicity as tenofovir [110].

Sofosbuvir

Sofosbuvir is a direct-acting antiviral agent that inhibits the NS5B RNA-dependent RNA polymerase (RdRp), and its efficacy has been confirmed in chronic HCV treatment. Sofosbuvir is likely an appropriate treatment option for COVID-19, as there are similarities between the HCV replication mechanism and that of coronaviruses [111]. Also, it has been reported that sofosbuvir, when combined with daclatasvir, reduces the number of patients with fatigue and shortness of breath after 30 days [112]. In research, combinations of polyvinyl alcohol (PVA) and chitosan biopolymers have been used to create nanohybrid materials (NHMs) for the delivery of the sofosbuvir drug. NHM of biopolymers exhibits biodegradability, nontoxicity, biocompatibility, antioxidant properties, and a high electron density. Also, PVA and chitosan are the most common biopolymers because they have bioactivity, antibacterial, and antifungal properties. Also, they have functional groups on their surfaces that facilitate drug loading and enhance absorption. Using PVA and chitosan nanohybrid for sofosbuvir delivery will lead to an increase in efficacy [113]. Considering the aforementioned, using this formulation in patients with COVID-19 may offer advantages that warrant further testing and validation.

Nelfinavir

Nelfinavir is a protease inhibitor confirmed by the FDA in 1997 to be used in the treatment of HIV infection in children over two years old and also in adults [114]. *In vitro* studies show that nelfinavir has an excellent inhibitory effect on SARS-CoV-2 replication [115]. Nelfinavir has disadvantages, such as low water solubility and low permeability. This is why PLGA nanoparticles have been used for the delivery of nelfinavir. The results show that the new formulation increases the oral bioavailability and therapeutic effect of nelfinavir [116].

Atazanavir

Atazanavir is a protease inhibitor used in HIV treatment in combination with other medicines [117]. Atazanavir can also inhibit various SARS-CoV-2 proteins [118]. It has been observed that a daily dosage of atazanavir will lead to serious liver problems. Also, one disadvantage of atazanavir in conventional oral dosage forms is its short duration of action, as the drug's absorption depends on its residence time in the gastrointestinal tract. In a study, Eudragit RL 100 nanoparticles were used for atazanavir loading. *In vitro* studies show a considerable increase in the speed and amount of atazanavir absorption [119].

Also, self-nanoemulsifying drug-delivery systems, as lipid-based nanocarriers that have recently shown effective roles in oral drug delivery, were used in another study to deliver atazanavir, leading to increased atazanavir bioavailability [120]. Using these two new formulations appears to be more effective than conventional oral atazanavir in patients with COVID-19.

Saquinavir

Saquinavir is a protease inhibitor that inhibits cathepsin L activity. Cathepsin L is an endosomal cysteine protease that plays a role in cleaving the S1 subunit of the coronavirus surface spike glycoprotein. Such cleavage is necessary for coronavirus entry into human host cells and for virus/host cell endosome membrane fusion [121]. Saquinavir has low bioavailability.

It was shown in a study that a gold nanoparticle-saquinavir conjugate will lead to an efficacy increase and sustained drug release [122]. As explained, the intrinsic antiviral properties of Ag nanoparticles alone have antiviral effects, and their use in combination with saquinavir

can be an appropriate therapeutic option for patients suffering from Covid-19. Hydroxypropyl-β-cyclodextrin and poly (alkyl cyanoacrylate) nanoparticles were used in a study for oral administration of saquinavir to treat HIV infection. This study revealed that using cyclodextrins has improved the loading capacity of nanoparticles [123].

Table 1: Utilizing nanomaterials as carriers for drug delivery of antiviral agents in COVID-19 patients.

Therapeutic agents	Nanocarriers	Situation (Study Type)	Advantages	Ref.
Hydroxychloroquine	magnetic nanoparticles	*in vitro* study	improved absorption and controlled drug release	[124]
ivermectin	polymeric nanoparticles (Alginate chitosan nanoparticles)	*in vitro*	sustained release	[125]
Remdesivir	remdesivir-PLGA core/lisinopril shell nanoparticles	computational molecular dynamic study	increase potency and reduce side effects	[126]
Favipiravir	solid lipid nanoparticles	*in vitro*	local delivery	[127]
Tenofovir	tenofovir into stable ProTide nanocrystals	*in vitro* and *in vivo* study	increases intracellular uptake and retention	[128]
Ribavirin	polymer nanoparticle poly (glycerol-adipate) as a drug-delivery system for ribavirin	*in vitro*	increase effectiveness in the management of viral infections through reducing ribavirin accumulation in red blood cells	[129]
Saquinavir	poly (ethylene oxide)-modified poly(epsilon-caprolactone) (PEO-PCL) nanoparticulate	*in vitro*	for intracellular delivery of saquinavir	[130]

