Metal Nanoparticles against Viruses

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This study is an actual review about of recent studies using metal nanocomposites as antivirals against coronavirus and structurally similar viruses. We wrote this review in a new perspective, within the scope of nanomaterials, the purpose of the review is to demonstrate the potential of nanoparticles in combating the COVID-19 pandemic.

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1. Metal Nanoparticles as Antivirals

The main strategies in the development of antivirals include the perception of viral structures and viral replication processes, making it possible to point out potential antiviral targets. Another possibility is the use of antivirals to strengthen the immune response to viral infection. The mechanism of one antiviral can vary as the target changes [1].

Among metallic nanoparticles, AgNPs are one of the best antimicrobials in efficiency against bacteria and viruses (**Table 1**) [2] because they are effective against several microorganisms even at a low concentration [3]. Lv and collaborators [4] tested different silver nanocomposites (20 nm AgNPs, 60 nm silver nanowires, 400 nm silver nanowires, and 10 nm silver colloids) with coated with Polyvinylpyrrolidone (PVP) against TGEV, porcine coronavirus, as a model of CoV. They demonstrated that all the nanomaterials, excepting silver colloids, showed an antiviral and inhibitory effect on TGEV entry and on apoptosis caused by the virus.

The antiviral effect of AgNPs is also showed by Chen and collaborators [5], inhibiting infection of feline coronavirus (FCoV) by blocking the entry to the host cells by physical biding. As other works demonstrated action of graphene oxide (GO) against coronaviruses (porcine epidemic diarrhea virus–PEDV) [6], Chen used nanocomposites of GO sheets along with silver against FCoV. They also address that due to the surface area/volume ratio and the possibility of tuning chemical and physical properties, no cytotoxicity is even presented at high concentrations. AgNP sized 11–12 nm from biological synthesis, using curcumin [2], also blocks the entry of RSV into Hep-2 cells, with nanoparticles possibly interacting with viral surface glycoproteins, and it is less toxic than AgNPs synthesized with citric acid in a chemical way.

Morris and collaborators [7] demonstrated the antiviral capacity of 8–12 nm AgNP, inoculated intranasally, against RSV during infection in vivo in BALB/c mice. Their suggestion of antiviral mechanism corroborates with the hypothesis of Yang and collaborators' [2] report, through interaction of AgNP with RSV surface glycoproteins,

inhibiting attachment of the virus to host cells. Silver nanoparticles with less than 5 nm in size were reported having antiviral effect against HIV, binding to the gp120 protein and affecting adsorption of the virus to CD4 host cell [8]. Smaller nanoparticles have a larger surface area/volume ratio; thus they are more prone to enter tissues and cells and to have better interaction with de virus; however, this penetration power can damage the host cells and cellular components, leading to a nanoparticle cytotoxicity increase [9].

Other metallic nanoparticles such as cooper nanoparticles also demonstrated antiviral activity. Fujimori and collaborators [10] showed antiviral activity of CuI nanoparticles against Influenza A virus (H1N1), inactivating the virus through generation of OH capable of degrading viral proteins, in a concentration-dependent manner. In their review, Sportelli and collaborators [11] affirm that coronaviruses are inactivated in copper surfaces due ROS created by copper ions release. Still, against H1N1 virus, zinc-oxide nanoparticles (ZnO-NPs) have antiviral activity after H1N1 infection to Madin-Darby canine kidney cells (MDCK-SIAT1), generating zinc ions and ROS that may potentially damage the host cell [12]. This toxicity can be decreased with surface coating with polymeric materials as polyethylene glycol as proposed to Ghaffari and collaborators [12].

Recently, a molecular docking of IO-NPs (Fe_2O_3 and Fe_3O_4) was performed to explore the interaction with the S protein receptor binding domain of SARS-CoV-2 (S1-RBD) [13]. As the interaction of Fe_3O_4 with S1-RBD involved the formation of four hydrogen bonds, it was considered stable and complex, and in addition, hydrophobic interactions of this IO-NP were detected with Leu455, Ser494 and Phe497 in the active site of S1-RBD, which could hinder virus adsorption to host cells [13]. Another approach with IO-NPs was validated against H1N1 influenza virus, where the 10 to 15 nm iron oxide nanoparticles (IO-NPs) show that may bind to the virus and inhibit its adsorption [14].

