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CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 11, Issue, 06 (E), pp. 39061-39067, June, 2020

ISSN: 0976-3031

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

GOOD THINGS IN SMALL PACKAGES: NANOPERIODONTICS- A COMPREHENSIVE REVIEW

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DOI: http://dx.doi.org/10.24327/ijrsr.2020.1106.5433

ARTICLE INFO

Article History:

Received 06th March, 2020
Received in revised form 14th April, 2020
Accepted 23rd May, 2020
Published online 28th June, 2020

Key Words:

Nanotechnology, Nanodentistry, diagnostics, periodontics, dentistry, therapeutics.

ABSTRACT

Development and advancements in the field of dentistry has been paving way for newer diagnostic and treatment approaches in the past few decades. Technology has proven to be an integral part of dental science and has provided increased efficacy, accuracy and minimally invasive techniques for effective patient management. One such technological marvel is the field of nanotechnology. Nanotechnology has become an integral and essential part of various fields, but its evolution in dentistry continues to be at the nascent stages. However, nano dentistry is now a rapidly growing science in terms of nano diagnostics, nanotherapeutics and nanorobotics. This paper highlights the various aspects of nanotechnology and its significant contributions in various fields of dentistry and periodontics.

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INTRODUCTION

Nanotechnology is an upcoming multidisciplinary field that covers a wide array of applications in departments such as medicine, engineering, chemistry and physics. The term nano derived from the word “dwarf”, signifies a metric scale ranging from 10-100 nm and is comparable to the size of an atom. Various definitions have been proposed to define nanotechnology in terms of its size, properties and uses. Nanotechnology mainly consists of the process of separation, consolidation, and deformation of materials by one atom or by one molecule (Taniguchi N,1974).According to the definition of the National Nanotechnology Initiative, nanotechnology is the direct manipulation of materials at the nanoscale (Kong LX *et al*,2006). It can also be defined as science & engineering involved in the design, synthesis, characterization & application of materials & devices whose smaller functional organization in at least one dimensions is on nanometer scale (Sahoo SK *et al*,2007)

History of Nanotechnology

The concept of nanotechnology was first described by Dr. Richard P. Feynman in his lecture titled “There’s plenty of room at the Bottom: An invitation to Enter a New Field of Physics” in 1959 (Feynman RP,1960). Norio Taniguchi in 1974 coined the term “nanotechnology” and the term was again independently used by K Eric Drexler in 1986 (Taniguchi N, 1974; Drexler KE,1986). The first book on nanomedicine was published byR. Freitas in 1999 (Freitas RA,2000).Between 2005 to 2010, 3D nanosystems like robotics, 3D networking and active nano products dominated the time period and from 2011 till date, it has been the era of molecular nanotechnology.

Properties of Nanomaterials

The following are the significant properties of nanomaterials

1. Clusters of atoms whose grain size is less than 100 nanometers (nm), fiber is less than 100 nm in diameter, or films less than 100 nm in thickness, or a combination of these.

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2. When compared to traditional materials, nanomaterials have greater stiffness, strength and toughness, more resistance to abrasion and scratches, increased heat resistance and decreased gas permeability.
3. Nanoparticles have a greater surface area per unit mass when compared with larger particles.
4. The important feature of nano structured materials is the property of self-assembly. They can arrange themselves in predefined structural organizations such as patterns or structures, without human intervention.

