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Review

Applications of Nanotechnology in Endodontics: A Narrative Review

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Abstract: The term "nanodentistry" was first introduced at the beginning of the 21st century. In recent decades, nanotechnology has progressed significantly, creating numerous opportunities for application in various biomedical fields. In particular, the use of nanoparticles in endodontics has attracted considerable interest due to their unique characteristics. As a result of their nano-size, nanoparticles possess several properties that can improve the treatment of endodontic infections, such as increased antibacterial activity, increased reactivity, and the ability to be functionalized with other reactive compounds. Materials whose size is less than 100 nm in at least one dimension are referred to as nanomaterials. Among nanoparticles can be found grains, fibers, clusters, nano-holes, or their combinations. The main feature of nanoparticles is their large surface area per unit mass compared to bulk matter. Due to their large surface area, nanoparticles have significantly modified the physical and chemical properties of the material in comparison to bulk matter. Nanoparticles with their modified and specific physicochemical properties, such as ultra-small size, large surface area/mass ratio, and increased chemical reactivity, have opened new prospects in endodontics. In this study, a comprehensive electronic search was conducted using MEDLINE (PubMed), Google Scholar, and open-access journals published by Elsevier. The search terms "nanotechnology", "nanotechnology in dentistry", and "classification of nanoparticles" were used in various combinations. In total, 40 articles were identified, out of which 16 were selected for inclusion in the study. These selected articles comprise both research and review articles. This review provides insights into the unique characteristics of nanoparticles, including their chemical, physical, and antimicrobial properties; limitations; and potential uses. Various studies concerning different methods of using nanoparticles in endodontics have been thoroughly studied. Based on previous clinical studies, methods of nanoparticle use in endodontics were evaluated. The findings indicate that nanoparticle applications in endodontics have a lot of potential.

Keywords**:** endodontics, nanodentistry, nanoparticles

1. Introduction

Dr. Richard Feynman first explained the concept of nanotechnology in 1959. In 1991, Dr. Sumio Lidjima introduced the concept of nanotubes. The term "nanodentistry" was coined by Dr. Freitas Jr. in 2000. He developed nanomaterials and nanorobots for the regeneration of dentition and developed "dentifrobots" – robots for cleaning teeth [1-3]. In general, materials with a size of less than 100 nm in at least one dimension are considered nanomaterials [4, 5].

Innovative endeavors have since led to nanotechnology being incorporated into a myriad of areas in clinical

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dentistry, such as direct restorative materials, materials used for dental prostheses, periodontal treatment, guided tissue regeneration, modifications of implant surfaces, and endodontics [6-8]. Due to their properties, benefits over other conventional materials, and mechanism of action, there has been an enormous increase in the application of nanoparticles in various fields of dentistry since their introduction (Figure 1).

