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“Nanotechnology-based strategies in diagnostic and therapeutic nanodentistry”

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Abbreviations

45S5: Calcium Sodium Phosphosilicate

ACP: Amorphous Calcium Phosphate

AFM: Atomic Force Microscopy

Ag: Silver

AgNPs: Silver Nanoparticles

BAG: Bioactive Glass

BFS: Biaxial Flexural Strength

Ca^{2+}: Calcium Ion

CaF_2: Calcium Fluoride

CaO: Calcium Oxide

CaOH: Calcium Hydroxide

CaP: Calcium Phosphate

CC: Calcium Carbonate

CdTe: Cadmium Telluride

CdSe: Cadmium Selenide

CHA: Carbonated Hydroxyapatite

cm^2: Square Centimeter

CNF: Cellulose Nanofiber

CNT: Carbon Nanotubes

CRP: C-Reactive protein

CS: Compressive Strength / Calcium Sulfate

CT: Computed Tomography

CuNP: Copper – Based Nanoparticle

DCPA: Dicalcium Phosphate Anhydrous

DEJ: Dentino-Enamel Junction

Dentifrobots: Nanorobots in Dentifrices

DNA: Deoxyribonucleic Acid

DTS: Diametral Tensile Strength

ECM: Extracellural Matrix

ENMs: Engineered Nanomaterials

F: Fluorine

FA: Fluorapatite

g: Gram

GF: Growth Factor

GIC: Glass Ionomer Cement

GNPs: Gold Nanoparticles

HA: Hydroxyapatite

KN: Ketac N100

MB: Methylene Blue

MRI: Molecular Resonance Imaging

mRNA: Messenger Ribonucleic Acid

MTA: Mineral Trioxide Aggregate

NaF: Sodium Fluoride

Nanobots: Nanoscale Robots

NaOCl: Sodium Hypochlorite

NCMS: Nano CaO Mesoporous Silica

NCS: Nuclear Localization Sequence

NIR: Near-Infrared

nm: Nanometer

NP: Nanoparticle

OSCC: Oral Squamous Cell Carcinoma

PDGF-BB: Platelet – Derived Growth Factor

PDL: Periodontal Ligament

PEG: Polyethylene Glycol

PLGA: Poly Lactic-co-Glycolic Acid

PMMA: Poly Methyl Methacrylate

PO_4: Phosphorous

PO_4^3: Phosphate

PVP: Poly(vinylpyrrolidone)

RGD: Arginine – Glycine - Aspartate

QACs: Quaternary Ammonium Compounds

QDs: Quantum Dots

ROS: Reactive Oxygen Spieces

SWNT: Single Walled Nanotubes

TEM: Transmission Electron Microscopy

TEOS: Tetraethoxysilane

TiO_2NPs: Titanium Dioxide Nanoparticles

TCP: Tricalcium Phosphate

TTCP: Tetra Calcium Phosphate

wt%: Percentage by Weight

w/w%: Weight by Weight

YbF3/BaSO4: Ytterbium Fluoride and Barium Sulphate

ZnONPs: Zinc – Oxide Nanoparticles

$ZrOCl_2$: Zirconyl Chloride

Contents

Abstract

Nanotechnology has rapidly spread into all fields of science, providing significant alternative approaches to scientific and medical questions and problems. Nanotechnology has also had a huge impact on the health-care industry, and its use is a benefit not only to modern medicine but also dentistry. It is expected to pervade and further redefine dentistry, with potential applications encompassing all facets of oral illnesses, diagnosis, prevention, and treatment. Materials' science in dentistry has embraced technology to create nanomaterials that are used in a variety of dental applications. These emerging technologies have the potential to provide significant benefits in the form of advancements in dental science and society [Sharan et al., 2017]. Manufacturers have included a variety of nanoparticles into dental materials in order to improve the chemical and physical properties of these materials. This field of research has been entitled 'nanodentistry' [Padovani et al., 2015]. Nanotechnology has been used in the development of restorative materials in dentistry with considerable success. The recent advances in nanodentistry and innovations in oral health-related diagnostic, preventive, and therapeutic methods required to maintain and obtain perfect oral health, have also been discussed. Recent breakthroughs in nanotechnology have the potential to bring about a paradigm shift in dentistry [Neel et al., 2015]. While oral health maintenance is a major challenge, various materials have been utilized to treat various dental problems, but the success of treatment is restricted by the biomaterials used. Materials including nanoparticles (NPs) can be employed in dental applications such as endodontics, periodontics, orthodontics, oral surgery, tissue engineering, and more to overcome these restrictions [Bapat et al., 2018]. Many applications of nanotechnology in dentistry are still in their early stages. A growing number of products are currently being studied, while some are commercially available [Mantri et al., 2021]. Nanotechnology is expected to have a significant impact on dental research and treatment approaches in the near future, resulting in enhanced oral health care [Sharan et al., 2017].

Purpose

This master thesis will review the recent advances in Nanodentistry and innovations in oral health-related diagnostic, preventive, and therapeutic methods.

Design

Perspective following literature review.

Methods

Research articles about nanotechnology-based strategies in diagnostic and therapeutic Nanodentistry were searched through Google Scholar and PubMed and the most representative of them in the last twenty years were reported.

