Review Article

Nanotechnology in Periodontal Management

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Abstract

Nanotechnology is a rapidly growing field, focused on the creation of functional materials, devices, and systems by controlling matter on a nanometer scale, and the utilization of novel phenomena and properties at that length scale. The application of nanotechnology in periodontology holds promise for the maintenance of comprehensive health care by using nanomaterials, including tissue engineering and nanorobots. A literature review was carried out on Google Scholar and PubMed about nanotechnology in periodontics, and the data have been taken from the selected articles and reviewed. This review gives an up-to-date view on nanotechnology, their role in diagnosis and management of periodontal diseases.

Keywords: *Nanomaterials, nanoperiodontics, nanorobots, nanotechnology*

Introduction

Nanotechnology is the science, engineering, and technology, managed at nanoscale, which ranges from 1 to 100 nm. It gives an idea of how any complex is made at the microscopic level and how its molecular arrangements can be exploited to alter the properties at the macroscopic level. Nanotechnology has become a thriving field in periodontics and its benefaction is gradually due to the ever-growing research field.[1]

The History

Fundamental concepts of nanotechnology

An object in a nanoscale can be defined as those whose size lies within the nanometric range, i.e., <100 nm in at least one dimension (between 0 and 100 nm). One nanometer is one-billionth of a meter, 0.000000001 or 10^{-9} m [Figure 1]. [2]

Properties of nanomaterials

Properties of nanomaterials were first put forward by Michael Farady in 1857 during the preparation of gold nanoparticles.[1]

1. The constituents of nanomaterials are <100 nm in a minimum one dimension
2. They have better performance properties than traditional materials and show remarkable surface effects, size effects, and quantum effects
3. They have different chemical, magnetic, optical, and electro-optical properties
4. The significant property of nanomaterials is the self-assembly by which they independently organize themselves into patterns or structures without any others intervention [Figure 2].[3,4]

The Manufacturing Techniques

Top-down technique

- In this approach, small objects are made from the larger ones by modeling and shaping, to make nanostructures in accurate patterns
- Objects turned down to nanoscale can exhibit unique and distinct properties than the larger objects, allowing it to be used in a different manner than the parent one
- As the size is brought down, there is increase in the ratio of surface area to volume and various physical phenomena will become noticeable, which includes statistical as well as quantum mechanical effects[2,5]
- Applications, where top-down approach is used, are nanocomposites, nano-impression materials,

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nanoparticles coating in dental implants, and nano-encapsulation materials.[6]

Bottom-up technique

- This approach arranges smaller objects into a complex structure. This starts by designing and production of custom-made molecules that can self-assemble into higher-order macroscale structures
- This approach could potentially be overwhelming as the size and complexity of the needed structure increases[2,5]
- Applications which uses bottom-up approach are local anesthesia, nanorobotics, tooth regeneration, and tissue biomimetics.[6]

Biomimetic approach

- This approach uses microorganisms including fungus, bacteria, or virus to produce nanoparticles
- It is in its initial stage and additional research is necessary to manifest its effectiveness [Figure 3].[1,3,7]

Classification of Nanomaterials

Generations of nanomaterials

1. First generation (2000–2005) – Passive (steady function nanostructures),
   for example, invasive, noninvasive diagnostics for rapid patient monitoring; nanostructured coatings – liposomes and contrast agents for imaging
2. Second generation (2005–2010) – Active (evolving function nanostructures),
   e.g., targeted cancer therapies; reactive nanostructured materials and sensors – quantum dots, nanoshells, and dendrimers
3. Third generation (2010–2015/20) – Integrated nanosystems,
   for example, artificial organs built from nanoscales; evolutionary biosystems
4. Fourth generation (from 2015/20) – heterogeneous nanosystems,
   e.g., molecules intended to self-assemble themselves; nanoscale genetic therapies.

Nanomedicine and Nanodentistry

Nanomedicine is a branch of medicine that involves the use of nanoscale materials, biotechnology, and genetic engineering for diagnosing, delivering, treating, and preventing diseases and injuries, which helps in preserving and improving human health.[3,4,9]

Nanodentistry is striving for the maintenance of near-perfect oral health and hygiene, with the help of nanoscale materials, nanorobotics, and biotechnology including tissue engineering.[2]

Nanoperiodontics

The applications of nanoscale particles in the field of periodontics have been increasing. Moreover, these can be broadly discussed under the concepts of prevention, diagnosis, and treatment.[1]

