AIMS Bioengineering

AIMS Bioengineering, 12(2): 265–282.
DOI: 10.3934/bioeng.2025013
Received: 28 February 2025
Revised: 22 May 2025
Accepted: 30 May 2025
Published: 23 June 2025

https://www.aimspress.com/journal/Bioengineering

Review

Tiny tools, big impact: the rise of nanoparticles in endodontics

Priyanka Bhojwani* Anuja Ikhar, Aditya Patel, Manoj Chandak and Shweta Sedani

Department of conservative dentistry and endodontics, Sharad Pawar Dental college, Datta Meghe Institute of Higher Education and research, Wardha, Maharashtra, India

Correspondence: Email: pbhojwani0000@gmail.com.

Abstract: Natural processes such as mineralization, natural disasters, and geological recycling of matter result in the constant formation of nanoparticles, which are found throughout the environment. In recent years, there has been a lot of interest in nanoparticles and their applications. Because of their unique physicochemical properties, nanoparticles provide promising new avenues for the prevention and treatment of dental infections. With potential applications of nanoparticles in clinical endodontics in the near future, robust research initiatives backed by collaborations between academia and industry are critical. These nanoparticles show a number of characteristics that may improve the way endodontic infections are treated, such as increased reactivity, improved antibacterial efficacy, and the capacity to functionalize with other reactive substances.

Keywords: Nanomaterial; advanced endodontics; bioglass

1. Introduction

Within the area of dentistry, endodontics is a specialized field that focuses on the morphology and physiology of the endodontium, which comprises the surrounding tissues and pulp. Numerous topics are covered in this field, such as prevention, epidemiology, aetiology, pathology, and, most importantly, the treatment of endodontic and periapical illnesses [1]. Remarkably, data from the American Association of Endodontists (AAE) indicates that, just in the US, almost 15 million root canal procedures are carried out each year [2]. The World Health Organization (WHO) also underscores the importance of endodontic care in global dental health initiatives [1]. A crucial element of successful endodontic therapy involves thoroughly disinfecting the root canal system [3].

The technique usually entails mechanical instrumentation to accomplish effective microbial reduction. An inert filler substance is then used to plug the canal. Still, getting rid of the bacterial biofilms that are present in the complex structure of the root canal system is a significant issue in root canal therapy [4]. The roots of nanoscience stretch back to ancient times, with early philosophical inquiries by Greek scholars like Democritus in the 5th century BC pondering the fundamental nature of matter—whether it consists of continuous, infinitely divisible substances or small, indivisible particles known as atoms. Even during the Roman era in the 4th century AD, humans already utilized nanoparticles and nanostructures. However, nanoscience was not recognized as a separate research branch until the 20th century. An important lecture given in 1959 titled "There's Plenty of Room at the Bottom" by Richard Feynman set the stage for future research into nanotechnology. Feynman laid the groundwork for contemporary nanotechnology by envisioning the direct manipulation of individual atoms and molecules to produce new materials and gadgets [5]. Since then, nanoscience has developed rapidly, with significant progress in materials synthesis, characterization techniques, and applications across diverse disciplines. In 1974, Norio Taniguchi defined "nanotechnology" as the manipulation and fabrication of materials at the scale of individual atoms or molecules, encompassing processes such as processing, separation, consolidation, and formation [6]. Following Feynman's seminal paper, "There's Plenty of Room at the Bottom", which was published in *Engineering and Science* in 1960 [7] and sparked significant interest among scientists, two distinct approaches have emerged to describe the various possibilities for synthesizing nanostructures. These approaches are categorized as top-down and bottom-up, differing in quality, speed, and cost [8,9].

The number of nanoparticle studies has significantly increased in the last several years. These particles, characterized by their size falling within the 1–100 nm range, possess an elevated surface-to-volume ratio due to their reduced dimensions. This attribute makes them highly effective in interactions with microbes [4]. Nanoparticles are increasingly integrated into various dental materials, serving as additives or coatings in applications ranging from implants to cement. The versatility of nanomaterials is prominently demonstrated in dental clinics, where they enable a diverse array of endodontic procedures. Applications include root restoration, obturation, medication delivery, pulp regeneration, and channel filling. In addition to the benefits of dental materials, such as their durability, ability to regenerate tissue, and bactericidal properties, a growing range of nanoparticles shows great promise for future development. These include bioactive glass, zirconia, chitosan, hydroxyapatite, silver particles, and zinc oxide [10]. Nanomaterials come in various shapes, encompassing nanotubes, nanorods, and nanowires, each offering versatile applications across various medical fields. In endodontics, nanotechnology is extensively utilized in sealers, obturating materials, composites, root repair materials, and disinfectants [11]. Functionalization is a crucial aspect of nanoparticle design, involving linker molecules with reactive groups at both ends. These molecules aid in binding several substances to the nanoparticle core, including antibodies, fluorophores, and biocompatible materials like dextran. The core nanoparticle can also offer a platform for building particles composed of both inorganic and organic components [11]. One of the primary functions of nanoparticles is to act as carriers for active ingredients used in imaging and therapeutic agents. Nanoparticles can be produced using a variety of approaches, including physical, chemical, and biological techniques. Among these, chemical reduction and green synthesis are widely adopted. In chemical methods, metal ions are reduced to nanoparticles using agents like sodium borohydride, citrate, or natural plant extracts.

Stabilizing agents—such as polyethylene glycol, polyvinylpyrrolidone, or biological molecules—prevent particle clumping and maintain stability. These substances also play a critical role in determining nanoparticle toxicity. While residues from chemical reagents can pose cytotoxic risks, biologically derived stabilizers used in green synthesis are typically more biocompatible. Furthermore, nanoparticle size, shape, surface charge, and solubility—shaped by the synthesis process—govern their interactions within biological environments. This underscores the importance of developing safe and precisely controlled fabrication methods [12]. Nanoparticles have several benefits, including biocompatibility, specificity, and targeting ability. Lipids, metals, silicon, silica, polymers, proteins, and carbon are just a few of the components that are used in nanoparticles [12,13]. Unlike bulk materials, nanoparticles have unique physical and chemical characteristics [1,14]. Furthermore, the adaptability of nanotechnology makes it possible to construct imaging, therapeutic, and diagnostic procedures that are safer and more successful [15,16]. In endodontics, various types of nanoparticles are employed. Biodegradable nanoparticles, such as polylactic acid, and inorganic nanoparticles like silica and metals like gold are among the most commonly utilized [17].

2. Materials and methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) database, accessible through the Cochrane Library and Medline via PubMed, to conduct our research. A variety of keywords were employed, such as “nanoparticles”, “dentistry”, “antimicrobial”, “applications”, “root canal therapy”, “endodontics”, “and”, and “or”. The inclusion criteria were useful literature not older than 1974. A preference for recent articles was given. To find any other research, we also carefully examined the reference lists of papers that might be pertinent. Studies retrieved from these computerized searches were included in our review, along with pertinent references located in the study bibliographies.

