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(Minireview)

Applications of Cerium Oxide Nanoparticles in Dentistry: A Review Article

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ABSTRACT

Nanotechnology is widely used nowadays in the medical and dental fields, it includes particles whom size is ranging from (1-100 nm), known as nanoparticles. The small particle size of these nanoparticles and their high surface area to volume ratio is the reason behind superior physical, mechanical, and biological properties. Metal and metal oxide nanoparticles become the research hotspot of the dental field. Cerium Oxide Nanoparticles (CeO_2NPs) are one of the metal oxide nanoparticles that have gotten a great attention during recent years owing to its superior properties. It exhibited redox potential, antibacterial activity, biofilm suppression and anti-inflammatory potential. Cerium oxide nanoparticles (CeO_2NPs) showed reduced toxicity to cells and unique antibacterial mechanism. In addition, Cerium Oxide Nanoparticles have superior scavenging abilities for the Reactive Oxygen Species (ROS), so they are recommended for different therapeutic applications. This review will present some applications of Cerium Oxide Nanoparticles in the dental field, such as the antimicrobial activity, dental caries prevention, modifications in dental materials, dental implant coating, tissue engineering, periodontal therapy and root canal disinfection.

Keywords: cerium oxide; nanotechnology; nanoparticles.

1- Introduction

Nanotechnology applications in dentistry involve the use of the nanoparticles for significant advancements in the dental care field. Nano-dentistry offers novel solutions in the field of diagnosis, therapeutics and tissue regeneration, resulting in the replacement of the traditional dental practice to a more recent and effective techniques [1].

Cerium oxide particles or nanoceria presents promising applications in the dental field because of its antioxidant, anticancer, antibacterial and anti-inflammatory properties. Cerium is a metal which belongs to the lanthanide group of the rare earth metals. It is present in different oxidation states; (Ce_3^+) and (Ce_4^+) states. The bioactivity of nanoceria is due to the change in valency between the $Ce3^+$ and $Ce4^+$ states [2].

The cerium atoms have the capability to adjust their electronic configuration that suits the surrounding environment as immediately as possible. Recent researches revealed that the small particle size of cerium oxide and the oxygen vacancies led to large lattice expansion owing to increased surface ratio. The oxygen vacancies of nanoceria make it a potent antioxidant for different therapeutic applications. This unique property of nanoceria makes it a potent bioactive material with various cells, tissues and micro-organisms. Some biological properties of CeO_2NPs are anticancer, antibacterial, antioxidant, neurotoxicity and cytotoxicity property. Cerium Nanoparticles with small molecules can be used as vectors to deliver drugs and genes [3]. The nanoceria coated formulations are found to be an effective drug therapy to prevent cancers since it exhibits cytotoxic properties against cancer cells. In addition, it can regulate the genes essential for a cellular defense mechanism. Biocompatibility studies indicate that Cerium Oxide Nanoparticles are non-toxic in short-term exposure. While, nanoceria reports toxicity potential for long-term periods. Cerium oxide-based bioactive scaffolds used for tissue regeneration revealed excellent results because they are non-toxic to cells, and exhibited enhanced osteoblastic differentiation. Based on the promising properties of nanoceria, it has been incorporated into some dental materials to improve their properties and to achieve various biological functions in the oral environment [4]. This review article provides a wide overview about various uses of Cerium Oxide Nanoparticles in the dental field. The use of Cerium Oxide Nanoparticles in dentistry includes antimicrobial activity, dental caries prevention, modifications in dental materials, dental implant coating, tissue engineering, periodontal therapy and root canal disinfection.

2- Dental applications of Cerium Nanoparticles

Cerium Oxide Nanoparticles (CeO_2NPs) introduced significant uses in the dental field owing to their superior biological activities which are in the growing phase.

2-1. Antimicrobial effect of Cerium Oxide Nanoparticles

Cerium is an effective long-lasting biocide in the prevention of bacterial infection because it is safe for human cells compared to other metal ions. Modified cerium nanomaterials are performed to improve the antimicrobial activities against different gram positive and gram-negative microbes. The antibacterial property of Cerium Oxide Nanoparticles was assessed commonly using agar well diffusion method, fluorescence cell viability assay and time-kill assay [5].

