



Review Article



Nanotechnology for better drug targeting

Current And Emerging Trends Of Nanotechnology In Interdisciplinary Dentistry- A Review

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Abstract: Nanotechnology comprising of nanoparticles, nanodiagnostics and nanorobotics have been intensively studied since they were found to fit perfectly in applicative fields, including medicine, chemistry, informatics and communication, industry, and energy generating. Nanosized particles can be used in medicine as nanomedicine for diagnosis, drug targeting and controlled delivery, or tissue engineering. Moreover, depending on their biological behavior, some bioactive or bioresorbable nanomaterials can be successfully used for both tissue reconstruction and as state-of-the-art implant biomaterial doping or coatings for improved mechanical properties, chemical stability, esthetic aspects, better host cell adhesion and antimicrobial effects. Application of nanotechnology in dentistry is promising for the maintenance of comprehensive dental care by employing nanomaterials including tissue engineering and ultimately nanorobots. This review summarizes the basics of nanotechnology, applications in dentistry with emphasizes on current and future perspective of nanotechnology in interdisciplinary dentistry and challenges faced by it in the current scenario.

Keywords: Nanotechnology, Interdisciplinary dentistry, Nanoparticles, Nanodiagnostics, Current and emerging, Nanorobots

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I. INTRODUCTION

The concept of nanotechnology was first elaborated in 1959 by Richard Feynman, a Nobel Prize winning physicist, in a lecture titled, "There's plenty of room at the bottom".¹ Derivation of the word "nano," is from the Greek word, "nanos "resembling" dwarf". One nanometer (nm) is a unit of length that equals 1 billionth of a meter.² Nanotechnology in dentistry (nanodentistry) is defined as the science and technology of diagnosing, treating and preventing oral diseases, relieving pain, preserving and improving dental health using nanostructured material.³ Nanomaterials include components sized from 1 to 100nm in at least one

dimension.⁴ They exhibit larger surface area –volume ratios and superior chemical, physical, biological, mechanical properties compared to their normal counterparts.⁵⁻⁸ Nanodentistry includes three branches⁹,

- Nanodiagnostics
- Nanorobotics
- Nanoparticles

Nanoparticles could be broadly classified based on its applications as antimicrobial nanoparticle, regenerative nanoparticle and therapeutic nanoparticle¹⁰ (Table I).

Table I. Types of nanoparticles in dentistry		
Antimicrobial nanoparticles	Regenerative nanoparticles	Therapeutic nanoparticles
<input type="checkbox"/> Silver	<input type="checkbox"/> Carbon Nanotubes & fibers.	<input type="checkbox"/> Hydrogels
<input type="checkbox"/> Gold	<input type="checkbox"/> Calcium phosphate	<input type="checkbox"/> Gold
<input type="checkbox"/> Metal oxides	<input type="checkbox"/> Calcium fluoride	<input type="checkbox"/> Dendrimers
<input type="checkbox"/> Chitosan	<input type="checkbox"/> Bioactive glass	<input type="checkbox"/> Solid lipids
<input type="checkbox"/> Quaternary Ammonium polyethylenimine	<input type="checkbox"/> Bioceramic	<input type="checkbox"/> Quantum dots
<input type="checkbox"/> Chlorhexidine		<input type="checkbox"/> Poly GA-PEG -cisplatin

1.1 Approaches to Nanodentistry

Nanoparticles can be classified as zero-dimensional, one-dimensional, two-dimensional, and three-dimensional.¹¹ Feynman had elaborated about manipulating individual atoms to produce new small structures with different properties from parent atoms.¹² Application of this basics in the synthesis of nanoparticles would produce nanomaterials with small size, larger surface area, high surface energy, large proportion of surface atoms; owing to these, it has some unique properties such as small size effect, quantum tunneling effect, surface effect and quantum size effect.¹³ The different approaches to fabricate a nanoparticle in nanotechnology are top down approach, bottom up approach, functional approach, biomimetic approach and speculative approach.¹⁴

