ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (*IJMACR*)

Available Online at: www.ijmacr.com

Volume – 5, Issue – 1, January –February - 2022, Page No. : 148 – 157

Small is the new big: A review on Nanomedicine in dentistry

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How to citation this article: Dr. Saba Khan, Dr. Nishita Gautam, Dr. B.N Padmavathi, Dr. Tulika Sharma, Dr. Pooja Dhakad, Dr. Sreeparna Das, "Small is the new big: A review on Nanomedicine in dentistry", IJMACR- January – February - 2022, Vol – 5, Issue - 1, P. No. 148 – 157.

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Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract:

Nanomedicine is a branch that includes Nano-diagnosis, nano-therapy and regenerative medicine. Nanomedicine can help treat smallest to largest areas in dentistry, it could be dental caries or even oral cancer. Nanotechnology is helping the dental areas in different fields. Drug-loaded Nano pharmaceuticals based on nanoparticles have been used widely in dentistry in recent years to cure tooth issues and promote near-perfect oral hygiene. The field of clinical dentistry is about to be transformed by nanotechnology. Rapidly developing inquiries will assure that future developments that appear impossible today will be possible.

Keywords: Nanomedicine, Quantum Dots, Nanotechnology, Nanoparticles, Preventive Dentistry, Nanostructures.

Introduction

Nano' is derived from the Greek word, meaning 'dwarf' [1,2]. The science and engineering involved in the design, synthesis, characterisation, and application of materials and devices whose smallest functional organisation in at least one dimension is on the Nanoscales scale can be characterised as nanotechnology (one-billionth of a meter). Nanomaterial or a Nanodevice can be considered as a particle with a maximum size of $1 \times 10{-}7$ m [1]. Nanotechnology can be applied to various medical Clinical diagnostics, immune system supplementation, cryogenic storage of biological tissues, protein detection, DNA structure probing, tissue engineering, tumour killing via heating (hyperthermia), biological molecule separation and purification of biological molecules and cells, magnetic resonance imaging (MRI) contrast enhancement, etc. [1]. The goal of this review is to assess the function of nanomedicine in fields such as monitoring, tissue regeneration, disease evolution control, protection and improvement of human biological systems, diagnosis, treatment and prevention, pain relief, health prevention, drug transport to cells, and so on [3].

History

The American Physicist Richard Feynman from his lecture titled "there is plenty room at the bottom" delivered at Caltech in 1959 was publicized as the one who provided the inspiration for the field of nanotechnology, but it was the Japanese scientist Norio Taniguchi of the Tokyo University of Science who first employed the term "nano-technology" in 1974. However, the term "nanotechnology" as against "nano-technology" was coined by Prof. Kevie E. Drexler in his 1986 book titled Engines of Creation: The Coming Era of Nanotechnology. [3,4]

Approaches to Nanotechnology [2,5]:

1. Bottom-up approach: This approach arranges smaller components into more complex assemblies.
2. Top- down approach: This approach creates smaller devices by using larger ones to direct their assembly.
3. Functional approach: This approach develops components of the desired functionality without much importance to their assembly or structure.
4. Speculative approach: This approach often takes a big picture view of nanotechnology, with more emphasis on its societal implications than the details of how such inventions could actually be created.

Nanomedicine has been defined by the European Science Foundation's forward Look Nanomedicine as follows: "Nanomedicine uses nano-sized tools for the diagnosis, prevention and treatment of disease and to gain increased understanding of the complex underlying patho-physiology of disease. The ultimate goal is to improve quality of life." [6].

Nanomedicine includes

- Nano diagnosis
- Nano diagnostics is the term used for the application of nanobiotechnology in molecular diagnosis.

Nano therapy

- Nano therapy addresses active nano-systems containing recognition elements to act or transport and release drugs exclusively in cells or affected areas in order to achieve a more effective treatment while minimizing side effects.

Regenerative medicine

- Regenerative medicine aims to repair or replace damaged tissues or organs using nanotechnology tools [3].