1. Introduction

Richard Feynman first discovered the concept of nanotechnology, which refers to materials with mechanical and chemical properties superior to those found on a larger scale, as well as a structural range at the atomic level of 1–100 nm [Choudhury et al., 2014]. In 1974 Professor Norio Taniguchi of the Tokyo University of Science first presented the term Nanotechnology [Kavoosi et al., 2018]. Nanocarriers with a diameter of 10 nanometers, for example, are 100 times larger than a hydrogen atom but 100 times smaller than a bacterium [Mitra et al., 2003]. As a result, nanotechnology is preoccupied with structures at the molecular and atomic levels [Neel et al., 2015]. Nanotechnology is thus defined as a technology that enabled the development and use of nanometer-sized items. Nanomaterials and nanoparticles have recently been employed to diagnose, prevent, and treat a variety of ailments. These substances have proven increasingly valuable in biomedicine, and they serve an important role in modern medicine by having applications in several sectors such as diagnosis, drug delivery systems, prosthetics, and implants [Faraji et al., 2009]. Materials with the same composition at the nanoscale have significantly different properties than materials with the same composition at a larger scale. At the nanoscale, qualities such as strength, conductivity, color, and toxicity can all change [Mantri et al., 2021]. Nanodentistry is defined as the science and technology of employing nanostructured materials in order to diagnose, treat, and prevent oral and dental disorders, relieve pain, preserve and improve dental health. There are numerous new dental products on the market, varying from implants to oral hygiene products that depend on the nanoscale properties. The use of Atomic Force Microscopy (AFM) and Optical Interferometry in dentistry is being examined, including the characterization of dental enamel, biofilms, oral bacteria, and the involvement of surface proteins in biomechanical and nanomechanical bacterial adhesions. Nanodentistry breakthroughs like saliva exosome-based diagnostics and the creation of biocompatible and antibacterial dental implants are transforming the area [Sharma et al., 2010]. Although the area of Nanodentistry is still evolving and many challenges remain unsolved, the new era of nanotechnology in dentistry has the potential to alter the public's perception of dentists. It promotes the idea of minimally invasive dentistry, resulting in a more dentist-friendly environment [Mantri et al., 2021]. One area of nanotechnology that has seen many applications in dentistry is the use of nanoparticles in composites. Nanoparticles are used for two reasons: 1) to improve the aesthetics of materials by making them more translucent, and 2) to improve (or at least affect) the wear qualities. The use of submicron grain size ceramics for the manufacturing of all-ceramic restorations is another area where nanotechnology has been used. The use of nanometer-sized powders in the creation of ceramic monoliths is based on aesthetics, wear characteristics, and increasing the ceramic's strength [Neel et al., 2015]. By enhancing the mechanical and physical qualities of materials, nanotechnology has transformed the medical and dentistry disciplines, allowing for the introduction of novel diagnostic techniques and nano-delivery systems [Kanaparthy R. et al., 2011]. The unique features of nanoparticles have prompted continuous research in the field of nanotechnology [Li et al., 2008]. The high surface to core ratio of nanoparticles is a unique physical property, implying that there are more atoms on the nanoparticle's surface than deep within its core. This is especially important since surface atoms have unbound surfaces compared to core atoms, which have the ability to form new and strong bonds, making nanoparticles more reactive than micro and macro particles [Binns et al., 2010]. Due to their high surface to core ratio, nanoparticles may be easily stacked in a variety of packing arrangements, allowing them to be easily manipulated and used in a variety of applications [Buffat et al., 1976]. Emerging nanoparticles for periodontal and endodontic treatments have been established in the field of nanodentistry. As healthy gums have a pocket depth of 4 mm between them and the teeth [López et al., 2002], nanoparticle penetration into the surrounding dental tissues is expected to be increased. This is also true for root canal therapy, which should be sterilized all the way up to the appical stenosis, the narrowest part of the canal [Vertucci et al., 2005]. Metals or metal oxide nanoparticles may be innately bactericidal, or they may be designed to encapsulate drugs within polymers in order to improve drug aqueous solubility for delivery into bacteria as well as achieving a regulated release. Multiple drug loading is also possible due to the large surface area to volume ratio, which can result in synergistic antibacterial activity and help overcome bacterial resistance [Benoit et al., 2019].

Meanwhile, nanoparticles are increasingly being employed to fill gaps in the resin matrix of prosthodontic and orthodontic composites, minimizing polymerization shrinkage and improving mechanical characteristics [Zhou et al., 2019]. Bond strength, fracture toughness, compressive strength, flexural strength, and hardness are all improved when mechanically strong nanoparticles like carbon nanotubes are used in the bulk material version [Gopinadh et al., 2015].

Caries control restorations, management of the oral biofilm, dental caries vaccine, tooth remineralization, management of dentinal hypersensitivity, root canal disinfection, infection control, local anesthesia, oral cancer therapy, and tissue engineering are some of the areas of interest in dentistry for the use of nanodrug delivery systems [Renugalakshmi A. et al. 2011]. Nanomedicines utilized as dental materials have unique physicochemical and biological characteristics that can be exploited to avoid the problems that occur with conventional dental treatments [Balazs et al., 2006]. Dental caries, periodontal disease, bad breath, tooth sensitivity, and oral precancerous and cancerous disorders can all be caused by damaged dental tissues. Therapeutic intervention and the usage of biocompatible synthetic materials can be used to treat such conditions. Although there is a widespread dearth of knowledge of such characteristics among the dentistry community, several forms of NPs and nanocomposites have been proven to imitate the properties of dental tissues [Zhang et al., 2016].

Currently many nanoproducts are available on the dental market for use. Some of the are depicted in the Table 1 below.