1.1.1 Top-down approach

In the top-down approach, synthesizing particles are done by grinding / milling, machining or lithography; these are mostly the extensions of methods employed previously in small-scale assembly at the micron scale achieving miniaturization. Increase in ratio of surface area to volume occurs as the size of system decreases and a number of physical phenomena becomes noticeably pronounced including statistical as well as quantum mechanical effects.¹⁴ Examples of top-down approach are nanoencapsulation, nanoneedles, nano coatings on implants, nanocomposites, nano based bone replacement cement and nano impression materials.¹⁵

1.1.2 Bottom-up (self assembly) approach

This approach arranges smaller components at the atomic or molecular levels with string covalent bonds into more complex assemblies. They recognize the molecules of their own breed and chemically assemble themselves by combination of two or more components to a new one.¹⁴ The examples pertaining to this approach are nanodiagnostics, local anesthesia, tooth regeneration, hypersensitivity cure, nano robots and oral tissue biomimetics.¹⁵

1.1.3 Functional approach

The functional approach does not give importance to the method of production of a nanoparticle; rather, it emphasizes on production of nanoparticle with a specific use. Thus the nanoparticles are developed based on the components of a desired functionality without regard to how they have been assembled.¹⁴

1.1.4 Biomimetic approaches

This approach uses biomolecules for applications in nanotechnology. Biomimetic nanotechnology relates to the recognition of the most basic aspects of the living systems and the transfer of their properties to human applications. It facilitates high potential in combination with inherent safety to be used for medical applications. Biomimetic approach is an example of the Biomimetic approach.¹⁴

1.1.5 Speculative approach

This approach particularly has a larger picture view of nanotechnology. It remarkably emphasizes more on social implications than the details of how such inventions could actually be created.¹⁴ The reason for the ongoing research in the arena of nano, is due to the unique properties that nanoparticles offer. Nanoparticles interacts on a molecular level, thereby increasing the overall efficacy and affinity in comparison with the micro or macro sized particles.¹⁶ The high surface area to core ratio, is a peculiar physical characteristic present in nanoparticles, which means that there are more atoms on the surface of the nanoparticle than deep within its core. This is specifically useful since the unbound surfaces on the surface atoms have the greater potential for creating new and strong bonds making nanoparticles more reactive in comparison to other biological particles which have more core than surface atoms.¹⁷ In comparison to the same material in bulk (macro or micro), nano particles can be easily arranged in different configurations due to their high surface area to core ratio and hence could be utilised in various applications. The thermal vibrations expressed by surface atoms is greater

which contributes to the lower melting temperature in nanomaterials compared to the same material in bulk¹⁸ which is particularly useful in dentistry while constructing porcelain fused to metal (PFM) crowns, cast post and cores, or denture frameworks. Nanotechnology is emerging in the interdisciplinary field of dentistry that is constantly undergoing rapid development. It has wide applications in dentistry like renaturalization of dentition, therapy for dentin hypersensitivity, single visit complete orthodontic realignment, intensifying the properties of root canal sealers, synthetic nanoparticles for dental restoration, targeted drug delivery and oral health maintenance using dentifrobots. In addition nanomaterial-based design mimics the mechanical and structural properties of the native tissue and thereby

could promote biointegration.¹⁹ This review focuses on the basics of nanotechnology and its applications in dentistry with emphasizes on current and future outlook of nanotechnology in the interdisciplinary dentistry along with a note on challenges faced by it in the current scenario.

1.2 Current perspective of nanotechnology in interdisciplinary dentistry

Nanotechnology has been potentially applied in all three forms in various fields of dentistry such as diagnosis and therapeutic, periodontics, prosthodontics, conservative dentistry and endodontics, oral surgery and orthodontics (Figure 1).

