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Review

Application of nanotechnology in periodontal therapy: Narrative review

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Abstract: The potential of nanotechnology to improve human health, optimize natural resource utilization, and reduce environmental pollution is remarkable. With the ever-growing advancement in dentistry, one of the breakthroughs is using nanotechnology. Nanotechnology in periodontics has touched every aspect of treatment modality, from non-surgical therapy to implant procedures, including regenerative procedures. Understanding their mechanism plays a pivotal role in more efficient usage of nanotechnology, better treatment procedures, and eventually better outcomes. In this paper, we review the application of nanotechnology in periodontal therapy. We performed the search for papers in Scopus using the key words and phrases as follows: "nanodentistry"; "dentistry and nanotechnology"; "dentistry and nanoparticles"; "dentistry and nanomedicine"; "dentistry and nanorobots". There were found 530 papers in total. Some papers belonged to two and more categories. It is revealed that the number of papers versus year does not follow any specific pattern, but the cumulative amount of papers versus year is fitted with the exponential regression. There were also selected papers using certain inclusion/exclusion criteria. Only the selected papers were analyzed. Nanomedicine is subjected to intensive studies nowadays. There are some promising results that will likely be implemented into praxis soon in the fields of medical diagnostics and clinical therapeutics. The appearance of nanotechnology can have a considerable impact on the treatment of periodontal diseases.

Keywords: nano dentistry; nanoparticle; nanotechnology; periodontal tissue; periodontal disease; treatment options

1. Introduction

Modern materials science is developing at a very fast pace. This development is felt in almost all areas of science and technology. New materials for sensors [1,2] and medical applications [3,4] evolve. Novel materials create excellent opportunities for researchers and engineers to solve long lasting problems. On the other hand, the conservative fields suffer from stagnation for many decades because the existing materials are prone to degradation [5], while new materials have not achieved the required level of performance yet. So to solve the problem of materials, a quite complex design of sensors and measurement systems is required [6,7]. Another topical direction of studies is the internet of things [8,9], which also has medical applications [9]. In this paper, we focus our attention only on nanomaterials for dentistry.

The field of dentistry is closely connected to materials and often requires the development of new therapeutic materials, along with the necessary equipment, instruments, and treatment techniques. Developing new materials and technologies can solve issues in traditional dental care [10]. Conventional dental treatment can often be uncomfortable, painful, and anxiety-inducing for patients due to invasive procedures such as carious cavity preparation, filling, and tooth extraction. Nano dentistry presents a promising alternative to these procedures by utilizing nanosized materials, tissue engineering, and dental nanorobots to diagnose, treat, and prevent oral and dental diseases. Patients may experience discomfort and hypersensitivity to dentine during recovery from procedures like root scaling, planning, and curettage of periodontal pockets. However, nanorobotics aims to overcome the drawbacks of conventional medical techniques. For instance, inserting medicaments into periodontal pockets and then protecting them with periodontal dressing may cause discomfort for a patient during eating or communicating, and it can also disrupt the mouth's esthetic appearance. Additionally, medicaments may seep out of the pocket. To combat these issues, nanoparticles can be carriers for targeted drug delivery.

Nanotechnology is the field of science and technology that involves manipulating materials at the scale of nanometers. The term 'nano' comes from the Greek 'Nanos,' which means 'dwarf'. Nobel Prize-winning physicist Richard Feynman introduced the concept of nanotechnology in a 1959 lecture titled "There is a Plenty of Room at the Bottom." He ended the lecture by concluding, "This is a development which I think cannot be avoided" [11–13]. In 1974, Norio Taniguchi coined the term 'nanotechnology' to refer to the ability to precisely engineer materials with the dimension of nanometers. Dogra et al. [14] and Hamissi et al. [15] first introduced the field of «nanomedicine». At the molecular level, nanostructures and nanodevices are used to observe, control, and treat biological systems within the human body [16,17]. It improved materials' mechanical and physical properties and introduced new diagnostic modalities and nanodelivery systems, revolutionizing the medical and dental fields [18]. The increasing interest in using nanotechnology in dentistry has led to the emergence of a new field called 'nano dentistry' [19,20]. Nano dentistry can be approached from two different perspectives. One is called the "Bottom-up approach," where atomic elements are combined to build particles. The other approach is the "Top-Down approach," which involves using equipment to create a mechanical nanoscale [21–23]. Nanotechnology has a wide range of applications for preventing, diagnosing, and treating oral diseases.

Periodontitis and gingivitis are prevalent periodontal diseases affecting millions of people worldwide [24]. Conventional treatment methods for these diseases involve mechanical debridement, antimicrobial agents, and surgery. However, the emergence of nanotechnology has opened up new possibilities in treating periodontal diseases. Periodontics has been used to develop novel drug delivery systems, such as nanofibers and nanoparticles, which can penetrate deep into the periodontal tissues and release drugs over an extended period. Moreover, nanotechnology has also been utilized to develop antimicrobial agents, which can effectively eliminate periodontal pathogens while minimizing toxicity and side effects. For example, silver nanoparticles have shown promising results in inhibiting the growth of periodontal pathogens, such as *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans*. In addition, nanotechnology has been applied in developing tissue engineering and regenerative medicine techniques, which aim to restore damaged or lost periodontal tissues. Nanofibrous scaffolds and nanoparticles have been used to promote cell adhesion, proliferation, and differentiation, forming new periodontal tissues. Integrating nanotechnology in the treatment modalities for periodontal diseases represents a significant advancement of periodontics and has a wide range of use (**Figure 1**). It offers new avenues for managing and preventing periodontal diseases, improving oral health outcomes that improve patients' quality of life.