Drug delivery of immunomodulatory and anti-inflammatory agents by nanomaterials

The use of nanomaterials in drug delivery for immunomodulatory and anti-inflammatory agents has gained significant interest in recent years. Nanomaterials offer several advantages for drug delivery, including improved pharmacokinetics, reduced toxicity, and the ability to target specific cells or tissues. One of the reasons that raises morbidity and mortality in COVID-19 patients is the release of cytokines from host cells [131], such as interleukins [132]. Although the specific infection mechanism of COVID-19 remains unclear, it appears similar to that of other viruses in the coronavirus family [133]. Immunomodulatory agents, such as cytokines and growth factors, play an important role in regulating the immune system and have potential therapeutic applications across a range of diseases, including cancer, autoimmune disorders, and infectious diseases. However, the use of these agents is often limited by their short half-life, rapid clearance, and potential for off-target effects. Nanomaterial-based drug-delivery systems can improve the pharmacokinetics of immunomodulatory agents by increasing their stability, solubility, and bioavailability, and reducing their clearance rate. These inflammatory responses may address systemic inflammation. In individuals infected with COVID-19, the levels of these cytokines are elevated [134].

Following COVID-19, many cells and a large number of immunoglobulins and interleukins play a role in inflammation. In intensive care unit patients, ARDS, shock, following infection, acute renal damage, and cardiac problems were much more powerful than in non-ICU patients [134]. Immunomodulators and anti-inflammatory agents may help us achieve these

objectives. A summary of the contents mentioned in this section can be seen in Table 2.

Baricitinib

Baricitinib, an oral Janus kinase inhibitor, has been utilized to treat rheumatoid arthritis (RA) and shown to be beneficial for COVID-19 infection via anti-cytokine effects and as a host cell viral growth inhibitor, using AI algorithms [135].

The nano-sedimentation approach produced baricitinib-encased PLGA nanoparticles with a compact size, a low polydispersity index, and a high entrapment efficiency. A nanoprecipitation approach was used to prepare PLGA nanoparticles encapsulating baricitinib. The *in vitro* release profile showed a consistent pattern, with 89% released in 12 hours and 93% released in 24 hours. In addition to its sustained-release properties and increased solubility, this sustained-release formulation can be used to reduce adverse effects by lowering the baricitinib dosage [136].

As a result, it's possible to infer that baricitinib can be utilized to treat and manage severe COVID-19 inflammation caused by calm storm cytokines, and that using PLGA nanoparticles can improve baricitinib efficacy.

Dexamethasone

Dexamethasone is the first medicine to show life-saving effectiveness in individuals infected with COVID-19. It is a corticosteroid that blocks the production of chemicals in the body that cause inflammation. Dexamethasone 6mg/day, either orally or intravenously, reduced fatality rates in COVID-19 patients in the ICU by 35% and by 20% in patients with mild to moderate COVID [137]. According to studies, dexamethasone is quite efficient against COVID-19 and can dramatically lower morbidity and fatality rates [138].

Dexamethasone is prescribed in the final phase of the disease and during the cytokine storm. In fact, the drug's positive effect occurs when the virus's direct role in the body is lost, and only inflammation, cytokines, and the immune system remain involved. Dexamethasone in severe COVID-19 modified IFN ^{active} neutrophils, downregulated interferon-stimulated genes, and activated IL-1R2+ neutrophils in addition to circulating neutrophils. Dexamethasone also increased immature neutrophils, which dampen the immune system, altering the nature of cellular communication by turning neutrophils from information consumers to information producers [139]. At the same time, its effects could affect TNF-α, IL-1α, IL-1β, IFN-α, IFN-β, and IFN-γ signaling, but not IL-6 signaling, indicating that the IL-6 pathway is not involved in the therapeutic action of dexamethasone in COVID-19 [140].