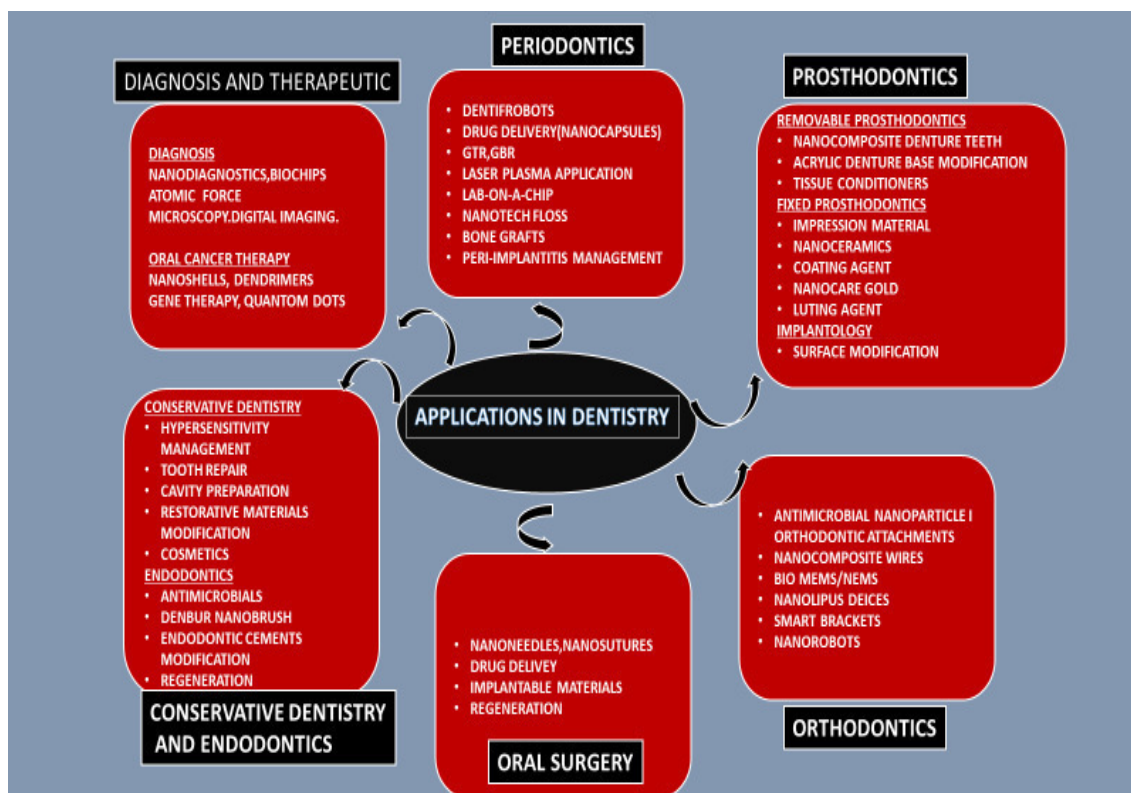


Fig 1. Application of nanotechnology in interdisciplinary dentistry²⁰

1.3 Diagnosis and Therapeutic Use

1.3.1 Nanodiagnosics/Nano-based molecular imaging

Nanodiagnosics provides the early identification of oral diseases at the cellular and molecular level. Nanotechnology has been applied in various diagnostic methods to improve the contrast and resolution of the image (Table 2).

Table 2. Nanotechnology-based detection and diagnostic methods

Diagnostic methods	Application of nanotechnology
Magnetic resonance imaging	Nano-contrast agents has the ability to recognize unique cell surface markers and prolonged blood circulation half-life ; thereby improving the contrast ²¹ Eg. Superparamagnetic iron oxide (SPIO) and ultrasmall superparamagnetic iron oxide (USPIOs) nanoparticles which can shorten T2 and T2*, folate pre conjugated chitosan and magnetic poly (lactide-co-glycolide) (PLGA) nanoparticles ²² , Gd3+ doped amorphous TiO2. ²³
Optical coherence tomography	Gold nanoparticles are biocompatible, easy to synthesize, and can provide localized surface plasmon resonances at near-infrared wavelengths and also avoids predominant absorption in tissues. ²⁴ Au nanoparticles with a diameter of 71 nm have been applied to enhance the contrast of Optical coherence tomography (OCT) images of oral dysplasia in a hamster model increasing the contrast to approximately 150%. ²⁵
Photoacoustic imaging	In photoacoustic imaging, the nanoparticles are considered a more attractive contrast agent due to their ability to conjugate biomolecules and their production of stronger photoacoustic imaging signals. ^{26,27}

