Journal of Pharmaceutical Research International

33(54B): 134-143, 2021; Article no.JPRI.78328
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Nanotechnology in Periodontics Revisited: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i54B33774
Editor(s):
(1) Dr. Rafik Karaman, Al-Quds University, Palestine.
Reviewers:
(1) Zenati Latifa, Benyoucef Benkhedda University of Algiers 1, Algeria.
(2) Hazim Mohamed Rizk, Mustaqbal University, Egypt.
Complete Peer review History, details of the editor(s), Reviewers and additional Reviewers are available here: https://www.sdiarticle5.com/review-history/78328

Review Article

Received 01 October 2021
Accepted 04 December 2021
Published 11 December 2021

ABSTRACT

Nanotechnology is the study of materials, devices, and systems that display features that are distinct from those found in larger systems. It is no surprise that medical and dental researchers have taken notice of this rapid advancement in technology, which has piqued their curiosity about how it may be used to cure and prevent disease. It is a relatively new science that deals with the manipulation of matter at the molecular level, including the manipulation of individual molecules and their relationships. High-level control of position and chemical characteristics are the primary goals of this method. Nanotechnology has become one of the most promising and significant areas of scientific research as a result, thanks to an increased interest in interpreting matter's property at this dimension. Nanotechnology has been used in dentistry to produce new materials and procedures for diagnosing, preventing, treating, and regenerating periodontal disease, which is the subject of this article. Cargoes and materials such polymeric nanoparticles, non-porous nanogels, nanotube scaffold matrices, and nanofibers have shown promise effectiveness, and their functions in disease treatment are of significant interest. The purpose of this review paper is to offer thorough recent updates on the numerous nanotechnology-based methods to periodontal disease treatment.

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Keywords: Nanotechnology; periodontics; nanoscience; nanosensor.

1. INTRODUCTION

Science and technology have been rapidly advancing for years now. It has an essential role in contemporary lives and has affected human civilization in several ways. Modern society and civilizations greatly depend on development in science and technologies and they have become an integral part of the survival of human life. The development of technology walks hand in hand with scientific breakthroughs and vice versa. Such advancements have made it possible to have deeper insights into the smallest functional and structural units- the atoms and the cells through nanotechnology. Some of these nano-technological advances are merely conceptual at this stage, but can revolutionize the field of dentistry. Who would have ever thought decades ago that a technology like mobile-phone would get the world at your fingertips! History and background: From the Greek word "Nanos," which means "dwarf," "nano" is derived. James Clerk Maxwell's visionary hypothesis concerning sub-microscopic creatures was the first to introduce the concept of nanotechnology in 1867. He named these entities “Maxwell’s Demons” which, according to him, would possess the capacity to handle individual molecules and atoms [1].

The late Nobel laureate Richard P. Feynman coined the phrase "There is plenty of room at the bottom" in a speech to the American Physical Society in 1959.He proposed the manufacture of machine tools that would be used to manufacture yet smaller tools and the cascade going on until it reached molecular level. According to Feynman, the use of such nano-machines, nano-robots, and nano-devices would lead to atomically precise instrumentation and manufacturing tools. He had the foresight that we could not avoid such a development. This was path-breaking for the emergence of nanotechnology [2]. To put it another way, nanotechnology refers to the practice of manipulating materials with a single atom or molecule. It was initially described in 1974 by Professor Norio Taniguchi of Tokyo University of Technology in Japan [3].

When Drexler wrote Engines of Creation: The Coming Era of Nanotechnology back in 1986 he used the word nanotechnology for the first time. When Feynman offered the notion of a nanoscale "assembler" that could make copies of itself and other objects of any complexity, there had a resemblance to this "assembler” [4]. Nanotechnology is a branch of science that deals with the manipulation of materials at the nanometer level. There is a lot more to nanotechnology than the study of the smallest of things. Research and development of materials, technologies, and systems that display physical, chemical, and biological features that are distinct from those seen on a large scale are all part of it. Nanotechnology is a synthesis of physics, materials science, engineering, chemistry, biochemistry, medicine, and optics [5]. “Nanomedicine” deals with the application of nanotechnology in the field of medicine [6]. It focuses on the detection, treatment, and prevention of illness and traumatic damage; pain relief; and the preservation and improvement of human health via the use of nanoscale-structured materials, genetic engineering, biotechnology, and sophisticated molecular machine systems and nanotechnology [7,8]. One of the most interesting components of nanomedicine and nano-dentistry are the “nano-robots” [2]. Nano-robots are controllable machines that can penetrate the cell membrane, and thus interact at cellular levels [1]. Nano-dentistry is an implication of nanotechnology for the field of dentistry, an offshoot of nanomedicine. The application of nano-dentistry will make the maintenance of near-perfect oral hygiene possible [2]. The term "nanomaterials" refers to substances whose components are smaller than 100 nanometers (nm) in at least one dimension. In addition, they include nanoparticles, such as atoms clustered together, as well as nanofibers, nanofilms, and nanocomposites that combine these [5].