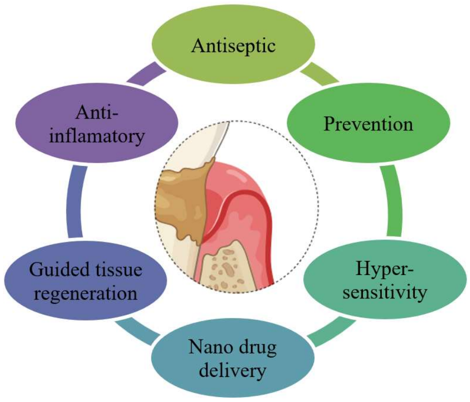

Figure 1. Areas of applications of nanotechnology in periodontics.

This review article aims to provide recent updates on nanotechnology-based approaches for periodontal disease therapy. Additionally, the present review will help the reader understand nanoscience and its benefits and limitations by addressing its ethical, social, and health implications.

2. The technique of data preparation

For this paper, we chose the form of narrative review [25]. For this narrative review, the search was performed within the Scopus database to identify the number of papers found for the keywords and phrases such as "nanodentistry"; "dentistry and nanotechnology"; "dentistry and nanoparticles"; "dentistry and nanomedicine"; "dentistry and nanorobots". The search considered works published in Scopus till 5th of November 2023 (included). Only relevant literature in English from the electronic search was selected for the present review. The nanoparticles had to be used in periodontics.

The found papers were subjected to the inclusion and exclusion criteria. The inclusion criteria are as follows: i) use of nanoparticles in periodontics; ii) full text journal articles written in English; iii) books and book chapters written in English; iv) scientific works published in 2013 and later (older works are mentioned only in the Introduction chapter).

The exclusion criteria are as follows: i) case reports (clinical trials); ii) conference papers; iii) materials published earlier than 2013; iv) randomized controlled studies; v) editorials; vi) errata. The search was carried out in Scopus, using the keywords and phrases "nanodentistry", "dentistry and nanotechnology", "dentistry and nanoparticles", "dentistry and nanomedicine", "dentistry and nanorobots".

In total, 530 records were found.

1) We excluded the types of papers that fit the exclusion criteria.
2) The first and second co-authors analyzed the remaining records for compliance with the inclusion and exclusion criteria. Some points were clarified with additional hand searching, in particular the peculiarities of the use of triclosan,

bone grafting, and data about periodontal disease. There were 27 additional records identified from the hand search.

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

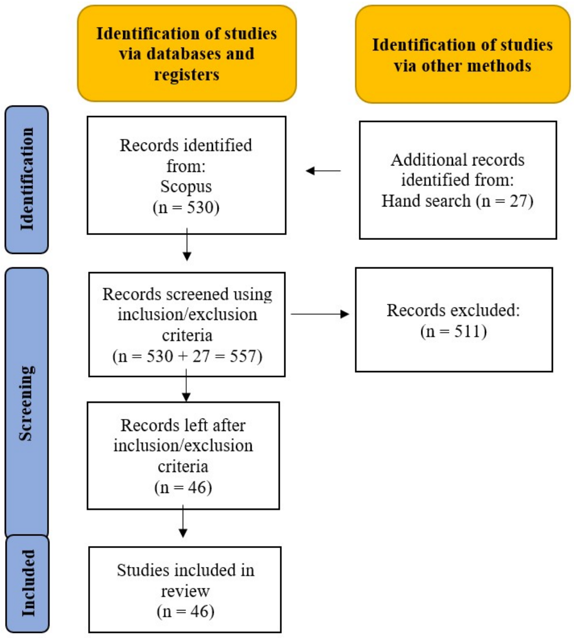

Figure 2. PRISMA (Preferred reporting items for systematic reviews and meta-analyses) flow diagram of inclusion/exclusion criteria.

3. Results

The results of the search are summarized in **Table 1** and explained in details below this table.

Table 1. Results of the search.

	Nano-dentistry	Dentistry and nanotechnology	Dentistry and nanoparticles	Dentistry and nanomedicine	Dentistry and nanorobots	Total (along row)
Nanodentistry	53	18	8	18	2	99
Dentistry and nanotechnology	18	148	19	15	0	200
Dentistry and nanoparticles	8	19	169	4	0	200
Dentistry and nanomedicine	18	15	4	75	0	112
Dentistry and nanorobots	2	0	0	0	1	3

The first column contains key words as well as the first row. The numbers on intersections of rows and columns indicate the number of papers belonging to both key words. The intersection of the key word along the row and column indicates the number of papers that belong exclusively to this particular key word. The table is symmetric, i.e., the number of papers on the intersection of a certain row and a certain column is the same as the number of papers on the intersection of a certain column and row with the same key words. The column entitled "Total (along row)" indicates the amount of papers that belong solely to a certain key word and in combination with other key words. Since the table is symmetric, the total amount of papers in each column equals to that of each row. The last row, "Total papers" indicates the total amount of papers.