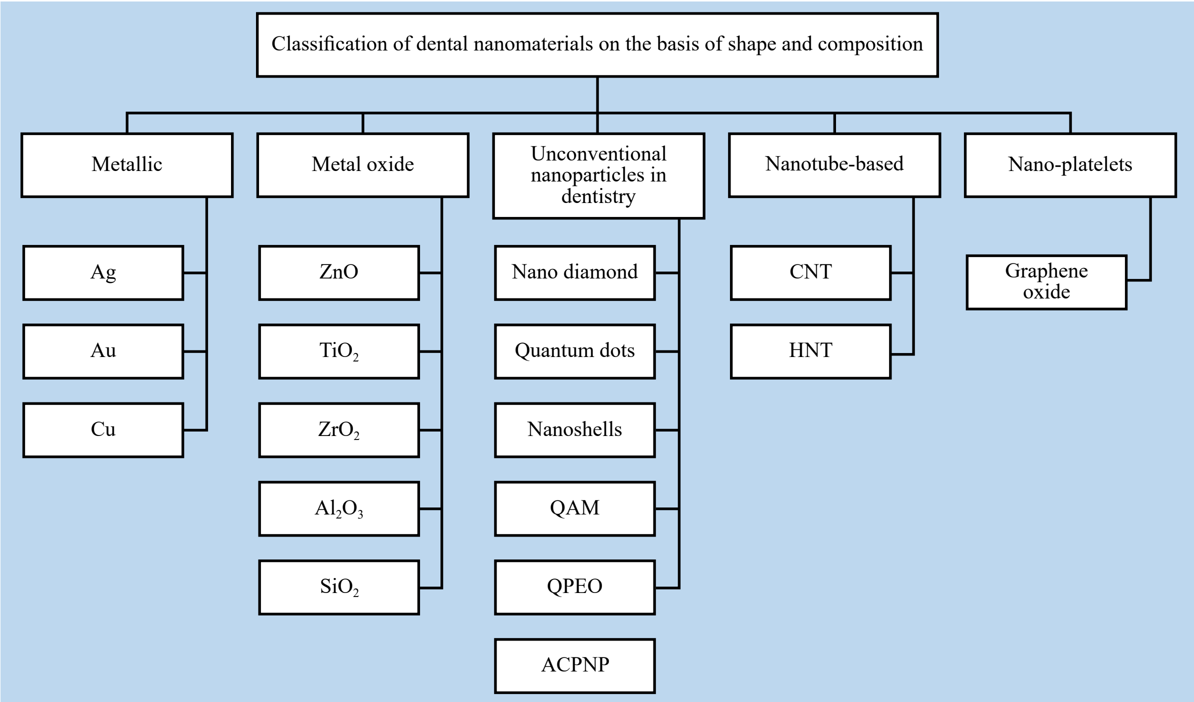

Figure 1. Classification of dental nanomaterials on the basis of shape and composition [9] (Abbreviations: QAM - quaternary ammonium; QPEI - quaternary ammonium polyethylenimine; ACPNP - amorphous calcium phosphate nanoparticles; CNT - carbon nanotubes; HNT - Halloysite nanotubes)

2. Materials and methods

Materials whose size is less than 100 nm in at least one dimension are referred to as nanomaterials. Nanoparticles possess specific physicochemical properties, such as ultra-small size, a large surface area to mass ratio, and increased chemical reactivity. Their properties are considerably different in comparison to bulk matter [4, 5].

For the present study, an electronic search was done using MEDLINE (PubMed), Google Scholar, and open-access journals which are published by Elsevier. For the search words and phrases such as: «nanotechnology», «nanotechnology in dentistry», and «classification of nanoparticles» were used in various combinations. 40 articles were found, from which 16 were selected. The selected items include research and review articles.

For this review article, a narrative review [10] was performed using a comprehensive literature search. The search considered works published from 2010 until November 2022 using the above-mentioned keywords.

Only relevant literature in English from the electronic search was selected for the present review. The nanoparticles had to be used in endodontics. The inclusion criteria are as follows: (i) use of existing commercial materials or their modifications in dental praxis; (ii) use of nanoparticles in endodontics; (iii) full-text journal articles written in English; (iv) books and book chapters written in English; (v) scientific works published in 2010 and later (only for the discussion chapter because there we review these relevant papers); (vi) books and book chapters of highly rated publishers (Wiley, Elsevier, and Springer). The exclusion criteria are as follows: (i) case reports (clinical trials); (ii) conference papers; (iii) materials published earlier than 2009; (iv) randomized controlled studies; (v) editorials.

(1) The search was carried out in MEDLINE (PubMed) and Google Scholar using the keywords «nanotechnology», «nanotechnology in dentistry», and «classification of nanoparticles» in various combinations. In total, 40

records were found.

(2) The first and third co-authors analyzed 40 records for compliance with the inclusion and exclusion criteria. An additional 15 records were identified from the reviewer's suggestions. In total, 24 records were deleted, i.e., 31 records remained.

(3) All selected records were distributed among all authors for reading the full-text articles and preparation of the manuscript. The procedure is shown in Figure 2 of the PRISMA flowchart.

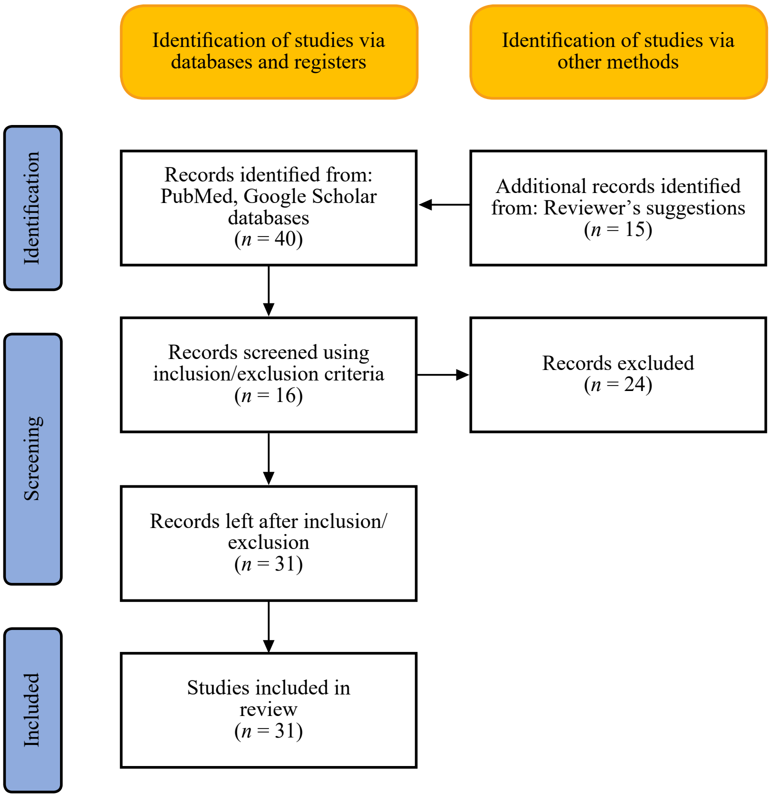

Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of inclusion/exclusion criteria