3. Literature review

Nanoparticles have garnered increasing attention in the field of endodontics due to their unique physicochemical properties, including a high surface area-to-volume ratio, enhanced reactivity, and nanoscale dimensions. These characteristics allow them to interact efficiently with biological tissues and microorganisms, making them ideal for applications such as root canal disinfection, sealing enhancement, drug delivery, and tissue regeneration. Several methods are employed for the synthesis of nanoparticles used in endodontics, each chosen based on the desired composition and application. Chemical reduction is a common method for synthesizing metal nanoparticles, particularly silver (AgNPs) and gold (AuNPs). In this process, metal salts such as silver nitrate ($AgNO_3$) are reduced using agents like sodium borohydride ($NaBH_4$) or natural plant extracts, often stabilized with polymers like polyvinylpyrrolidone (PVP) to control particle size and prevent agglomeration [16]. The sol-gel method is widely used to produce ceramic-based nanoparticles like zinc oxide (ZnO), silica, and hydroxyapatite (nHAp). This involves the hydrolysis and condensation of metal alkoxides to form a gel, which is then dried and calcined to obtain nanoparticles. Co-precipitation is frequently employed for the synthesis of magnetic nanoparticles such as iron oxide (Fe_3O_4). This technique involves the simultaneous precipitation of ferrous and ferric ions in an alkaline medium, yielding uniform and crystalline nanoparticles [15]. Ionotropic gelation is typically used for synthesizing biopolymer-based nanoparticles like chitosan, where positively charged chitosan interacts with a polyanion such as tripolyphosphate (TPP), leading to spontaneous nanoparticle formation. In recent years, green synthesis approaches have gained popularity due to their environmental friendliness and biocompatibility. These methods use biological agents such as plant extracts or microbial cultures to reduce metal salts into nanoparticles without toxic byproducts [17].

3.1 Classification of nanoparticles in endodontic/periodontal applications

Nanoparticles can be classified based on various factors, including origin, dimension, and structural configuration. Origin is a primary factor in nanoparticle classification, dividing them into two main groups. Natural nanoparticles are composed of substances used as nanoparticles in recent decades, and whose medicinal qualities have long been known. These substances include different polysaccharides, such as pullulan, and natural polymers, such as cellulose, gelatine, gliadin, copper, silver, and chitosan. These polymers, derived from fungi, bacteria, plants, and animals, are frequently separated into protein-based polymers and polysaccharides [18]. On the other hand, polyesters are the source of synthetic or artificial nanoparticles [19,20]. These synthetic polymers offer tailored properties and controlled release characteristics, contributing to their wide-ranging applications in various fields, including medicine and biotechnology. Among the relatively recent artificially formed nanoparticles is graphene, which can be synthesized using the arc discharge method in the presence of an H_2 atmosphere. The resulting graphene typically consists of two to three layers with a flake size ranging from 100 to 200 nm [21,22]. Additionally, rapid heating through arc discharge in an air atmosphere has been shown to produce graphene nanosheets primarily with two layers and a width of approximately 100–200 nm [23,24].

3.1.1. Silver nanoparticle

In a 2014 study by Samiei et al. [25] titled “Antibacterial Efficacy of Silver-Crosslinked Hydrogel Nanocomposite Versus Sodium Hypochlorite and Chlorhexidine on Enterococcus faecalis for Use in Root Canal Infection”, the researchers looked at the in vitro efficacy of the silver-crosslinked hydrogel nanocomposite (SCHNC) against *Enterococcus faecalis* that had been seeded into root canals. The findings showed that SCHNC retained its antibacterial activity and did not show substantial antimicrobial efficacy in irrigation. In a 2014 study by Daming Wu et al., “Evaluation of the Antibacterial Efficacy of Silver Nanoparticles Against Enterococcus faecalis Biofilm”, the effectiveness of silver nanoparticles against *Enterococcus faecalis* biofilms generated on root canals was investigated in vitro [26]. The results demonstrated that although silver nanoparticles did not exhibit strong antibacterial qualities when used as an irrigant, they could be helpful as a medication to target bacterial biofilms after root canal cleaning. In 2000, K. Kawahara and colleagues conducted a study titled “Antibacterial Effect of Silver-Zeolite (SZ) on Oral Bacteria Under Anaerobic Conditions”, which looked at the effectiveness of silver-zeolite against different oral bacteria in anaerobic circumstances in vitro. According to their research, SZ may be helpful in providing dental materials with antibacterial activity, especially in anaerobic settings like deep periodontal pockets [27].

3.1.2. Zinc nanoparticles

The adhesion of *Enterococcus faecalis* to dentin, as well as the prevention of bacterial recolonization and biofilm formation, were assessed in vitro in a study led by Anil Kishen in 2008 and titled "An Investigation on the Antibacterial and Antibiofilm Efficacy of Cationic Nanoparticulates for Root Canal Disinfection". The outcomes demonstrated the possible benefits of applying zinc oxide nanoparticles and chitosan nanoparticles to enhance the antibacterial efficacy of endodontic sealers and prevent bacterial recolonization in root canals [28]. According to the study "Polymeric Zinc-Doped Nanoparticles for High Performance in Restorative Dentistry", effective bioactive materials in restorative dentistry should promote both intrafibrillar and interfibrillar remineralization. This dual approach is essential for restoring the structural integrity and function of dentin by enabling mineral deposition both within and between collagen fibrils [29].

3.1.3. Chitosan nanoparticles

In a 2009 study by Annie Shrestha titled "Delivery of Antibacterial Nanoparticles into Dentinal Tubules Using High-Intensity Focused Ultrasound", researchers conducted in vitro experiments to evaluate the effectiveness of delivering antibacterial nanoparticles into dentinal tubules. The study explored the use of high-intensity focused ultrasound (HIFU) as a method to enhance root canal cleaning by facilitating deeper and more efficient penetration of nanoparticles into the tubules. According to the results, HIFU significantly facilitated the entry of antimicrobial nanoparticles in tubules [30]. In endodontics, chitosan nanoparticles are employed primarily for their antimicrobial properties and drug delivery potential. CNPs have demonstrated significant efficacy against common endodontic pathogens, including *Enterococcus faecalis*, a bacterium often associated with persistent root canal infections. When incorporated into root canal irrigants or intracanal medicaments, chitosan nanoparticles can penetrate dentinal tubules and eliminate bacterial biofilms more effectively than conventional solutions such as sodium hypochlorite or chlorhexidine. Furthermore, their ability to carry and release antimicrobial agents in a controlled manner makes them an ideal vehicle for local drug delivery within the root canal system. Studies have also shown that chitosan nanoparticles can be integrated into endodontic sealers, enhancing their antibacterial activity and improving the sealing quality by reducing microleakage.