<i>Surface plasmon resonance scattering</i>	High optical signals were produced by enhanced surface plasmon resonance when the nanoparticles gathered around the target cancerous cells, due to their conjugation with anti-EGFR increasing the sensitivity to 70%. ²⁸
<i>Surface-enhanced Raman spectroscopy</i>	Nanoparticles have been applied as exogenous contrast agents to acquire Raman signal with high speed and resolution. RB-GNR platform increases the detection sensitivity of 2000 cells/ml. ²⁹
<i>Diffusion reflection imaging</i>	Nanoparticles specifically gets attached to areas histologically identified as OSCC, with high reflectance at 780 nm over 17 intensity units. ³⁰
<i>Quantum dots imaging</i>	Quantum dots with an emission wavelength of 800 nm conjugated with EGFR monoclonal antibodies or arginine–glycine–aspartic acid sequence has the potential to generate high quality images of OSCC offering great potential in personalized therapy for OSCC. ³¹⁻³³

In oral diagnosis, Atomic Force Microscopy provides a real time scanning of live bacterial cells with high sensitivity using nanomechanical biosensors thereby adding information on cell adherence and elasticity at both nanoscale and picoscale levels. It helps to detect the disease progression by identifying the structure of biofilms and aids in the development of therapies against drug-resistant bacteria.³⁴ Biochips are integrated and automated system that enables rapid detection of multiple salivary proteins and nucleic acid targets. It rapidly detects premalignant and malignant lesions in oral cancer.³⁵ Integrated Microfluidic Platform detects proteins such as TNF-alpha, IL-6 in pico molecular levels within 10 minutes there by indicating the severity of periodontitis.³⁶ In addition High quality digital imaging could be obtained using nanophosphor scintillators.⁶

1.4 Periodontics

Nanorobotic Dentifrices/dentifrobots (1 to 10 microns) are deposited on the tooth surfaces by toothpaste or mouthrinses, moves 1 to 10 microns and gets deactivated when swallowed. They help in the reduction of both supragingival and subgingival plaque sparing only the harmless oral species.³⁷ Nanohydroxyapatite dentifrices occludes the dentinal tubules thereby providing a quick relief from dentin hypersensitivity.³⁸ When properly designed, dentifrobots could identify and destroy pathogenic bacteria residing in dental plaque and elsewhere, while sparing the 500 species of harmless oral microflora and allowing them to flourish in a healthy ecosystem.³⁹ Nanotech floss are Ultra-thin, ultra-glide, completely non-shredding with excellent tensile strength. The unique nanostructure of dental tape allows for the addition of flavours, and delivery of medication.² Functionalized nanoparticles like nanocapsules are used in drug delivery for periodontal diseases as they reach the inaccessible areas, smart release of drugs when triggered by bacteria, provides uniform and controlled release, combats antibiotic resistance compared to micro-sized particles. Drug like Chlorhexidine (CHX), tetracycline, Metronidazole, silver and leaf extracts are loaded in suitable nanofibers for sustained release in pockets.⁴⁰ Presolving mediators has been incorporated into Nanopore solving medicines(NPRM) which targets specific tissues reduces inflammation and facilitates bone formation in periodontitis.⁴¹ For periodontal therapy, the functional graded material (FGM) nCHAC/PLGA membrane was prepared that consisted of three layers with 8 wt% nCH + PLGA/4 wt% nCHAC + PLGA/PLGA, where one face of the membrane is porous, thereby allowing cell growth and the opposite face of the membrane smooth, thereby inhibiting cell adhesion.⁴² Laser plasma application using nanosized titanium particle emulsion are used clinically in soft tissue incisor without anaesthesia and periodontal therapy.⁴³