Numerical analysis of publication in a certain field can be interesting and useful. It can reveal some patterns of development, ties to other fields, and trends of development [19,26].

The total list of unique papers contains 530 ones. This number can also be found when we add the numbers on intersections of a row and a column with the same key word, i.e., along the diagonal. These include 6 editorials, 7 conference papers, 103 book chapters, 222 journal articles, 187 reviews, and 5 other articles (errata, notes, etc.).

The distribution of papers by year and cumulative amount of papers by year are given in **Table 2**.

Table 2. The amount of paper year by year and cumulative amount of papers by year.

Year	Papers by year	Cumulative number of papers
2000	2	2
2006	1	3
2007	1	4
2009	2	6
2010	3	9
2011	14	23
2012	9	32
2013	8	40
2014	9	49
2015	14	63
2016	10	73
2017	9	82
2018	16	98
2019	17	115
2020	56	171
2021	76	247
2022	117	364
2023	166	530

The cumulative amount of papers by year can be expressed with the formula [27].

$$N(X \leq x) = \sum_{(x_i \leq x)} n(x_i) \quad (1)$$

where $N(X \leq x)$ is the cumulative amount of papers for a certain year x; $n(x_i)$ is the amount of papers for i-th year.

These data are also given in **Figure 3**. The left-hand side Y-axis is for the blue curve, which shows the amount of papers each year. The right-hand side Y-axis is for the orange curve, which shows the cumulative distribution of papers, i.e., the sum of papers for this particular year and all years prior to this one.

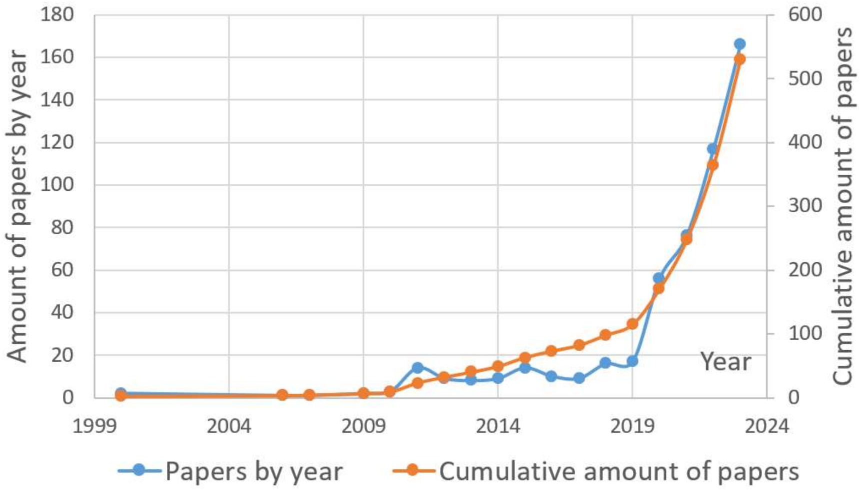

Figure 3. The amount of paper versus year (left hand side axis Y) and cumulative amount of papers (right hand side axis Y).

As can be seen from **Figure 2,** the number of papers published within 2020–2023 has sharply increased. This rise agrees with the prediction made in the study by Kochan [19]. However, it seems to us as a new trend, so it is impossible to fit any curve to describe the data and make any prediction for the field's future development.

We try to fit the curve to data. There are several tools, such as regression analysis [28] and neural networks [29,30] to solve such a task. However, according to Spiegelhalter [31], it is preferable to use regressions in relatively simple tasks like this. We applied this approach in the study by Kochan [19], and we will follow it in this paper too.

We failed to fit the curve to the amount of paper versus year because there is no such a typical equation [28] to fit the amount of papers by year.

However, we can fit the cumulative amount of papers. To do it, we need to preprocess the data. First of all, we eliminate the data prior to 2006 to avoid gaps in the independent variable (year). Then, to simplify the coefficients, we subtract 2000 from each year (i.e., we use only two last digits to denote a year), and plug is in Equation (2). From **Figure 3**, we assume the data can be fitted with the model as follows:

$$Cumulative\ Amount\ of\ Papers = a_0 \cdot a_1^{year} \tag{2}$$

To estimate the unknown coefficients a_0 and a_1 we log both sides, so the linear model is as follows:

$$Log(Cumulative\ Amount\ of\ Papers) = log(a_0) + year \cdot log(a_1) \tag{3}$$

Equation (3) is the simple linear regression [27,28]. Having applied the conventional procedure of the least squares we got coefficients of Equation (3). The distribution of residuals is given in **Figure 4**.

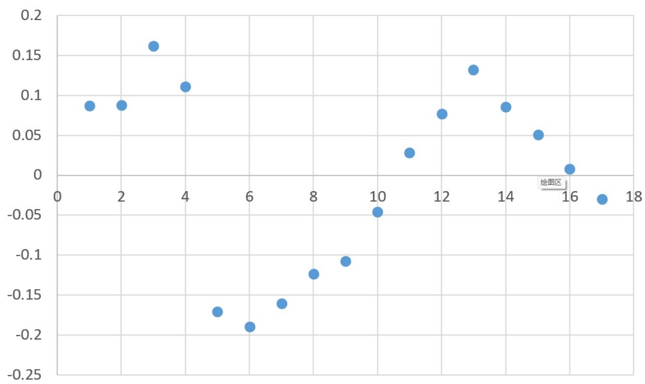

Figure 4. The distribution of residuals for linearized Equation (3).