Discipline	**Available Materials**
Restorative Dentistry	Ketac™ (3M ESPE, St. Paul, MN, USA), Ketac N100; Nano-ionomers (3M ESPE), Filtek Supreme XT (3M ESPE), Fuji IX GP (GC, Leuven, Belgium), Nano-primer, Premise™ (Kerr/Sybron, Orange, CA, USA), Adper™ Single bond plus Adhesive (3M ESPE), Ceram X™ (DENTSPLY International, Milford, CT, USA).
Regenerative Dentistry and Tissue Engineering	Ostim® (Osartis GmbH, Elsenfeld, Germany), VITOSSO™ (Orthovita-Inc, Malvern, PA, USA), Nano-Bone® (ARTOSS, Rostock, Germany).
Periodontics	Arestin® (Valeant, Bridgewater, MA, USA), Nanogen® (Orthogen, Springfield, IL, USA).
Preventive Dentistry	NanoCare® Gold (Nano-Care, Saarwellingen, Germany).
Orthodontics	Ketac™ N100 Light Curing Nano-Ionomers (3M ESPE), Filtek Supreme Plus Universal (3M ESPE).
Prosthodontics	Nanotech elite H-D plus (Zhermack, Badia Polesine, Italy), GC OPTIGLAZE color® (GC).
Oral Implantology	Nanotite™ Nano-coated implant (BIOMET 3i, Palm Beach Gardens, FL, USA).
Endodontic	AH plus™ (DENTSPLY International), Epiphany (Pentron Clinical Technologies, Wallingford, CT, USA), Guttaflow® (Coltène, Altstätten, Switzerland).

Table 1. Currently available products in dentistry through the applications of Nanotechnology.

Nanostructures appear in a variety of shapes and forms [Gleiter H. et al., 2000]. They also come in a variety of compositions, allowing for a broad spectrum of altered characteristics to support the development of new dental applications [Elkassas D. et al., 2017]. Some of them are mentioned below.

Nanopores

A nanopore is an extremely small hole with a diameter in the nanoscale range of up to 100 nanometers [Luo et al., 1997]. Nanopore silica fillers have been shown to increase wear resistance in posterior composite restorations.

Nanotubes

Carbon nanotubes are long, thin carbon cylinders formed of a graphite sheet folded into a cylinder, and they are the most frequent form utilized in dentistry. Nanotubes are available in single-walled or multi-walled configurations. They exhibit exceptional mechanical qualities like stiffness, strength, and tenacity, as well as exceptional bioactive capabilities [Wepasnick et al., 2010]. Carbon nanotubes were shown to improve the flexural strength and modulus of elasticity of dental composites, as well as they appear to reduce polymerization shrinkage and water resorption, resulting in more lasting and improved restoratives [Shin et al., 2011].

Quantum dots

Quantum dots are microscopic particles of specific materials, most often semiconductors that have unique optical characteristics. They also demonstrated fluorescence potential that can be altered by carefully controlling the size of the dots. Tooth enamel also exhibits fluorescence characteristics that are difficult to replicate in cosmetic restorations. Certain quantum dots, formed of core-shell complex of cadmium selenide in the inner layer and zinc sulfide at the outer layer can lead to providing restorations with improved esthetics [Alves et al., 2010].

Nasnoshells

Nanoshell nanoparticles have a dielectric core surrounded by a thin metallic shell. Nanoshells of different thicknesses may absorb different wavelengths of light. Light absorption by nanoshells generates intense heat, which can be deadly to cancerous cells while leaving normal cells unharmed. As a result, it may be effective in treating of oral cancer [Wong D. T. et al., 2006]. Nanoshells can also help with regulated site-specific medication delivery into periodontal tissue.

Dendrimers and dendritic copolymers

Dendrimers are nanometer-sized molecules or monomers that are repetitively branched around an inner core [Astruc D. et al., 2010]. They appear to enhance the efficiency of dental restorations.

Liposomes

One or more phospholipid layers surround a fabricated small vesicle with an aqueous core. Its dental use may help minimize the risk of dental caries [Yamakami K. et al., 2013].

Nanorods

It has been discovered that hydroxyl apatite (HA) nanorods have a new influence on improving the characteristics of dental adhesives. The addition of 0.2-0.5 wt.% HA-nanorods to the dental adhesive increased the bulk mechanical characteristics and micro-shear strength to the dentin substrate considerably [Sadat-Shojai M. et al., 2010].

Fullerenes

The discovery of fullerene led to the creation of a new class of nanostructures. They are hollow spherical caged molecules with a single atom in the corner of a polyhedral temple constructed in pentagons and hexagons. These new nanostructures have biological applications in the fields of cancer treatment and photosensitive antibacterial agents [Mizuno K. et al., 2011; Pacor S. et al., 2015].

Nanospheres

The nanospheres are nanometer-sized spherical particles. The incorporation of peptide nanospheres into composite restoratives and dental adhesives have resulted in substantial mechanical property reinforcement and improvement [Saunders S. A. et al., 2009]. Nanospheres have been proposed to have a possible therapeutic impact in tissue engineering by releasing growth factors in a sustained manner over a long period of time [Kim T. H et al., 2014].

Nanowires

A nanowire is a long, very thin structure with a diameter ranging from 20 to 80 nanometers [Lin K. et al., 2009]. Nanowires have the potential to be used in dentistry. It has been observed that hydroxyapatite nanowires have the ability to restore enamel and remineralize carious lesions [Chen H. et al., 2006]. HA-nanowires may be utilized to strengthen and enhance the mechanical characteristics of polymer composites [Costa D. O. et al., 2012].

Nanobelts

Nanobelts are nanostructures that have a rectangular cross section and appear in the shape of bands. According to the application, they are oxides of various elements. Biomimetic uses of this new nanostructure have been suggested in dentistry.

Nanorings

A nanoring is a crystal created in the shape of a ring. The increased surface area of the nanorings fostered excellent interface bonding, which resulted in improved mechanical performance for the HA nanoring composite [Nathanael A. J. et al., 2012].

Nanofibers

A wide range of nanofibers with high promise in the dentistry sector are currently accessible.Nanofibers were shown to improve the mechanical properties of dental composites. The mechanism of the reinforcing effect may be ascribed to the existence of a strong interfacial binding force between the distinct phases of the restorative material and an homogeneous distribution of the impregnated nanofillers preventing crack development [Saunders S. A. et al., 2009].