3. Results

Biofilms are highly organized, surface-adjacent structures of microcolonies [11]. The main component of biofilms is an exopolymeric matrix consisting of polysaccharides, proteins, enzymes, and bacterial metabolites [12, 13]. Exopolysaccharides are synthesized both intracellularly and extracellularly and perform skeletal functions [14]. The extracellular matrix of the biofilm is secreted by bacteria and consists of metabolic polymers that firmly adhere to surfaces. Biofilms develop in stages: initial attachment of microbes to the surface or bacterial cell, formation of microcolonies, maturation, and finally, expansion of the biofilm [15, 16].

Persistent microflora in the lumen of numerous dentinal tubules is practically not amenable to medicinal and instrumental treatment of root canals. Chemical irrigation solutions, intracanal preparations, and topical antibiotics have been used for years to eliminate biofilms. However, over time, microorganisms can develop resistance to these antimicrobial agents. Therefore, research has focused on new anti-biofilm strategies [17, 18]. The diameter of dentin tubules is only 200-300 nm, which prevents the penetration of even the strongest antiseptics. The inclusion of metal nanoparticles in antiseptics for root canals can help cope with resistant microflora (*Enterococcus faecalis*) after one week [19, 20].

In endodontic treatment, nanotechnology plays an important role in the development of advanced endodontic materials. The properties of endodontic materials can be improved through the use of nanotechnology by incorporating antibacterial nanoparticles, which can prevent the recurrence of infection and the ineffectiveness of root canal treatment [9, 21].

These nanoparticles can be incorporated into sealers, obturation material, intracanal medications, and irrigation solutions to achieve desired results [8] (Figures 3 and 4).

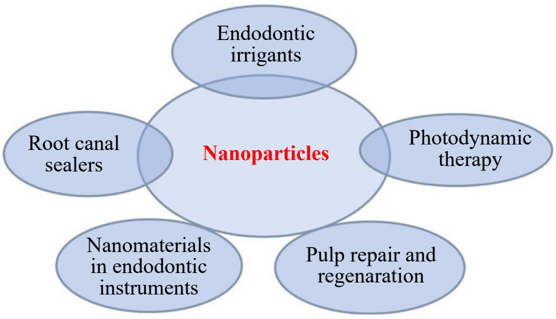

Figure 3. The applications of nanoparticles in endodontics [22]

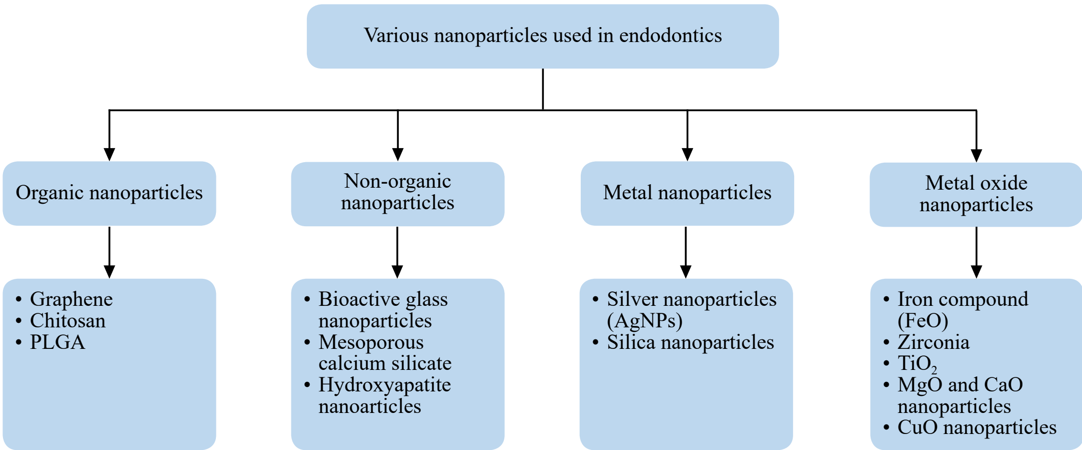

Figure 4. Variety of nanoparticles used in endodontology

3.1 *Modern methods of bacterial disinfection*

Modern cleaning and shaping of root canals are based on the application of chemical mechanical processing to achieve optimal bacterial disinfection. The purpose of root canal irrigation is chemical dissolution or destruction and mechanical removal of the pulp tissue, debris of dentin and smear layer, microorganisms and their byproducts from the wall of the root canal, and debridement of the entire root canal system.