We use the coefficients of the linearized model to compute the coefficients of Equation (2) according to the procedure described in the study by Mendenhall et al. [28]. We plug numerical values of coefficients in Equation (2) to get the formula that can be used for calculating the cumulative amount of papers:

$$Cumulative\ Amount\ of\ Papers = 0{,}649 \cdot 1{,}334^{year} \quad (4)$$

The coefficient of determination is 0.97, which means the model explains the variation of 97% of the data. According to DeCoursey [27] and Mendenhall et al. [28], in a fully valid linear model, residuals have to be distributed randomly. This was the case in the study by Kochan et al. [19]. However, **Figure 4** shows some pattern in distribution, so the model can be used with some care; that is why we do not use it for forecasting, unlike Kochan et al. [19], despite a very high value of the coefficient of determination. However, the forecast can be made according to the technique given in the study by Hu et al. [9].

4. Discussion

4.1. Properties of nanomaterials

Nanotechnology refers to the science and art of engineering materials on a scale of less than 100 nanometers [29–31]. The term “nanotechnology” was initially coined by Norio Taniguchi, a professor at Tokyo Science University, in 1974. According to scientific research, nanotechnology involves processing materials by manipulating them at the level of individual atoms or molecules [32]. Materials with components measuring less than 100 nanometers in at least one dimension are called nanomaterials. This includes synthetic or natural materials such as clusters of atoms, grains less than 100 nanometers in size, fibers with a diameter of less than 100 nanometers, films less than 100 nanometers in thickness, nanoholes, and composites that are a combination of these [33,34].

Unique physical and chemical properties are possessed by materials on the nanoscale, commonly referred to as nanomaterials. Nanostructures, another name for nanomaterials, can be classified based on their dimension. Zero-dimensional nanostructures are known as nanoparticles, while nanowires and nanorods are considered one-dimensional nanostructures. Two-dimensional nanostructures are referred to as thin films. All of these structures meet the definition of a nanomaterial or nanostructure, being smaller than 100 nm in at least one dimension (**Figure 5**) [35].

The characteristics of the material have been enhanced, resulting in improved toughness, stiffness, and transparency, as well as increased resistance to scratches, abrasions, solvents, and heat. Furthermore, nanoparticles possess distinctive attributes that distinguish them from other particles, such as varied chemical, optical, magnetic, and electro-optical properties, which are not found in bulk species or individual molecules [35].

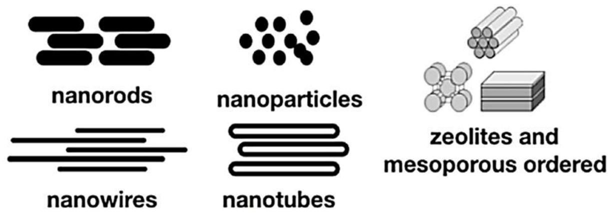

Figure 5. Representation of the structure of nanomaterials that are highly beneficial for medical purposes.

The shape of nanoparticles and their size distribution vary depending on the method of synthesis used. Both top-down and bottom-up approaches can be utilized in the creation of nanoparticles. The synthesis methods for nanoparticles depend on the material classification of the particle, such as metal, ceramic, or polymer.

Silver nanoparticles are commonly used in dental materials because of their ability to destroy microbes. Metal complexes are typically reduced in dilute solutions under carefully controlled reduction reaction conditions to create metal colloidal dispersions containing metallic nanoparticles [36]. Drug delivery often employs polymer nanoparticles, such as nanospheres and nanocapsules, which often contain active pharmaceutical ingredients within each particle or have macromolecular substances adsorbed on their surface. Polymerization-based methods like emulsion polymerization, dispersion polymerization, interfacial complexation, and polymer participation methods such as single/double emulsion, solvent displacement, or salting out can be used to prepare polymer nanoparticles. Drugs can be incorporated either during nanoparticle preparation or after [37]. Typical polymers for polymer nanoparticles include chitosan, polyacrylamide, polyacrylate, and polyesters. Biodegradable polymer nanoparticles are often employed to release drugs from nanoparticles into the human body. Polymer nanoparticles can be used as a drug delivery mechanism, which offers many benefits over traditional drug applications. These benefits include the ability to target specific tissues and cells through ligand specificity, efficient absorption of polymer nanoparticles into cells, lower doses of drugs required for treatment, reduced toxic effects, sustained release of drugs at the target site, and improved therapeutic potential [38]. The fusion of nanotechnology in the treatment modalities for periodontal diseases can be considered one of the breakthroughs in periodontics.

4.2. Periodontal diseases

Periodontal disease, which is a major dental illness, affects millions of people across the globe. The disease is one of the significant public health problems in many countries [39,40], as it possesses the criteria such as being widespread and having severe consequences on individuals, communities, and health services in terms of social, psychological, and economic aspects [41,42].