The antibacterial mechanism of Cerium Oxide Nanoparticles depends on interacting with the bacterial cell membrane by electrostatic attraction which produces ROS which helps in bacterial cell death. There are four steps included in this antibacterial activity of cerium oxide. The first is the adsorption of Cerium Oxide Nanoparticles onto the -ve charged bacterial cell wall through direct contact by electrostatic attraction. Cerium Oxide Nanoparticles (CeO2NPs) maintain on the bacterial surface for a long time without penetrating the cell membrane because of the electrostatic interaction, blocking the bacterial cell wall and modifying bacterial membrane diffusion, reduces specific ionic pumps, finally disrupting bacterial cell growth. The second step targets the proteins, where cerium ions modify the electron flow and bacterial respiration [6]. Further, Cerium Oxide Nanoparticles impair nutrient transportation by getting absorbed onto transporters. Furthermore, cerium oxide particles with rough edges lead to damage of the bacterial membrane physically especially those of gram-positive bacteria [7]. Oxidative stress is resulted through production of the reactive oxygen species (ROS) through the change between Ce (III) and Ce (IV) on the bacterial cell membranes. This ROS results in chemical degradation of the organic constituents of the bacteria such as polysaccharides, proteins, lipids, DNA and RNA, with severe damage to the bacterial cell. The cerium-based nano-enzymes cleave the extracellular DNA of Streptococcus sanguinis, Porphyromonas gingivalis and Fusobacterium nucleatum which are important components of biofilm formation by exhibiting mimetic activity with deoxy ribonuclease. Therefore, the cerium-based nanoenzymes disrupt and eliminate the established biofilms [8].

2-2. **Role of Cerium Oxide in Caries prevention**

The process of caries prevention includes mainly three procedures; destroying the cariogenic bacteria, controlling the oral biofilm, and altering the tooth surface [9]. The use of nanotechnology in dentistry provides great possibilities of using various metal oxides for dental caries elimination. Cerium Oxide Nanoparticles revealed good impact on caries elimination [10]. The role of CeO_2NPs in inhibition of biofilm cariogenic bacteria is considered an important strategy of caries inhibition. It inhibits the production of a sucrose-based biofilm by Streptococcus mutans [11]. The second strategy in caries prevention by Cerium Oxide Nanoparticles is based on its superior antibacterial effect against Streptococcus mutans. Santos et al. [12] evaluated the antibacterial potential of CeO_2NPs against S. Mutans. Results revealed an important correlation between the purity of the nanoparticles and their size with their antibacterial activity. This study also demonstrated an antibacterial effect against other microbes as E. coli and B. subtilis through the reactive oxygen species. The third strategy regarding caries prevention include altering of the tooth structure. Hydroxyapatite (HAP) is the structural unit of tooth enamel which is mainly constructed of calcium molecules and phosphorus molecules. There were several trials to enhance the crystallinity, solubility and hardness of the hydroxyapatite to make the tooth enamel more acid resistant. One of these attempts is replacement of Ca^{+2} ions of enamel with metal ions. The doping of Cerium Oxide inside hydroxyapatite is possible because the radius and the electronegativity of Ce^{3+} are quite close to that of calcium ions $Ca^{2+.}$ Zhang et al. [13] examined the effect of lanthanide metals as cerium and lanthanum on root carious lesions compared to fluorides. It was revealed that the resistance of lanthanide metals to acids showed comparable values to that of fluoride group. While, the effect of both fluoride and cerium together exhibited more acid resistance. A study by Wegehaupt et al. assessed the anti-erosive capability of cerium chloride, laser irradiation and amine fluoride on dentin. The results revealed that the combination of amine fluoride and cerium chloride had the highest anti-erosive potential on dentin. The mechanism by which the cerium increases the HAP acid resistance is through replacing calcium in the hydroxyapatite with cerium ions, because it has the same atomic radius of calcium, and high electric charge valence that influences the apatite stability [14].

2-3. **Modifications of dental materials:**

Recently, incorporation of nanoparticles into different dental materials are of great importance to improve their properties. Metal oxides as Cerium Oxide Nanoparticles (CeO2NPs) in various types of restorations as glass ionomer restoration, resin composite, pit and fissure sealants, porcelains and adhesives.