3.1.4. Rose Bengal chitosan nanoparticles

Rose Bengal (RB) combined with green laser light has shown effectiveness against nail infections caused by *Trichophyton rubrum*, but its application is limited due to poor penetration and dilution. To address this, researchers developed RB-encapsulated chitosan nanoparticles (~200 nm) that enhance tissue penetration and generate high levels of reactive oxygen species (ROS). These nanoparticles achieved over 99% fungal spore kill for major onychomycosis pathogens (*T. rubrum*, *T. mentagrophytes*, and *T. interdigitale*) and were found to be non-toxic to human fibroblasts, supporting their potential for safe clinical use [31]. In an investigation headed "Antibacterial Efficacy of Photosensitizer Functionalized Biopolymeric Nanoparticles in the Presence of Tissue Inhibitors in Root Canal", carried out by Annie Shrestha in 2014, scientists conducted in vitro tests to evaluate the efficacy against planktonic *Enterococcus faecalis* in the presence of various inhibitory agents. According to the findings, in the presence of tissue inhibitors, Rose Bengal-functionalized chitosan nanoparticles showed a persistent antibacterial action following photodynamic therapy [32].

3.1.5. Triclosan-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles

In a study conducted in 2005, titled "Preparation and Characterization of Triclosan Nanoparticles for Periodontal Treatment", studies were conducted to evaluate the in vitro release profile of triclosan from nanoparticles for early in vivo research. Two noteworthy results were identified: Due to the large surface area of the nanoparticles, there is 1) a rapid release of triclosan and 2) a reduction in gingival inflammation [33]. Potential changes to enhance endodontic treatments' sealing and therapeutic benefits include nanosilver particles and nanodiamonds. Silver nanoparticle-coated gutta-percha has shown antibacterial activity and antiseptic qualities against various pathogens, including *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Enterococcus faecalis*, frequently linked to root canal infections [34].

3.1.6. Graphene nanoparticles

Graphene nanoplates demonstrate antimicrobial characteristics attributed to the sharp edges of graphene nanoplate flakes, which penetrate the delicate cell wall of bacteria, resulting in entrapment and reduction in size [35]. These findings propose a potential strategy for combating *Streptococcus mutans*, the culprit behind human dental caries. When applied as a coating on titanium implants, graphene holds promise in enhancing osseointegration properties, expediting tissue healing, and restraining microbial proliferation [36]. Investigations have revealed that graphene, when combined with silver nanoparticles, exhibits robust antibacterial qualities with diminished cytotoxic effects on soft tissues and bones in contrast to 3% sodium hypochlorite [37]. Such attributes position graphene as a prospective material for future use as an irrigant in infected root canals.

3.1.7. Zirconia nanoparticles

In their study, Tanamaru et al. discovered that zirconia nanoparticles could serve as an efficient radiopacifier when added as a supplement to Portland cement without detrimentally affecting its biocompatibility. The study examined two groups of zirconia oxide particles, one micro-sized and the other nano-sized, demonstrating enhanced radiopacity properties consistent with ISO/ADA standards of 3 mm Al [38]. In endodontics, zirconia nanoparticles are mainly incorporated into endodontic sealers, obturation materials, and posts to improve physical properties such as strength, durability, and radiopacity. Zirconia has been used as a radiopacifier in calcium silicate-based sealers, providing an alternative to bismuth oxide with fewer concerns regarding discoloration or cytotoxicity [39]. In periodontal therapy, zirconia nanoparticles demonstrate potential in bone grafting and coating applications due to their osteoconductive behavior and ability to support cell proliferation and differentiation. Their use in periodontal scaffolds and membranes has been investigated to promote hard tissue regeneration [29]. Furthermore, recent studies suggest that zirconia nanoparticles may exhibit antibacterial activity, especially when doped with other elements (e.g., silver or copper) or when combined with antimicrobial agents. This property enhances their potential to reduce bacterial colonization around implants or within periodontal pockets [40].

3.1.8. Titanium oxide nanoparticles

In his study titled "Effect of Nano-Titanium Dioxide with Different Antibiotics against Methicillin-Resistant Staphylococcus Aureus" [29], Aashis S. Roy examined various concentrations of nano-scale TiO_2 to determine the optimal concentration with the most potent antibacterial activity against methicillin-resistant *Staphylococcus aureus* cultures. The results indicate that TiO_2 nanoparticles enhance the antimicrobial efficacy of beta-lactams, cephalosporins, aminoglycosides, glycopeptides, macrolides, lincosamides, and tetracycline, suggesting a potential for utilizing nano compounds in combination therapy against methicillin-resistant *Staphylococcus aureus* [41]. In endodontics, TiO_2 nanoparticles are often incorporated into root canal sealers, composites, and irrigants to enhance their antimicrobial properties. Studies have demonstrated that TiO_2 NPs can inhibit the growth of *Enterococcus faecalis*, a resilient pathogen frequently involved in persistent root canal infections. When exposed to light, especially UV or near-UV, TiO_2 exhibits photocatalytic antimicrobial action, making it a potential additive in light-activated disinfection systems for root canals. In periodontal applications, titanium dioxide nanoparticles are widely studied for their anti-inflammatory, antimicrobial, and osteoconductive properties. TiO_2 NPs can be incorporated into periodontal gels, scaffolds, and membranes to aid in the regeneration of alveolar bone and periodontal ligament. They help inhibit the colonization of pathogens such as *Porphyromonas gingivalis* and promote the proliferation of fibroblasts and osteoblasts, which are critical for tissue regeneration.

3.1.9. Copper oxide nanoparticles

Numerous studies have explored the antibacterial properties of copper nanoparticles, but comparatively fewer have investigated their antiviral effects. These studies have revealed that copper nanoparticles specifically target the viral genome, particularly the genes responsible for viral infections [42,43]. Additionally, some research has illustrated a similar mechanism involving reactive oxygen species within the viral envelope or capsid, akin to antibacterial activity [42]. Viruses are particularly susceptible to damage inflicted by copper nanoparticles due to their lack of a repair mechanism, unlike bacteria and fungi, resulting in rapid cell death [44]. This phenomenon, where microbes are instantly inactivated upon contact, is called "contact killing" [45]. In numerous studies, researchers have used this "contact killing" attribute to develop antiviral surfaces functionalized with copper nanoparticles.

3.1.10. Iron nanoparticles

Iron oxide nanoparticles have demonstrated peroxidase-like activity when incorporated into an irrigating solution and hydrogen peroxide, leading to antibiofilm and bactericidal effects against *Enterococcus faecalis* [46]. Nonetheless, like silver nanoparticles, metal and metal oxide nanoparticles may carry some level of cytotoxicity. Therefore, conducting risk assessments and biocompatibility studies is crucial before advancing to in vivo research [47].

3.1.11. Hydroxyapatite nanoparticles

Nanohydroxyapatite molecules have been shown by Benita Wiatrak et al. [48] to be able to stimulate nerve regeneration. A relationship has been seen between the onset of nerve inflammation and increased mitochondrial activity in neurons treated with hydroxyapatite nanoparticles. Because it remineralizes teeth, nano-hydroxyapatite is important in dentistry. Hydroxyapatite facilitates the precipitation of calcium and phosphate ions, which leads to remineralization, particularly during partial demineralization of the collagen matrix [49–51]. Allaker et al. and Rana S. Al-Hamdan et al. demonstrated how adding nano-hydroxyapatite particles to adhesive resins enhances the materials' biomechanical qualities. Additionally, the tooth's lifetime and structural integrity are improved by this combination [49,52].