Application of nanotechnology in dentistry

Nano dentistry refers to the use of nanotechnology for diagnosing, treating and preventing oral and dental diseases. Thus to preserve and improve oral/dental health using nanostructured materials it is done. The field of nanotechnology has a great potential. If it is developed in an absolute manner and is done efficiently

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it will be of great use to the human population in terms of better treatment resulting in better health [7]. Application of nanotechnology in dentistry include:

1. Diagnostic dentistry
2. Preventive dentistry
3. Regenerative dentistry
4. Therapeutic dentistry

Diagnostic dentistry

Nanomaterials in biomedical imaging applications: Imaging plays a important role in cancer diagnosis, staging, and assessment of treatment efficacy. A wide range of nanomaterials used in biomedical imaging which includes NIR-absorbing carbon (such as graphene and carbon nanotubes), metal (Au, Ag, Pt, Pd), quantum dots (such as CdTe, CdSe) based nanostructures, magnetic (iron oxides) and up conversion composite NPs (e.g., NaGdF4: Yb: Er) [8]. Some of them are:

Quantum dots (QDs): QDs are fluorescent semiconductor nanocrystals with unique optical and electrical properties and about 3–8 nm in size. QDs possesses a narrow linewidth in the emission spectra, wide array of optical properties when compare to other organic fluorophores, continuous emission maxima as a result of quantum size effects, a comparatively long fluorescence lifespan and insignificant photobleaching over minutes to hours. These properties make QDs good for medical imaging applications after conjugation with specific bioactive moieties. Gao et al., have also developed a new class of polymer-encapsulated and bioconjugated QD probe for in-vivo cancer imaging and targeting. These NP probes have triblock polymer structure, targets tumour sites using both passive and active mechanisms and allow sensitive and multicolour imaging of cancer cells in living animals when coupled with wavelength resolved imaging. A hybrid QD was developed by combination of Gd3þ and QDs as dual modal agent for in vivo imaging and magnetic resonance imaging (MRI). Dubertret et al., showed that encapsulated QDs in phospholipid block-copolymer micelles acted excellently as a fluorescent probe by providing significant reduction in photobleaching and low non-specific adsorption [8].

Gold nanoparticles (AuNPs): AuNPs are valuable X-ray contrast agents when compared with existing agent because they present novel pharmacokinetic and physical benefits and also, AuNPs have a distinctive optical property due to their localized surface plasmon resonance (SPR), facile conjugation to biomolecules and biocompatibility. Au nanorods have also been conjugated with UM-A9 antibodies in squamous cell carcinomas of the head and neck (SCHNN). The increased assembly of AuNPs on targeted SCHNN cells generated efficient X-ray attenuation when compared with normal cells or untargeted cells [9].

Magnetic nanoparticles: Magnetic nanoparticles (MPs) are gaining popularity as tools in biomedical field based on their biocompatibility and functional surfaces. Recently emerging magnetic particle imaging (MPI) techniques have employed a non-ionizing imaging technique for specific non-invasive diagnostic imaging, with better temporal and spatial resolution. This takes advantage of the dynamic quantifiable superparamagnetic nature of magnetic nanoparticles during cellular binding to achieve tissue specificity and lower toxicity levels. Xie et al., synthesized ultrasmall c(RGDyK)-coated Fe3O4 NPs by thermal decomposition of Fe (CO)5 with 4-MC followed by air oxidation. The study documented a novel method of synthesizing and functionalizing Fe3O4 NPs as contrast tool for probable in vivo tumour-specific targeting

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abilities using MRI. Montet et al., (2006) designed a magneto/fluorescent nanoparticle conjugate that enhanced visualization of normal and tumour cells by MRI [8].

Superparamagnetic iron oxide nanoparticles (SPIONs) These are multi-layered polymeric shells with an iron oxide core. These shells can carry contrast agents with different aqueous solubilities. Specific surface anti-nucleosome antibodies help identify targeted tumor sites, where the compromised clearance mechanisms of the tissues help in their retention and improved MRI imaging [10].

Nanopunch

This is a paramagnetic biopsy tool consisting of layered copper, nickel, silicon, and chromium, in the shape of a claw. With temperature change, the differing coefficients of expansion cause the claw to open and close to collect the specimen. Once tissue is harvested from the site, the punch could be collected from the urine sample by a magnetic trap [10].