3.1.1 *Endodontic irrigation*

One of the most important elements of root canal treatment is their disinfection by irrigation.

Irrigants facilitate the removal of microorganisms, tissue remnants, and dentinal debris from the root canal; prevent the compaction of hard and soft tissues in the area of the apical hole and the intrusion of infected remnants into the periapical area; dissolve organic and inorganic tissues in the root canal. Irrigation makes it possible to remove infected tissues that are inaccessible to mechanical debridement alone. Theoretically, the irrigation liquid is able to reach all areas of the canals, removing pathological tissues from them without damaging the healthy tissues of the root canal [23].

During the preparation of hard tooth tissues with manual or rotary tools, a smear layer is formed on the dentin surface, which is characterized by a high content of organic components in the form of pulp tissue remnants, odontoblasts, and weakly mineralized pre-dentine. To remove the smear layer from the inner walls of the root canal, liquids that are effective for both organic and mineral component removal are required. Thus, effective chemo-mechanical treatment is important to eliminate root canal infection [7, 24].

The most commonly used irrigants are chlorhexidine (CHX), ethylenediaminetetraacetic acid (EDTA), and sodium hypochlorite (NaOCl) (Table 1).

Table 1. Most widely used endodontic irrigants and their properties

Conventional irrigants	Properties	Drawbacks
NaOCl 0.5% to 5.25%.	Tissue dissolving and antimicrobial properties	Breakdown and weakening of the organic dentin matrix. Damage to the periapical tissues.
CHX 2%	Antibacterial properties and substantivity	Inability to degrade necrotic tissue. Reduced efficacy against Gram-negative microbes.
EDTA 17%	Chelating agent	Excessive use can lead to dentin demineralization and erosion.

It is necessary to influence the organic substance of dentine of the root canal with NaOCl in the form of 0.5-5.25% solutions. To influence the inorganic substance in the root canal, drugs based on EDTA-ethylenediaminetetraacetate 15-17% are used. The mechanism of action of CHX is associated with the adsorption of the solution on the wall of microorganisms, which causes the leakage of their intracellular components. It is bacteriostatic in low concentrations, and bactericidal in high concentrations.

Although the aforementioned irrigants have proven to be effective antimicrobial agents, they do not guarantee complete disinfection of the root canal space, and none of the existing technologies guarantee complete removal of endodontic biofilms.

The introduction of antimicrobial nanoparticles is considered a new strategy for increasing the effectiveness of root canal irrigants. Formulations based on nanoparticles have been found to have better penetration, and a slow and controlled release of active ingredients at target sites [25, 26]. The antimicrobial properties of metal nanoparticles are well known and are of great importance in strategies designed to eradicate chronic infections [27]. The most popular metal nanoparticles are silver nanoparticles.

3.1.2 *Photodynamic therapy*

Biofilm disruption and disinfection of root canals are the most critical steps during the treatment of an infected root canal system, which are essential to avoid the persistence of microbial infection and achieve endodontic success [28]. Total asepsis of the root canal is not possible to achieve despite effective current instrumental techniques and modern antiseptics. Antimicrobial photodynamic therapy (aPDT) has emerged and provided excellent experimental results, anticipating a new era in endodontic disinfection [29]. The chlorophyll derivative Zn(II)e_6Me showed adequate antimicrobial efficacy, performing better in mixed biofilm removal [30].

PDT is an adjunctive, conservative, non-selective approach to eliminating bacteria. The technique of a PDT is used to improve root canal disinfection without inducing bacterial resistance [31]. The PDT principle is not only effective against bacteria but also against other microorganisms, including viruses, fungi, and protozoa [32-34]. PDT uses a photosensitizer and light of a specific wavelength, e.g., toluidine blue at 600 nm wavelength. Effective oral biofilm destruction with methylene blue dye (photosensitizer) encapsulated within poly(D, L-lactide-co-glycolide) (PLGA) nanoparticles (≈ 150 nm to 200 nm in diameter) [35].

3.2 *Nanomaterials in endodontic instruments*

The introduction of nickel-titanium (NiTi) alloys and the subsequent automation of mechanical preparation were the first steps toward a new era in endodontics. Endodontic files are used to make the instrumentation of the root canal in the endodontic procedure. NiTi file systems have been introduced to minimize the chance of endodontic procedure errors. Despite high flexibility and increased torsional fracture resistance when compared with conventional stainless-steel instruments, NiTi files are very subject to cycle fatigue and risk fractures that occur unexpectedly and frequently without being preceded by visible defects resulting from permanent deformation [36].