3.1.12. Calcium hydroxide nanoparticles

Compared to their traditional counterparts, calcium hydroxide nanoparticles have several advantages, such as greater antibacterial activity, higher solubility, increased surface area contact with pathogens, and deeper penetration [53–55]. Compared to conventional calcium hydroxide, numerous investigations have shown nano-calcium hydroxide to exhibit higher antibacterial effectiveness against *Enterococcus faecalis* and deeper penetration into dentinal tubules [53–56]. Furthermore, compared to traditional calcium hydroxide dressing, nano-calcium hydroxide results in a smaller decrease in dentine microhardness [57]. Conventional calcium hydroxide treatment causes a larger reduction in fracture resistance than its nanosized equivalents [54]. Although this difference was not statistically significant, it was shown that nano-calcium hydroxide had somewhat higher cytotoxicity levels than ordinary calcium hydroxide [58]. Figure 1 shows the nanoparticles used frequently in endodontics.

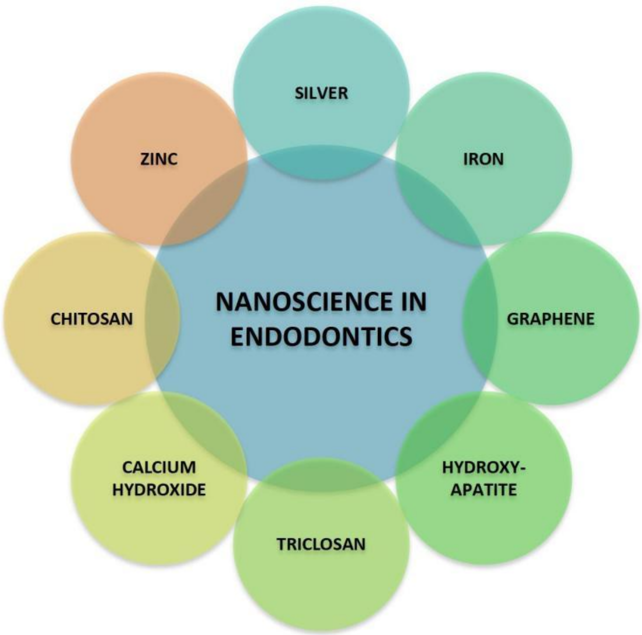

Figure 1. Nanoparticles frequently used in endodontics. Other nanoparticles are still being explored.

4. Discussion

Three dimensions can be used to group nanoparticles: zero dimension, which is associated with nanostructures; one dimension, which is associated with nanorods; and two dimensions, which is associated with thin films. Furthermore, nanoparticles can be classified based on their structural configuration, including carbon-based nanoparticles like graphene and metals like iron oxide, silver, and dendrimers. Because of their unique physical, electrical, magnetic, and optical qualities and their magnetic, radioactive, and plasmonic capabilities, metal nanoparticles are desirable for imaging, photothermal therapy, and diagnostics [59]. Nanoparticles can be further classified based on their composition as either organic or inorganic. In terms of shape, they exhibit diversity, ranging from particles and spheres to tubes, rods, plates, and other geometries. Among the primary inorganic materials used for nanoparticle synthesis are silicon, graphene, and silica [60]. Inorganic materials offer exceptional properties such as high chemical, thermal, and mechanical resistance, rendering them well-suited for various applications. Among these materials, silica nanoparticles are particularly noteworthy due to their distinctive attributes. Silica nanoparticles have the capacity to degrade into silicic acid or smaller silica species in specific aqueous environments, endowing them with biocompatibility and versatility for a wide array of applications [61]. The top-down and bottom-up approaches represent two fundamental strategies for fabricating and synthesizing nanoparticles, each offering distinct advantages and applications.

4.1. Top-down approach

This method involves reducing bulk materials to obtain nano-sized particles. Advanced techniques like precision engineering and lithography are utilized for this purpose. Precision engineering, refined by industry over decades, supports the microelectronics industry by enabling the production of high-performance components. Through precise manipulation, top-down techniques fabricate nanostructures with tailored properties and dimensions [62].

4.2. Bottom-up approach

Bottom-up techniques use controlled self-assembly processes of atoms and molecules to build nanostructures with intricate architectures and functionalities. The field of bottom-up nanotechnology gained momentum in the 1980s, driven by advancements in cluster science and the development of powerful tools like the scanning tunnelling microscope [62].

Eric Drexler's influential book, *Engines of Creation: The Coming Era of Nanotechnology*, published in 1986, further popularized the concept of nanotechnology and its potential applications [63]. Nanoparticles exert their effects through diverse mechanisms, each contributing to their wide-ranging applications in medicine, agriculture, and environmental science. Understanding these mechanisms is crucial for maximizing their potential. Some key mechanisms of nanoparticle action are as follows: A) Reactive oxygen species (ROS) and toxicity. Nanoparticles can induce ROS; elevated ROS levels, triggered by nanoparticles, can lead to cytotoxic effects in plants and other organisms. B) Electrostatic interactions. Nanoparticles interact with cell membranes via electrostatic interactions, particularly through positive-negative charge attractions. This interaction disrupts the cell membrane structure, increasing permeability and potentially compromising vital cellular functions like respiration, division, and DNA replication. These mechanisms highlight how nanoparticles can impact biological systems, underscoring the importance of understanding their interactions and effects for various applications. Furthermore, the imbalance in metal ion homeostasis, crucial for metabolic functions in microbes, can be disrupted by excess metal nanoparticles. This disruption can result in irreversible damage, growth retardation, or microbial death. Researchers have shown great interest in biodegradable nanoparticles because of their advantageous characteristics and fewer adverse effects. Of them, chitosan—also known as poly[1,4-β-D-glucopyranosamine]—emerges as the most frequently used polymer in endodontics. Derived from deacetylated chitin, chitosan shares structural similarities with components found in the extracellular matrix, enabling it to strengthen collagen structures [64]. Its outstanding antibacterial, antiviral, and antifungal characteristics, demonstrated in various forms and functions, demonstrate its adaptability and have generated a great deal of attention in the field of biomedicine [65].