2-3.1. Cerium oxide-based glass restoration

Glass ionomer (GI) is one of the most popular restorative material used in dentistry. It has been used in restoration of primary teeth, carious and non-carious cervical lesions, cementation of fixed restorations, sandwich technique restoration and restoration in atraumatic restorative therapy [15]. Glass ionomer (GI) is characterized by its ability to bond chemically to the tooth structure and it has a low coefficient of thermal expansion and contraction nearly the same to that of the tooth structure, besides its ability to release fluoride with its characteristic antibacterial effect. Despite these advantages, surface roughness, low fracture toughness, the internal cracks with high porosity of glass ionomer resulting in unfavorable microleakage with subsequent secondary caries. Because of the glass ionomer disadvantages, the inclusion of metal nanoparticles with a promising antibacterial potential were performed. Nanoparticles make a positive interaction with the oral microbes increasing the antibacterial effect. Therefore, CeO2-NPs can eliminate the occurrence of recurrent caries adjacent to restorations improving its clinical durability [16]. Glass ionomer incorporated with Cerium Oxide Nanoparticles (CeO2-NPs) revealed an antibacterial activity, not only reducing bacterial proliferation but it also affects the function of the mitochondria, cell division and DNA replication resulting in changes in oxidative stress produced by reactive oxygen species and microbial cell damage [17]. Several studies evaluated the ability of the addition of CeO2-NPs into glass ionomer to enhance its physical as well as its mechanical properties. Jairam et al. [18] concluded that the Cerium-modified glass ionomer cement revealed an improvement in microhardness, tensile and compressive strength with CeO2 NP-GIC (8%) and an antibacterial activity against *S mutans*. Cytotoxicity was also examined by MTT assay confirmed the non-toxic effect of the material proving it safe for dental applications. Evaluation of the optical properties CeO2 NPs modified glass ionomer cement showed color values which closely resemble those of natural teeth.

2-3.2. Cerium oxide-based pit and fissure sealants

Lee et al. [19] assessed the degree of adhesion of S. Mutans and the surface roughness of a pit and fissure sealant containing CeO_2NPs. The results revealed no significant difference in surface roughness between cerium oxide-based pit and fissure sealant and the pit and fissure sealant without nanoparticles (control). Regarding the antibacterial capacity of CeO_2NPs with various concentrations (1% & 2%) revealed an improved antibacterial activity. Another study by Jeong et al. [20] the physical properties of cerium nanoparticles with (0-4.0 Wt%) was included to the commercial pit and fissure sealant (Concise TM). The depth of polymerization, the degree of solubility and the degree of water absorption were assessed. MTT assay was used to assess the cell viability. Results showed that the depth of polymerization was reduced by increasing the CeO_2NPs amount. The degree of solubility of the pit and fissure sealant containing 2.0 wt% CeO_2NPs showed lower values than the control group. While, there was no statistically significant difference regarding water absorption of the pit and fissure sealant containing CeO_2NPs with the control group. The cytotoxicity test revealed high survival values for the experimental groups. It was concluded that pit and fissure sealant exhibited excellent cell viability without weakening the physical properties with no cytotoxic effect.

2-3.3. Cerium oxide fillers-based Resin Composite

Numerous studies have revealed that resinous restorative dental materials enhance the production of oral biofilm. This bacterial biofilm is formed by the by-products of the breakdown of the dental monomers of the resinous restorative materials, as Triethylene glycol Dimethacrylate (TEGMA) and Bisphenol A-glycidyl dimethacrylate (BisGMA) that enhance *S. mutans* growth [21]. Metal as well as metal oxide nanoparticles have antioxidant potential against oral microbes. This antioxidant activity is referred to the free electrons transfer from the oxygen molecules of metal oxides to that exist on the microbes [22]. The metal oxide within the lanthanide group, as cerium oxide (CeO_2), have a promising antibacterial potential and could be used to efficiently eliminate oral microbes. In addition, the CeO2 nanoparticles' antioxidant property and their ability to delay the release of metal oxide ions are unique properties that make them better than other metal nanoparticles. Addition of Cerium Oxide Nanoparticles to resin-based restorations can improve their mechanical properties [23]. The rate of occurrence of recurrent caries for polymer restorative materials is very high which represents about 60% of the main reasons of resin composite restoration failure [24]. Application of Cerium Oxide Nanoparticles to resin composite restoration has been considered due to its antibacterial activity, but it may be limited because of the deterioration of the mechanical properties. Therefore, a study by Sung‑Yun Byun et al., examined mesoporous silica (MCM-41) coated with CeO_2NPs regarding its antibacterial effect and mechanical properties when incorporated into resin composite restoration. The mesoporous silica -coated with CeO_2NPs were examined for their antibacterial activity against *S. Mutans*. The mechanical properties including depth of cure and flexural strength were assessed based on ISO 4049. The mesoporous silica-coated Cerium Oxide Nanoparticles exhibited significantly improved antibacterial capacity in comparison to that of the control group. The flexural strength showed a decrease as the amount of mesoporous silica (MCM-41) coated with CeO_2NPs increased [25].