"Top-down" and "bottom-up" manufacturing methods are used to build nanoscale structures [9]. It is a bottom-up technique that deals with the organisation of smaller components into more complicated assemblies, while the top-down approach builds smaller devices by employing bigger ones to control their assembly. Nanotechnology in a top-down approach includes salivary diagnostics powered by nanotechnologies, nanocomposites nanotech-nology for glass ionomer cement, nano-ceramic technology, nano-bonds, nano-solutions, coating agents, nanotechnology for impression materials, nano-composite denture teeth, implants laser-plasma application for periodontia, nano-needles, nano bone replacement materials, nano bone fibres, nanoparticles as antimicrobial agents, and nanotechnology-based root-e. The bottom-up approach to nanotechnology includes anaesthesia (local anaesthesia), hypersensitivity cure, tooth repair, nano-robotic dentifrice (dentifrice), orthodontic nanorobots, dental durability, cosmetics, halitosis, nanotech floss, photosensitizers and carriers, diagnosis of oral cancer, and treatment of oral cancer [4]. Nanotechnology in periodontology has its application in diagnostics, dentin tubule blocking agents, dentifrices, floss, anesthesia, bone replacement materials, drug delivery agents, nano-needles, lasers, regenerative therapies, and implants. Applications of nanotechnology in periodontology: The human body supports various niches for harboring bacteria- both commensals and pathogenic. The oral cavity provides hard, non-shedding surfaces which aid in bacterial colonization, forming a biofilm. Plaque, which is a primary etiologic factor for gingival and periodontal diseases, is also a biofilm that harbors a plethora of bacteria. GCF and saliva form a planktonic stage with free-floating bacteria. The plaque matrix acts as a barrier and leads to the retention and concentration of various substances produced by bacteria to foster metabolic interactions among the bacteria. Such bacterial products act as chemokines for the inflammatory cells and disease sets in. Inflammation and/or attachment loss are the two features that help in indicating the disease's presence [10]. These disorders can be diagnosed and treated with the use of nanotechnology. The periodontal diagnostic aids using nanotechnology involve the detection of certain biomarkers. The management of diseases using nanotechnology encompasses non-surgical and surgical therapies and even oral implantology. Application in diagnosis: As stated earlier, the bacteria in the plaque initiate the inflammatory diseases of the periodontium, causing either tissue degradation because of the virulence factors of pathogens or inducing a host response. Activation of host response leads to the release of biological mediators, which leads to tissue destruction. Salivary indicators originating from bacteria and hosts, including as enzymes, proteins, and other inflammatory mediators, have great promise for the detection of periodontal disorders. IL-1, TNF, MMP-8, CRP, and IgA have all showed a substantial rise in saliva in individuals with active periodontal disease. Chairside salivary biomarker detectors can be used for illness screening and detection at the point of care [11].

One of the most commonly used chairside diagnostic kits, the Oral Fluid NanoSensor Test (OFNASET) provides an evaluation for four mRNA biomarkers and two protein biomarkers in saliva, which can be used to diagnose a wide range of conditions, such as diabetes, cardiovascular disease, cancer, and other conditions [12].

2. ORAL CANCER DETECTION WITH THE OFNASET

2.1 Ofnaset Kit

- The mechanics: Probes in the electrochemical sensor are designed to capture or bind with antibodies that are associated to antigens. As a result, a capture probe secures a target, while a detection probe sends out an alert to the sensor through a reporter molecule.
- Antibody pairs will be used instead of oligonucleotide probes for salivary genetic marker detection, such as IL-8.
- When a salivary proteomic signature is detected, it means that Anti-fluorescein conjugated horseradish peroxidase (HRP) reporter enzyme can be bound to the target–probe complex by fluorescein-modified detection probe or antibody. The electrochemical sensor measures the current generated by an HRP-mediated redox cycle when a redox substrate is added and a fixed voltage is applied between the working and reference sensor electrodes. The magnitude of the electro-reduction current reflects the concentration of target–probe complexes on the sensor surface [13].