A study by Ke Zhang et al. in 2013, titled "Effects of Dual Antibacterial Agents 12-methacryloyloxydodecylpyridinium bromide (MDPB) and Nano-Silver in Primer on Microcosm Biofilm, Cytotoxicity, and Dentine Bond Properties", included evaluating in vitro the production of lactic acid [66]. Daming Wu et al. established the MDPB-NAG primer's antibacterial efficiency by demonstrating its capacity to prevent oral biofilms and secondary caries while preserving dentin bond strength and biocompatibility. Comparable results were documented by L. Cheng et al. in their 2012 work, "Anti-Biofilm Dentin Primer with Quaternary Ammonium and Silver Nanoparticles" [67]. In 2012, Moghadas et al. looked into the antibacterial activity of a brand-new endodontic irrigation solution based on nanotechnology [68]. According to their findings, it is as effective as NaOCl at stopping the growth of common root canal bacteria such as *Staphylococcus aureus* and *Enterococcus faecalis*. In "Development of Intracanal Formulation Containing Silver Nanoparticles", a study published in 2014 [69] by João Felipe Bonatto Bruniera et al., silver nanoparticles showed antibacterial activity against all species examined. Moreover, silver nanoparticles integrated into hydroxyethylcellulose polymer gel demonstrated appropriate homogeneity and fluidity for their intended purpose. In an additional 2010 study by Tom C. Pagonis titled "Nanoparticle-Based Endodontic Antimicrobial Photodynamic Therapy", scientists tested the efficacy of treatment against *Enterococcus faecalis* biofilm-infected root canals using in vitro studies. The uptake and dispersion of nanoparticles in the *Enterococcus faecalis* suspension were investigated using transmission electron microscopy. The outcomes showed that light and methylene blue-loaded nanoparticles significantly lowered the number of bacteria in the planktonic phase and inside the root canals [70]. As the by-product of chitin's deacetylation, chitosan is the second most prevalent naturally occurring biopolymer. Its versatility has drawn much interest in biomedicine since it may be employed in many forms, such as powder (including micro- and nanoparticles), capsules, films, scaffolds, hydrogels, beads, and bandages [71]. Chitosan is an ideal reinforcement material for collagen structures because of its structural similarity to extracellular matrix components [72]. The preparation of chitosan nanoparticles can be achieved through several methods outlined in the literature. Emulsification and crosslinking are two frequently used techniques that use the amino groups in chitosan and the aldehyde groups in a crosslinking agent [73]. Additional approaches, such as reversed micelles (microemulsion) and precipitation methods, rely on covalent crosslinking to make chitosan nanoparticles. These diverse approaches offer flexibility in tailoring chitosan nanoparticles for various biomedical applications [72].

Yazdan et al.'s in vitro research [34] revealed that gutta-percha coated with nanosilver might have better antibacterial properties than regular gutta-percha when used in endodontic procedures. However, utilizing dye and bacterial leakage methods, a 60-day comparison of conventional gutta-percha and nanosilver-coated gutta-percha indicated no statistically significant difference in the dye or bacterial leakage results between the two fillers. Furthermore, by improving mechanical qualities with a suggested nanodiamond-gutta-percha composite functionalized with amoxicillin, Lee et al. [74] sought to reduce the incidence of root canal reinfection. This innovative approach aims to improve the efficacy of root canal treatment by incorporating nanodiamonds and antibiotics into the gutta-percha composite, potentially enhancing antimicrobial properties and treatment outcomes. Incorporating nanodiamonds with an antibiotic could potentially enhance the eradication of residual bacteria following endodontic treatment. The study also demonstrated broad bactericidal properties against pathogens in lateral or additional canals. Nanodiamond-gutta-percha has been suggested to improve treatment efficacy and complement conventional endodontic therapy procedures.

Moreover, ZrO_2 nanoparticles enhance the compressive strength and sealing ability of these materials, which are critical in preventing microleakage and reinfection. Due to their bioinert and non-toxic nature, zirconia nanoparticles have also shown good cytocompatibility with periodontal ligament fibroblasts and osteoblasts, making them suitable for regenerative endodontic materials. Additionally, zirconia nanoparticle-coated implants have demonstrated reduced biofilm formation and improved gingival tissue response, which is essential for the long-term success of dental implants in periodontally compromised patients. Furthermore, the inclusion of TiO_2 nanoparticles in bioceramic sealers has been shown to improve their compressive strength, reduce setting time, and enhance antibacterial activity without compromising biocompatibility [39]. Additionally, TiO_2 coatings on dental implants have been shown to improve osseointegration, reduce biofilm formation, and enhance surface hydrophilicity—factors essential for the long-term success of implants in periodontally compromised patients [75].

Chlorhexidine, which has demonstrated significant efficacy in eliminating bacteria and biofilms linked to specific oral illnesses, is one of the active chemicals that chitosan can transport [75]. Because of its positive charge, chitosan interacts electrostatically with negatively charged bacterial cell membranes. This contact may disrupt permeability in the cell wall, which could result in cell rupture, intracellular protein and component leakage, and, ultimately, microbial death [76]. Chitosan nanoparticles have demonstrated the potential to access the dentinal tubules of infected root canals and enhance root canal disinfection despite the challenging anatomical hurdles involved. Furthermore, chitosan nanoparticles remain beneficial when combined with efflux pump inhibitors, which mitigate the effects of biofilm resistance to antimicrobial medications [76]. Moreover, it has been shown that chitosan nanoparticles are still effective in the presence of inhibitors that target the efflux pump, a mechanism by which biofilms evade antibiotics [77].

Some commonly utilized biological models for toxicity studies include (1) cell cultures, where cultured cells are exposed to nanomaterials to monitor responses such as cell viability, proliferation, apoptosis, and oxidative stress; (2) aquatic organisms like embryonic zebrafish (*Danio rerio*), frequently used due to their sensitivity, optical transparency, rapid development, and genetic similarity to humans, making them suitable for developmental toxicity evaluations; and (3) whole-animal tests with rodents, including mice and rats, which assess systemic effects such as organ toxicity, immunotoxicity, neurotoxicity, and reproductive toxicity following nanomaterial exposure. By employing diverse biological models, toxicity studies can provide comprehensive insights into the potential adverse effects of nanomaterials on various physiological systems. These findings are crucial for informing regulatory decisions and ensuring nanotechnology's safe development and application.

In urban environments, particulate matter from diesel- and gasoline-fueled vehicles and stationary combustion sources contains nanomaterials. Ongoing research into the toxic effects of these particles is essential, with regulatory focus shifting toward finer-sized particles. Nanotechnology encompasses various products classified into compound classes, including metals, metal oxides, carbon-based materials, and semiconductor nanomaterials [25].

Nanoparticles can harm biological systems through several mechanisms, including the induction of carbonyl formation. They have been shown to catalyze the oxidative modification of amino acid chains, resulting in the formation of carbonyl groups. These carbonyl groups can bind to proteins, leading to protein degradation, enzyme inactivation, and disruption of catalytic activity. This process compromises the function of essential cellular proteins and enzymes, contributing to cellular dysfunction and oxidative stress [78,79].

Additionally, nanoparticles possess electrical properties that allow them to interact with nucleic acids, such as chromosomal and plasmid DNA. These interactions can adversely affect DNA replication by disrupting the normal structure and function of DNA molecules. Consequently, nanoparticles may inhibit DNA-mediated signal transduction processes, impairing critical cellular functions including gene expression, cell proliferation, and differentiation. Such interference with DNA replication can have profound effects on cellular homeostasis and genomic stability [80,81].

Overall, the ability of nanoparticles to induce carbonyl formation and interact with nucleic acids highlights their potential to disrupt fundamental cellular processes and cause adverse biological effects. Understanding these mechanisms is crucial for accurately assessing the safety and risks associated with nanoparticle use across various applications.