Gold is extensively used for diagnostic devices and vaccines for being chemically inert and relatively nontoxic [15]. Zacheo and collaborators [16] successfully tested gold nanoparticles (AuNPs) sized 4–5 nm with sulfonated group ligands varying in number, size, orientation and the sugar as head groups against Dengue virus (DENV). With a moderate toxicity and virucidal effect, a complex multi-sulfonated with glucose as head group was found to be the most effective against DENV-2, suggesting that this complex of AuNP interacts with DENV-2 envelope protein, inhibiting the virus permanently. AuNPs can also break disulfide bonds of the highly conserved protein Hemagglutinin (HA) of influenza viruses. Kim and collaborators [17] synthesized porous AuNPs without surfactant that decrease infectivity of various influenza virus strains (H1N1, H3N2 and H9N2). These strategies are promising and should be considered when studying antiviral approaches against SARS-CoV-2 because hemagglutinin esterase is a structural glycoprotein of some coronaviruses [18].

2. Nanoparticulated Delivery Systems against Viruses

Many medicines, including antiviral drugs marketed today, have issues that decrease their effectiveness, such as difficulties with solubility, permeability and absorption, affecting the drug bioavailability. Consequently, it is necessary to administer intravenous high doses to increase the frequency of medication administration or prolonged treatment duration, which may negatively affect the patient leading to major adverse effects. As a

solution, nanoparticulated delivery systems can overcome these issues by improving the action of existing drugs, carrying bioactive compounds, immunogenic drugs or proteins that stimulate the host immune system [19].

Nanocarriers are well studied against HIV, improving the spreading of already anti-HIV used drugs in different tissues [20][21]. Because there have been no known drugs until now that effective interfere with SARS-CoV-2 replication, this type of strategy—drug nanocarrier—is not addressed in this work.

On the other hand, nanoparticulated systems can also carry molecules that somehow may interfere with viral replication. Aiming specific Dengue virus genes, Paul and collaborators [22] investigated the antiviral efficacy of biocompatible gold nanoparticles carrying small interfering RNA in a cationic complex AuNP-siRNA capable of inhibiting the replication of the dengue virus (DENV) in vitro. The complex interferes with the viral entry due its viral surface positive charging, binding to the host's negatively charged cell membrane. This linkage releases siRNAs constructed to attach to the genes responsible for the expression of capsid or β-actin, and the decreased expressions were verified by qPCR, plaque forming assay and an immunostaining assay [22]. This strategy can be studied for usage against coronaviruses and other emergent microorganisms; however, in vivo testing is necessary, considering aspects as size regulation, configuration, and surfaces modification to achieve the best balance between host toxicity and antiviral effectiveness.

3. Metallic Nanoparticles in COVID-19 Diagnosis

COVID-19 early diagnosis is fundamental to contain development of the patient's disease, also to avoid SARS-CoV-2 transmissibility and to manage the pandemic to its final course, especially at the time when there were not vaccines available. In order to develop low-cost approaches, seeking fast, accessible and trustworthy SARS-CoV-2 detection, research in novel devices and methods to detect the virus in different patient samples increased significantly in the past two years. In this context, nanotechnology is undoubtedly a weapon in the fight against COVID-19 [23].

COVID-19 diagnosis relies on viral gene sequences, patients' antibodies or SARS-CoV-2 antigens detection from nasopharyngeal or oropharyngeal swab sample from patients (the gold standard of sampling) [24]. Combining diagnosis with the ability to tailor a metallic nanomaterial with a specific size and shape and high surface-to-volume ratio opens possibilities to design various biosensing methods. Gold nanostructures and their optical properties, for example, were already exploited in SARS-CoV-2 detection within a chip where these nanomaterials were functionalized with DNA receptors, and when hybridized with antigen nucleic acid, the combination of plasmonic photothermal and the surface plasmon resonance could be read by a laser beam, leading to an accurate detection [25].

Nanogold is also exploited in naked eye colorimetric assays, as well as lanthanide with its luminescence properties, detecting antigens from the virus or antibodies from the patient [25]. These naked-eye type detections are useful in point-of-care testing where the detection system is assembled in accessible and uncomplicated kits or paper-like membrane/lateral flow strip, enabling the home diagnosis [26].

Magnetic nanoparticles bring easy and effective possibilities in SARS-CoV-2 detection, through electrochemical, fluorescence or magnetic resonance properties [25]. Nucleic acid extraction, an important part of for COVID-19 diagnosis based on nucleic acid detection strategies, can be simplified through SARS-CoV-2 RNA separation with magnetic nanoparticles coated with carboxyl polymer, increasing the sensitivity of detection based on amplification methods [26].

Giovannini, Haick and Garoli (2021) [24] brought in their study a distinguished method to diagnosis COVID-19 from exhaled breath condensate (breath's liquid phase), where the detection can take place in an electrochemical device build with modified gold nanoparticles where the patient is asked to cough or exhale with the month for 30 min aiming the device. Detection is possible due differences in electrical resistances between comparison of three samples: from sick and cured patients, and a control sample.

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