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Exploiting Nanotechnology to Target Viruses

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Abstract

Since the early years, different civilizations have been affected by infectious diseases caused by bacteria, fungi, parasites, and, mainly, by viruses. Viruses from the beginning impacted socio-economic development, as well as leveraging different public health problems. Treatments with traditional methods, such as drugs and vaccines, are used to contain the spread of infectious diseases. However, these treatments are not enough. Thus, it is necessary to develop new therapeutic strategies, and the nanotechnology associated with medical devices stands out with great potential for diagnosis, prevention, and treatment of various infectious diseases. This review will present an overview based on nanotechnological concepts and applications with the main focus on viral infections.

Keywords: Nanotechnology; Nanoparticles; Nanotechnological applications; Virus; Antiviral; COVID-19

Introduction

Infectious diseases caused by microorganisms of the most varied natures and by viral entities cause millions of deaths every year [1]. Around the world, viral infections have impacted civilizations' circumstances since the earliest times, including the current panorama of the SARS-CoV-2 pandemic known as coronavirus disease in 2019 (COVID-19). In this sense, in the last century, it is possible to mention some pandemics with global epidemiological repercussions. With a pandemic peak in 1918, the so-called 'Spanish flu' caused by the Influenza A virus of the H1N1 subtype, infected more than 500 million people and caused 50 to 100 million deaths worldwide [2]. According to the Centers for Disease Control and Prevention (CDC), the Asian flu pandemic, which began and peaked in the years 1957-1958, caused more than 1.1 million deaths worldwide [3]. Another highly relevant pandemic occurred in 1968, where the so-called 'Hong Kong flu' was caused by the Influenza A virus of the H3N2 subtype and caused more than 1 million deaths across the globe [4]. It is estimated that the virus Influenza A H1N1pdm09, which caused the 2009 pandemic, caused 151,700 to 575,400 deaths in the first 12 months of circulation of the viral entity [5]. Currently, the World Health Organization estimates that there are 290 to 650 thousand deaths per year caused by seasonal infections of Influenza virus subtypes [6]. The pandemic caused by COVID-19, with a pandemic peak in the current year of 2020, confirms several questions about the real perspective of the mortality rate of the disease, the possibilities of sequelae after the cure of the infection, among other vital issues in the areas of health and of society [7]. It is worth mentioning that several data demonstrate that the majority of infected people are not documented because they are asymptomatic or have mild symptoms, which facilitates the spread of COVID-19 [8].

Nanoscience appears with the proposal to find alternatives that reduce or prevent the spread of virions. The use of nanoparticles can inactivate the viral particle or decrease its resistance on abiotic surfaces and in the intracellular environment [9]. Besides, there is also the development of nanotechnologies capable of combating viral diseases. The use of nanosystems that target drugs, quantum dots, among other biomedical technologies, can attack the infections by directing them to the target site.

There is also the use of viral substrates as vehicles or molecular additives. Starting their physical-chemical

and biological properties, the fight against tumors occurs with the activation of the immune system directed to that region of hyperplasia [10,11]. Therefore, in this article, we will address several possibilities for timely nanotechnological applications. It will be possible to highlight the potential of nanosciences in combating the viral entity.

Physico-Chemical Influence of Organic Materials on the Biosynthesis and Stabilization of Nanoparticles

In recent years, the development of ecologically correct scientific techniques has gradually grown to find new medicinal solutions that do not pose a risk to human and animal health, as well as the environment [12]. In this way, nanoparticle biosynthesis adapts to sustainable routes using organic materials as nanoparticles' formers and stabilizers instead of harmful toxic components [13]. The biosynthesis of nanoparticles begins with a reduction process between the ions, followed by the growth and nucleation stage of the nanoparticles to establish a colloidal matrix with active principles. About this, the nanosystem may have antimicrobial, antioxidant, anti-inflammatory properties, among others [14,15].

Besides, nanoparticle biosynthesis can be mediated by different organic materials available in nature, whether they are of plant or animal origin [16]. As an example of this, we can mention plants that have different specialized structures capable of secreting essential oils due to the accumulation of secondary metabolites. Beyond as inputs of animal origin, for example, propolis has substances that compose the group of polyphenols, such as phenolic and flavonoid compounds [17,18]. Therefore, these substances are directly related to the antioxidant potential of the nanosystem, since it is a fundamental characteristic for the determination of an efficient system that has a colloidal dispersion and stabilization of nanoparticles [19]. Therefore, this nanosystem, as well as others, has characteristics and properties that can be adjusted in detail for different functions and applications that provide efficient antiviral mechanisms of action.