Classification of Nanomaterials

Nanomaterials have been classified based on various aspects depending upon their dimensional arrangement, composition of material and generation of nanomaterials

Based on dimensional arrangement

The dimensional arrangement of nanomaterials can be classified as a zero-dimensional arrangement such as spheres & clusters, one- dimensional arrangement such as nanofibers, rods & wires, two-dimensional arrangement such as films & plates or a three-dimensional arrangement such as quantum dots / bulk materials.(Fig 1)

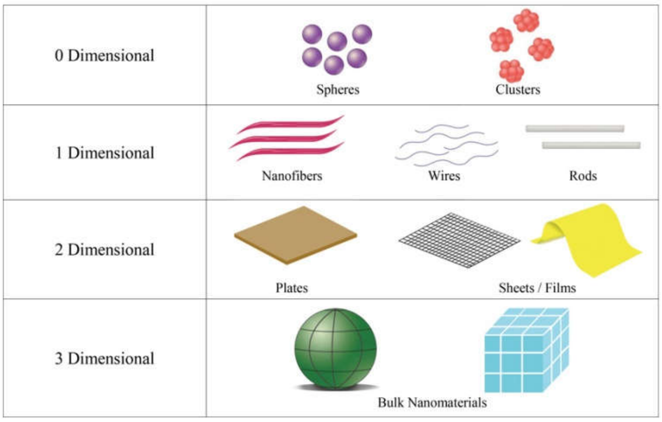

Figure 1 Classification of nanomaterials based on dimensional arrangement

Based on the composition of material

Based on composition, nanomaterials can be classified as organic nanomaterials and inorganic nanomaterials. Organic nanomaterials are natural polymers such as collagen, chitosan, gelatin and alginate or inorganic nanomaterials. Inorganic nanomaterials mainly comprise of synthetic polymers such as polyhydroxy esters,dendrimers, ceramic nano particles, metallic and magnetic nanoparticles and silica based nanoparticles.

Based on generations of nanotechnology

Over a period of time, nanotechnology is classified as various generations. (Table 1)

Table 1 Generations of nanotechnology

First generation (From 2000)	Passive (steady function nanostructures) E.g., Nanostructured coatings invasive; noninvasive diagnostics for rapid patient monitoring
Second generation (From 2005)	Active (evolving function nanostructures) E.g. Reactive nanostructured materials and sensors; targeted cancer therapies
Third generation (From 2010)	Integrated nanosystems E.g. Artificial organs built from nanoscales; evolutionary biosystems
Fourth generation (From 2015/20)	Heterogenous nanosystems E.g. Nanoscale genetic therapies; molecules intended to self-assemble themselves

Manufacturing of Nanoparticles

There are three different approaches proposed for the fabrication of nanoparticles. They are thetop-down approach**,** bottom-up approach and the functional approach.

Top-down approach

In this technique, smaller particles are arranged into larger complex structures, which are directed by specified devices. Top down technique is mainly used for the fabrication of complex structural organisations consisting of millions of precisely positioned nanostructures. The physical characteristics of the particles are greatly enhanced due to the reduction in particle size and increase in ratio of surface area to volume (Ashley S,2001).

Bottom-up approach

In this technique, a complex is assembled by arranging small molecules into different definitive arrangement. Many pharmaceutical drugs and chemicals are manufactured using this fabrication process. Even though the main advantage of this technique is that it is cheaper than the top down technique, it carries an inherent disadvantage of overwhelming size and complexity of the assembled structures (Herzog A,2002).

Functional approach

The functional approach mainly focuses on the specific use of the nanoparticle being produced and does emphasize on the method of production of a nanoparticle (Wong TS *et al*,2009) .

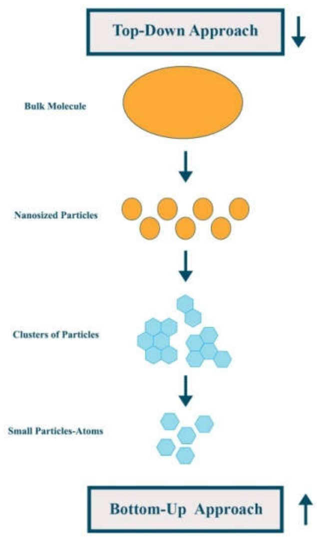

Figure 2 Techniques of nanotechnology

Nanotechnology & Its Applications

Nanotechnology has been implemented for a wide array of applications in the field of medicine and dentistry. Their field of usage can be broadly classified as nanorobotics, nanotherapeutics and nano diagnostics.