2-3.4. Dental adhesives incorporated cerium dioxide particles

Secondary caries is considered one of the most frequent types of failure of resin composite restorations. Secondary caries is difficult to be diagnosed during clinical examination, so radiographic examination is mandatory for confirmation of the lesion. During the radiographic examination of secondary caries, there will be mis-judgement of radiographic image due to the radiolucency of dental adhesives. To overcome this problem radiopaque inorganic filler with high atomic weight is added into the dental adhesives, since its radiopacity depends on the filler content [26]. Therefore, Cerium Oxide Nanoparticles were added to dental adhesives to enhance the radiopacity and to easily detect dental adhesives below resin composite restorations. Inclusion of Cerium Oxide Nanoparticles to dental adhesives effectively increased their radiopacity and showed the same degree of conversion compared to commercially available dental adhesives. A study evaluated the radiopacity of cerium oxide-incorporated adhesive in comparison to a dental adhesive without fillers, it was revealed that CeO_2NPs could be considered a potent radio-opacifier when added to dental adhesives [27].

2-3.5. Cerium oxide-based glass ceramics

Recently, glass ceramics have been used for different dental uses due to their superior characteristics. Glass ceramics characterized by their superior aesthetic appearance compared to metal-ceramic restorations, high compressive strength, translucency, biocompatibility, superior chemical stability in the oral environment, low thermal conductivity and high abrasion resistance. Dental glass-ceramic suffers from several drawbacks as brittleness, low fracture toughness and tensile strength as well as sensibility to crack propagation. Therefore, several trials have been introduced to improve their mechanical properties. It was revealed that cerium oxide particles act as a glass network-modifier of silicate-based glasses and could improve crystallization by reducing glass viscosity [28]. While, other studies showed that there was an increase of the viscosity of silicate melts when Cerium Nanoparticles were found in the glass constituents. An increase of the amount of cerium oxide in the glass constituents enhances glass network connectivity by reducing non-bridging oxygens. It was concluded that the chemical stability of cerium oxide-based glass ceramics was improved mainly by the improvement of the chemical stability of the residual glass phases [29].

2-3.6. Cerium oxide-based mineral trioxide aggregate (MTA)

Mineral trioxide aggregate is a bio-material which have the ability to improve tertiary dentin formation and promoting the odontoblastic differentiation [30]. Cao et al. [31] examined the effect of adding CeO_2NPs as a potent antioxidant within a commercially available MTA on the differentiation and proliferation of dental stem cells. Results revealed that the addition of CeO_2NPs into mineral trioxide aggregate significantly increased the differentiation of stem cells as indicated by alkaline phosphatase activity.

2-3.7. Cerium oxide acting as a decolourizer

Cerium oxide was included into the porcelain material using different concentrations (0.10 wt.%-0.20 wt.%), resulted in decrease in the staining of porcelain [32]. Cerium oxide is commonly used as a strong decolourizer for iron and also to get a colourless feldspar glass. Vargin and Osadchaya [33] revealed that cerium oxide particles have an excellent decolourizing effect at concentrations from (0.15% - 0.40%). The incorporation of silver-based alloy during the fabrication of porcelain fused to metal crowns imparts unpleasant yellow-green colour. Therefore, attempts had been made to decrease the silver staining in the dental porcelain crown. Cerium oxide has the ability to reduce this silver staining by its oxidizing property of the tetravalent cerium which helps in prevention of colloidal silver precipitation [34].

2-4. **Cerium oxide in Tissue engineering**

The tissue engineering process involves three essential components which are; stem cells, growth factors and scaffolds. Mesenchymal stem cells (MSCs) are extensively used for tissue regeneration but they unfortunately exhibited a slow rate of cell proliferation. Cerium oxide has been frequently used in the field of tissue engineering. It has been used as nano-cerium embedded films, hydrogels and nano-fiber scaffolds with satisfactory results. For cell growth improvement, nano-crystalline cerium oxide combined with gadolinium that is considered as a growth stimulator, increasing the proliferation rate of cells. Therefore, it was concluded that CeO_2NPs can be considered as a cost-effective stimulator for proliferation of the dental pulp stem cells (DPSCs) [35]. Cerium oxide and yttria nanoparticles could improve the proliferation of DPSCs due to the antioxidant potential of CeO_2 and yttrium oxide nanoparticles [36].

ROS threaten the survival and differentiation of mesenchymal stem cells. Since CeO_2NPs can scavenge ROS, it was used in protection and preservation of MSCs from the oxidative stress. Two morphologies of Cerium Oxide Nanoparticles were introduced which either; short nanoparticles or long nanowires. The penetration rate of short nanoparticles into stem cells is faster than the penetration rate of the long particles. Because of this difference in penetration rate, there are both intra and extra-cellular suppression of reactive oxygen species (ROS) which lead to a prominent viability of stem cells [37]. The superior protective effect of CeO_2NPs on mesenchymal stem cells provides a promising future for its use in tissue engineering.