Nanocapsules

They are polymeric membrane vesicular structures that enclose an interior liquid core. The encapsulation approach has several advantages in terms of protecting encapsulated compounds from harmful environmental impacts, precise targeting, and controlled release of active components [Elkassas D. et al., 2017].

Widely studied are also the metal and polymer-based nanoparticles in dentistry. Thus, frequently studied nanoparticles in the dental field are silver nanoparticles, gold, iron oxide and copper oxide nanoparticles, silica nanoparticles, calcium phosphate, hydroxyapatite, and titanium dioxide nanoparticles, as well as calcium fluoride and calcium phosphate nanoparticles. Chitosan nanoparticles, zirconia nanoparticles, PLGA and zinc oxide nanoparticles have also been found to have different dental applications [Bapat et al., 2018].

2. General Information about the oral cavity and dental tissues

2.1. Properties of saliva

Saliva is a complicated mucous fluid that helps to keep the oral cavity's pH balanced, mostly through bicarbonate and calcium phosphate buffering [Pedersen A. M. et al., 2002]. To avoid acidic erosion of the teeth, acids produced from the nutrition and beverages, as well as bacterial metabolism, are neutralized by bicarbonate [Edgar W. M. et al., 1994; Stookey G. K. et al., 2008]. Saliva also has a cleaning effect on teeth and helps to remove germs, but it also includes antimicrobial proteins and immune system components. Saliva is made up of 99 % water and is a medium with a high ionic strength and a plethora of electrolytes. Saliva includes in mmol l^{-1}: phosphate (2-22), sodium (2-26), potassium (13-40), calcium (0.5-2.8), bicarbonate (0.1-8), chloride (8-40), iodide (2-22), magnesium (0.15-0.6), and a tiny quantity of fluoride. These concentrations may be greater in saliva that has been recently stimulated. When the F^- ions in saliva react strongly with the free Ca^{2+} and $HPO_4{}^{2-}$ ions in enamel's hydroxyapatite (HA), fluorapatite crystals that are less soluble and acid resistant than pure HA are developing. This is one of fluoride's effects in combating dental cavities. The oral cavity's solute concentrations are also controlled by the salivary flow rate. Saliva quantity (and quality) can be affected by a variety of factors, including age, health condition, and medicines. When salivary flow is reduced or absent, food retention increases, and when the salivary buffering capability is lost, an acidic environment is favored, leading to enamel demineralization. The unstimulated (resting) salivary flow rate in healthy people is 0.3-0.4 ml min^{-1} and can rise to 1.5-2.0 ml min^{-1} [Besinis et al., 2015]. When saliva is first produced, it is sterile, but the bacterial content can rise to 109 ml^{-1} over time. The flow rate of saliva is usually too high for bacterial growth and proliferation in the fluid [Dawes C. et al., 2003]. To live in the long run, bacteria must attach to oral surfaces (teeth, mucosa). Saliva production is primarily regulated by cholinergic parasympathetic innervation of the salivary glands, which stimulates saliva release from the acinar cells, whereas sympathetic nerve stimulation tends to increase protein content, leading to more viscous saliva [Proctor G. B., 2007]. Saliva also contains antibacterial proteins and immunological components.

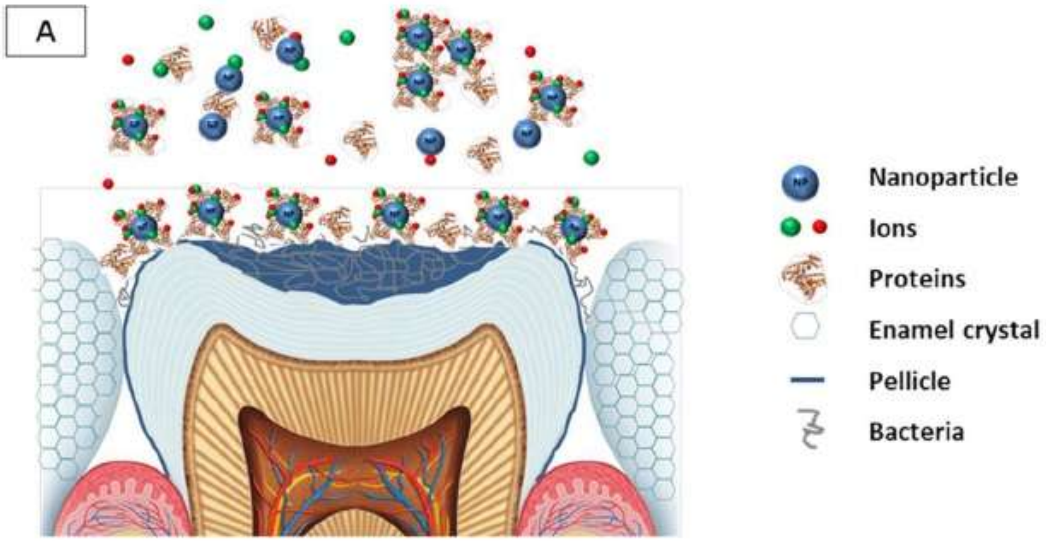

Figure 1. A. Diagram depicts the presence of NPs (isolated particles or agglomerates) in saliva as well as the microstructure of dentinal tissues. The pellicle covers the surface of the enamel, and the oral biofilm forms on the pellicle surface. The enamel crystallites' distinctive hexagonal form is visible, as is the presence of tubules in the dentine underlying tissue. The NP-ion-protein complexes do not attach to the tooth surfaces directly, but rather to the pellicle layer or the growing biofilm.