Nanorobotics

A nanorobot is defined as "an artificially fabricated objects able to freely diffuse in the human body & interact with specific cell at the molecular level by itself". Nanorobots that are used for drug delivery are called "Pharmacytes".The function of nanorobots can be controlled using onboard computers and communication is transmitted using a broadcast type acoustic signalling. The nanorobot scans the cell surfaces for specific antigenic detection and distinguishes the various types of cells using chemotactic sensors keyed to these specific antigens on the target cells. Once the task is completed, they can exit through the human excretory channels or they can be retrieved using scavenger systems.

Nanodiagnostics

Various forms of nanoparticles, in varied arrangements and structures are used for diagnostic purposes, especially at the molecular and genetic level. The different types of nanoparticle arrangements are as follows.

***Nanoscale Cantilevers**:* Flexible beams resembling a row of diving boards that can be engineered to bind to molecules associated with cancer.

Nanotubes: They are chiefly rods made of carbon, which constitute about half the diameter of a molecule of DNA. The main function of a nanotube is to identify the presence of genetic alterations in the DNA/RNA and assist researches locate the exact location of these changes.

***Nanowires**:* Nanometer scale wires may help monitor local chemical, electrical, or physical property changes in cells or tissues

***Iodinated Nanoparticles**:* Iodinated nanoparticles can be confined to the lymph nodes after bronchoscopic instillation,and can be visualized precisely using computerized tomography (CT).

Nanoshells: A nanoshell is a spherical nanoparticle consisting of a core which is usually dielectric and composed of silica. The core is encapsulated by a thin metallic shell made of gold. By modifying the core-to-shell ratio, these shells can absorb near-infrared light creating a powerful heat that is mortal to cancer cells, without affecting adjacent normal cells.

Dendrimers and Dendritic Copolymers: Dendrimers are man-made molecules about the size of an average protein and have a branching shape which amounts to increased surface area and is used extensively as a filler material in dental restorative composites.

Nanobelt: Nanobelts are millimeters long and have multiple advantages over tubes in terms of price, flexibility, and practicality. For making nanobelts, an oxide containing zinc, tin, cadmium, gallium, orindium is evaporated for 2 hours and is then deposited as a wool-like product. These particles have a rectangular cross section with a width of 30–300nm and a thickness of 10–15 nm. Because the material is already an oxide, it does not undergo any further chemical reaction and has a pure, flawless surface

Nano electromechanical Systems (NEMS): NEMS biosensors that exhibit exquisite sensitivity and specificity for analyte detection, down to single-molecule level, are being developed. They convert biochemical signals to electrical signals, thus monitoring health status, disease progression, and treatment outcome through noninvasive means

Optical Nanobiosensor: The nanobiosensor is a unique fiberoptics-based tool which allows the minimally invasive analysis of intracellular components. Components such as cytochrome C, an important protein involved in the production of cellular energy as well as in apoptosis, can be analyzed.

Nanotherapeutics

Nanotechnology will eliminate the solubility problems of the drug and lead to a reduction in the dosage of drug and reduce the adverse effects. It also provides a prolonged sustained release of the drug, thus enhancing its efficiency. The pharmacokinetic and pharmacodynamic aspects of the drug determine the nature of ideal nano delivery system to be used for its treatment. This method may be utilized in treating Alzheimer's disease, Parkinson's disease, brain disorders, ocular defects, nanoparticles loaded contact lenses, etc

Nanotechnology in Dentistry

Dentistry like many other fields has commenced the utilisation of nanoservices in its various branches in terms of diagnostic and therapeutic approaches. The following are some of the applications of nanotechnology in various specialities of dentistry.

Nanocomposites

Nanocomposites have superior hardness and strength mainly atttributed to the homogenous distribution of non agglomerated discrete nanoparticles in resins or coatings. They also have increased flexible strength, modulus of elasticity, translucency, esthetic appeal, excellent colour density, high polish retention & excellent handling properties(Yang J *et al*,20200. Filler materials commonly used are silica/zirconia nanofillers or clusters and carbomised flourapatite/hydroxyapatite (Ficai A *et al*,2016).