Nanosystems and Antiviral Mechanisms

One of the most intriguing characteristics associated with viruses refers to the fact that they do not have their metabolism and independent reproduction. Thus, they are not considered as living beings, as they need host cells to ensure survival. They need the cellular machinery of the host cell to replicate its genetic material, whether DNA or RNA, and produce new viral particles, so they are mandatory intracellular parasites [20,21]. Scientists around the world are looking for solutions using existing drugs. Besides that, new drugs that are successful *in vitro* may not be efficient when administered to patients [22]. The significant advantage of nanotechnology is that the size of the nanoparticles. The permeation in targets that are anatomically inaccessible with common drugs is a different ability [23]. The ability to change its surface charge, through supramolecular interactions, allows for permeation through the cell membrane. It can be a possible alteration of its surface charge, which integrates the nanosystem efficiently [24,25]. Many antiviral activities were established for nanosystems. (Figure 1).

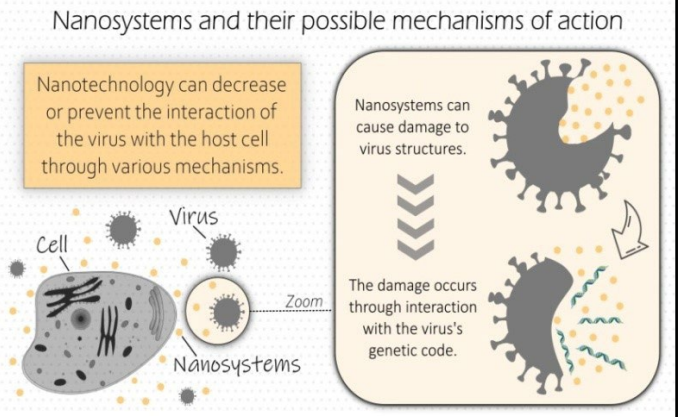

Figure 1: Possible interactions of nanosystems with viral particles.

Nanomaterials have also been investigated to optimize the methods of drug administration already used. This new approach would make it possible to reduce toxicity. Also, it prevents the degradation of drugs by metabolism. It is possible to increase absorption and greater targeting of drugs to target cells and tissues [26].

Silver nanoparticles (AgNPs) have broad antiviral action for herpes simplex viruses (HSV), human immunodeficiency viruses (HIV), Hepatitis B virus (HBV), among others [27]. AgNPs still have the advantage of having efficient, eco-friendly synthesis routes. The antiviral properties of nanoparticles can involve interaction with nucleic acids or thiol groups of proteins [28]. Besides, other mechanisms have been reported. The interaction and fusion of HIV-1 to host cells were prevented by the binding of AgNPs (coated by PVP, BSA, and carbon) to the gp120 glycoproteins of the viral envelope. These proteins are essential for the admission of the virus into host cells, such as lymphocytes, by binding to CD4 receptors. It was also seen that AgNPs were able to inhibit infection regardless of tropism and is non-toxic concentrations to cells [29]. In another study, AgNPs coated with 30-50 nm PVP added to neutralizing

antibodies increased their ability to prevent infection of cells by HIV-1. These interactions are dependent on the shape and size of the nanostructures. AgNP activity against the hepatitis B virus (HBV) has also been reported. The binding of AgNPs inhibited the replication of the virus to DNA. The synthesis of RNA and the formation of virions was prevented [30].

The gold nanoparticles (AuNPs) synthesized by the green route are not yet so evident [31]. AuNPs functionalized with sialic acids had the potential to inhibit infection by the Influenza A virus. The binding of the virus to the surface of host cells and subsequent infection depends on the recognition of the sialic acid present in these cells by the hemagglutinin protein present on the viral surface. It is believed that AuNPs functionalized with sialic acid were able to block the interaction of hemagglutinin with sugar. Thus, the virus cannot enter the cell [32]. It was observed that nanoparticles that are 10 nm bound more efficiently to the surface of the HIV-1 viral envelope. They would be associated with interaction with residues exposed in the existing gp120 glycoproteins [33]. AuNPs coated with glucose conjugated to the drugs abacavir and lamivudine be able to inhibit viral replication in cell assays [34].

Also, AuNPs were coated with mercaptobenzoic acid and conjugated to SDC-1721, a derivative of the antagonist TAK-779 for the CCR5 receptor. This receptor is essential for the entry of HIV-1 into T lymphocytes. The SDC-1721 and AuNps alone did not show inhibitory effects for virus infection. However, when AuNPsare conjugated to SDC-1721, the results showed similar effects to TAK-779. There is an efficient inhibition of the fusion and entry of HIV-1 with T lymphocytes. With these results, it is seen that small, therapeutically inactive organic molecules can be converted into highly active drugs by conjugating them to metallic nanoparticles [35].