3. LAB-ON-CHIP TECHNOLOGY

An further use for nanotechnology is the use of Lab-on-chip (LOC) technology for the detection of IL-1, MMP-8, and C-reactive protein (CRP) biomarkers in the identification of periodontal disease (CRP). Assists in determining the severity of periodontal disease. Periodontal disease may be diagnosed at the point of treatment using this new method [14]. As a result of its reduced sample volume and higher sensitivity, the LOC is well-suited to a wide range of saliva-based diagnostic and therapeutic applications.

Bead Preparation, Sieving, Activation, and Antibody Conjugation: Using agarose beads, the

LOC test relies on the consistency of the beads' diameters. At this size, microspheres are subjected to the sifting process, which ensures that the population is uniform. Sodium borohydride and glycidol are added to a 10-mL solution of sodium hydroxide and gently stirred overnight to form reactive aldehyde groups in the matrix. Washing with water is followed by exposure to a solution of sodium periodate (0.16%). Antibody-specific and control antibodies are linked to beads by the use of a chemical reaction known as reduction.

CRP, tumour necrosis factor, IL-6, myeloperoxidase MPO, MMP-8, and IL-1 antibodies are used in the LOC Assays.

Beads are placed in an array on the LOC and then encased in a flow cell for an assay run. Optic and charged-coupled devices secure flow cell in position (CCD). As a precaution, wash buffer (PBS), detecting antibody, blocking agent (3 percent bovine serum albumin in PBS), as well as sample are loaded into the system to minimise the entrance of air bubbles into the analysis region. To prevent non-specific binding, 3 percent BSA/PBS is utilised to inhibit the bead components. The protein standards or the unknown sample are given to the array for analysis by a technician. A particular antibody coupled to AlexaFluor-488 detects the analyte on the beads following a wash with PBS. Washing with PBS removes any remaining antibodies from the specimen. The final image is taken using a CCD camera and saved for further analysis. An individual micro-reactor is created by the use of each bead. The signal intensity is transformed to a quantitative measurement using the standard curve that has been prepared in advance [15].

A scanning electron micrograph of the assay platform of the LOC system: It is made up of a silicon microchip with a micro-etched array of addressable wells that host beads sensitized to analyses of interest

(B) A bead-loaded microchip is sandwiched between two PMMA inserts and encased in a housing. The LOC system's analytical flow cell is created in this way [15].

3.1 Bead-based Immunoassays Sandwiched between two Plates on the LOC System

(A) An antigen on the bead is sequestered by an analyte-specific capturing antibody.

(B) Delivery of sample and detecting agents to the beads from the top
(C) Image of an array of beads [15].

Application in management of periodontal diseases: The management of periodontal diseases encompasses three major goals: short, intermediate, and long-term objectives are all included.

To eradicate any infections and inflammatory processes and other oral disorders that may affect the patient's overall health are the immediate objectives. From a periodontal point of view, achieving this goal is important because it involves corrections of conditions that cause and/or perpetuate gingival and periodontal diseases.

Intermediate goals: To reconstruct a healthy dentition that not only fulfills functional and esthetic requirements but also has longevity. Immediate goals depend on age, health, desires, and also the financial aspects of the patients. They also depend on the complexity of the case and the therapy involved. They may achieve these goals quickly or may need a long span, ranging from months to years.

Long-term goals: It mainly involves preventive and supportive periodontal therapy to maintain the health of the patient. Once the active disease is under control with the elimination of infectious and inflammatory processes and it achieves health, the lifelong maintenance of the same is of prime importance. The treatment plan itself acts as a blueprint. The overall treatment plan is the coordinated achievement of the immediate, intermediate, and long-term goals and often requires an interdisciplinary approach. This will help in attaining a well-functioning dentition in a periodontally sound and healthy environment [10].