Nanobiosensors: Replacing micro sized particles with nanosized ones 220 transforms the biosensor into a nano biosensor, with the advantage of rapidly identifying targeted biological tissues at an ultra-low molecular level. Its high sensitivity is particularly useful in cases of cancer diagnosis for example, as nano biosensors in comparison to conventional biosensors are able to detect cancer cell molecules at very early stages and in very low concentrations (Touhami, 2014; Foster, 2005). Nano biosensors are also mechanically compliant, as they are easily displaced and deformed in response to very low forces, therefore, sensitive enough to detect breaking of chemical bonds (Arlett et al., 2011). This is attributed to its nano size effects, as the high surface area to core ratio increases the level of sensitivity, electrical properties, and response time of the biosensor [11].

The Oral Fluid Nano Sensor Test (OFNASET, The Wong Lab, University of California, Los Angeles) is a highly sensitive, specific, portable, and automated nanoelectromechanical system, which enables point-of-care detection of salivary proteomic biomarkers and nucleic acids specific for oral cancer, including 4 mRNA biomarkers (SAT, ODZ, IL-8, and IL-1β) and 2 proteomic biomarkers (thioredoxin and IL-8) [12].

Atomic Fluorescence Microscopy and oral biofilms: AFM, has the capability to directly interact with and image live cells without any disruption of their morphology and properties, offers a breakthrough in characterization of bacteria as well as measurement of their adhesion to different substrates. With nanomechanical biosensors, AFM cantilever, a real-time scanning of a live bacterial cell with high sensitivity was made possible. Furthermore, information on a cell's elasticity and the membrane-molecules' properties become available. The way by which bacteria adhere to tooth surfaces or dental implants has been revealed using AFM [13].

Biochips and salivary biomarkers: Biochips are very small devices (less than a few millimeters) on which a collection of miniaturized test sites (microarrays) are arranged. The main advantage of the microchips over more traditional approaches is that many tests (diagnostics) can be performed simultaneously in order to achieve higher throughput and speed [14].

Microfluidics and microelectromechanical systems (MEMS) for saliva diagnostics with the aim to identify technologically viable systems and support their advancement toward commercialization. This unique venture focused on the development of microfluidic and

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MEMS technologies for measuring DNA, gene transcripts (mRNA), proteins, electrolytes, and small molecules in saliva, as well as overall profile correlates of a particular disease state, such as cardiovascular disease [13]. These devices exhibit exquisite sensitivity and specificity for analyte detection, down to single-molecule level.

In the field of periodontal diseases, Christodoulides et al have developed an electronic microchip-assay to detect C-reactive protein (CRP), which is a biomarker for inflammation associated with periodontal disease at the picogram per millilitre level. CRP is known to be a systemic marker produced as a response to inflammatory stimuli that can be used to differentiate in serum, between a healthy state and the presence of periodontitis and saliva [13].

Digital dental imaging

Advances in digital dental imaging techniques are also expected with nanotechnology. The radiation dose obtained using digital radiography with nanophosphor scintillators is diminished and high-quality images obtained [4].

Preventive dentistry: Nanotechnology offers new approaches for preventive therapies in oral diseases, particularly dental caries and periodontal diseases [5].

Dental caries: Dental caries is one of the most prevalent destructive diseases affecting tooth structures. It is caused by bacteria, e.g., Streptococcus mutans, Streptococcus sobrinus, and Lactobacillus spp [13].

Antibacterial Nanotherapy: Several nanoparticles (e.g., zinc oxide, silver, and polyethylenimine) have been incorporated into dental composites or dental adhesives to inhibit the bacterial growth through several mechanisms. These mechanisms include disruption of the bacterial cell membrane, inhibition of the active transport as well as the metabolism of sugars, generation of reactive oxygen species, displacement of magnesium ions required for the enzymatic activity of oral biofilms, disturbance of the electron transportation across the bacterial membrane, and prevention of DNA replication. These nanoparticles were effective in reducing the S. mutans and Lactobacillus acidophilus biofilms in an in vitro model [5].

Biomimetic remineralization – reversing an incipient caries: Owing to their colloidal particle size and potential for delivery of calcium ions, calcium carbonate (CC) nanoparticles can have good retention on oral surfaces. They act as a delivery vehicle for slow continuous release of high concentrations of calcium ions into the surrounding oral fluids (saliva and dental plaque). CC nanoparticles also have the potential to increase the surrounding fluid pH.