1.5 Prosthodontics

1.5.1 Removable prosthodontics

Carbon nanotubes at 0.5% and metal nanoparticles are added to monomer of heat activated acrylic dentures preventing the shrinkage and promoting better colour stability, better denture fit and antibacterial effect.⁴⁴ Nanometal oxides has been added to silicone materials in maxillofacial prosthesis to improve the tensile and tearing loads and to improve the anti-thermal aging properties. Eg titanium oxide, polyhedral oligomers silsesquioxanes.⁴⁵ Nanocomposite denture teeth has been fabricated using PMMA to overcome the disadvantages of high rate of wear in acrylic teeth.⁴⁶ Tissue conditioners are added with silver nanoparticles which displayed antimicrobial activity against staphylococcus and candida improving its clinical use.⁴⁷

1.5.2 Fixed prosthodontics

Nanosized fused silica is added to polyvinyl siloxane impression material to change its working and setting time, and for accurate reproduction of tissue details . Eg Nanotech Elite H-D+⁴⁸

1.5.2.1 Nanoceramics

To overcome the brittleness of ceramics, nanoceramics with nanofillers, Nanopigments and Nanomodifiers was manufactured. It shows good toughness, superplasticity, ductility, translucency and strength.⁴⁹ Coating Agents like G-coat plus is added to esthetic restorations to have higher luster and wear resistance. Nanocare gold is added directly to crowns, inlays, onlays before luting to increase the adhesion to tooth and improve the antimicrobial effect.²⁰ Nanoparticles are added to luting cement to increase the flexural strength, knoop hardness and to reduce film thickness.²⁰

1.5.2.2 In implant dentistry

Nanoscale surface modifications has been done in the implant using ion beam deposition, nanoparticle compaction making nanostructures thereby increasing the cellular interactions and the bone implant interface strength. Nano Functionalization using biomolecules like DNA, proteins enhances the osteoblast attachment and differentiation. Eg. Nanotite implant, Biohelix implant. Structural implant materials and Bioresorbable materials has been fabricated using nano Hydroxyapatite and calcium phosphate appetite in paste form are used as bone substitutes.^{20,50}

1.6 Conservative dentistry

Nanocomposites includes both Nanohybrid and nanofilled composites with dimension of 5100 nm paving the way for increased filler content thereby improving mechanical properties and wear resistance. Moreover, the small size of filler particles improves the optical properties, polishability and gloss retention compared to universal composites .eg Filtek supreme universal restorative.⁵¹ Pathogenic microorganisms are capable of colonising the marginal gaps between an existing restoration and tooth leading to secondary caries. To overcome this, Antibacterial nanoparticles (10 nm) containing oxides of gold, silver, titanium, zinc, copper, quaternary ammonium salts, chlorhexidine or combination of these have been incorporated into composites. They act via generation of free radicals having an effect on cell wall, DNA, enzymes leading to destruction.⁵² Monocalcium phosphate, dicalcium phosphate, tetracalcium phosphate, octacalcium phosphate and amorphous calcium phosphate containing nanoparticles have been incorporated into composites, releases calcium and phosphate over time preventing caries activity and helping in Remineralization. Calcium fluoride nanoparticles has been listed under smart materials because they are able to release fluoride ions whenever there is a decrease in Ph. Due to the higher surface area of nano calcium fluoride they are able to provide sustained release of fluoride over 70 days. Addition of reinforced glass fillers, bioactive glass and providing a combination of nanoparticles leads to improved mechanical, remineralizing and antibacterial properties.⁵³ Similar nanoparticles in the form of nanorods, nanogels, nanoclay are added in adhesives at 0.2 to 10% reducing the bacterial load before and after curing, and also reducing pulpal inflammation and Remineralization. Eg Prime & bond NT adhesive, GC-G Bond.⁵⁴ Replacement of 10 to 20 % of microgranular fillers in glass ionomer cement with nanogranular fillers improves its physical and mechanical properties. In addition to this surface modified nanoparticles containing silver, Titanium oxide, Hydroxyapatite, chlorhexidine hexametaphosphate are added to provide antibacterial, polish and abrasion resistance of GIC.⁵⁵⁻⁵⁶ Silanated silica nanoparticles are added upto 2.5% improving the flexural strength. Rely X Arch contains silver nanoparticles with 5nm providing antibacterial action. Nanoparticles has also been added in temporary restorative material increasing the sealing ability and possessing antibacterial ability. In cosmetic dentistry upper enamel layers could be replaced with diamond or sapphire carbon nanotubes making the teeth appear more esthetic and improving its fracture resistant.⁵⁵ Radio-opacity could be incorporated into cements and instruments by using nanoparticles instead of heavy metals to reduce the toxicity. Laser plasma application using nanoparticles are also used in cavity preparation. Multiple nano robots working on the teeth in union, invisible to the naked eye, may be used for cavity preparation and restoration of teeth. The cavity preparation is very precisely restricted to the demineralised enamel and dentin, thus providing maximum conservation of sound tooth structure.⁵⁷ With the combination of finishing procedures, nanotechnology liquid polish application provides a glossier surface for resin composite restorations.²⁰ Smart composites, a light activated nano-filled glass restorative material releases calcium, fluoride and hydroxyl ions when the ph drops below 5.5 e.g. Ariston pHc.⁵⁸