In the study with the functionalized gold nanoparticles, only those with 14 nm were able to block the Influenza A virus infection. The 2 nm AuNPs did not show significant results. With the change in the shape of the gold nanostructures, there are studies associated with vaccines based on gold nanorods that were tested for the respiratory syncytial virus (RSV) because there is the induction of production of T lymphocytes, which are cells of the immune system [36].

Copper nanoparticles (CuNPs), as well as AgNPs, have also shown broad activity against different organisms. Copper is cheaper and readily available than silver [37]. The antiviral potential was evaluated by copper iodide nanoparticles (CuINPs) against the strain of Influenza A virus that caused the 2009 epidemic. CuINPs were able to act on viral proteins such as hemagglutinin and neuraminidase, leading to degradation and inactivation of the virus through the formation of reactive oxygen species (ROS) [37]. CuINPs have also been studied against the feline Calicivirus (FCV). A non-enveloped virus that is highly resistant to organic solvents and surfactants, unlike enveloped ones. This virus was considered as a substitute for human norovirus that is associated with gastroenteritis [38]. The virus infection capacity was significantly reduced during the exposure of Crandell-Rees feline kidney cells (CRFK) to 1000 $\mu g.ml^{-1}$ CuINPs for 60 min, reaching a reduction of 7 orders of magnitude under these conditions. This effect was also hypothesized to be the result of the production of ROS and the sequential oxidation of capsid proteins [38].

It is urgent to establish options for human coronavirus (HCoV). However, anti-virus therapy is challenging, as coronaviruses mutate rapidly and have wide diversity. The first generation of nanostructures that demonstrated the inactivation of the virus was derived from hydrothermal carbonization of ethylenediamine/citric acid as carbon precursors and post-modified with boronic acid ligands, called carbon quantum dots (CQDs). These nanostructures showed concentration-dependent virus inactivation. CQDs derived from 4-aminophenyl boronic acid are the second generation of anti-HCoV nanomaterials. These nanostructures showed concentration-dependent virus inactivation. CQDs derived from 4-aminophenyl boronic acid are the second generation of anti-HCoV nanomaterials. With an average size of 10 nm, have excellent dispersion in water. Have no toxicity associated with animals, so promise to be an advance associated with nanomedicine [39]. Characteristics of the nanostructures related to shape, size, and chemical surface are essential for the access of these nanometric structures to the attack target. The interactions with the biological environment and properties of the cell membrane, as a particular charge and affinity with water (hydrophilicity or hydrophobicity), can influence the cell absorption ways. This feature would allow drugs to efficiently access virus reservoirs. In the case of SiO_2NPs nanoparticles, these nanostructures interact strongly with viral particles due to hydrophobic or hydrophilic properties. It can establish stronger interactions with a specific virus envelope with similar surface properties. The antiviral activity of SiO_2NPs particles suggests a mechanism of antiviral action for anti-HIV therapy, based on surface interactions between silica, cells, and viruses [40]. For H1N1 influenza virus types A and B, one of the most widely used antiviral drugs are oseltamivir (OTV). When there is an association of this drug with selenium nanoparticles (SeNPs), the delivery of the drug, through the use of an association between OTV and SeNPs, is much more efficient to prevent H1N1 infection with low toxicity [41]. Bacterial viruses are called when the virus infects

the bacteria. The bacteriophage virus MS2 is an example that infects the bacteria *Escherichia coli*. Studies indicate that titanium dioxide (TiO_2) nanoparticles modified with silver commenced inactivation to the MS2 virus about five times higher when compared to titanium nanoparticles without doping. The evolution of virus inactivation was favored by the increase in silver doping, due to the action already mentioned above [42].

Conclusion

The potential of nanomaterials has attracted several interests in approaches to viral infections since they can be designed to act directly against viruses or increase the capacity of drugs already used today. In this sense, further studies will be necessary to deepen the knowledge about antiviral mechanisms. Therefore, various tests must take place *in vitro* and *in vivo* to apply nanosystems associated with reducing the spread of viruses, in addition to expanding the advantages of using nanostructures in new therapies or vaccines capable of stopping the rapid action of these viral particles. From this, it is worth emphasizing the importance of knowledge about the immune system, since it interacts and responds to these nanomaterials to optimize better constructions and avoid toxic effects on the body. Therefore, through all the data cited in the text above, it can be observed that nanotechnology has been a promising science in the search for alternatives to conventional treatments against diseases caused by viral particles.

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