3.2 Periodontal Treatment Plan [16]

The preferred treatment plan: [16] Nanotechnology in the management of gingival and periodontal conditions finds its place in the maintenance of oral hygiene, drug delivery systems, control of dentinal hypersensitivity as a part of non-surgical therapy. Whereas surgical therapy it finds its applications in the administration of anesthesia, bone regenerative materials, laser therapy, needles, and even implantology. Nanotechnology in the maintenance of oral hygiene: Elimination of the etiologic agent, plaque, is the mainstay of periodontal treatment. Various home care or professionally used chemical, mechanical or chemo-mechanical techniques are used to achieve this. Though theoretical at this stage, the nano-robots impregnated in dentifrices or mouthwashes may revolutionize the maintenance of oral hygiene. Known as the dentifrobots, they can move with a speed of 1^{-10}/seconds [17]. Mouthwashes and toothpaste can reach the subgingival zones and convert organic materials into harmless and odourless gases. These can also recognise and eliminate the harmful bacteria present in the plaque if they are designed correctly. These purely mechanical devices will inactivate themselves even if swallowed [18].

Since the metabolism of bacteria may alter, it will also help in the control of halitosis [4]. Dentifrobots People use floss as an interdental cleaning aid. The application of nanotechnology to floss has yielded floss with excellent tensile strength, which is ultra-thin, ultra-gliding, and non-shredding. The nanostructure also enables the addition of flavors and medications [4]. Nanotechnology in controlling dentinal hypersensitivity: Exposure of dentin following removal of plaque and calculus and their products from the tooth surface end up with dentinal hypersensitivity. Stimulation of the odontoblastic processes within the dentinal tubules leads to stimulation of nerve endings in the pulp or pulpal region of dentin, leading to hypersensitivity. Another mechanism is the displacement of dentinal fluid within the tubules commonly termed as the hydrodynamic mechanism.

3.3 Following Methods Proposed by Trowbridge and Silver, 1990, are used to Control Hypersensitivity

1. Burnishing the exposed surface to form a smear layer
2. Formation of insoluble precipitates by application of topical agents.
3. Use of plastic resins for impregnation of tubules.
4. Use of plastic resins for sealing of tubules.

The most likely mechanism of action of the desensitizing agents is by reduction of the diameter of dentinal tubules to reduce the displacement of fluid in them. Desensitizing agents are either home applied or office applied [16].

We can use nanotechnology in various ways for desensitization. Dentifrice containing carbonate/ hydroxyapatite nano-crystals has shown a significant reduction in hypersensitivity compared to sodium fluoride/potassium nitrate containing dentifrice. We consider hydroxyapatite crystals as the main synthetic bio-filler materials. However, the limited application is owing to the high cost of these dentifrices and mouth rinses. The bottom-up approach for the synthesis of micro-nano-sized hydroxyapatite crystals is quite significant. Such hydroxyapatite crystals will have an improved response to the biological hydroxyapatite crystals and help in desensitization [19]. An in vitro study conducted using gold nanoparticles for two independent techniques of occluding dentinal tubules has shown promising results for clinical use [20]. Dentinal tubules can be blocked by nano-robots and other approaches employing local, native materials. As a result, it has the potential to offer both immediate and long-term relief [18]. Nanotechnology in drug-delivery systems: For biofilm-dependent diseases in the oral cavity, nanotechnology-based drugs might act against the biofilm-forming organisms without altering the flora at specific sites such as gingival crevices or periodontal pockets. Thus, they offer possibilities of specific and efficient treatment by the drugs based on nanotechnology [21]. Common dental diseases, development of biofilm and applicability of drug-delivery; [21] Nano drug delivery systems: Nanoparticles: Nanospheres & Nanocapsules Image showing (a) nano-capsule (b) nanosphere [22] For the delivery of recombinant proteins, therapeutic drugs, genetic material, and vaccines, nanoparticles are of significant value. Nanoparticles coupled with nano-spheres and nano-capsules can alter the kinetics, distribution, and release of an entrapped drug. These can either be polymer-based or non-polymer-based. PLGA (poly-lactic-glycolic acid), PGA (polyglycolic acid), PLA (polylactic acid), PEG (polyethylene glycol) are a few commonly used polymers to synthesize these nanoparticles. As compared to microparticles and emulsion-based delivery systems, the nano-particulate systems have the following advantages: [21-22].