Nanosized calcium fluoride (CaF2), as a labile reservoir for fluoride (F), has been shown to be highly soluble and reactive with dicalcium phosphate dihydrate compared to its macro counterpart [5].

Biomimetic remineralization – recurrent decay: Different forms of nano calcium phosphates were used as Ca2+ - and PO4 3− -releasing fillers, eg, dicalcium phosphate anhydrous, tetra calcium phosphate, monocalcium phosphate monohydrate, and carbonate hydroxyapatite. The release of Ca and PO4 is dependent on degradability and volume fraction of Cap form. The chemical binding ability of nano calcium phosphate fillers, eg, carbonate hydroxyapatite, these nanoparticles bind to eroded enamel and dentin, forming a protective coating, and then reverse the action of acid or bacterial attack [4].

Caries vaccine: These vaccines include pcDNA3-Pac, pCIA-P, pGJGLU/ VAX, and pGLUA-P. Most of the

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anticaries vaccines work by preventing bacterial accumulation either by blocking the surface protein antigen PAc or inactivation of glucosyltransferases enzyme. Both surface protein antigen PAc and glucosyltransferases are the virulent factors responsible for the adhesion of S. mutans to tooth surface [13].

Periodontal diseases: Nanotechnology has been used to prevent bone loss in an experimental periodontal disease model by local application of nanostructured doxycycline gel.

Mouthwashes containing nanoparticles loaded with triclosan and silver nanoparticles have demonstrated plaque control potential. Mouthwashes containing biomimetic carbonate-hydroxyapatite nanocrystals have been shown to preserve the implant titanium oxide layer by protecting it against surface oxidative processes. These nanocrystals also reduce implant surface roughness by depositing hydroxyapatite into the streaks present on the titanium surface. This decrease in surface roughness provides better prevention against plaque accumulation and peri implant pathologies [10].

Nanorobots (dentifrobots) mouthwash or toothpaste left on the occlusal surfaces of teeth with their continuous and fast movement (1–10 µm/ second) across the supra and subgingival surfaces continuously removes the organic residues and prevents the calculus accumulation. These nanorobots can be safely deactivated when they are swallowed [13].

Regenerative dentistry

Bone grafting: Most popular ones to date are nano Hydroxy apatite particles (n-HAP) bone grafts, which are available in crystalline, chitosan-associated and titanium-reinforced forms. These n-HAP composite bone graft scaffolds are highly biocompatible, have superior mechanical properties, and induce better cellular response. The use of an NHAP paste significantly improved the clinical outcome when compared to open flap debridement. Commonly used nanoparticles of HA used for the treatment of bone defects are NanOSSTM HA (Angstrom Medica, USA), Vitosso (Orthovita, Inc, USA) HA + tri-calcium- phosphate (tri CaP), and Ostim HA (Osartis GmbH, Germany) [2].

Nanosized crystals of conventional $CaSO_4$ bone grafts have now developed, with particulate sizes ranging from 200-900 nm, while the conventional $CaSO_4$ bone graft particle size ranges from 30-40 µm. These nanoparticles are further condensed into pellets of 425-1000 µm. This nanotization of particles results in a graft material which is more resistant to degradation and lasts longer (12-14 weeks) than conventional $CaSO_4$ (4-6 weeks) [15].

An antibacterial nanoceramic composite material has recently been developed by impregnating nano calcium phosphate, walled carbon nanotubes, and zinc oxide (ZnO) nanoparticles into an alginate polymer matrix. Carbon nanotubes provide a strong, flexible, and inert scaffold on which cells could proliferate and deposit new bone, while the ZnO nanoparticles provide the antibacterial properties. This material enhances HAP formation in bone defects. The use of nanoparticulate bone grafts show promise in post extraction ridge preservation, intrabony defects regeneration, root perforations, sinus-lift procedures, implant dehiscence, and fenestration corrections [16].