Inflammation and damage to the supportive tissues surrounding the teeth, including the periodontal ligament, alveolar bone, cementum, and gum, often occur due to the invasion of anaerobic Gram-negative bacteria (**Figure 6**). This condition is commonly known as periodontal disease [43]. The cause of periodontal disease is the imbalance between the colonization of bacterial pathogens and the host's immune response toward infection [44,45].

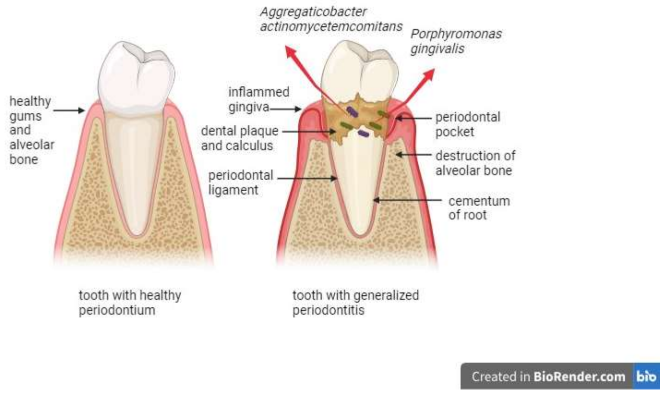

Figure 6. Schematic representation of healthy periodontal tissues and generalized periodontitis.

Periodontal treatment aims to address infections and restore the function and structure of periodontal tissues, including cementum, periodontal ligament (PDL) fibres, and bone. However, it is still difficult to fully recover these three tissue types and re-establish the strong attachment of PDL fibres to the new cementum and alveolar bone [46,47].

Recent developments in nano-materials and nano-technology have created promising possibilities for the efficient management of periodontitis. Various newer techniques, such as the use of bio-adhesive polymers to achieve extended drug release, enhancing intrapocket drug penetration, improving mechanical features through chemical cross-linkers, and the potential of loading multiple drugs in a single delivery system, offer several significant advantages. These benefits pave the way for further research opportunities in advancing dental therapeutics through the development of drug delivery systems [48–51].

4.3. Applications of nanotechnology in periodontics

Antiseptic treatment of periodontal diseases involves using disinfectants, which can contain irritating compounds and cannot be applied to soft tissues like mucosa. An exciting alternative to these strong disinfectants is the development of Ozone water. Unlike other disinfectants, Ozone water does not damage skin cells, and repeated use does not result in skin roughness or oral mucosa irritation. After use, ozone decomposes to oxygen and leaves no harmful residues. Additionally, ozone nano-bubble water, which has been stable for over six months in storage in an electrolyte solution, has been created [52].

Nanotechnology in periodontics has touched every aspect of treatment modality, from non-surgical therapy to implant procedures, including regenerative procedures (**Table 3**).

Table 3. Overview of advancements in nanomaterial, and nanotechnology in periodontics.

Active ingredient/brand name	Properties and advantages	Reference/year
Ozone water	Ozone water is an exciting alternative to strong disinfectants (i.e. Alcohol, povidone iodine) used in antiseptic treatment of periodontal diseases. It can be used on soft tissues like mucosa and does not contain irritating compounds.	[52]/2017 year
Antimicrobial and antibiofilm activity of curcumin-silver nanoparticles	Curcumin-silver exhibited excellent antibacterial activity against both Gram-positive and Gram-negative bacteria and were less toxic to human keratinocytes. Cur-AgNPs were effective in inhibiting biofilm formation and exhibited anti-inflammatory effects on human macrophages.	[53]/2018 year
Triclosan	It is a noncationic antimicrobial agent that has been proven efficacious against several plaque forming bacteria.	[54]/2020 year [55]/2021 year
Tetracycline microspheres	Tetracycline Microspheres(TM) were more effective in treating chronic periodontitis through clinical parameters and microbiological analysis. Additionally, TM had a superior method of local drug in terms of usage and application.	[56]/2017 year
Minocycline Microspheres, Arestin®	The microspheres are combined with the person's saliva as they are dispensed. This mixture transforms into a semi-solid gel that fills the small crevices of the gum pocket and tooth. The microsphere gel compound can move around the mouth after inoculation, better coating the infected area. The microspheres slowly dissolve over three weeks to a month, releasing minocycline. This allows the drug to target the biofilms around the area and directly attack these species.	[57]/2023 year
Harungana madagascariensis (Hypericaceae)	H. madagascariensis, a plant found in tropical Africa and Madagascar, has medicinal properties that have been traditionally used to cure diseases. It has antibacterial potential against both sensitive and MDR bacteria. Its anthranoids constituents show promise in developing herbal medicine and pharmaceuticals to combat bacterial drug resistance.	[58]/2023 year
Tricalcium phosphate scaffolds for bone regeneration/Vitosso (Orthovita, Inc., USA) HA+tricalcium phosphate	Biomaterials made of ceramics, such as CaP, are excellent choices for restoring lost function and hard-tissue engineering. The minerals in them are comparable to those found in bones, and they have the ability to induce the growth and specialization of cells.Additionally, their relatively low degradation rate can facilitate prolonged guided tissue remodeling and structural support.	[59]/2017 year
Nano-Hydroxyapatite for Bone Tissue Engineering, Nano crystalline particles of HA Ostims commercially available in a syringe as a ready-to-use paste (Heraeus Kutzer, Hanau, Germany)	HAp can promote new bone ingrowth through osteoconduction mechanism without causing any local or systemic toxicity, inflammation or foreign body response. Nanocrystaline hydroxyapatite (nHA) is a drug delivery carrier that can be used instead of HA ceramics. The reason for this is that it has a reactive surface area that is quite high, nanoscale porosity, and it is capable of in vivo degradability	[60]/2019 year
Chitosan Nanohydrogel as a Bone Regenerative Material	It has the potential to act as a scaffold material that can enhance the differentiation of osteoprogenitor cells, chitosan hydrogel in combination with a bone graft showed superior bone regenerative potential and could prove to be an excellent candidate for bone regeneration.	[61]/2021 year
Chitosan hydrogels for drug delivery	The study tested a prototype toothpaste containing $CaCl_2$/chitosan microspheres for remineralization of human tooth enamels. The toothpaste was found to be effective in increasing calcium contents and Ca/P weight ratios in treated enamels, resulting in larger remineralization bands compared to the negative control group.	[62]/2018 year
Micro-nanorobots	Dental nanorobots can quickly relieve dentine hypersensitivity by closing specific dentinal tubes. Dentifrobots can prevent cavities by targeting harmful bacteria and allowing good bacteria to thrive. Utilizing micro/nanorobots, stem cells have been transported to a damaged area for the purpose of restoring tissue. These uses exemplify that micro/nanorobots could act as foundations for cell-based therapy and regenerative medicine. This has the potential to be particularly advantageous during the later phases of life, as organs and systems may begin to deteriorate.	[63]/2023 year [64]/2018 year