Prevention

Antibacterial agents

Agents with nanoparticles of silica, silver, copper, and zirconia, are seen to have superior effects due to their large surface area. Eco-True, is a commercially available nanosilver salts-based disinfectant, used for disinfecting instruments and surgical areas.[1]

Personal protective equipment

Nanoparticles with antibacterial effect which are incorporated with PPE and masks have shown enhanced protection.[1]

Surface coatings

Paints, medical instruments, and other highly contagious surface with nanomaterial coatings can be used to control the spread of diseases.[1]

Oral hygiene maintenance

Mouthwashes integrated with selenium nanoparticles and nanorobots help to control halitosis by the destruction of volatile sulfur compounds-producing bacteria. Dentifrices integrated with nanorobots can be used to destroy pathogens while preserving commensals are under the study.[1]

Nanorobotic dentifrices

Subocclusally staying nanorobotic dentifrices could monitor all supra and subgingival surfaces at least once a day, processing trapped organic matter into nontoxic vapors and perform continuous calculus debridement. These nano dentifrobots (1–10 µ), moving at 1–10 µ/s, would be inexpensive mechanical devices, that would safely inactivate themselves if swallowed and can be programmed with strict occlusal avoidance arrangement.[2,9,10]

Detection

Nanoscale cantilevers

These are structured as flexible beams and can be put together to bind to molecules associated with cancer.[2]

Nanopores

These resemble tiny holes through which DNA passes by one strand at a time for sequencing DNA.[2]

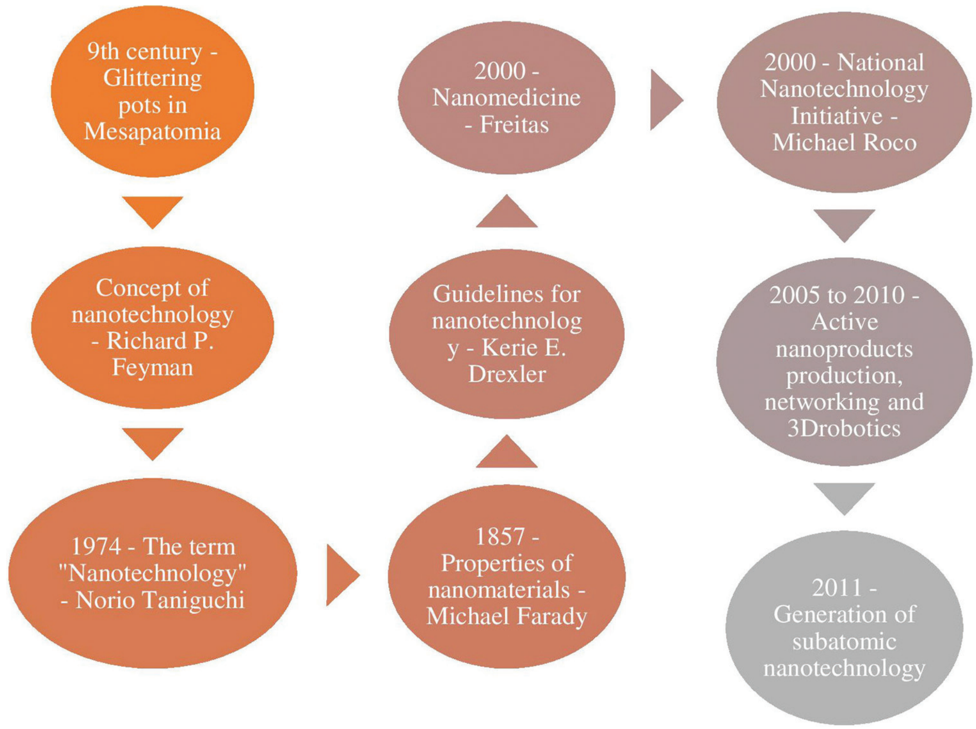

Figure 1: The history of nanotechnology [1]

Nanotubes

These are carbon rods measuring about half the diameter of a molecule of DNA. It helps in the detection of the presence of altered genes and can also pinpoint the exact location of those altered.[2]

Quantum dots

These nanoparticles glow when illuminated with UV light. Hence, these can be made to bind to specific molecules by coating them with materials that makes them attach to it. They can attach to proteins distinctive to cancer cells, literally lighting up tumors.[2]

Nanobelts

Similar to nanotubes in their application, these are cost-effective and technique insensitive comparatively.[1]

Nano electromechanical systems

These biosensors are being developed for exquisitely sensitive and specific detection of an analyte by converting the biochemical signal into electrical.[2,11]