The potential toxic effects of nanomaterials depend on several factors, including their base material, size, shape, and surface coatings. Interpreting these effects requires careful consideration of experimental conditions, as differences in methodologies across studies can make comparisons challenging. Therefore, toxicity studies employing diverse biological models are essential to comprehensively evaluate the harmful effects of nanomaterials on living organisms.

5. Conclusion

The advancement of nanotechnology has the potential to revolutionize endodontic therapy. Recent research highlights a broad range of applications for nanoparticles in endodontics, including obturation materials, photodynamic therapy, disinfection methods, and tissue regeneration. However, it is essential to tailor nanoparticle-based approaches to specific clinical needs, as different materials, formulations, and combinations exhibit unique properties that can be both beneficial and potentially harmful. While the promise of nanoparticles in endodontics is significant, further research and clinical validation are necessary to fully realize their potential benefits.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization: Priyanka Bhojwani, Anuja Ikhar; Literature Review and Data Curation: Priyanka Bhojwani, Aditya Patel; Writing – Original Draft Preparation: Priyanka Bhojwani, Manoj Chandak; Writing – Review & Editing: Shweta Sedani; Visualization and Figure: Priyanka Bhojwani; Supervision: Priyanka Bhojwani; Project Administration: Priyanka Bhojwani. All authors have read and agreed to the published version of the manuscript.

References

1. Couvreur P (2013) Nanoparticles in drug delivery: past, present and future. *Adv Drug Deliv Rev* 65: 21–23. https://doi.org/10.1016/j.addr.2012.04.010
2. Wong J, Zou T, Lee AHC, et al. (2021) The potential translational applications of nanoparticles in endodontics. *Int J Nanomed* 16: 2087–2106. https://doi.org/10.2147/IJN.S293518
3. Shrestha A, Kishen A (2016) Antibacterial nanoparticles in endodontics: a review. *J Endod* 42: 1417–1426. https://doi.org/10.1016/j.joen.2016.05.021
4. Yin IX, Zhang J, Zhao IS, et al. (2020) The antibacterial mechanism of silver nanoparticles and its application in dentistry. *Int J Nanomed* 15: 2555–2562. https://doi.org/10.2147/IJN.S246764
5. Feynman RP, Leighton RB, Sands M (1987) Six Easy Pieces. New York: Anchor. Available from: https://www.amazon.in/Six-Easy-Pieces-Richard-Feynman/dp/0465025277
6. Yao C, Storey D, Webster TJ (2007) Nanostructured metal coatings on polymers increase osteoblast attachment. *Int J Nanomed* 2 :487–492. https://doi.org/10.2147/IJN.S2.3.487
7. Aston D (2011) Nanotechnology: the stuff of science fiction or science fact?. *Sch Sci Rev* 92: 71–75.
8. Listl S, Galloway J, Mossey PA, et al. (2015) Global economic impact of dental diseases. *J Dent Res* 94: 1355–1361. https://doi.org/10.1177/0022034515602879
9. Raura N, Garg A, Arora A, et al. (2020) Nanoparticle technology and its implications in endodontics: a review. *Biomater Res* 24: 21. https://doi.org/10.1186/s40824-020-00198-z
10. Zakrzewski W, Dobrzyński M, Zawadzka-Knefel A, et al. (2021) Nanomaterials application in endodontics. *Materials* 14: 5296. https://doi.org/10.3390/ma14185296
11. Jhajharia K, Parolia A, Shetty KV, et al. (2015) Biofilm in endodontics: a review. *J Int Soc Prev Comm Dent* 5: 1–12. https://doi.org/10.4103/2231-0762.151956
12. De Jong WH, Borm PJ (2008) Drug delivery and nanoparticles: applications and hazards. *Int J Nanomed* 3: 133–149. https://doi.org/10.2147/IJN.S596
13. Wolfram J, Zhu M, Yang Y, et al. (2015) Safety of nanoparticles in medicine. *Curr Drug Targets*16: 1671–1681. https://doi.org/10.2174/1389450115666140804124808
14. Farges J-C, Alliot-Licht B, Renard E, et al. (2015) Dental pulp defence and repair mechanisms in dental caries. *Mediators Inflamm* 2015: 230251. https://doi.org/10.1155/2015/230251
15. Yohan D, Chithrani BD (2014) Applications of nanoparticles in nanomedicine. *J Biomed Nanotechnol* 10: 2371–2392. https://doi.org/10.1166/jbn.2014.2015

16. Baetke SC, Lammers T, Kiessling F (2015) Applications of nanoparticles for diagnosis and therapy of cancer. *Br J Radiol* 88: 20150207. https://doi.org/10.1259/bjr.20150207
17. Moraes G, Zambom C, Siqueira WL (2021) Nanoparticles in dentistry: a comprehensive review. *Pharmaceuticals* 14: 752. https://doi.org/10.3390/ph14080752
18. Dodwad V, Kukreja BJ. Biomimetics—the new pathway for regenerating tissue. *J Pharm Biomed Sci (JPBMS)* 16: 1–4.
19. Osorio R, Alfonso-Rodríguez CA, Medina-Castillo AL, et al. (2016) Bioactive polymeric nanoparticles for periodontal therapy. *PLoS ONE* 11: e0166217. https://doi.org/10.1371/journal.pone.0166217
20. Harrington GW, Natkin E (1992) Midtreatment flare-ups. *Dent Clin North Am* 36: 409–423. https://doi.org/10.1016/S0011-8532(22)02504-6
21. Subramanian AK (2021) The Applications and the current status of silver nanoparticles in the field of Orthodontics. *J Contemp Issues Bus Gov* 27: 3620. https://doi.org/10.47750/cibg.2021.27.02.370
22. Rao CNR, Subrahmanyam KS, Ramakrishna Matte HSS, et al. (2010) A study of the synthetic methods and properties of graphenes. *Sci Technol Adv Mater* 11: 054502. https://doi.org/10.1088/1468-6996/11/5/054502
23. Wu Z-S, Ren W, Gao L, et al. (2009) Synthesis of graphene sheets with high electrical conductivity and good thermal stability by hydrogen arc discharge exfoliation. *ACS Nano* 3: 411–417. https://doi.org/10.1021/nn900020u
24. Ohya Y, Shiratani M, Kobayashi H, et al. (1994) Release behavior of 5-Fluorouracil from chitosan-gel nanospheres immobilizing 5-Fluorouracil coated with polysaccharides and their cell specific cytotoxicity. *J Macromol Sci A* 31: 629–642. https://doi.org/10.1080/10601329409349743
25. Samiei M, Davaran S, Davari A, et al. (2014) Antibacterial efficacy of silver-crosslinked hydrogel nanocomposite versus sodium hypochlorite and chlorhexidine on *Enterococcus faecalis* for use in root canal infection. *J Dent Res* 3: 2316–2332.
26. Wu D, Fan W, Kishen A, et al. (2014) Evaluation of the antibacterial efficacy of silver nanoparticles against Enterococcus faecalis biofilm. *J Endod* 40: 285–290. https://doi.org/10.1016/j.joen.2013.08.022
27. Kawahara K, Tsuruda K, Morishita M, et al. (2000) Antibacterial effect of silver-zeolite on oral bacteria under anaerobic conditions. *Dent Mater* 16: 452–455. https://doi.org/10.1016/s0109-5641(00)00050-6
28. Kishen A, Shi Z, Shrestha A, et al. (2008) An investigation on the antibacterial and antibiofilm efficacy of cationic nanoparticulates for root canal disinfection. *J Endod* 34: 1515–1520. https://doi.org/10.1016/j.joen.2008.08.035
29. Bhojwani P, Ikhar A, Patel A, et al. (2024) Recent advances in antimicrobial and biosynthesis properties of bioglass and nanoparticles: a narrative review. *Multidisciplinary Reviews* 7: 2024286. https://doi.org/10.31893/multirev.2024286
30. Shrestha A, Kishen A (2014) Antibacterial efficacy of photosensitizer functionalized biopolymeric nanoparticles in the presence of tissue inhibitors in root canal. *J Endod* 40: 566–570. https://doi.org/10.1016/j.joen.2013.09.013

