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Applications of Nanotechnology in Dentistry: A Review

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Abstract

Objective: Maintaining the health of oral tissues is a major goal in dentistry. However, limitations in dental materials, instruments, procedures and medications prevent achievement of this goal. Advances in nanotechnology have paved the way to approach this goal. This study reviews the advances on nanotechnology in dentistry.

Review of Literatures: In this review study, Google Scholar, PubMed, Science Direct, Medline and Cochrane databases were searched for relevant English and Farsi papers from 1981 to 2013. The searched key words were: "nano-characterization", "antimicrobial agent", "nano-dentistry", "nanotechnology", "nanoparticles", and "nano-medicine".

Conclusion: Studies indicated extensive applications of nanotechnology in various fields of dentistry such as prevention, diagnosis and treatment. Use of nanoparticles as antimicrobial agents in conjunction with other oral hygiene tools such as toothpastes may prevent many oral and dental conditions. Also, application of nanostructures enables faster and easier detection of oral cancers and assessment of the saliva for presence of viruses, proteins or specific markers. Last but not least, nano-capsules, nano-coatings and nano-antibiotics enable more efficient treatments.

Key words: Antimicrobial agent, Nano-characterization, Nano-dentistry, Nano-medicine, Nanoparticles, Nanotechnology.

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Introduction:

Maintaining oral health is a major goal in dentistry, which can be evaluated in prevention, diagnosis and treatment levels. In other words, clinicians must be able to prevent possible complications by using proper tools and materials even in ideal health conditions. Also, by accurate and prompt diagnosis, a clinician can prevent serious complications due to delayed diagnosis. In the level of treatment, a clinician must provide patients with the latest, most efficient treatment protocols. However, limitations in dental materials, instruments, procedures and medications prevent achievement of this goal and emphasize the need for a more efficient technology.

Dr. Richard Feynman was the first to introduce the concept of nanotechnology in 1959. He discussed his viewpoint in this regard in his lecture in the American Association of Physicists in Medicine entitled "Nanotechnology: It's a small world" (1). One nanometer is equal to one billionth of a meter (2). In this scale, particles have properties much different from those of the same material in mass scale. This concept led to the development of lighter but stronger materials with higher chemical and mechanical properties (3). Since then, nanotechnology has greatly advanced in different fields of science and dentistry has been no exception.

Application of nanotechnology in medicine aims at using equipment, Nano-materials and theories to enhance prevention, diagnosis and treatment of conditions via detection and reconstruction of injured tissues at the molecular and micromolecular levels (3). This study aimed to review the advances of nanotechnology in dentistry.

Review of Literatures:

In this review study, data were collected by searching Google Scholar, PubMed, Science Direct, Medline and Cochrane databases for the keywords: "nano-characterization", "antimicrobial agent", "nano-dentistry", "nanotechnology", "nanoparticles", and "nano-medicine." Relevant articles published from 1981 to 2013 in English and Farsi were retrieved (Diagram 1).