Oral fluid nano sensor test

This technology combines bio-nanotechnology, self-assembled monolayers cyclic enzymatic amplification, and microfluidics for distinguishing salivary biomarkers for oral cancer.[2,12]

Optical nanobiosensor

The nanobiosensor is a unique fiberoptics-based tool which allows the minimally invasive analysis of intracellular components such as cytochrome C, an important protein involved in the production of cellular energy as well as in apoptosis, or programmed cell death.[2,13]

Lab on a chip method

Lab on a chip (LOC) is a device which combines several complex laboratory assays on a single chip. These assays are performed on etched silicon wafers with chemically sensitized beads which have embedded fluid handling and optical detection capabilities. LOC methodologies have been used to assess the levels of interleukin-1β, C-reactive protein, and matrix metalloproteinase-8 in whole saliva.[1,2,14,15]

Nanoplasmic sensors

These are used as rapid detection kits which help in detecting live viruses using their antibodies.[1]

Treatment

Nanovectors

Calcium phosphate nanoparticles serve as nanovectors that is used for delivering target genes to fibroblasts for periodontal regenerative purposes *in vitro*.[2,16]

Local anesthesia

Nanorobots, which are guided by a combination of chemical gradients, temperature differentials and even positional navigation under the control of nanocomputers, are used for the purpose of local anesthesia. They

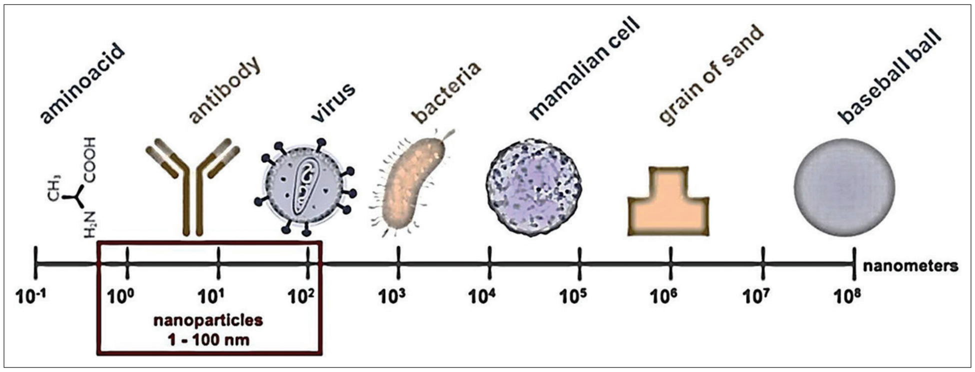

Figure 2: Size of nanoparticles compared with other materials

Based on ORIGIN:	Based on COMPOSITION:	Based on DIMENSIONS:	Based on STRUCTURE:
Natural	Organic	0 - dimensional	Liposomes
Synthetic	Inorganic	1 - dimensional	Dendrimers
		2 - dimensional	Carbon based
		3 - dimensional	Metal based

Figure 3: Classification of nanomaterials [1,2]

establish control over the nerve impulses; they can be commanded to shut down all the sensitivity of desired teeth that requires treatment. Nanorobotic analgesics offer great comfort and reduce patient anxiety and seem to be better than the conventional methods.[2,9]

Nanoencapsulation

Nanocapsules can be used to deliver vaccines, antibiotics, and also could be engineered to target oral tissues, including the cells from the periodontium, in future.[2,10]

Wound healing

Polymer and lipid-based materials show good antimicrobial and anti-inflammatory properties with increased wound-healing capacity. Carbon-based particles also reveal good wound healing and angiogenesis, and scarless healing is shown by the metal-based nanoparticles.[1,17]

Periodontal wound dressings

Nanocrystalline silver particles are embedded into wound dressings (Acticoat TM, UK), which is a broad-spectrum antiseptic and can act against methicillin-resistant *Staphylococcus epidermidis*, methicillin-resistant *Staphylococcus aureus*, and even vancomycin-resistant strains.[2,10,18]

Nanotechnology in dental biofilm

Nanoscale materials such as zinc oxide, titanium dioxide, copper oxide, chitosan, carbon nanotubes, gold particles, and quaternary ammonium compounds exhibit anti-biofilm activity by disrupting bacterial cell membrane through the generation of reactive oxygen species.[1,19]

Drug delivery

Controlled drug release using nanomaterials has been tested using nanospheres, core-shell structures, nanotubes, and nanocomposites. Recently, triclosan-loaded nanoparticles were found to help in the reduction of inflammation.[20,21] Microspheres containing tetracycline is available as Arestin, which is used as local drug delivery (LDD) into periodontal pocket.[4] 8.5% doxycycline gel was experimented and observed to preserve periodontal surface in rats.[2,22]