NiTi alloy was originally developed for the U.S. space program at the Naval Ordnance Laboratory, in 1963, and was given the generic name "Nitinol" [37]. In dentistry, it was first used in 1971 by Andreasen and Hilleman, in the manufacture of orthodontic wires, due to its low modulus of elasticity, shape-memory effect, and super-flexibility. Specifically in endodontics, Civjan et al. [38] were the first to conceptualize the fabrication of endodontic instruments from the NiTi alloy, in 1975. Later, in 1988, Walia et al. [39] introduced the first handheld NiTi endodontic instruments, made by machining orthodontic wire. Thereafter, technological advances in the production of NiTi instruments allowed them to be manufactured by machining processes with significant changes in the configuration of the active part, variations in the helical angle and cut angle, and different increases in taper within the same instrument, no longer following the ISO standards published in 1958 for manual instruments [40].

From a future perspective, coating the files with nanoparticles will improve their resistance to cyclical fatigue. Also improved the resistance to corrosion by the endodontic irrigants. Cobalt coatings of the NiTi file with impregnated fullerene-like WS_2 nanoparticles significantly improved the fatigue resistance and breakage time of coated files were observed stemming from reduced friction between the file and the surrounding tissue [41].

3.3 *Root canal sealers*

Sealer forms an integral part of obturation. They hold gutta percha within the root canal space. Ideal properties of a sealer include: ease of handling, non-toxicity, biocompatibility, absence of shrinkage upon setting, effective working time, hydrophilic properties, antibacterial property, ease of retreatment, etc.

Apart from antibacterial efficacy, nanoparticle-based modifications are used to enhance other physicochemical properties of endodontic sealers, including bioactivity and radiopacity. A study by Al-Bakhsh et al. [42] found that the inclusion of bioactive glass and hydroxyapatite nanoparticles enhanced the bioactivity of an epoxy resin-based sealer.

Calcium hydroxide paste is the most commonly used material. It initiates the release of hydroxyl ions that increase the pH within the root canal, distressing the DNA, cytoplasmic membranes, and enzymes of microorganisms. Silver nanoparticles (the size of 20 nm) can be mixed with calcium hydroxide, which showed increased antibacterial action when calcium hydroxide was used alone or in combination with CHX [43].

Zinc oxide is mainly used for its antimicrobial properties. The process takes place through the electrostatic interaction of nanoparticles with the bacterial cell membrane (nanoparticles are charged positively, and the membrane is negatively charged). As a consequence of the accumulation of nanoparticles, the permeability through the membrane is inhibited, which is a further cause of bacterial cell death [44].

A bioceramic-based nanomaterial (Endo Sequence BC sealer) used as a sealer that is composed of calcium phosphate, calcium hydroxide, calcium silicates, zirconia, and a thickening agent was developed recently. Nanoparticles have improved physical properties. The nanocomposite structure of hydroxyapatite and calcium silicate forms during the hydration reaction in the root canal. This hydration reaction and setting time are affected by the availability of water, and setting time may be prolonged in overly dried canals. Nanosized particles facilitate the delivery of material from 0.012 mm fine needles and adapt to irregular dentin surfaces, providing excellent seal and dimensional stability [45].

This type of hydraulic calcium silicate cement, bioceramic, is associated with color change in the medium/long term in contact with blood [46]. It was also important to know how far one could fill the canal with these techniques without interfering with discoloration or minimizing this impact. This impact agent (oxide bismuth) has an effect on discoloration [47].

Other drawbacks of mineral trioxide aggregate (MTA) cement were lower values of shear bond strength and the fracture pattern, which were all cohesive in bioceramic. Palma et al. [48] suggest that all tested biomaterials (Biodentine and TotalFill BC) present suitable alternatives that allow performing restorative procedures immediately after pulp capping biomaterial placement (3 or 12 min), depending on the bioactive cement.

Hydraulic calcium silicate-based cement (HCSC) has gained increasing clinical relevance, enabling a more conservative approach based on pulp preservation and regeneration. To overcome some of MTA's conventional limitations, new cement has been developed; Xavier et al. [49] tested how the additional hydrophobic bonding layer and restoration time affected the bond performance and ultra-morphological interface between composite adhesive restoration and HCSC.

3.4 *Pulp repair and regeneration*

Regenerative endodontics is referred to as a biologically based procedure intended to physiologically replace damaged tooth structures, including dentin and root structures, as well as the pulp-dentin complex [50].

Regeneration of dental pulp is a dream for dental clinicians all over the world and will definitely be a game changer in clinical practice. With advancements in technology, it has become a fruitful reality. Theoretically, it is possible to regrow dental pulp inside a pulpless tooth by using growth factors, scaffolds, and stem cells [51].