Guided tissue regeneration: The concept of guided tissue regeneration (GTR) is being researched to replace earlier functional graded membranes with novel 3-layered membranes. A novel system has come up with a 3-layered GTR membrane composed of an innermost layer made of 8% nano carbonated hydroxyapatite/collagen/polylactic-coglycolic acid

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(nCHAC/PLGA) porous membrane, a middle layer of 4% nCHAC/ PLGA, and an outer layer of PLGA nonporous membrane. These 3 layers combine to form a highly flexible, biocompatible, osteoconductive, and biodegradable composite membrane. When osteoblastic cells were cultured on this membrane, they showed a more positive response compared to a pure PLGA membrane [10].

Tissue engineering: A gene-activated matrix (GAM) provides a platform to combine these 2 techniques. GAM provides a structural template for therapeutic gene expression and fills the defects for cell adhesion and proliferation, as well as the synthesis of extracellular matrix. A recent development in this aspect is a GAM composed of chitosan/collagen scaffold acting as a 3-dimensional carrier, incorporated with chitosan/plasmid nanoparticles that encode platelet-derived growth factor. This matrix demonstrated a sustained and steady release of condensed plasmid DNA over 6 weeks, which resulted in a high in vitro proliferation of cultured periodontal ligament fibroblasts, thus demonstrating potential for periodontal tissue engineering [10].

Nerve regeneration: Nanoparticles can also be applied to reconstruct damaged nerves, with self-aggregating rod-like nanofibers called amphiphiles. Aggregated amphiphiles may reach up to several micrometers in length and can be utilized in vivo to bridge tissue defects in the spinal cord. This application holds huge potential in the oral surgical arena, such as the possible reconstruction of a damaged inferior alveolar nerve after extensive oral surgical procedures [10].

Pulp regeneration

Nanotechnology has potential in the region of dental pulp regeneration. The development of tissues to replace diseased or damaged dental pulp can provide a revolutionary alternative to pulp removal. The α-melanocyte-stimulating hormone (α-MSH) is known to possess anti-inflammatory properties. Recently, it has been suggested that nanofilms containing α-MSH could help revitalize damaged teeth. Further research is needed to evaluate these proposed therapeutic and regenerative approaches [10].

TMJ regeneration: The regeneration of the temporomandibular joint, delivering molecules to target two different tissues (cartilage and bone) is required; thus, the use of dual factors such as BMP2 (bone morphogenetic protein) and TGF-β (transforming growth factor) may be an appropriate delivery option [17].

Therapeutic dentistry

The use of nanotechnology in treating dental diseases has found a great interest. Its use has been extended from treating dentin hypersensitivity, root canal disinfection, and oral cancer to the most recent use in tissue engineering and drug delivery applications [13].

Dentinal hypersensitivity: Dental nanorobots could selectively and precisely occlude selected tubules in minutes using native logical materials, offering patients a quick and permanent cure [10].

Nano anaesthesia: Application of nanotechnology can be used to induce anaesthesia. The gingiva of the patients is instilled with a colloidal suspension containing millions of active, analgesic, micron-sized dental robots that respond to input supplied by the dentist. After contacting the surface of crown or mucosa, the ambulating nanorobots reach the pulp via the gingiva sulcus, lamina propria and dentinal tubules, guided by chemical gradient, temperature differentials controlled by the dentist. Once in the pulp, they shut down all sensation by establishing control over nerve-impulse traffic in any tooth that requires treatment. After

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completion of treatment, they restore sensation thereby providing patient with anxiety-free and needless comfort. Anaesthesia is fast acting, and reversible, with no side effects or complications associated with its use [18].

Nanomaterials for periodontal drug delivery: Nanomaterials such as nanotubes, hollow tubes and spheres, core-shell structure and nanocomposites have been widely experimented for local drug delivery system. These nanomaterials are made up of biodegradable polymer that allows the drug delivery to the site-specific region of the tooth at regular intervals as these materials disintegrate. E.g., Arestin, in which tetracycline is incorporated into microspheres for drug delivery by local means to a periodontal pocket [5].

Nanotechnology coupled laser plasma application, Nanoparticles of titanium dioxide (TiO_2) when applied on human skin surface by means of gel like emulsion, exhibits extraordinary properties and effects-like shock wave, microabrasion, and stimulation of collagen production by degradation when irradiated with laser pulse. This remarkable properties of TiO_2-based nanoparticles coupled with laser irradiation can be utilized in varieties of procedures such as depigmentation of gingiva, soft-tissue incision without anesthesia and periodontal disease treatment [2].