1.7 Endodontics

1.7.1 Irrigants and Intracanal medicaments

Nanoparticles with silver, chitosan, magnesium oxides has been added to the irrigants which provides increased solubility, low viscosity, release of free radicals thereby eradicating the resistant *E faecalis* strains. Due to their increasing time of contact with the microorganism, it could also be used as an effective intracanal medicament. Nanocare plus, a commercial intracanal medicament is a combination of silver, gold nanoparticles in alcoholic solution. Denbur Nanobrush could penetrate the tubules and lateral canals and achieves better cleaning of the canal space.²⁰

1.7.2 Obturation

Silver nanoparticles coated gutta percha, sealers containing ZnO, CHX, QPEI, Cs nanoparticles and its combination prevents microleakage by reducing bacterial adherence without affecting its mechanical properties.²⁰ Photosensitizers are combined with nanoparticles like chitosan in photodynamic therapy which increases the specificity, uptake and lower cytotoxicity compared to Photosensitizers used alone.⁵⁹

1.7.3 Perforation repair

Nanomodified faster setting MTA with metal oxides is possible which sets within 6 minutes due to the larger surface area, resistant to acids, efficient nucleation sites thereby increasing the hydration reaction. ZrO₂ nanoparticles in addition to improving mechanical properties also serves as a radio opacifier replacing the disadvantages of bismuth oxide. Nanocomposites prepared using C²¹ organoclay nanoparticles provides superior apical seal in invitro conditions.⁶⁰ Synthesis of nanostructured biomaterials based on highly active calcium silicate, calcium carbonate; super elastic, quick bonding endodontic mixtures increases efficiency and provides quicker bonding suitable for endodontic applications.

1.7.4 Regeneration

Nanosized scaffolds manufactured using electrospinning, self-assembly and phase separation procedure mimics the extracellular matrix in tooth providing better attachment of stem cells. Antibiotic containing nanofibers introduced by Bottino et al helps in the controlled release of TAP for a period of 30 days reducing its cytotoxicity to stem cells. Further nano bioactive glass is more potent in inducing the differentiation of DPSCs.^{61,62} Calcium phosphate nanoparticles releases osteocalcin and bone sialoprotein providing better cell differentiation and could be also used in drug delivery systems and as gene vectors in regeneration. In direct pulp-capping procedure MTA could be combined with PCL nanofiber mesh producing thicker reparative dentine formation compared to MTA alone.⁶³ An attempt has been made by Chen et al. (2005)⁶⁴ in recreating the whole tooth followed by Bhardwaj et al. in 2014⁶⁵ was able to recreate the structure of enamel by nanorods.