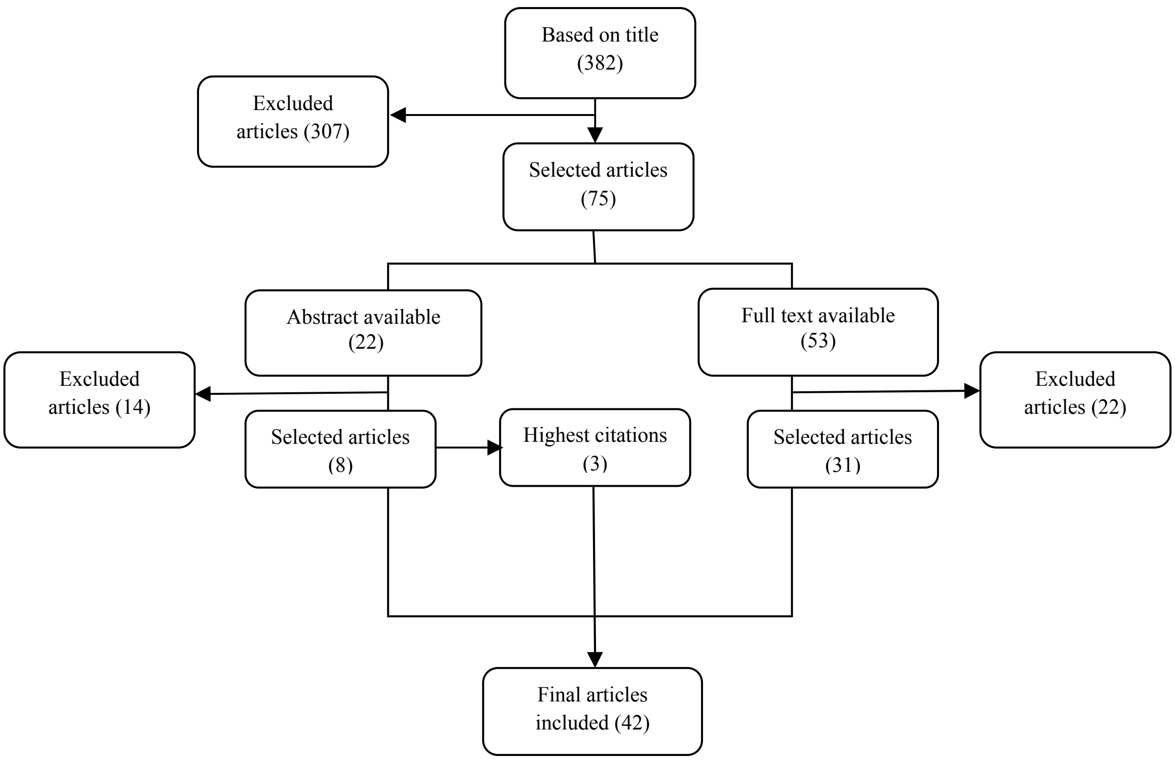

Diagram 1- Flowchart of article selection

A. A review on the applications of nanotechnology in the field of treatment:

1. Antimicrobial agents:

Unnecessary long-term antibiotic therapy often results in occurrence of antibiotic-resistance. Recent microbiological studies have focused on developing novel antimicrobial agents with higher efficacy while being non-invasive and non-toxic and not causing drug resistance (4, 5). Use of nanoparticles with antimicrobial properties is one efficient method for this purpose.

Metal nanoparticles:

The mechanism of the antibacterial activity of metals has yet to be fully elucidated. However, evidence shows that the reaction between the positively charged metal particles and negatively charged membrane of the microorganisms plays an important role in this respect (6).

Metal nanoparticles may be used in oxidized form. In this state, particles have high antimicrobial properties because their higher surface area and unconventional shape of crystals cause numerous highly reactive corners (7).

Metal nanoparticles have variable affinity for different microorganisms. For instance, silver nanoparticles have higher affinity for Gram-negative (8) and anaerobic (9) bacteria; which is related to the lower peptidoglycan content in Gram-negative bacteria. Also, the difference in affinity for aerobic and anaerobic bacteria is attributed to the different ability of nanoparticles for bonding to enzymes containing sulfhydryl (SH) groups. This may explain the lower effect of nanoparticles on Porphyromonas gingivalis (10).

Other factors such as the concentration (11) and size of particles (12) and their shape (13) also affect the efficacy of these materials against microorganisms. For instance, triangular silver nanoparticles with meshed surface are more effective than tubular and round nanoparticles (14). Further decrease in size of nanoparticles increases their antimicrobial efficacy due to increased surface area and consequently improved biocompatibility (12). On the other hand, using silver nanoparticles in inadequately low concentrations can cause bacterial resistance (11).

The antimicrobial efficacy of metal nanoparticles is variable and silver has higher efficacy than copper, zinc, titanium, magnesium and gold in lower concentrations (15).