Understanding their mechanism plays a pivotal role in more efficient usage of nanotechnology, better treatment procedures, and eventually better outcomes. Effectively treating periodontal disease involves utilizing NPs that can eradicate pathogenic bacteria, as bacterial colonization is among the initial stages that cause this condition. According to available reports, combining azithromycin and clarithromycin with silver nanoparticles (AgNPs) has been found to have a synergistic antimicrobial effect against microorganisms that cause periodontal disease [53, 65]. In another study, produced glutathione-capped bimetallic NPs with great antibacterial potential against the anaerobic oral pathogen *Porphyromonas gingivalis* was suggested [53]. Curcumin-silver nanoparticles (Cur-AgNPs) exhibited excellent antibacterial activity against both Gram-positive and Gram-negative bacteria and were less toxic to human keratinocytes [66]. Moreover, Cur-AgNPs exhibited anti-inflammatory effects on human macrophages by reducing the secretion of pro-inflammatory cytokines IL-6 and TNF-α compared to chemically synthesized AgNPs. Implants can be coated with titanium oxide nanotubes and infused with silver nanoparticles to help prevent infections and prolong the lifespan of the implants [67].

4.4. Dentinal hypersensitivity

Dentin hypersensitivity is an area where dental nanorobots may find their use. Dentin hypersensitivity is a condition that occurs when changes in pressure are transmitted through the surface of the tooth, affecting the pulp [68].

The density of dentinal tubules on hypersensitive teeth is eight times higher than on non-sensitive teeth. Additionally, the diameter of these tubules is twice as large. It is possible to use dental nanorobots to occlude these tubules within a few minutes. This procedure offers patients a fast and permanent solution to their hypersensitivity [69]. The dentinal tubules are reached by tiny nanorobots that move towards the pulp while being directed by chemical gradients and temperature changes, all controlled by a nanocomputer. These nanorobots can get the pulp within 100 s, providing quick relief from sensitivity [63,70].

4.5. Drug delivery

In periodontal treatments, local drug delivery is necessary for reliable outcomes. Drug delivery systems based on triclosan-incorporated nanoparticles have been developed. Triclosan-loaded nanoparticles have been produced by emulsification-diffusion to obtain a novel delivery system for the treatment of periodontal disease. In this research article [54], the authors investigated the properties of triclosan (TCS), a hydrophobic antibacterial agent with broad-spectrum activity. To improve its antimicrobial and bacteriostatic effects, a novel amphiphilic copolymer containing tertiary amine groups, called monomethyl ether poly (ethylene glycol)-b-poly{α-[4-(diethylamino)methyl-1,2,3-triazol]-caprolactone-co-caprolactone} (mPEG-PDCL), was synthesized and designed. This copolymer was used to create micelles that served as carriers for TCS. Micelles released the cargo faster in acidic environments and demonstrated excellent antimicrobial ability against *S. aureus* and *E. coli.* Significant regeneration of the lost bone was revealed for the nanogels-treated group as per another study [55] based on morphometric findings. The developed nano-gel system, loaded with antimicrobial TCS and anti-inflammatory FLB (flurbiprofen-loaded nanogels), showed a superior healing effect in treating periodontitis based on the overall results.

The use of microspheres containing tetracycline is presently being evaluated for treating periodontal pockets. Based on the study by Kumar et al. [56], it was concluded with the help of clinical parameters and microbiological analysis that Tetracycline Microspheres (TM) were more efficient than commercially available Tetracycline Fibers (TF) (Periodontal Plus AB) in the treatment of chronic periodontitis. Also, TM had a better mode of local drug delivery in comparison to TF for both dentists and patients in terms of usage and application.