The use of nanoscale scaffold materials for tissue regeneration has already been established. Nanoscaffolds comprising nanofibers of biodegradable collagen type I or fibronectin can be used for pulp regeneration. Self-assembling polypeptide hydrogels have been used for pulp tissue regeneration [52]. Poly(l-lactic acid) (PLLA) is a common synthetic polymer that can be applied in nanoform and has the ability to participate in tissue engineering.

To address this challenge of pulp regeneration, Li et al. [53] designed and synthesized a unique hierarchical growth factor-loaded nanofibrous microsphere scaffolding system. In this system, vascular endothelial growth factor (VEGF) binds with heparin and is encapsulated in heparin-conjugated gelatin nanospheres, which are further immobilized in the nanofibers of an injectable PLLA microsphere. This hierarchical microsphere system not only protects the VEGF from denaturation and degradation but also provides excellent control over its sustained release. In addition, the nanofibrous PLLA microsphere integrates the extracellular matrix-mimicking architecture with a highly porous injectable form, efficiently accommodating dental pulp stem cells (DPSCs) and supporting their proliferation and pulp tissue formation.

Regenerative endodontic procedures (REPs) demonstrate excellent success rates for the resolution of periapical pathology and increase the survival of the immature tooth. Moreover, recent histologic findings from animal studies [54] and human clinical cases [55] give information about the nature of the newly formed tissues after REPs.

Thus, based on the various research conducted over the years, it is worth saying that nanotechnology has gained significant development in the field of regenerative endodontics. The regeneration of pulp in a pulp-less tooth will soon be a reality.

3.4.1 *Organic nanoparticles*

3.4.1.1 *Graphene*

Graphene, an allotrope of carbon, is the thinnest material and forms an even crystal lattice without any structural dislocations. This nanoparticle is used for diagnosis and detection of disease and the formation of antibacterial surfaces [56].

Graphene nanoplatelet, a derivative of graphene, also showed antimicrobial properties against various microorganisms, especially *Streptococcus mutans*, in a study performed by Rago et al. [57]. The SEM (scanning electron microscopy) images showed that a strong mechanical bond exists between the graphene nanoplatelet and cells, which involves shrinking and trapping of cells, ultimately leading to the death of these microorganisms.

3.4.1.2 *Chitosan nanoparticles (Cs-NPs)*

Cs-NPs are one of the commonly investigated polymeric nanoparticles in endodontics. Chitosan is a natural polysaccharide that is obtained by deacetylation of chitin, one of the most abundant polysaccharides in nature that forms most of the external skeleton of arthropods such as crabs and shrimps [58-61].

The mechanism of action of Cs-NPs is based on the principle of electrostatic interaction leading to cell membrane disruption. This results in increased permeability of the cell wall, eventually causing cell death and microleakage of its intracellular components [62].

Cs-NPs have shown enhanced antibiofilm efficacy and have the potential to disable bacterial endotoxins. These nanoparticles cause enhanced bacterial degradation, as demonstrated by the organized release of singlet oxygen species. They are suggested for usage as a finishing rinse in the irrigation of root canals as they are non-toxic to eukaryotic cells [56, 63, 64].

3.4.1.3 *PLGA*

PLGA is a biodegradable polymer used in a wide range of medical applications. In particular, PLGA materials are also being developed for the dental industry in the form of scaffolds, biofilms, membranes, microparticles, or nanoparticles [65]. Biocompatibility, biodegradability, flexibility, and minimal side effects are the main advantages of using this polymer for biomedical purposes. PLGA microparticles were successfully studied in a wide range of dental applications, such as endodontic therapy [66]. In endodontics, PLGA and zein microspheres are able to deliver significant amounts of amoxicillin into the root canal and exceed concentration levels required for appropriate endodontic disinfection. Amoxicillin was chosen because it is effective against *E. faecalis*. This microorganism is responsible for endodontic failure and retreatment cases. *E. faecalis* is the most resistant to root canal debridement and intracanal dressings [67].

3.4.2 *Non-organic nanoparticles*

3.4.2.1 *Bioactive glass*

In 1960, Piotrowski et al. [68] developed bioactive glass, which consisted of strictly defined proportions of sodium oxide, calcium oxide, phosphorus pentoxide, and silicon dioxide. SiO_2, Na_2O, and P_2O_5 in different concentrations form the main components of bioactive glass. Their size ranges from 20 to 60 nm [69].

Bioactive glass in micro- and nanoforms is used for the disinfection of root canals. Bioactive glass has antibacterial properties. This is possible when several factors work together [70]. These include high pH, Ca/P deposition, and osmotic effects.

An increase in pH occurs when bioglass dissolves in water and thus releases ions. In turn, deposited Ca/P ions initiate mineralization on the surface of bacteria, and an increase in osmotic pressure above 1% inhibits numerous bacteria [71].