Nano-chitosan:

Chitosan is a positively charged polysaccharide from the chitin family (16) and has high biocompatibility and coagulative properties (17). It is not an allergen (18, 19) and the antimicrobial activity of this material makes it a suitable choice for use in areas susceptible to infection (17, 20).

Carbon nanotubes:

Carbon nanotubes are allotropes of carbon with a cylindrical nanostructure (21). These tubes are categorized into two main groups of single-walled nanotubes and multi-walled nanotubes. The structure of a single-walled Nanotubemay be conceptualized by wrapping a one-atom-thick layer of graphite into a seamless cylinder; while multi-walled tubes are comprised of multiple concentric rolled layers of grapheme (22). Literature shows that single-walled nanotubes have antimicrobial activity (23). These nano tubes may be used for water filtration and surface coating (24); thus, they can be used in dental water filtration systems and manufacture of dental equipment.

Nano quaternary ammonium:

As an antimicrobial agent, this material can disintegrate the cell membrane and kill microorganisms. At w/w[1] concentration, it can prevent biofilm formation. This material is capable of eliminating 50% of oral bacteria. An important issue is that the effect of this material is not limited to the bacteria in direct contact to it; because cohesion of particles is so strong that the material does not disseminate into the adjacent tissues and consequently it penetrates deep into the layers of biofilm (25) (Table 1).

Table 1- Nanoparticles with antimicrobial activity and their mechanism of action

Nanomaterial	Antimicrobial mechanism	Reference
Silver	Release of Ag ions, disruption of bacterial cell membrane, impairing the electron transfer system, DNA damage	27
Zinc oxide	Accumulation of nanoparticles inside the cells, disruption of cell membrane, generation of H2O2, Release of zinc ions	28, 29
Copper oxide	Disruption of bacterial cell membrane as the result of lipid oxidation by reactive oxygen species and hydroxyl free radicals	30
Titanium dioxide	Production of reactive oxygen species, disruption of bacterial cell membrane and cell wall	31
Gold	Reaction with bacterial cell membrane and strong electrostatic effects	32, 33
Chitosan	Increased membrane permeability and leakage of intracellular components, deactivation of bacterial enzymes	34
Carbon nanotube	Cell membrane disruption by reactive oxygen species, oxidation of proteins and lipids within the cell membrane	23, 35
Quaternary ammonia	Penetrating through the bacterial cell wall and its disruption	36

2. Delivery systems:

These systems can be used for the delivery of drugs, proteins, growth factors, genes and cells to the target sites.

Nano-capsules:

Encapsulation of drugs into nanoparticle shells is one method of protecting the drug during delivery and also protecting the body against very toxic drugs. Encapsulation of drugs into nanoparticle shells or loading them onto the surface of nanoparticles enables controlled drug release. Such sustained release of drugs occurs during a specific time period through the nanoparticle capsule or following disintegration of the capsule at specific target locations resulting in burst release of drug. Evidence shows that capsules made of nanoparticles measuring 1-100 nm in size have higher surface/volume ratio and smaller porosities in capsule membrane and consequently more efficient solubility in comparison with capsules fabricated of larger nanoparticles (microns). Such properties affect the diffusion of drug through the capsule (26-36).

Nano-scaffolds:

Nano-fiber scaffolds were first used for drug and hormone delivery purposes but later, researchers found that these materials were capable of preserving, and delivery of cells to human body (37).

At present, scaffolds are used for delivery of drugs to the target sites (38). Disintegration of scaffolds while not triggering any immune response in the body is among their main advantages. Method of fabrication of these scaffolds and their constituents vary depending on the target. These scaffolds have many applications in dentistry for regeneration of oral and dental tissues like the alveolar bone, periodontal ligament, dental pulp and even mineralized tissues like enamel, which have lost their regeneration potential due to the apoptosis of the cells secreting them during the process of growth and development (39-48) (Table 2).