Resin-Modified Glass Ionomer Cement

Resin-modified GIC has been improved by incorporating nanosized fluoroapatite (NFA) or fluorohydroxyapatite (NFHA) particles at 25% concentration. However, there was a significant reduction in shear bond strength and the fluoride release nearly tripled after 70 days (Olegario *et al*,2015).Nanohydroxyapatite (Nano-HA) has also been added to orthodontic banding cement to prevent microleakage under orthodontic bands.

Nanosolutions

Nanosolutions are prepared by preparing a homogenous adhesive material dispersed with fine nanoparticles and are incorporated into bonding agents. These solutions show superior dentin and enamel bond strength, high stress absorption, longer shelf life, durable marginal sealand separate

etching is not required. Nanoparticles such as nano hydroxyapatite and fluorapatite can be used and they seem to offer a sustained fluoride release, which reduces the cariogenicity and confers additional protection to the tooth.
Trade name: 3 M ESPE Adper Single Bond Plus Adhesive Single Bond

Nanoparticles as Enamel Remineralizing Agents

Demineralization and white spot lesions are common problems encountered and nanoparticles are being used for remineralization of decalcified enamel. A paste containing calcium nanophosphate and nano hydroxyapatite has been devisedand have shown to increase the surface area and wettability of HA (hydroxyapatite) nanoparticles which in turn helps in remineralization of the enamel.

Nano impression materials

Nanofillers such as nanosilica and silicon dioxide are integrated into the vinyl polysiloxanes, producing a unique addition siloxane impression material. These materials have improved hydrophilic properties, better flow, fewer voids at margin and enhanced detail precision.

Trade name: Nanotech elite H-D+ and Imprint 2 Penta H Nanotech Elite H-D+

Application of nanotechnology in dental anesthetics

Local anaesthetic application plays a pivotal role in providing a painless dental procedure. The application of anaesthesia by itself can cause anxiety and fear among patients and improper anaesthetic techniques can lead to a traumatic dental experience. However, with the usage of nanotechnology, anaesthetic effect can be achieved easily with more accuracy and predictability. A colloidal suspension containing millions of active, analgesic and microsized are injected into the gingiva of the patients. The ambulating nanorobots travel through the gingival sulcus, lamina propria and dentinal tubules to achieve pulpal anaesthesia. The chemical and temperature gradient mechanisms aid the dentist to control the nanorobot. Once in the pulp, they take control of the nerve-impulse traffic in the tooth and they shut down all sensation, hence producing adequate anaesthesia. On completion of the planned therapy, the operating dentist can withdraw the nanorobots, leading to reversal of sensation.

Tooth Repositioning using nanorobots

Painless orthodontic tooth movement is achieved through orthodontic nanorobots which guide the movement of the tooth by controlling the periodontal structures namely the gingiva, cementum, periodontal ligament and alveolar bone.

Applications of Nanotechnology In Periodontics

Nanotechnology is being used in periodontics since its introduction in field of dentistry. Ranging from periodiagnostic techniques, plaque control measures, to latest advancements in periodontal regeneration using nanomodified materials and dental implant surface modifications, nanotechnology is now an integral part of periodontics. The following are the uses of nanotechnology in periodontics.

Diagnosis

Oral Fluid Nanosensor ASSAY Test (OFNASET)

OFNASET uses the concept of microfluids for the detection of oral cancer biomarkers in saliva. It is made up of a combination of self-assembled monolayers and a cyclic amplification technique for performing the enzyme analysis. It has high sensitivity and specificity and can detect both salivary proteomic and mRNA biomarkers (Gau V and Wong D, 2007).