1.8 Oral surgery and implants

Millions of nanorobots are instilled into the gingiva which reaches the pulp and provides needle free nanoanesthesia.²

Nanoshells, carbon nanotubes, dendrimers, nanodiamonds, Lipid based and gold nanoparticles are used for targeted delivery of anticancer drugs.⁶⁶ Quantum dots along with photodynamic therapy mediate the targeted cellular destruction of cancer cells.⁶⁷ Implant surface modification using ceramic coatings, surface functionalization and nanoscale patterning mimics the extracellular matrix resulting in faster healing and bone formation). In addition, Implant surfaces should be designed towards regulating the neovascular morphogenesis providing better endosseous healing.⁶⁸

1.9 Orthodontics

Nanofillers has been added to orthodontic composites to create nanocomposites thereby increasing the bond strength to orthodontic attachments like brackets, temporary anchorage devices and ligature wires.⁶⁹ Antimicrobial nanoparticles like silver, zinc oxide, chitosan and remineralizing agents like nano – HA has been added to prevent caries risk and improving remineralization.⁷⁰ Nanocoated orthodontic archwire using fullerene-like tungsten disulfide and nickel nanoparticles could be used as a replacement of regular archwire to reduce the frictional forces on orthodontic mechanics. Eg. Sandvik nanoflex and MBT archwires.⁷¹ Nanotechnology orthodontic brackets has been manufactured by incorporating hard alumina nanoparticles to provide higher strength, lower friction and biocompatibility.⁷² Nanomechanical sensors could be attached to the brackets to measure the real time forces and moment applied to tooth.⁷³ Nanophase coatings using ZnO, TiO₂ reduce the S. Epidermidis adhesion and increase osteoblast function in orthopaedic implants.⁷⁴

1.10 Future Scenarios

1.10.1 Nanotweezers

Single cell surgery could be made possible Nanotweezers and nanoneedles which is under development². Gene therapy could transfer genetic material into the tumour cells inhibiting the tumour progression.⁷²

1.10.2 Nanorobots

Dental nanorobots penetrate the human tissues via specific motility mechanisms, takes up the orders via acoustic signals and modify the surroundings in real time. Nanorobots coupled with smart brackets could be used in the near future to bring accelerated tooth movement with low forces.⁷⁵

1.10.3 Nano orthodontics – A futuristic approach

Hollow NiTi wires and esthetic Orthodontic wires made of shape memory nanocomposite polymer could be a futuristic application in orthodontics. Biological microelectromechanical system built using nanostructures

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with high electrical conductivity could enzymatic tooth movement in orthodontics Nano LUPUS devices which uses ultrasound energy could be used to enhance the bone growth and prevent root resorption.⁷²

1.11 Future perspective and challenges

Along with the growing interest in nanotechnology, there are also significant challenges faced by it which includes inadequate clinical research, financial concerns, Ethical acceptance, risk assessment and manufacturing and synchronisation of nanoscale parts. Further toxicity could be a major concern as the nanoparticles is able to cross the blood brain barrier and due to the larger surface area may lead to oxidative stress. Hence the future of nanotechnology should be aimed towards the development of more Randomized Clinical Trials which compares the Nano product with a Non-Nano product to propagate Evidence Based Medicine, and to examine the feasibility, toxicity, precision of materials and patient compliance.

2. CONCLUSION

The rapid phase of growth and dental application of nanotechnology has led to the emergence of a new field called Nanodentistry. Nanotechnology in interdisciplinary dentistry aims to ensure comprehensive oral healthcare of the patient and emphasizes the primary prevention of oral diseases. With the availability of nanodiagnostics, a number of oral diseases can be prevented or treated at early signs, thereby minimizing the complications which could occur at the later stage. Research to improve upon existing nanomaterials is still ongoing, with future directions towards cost effective and more efficient nano-biosensing devices. Although the science behind nanotechnology is intriguing, the lack of long term clinical evidence addressing their clinical performance is restricting their wide clinical use. Though the science of nanotechnology may appear as fiction in the present scenario, the future holds strong promise for the benefit of mankind by utilizing and maximizing this technology. Hence if the challenges are surpassed, nanodentistry will be reassuring to provide efficient and highly effective personalized dental treatments in the long run.

3. AUTHORS CONTRIBUTION STATEMENT

DR Vinothini conceptualized and gathered this information with regard to this work. Prof Dr Ramaprabha MDS analyzed this information and necessary inputs were given towards the designing of the manuscript.

4. CONFLICT OF INTEREST

Conflict of interest declared none

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