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Cerium Oxide (CeO_2) Nanoparticles Could Have Protective Effect Against COVID-19

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Abstract: The COVID-19 pandemic has been incredibly influential on public health, life, and economy for one year, and this type of virus could be our life in the future. Currently, there are some vaccines or combination therapies of anti-viral drugs. However, the mutation rates of the virus could be unpredictable, and the known treatments could be ineffective in fighting the virus's diseases. Nanotechnology included metal nanoparticles, has been used due to their antivirus, antibacterial or antioxidant properties. CeO_2 (Cerium oxide) metal nanoparticles have great potential against viruses or bacteria. Also, CeO_2 metal nanoparticles have antioxidant properties and immunomodulatory effects. Thus, this paper suggests the PEGylated CeO_2 metal nanoparticles as a new approach for treating COVID-19.

Keywords: COVID-19; CeO_2; metal nanoparticle; nanoparticle; PEGylation; targeted system.

1. Introduction

The introduction should briefly place the study in a broad context and highlight the importance of COVID-19, which emerged in the last months of 2019 and is considered a pandemic by WHO, continues to increase day by day. Although prophylaxis was tried with vaccines, the desired reduction in transmission rate could not be achieved due to insufficient production of vaccines for social immunity worldwide. In addition, seeing different mutations in the virus that increase the rate of spread of the disease causes the problem to get worse. For this reason, it is essential to develop agents with antiviral activity to eradicate the virus with the vaccine. Regulation of oxidant damage and cytokine storm, which occur mainly during viral infections but are more severe in this virus, are essential for mortality and morbidity.

Although different approaches are applied in this direction, the high potential of side effects leads to searching for an alternative treatment. It has been shown in previous studies that nanoparticles have antiviral and immunomodulatory properties [1,2]. Nanoparticles can effectively diagnose and treat viral diseases such as COVID-19 and their special properties such as shape, superparamagnetism, bioavailability, biocompatibility, and immunity. Especially, metallic nanoparticles have promising properties due to their antiviral, antibacterial, anti-inflammatory, anti-fungal, anti-cancer effects [3-6]. In addition, metal nanoparticles can

be stabilized to long-term stabilization by polymers, dendrimers or microgels, or hydrogels [7-10]. Also, stabilization increases the biocompatibility of metal nanoparticles can adversely affect lung and kidney nanoparticles [11,12].

PEGylation has been used to stabilize different types of metal nanoparticles or for encapsulation for biological and pharmaceutical applications [13-15]. Additionally, PEGylation provides surface modification for targeted systems. Targeted nanoparticle systems have great potential for therapeutic effects [16-18]. These nanoparticles reduce the side effects of conventional antiviral drugs in the treatment and increase the concentration of metal nanoparticles or drug molecules in certain organs or tissues. In addition, targeted metal nanoparticles can prevent the spread of the virus and infections to vital organs. In this regard, PEGylated cerium oxide nanoparticles have been proposed against COVID-19 because of their antiviral, antioxidant, and immunomodulatory properties demonstrated in previous studies [19-21].

2. Antiviral effects of nanoparticles

Antiviral effects of metallic nanoparticles have well-known properties; these nanoparticles can be gold nanoparticles, silver nanoparticles, iron oxide, zinc oxide nanoparticles [22]. Generally, protein S-receptor or spike, N, envelope (E), and membrane protein interactions have been used for the antiviral effects. Still, nanoparticles can effectively target vacuolar ATPase (V-ATPase) [23]. In addition, nanoparticle-based drug delivery systems have been used as antiviral systems by blocking receptor cell entry, stopping viral replication, and multiplying [24]. Potential antiviral effects of metallic nanoparticles against COVID-19 have been analyzed by Fouad [25]. According to this review, Au nanoparticles, Ag nanoparticles, iron oxide nanoparticles (IONPs), zinc oxide nanoparticles (ZnONPs), graphene oxide, titanium dioxide, selenium nanoparticles promise potential antiviral effects against COVID-19 due to their known antiviral effects.