Subgingival irrigation

Ozone nanobubble water is being experimented in subgingival irrigation and the results have shown that it can be used as an addition to periodontal therapy because of their enhanced antibacterial capacity.[1,23]

Nanomembranes

Nanoguide, which has silk fibroin nanomembrane, used in guided bone regeneration, is shown to exhibit superior bone formation in comparison to biomesh.[1,24]

Nanoneedles and nanotweezers

Nano stainless-steel crystals incorporated into suture needles have been developed. Nanotweezers which will help in the possibility of cell surgery are under development.[10]

Bone growth inducers

If the particle size is smaller, the surface area will be larger in volume. Nanobone uses this principle. They have nanopores situated between nanocrystallites of bone, which are interconnected.[2,25]

Hydroxyapatite nanoparticles used in the treatment of bone defects are:

- HA – Ostium (Osartis GmbH, Germany)
- HA + TCP–VITOSSO (Orthovita. Inc., USA)
- HA – NanOSSTM (Angstrom Medica, USA).

Nanobioactive glass was found to be biocompatible with gingival fibroblasts in a recent *in vitro* study.[2,26] BoneGen-TR, which resorbs slowly and regenerates bone consistently, has been developed.

Bone replacement materials

Nanocarriers and nanocomposites with calcium phosphate, interdigitates with bone supporting its growth.[25] Nanoscale bone rafts have been successfully used in the treatment of intrabony defects,[27] socket preservation,[28] and sinus augmentation procedures.[1,29]

Dental implants

Nanotechnologies are increasingly use for surface modifications of dental implants like creating nanogrooves, nanopillars, etc.,[30,31] and chemical coatings with nanoparticles of diamond,[32,33] hydroxyapatite – NanoTite BIOMET,[33,34] graphene, titanium oxide, and metalloceramic-based nanomatters are also used.[1,30,33]

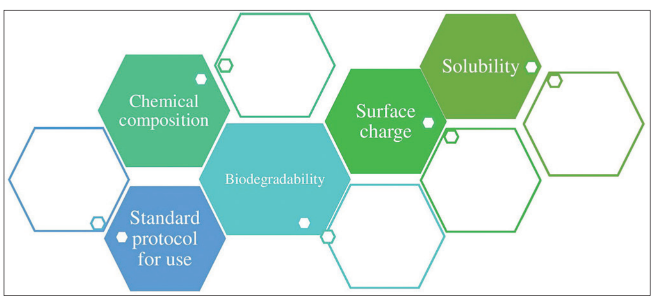

Figure 4: Physicochemical properties of nanomaterials leading to nanotoxicity[1]

Studies have shown that nanophase ZnO and TiO2 may reduce the adhesion of *S. epidermidis* and increase the osteoblastic functions to upgrade the efficacy of orthopedic implants.[2,35] Nano-structured self-assembling implants are shown to have decreased marginal bone loss and better osseointegration than the conventional implants.[1,36]

Management of peri-implantitis

Using nanohydroxyapatite on citric acid conditioned surface can enhance the clot stability. Moreover, it has been demonstrated that PDGF-BB delivered using calcium phosphate nanoparticle has increased the fibroblast proliferation.[1,16]

Host immunomodulation therapy

It has been highlighted in a study that host modulating agents delivered through nanocarriers have shown to decrease the level of proinflammatory and bone resorbing T cells such as Th-1, Th-22, Th-17 and increases the differentiation of Th-2 and Treg cells.[1,37]

Local drug delivery

Nanotechnology-based LDD has been put together as they have enhanced biocompatibility, decreased antimicrobial resistance, targeted release, long duration of action, and less toxicity. Various LDD agents include liposomes,[38] dendrimers,[39] micelles,[40] polymers,[21] nanowires,[41] nanorattles,[42] and niosomes.[43]

Nano antibiotics

These are antibiotics delivered through nanocarriers, which have shown to manifest the broad spectrum of activity and decreased probability of secondary infections. Nanoscale particles and antibiotics have demonstrated positive interactions.[1,44]