31. Bekmukhametova A, Antony A, Halliday C, et al. (2024) Rose bengal–encapsulated chitosan nanoparticles for the photodynamic treatment of *Trichophyton* species. *Photochem Photobiol* 100: 115–128. https://doi.org/10.1111/php.13839
32. Shrestha A, Fong S-W, Khoo B-C, et al. (2009) Delivery of antibacterial nanoparticles into dentinal tubules using high-intensity focused ultrasound. *J Endod* 35: 1028–1033. https://doi.org/10.1016/j.joen.2009.04.015
33. Piñón-Segundo E, Ganem-Quintanar A, Alonso-Pérez V, et al. (2005) Preparation and characterization of triclosan nanoparticles for periodontal treatment. *Int J Pharm* 294: 217–232. https://doi.org/10.1016/j.ijpharm.2004.11.010
34. Corrêa JM, Mori M, Sanches HL, et al. (2015) Silver nanoparticles in dental biomaterials. *Int J Biomater* 2015: 485275. https://doi.org/10.1155/2015/485275
35. Lee MJ, Seo YB, Seo JY, et al. (2020) Development of a bioactive flowable resin composite containing a Zinc-doped phosphate-based glass. *Nanomaterials* 10: 2311. https://doi.org/10.3390/n
36. Pranno N, La Monaca G, Polimeni A, et al. (2020) Antibacterial activity against staphylococcus aureus of titanium surfaces coated with graphene nanoplatelets to prevent peri-implant diseases. an in-vitro pilot study. *Int J Environ Res Public Health* 17: 1568. https://doi.org/10.3390/ijerph17051568
37. Wu X, Ding SJ, Lin K, et al. (2017) A review on the biocompatibility and potential applications of graphene in inducing cell differentiation and tissue regeneration. *J Mater Chem B* 5: 3084–3102. https://doi.org/10.1039/C6TB03067J
38. Moradi F, Haghgoo R (2018) Evaluation of antimicrobial efficacy of nanosilver solution, sodium hypochlorite and normal saline in root canal irrigation of primary teeth. *Contemp Clin Dent* 9: S227–S232. https://doi.org/10.4103/ccd.ccd_95_18
39. Hu C, Sun J, Long C, et al. (2019) Synthesis of nano zirconium oxide and its application in dentistry. *Nanotechnol Rev* 8: 396–404. https://doi.org/10.1515/ntrev-2019-0035
40. Raura N, Garg A, Arora A, et al. (2020) Nanoparticle technology and its implications in endodontics: a review. *Biomater Res* 24: 21. https://doi.org/10.1186/s40824-020-00198-z
41. Roy AS, Parveen A, Koppalkar AR, et al. (2010) Effect of nano-Titanium dioxide with different antibiotics against methicillin-resistant staphylococcus aureus. *J Biomater Nanobiotechnol* 1: 37. https://doi.org/10.4236/jbnb.2010.11005
42. Vincent M, Duval RE, Hartemann P, et al. (2018) Contact killing and antimicrobial properties of copper. *J Appl Microbiol* 124: 1032–1046. https://doi.org/10.1111/jam.13681
43. Warnes SL, Summersgill EN, Keevil CW (2015) Inactivation of murine norovirus on a range of copper alloy surfaces is accompanied by loss of capsid integrity. *Appl Environ Microb* 81: 1085–1091. https://doi.org/10.1128/AEM.03280-14
44. Borkow G (2012) Using Copper to fight microorganisms. *Curr Chem Biol* 6: 93–103. https://doi.org/10.2174/187231312801254723
45. Bleichert P, Espírito Santo C, Hanczaruk M, et al. (2014) Inactivation of bacterial and viral biothreat agents on metallic copper surfaces. *Biometals* 27: 1179–1189. https://doi.org/10.1007/s10534-014-9781-0

46. Bukhari S, Kim D, Liu Y, et al. (2018) Novel endodontic disinfection approach using catalytic nanoparticles. *J Endodont* 44: 806–812.https://doi.org/10.1016/j.joen.2017.12.003
47. Beyth N, Houri-Haddad Y, Domb A, et al. (2015) Alternative antimicrobial approach: nano-antimicrobial materials. *Evid-Based Compl Alt* 2015: 246012. https://doi.org/10.1155/2015/246012
48. Wiatrak B, Sobierajska P, Szandruk-Bender M, et al. (2021) Nanohydroxyapatite as a biomaterial for peripheral nerve regeneration after mechanical damage—in vitro study. *Int J Mol Sci* 22: 4454. https://doi.org/10.3390/ijms22094454
49. Al-Hamdan RS, Almutairi B, Kattan HF, et al. (2020) Influence of hydroxyapatite nanospheres in dentin adhesive on the dentin bond integrity and degree of conversion: a scanning electron microscopy (SEM), Raman, Fourier transform-infrared (FTIR), and microtensile study. *Polymers* 12: 2948. https://doi.org/10.3390/polym12122948
50. Liu Y, Tjäderhane L, Breschi L, et al. (2011) Limitations in bonding to dentin and experimental strategies to prevent bond degradation. *J Dent Res* 90: 953–968. https://doi.org/10.1177/0022034510391799
51. Herman K, Wujczyk M, Dobrzynski M, et al. (2021) In vitro assessment of long-term Fluoride Ion release from nanofluorapatite. *Materials* 14: 3747. https://doi.org/10.3390/ma14133747
52. Allaker RP, Ren G (2008) Potential impact of nanotechnology on the control of infectious diseases. *Trans R Soc Trop Med Hyg* 102: 1–2. https://doi.org/10.1016/j.trstmh.2007.07.003
53. Dianat O, Saedi S, Kazem M, et al. (2015) Antimicrobial activity of nanoparticle calcium hydroxide against *Enterococcus faecalis*: an in vitro study. *Iran Endod J* 10: 39–43. https://doi.org/10.22037/iej.v10i1.6379
54. Sireesha A, Jayasree R, Vidhya S, et al. (2017) Comparative evaluation of micron- and nano-sized intracanal medicaments on penetration and fracture resistance of root dentin—an in vitro study. *Int J Biol Macromol* 104: 1866–1873. https://doi.org/10.1016/j.ijbiomac.2017.05.126
55. Louwakul P, Saelo A, Khemaleelakul S (2017) Efficacy of calcium oxide and calcium hydroxide nanoparticles on the elimination of Enterococcus faecalis in human root dentin. *Clin Oral Investig* 21: 865–871. https://doi.org/10.1007/s00784-016-1836-x
56. Zand V, Mokhtari H, Hasani A, et al. (2017) Comparison of the penetration depth of conventional and nano-particle Calcium hydroxide into dentinal tubules. *Iran Endod J* 12: 366–370. https://doi.org/10.22037/iej.v12i3.16421
57. Naseri M, Eftekhar L, Gholami F, et al. (2019) The effect of calcium hydroxide and nano–calcium hydroxide on microhardness and superficial chemical structure of root canal dentin: an ex vivo study. *J Endod* 45: 1148–1154. https://doi.org/10.1016/j.joen.2019.06.002
58. Dianat O, Azadnia S, Mozayeni MA (2015) Toxicity of calcium hydroxide nanoparticles on murine fibroblast cell line. *Iran Endod J* 10: 49–54. https://doi.org/10.22037/iej.v10i1.7005
59. Sánchez-López E, Gomes D, Esteruelas G, et al. (2020) Metal-based nanoparticles as antimicrobial agents: an overview. *Nanomaterials* 10: 292. https://doi.org/10.3390/nano10020292
60. Parra-Nieto J, Del Cid MAG, de Cárcer IA, et al. (2021) Inorganic porous nanoparticles for drug delivery in antitumoral therapy. *Biotechnol J* 16: e2000150. https://doi.org/10.1002/biot.202000150