Lab-on-a-chip method

As the name implies, ‘Lab on a chip’ incorporates various lab functions in a single chip.It is used to assess the levels of IL-1β, CRP, & MMP-8 in whole saliva, and categorizing the severity & extent of periodontitis (Gardeniers JG and Van den Berg A,2004) .

Management of Dentinal hypersensitivity

Dentinal hypersensitivity occurs mainly due to the exposure of dentinal tubules, which can cause fluid movement within the tubular structure. Reconstructive dental nanorobots uses specific native surface markers and selectively attaches itself to the dentinal tubules, thus occluding it. This will provide immediate relief and long-term comfort for the patients in a short span of time. The material of choice is the Nano-hydroxyapatite (n-HAP). It is a material in rising popularity in the field of dentistry, mainly attributed to its structural resemblance to the crystals of the tooth enamel and is a biocompatible and a bioactive material. n- HAP-containing toothpaste was found to be effective in reducing dentin hypersensitivity and can be advocated for the management of hypersensitivity. A study performed by Wang *et al*, stated that nano-hydroxyapatite formulations (with or without home-care product association) were as effective as the other treatment modalities in reducing dentin hypersensitivity (Wang L *et al*,2016).

Nanorobotic Dentifrices

Nanorobotic dentifrices also known as ‘dentifrobots’, are designed with the chief purpose of providing lytic activity against the pathogenic microorganisms, while sparing the commensal flora to flourish in the healthy ecosystem. Dentifrobots also help in relieving oral malodour as they prevent bacterial putrefaction of the substrate, which is the major step in formation of Volatile Sulphur Compounds (VSC) involved in production of malodour.

Applications of Nanorobots in mouthwash

Mouthwash incorporated with nanorobots can easily identify and destroy disease causing microorganisms, and with the added advantage of being in liquid, they can reach area which toothbrushes and floss cannot reach. They also help in providing a continuous barrier for halitosis. Other agents used in mouthwashes are

Silver nanotechnology – It is proven to be effective against biofilms as silver disrupts critical functions in microorganism. The silver particles posses a high affinity towards the negatively charged cell surface on biological molecules and hence inactivates cell wall synthesis, membrane transport functions, nucleic acid synthesis (DNA and RNA) and function and electron transport mechanisms.

Zinc Oxide (ZnO) Nanoparticles: Zinc oxide (ZnO) nanoparticle-coated titanium disks have demonstrated anti-adhesion properties and reduce viable bacteria like

Staphylococcus aureus and *streptococci* without cytotoxic effect on osteoblasts and human mesenchymal cells.

Chitosan: Chitosan is a biopolymer obtained by deacetylation of chitin which is a natural polymer,and has been used extensively in biomedical applications due to its high biocompatibility and antimicrobial properties.

Local drug delivery

The main advantage of nanomaterials in local drug delivery mechanism is the timed release of drugs which may occur from biodegradable nanospheres. (Table 2)

Table 2 Literature references of various nano drug delivery systems

Delivery system	Role(s)	References
Nanoparticles	Triclosan-nanoparticles could help decrease gingival inflammation.	Pinon-Segundo *et al,* 2005
	Minocycline-loaded nanoparticles could significantly decrease symptoms of periodontitis	Yao *et al,* 2014
	Calcium and zinc-loaded nanoparticles can aid in periodontal regeneration.	Osorio *et al,*2016
Nanogels	Nanogels of cholesterol-bearing pullulan modified with amino groups (CHPNH2) was utilized as a carrier to introduce Quantum Dots into PDL cells.	Fukui *et al,* 2007
	Redox injectable gel act locally as specific Reactive Oxygen Species scavenger for the treatment of periodontitis.	Saito *et al,* 2016
	Subgingivally delivered nanostructured doxycycline gel (nDOX) used as an adjunct to SRP.	Madi *et al,* 2017
Nanocomposites	Nanocomposite hydrogels offer flexibility for local placement of drugs at the disease site.	Bako *et al,* 2008
	Nanocomposite composed of 2-methacryloxyethyl phosphorylcholine and dimethylamino hexadecyl methacrylate used for Class V restorations inhibit periodontal pathogens.	Wang *et al,* 2016
Nanofibers	Poly-ε-caprolactone nanofibers containing metronidazole used as a local drug delivery system for metronidazole to treat periodontitis.	Zamani *et al,* 2010
	Nanofibers containing doxycycline showed sustained drug release and can be used for the treatment of periodontal diseases.	Chaturvedi *et al,* 2013