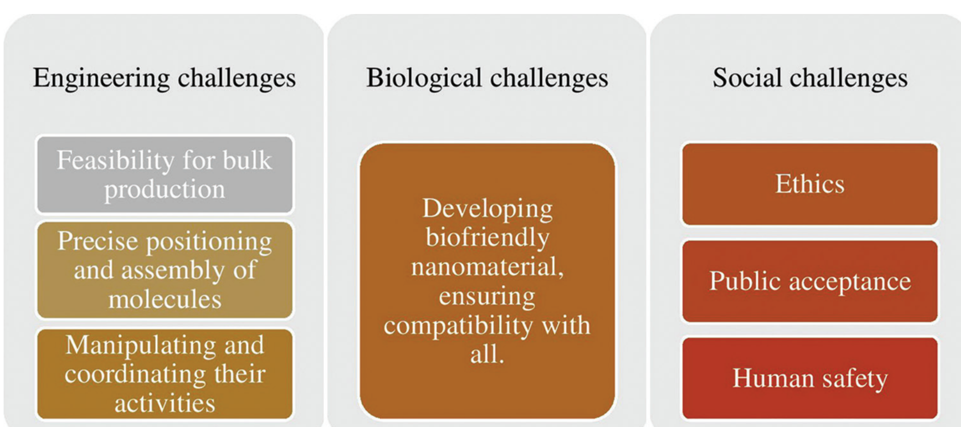

Figure 5: The challenges faced by nanotechnology[6]

Laser therapy

Nanotitanium particles coated surface on laser irradiation have shown to increase collagen production. Based on this, gingival depigmentation and other periodontal procedures can be performed. Diode laser along with nanoparticles can be used to decontaminate the dentin surface.[1,45]

Photodynamic therapy

Recently, PLGA nanoparticles along with methylene blue were found to provide enhanced drug delivery and photodestruction of oral biofilms. Indocyanine green – loaded nanospheres with low level laser therapy might also serve as a useful photodynamic periodontal therapy.[2,46]

Self–assembly

Polyelectrolyte materials such as polyallylamine/polystyrene sulfonate and diazo resin are studied, because these are most commonly used for self-assembly as they enable stable, smooth, homogenous films to form with a number of functional groups.[4,47] Recently, a pH-induced self-assembling nanofibrous scaffold has been developed, which are able to direct mineralization of hydroxyapatite mimicking periodontium.[2]

Periodontal tissue engineering

Polymer-based scaffold for growth factor delivery, cell seeding, and tissue engineering through nanoparticles embedded in the site of tissue damage can be constructed.[48] Although the idea of tissue engineering using nanoscale particles is fascinating, their use clinically remains unreal [Figure 4].[1]

Nanohazards

Potential hazards of nanotechnology are unknown, since it is a very recent discovery and the long-term effects are yet to be discovered. Various factors can modify the properties of nanomaterials such as their physiochemical properties, quantity, and time of exposure.

- Environmental factors such as temperature, pH, different biologic conditions, and presence of other pollutants, can modify the nanomaterials
- Accidental contact of nanoparticles may occur during production or use through lungs or skin, from which translocation to other organs can occur through bloodstream
- Carbon black nanoparticles have been shown to be interfering with cell signaling and can also have unwanted effects on DNA of the cells.

There is a need for monitoring, recording, and developing solutions for the potential hazards to achieve safety for human health and environment.

Nanotoxicity

The people working with nanotechnology would be the first to get involved in nanotoxicity. Studies on people handling nanomaterials have shown depression of antioxidant enzymes, increased expression of cardiovascular markers, and apoptosis of cells.[49,50] Evidence also states that nanoparticles can get assimilated into the body through lungs, skin, and gastrointestinal tract [Figure 5][6,51-53]

- Although increase surface area seems beneficial, it can also cause increase in toxicity by increased duration of action, drug solubility, and their ability to cross blood − brain barrier
- Other drawbacks include difficulty associated with bulk synthesis and cost ineffectiveness.[1]

Challenges Faced

Problems for research in India

The production and application of nanorobots in India might face these problems:

- Poor and slow tactical decisions
- Improper funding
- Lack of involvement of private agencies
- Inadequate trained manpower
- And the problem of retaining them.[6,10,54]

Future Scope

More research in nanotechnology can be expected in its applications in various aspects such as drug delivery, gene therapy, cell surgery, detection and modification of molecular signaling, and patient-specific treatment.

Conclusion

Dr. Richard Smalley, a Nobel Laurette in chemistry, believes that "influence of nanotechnology on wealth, health, and standard of living, will be at least analogous to the combined influences of microelectronics, medical imaging, computer-aided engineering, and man-made polymers in this century."[55] Further developments in nanomaterials and nanotechnology will upgrade dentistry, health care, and human life, still more. Overcoming the challenges should also be considered to get better. A successful future of nanotechnology is only based on sharing ides of research, discussion, testing, and commercial exploration.[2,3]

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Conflicts of interest

There are no conflicts of interest.

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