2.2. Tooth surface microenvironment

Saliva contains substances that interact with tooth enamel through a fine layer referred as the pellicle, which typically covers the teeth. The pellicle is an acellular proteinaceous film that originates from saliva, develops in minutes and is so firmly attached to the enamel that it is impossible to remove even with tooth cleaning. Salivary glycoproteins, phosphoproteins, lipids, and, to a lesser extent, components from the gingival crevicular fluid are the primary components of pellicle [Yao Y. et al., 2001]. Because it passively regulates the passage of ions in and out of the dental tissues, the pellicle plays a crucial role in the tooth demineralization and remineralization processes. As a result, it's a selective semi-permeable structure that acts as a chemical buffering barrier, preserving the enamel's mineral content from bacterial [Zahradnik R. T. et al., 1977] and nutritional acidic demineralization [Hannig M. et al., 2001; Hara A. T. et al., 2006]. The enamel-pellicle junction is not uniform, but rather has a multi-layered spherical shape [Lendenmann U. et al., 2000]. The colloidal and physico-chemical properties of the macromolecules in saliva, such as charge density, hydrophobicity, and relative concentration of each component, are presumably controlled by the colloidal and physico-chemical properties of each component to compete for binding on the tooth surface to form the organic layer of the pellicle.

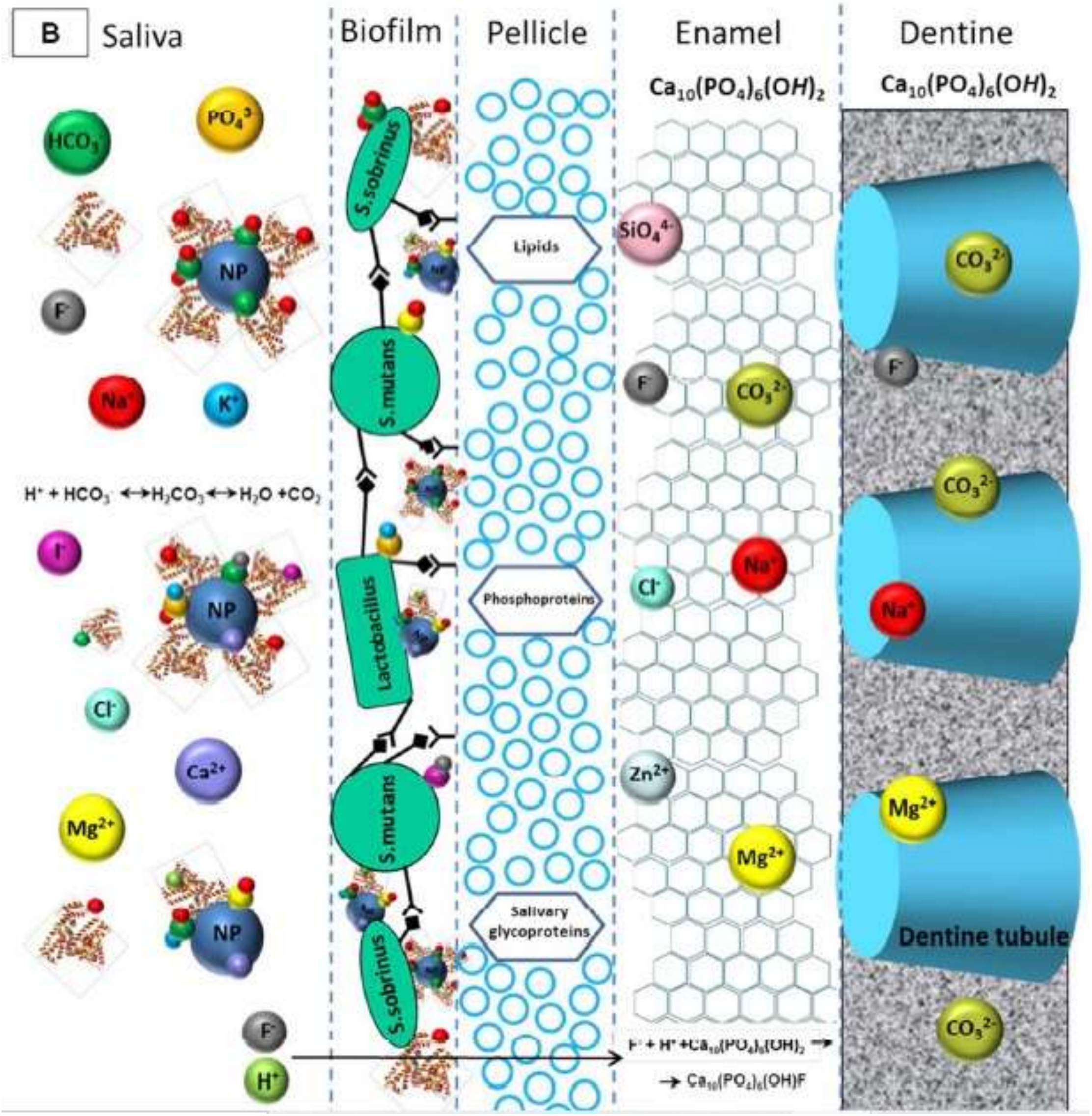

Figure 1. B. The distribution of NPs and ions in the oral environment, oral biofilm, and dentinal mineralised tissues is depicted in a schematic figure of the oral environment, oral biofilm, and dentinal mineralised tissues. Natural saliva includes a variety of ions and proteins. NP-ion-protein complexes develop in the presence of NPs. Particle agglomeration is promoted by oral environment, resulting in particle deposition on dentinal surfaces. The

pellicle has a globular form, and its proteinaceous layer aids the adhesion of the early colonizing species required for the establishment of the oral biofilm. NPs are prevented from reaching the enamel-pellicle contact by the oral biofilm and pellicle acting as diffusion/permeation barriers. Certain ions are more prevalent at the exterior surface of enamel (F-, Cl-, SiO4 4-, Zn2+), whereas others (Na+, Mg2+, CO3 2-) are found in larger quantities near the dentino-enamel junction (Na+, Mg2+, CO3 2-). F-, Na+, Mg2+, and CO3 2- are the most frequent ions detected in dentine.