1. Accessibility to sites inaccessible by other release systems
2. Improved dispersibility in body fluids
3. Controlled-release
4. Improved stability
5. Easy preparation
6. Diversity in preparation

7. Batch-to-batch reproducibility
8. Easy large scale manufacturing Administration of nano-particles in the pocket [22].

Minocycline-loaded PEG-PLA nanoparticles as local drug delivery systems have shown to produce better results than minocycline hydrochloride (99%) solution and Periocline® in beagle dogs [23]. The phosphotungstic acid solution coloured the minocycline-loaded nanoparticles adversely, as shown in this transmission electron microscopy picture [23].

Scaling and root planing coupled with silver nanoparticles, with or without tetracycline films as local drug delivery systems have shown reduced pocket depths, better gain in attachment levels, and a decrease in bacterial count than mere scaling and root planning [24].

In addition to scale and root planing, nanoparticles of Nano-bio-fusion gel, which was employed as an adjunct, improved attachment and reduced pocket depth [25]. Benzocaine nanoparticles are also said to be used for effective pain control. Parenteral administration is possible with a single dose for a prolonged effect [26]. Nanoparticles loaded with Auranofin, an anti-rheumatic drug, have shown anti-inflammatory effects with reduced bone loss and can significantly improve the outcome of therapy when used as an adjunct [27]. Minocycline, which is available as Arestin, is also a nanotechnology-based local drug delivery system [4].

Nanofibers: These are fibers less than 100 nm in diameter and can be flexible or rigid. The use of Electrospinning, force-spinning or interfacial polymerization can be of significance in their synthesis. Their inherent flexibility widens their range of application. Complex formation and difficulty in insertion make these fibers secondary to the nanoparticles [21].

(a) Post-treatment of nanofibers.
(b) Immobilization or incorporation of drug-loaded nanocarriers to nanofibers.
(c) Co-electrospinning of drug/polymer blends.
(d) Coaxial (or emulsion) electrospinning" [28].

Dendrimers: These are 3D, hyperbranched, globular nanopolymers. In a dendrimer, the inner core is surrounded by a dendritic structure (the branches), while the outside surface is covered in functional surface groups. The peripheral functional groups can be modified to enhance the versatility. The terminal functional groups provide a platform for drug moiety. These can be used for hydrophobic drugs with limited water solubility. These delivery systems with their modifications can encapsulate active drugs. e.g. Polyamidoamine dendrimers encapsulate triclosan for controlled release in the oral cavity [21].

Dendrimers Liposomes: These are spherical vesicles with a lamellar phase lipidic double layer. Following are the methods to achieve drug loading in liposomes:

1. "Formation of liposomes in an aqueous solution with a saturation of soluble drug.
2. Using organic solvents and solvent exchange mechanisms
3. Lipophilic drug usage"
4. Methods involving pH gradient Drugs are trapped in the central core by the hydrophobic region.

Ligands can be used to functionalize the outer surface [26] Liposomes reach the target site via the bloodstream and attach by active or passive mechanisms.

Active mechanism: Binding to the receptor site of the cell through ligand leads to internalization and subsequent drug delivery.

Passive mechanism: Internalization or local high concentration drug release [26].

Mechanism of reaching the target site: Active and Passive [26].

Role of nano-robots in the administration of local anesthesia: Nanorobots when suspended in colloidal solution will reach the dental pulp through the gingival sulcus, dentinal tubules, and the lamina propria when instilled on the gingival surface and can be externally controlled by the operator.

Nanorobots are assumed to reach the pulp in 100 seconds, considering the path length of 100 mm and travel speed of 100/sec.

When instilled in the pulp, the nanorobots will block the impulse traffic and produce analgesia in the region controlled by the operator. Once the requirement is over, the nanorobots can be commanded to stop their function, release the traffic of impulses, and exit via the same path of ingression.

After this, aspiration can be followed. Thus, the nanorobots will be able to provide needleless anesthesia and better patient comfort with reduced anxiety. Greater selectivity, controllability, fast action, and complete reversal of anesthesia are added benefits of nanorobots [29]. Nanorobots in local anesthesia [29] Application of nanotechnology in periodontal regeneration: Periodontal diseases may sometimes lead to intra-bony and furcation defects. Such defects should be managed by periodontal regeneration. The concepts of regeneration have evolved over the years. The current status of regenerative therapy has changed and improved due to a better understanding of the tissues that constitute the periodontium. Bone regenerative grafts, guided tissue regeneration (GTR), understanding of biologic mediators, and tissue engineering have made regenerative therapy more predictable and available as a choice [10].