Nano-coatings:

Silica nanoparticles can be used for the delivery of antibacterial agents like triclosan (49). Also, incorporation of nitric oxide into the Nano-silica coat enhances its diffusion into oral biofilm and subsequent elimination of bacteria (50).

This system is also used for the incorporation of PSs like methylene blue into the Nano-silica (51). Nano-silica with magnetic properties may be used for delivery of these materials (52) or PSs may be loaded onto the surface of gold nanoparticles bonded to a specific antibody against a target microorganism (53). Under such circumstances, laser irradiation can stimulate the PS. PS transfers its energy to a neighboring oxygen molecule, moving it to the lowest excited state. Singlet oxygen is a highly reactive, electrophilic molecule and reacts with a wide range of bacterial enzymes and proteins, causing the death of microorganisms (54). Since endodontic and periodontal diseases are mainly caused by the activity of pathogenic microorganisms, these materials may be used in conjunction with other treatment modalities to decrease the sub gingival microbial count.

Nano-shells:

Nano-shells are nanoparticles with a di-electric (like silica) core and a thin metal coating i.e. by gold nanoparticles. Infrared light stimulates the Nano-shell and generates heat and thus, can be used for thermal destruction of bacteria, cancer cells, ligature of the vessels, wound healing and decreased angiogenesis. This method minimizes the risk of trauma to the adjacent tissues. Nano-shells loaded with anti-bodies, proteins or other cell-targeting agents can be used for targeted drug delivery (55).

Quantum dots:

Quantum dots are a group of semi-conductive nanoparticles like lead sulfide, zinc sulfide and indium sulfide that can radiate light based on the amount and wavelength of light radiated to them. The importance of semi-conductive nature of these materials is that their conduction state can be changed by external stimulants like magnetic field or light irradiation. These materials may be used as drug or gene carriers. They are also used as PSs in photodynamic therapy. Coating them with specific substances can enhance their attachment to cancer cells. Upon attachment, radiating UV light to them initiates UV light emission and enhances the detection of oral cancers. Wavelength and color of emitted light depend on the size of crystals (56). Thus, quantum dots can be used for treatment of head and neck diseases via drug delivery and correction of genetic defects. Also, they may play a role in prevention of oral cancer.

Table 2- Examples of Nano-scaffolds and their applications in dentistry

Application	Nano-scaffold	Loaded drugs	Description	Reference
Drug delivery	PIHCA	Ampicillin	Increased antibiotic activity inside phagocytes with adequate and efficient release of antibiotics into inter-cellular matrix	41
	PAA	Penicillin	Increased antibacterial activity against penicillin-resistant bacteria by protecting the drug from the effect of destructive enzymes and enhanced antibiotic delivery by appropriate bond of PAA to bacteria	42
	PLGA	Doxycycline	Sustained release of doxycycline within 6 weeks	43
	+PLGA	Nano-hydroxy apatite and Nano-collagen	Regeneration of bone and tissue collagen in periodontal disease	44
	PLGA	Methylene blue and Nano-gold particles	Photosensitizer (PS) materials were guided to the target site in this system. Nanogold particles enhanced penetration into the tissues. The system was attached to the target microorganism, methylene blue diffused into the microorganisms; red light radiation at 665 nm wavelength caused the death of the microorganisms. Positively charged PLGA enhanced the release of PS material and had higher toxicity.	45,46
	Chitosan	Silver nanoparticles	Chitosan polysaccharide is capable of absorbing metal ions like silver due to having functional groups and is used in infected areas like open wounds.	47
Cell delivery	PLGA+ PLLA	Platelet derived growth factor	This factor is used as a growth stimulator for periodontal ligament and bone cells	48
	RGDS	Ameloblast-like cells and primary tooth bud epithelial cells	Increased expression of genes coding for amelogenin and ameloblastin proteins that play a role in enamel formation in vitro	40
	Peptide amphiphiles	Stem cells from human exfoliated deciduous teeth and dental pulp stem cells	Group 1 stem cells were proliferated in vitro and secreted collagen matrix. Group 2 stem cells differentiated into odontoblast-like cells and secreted minerals; thus, they enhanced regeneration of hard and soft dental tissues.	41

- PIHCA, polyisohexylcyanoacrylate; PAA, polyacrylate; PLLA, Poly-L-Lactase Acid; PLGA, Poly lactic Co Glycolic Acid.