2.3. Fine structure and chemistry of the tooth

Teeth are made up of four distinct tissues, three of which are mineralized (enamel, dentine, and cementum) and enclose an inner core of loose connective tissue known as the dental pulp [Figure 2].

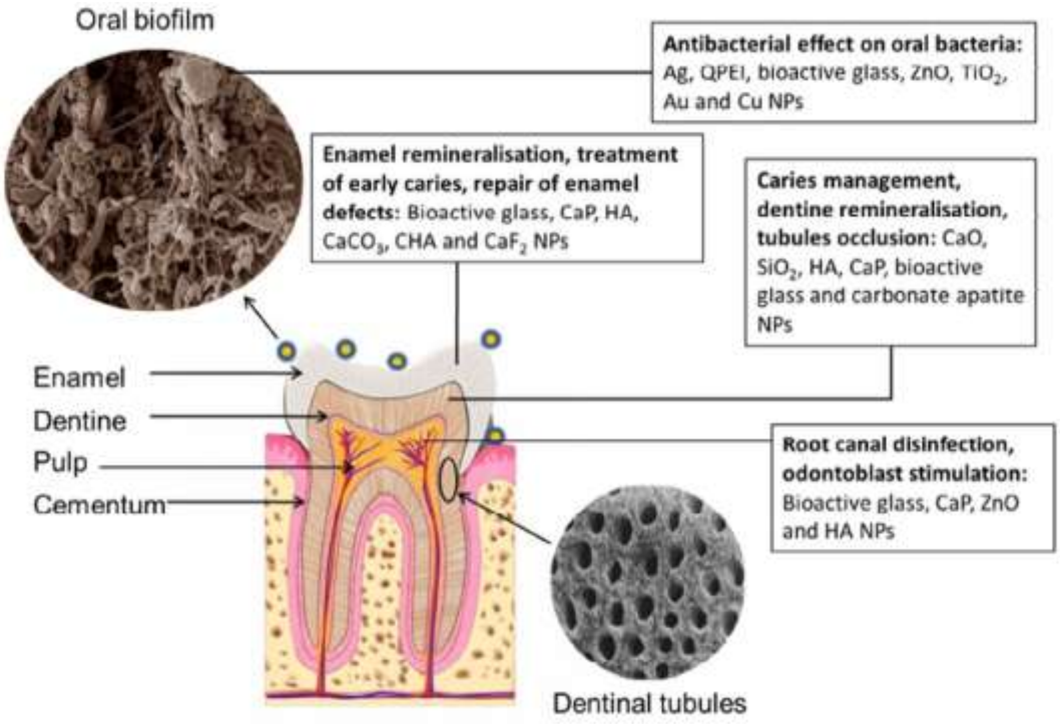

Figure 2. Tooth anatomy illustrating the four major components of the tooth (enamel, dentine, cementum and pulp). Details of the complex oral biofilm that forms on the tooth surfaces, as well as the distinctive tiny channels (dentinal tubules) that permeate dentine, are also depicted. Dental research studies have looked at the usage of a wide variety of ENMs in a variety of clinical applications such as enamel remineralization methods, antibacterial applications, caries management, dentine hypersensitivity, and root canal disinfection.

2.3.1. *Enamel*

Enamel is the toughest and most highly calcified tissue in the body, covering the crown of the tooth. Its thickness varies with site and age [Park S. et al., 2008], and may range from 2.6 mm across the cusps of healthy adult teeth to as little as 1.2 mm on the lateral surfaces [Grine F. E. et al., 2001]. Minerals account for 96% of the enamel's weight, with water and organic material responsible for the rest [Weatherell J. A. et al., 1975]. The most abundant mineral phase in enamel is calcium hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$, however non-apatitic mineral phases such as octacalcium phosphate can be found in small amounts (less than 2%). Calcium hydroxyapatite is not usually found in its purest form, and various variants are frequently seen. Calcium ions and hydroxyl groups are commonly absent, while other ions found in enamel, such as fluoride, carbonate, chlorine, silicon (generally as $SiO_4{}^{4-}$), sodium, magnesium, and zinc, take their place. These ions are not evenly distributed across the enamel layer. Some of them (F^-, Cl^-, Si, Zn^{2+}) are more plentiful at the enamel's exterior surface, whereas others (Na^+, Mg^{2+}, $CO_3{}^{2-}$) are more prevalent near the dentino-enamel junction (DEJ). Enamel apatite crystals are at least 100 µm long, 30 nm wide, and 90 nm thick, and they are extremely crystalline [Piesco N. P., 2002, pp 153-171]. The majority of crystals are hexagonal, however owing to crowding, some can be deformed. Near the tooth surface, dental enamel contains 558 crystallites/mm^2 [Kerebel B. et al., 1979] and the spacing between neighboring crystallites is 20 nm. A thin layer of tightly linked water surrounds [Diekwisch T. G. et al., 1995] HA crystals (2 wt. %). The presence of water is related to the tissue's porosity. The organic matrix makes up the remaining 2% of mature enamel. Enamel does not include collagen, but it does contain two distinct protein families known as amelogenins and enamelins.