Nano-formulated dexamethasone may improve the management of COVID-19. Several disorders, including as RA and inflammatory bowel disease, have previously been effectively treated using dexamethasone nanomedicines at the preclinical stage. Nano-formulating dexamethasone could improve the efficacy of anti-COVID-19 treatments by targeting highly activated immune cells. On the other hand, i.v. Delivery allows the use of liposomes and other nanoparticle-based formulations to deliver dexamethasone to phagocyte-rich myeloid and lymphoid regions, such as the spleen and bone marrow. It also allows for efficient and relatively selective delivery of the powerful corticosteroid drug to inflammation sites where the vasculature is leaky and large numbers of phagocytes have infiltrated, thereby reducing the production of pro-inflammatory cytokines, matrix-degrading enzymes, and other signaling molecules that contribute to edema formation and progressive tissue damage in COVID-19. This improves regulation of cytokine storms, which have been linked to COVID-19-related deaths. As a result, critically ill patients receiving ventilation or oxygen therapy should recover faster and more effectively than those receiving the free medicine [137, 141].

Nano-formulating dexamethasone can improve its efficacy by targeting highly activated immune cells and delivering the drug to phagocyte-rich regions such as the spleen and bone marrow. This allows for efficient and selective delivery of the drug to inflammation sites where the vasculature is leaky and large numbers of phagocytes have infiltrated, reducing the production of pro-inflammatory cytokines and other signaling molecules that contribute to tissue damage in viral diseases. This improves regulation of the cytokine storm, which has been linked to viral disease-related deaths. As a result, it's acceptable to conclude that dexamethasone may be utilized to treat and manage severe COVID-19 inflammation caused by calm

storm cytokines, and that employing Nano-formulated dexamethasone can improve dexamethasone's effectiveness.

Tocilizumab:

Tocilizumab is an immunosuppressive medication that is used to treat RA and systemic juvenile idiopathic arthritis in children. It's a humanized interleukin-6 receptor monoclonal antibody. RA is a chronic inflammatory immunological disease that causes synovial membrane inflammation and articular cartilage loss. [142]. Because the inflammatory conditions of COVID-19 and RA are comparable in several ways, it is logical to use the same treatment for both illnesses [143]. Monoclonal antibodies can be used as antagonists of the receptor that cytokines bind to, which is one of the best treatments [144].

Preparation of a hyaluronate gold nanoparticle/tocilizumab (HA-Au NP/TCZ) combination for the treatment of RA is advantageous [145]. Au NP, a medicinal carrier, inhibits angiogenesis. TCZ is a humanized monoclonal antibody that inhibits IL-6 effects [146]. The therapeutic efficacy of the HA-Au NP/TCZ combination in RA was confirmed in a collagen-induced arthritis model. One of these studies shows that HA-Au NP/TCZ can block IL-6 receptors and reduce the effects of inflammatory cytokines in people infected with COVID-19 [145].

Infliximab

A chimeric monoclonal antibody called infliximab is used to treat a variety of autoimmune disorders. It appears to attach to TNF-alpha and neutralize it, as well as prevent it from connecting with the cell's receptors. TNF-alpha is a cytokine that performs a regulatory role in the immune response [147].

Furthermore, it was shown to be overexpressed in the inflamed region or even in the blood of people suffering from autoimmune disorders like RA [148]. TNF inhibitors have been shown to protect patients with severe COVID-19. TNF may worsen lymphopenia by modulating T-cell function via the TNF/TNFR1 pathway. As a result, anti-TNF therapies may be a viable alternative in severe COVID-19 cases [149]. In a clinical trial examining the effectiveness of infliximab in COVID-19, a rapid , and at least a temporary reduction in pro-inflammatory cytokines, such as IL-6, was observed in all Infliximab-treated patients, coupled with clinical improvement in 6 of 7 patients [150].

In addition, nanomaterials and nanomedicines were investigated to determine whether they could enhance the effectiveness of infliximab. The potential of novel biodegradable poly (ester urethane) polymers, including its PEGylated variant, as nanocarriers for infliximab to treat inflammation was examined in an *in vitro* epithelial model. None of the NPs tested positive for cytotoxicity. Cellular interaction was higher when PEG-NPs were matched. The potential of PU-PEG-NPs for drug delivery and targeting in the treatment of gastrointestinal inflammation is fascinating and warrants further investigation [151].

As a consequence, it's reasonable to deduce that infliximab may be used to treat and control severe COVID-19 inflammation produced by calm storm cytokines, and that using PEG-NPs nanoparticles can help infliximab work better.

Interferon beta-1b

In individuals with severe COVID-19, interferon beta-1b (IFN-1b) reduced time to clinical improvement without causing substantial side effects. In addition, ICU admissions dropped when IFN-1b was administered. Although the IFN group had a lower 28-day mortality rate, more randomized clinical trials with larger sample sizes are needed to determine the specific survival advantage of IFN-1b [152], or a better formulation might have a greater impact on this population. In contrast to intravenous treatment, prior studies have shown that intranasal administration of IFN-1b leads to effective cytokine accumulation in the central nervous system [153].