Arestin is a famous brand of antibiotic minocycline that is claimed to aid in regaining at least 1 mm of gingival reattachment height. This treatment does not require bandages or stitches and is bio-adhesive and bioresorbable, which means that it will not leak or fall out and does not need to be removed by the dentist or hygienist in a follow-up visit. When combined with deep cleaning, using Arestin to treat periodontal disease can help keep gum pockets below the threshold for surgical intervention. Moreover, the application of Arestin is comfortable and does not require anaesthesia. Clinical trials have demonstrated that a single dose of microspheres introduced into an infected gum pocket can be released for over three weeks, compared to minocycline oral capsules, commonly prescribed for 15 days [57]. Arestin® doses, which contain minocycline hydrochloride impregnated within a polymer, are delivered in 1 mg increments into the gum pocket, allowing the minocycline to be released slowly over three weeks to a month.

Although several chemical agents are available commercially, the search for alternatives persists, and traditional medicinal plants are considered a viable option, as they contain natural phytochemicals that could serve as substitutes.

An African plant called Harungana madagascariensis (Hypericaceae) possesses antimicrobial properties and contains various antimicrobial components. The leaves were subjected to successive Soxhlet solvent extractions to prepare an ethyl acetate extract, which was then tested against several oral pathogens. The extract killed all oral bacteria tested, including Actinomyces, Fusobacterium, Lactobacillus, Prevotella, Propionibacterium, and Streptococcus species. However, the activity of poly(d,l-lactide-co-glycolide) nanoparticles containing the extract was enhanced. The authors suggested that the polymer's bioadhesive properties might have led to the extract being in contact with the bacteria for prolonged periods [58].

4.6. Bone regeneration

Bone loss is a significant hallmark of periodontitis. Losing bone support causes tooth movement and dislocation, ultimately resulting in tooth loss [71]. Biologic or synthetic biomaterial intended for human implantation to restore bone health, preserve bone structure, or fill bone loss is considered a bone substitute [72]. Bone grafts can be conveniently divided into four groups:

- The patient himself (autogenous grafts)—"gold standard" for bone replacement [73];

- Different donors from the same species (allogeneic grafts), including freeze-dried bone allografts and demineralized freeze-dried bone allografts [74];
- Donors from different species (xenogeneic grafts), for example, Bio-Oss [75];
- Synthetically created materials (alloplastics), for example, tricalcium phosphates [59], a calcium-layered polymer of polymethyl methacrylate and hydroxyethyl methacrylate [76], bioactive glass [77], and hydroxyapatite (HA) [78].

Hydroxyapatite (HAp) is the primary mineral constituent of vertebrate bones and teeth. Hydroxyapatite (HAp) powder has been used for biomedical applications such as bone implant substitutes, scaffolds for complex tissue engineering, or superficial coating of implants due to a great chemical similarity with biologically calcified tissues. Synthetic HAp has been of interest for decades due to its excellent biocompatibility, affinity to biopolymers, and high osteogenic potential. It has been well documented that HAp can promote new bone in growth through osteoconduction without causing local or systemic toxicity, inflammation, or a foreign body response [79]. Among the various HAp structures, nanosized HAp, also known as HAp nanoparticles, with appropriate stoichiometry, morphology, and purity, have stimulated great interest in basic scientific research and various biomedical applications.

Nanosized HAp, which has a grain size less than 100 nm in at least one direction, has high surface activity and an ultrafine structure, similar to the mineral found in hard tissues. In recent years, bioceramics and biocomposites based on nanosized HAp have been the most promising materials for a variety of biomedical applications. Nanocrystaline hydroxyapatite (nHA) is a drug delivery carrier that can be used instead of HA ceramics. The reason for this is that it has a reactive surface area that is quite high, nanoscale porosity, and it is capable of in vivo degradability. Numerous techniques have been created for linking nHA with a broad range of antibiotics, especially tetracyclines, gentamicin, and vancomycin. The effectiveness of the delivery mechanism relies on the interplay of antibiotics with the surface of nHA, the scaffold's porosity, the capacity of antibiotic loading on the nHA nanoparticles, and the gradual release of antibiotics in the defect [60]. Apart from its therapeutic activity, nHA also acts as a bioactive matrix for newly formed bone, which may be improved with metal (Zn^{2+} and Sr^{2+}) and carbonate substitution (CO_3^{2-}) in the apatite structure. Methods for the preparation of HAp nanoparticles are given in **Figure 7** [80].

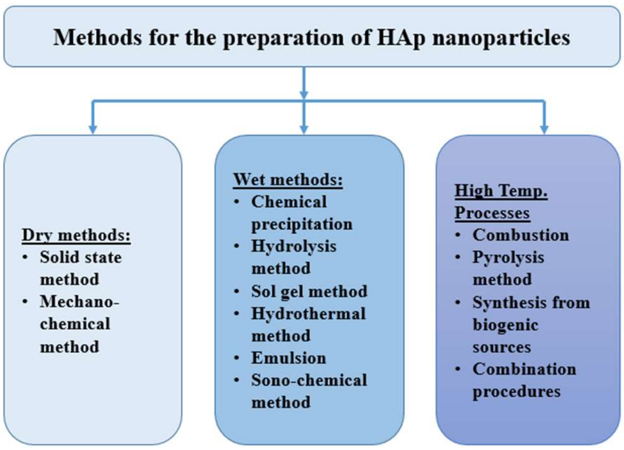

Figure 7. Methods for the preparation of HAp nanoparticles.