2.3.2. Dentine

Dentine is composed of around 70% inorganic, 20% organic, and 10% water by weight [Piesco N. P., 2002]. Dentine crystals contain a lower calcium concentration and are more carbonate-rich than stoichiometric HA, and the mineral phase is HA, much like enamel. Crystallites with a hexagonal or plate-like shape and sizes of 3-30 nm in cross-section and around 50 nm in length are significantly smaller than those seen in enamel [Lees S. et al., 1979; Lees S. et al., 1988]. The HA crystals are therefore naturally produced nanocrystals, and the dentine has a broad and chemically reactive surface area due to the high content of carbonate (4.6 wt%) [Marshall G. W. et al., 1997]. Fluoride, sodium, and magnesium have all been found in low quantities in dentine. Dentine's inorganic component is mostly type I collagen, which serves as a structural basis for the apatite crystallites. Dentine collagen fibrils range in size from 60 to 200 nanometers [Kinney J. H. et al., 2001]. Dentine is pervaded by dentinal tubules, which are tiny channels that run through it. They have a diameter of 2.5 µm in the pulp, 1.2 µm in the center of the dentine, and 900 nm at the DEJ. The tubule density differs as well and it depends on location. Near the pulp, there are 45,000 mm^{-2} tubules, which cover 22% of the entire surface area of dentine; in the middle, there are 29,500 mm^{-2} tubules; and near the DEJ, there are 20,000 mm^{-2} tubules, which cover just 1% of the total surface area of dentine [Garberoglio R. et al., 1976; Marshall G. W. et al., 1997].

2.3.3. Cementum

Cementum is a thin, calcified, fibrillated bone tissue that protects the root's dentine. The cementum is composed of roughly 65 % inorganic material (mostly HA), 23% organic material (collagen type I, proteins, and polysaccharides), and 12% water. Cementum contains thin, plate-like HA crystals with an average dimension of 55 x 8 nm. Cementum thickness is significantly larger at the root apex (50-200 µm) than in the cervical portion of the tooth (10-15 µm) [Bosshardt D. D. et al., 1997].

2.3.4. Pulp

The pulp chamber, which fills the middle section of the tooth, is where the pulp is situated. The nerves in the pulp allow for the detection of sensory input and are responsible for teeth's sensation. The pulp's primary job is to produce dentine [Chandra S. et al., 2008]. Dentine is formed by odontoblasts, which are found on the perimeter of the pulp. Fibroblasts, macrophages, pre-odontoblasts, and T lymphocytes are among all the other cells found in the pulp [Besinis et al., 2015].

3. Oral cavity diseases and diagnosis

3.1. Conventional diagnostic methods

Dental problems are still frequently diagnosed in clinics today, following a set of principles developed by the standard practice in the profession. To review the data and establish the real reason, the dentist will do a thorough oral examination. A full oral exam includes a detailed medical history, x-rays, and sending samples and swabs to a lab for sores or unusual tissue growths. Computed tomography (CT), x-rays, molecular resonance imaging (MRI), and ultrasound are examples of common diagnostic imaging modalities. It can be used to check for unerupted teeth, retained root segments, unanticipated bone cysts, tumors, as well as to confirm the location and morphology of a partly erupted third molar. Blood tests can also be used to confirm a diagnosis of a specific illness, such as anemia, or as a general screening tool. Dental diagnostic casts can be put in a semi-adjustable articulator and used to evaluate occlusion changes in patients. The definitive diagnosis of a problem, no matter how basic or complicated, is only made after the history, clinical examination, and numerous necessary specific investigations. For specific diseases, such as caries or tooth crack syndrome, some of these principles haven't altered in decades. As a result, bringing novel ways to developing a treatment plan for patients while assuring the greatest outcomes has been proven tough. As a consequence, unlike medicine, dentistry has failed to make a significant shift from research lab techniques to clinical practice. Nanotechnology's influence on the diagnosis of dental problems has received relatively little attention from the scientific and clinical sectors.

3.2. Novel nanotechnology-based strategies for diagnosis

Contributions from nanotechnology in dentistry have mostly been produced in three areas over the last two decades: atomic force microscopy (AFM), imaging contrast enhancement, biosensors and biochips [Neel et al., 2015].

3.2.1. AFM and oral biofilms

For the prevention or treatment of biofilm-dependent oral illnesses, a complete picture of bacterial adhesion, the primary factor in bacterial colonization and pathogenicity, as well as bacterial nanomechanics, is required [Chen C. et al., 2014]. Bacteria can attach to other bacteria of the same or other species, as well as to complex surfaces, such as teeth and implants [Subramani, K. et al., 2009; Abe Y. et al., 2012]. AFM [Yang X. et al., 2010] offers a breakthrough in bacterial characterization, as well as assessment of their adherence to various substrates due to its ability to directly interact with and capture living cells without disrupting their shape and characteristics [Pinzón-Arango et al., 2010], [Zhang T. et al., 2011]. A real-time scanning of a live bacterial cell with great sensitivity was made feasible using nanomechanical biosensors and an AFM cantilever [McKendry R. A. et al., 2012]. The docking step is where nonspecific reversible attachments between bacteria and substrate are formed due to van der Waals and electrostatic forces. Bacterial adherence to tooth surfaces fluctuates by species; microbiomes, for instance, have greater adhesion forces than planktonic bacteria.This might refer to the relevance of early adherent bacteria in the development of biofilms [Wessel S. W. et al., 2014]. AFM also provides specific data on the biomechanical interactions of antibacterial drugs with bacterial cells and this could support the development of antibacterial therapies against drug-resistant bacteria.