61. Zhou H, Ge J, Miao Q, et al. (2020) Biodegradable inorganic nanoparticles for cancer theranostics: insights into the degradation behavior. *Bioconjug Chem* 31: 315–331. https://doi.org/10.1021/acs.bioconjchem.9b00699
62. Iqbal P, Preece JA, Mendes PM (2012) Nanotechnology: the "top-down" and "bottom-up" approaches, In: Gale PA, Steed JW (eds.) *Supramolecular Chemistry,* Wiley. Available from: https://onlinelibrary.wiley.com/doi/10.1002/9780470661345.smc195.
63. Drexler E (1987) *Engines of creation: The coming era of nanotechnology*. New York: Anchor.
64. Tan W, Krishnaraj R, Desai TA (2001) Evaluation of nanostructured composite collagen–chitosan matrices for tissue engineering. *Tissue Eng* 7: 203–210. https://doi.org/10.1089/107632701300062831
65. Parolia A, Kumar H, Ramamurthy S, et al. (2020) Effectiveness of chitosan-propolis nanoparticle against Enterococcus faecalis biofilms in the root canal. *BMC Oral Health* 20: 1–14. https://doi.org/10.1186/s12903-020-01330-0
66. Zhang K, Cheng L, Imazato S, et al. (2013) Effects of dual antibacterial agents MDPB and nano-silver in primer on microcosm biofilm, cytotoxicity and dentine bond properties. *J Dent* 41: 464–474. https://doi.org/10.1016/j.jdent.2013.03.003
67. Cheng L, Zhang K, Melo MAS, et al. (2012) Anti-biofilm dentin primer with quaternary ammonium and silver nanoparticles. *J Dent Res* 91: 598–604. https://doi.org/10.1177/0022034512444128
68. Moghadas L, Shahmoradi M, Narimani T (2012) Antimicrobial activity of a new nanobased endodontic irrigation solution: in vitro study. *Dent Hypotheses* 3: 142. https://doi.org/10.4103/2155-8213.106838
69. Bruniera JFB, Silva-Sousa YTC, Lara MG, et al. (2014) Development of intracanal formulation containing silver nanoparticles. *Braz Dent J* 25: 302–306. https://doi.org/10.1590/0103-6440201302431
70. Pagonis TC, Chen J, Fontana CR, et al. (2010) Nanoparticle-based endodontic antimicrobial photodynamic therapy. *J Endod* 36: 322–328. https://doi.org/10.1016/j.joen.2009.10.011
71. Agnihotri SA, Mallikarjuna NN, Aminabhavi TM (2004) Recent advances on chitosan-based micro- and nanoparticles in drug delivery. *J Control Release* 100: 5–28. https://doi.org/10.1016/j.jconrel.2004.08.010
72. Muzzarelli RA, Isolati A, Ferrero A (1974) Chitosan membranes. *Ion Exch Membr* 1: 193–196.
73. Machida Y, Nagai T, Abe M, et al. (1986) Use of chitosan and hydroxypropylchitosan in drug formulations to effect sustained release. *Drug Des Deliv* 1: 119–130.
74. Shantiaee Y, Maziar F, Dianat O, et al. (2011) Comparing microleakage in root canals obturated with nanosilver-coated gutta-percha to standard gutta-percha by two different methods. *Iran Endod J* 6: 140–145. https://doi.org/10.22037/iej.v6i4.1949
75. Araujo HC, da Silva ACG, Paião LI, et al. (2020) Antimicrobial, antibiofilm and cytotoxic effects of a colloidal nanocarrier composed by chitosan-coated iron oxide nanoparticles loaded with chlorhexidine. *J Dent* 101: 103453. https://doi.org/10.1016/j.jdent.2020.103453
76. Rabea EI, Badawy ME-T, Stevens CV, et al. (2003) Chitosan as antimicrobial agent: applications and mode of action. *Biomacromolecules* 4: 1457–1465. https://doi.org/10.1021/bm034130m

77. Upadya M, Shrestha A, Kishen A (2011) Role of efflux pump inhibitors on the antibiofilm efficacy of calcium hydroxide, chitosan nanoparticles, and light-activated disinfection. *J Endod* 37: 1422–1426. https://doi.org/10.1016/j.joen.2011.06.017
78. Jasso-Ruiz I, Velazquez-Enriquez U, Scougall-Vilchis RJ, et al. (2019) Synthesis and characterization of silver nanoparticles on orthodontic brackets: a new alternative in the prevention of white spots. *Coatings* 9: 480. https://doi.org/10.3390/coatings9080480
79. Song W, Ge S (2019) Application of antimicrobial nanoparticles in dentistry. *Molecules* 24: 1033. https://doi.org/10.3390/molecules24061033
80. Kirsch C (2007) Oral cavity cancer. *Top Magn Reson Imaging* 18: 269–280. https://doi.org/10.1097/RMR.0b013e3181572caa
81. Wanasathop A, Li SK (2018) Iontophoretic drug delivery in the oral cavity. *Pharmaceutics* 10: 121. https://doi.org/10.3390/pharmaceutics10030121