Certain bone replacement materials that are modified by nanotechnology can attain effective regeneration. Natural bone; in itself, is a nanostructure made of collagen as the major constituent of the organic matrix and hydroxyapatite crystals as the major constituent of the inorganic matrix. Ideally, these replacement materials should mimic the natural structures. Nanotechnology aims at emulation of bone for various applications [30]. Nanobone fibers: These are available as polyphosphazene nanofibers [4].

The biodegradable polyphosphazene fibers are of growing interest because of their great biocompatibility and neutral and non-toxic degradation byproducts. Using electrospinning, nanofiber matrices containing polyphosphazene and nanohydroxyapatite were created as scaffolds for bone tissue engineering. These nano hydroxyapatite-loaded fibers are called composite nanofibers. The matrices formed from these fibers have shown better cell adhesion, proliferation, and alkaline phosphatase activity compared to matrices formed by simple polymeric nanofiber [30]. Scanning electron microscopy images of composite nanofibers at 10000x magnification.

(a) loaded with 50% nano-hydroxyapatite
(b) 70% nano hydroxyapatite [30]

Bone grafts: Periodontal bone grafts used as replacement materials have hydroxyapatite nanocrystals with loose microstructures and nano-pores between the crystals. The nano-pores can be surface modified for better adsorption of proteins. Such pores with nano-porosity have the greater surface area and thus allow for ideal bone regeneration [4,21].

Bone replacement materials with modified nanoparticle hydroxyapatite are available as [31] Ostim H.A.'s (Osartis GmbH, Germany) The name Vitosso is derived from the Latin word "vitus (Orthovita, Inc) TCP and HA (tricalcium phosphate) The NanOSSTM HA is a high-performance HA (Angstrom Medica) These materials, Nanogen and BoneGEN TR, have a moderate rate of resorption and consistent bone growth that makes them ideal for regenerating bone in vast lesions [32].

Application of laser-plasma: Nanoscale TiO2 particles (20-50 nm diameter) when present on the skin, form gel-like emulsion. These particles, when irradiated by laser, get optically broken down, stimulating collagen production and micro-abrasion of hard tissues for treatments, including melanin depigmentation and soft tissue incision without anesthesia [4]. Application in needles and tweezers: They have developed Nano-needles using nanotechnology. These can reach the intercellular nano-scale structures of a single living cell. They market these under the trade name Sandvik Bioline, RK 91™ needles. The nano-tweezers are still under development that can be of use in the future to carry out cell surgeries [4].

Application in implantology: Osseointegration is desirable for the long-term success of an implant. Nanotechnology is used for surface bio-modification of the implant to improve osseointegration. Nanoscale deposits of hydroxyapatite and calcium phosphate activate the osteoblasts. Such activation of osteoblasts alters the implant surface and creates a suitable medium for osseointegration [4]. Examples of nanostructured implant coatings are:

i. Nanostructured diamond: These provide improved hardness and toughness over micro-structured diamonds. In addition, they have low friction and good adhesion to titanium alloys.
ii. Nanostructured processing applied to hydroxyapatite crystals: These show increased surface reactivity, osteoblast

adhesion, proliferation, and matrix mineralization.

iii. Metallo-ceramic coatings with nanostructured metallic bonds at the interface and strong ceramic bonds on the surface give a wide range of options for a variety of applications [29].

The peri-implant mucosa or the bone might show some pathological changes leading to peri-implant mucositis and/or peri-implantitis. Some in vitro studies have shown that bone substitutes having nano-hydroxyapatite crystals used on implants obtained from sites affected by peri-implantitis show better capability to interact with specific proteins. Thus, this may show potential advantages in promoting bone cell responses.

This is said to be likely because of the great structural similarity of the nano-hydroxyapatite crystals to the natural hydroxyapatite of the bone [33].

4. CONCLUSION

Nanotechnology is looked up to have great potential in changing the dental care systems radically. As with any technology, nanotechnology comes with its own pros and cons. The current research lies in the development of nanoscale materials for their use in dentistry. Although many studies using nanomaterials have been published, research and development of specific nanomaterials that can be used to manage periodontal patients have a long way to go. Also, the cost factor in the development and use of these materials should not be neglected. If it is possible to overcome the challenges pertaining to nanotechnology, nanotechnology will be the future of dentistry because science has no bounds and the sky's the limit.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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