2-5. **Periodontal therapy**

Periodontal therapy is based on preservation of the healthy periodontium and bone. Cerium Oxide Nanoparticles revealed noticeable suppression of the osteoclasts and reducing bone resorption which are the main goals of periodontal therapy [38]. A study evaluated the impact of artemisinin-based cerium-doped mesoporous calcium silicate nano-particles on proliferation of fibroblastic cells of the periodontal ligament, it was revealed that proliferation of fibroblasts was increased [39]. In addition, Popov et al. [35] concluded that nanocrystalline cerium oxide is an effective material for stem cells culture.

2-6. Cerium oxide for dental Implant coating

Microbial-induced peri-implantitis is one of the causes of failure of most dental implants. The clinical durability of dental implants is based on the anti-inflammatory, antibacterial and osseointegration properties. Since Cerium Oxide Nanoparticles introduce all these properties, dental implants are coated with this nano-material. Cerium oxide with a prominent antioxidative capacity protects the osteoblasts from oxidative stress through the reversal of antioxidant defense system intracellularly. Yue *et al*. [40] coated a titanium-based dental implant with cerium oxide processed by plasma spraying technique. They concluded that cerium oxide coated on titanium dental implant exhibited excellent antibacterial, biocompatibility and osteogenic properties which is important for peri-implantitis prevention.

2-7. Dentin remineralization and disinfection of root canal

Root canal treatment is an endodontic procedure for management of teeth with apical periodontitis and/or irreversible pulpitis [41]. Achieving thorough cleansing of the root canals remains a great challenge because of the complicated anatomical structure of the root canals, for example, C-shaped canals and lateral canals [42]. Although the performed dental procedures during root canal treatment can approach the full length of the root canal, there are some sources of infection may still in some regions where the used dental instruments and disinfectants are inaccessible [43]. Inadequate achievement of an apical-coronal seal leads to permeation of tissue fluids with large amounts of glycoproteins inside the root canal, resulting in an environment suitable for the oral microbes to flourish, with initiation of a peri-radicular infection [44]. The above-mentioned problems of the chemical and mechanical preparations of root canal treatment, intracanal medicaments are commonly used to decrease the bacterial count. Although numerous intracanal medicaments as $Ca(OH)_2$ have been widely recommended, they have concerns regarding potential allergenic and mutagenic effects. Nowadays, metal nanoparticles-based disinfectants have gained an increasing interest within the field of endodontics. Among these nanoparticles, is Cerium Oxide Nanoparticles that have been used for the prominent antifungal, anti-inflammatory, antibacterial, antibiofilm properties regarding the disinfection process of the root canals [45]. Extensive researches have proved the capability of CeO_2NPs to affect the bacterial growth, especially S. mutans and E. Faecalis while keeping superior biocompatibility. However, if CeO_2NPs are used as canal disinfectants, they do not introduce an antibacterial effect for a prolonged duration compared to nanoparticles of other metals. The Biomimetic Mineralization process simulates the natural mineralization by replacement of water within the demineralized-organic matrix with the apatite crystals, which is considered an advanced approach [46]. This process of remineralization was used for sealing of dentinal tubules of the root, reinforcing the root dentin with the improvement of its mechanical properties based on the use of hydroxyapatite during root canal therapy. Cerium Oxide Nanoparticles (CeO_2NPs) deposited into the demineralized collagen fibers of root dentin seals the regions which are inaccessible to the performed mechanical and chemical procedures. In addition, it also burdens any remaining bacteria. Besides, the re-mineralized root dentin has the ability to leach antibacterial agents for a long-lasting antibacterial purpose [47].

3- Conclusion

Cerium Oxide Nanoparticles (CeO_2NPs) showed promising applications in ~~the medical~~ ~~and~~ dental fields. It can be used in the dental field safely because it exhibits biocompatibility with a wide range of antibacterial, antioxidant and cell differentiation potential. Cerium Oxide Nanoparticles have many beneficial uses because of its unique surface reactivity and physicochemical properties. Further research is warranted regarding the prospected applications of Cerium Oxide Nanoparticles (CeO_2NPs) in biological simulated models and animal studies. Long-term toxicological studies are necessary to determine the long-term impacts of Cerium Oxide Nanoparticles (CeO_2NPs).

- **Conflict of Interest**

The author declares no conflict of interest.

4. References

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