Various techniques have been developed to enhance the osteogenesis process, including bone grafts [81], scaffolds [82], stem cells [83], and growth factors [84]. All of these techniques have significant clinical drawbacks. Autologous grafts are limited in availability, growth factors are often unstable, and biomaterials have a high failure rate. Consequently, there is a great need for treatments that are highly effective and efficient in order to pave the way for periodontal tissue renewal. Designing scaffolds that imitate the intricate shape and organization of periodontal tissues is a significant challenge in regenerative periodontology.

Ceramics and polymers are the most commonly used materials for restoring and replacing lost oral tissues in periodontal regeneration. Ceramic biomaterials, such as calcium phosphate (CaP), calcium sulfate (CS), and bioactive glass (BG), are highly suitable for the construction of complex tissues. They can effectively restore lost function due to their similar composition to bone minerals, ability to stimulate cell proliferation and differentiation, and relatively low degradation rate. The latter is particularly beneficial for promoting long-term guided tissue remodelling and structural support. Nevertheless, these materials' brittleness and low ductility should be considered. Polymers, such as polylactic acid (PLA), polyglycolic acid (PGA), the copolymer poly (lactic-co-glycolic acid), and PCL, are highly adjustable and can be mass-produced [59].

Although many options are available, achieving complete regeneration is still challenging. Therefore, there is a focus on utilizing natural materials to overcome the limitations of synthetic ones. Chitosan is a naturally occurring biopolymer that is abundant [85]. It has the potential to act as a scaffold material that can enhance the differentiation of osteoprogenitor cells, which in turn promotes bone regeneration [86]. The study's outcome showed that chitosan significantly improved clinical and radiological parameters [61]. When bone grafts were mixed with chitosan gel and used to treat defects, it substantially reduced probing depth, improved clinical attachment loss, and achieved significant defect resolution at six months [87].

4.7. Prevention

Delivery of nanorobotic dentifrice is possible through toothpaste or mouthwash, allowing it to patrol all surfaces above and below the gum line. It can metabolize trapped organic matter into harmless, odorless vapors while performing continuous calculus debridement [88].

Mouthwash or toothpaste can release tiny robots called dentifrice nanorobots (or dentifrobots) onto the surfaces of teeth. These robots, which can be as small as 1–10 microns, move quickly (at a rate of 1–10 microns/second) and can clean up organic residues on both the supragingival and subgingival surfaces of teeth. By doing so, they can continuously prevent the buildup of calculus. Dentifrobots are designed to be safe for humans; they are deactivated when swallowed. Additionally, if they are correctly configured, dentifrobots can detect and eliminate harmful bacteria that may be present in dental plaque [64].

In scientific research [62], we tested a prototype toothpaste containing $CaCl_2$/chitosan microspheres for remineralization of human tooth enamels. The toothpaste was found to be effective in increasing calcium contents and Ca/P weight ratios in treated enamels, resulting in larger remineralization bands compared to the negative control group.

Antimicrobial peptides can be immobilized on the surface of medical devices and instruments to provide them with antimicrobial properties [89].

4.8. Challenges faced by nano dentistry

The healthcare industry is set to undergo a significant transformation through the utilization of nanotechnology, which provides new possibilities for disease diagnosis and prevention, drug delivery, and gene therapy. Despite the groundbreaking methods and equipment introduced by nanotechnology in the dental field, certain apprehensions must be addressed (**Table 4**). These include cost-effective mass production of nanorobots, ethical dilemmas and human safety, biocompatibility issues, and the necessity for precision positioning and technical expertise in nanotechnology [90–94].

Table 4. Problems and challenges of nanotechnology.

Area	Problems and challenges
Engineering	Feasibility of mass production technique
	Assembly lines for mass production
	Precise monitoring and control of production processes
	Metrological service of measuring instruments
Biological	Development of biofriendly nanomaterial
	Development of safe materials for human beings
	Biocompatibility the human body
Social	Ethics
	Public opinion and acceptance
	Regulation and human safety
	Affordability
	Accessibility

5. Conclusion

The field of nanotechnology is relatively new and holds immense potential for advancements. There are numerous paths for its development and progress. It is a rapidly growing area with the potential to produce advanced clinical tools and devices for oral healthcare.

The future of periodontics looks incomplete without incorporating nanotechnology in routine periodontal therapy, be it surgical or non-surgical; however, it will take extensive research to develop nanoscale biomaterials, which can be safely instilled in the human body. Nanotechnology promises to play an essential role in minimizing patient discomfort and, at the same time, maximizing the effects of a particular periodontal therapy.

Numerous nanomedicine approaches are being pursued today, and their successful development will likely occur very soon. These approaches are already close enough to the realization that their subsequent incorporation into valuable medical diagnostics or clinical therapeutics is almost inevitable. The fusion of nanotechnology in the treatment modalities for periodontal diseases is one of the breakthroughs in periodontics.

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