1. Tissue regenerators:

Demineralization of enamel and dentin, degeneration of soft tissue and periodontal ligament and resorption of cementum and alveolar bone during the course of periodontal disease are among the common problems in the oral cavity. To achieve the final goal of periodontal therapy namely regeneration of the lost tissues, several methods have been introduced such as bone grafting (57, 58), use of bone substitutes (57), guided tissue regeneration or a combination of all (59). Nanotechnology can also help in this respect. For instance, nanotubes and carbon Nanofibers can enhance bone regeneration (60).

Nano-hydroxy apatite (HA) particles with a mean size of 18nm are a good substitute for the resorbed bone (61). These particles may also play a role in remineralization of tooth structure following exposure to acidic agents such as carbonated beverages and can prevent erosive lesions (62).

2. *Nano-coatings:*

Implant surface coating:

Titanium is a suitable material for the reconstruction of the lost tissues in orthopedics and dentistry. This material has high fracture resistance and ductility and adequate strength/weight ratio; however, it does not enhance cell adhesion or proliferation of osteoblasts (63). To solve this problem, Arg-Gly-Asp-Ser (RGDS) Nano-fibers were used in combination with nickel titanium alloys to increase the adhesion of pre-osteoblasts cultured under in vitro conditions; since these cells do not attach to regular nickel titanium. Pre-osteoblasts can survive and proliferate within this compound and differentiate into osteoblasts and form bone (64). On the other hand, implant surface can be coated with many substances. These coatings must have a porous structure in order to provide nutritional supply for the growing cells. Also, they must have high strength because dental implants are subjected to high mechanical loads and stress. There is a theory that HA Nano-crystals can enhance the process of bone formation when used as coating on implant surface; however, studies have demonstrated that this material plays no role in stimulating bone response around implants (65, 66).

Another proposed theory in this respect is use of HA coating in conjunction with silver nanoparticles to have both osteogenesis and antibacterial properties (49). In an in-vitro study on this subject, silver nanoparticles were mixed with an amorphous carbon membrane measuring 40-60 nm in size. The results showed significant reduction in biofilm formation compared to standard titanium (67).

Surface coating of root canal filling materials:

Microleakage of bacterial products is one major drawback of root canal filling materials like gutta percha. Silver nanoparticles have been used as coating for gutta percha in an attempt to decrease the rate of microleakage (68).

1. *Nano-fillers:*

Polymerization shrinkage of composite resins results in gap formation at the tooth-restoration interface, leading to biofilm accumulation and development of secondary caries (69). To solve this problem, low molecular weight particles like silver and iodine used to be incorporated into the composite resins resulting in their sustained release. However, aside from their biological side effects, they had adverse effects on the mechanical properties of composites. On the other hand, difficult control of their release and diffusion was a major drawback of this method (70). Thus, quaternary ammonium nanoparticles were added to composites as an antibacterial agent. Hydrophobic nature and positive charge of this material enhances its antimicrobial activity (71). Addition of zinc nanoparticles also decreases bacterial activity and prolongs the clinical service of composite restorations (69, 72).

Titanium dioxide nanoparticles increase the hydrophilic activity of composites and prevent adhesion of microorganisms and biofilm formation (73).

Moreover, Nano-silica decreases the shrinkage and increases the strength and thermal stability of composites (74).

B. A review on the applications of nanotechnology in the field of prevention:

Toothpaste:

Toothpastes of higher quality and greater efficacy can promote oral hygiene care and prevent the need for future complex dental procedures. Nanotechnology can help in this respect.