3.4.2.2 *Mesoporous calcium silicate*

These are nanoparticles with sizes ranging from 80 to 100 nm and a high specific surface area and pore volume ratio. These nanoparticles find their use in the filling of the apical third of the root canals due to their property of being highly viscous in nature [72]. Its other advantages in endodontics include drug delivery, antibacterial efficiencies, injectability, apatite mineralization, and osteostimulation [73].

3.4.2.3 *Hydroxyapatite nanoparticles*

Hydroxyapatite (HA) is one of the most studied biomaterials in the medical field for its proven biocompatibility and for being the main constituent of the mineral parts of bone and teeth. Nano-hydroxyapatite presents crystals ranging in size between 50 and 1000 nm. HA ($Ca_5(PO_4)_3OH$) possesses superior qualities such as high biocompatibility, properties similar to human hard tissues, antibacterial properties, and bioactivity.

Their main function is to integrate into the dentinal tubules and seal their opening, preventing the exposure of nerves to external stimuli. Also, they have an important role in decreasing dentin hypersensitivity. HA is very biocompatible, is capable of reducing local or systemic inflammatory reactions, and can be used as an agent in periapical healing [74].

3.4.3 *Metal nanoparticles*

3.4.3.1 *Silver nanoparticles (AgNPs)*

The biological activity of AgNPs, like other products containing silver, occurs through the gradual release of silver as a consequence of redox reactions in the presence of water [75]. One of the most important mechanisms of action of AgNP is represented by the induction of reactive oxygen species (ROS) production, and hydroxyl radicals are the main species responsible for oxidative damage [76].

AgNPs can easily penetrate the bacterial cell membrane due to their larger surface area and small sizes causing rapid bactericidal action. It is biocompatible, shows low bacterial resistance, low toxicity, and longstanding antibacterial activity. Biologically produced AgNPs have shown effective antibacterial properties against *E. faecalis* [77]. When used as an irrigating solution, poly(vinyl alcohol) (PVA)-coated AgNPs were efficient against *Pseudomonas aeruginosa*, *Candida albicans*, and *E. faecalis* [78]. Irrigating with AgNPs solutions may influence the physical and structural properties of root dentine. Using an AgNP-based irrigant as a final rinse almost doubled the fracture resistance of endodontic-treated teeth compared to when only NaOCl was used [79-81].

3.4.3.2 *Silica nanoparticles*

Silica nanoparticles have a positive impact in the field of dentistry, more so in conservative dentistry than in Endodontics. These nanoparticles have shown excellent biocompatibility and a large surface area with low levels of toxicity and density. They are widely used as dental fillers in various restorative materials and also as a polishing agent due to their ability to lower roughness of the polished surface [3].

3.4.4 *Metal oxide nanoparticles*

3.4.4.1 *Iron compound (FeOx)*

Iron compound (FeOx) nanoparticles have an important role in biology and the medicinal field. Magnetite and Maghemite, the two common forms of iron oxide nanoparticles, are most popular in biomedical science due to their biocompatibility and non-toxic properties to humans. They possess superparamagnetic properties at certain sizes. This allows them to have properties that make them suitable contrast agents, drug delivery vehicles, and thermal-based therapeutics [82, 83].

3.4.4.2 *Magnesium halogen-containing nanoparticles*

Magnesium-containing nanoparticles were suggested for use as antimicrobial agents against endodontic pathogens due to their known antibacterial properties against Gram-positive and Gram-negative bacteria, spores, and viruses [84]. Magnesium-containing nanoparticles are either magnesium-oxide nanoparticles or magnesium-halogen-containing nanoparticles such as chlorine, bromine, and fluorine [85, 86].

The main mechanism is penetration inside the bacterial cell, causing a disturbance in the membrane potential. The lipid peroxidation and DNA binding effects of the nanoparticles were facilitated by penetration, causing more destruction of the bacterial cell [87].

3.4.4.3 *Zinc oxide nanoparticles (ZnONP)*

Zinc oxide nanoparticles (ZnONPs) are used because of their bactericidal properties and a mechanism of action similar to that of AgNPs. A ZnONPs-based irrigant was found to eliminate planktonic *E. faecalis* and disrupt the biofilm matrix while retaining its antibacterial activity after 90 days of aging [22, 88].

Zinc oxide nanoparticles showed high antibacterial effectiveness, destroying microbial cells in a higher pH environment. The antibacterial mechanism of zinc oxide nanoparticles is similar to that of other types of nanoparticles, causing increased permeability of the cell wall membrane, a release of cytoplasmic content, and cell death [89-92]. However, its antibacterial efficacy was less pronounced against biofilm bacteria compared to their planktonic equivalents.