Subgingival irrigation using nanobubble technology

Ozone nano-bubble water (NBW3) using nanobubble generating technology is being used for subgingival irrigation of periodontal pockets. The ozone concentration is achieved at 1.5 mg/litre and it produced using a nanobubble generator. Hayakumo *et al.*, showed a significant reduction in the mean total number of bacteria in subgingival plaque in chronic periodontitis patients and subgingival irrigation using NBW3 which may be a valuable adjunct for periodontal treatment **(**Hayakumo S *et al*,2014**).**

Nanocrystalline Bone Grafts in Bone Regeneration

Bone grafts in nano sized particles mimic the natural bone mineral in its size, composition&morphology is said to have better osteo-conductive property than the conventional bone grafts. Various nano modified materials are also used as bone grafts namely Nano-hydroxyapatite (CA-NHA) composite graft, nanocrystalline hydroxyapatite, titanium reinforced nanohydroxyapatite grafts, nanosized crystals of calcium sulphate, nanoceramic composite materials and chitosan nanofiber membranes. Nanosized ceramics may represent a promising class of bone graft substitute in intrabony defects due to their improved osseointegrative properties. Tran *et al*. evaluated the effect of osteoblast function on nano hydroxyapatite and conventional hydroxyapatite. They concluded that the osteoblast adhesion as well as proliferation were significantly greater on nanocrystalline (50nm grain size) than on conventional (250 nmgrainsize) hydroxyapatite at all time periods tested (Tran N and Webster TJ,2011)

Periodontal tissue engineering

Nonbiologic self assembly systems for tissue engineering modalities are designed effectively using nanotechnology methods. It is possible to create polymer scaffolds for cell seeding, growth factor delivery and tissue engineering via nanodevices implanted to sites of tissue damage.

Tissue Regeneration Scaffolds

Nanotechnology can develop molecular sensitive polymers using the optical properties of nanoparticles as control system, manipulating the stiffness, and strength of scaffolds using hybrid nanostructures and for the preparation of molecular imprints to maximize long-term viability and function of cells on scaffold surfaces. Surface modification of scaffolds are done using various nanoparticles such as Graphene oxide, titanium oxide, hydroxyapatite, ceramic coatings etc. Modification is also done for immune cell activation and infiltration using a gelatin hydrogel scaffold coated with heparin.

Socket preservation and sinus lift procedures

To overcome rapid degradation of conventional allograftsnanocrystalline form of calcium sulfate (nCS) is used for socket preservation and sinus lift procedures. The particle size is 200-900nm and is premixed with medical-grade calcium sulphate hemihydrate powder. It degrades over a period of 3 to 4 months.

Nanotechnology and Dental Implants

Nanotechnology has been used extensively in the field of dental implantology to enhance the implant surface topography and chemical composition of the implant material. This would allow predictable and enhanced tissue-integration around implants.