Nanotechnology in endodontics

Nanoparticles as antimicrobial agents: Nano particulates display higher antibacterial activity because of their polycationic or polyanionic nature, which extends their applications. Treatment of bacterial biofilms and wound healing gets the benefit from nanoparticles primarily because of their antimicrobial properties and biocompatibility. These disinfect the canal by removing the residual microbes in the canal and enhance the antibacterial action of the intra canal medicaments.

The nanoparticles evaluated on endodontics include Chitosan, zinc oxide and silver. The efficacy of chitosan and zinc oxide nanoparticles against Enterococcus fecalis has been attributed to their ability to disrupt the cell wall. In addition, these nanoparticles are also able to disintegrate the biofilms within the root canal system. Silver nanoparticles are being evaluated for use as root canal disinfecting agents. It has been shown that 0.02% silver nanoparticle gel is able to kill and disrupt Enterococcus faecalis biofilm [19].

Bioactive glass (SiO_2 -Na_2O-CaO-P_2O_5): The use of SiO_2 -Na_2O-CaO-P_2O_5 has been suggested for root canal disinfection. The antimicrobial effect of bioactive glass is due its ability to maintain an alkaline environment over a period of time. The efficacy of 45S5 bioactive suspension – nanometric/micrometric hybrid as an antimicrobial agent showed that a ten-fold increase in silica release and 3 units of pH elevation was found with the nanometric bioactive glass [19].

Oral cancer: In cancer chemotherapy, nano delivery vehicles (eg, naringenin loaded nanoparticles in 7,1-dimethylbenz(a)anthracene) were used for improving the stability as well as targeted and controlled delivery of chemotherapeutic drugs [8].

In photothermal therapy, this relies on the use of a plasmonic probe and NIR (near-infrared spectrum) light, recently introduced as a minimally invasive technique for the treatment of deep tissue malignancy such as OSCC. In this therapy, GNPs (gold nano particles), with their enhanced NIR absorbance and ability to convert the absorbed light into heat energy, were used as a plasmonic nanoprobe. The nano dimension of this probe ensures its easy absorption by the localized tissue,

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reduces its toxicity, and allows its removal from the body after the treatment. Further enhancement of their biocompatibility, coating the gold nanostructures with thermo and pH-responsive polymers, for example poly (N-isopropylacrylamide-co-acrylic acid), has been attempted. RGD (arginine-glycine-aspartate) and NLS (nuclear localization sequence) peptides-conjugated nuclear targeting gold nanostructures can be easily captured by cancerous cells (e.g., OSCC), subsequently disturb their functions (DNA damage, induces cytokinesis arrest in cancer cells) inducing cell apoptosis and necrosis. Selective inhibition of cancer cell growth through mitochondria-mediated autophagy has been obtained by iron-core–gold shell nanoparticles [13].

A nano delivery trans buccal system was developed to rapidly and efficiently deliver the opioid analgesia at a consistent and controlled diffusion into the target tissue. Accordingly, it minimizes the risk of overdosing in patients and also protects the patients from needle injection. It also avoids the enzymatic and spontaneous degradation of the drug associated with oral administration [13].

Nanotoxicology: Nanotechnology has its role in every field and it can make our life easy and faster. But it has few limitations relating to our safety concerns. Nanomaterials have large surface area volume ratio due to which atoms present at the surface also increase. Thus, nanomaterials are more reactive and have increased rate of absorption through skin, lungs, and digestive tract and after a prolonged use, these will get accumulated in different organs and will be transported to the other organs via blood. In the lungs, they may cause inflammation of the alveoli and subsequent cell damage. These small particles can also react with DNA, RNA, and other intracellular components and can cause mutations [20].

Conclusion

Nanotechnology is set to revolutionize clinical dental practice. The field of dentistry is receiving unprecedented support from the biotechnological sector, in the form of novel innovations that include improvised diagnostic aids and treatment devices. In the near future, oral health care services will become less stressful for the dental surgeons, more acceptable to patients and the outcome will significantly become more favorable. Rapidly progressing investigations will ensure that developments that seem unbelievable today are possible in the future. For now, medical and dental practitioners still require guidance on the use of nano-incorporated products with respect to patient safety and occupational health.

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