Because SARS-CoV-2 can cause central nervous system (CNS) issues [154], accumulating this medication in the CNS may be more effective at reducing symptoms and preventing a cytokine storm. The nano-vehicle, constructed from biodegradable and biocompatible materials, had a high affinity for IFN-1b, which remained biologically active after release from the nanostructure. In a preclinical model of multiple sclerosis, intranasally delivered IFN—NPs were substantially more efficacious than systemic administration of free cytokine. Controlling cell activation by delivering IFN from NPs into the CNS resulted in a considerable reduction in clinical symptoms, improvement in

motor impairment and neurological damage, and control of neuroinflammation [153].

Vitamin D

Many studies have demonstrated that vitamin D supplementation can have a critical effect on SARS-CoV-2 disease and can reduce the risk of COVID-19 Infections and Deaths [155-157]. For instance, vitamin D lowers blood levels of C-reactive protein (CRP), an inflammatory marker associated with severe COVID-19 [158, 159]. Vitamin D and its derivatives have gained popularity as active ingredients for incorporation into drug delivery systems, owing to their numerous beneficial properties. Oral administration is the easiest and most cost-effective way to raise 25(OH)D levels, especially given that a substantial percentage of the population is affected. In one study, it was evaluated that microencapsulation is a suitable method for designing vitamin D nanomaterials [160]. In another study, an oral nanoliquid formulation of vitamin D3 (60,000 IU) was shown to exert therapeutic effects in ulcerative colitis [161].

Table 2. Use of nanomaterials in host-directed therapy for COVID-19 patients.

Medication	Types of NPs	Study design	Results of using NPs	Ref.
Baricitinib	encapsulated PLGA nanoparticles	*in vitro*	sustained-release behavior, enhancing solubility	[136]
	baricitinib-loaded lipids (stearin)-polymer (Poly(d,l-lactide-co-glycolide)) hybrid nanoparticles	*in vitro*	enhanced bioavailability	[167]
Dexamethasone	PEGylated liposomal	clinical trial	accumulation in inflammatory macrophages and better outcomes	[138]
	dexamethasone-loaded ROS-responsive polymer nanoparticles	*in vivo*	more efficiently suppress inflammatory cells, ROS signaling pathways, and cell apoptosis	[168]
Tocilizumab	HA-AuNP/TCZ complex	*in vitro* and *in vivo*	decrease the effect of inflammatory cytokines	[145]
Interferon beta-1b	CS and SBE-β-CD	*in vivo* study	Led to a significant amelioration of clinical symptoms, improvement of motor impairment and neurological damage, and control of neuroinflammation	[153] [153]
Infliximab	polyurethane-based nanoparticles and Carbosilane dendrimers	*in vitro* and *in vivo* study	Highest cellular interaction, uptake and permeability across inflamed epithelial Caco-2 cell monolayer, rapid recovery of epithelial barrier function	[151]
	infliximab loaded- chitosan/ carboxymethyl chitosan and alginate	In vivo	Alleviate colitis by ameliorating inflammation more efficient	[169]

Poly(lactic acid) (PLA) NPs [162], quantum dots [163], and HAp-PLGA NPs [164] have been used as nanocarriers to deliver vitamin D more effectively [165]. The nanoprecipitation process, for example, was used to make NPs. Rapid solvent diffusion induced polymer precipitation, resulting in the formation of NP. The nanoencapsulation of vitamin D3 active metabolites could provide a new, potentially practical approach to overcoming the limitations of vitamin D3-based chemotherapy [162]. Given that COVID-19-induced colitis has been observed, it can be inferred that there is a link between the two diseases [166]. Therefore, these studies can inform lifesaving vitamin D treatment for COVID-19 patients.

The lessons learned from the COVID-19 pandemic can guide future research and development of nanomaterial-based drug-delivery systems for the treatment of inflammatory stages of viral diseases. By investing in research and development, implementing effective public health measures, and exploring innovative approaches, we can improve our ability to detect, prevent, and control future viral outbreaks. The use of nanomaterials as carriers for anti-inflammatory agents, such as dexamethasone, offers significant promise for the treatment of viral diseases and for improving patient outcomes. One key advantage is the ability to improve the selectivity of anti-inflammatory agents, such as dexamethasone, by targeting specific cells or tissues. This can reduce off-target effects and drug toxicity and improve its efficacy. Nanomaterial-based drug-delivery systems can also improve the pharmacokinetics of anti-inflammatory agents by increasing their stability, solubility, and bioavailability, and reducing their clearance rate. This can improve drug efficacy and reduce dosing frequency. Overall, the use of nanomaterial-based drug-delivery systems for the treatment of inflammatory stages of viral diseases offers significant promise for improving patient outcomes. However, further research is needed to fully understand the pharmacokinetics and toxicity of these nanomaterial-based drug-delivery systems and to optimize their efficacy and safety. By investing in research and development, implementing effective public health measures, and exploring innovative approaches, we can improve our ability to detect, prevent, and control viral outbreaks in the future.