Nano- Coated Implant

Titanium implant surfaces can be coated using antibiotics or growth factors incorporated in calcium phosphate. eg: Nanotite™. Implant surface could be improved by mimicking the surface topography formed by extracellular matrix components of natural tissues (Bohl KS *et al,*1998). Nano patterned surface also provides better fibrin clot adhesion that forms immediately after implant placement, enabling the migration of osteogenic cells to the material surface(Albrektsson T and Johansson C,2001). Titanium nanotubes can increase the density of osteoblast cells on the implant that may lead to better implant stability. Titanium oxide nanotubes on Titanium implants improved the production of alkaine phosphatase by osteoblasts, which is a marker of osteoblast activity.Aluminium oxide nanoparticles help in osseointegration and in the healing process by new bone formation with haversian canals, osteoblast, and osteocyte around implant. Silver nanoparticles coating helps to prevent the growth of bacteria and thus helps in osseointegration. Flores *et al*. studied the antibacterial potential of silver nanoparticles against Pseudomonas aeruginosa (Flores *et al*,2018). Zhao *et al*. showed that titanium nanotubes immersed in silver nitrate solution followed by ultraviolet light radiation can kill bacteria in the suspension (Zhao L *et al*,2011).Multiwalled carbon nanotubes are also used as implant coating materials and are found to be effective enhanced implant osseointegration as they mimic the triple helical structure of natural collagen(Song XR *et al,* 2016*)*

Nanotechnology in the Management of Peri-implantitis

Peri-implantitis affected surface conditioning with citric acid improves nanoparticle- sized hydroxyapatite binding and clot adhesion to titanium implant surfaces (Alfarsi MA *et al*,2014). Platelet-derived growth factor isotype BB (PDGF-BB) gene delivery in fibroblasts using nanosized calcium phosphate particles (n CaPP) as vectors, has found to significantly enhance fibroblast proliferation (Elangovan S *et al,* 2006)

Nanotechnology in Laser Plasma Application

Nano sized titanium particles can be applied as emulsion on human skin followed by a laser irradiation session which leads to the disintegration of the particles. It also leads to formation of shock waves, producing microabrasion of hard tissues and stimulates collagen production. Hence, it can be used for periodontal therapy, gingival melanin depigmentation, and soft tissue incision even without local anaesthesia.

Dentition Replacement Therapy

Nanotechnology may utilize genetic engineering, tissue engineering concepts for a whole tooth repair. Entire enamel regeneration using nano hydroxyapatite crystals were done by Chen *et al*, which lead to increasing interest in this field (Chen HF *et al*,2006). Tissue regeneration is done initially followed by growing whole new teeth in vitro & then installation. Eventually, production and installation of an autologous tooth leading to complete dentition replacement therapy in single visit office is still in hope.

Nanotechnology in Surface Disinfectants

Nanotechnology is used to produce a surface disinfectant called Eco-True, which is reported to have a 100% destructive efficacy on Human Immunodeficiency Virus(HIV). This disinfectant is mainly used for sterilization of instruments and incisions for the purpose of preventing post-operative infections.

Role of Nano-Proresolving Medicines (Nprm) In Management of Periodontal Diseases

Non soluble communication between cells have emerged as an efficient means of long-range communication beyond soluble cytokines and autacoids. Microparticles, which are membrane-shed vesicles are used to construct nano- proresolving medicines (NPRM) which are incorporated with proresolving lipid mediators (LMs). These mediators can target specific tissues without getting diluted or inactivated. NPRM-bLXA4, is a lipoxin derivative which vividly reduced inflammatory cell infiltration into chronic periodontal disease sites treated surgically and increased new bone formation and enhanced regeneration of the periodontal tissues.

CONCLUSION

The quote "There's plenty of room at the Bottom" proposed by Dr.Richard Feynman still stands true in this current 21st century. Research in nanotechnology has gained immense importance and has taken a huge leap in every potential field of application. But there are many more dimensions of this field to be further explored and implemented. Nanotechnology like other emerging molecular arenas, will bring enormous changes in medicine and dentistry. With time, newer developments, economical & technical resources and human needs will determine which of the applications should be realized first and laid to function for the betterment of human health.

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How to cite this article:

Dr. Shruthi Chandrasekaran and Dr Jaideep Mahendra.2020, Good Things in Small Packages: Nanoperiodontics- A Comprehensive Review. *Int J Recent Sci Res.* 11(06), pp. 39061-39067. DOI: http://dx.doi.org/10.24327/ijrsr.2020.1106.5433

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