Enamel is made of HA crystals. HA has a porous structure; therefore, stains can lodge and deposit onto the tooth surface. These porosities enhance the accumulation and proliferation of bacteria as well (75).

Nano-HA crystals can penetrate into these porosities and act as a whitening agent. This property is due to their increased surface area and stain removal from the dental surfaces as well as filling the pores on the tooth surface and lighteningitscolor (76, 77). At present, titanium oxide nanoparticles are used as whitening agents and zinc citrate or acetate is used for biofilm control (78).

Nano-toothbrush:

Colloidal silver or gold can be used in-between toothbrush bristles to prevent gingivitis, periodontal disease or tooth caries since this technology enhances removal of microbial plaque (79).

C. A review on the applications of nanotechnology in the field of diagnosis (80-83):

Use of nanotechnology for diagnostic purposes enables the clinicians to perform tests with higher sensitivity, accuracy and simplicity without affecting the cells; as the result, costs decrease and the limited samples obtained from patients can be re-used.

Successful treatment of head and neck cancers especially those of the oral cavity highly depends on their prompt diagnosis. The following nanostructures can greatly help in this respect:

1. Cantilevers:

Cantilevers are tools comprising of flexible, small rods with endings that attach to cancer-related molecules, changed DNA sequences, or specific proteins expressed during the course of some cancers. Under these circumstances, the flexible end bends and helps detection and diagnosis of specimen.

2. Nano-pores:

Nano-pores are small pores that enable the passage of one strand of DNA only. Thus, shape and electrical properties of each base on a DNA strand may be assessed and genetic defects with potential risk of carcinogenesis can be detected.

3. Nano-tubes:

Nano-carbon tubes have a diameter half that of a DNA. By using them, change in DNA sequence or more importantly, the exact location of defect can be detected.

Another application of Nano-carbon tubes is in electron microscopes. By attaching them to the electron microscope tip, very small structures can be felt. This enables tracing of specimens as small as a few nanometers in size. This is a tool with high differentiation ability for detection of complex biomolecules and their interactions. In dentistry, these tubes can be used for evaluation of dentin collagen network, dentin pores and their effects on tooth hypersensitivity, surface of dental implants, colonies formed on the tooth surface and comparison of post-operative results (84).

4. Dendrimers:

Dendrimers have a central core with polymer branches located radially around the core. These structures are a type of delivery system. These nanoparticles have the ability to be used for both diagnostic and therapeutic purposes. One property of these branched molecules is their wide surface area and thus, they can simultaneously carry one molecule for diagnosis and another one for elimination of cancer cells in the oral cavity.

5. Nanowire sensors:

Saliva is an important indicator of health status. Silicon Nano-wires can detect proteins, viruses, genes, etc. in saliva samples within minutes. Such detection has also been done successfully in tiny amounts of the sample where conventional sensors are inefficient.

Nano-robots:

Using Nano-technology, scientists have designed bio-Nano-robots playing protective and therapeutic roles in the human body. These intelligent Nano-machines can make copies of themselves and replace or repair the damaged or injured tissues. Nano-robots can be used in dentistry for local anesthesia and tooth restoration, treatment of tooth hypersensitivity, surgery, etc. These robots are injected into the gingiva in a colloidal suspension containing millions of robots. Upon entry, they move around and reach dental pulp via dentinal tubules, gingival sulcus and lamina dura or exert their function in other areas as ordered by the dentist (85).

Conclusion:

Nanotechnology is a new approach in dentistry. By providing novel methods, it increases efficacy, accuracy and speed of treatment while decreasing costs. However, similar to other technologies, nanotechnology can cause problems as well if not appropriately employed. Using unique features of nanotechnology in developed countries has enhanced treatment protocols and paved the way towards science-based economics. The current review article shed light on the potentials and capabilities of nanotechnology in dental field. In near future, this technology may become the core of dental and medical science and accurate programming in this regard can bring about favorable social and economic outcomes.

Conflict of Interest: "None Declared"

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