On the other hand, cerium dioxide nanoparticles have been proposed as antivirals against some important diseases such as Herpes simplex virus 1 (HSV-1), HSV-II, and A / FM / 1/47 (H1N1) [26,27]. In addition, we think that cerium dioxide could be a step forward for the radical treatment of COVID-19, thanks to its antioxidant and anti-inflammatory properties.

3. Antioxidant effects of CeO_2 nanoparticles

The findings obtained with free oxygen radicals in studies with CeO_2 nanoparticles are controversial. This is thought to be due to the difference between dose and cells. It has been found to have pro-oxidant properties against cancer cells and viral infections and exerts antioxidant and antiapoptotic effects in the inflammatory process. Due to these cell-selective properties, it is thought that COVID-19 can suppress the inflammatory process and reduce the expression of cytokines by suppressing the oxidative stress caused by the virus by exerting a viral effect on SARS-CoV-2. CeO_2 nanoparticles have great efficient antioxidants. COVID-19 infection triggers ROS formation, resulting in multi-organ failure [28]. In addition, cerium oxide nanoparticles initiated caspase-3 activity in rat brain tissue by increasing the thiol content and the level of antioxidant enzymes such as superoxide dismutase and catalase. This is important for reducing oxidative DNA damage and lipid peroxidation [19]. Another study suggested that reducing CeO_2 nanoparticles could achieve the stimulation of dendritic cells (DCs) to produce interleukin 10 (IL-10), which is important for regulating cytokine restriction

[29]. Also, CeO_2 nanoparticles have an oxidative stress protection effect [30,31]. On the other hand, CeO_2 nanoparticles can reduce cellular structural damage by removing and inhibiting reactive oxygen species (ROS); these properties are crucial for maintaining normal cellular function against inflammation [32-35]. As a result of this information, CeO_2 metal nanoparticles can be a great agent for COVID-19.

4. Anti-inflammatory properties

Cerium Oxide has the feature of a bi-directional immunomodulator. It has been observed that it shows immunostimulatory properties with T cell activation against viral infections. In particular, it has been shown to regulate TNF α and IL-1β levels. In cases of inflammation, it has been reported to have a negative effect on T cell activation, suppressing inflammatory pathways and thus reducing cytokine expression [36]. Additionally, it has been reported that it can inhibit matrix metalloproteinase activation, which is activated during inflammation [37]. Another study demonstrated that CeO_2 nanoparticles did not exhibit remarkable inflammatory response on human aortic endothelial cells using IL-8, ICAM-1, and MCP-1 [38]

SARS-CoV-2 infection is known to cause cytokine storms by activating inflammatory pathways such as MAPkinase, NF-κB, STAT3, iNOS, and COX. In experimental studies with CeO_2, it is important to show that it suppresses inflammatory pathways during inflammation to prevent multiple organ damage.

5. Conclusions

Polymers can stabilize CeO_2 nanoparticles with antiviral, antioxidant, and immunomodulatory, anti-inflammatory properties, and this polymer can be a PEG polymer for stabilization. Stabilization can increase the long-term use of CeO_2 nanoparticles and increase metallic nanoparticle toxicity. In addition, stabilized CeO_2 nanoparticles can target specific tissue or organs undergoing viral infection using specific organ or tissue receptors.

This short review suggests that CeO_2 nanoparticles may effectively treat the disease, thanks to their ability to inhibit oxidant and inflammatory pathways that cause multiple organ damage, especially during COVID-19. It is also essential to prevent side effects seen during antiviral therapy because it shows cell-specific activation. The ability to prepare nanoparticles together with other drugs increases the importance of these structures day by day, creating a new treatment option for all kinds of diseases.

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Conflicts of Interest

The authors declare no conflict of interest or personal relations that could have influenced the work reported in this paper. Author contribution statement: All authors have equally contributed to the study.

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