3.4.4.4 *Magnesium oxide and calcium oxide (MgO and CaO) nanoparticles*

Magnesium oxide nanoparticles (MgONPs) have proven multiple antimicrobial effects, and because of this, they are used in endodontics. MgO and CaO nanoparticles were proven to be efficient against both Gram-positive and Gram-negative microorganisms. Both MgO nanoparticles at a concentration of 5 mg/L and chitosan nanoparticles demonstrated long-lasting efficacy in the eradication of *E. faecalis* [93].

Metal oxides like zinc oxide and magnesium oxide have great antibacterial properties in various forms. The antibacterial and mechanical properties of the materials in which MgONPs were incorporated were tested, showing a significant reduction in the growth of *Staphylococcus aureus* [74, 94].

3.4.4.5 *Cuprum oxide nanoparticles (CuONPs)*

These nanoparticles are effective against Gram-positive and Gram-negative bacteria as they cross the bacterial cell membrane and damage the vital enzymes of the bacteria. CuONPs penetrate the bacterial cell membrane and are highly effective against Gram-positive and Gram-negative bacteria. They also possess certain antifungal properties. However, their application in the field of endodontics is limited, and further studies are required to evaluate their efficacy [3, 95].

Antibiotic-mediated synthesis of gold nanoparticles with potent antimicrobial activity researched by Rai et al. [96] suggest that the combined action of cefaclor, which inhibits the synthesis of the peptidoglycan layer, and gold nanoparticles, which cause "holes" in bacterial cell walls, results in the leakage of cell contents and eventually cell death [97].

Despite some limitations, such as low residence time in the blood circulatory system, susceptibility to proteases, and an alkaline wound environment, antimicrobial peptides (AMPs) are considered alternatives to antibiotics due to the increasing number of multidrug-resistant bacteria [98]. AMPs, such as LL37 peptides, may be immobilized on the surface of medical devices, such as dental implants, to render them antimicrobial and angiogenic properties (conjugated to gold nanoparticles) [99].

3.4.4.6 *Titanium dioxide (TiO_2) nanoparticles*

The TiO_2 nanoparticles are safe enough to be used in various areas of medicine and dentistry as a result of their biocompatibility, biosafety, and non-allergic reactions with human tissues. TiO_2 nanoparticles have a great range of uses in medical and dental applications (bone grafting, dental implants, etc.) and have been explored in recent years as antimicrobial agents [100].

3.4.5 *Possible perils of endodontic nanotechnology*

Nanoparticle-based endodontic therapies are not without disadvantages, such as the potential for cytotoxic effects on periapical and pulpal tissues.

Nanoparticles may enter into the human body in diverse ways, including the lungs, skin, gastrointestinal tract, and systemic administration. Given that nanoparticles have similar dimensions to biological molecules, they are readily absorbed by various organs and tissues and can accumulate in the lungs, liver, and reticuloendothelial system [101-103].

The environmental concerns associated with the use of nanoparticles are present as well. Nanoparticles may act as pollutants and accumulate in the environment, and given that, the toxic effects are often concentration-dependent. Bioaccumulation could result in subsequent systemic toxicity for exposed living organisms [104].

4. Conclusions

A large number of nanoparticle-containing materials are available on the market today. They provide multiple choices for their use in the medical field. The impact of nanoparticles in the field of endodontics is quickly advancing. Their applications in the diagnosis and treatment of infections and in regenerative procedures are increasing. Their unique properties, like larger surface areas and better reactivity, result in better antibacterial actions in contrast to their bulk counterparts. The era of nanoendodontics paves the way for the wider use of nanoparticles in dentistry in the future.

In this paper, we considered the pros and cons of nanoparticles with respect to endodontics. The main advantage of nanoparticles in endodontics is their application to improve existing conventional materials due to their higher reactivity with host tissues.

However, nanoparticles also have some drawbacks. First of all, they can be toxic for humans as well as for nature. It should be noted that this side is not studied enough. Another drawback is their synthesis. Nanoparticles must be safe for humans, environmentally friendly, and cost-effective. It is quite challenging to synthesize nanoparticles with the properties listed above.

It is obvious that additional clinical investigations are required to further enhance their properties and applications as well as study the possible perils of nanoparticles. We expect considerable growth in papers in this field in the near future. For instance, in [5], there is a forecast of future papers related to studies of nanoparticles in dentistry. According to the forecast made in [5], the 95% confidence interval for the number of papers published in 2022-2026 lies within the range of 256-360 papers. Thus, we can expect at least a twofold growth in papers in this field. We hope future studies will study the possible negative effects of nanoparticles on humans and nature because this field is underrepresented in scientific studies.

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Conflict of interest

There is no conflict of interest for this study.

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