Challenges and Limitations

Potential risks, toxicity, and long-term effects

While nanomaterials offer notable antiviral and immunomodulatory advantages, their safety profiles remain an important unresolved challenge. The physicochemical characteristics that enable strong biological interactions—such as high surface reactivity, small size, and the ability to cross cellular barriers—may also lead to unintended cytotoxicity, oxidative stress, or immune dysregulation [170]. Toxicity can vary widely depending on particle composition, surface charge, solubility, and functionalization, often making it difficult to generalize findings across nanomaterial classes. Another critical limitation is the insufficient understanding of long-term biodistribution and clearance. Many nanomaterials exhibit slow degradation or persistent retention in organs such as the liver, spleen, and lungs, raising concerns about chronic accumulation and late adverse effects. These risks highlight the need for systematic toxicological studies under conditions that closely mimic clinical exposure [171].

Regulatory and ethical considerations.

Regulatory frameworks for nanomedicines remain fragmented and underdeveloped, creating uncertainty in the translational pipeline. Current standards for evaluating safety, pharmacokinetics, and manufacturing quality were primarily designed for conventional small molecules and biologics, and may not fully capture the complex behavior of nanoscale systems. As a result, regulatory agencies often require case-by-case assessments, which increase development time and costs. Ethical considerations also arise, particularly regarding informed consent, environmental impact of nanoparticle production and disposal, and equitable access to advanced nanotherapeutics. Ensuring transparency, traceability, and comprehensive risk–benefit evaluation is essential for responsible clinical deployment [172].

Production and scalability issues

Despite significant progress in laboratory-scale synthesis, large-scale production of nanomaterials suitable for clinical use remains challenging. Many nanoparticle systems rely on precise control of size, shape, and surface chemistry, which are difficult to maintain consistently during industrial manufacturing.

Batch-to-batch variability, storage instability, and high production costs continue to impede commercialization. Furthermore, specialized equipment and stringent quality-control measures are required to achieve Good Manufacturing Practice standards, increasing the complexity of scale-up efforts [173]. These barriers must be addressed through standardized protocols, scalable synthesis methods, and improved process engineering to support widespread clinical translation [174].

Conclusion

In this study, we investigated the innate antiviral effects of various nanomaterials on viral infections, including AgNPs, AuNPs, and Fe3O4. Additionally, nanomaterials could serve as excellent platforms for delivering antiviral and anti-inflammatory agents such as remdesivir or dexamethasone to boost their effectiveness. In the future, these functional nanoparticles may provide a platform for bio-safe manufacturing. A major challenge in treating viral diseases is developing effective antiviral drugs that target the virus without harming healthy cells. Nanotechnology-based medicines and delivery systems can overcome this challenge by targeting specific cells or tissues, thereby reducing off-target effects. For example, liposomes and nanoparticles can encapsulate antiviral drugs and deliver them directly to infected cells or tissues, increasing efficacy and reducing toxicity. However, further research is necessary, including examining nanomaterials—particularly those targeting SARS-CoV-2—using various models such as computational studies, *in vitro* and in vivo experiments, and ultimately clinical trials to assess their effectiveness against COVID-19. One of the biggest hurdles in these approaches is that public access to nanomedicines requires large-scale manufacturing, significant capital, and infrastructure. Nonetheless, the ability to manage situations effectively with nanomaterials remains a valuable asset.

The development and implementation of effective vaccination programs, public health measures, and innovative approaches like nanotechnology can help prevent and control future outbreaks. Additionally, the collaboration among researchers, healthcare professionals, and policymakers during the COVID-19 pandemic has shown the importance of coordinated efforts to address global health challenges. Building on the lessons learned from COVID-19, we can better prepare for and respond to future viral diseases. Overall, developing nanotechnology-based therapeutics and drug-delivery systems could greatly impact how we treat viral diseases. By harnessing the unique properties of nanomaterials, researchers can create more effective and targeted antiviral drugs.

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