3.2.2. *Imaging contrast enhancers and oral cancers*

The detection of oral cancer lesions is one of the most major accomplishments of nanotechnology in the field of dentistry. The capacity to scan these lesions is crucial in cancer management and treatment plan development. Structural imaging techniques include conventional diagnostic imaging modalities such as computed tomography (CT), molecular resonance imaging, and ultrasound. As a result, they can support the identification of anatomical patterns as well as provide basic information on tumor location, size, and spread based on contrast levels. However, for cancers and metastases smaller than 5 mm in size, these imaging methods become less accurate in differentiating between benign and malignant tumors [Popovtzer R. et al., 2008; Reuveni T. et al., 2011]. Another application of nanotechnology is the identification of malignancies by the use of near-infrared (NIR) luminous quantum dots (QDs). Due to their dimensional similarities with biological macromolecules, metal and semiconductor nanoparticles in the size range of 2–6 nm are of great interest. QDs can be coupled to biomolecules in the same way as GNPs can. OSCC (head and neck squamous-cell carcinoma) is one of the most prevalent forms of cancer in oral oncology, accounting for around 6% of all cases, an estimated 650,000 new malignancies and 350,000 cancer deaths worldwide each year [Parkin D. M. et al., 2005; Seiwert T. Y. et al., 2005]. Due to the lack of specificity in existing medicines, selectively targeting squamous cancers has been a long-standing issue. Yang et al [Yang C. C. et al., 2011] utilized cell-penetrating peptides to successfully combine NIR QDs for cancer diagnosis in 2011. They used a novel method to mark OSCC with QD conjugates through endocytosis for visually in vivo imaging on a mouse model.

3.2.3. Biochips and salivary biomarkers

The idea of nanobiosensing was created to enhance medical diagnoses. A biosensor is defined as "an analytical device which incorporates biologically active element with an appropriate physical transducer to generate a measurable signal proportional to the concentration of chemical species in any type of sample." Clark and Lyons first presented biosensors in 1962, and since then, considerable research and development has been conducted using multiple detection methods, with potential applications in the health industry [Touhami et al., 2014]. Nanobioreceptors, which incorporate nanotubes, nanowires, and nano-dots in the sensing assembly, were created to improve the biorecognition procedure and overall bioreceptor function [Sagadevan and Periasamy, 2014]. The top down, bottom up, or molecular self-assembly techniques are used to generate nanoparticles [Foster et al., 2005]. Nanobiosensors are also mechanically responsive, meaning they can be readily moved and deformed in response to extremely low pressures, making them sensitive enough to detect chemical bond breakage [Arlett et al., 2011]. This is due to the nano size effects, since the large surface area to core ratio enhances the biosensor's sensitivity, electrical characteristics, and reaction time. Metallic nanoparticles such as gold, silver, platinum, and palladium are widely used in nano biosensor transduction/bioreception systems because they can quickly react with most biological substances without interfering with their function [Sagadevan and Periasamy, 2014]. The potential of gold nanoparticles to increase the electrical signal when the bio receptor detects the analyte at extremely low concentrations has been extensively explored. For example, gold nanoparticle altered DNA by receptor recognizes a concentration of an analyte as low as 0.05 nm [Su et al., 2003]. Its great sensitivity is important in cancer detection since nanobiosensors, as opposed to traditional ones, can identify cancer cell chemicals at very early stages and at low concentrations [Touhami et al., 2014; Foster et al., 2005]. The introduction and development of biochips is probably one of the most intriguing uses of nanotechnology in oral health diagnostics [Li Y. et al., 2005]. Biochips are tiny devices that include a set of miniature sampling sites (microarrays). The major benefit of microchips over more traditional techniques is that they can run several tests at the same time, resulting in increased efficiency and speed. For analyte detection, these instruments have exceptional sensitivity and specificity, even down to single molecules. Gau and Wong proposed in 2007 that the oral fluid nanosensor test to be used for point-of-care multiplex detection of salivary biomarkers for malignancy [Gau V. et al., 2007]. Carbon nanotubes were also used to identify cancer cells that were circulating in the body. Layer-by-layer assembly was used to organize the carbon nanotubes, which were then chemically coupled to antibodies of a particular carcinogenic marker that selectively attaches to cancer cells, resulting in a more efficient and helpful diagnostic tool [Hasanzadeh and Shadjou, 2016]. Another biochip effort is the work of Weigum et al on the creation of a diagnostic cytology-on-a-chip technology that identifies premalignant and cancerous cells quickly and with great sensitivity and specificity [Weigum S. E. et al., 2010; Weigum S. E. et al., 2007]. They created a sensor for OSCC diagnostics that combines several laboratory procedures onto a microfluidic substrate in three phases. At the pictogram per milliliter level, Christodoulides et al. [Christodoulides N. et al., 2005] developed an electronic microchip-assay to detect C-reactive protein (CRP), a biomarker for inflammation related to periodontitis. CRP is a systemic biomarker that is produced in response to inflammatory stimuli and may be used to distinguish between a healthy condition and periodontitis [Pasceri V. et al., 2000; Joshipura K. J. et al., 2004; Pederson E. D. et al., 1995; Loos B. G. et al., 2000].

4. Oral cavity diseases and treatments

4.1. Conventional treatments

4.1.1. Dentin Hypersensitivity

Enamel in the crown and cementum in the root protect the dentin from external stimulation. The loss of this protective layer exposes the below dentinal tubules, modifying the fluid pressure hydrodynamics of the fluid inside the dentinal tubules and is thought to be the cause of dentin hypersensitivity [Neel et al, 2015]. Dentin hypersensitivity is defined as a brief, acute pain that arises from the exposed dentin in reaction to thermal, evaporative, haptic, osmotic, or chemical stimuli and cannot be attributed to any other dental problem or disorder [Addy M. et al., 1992; Holland G. R. et al., 1997]. Dentinal tubules occlusion is the most prevalent conservative technique to managing dentin hypersensitivity, and it involves the use of chemicals capable of producing precipitation and/or entering dental tubules and blocking external stimuli, resulting in a painless treatment for this issue. Other therapeutic options for dentin hypersensitivity include topical treatments of pastes containing calcium, sodium, potassium, strontium, nitrate, and fluoride ions, as well as restorative materials such as oral laser applications used to occlude the open dentin tubules.

4.1.2. Endodontics

Even though bacteria have been shown to resist conventional disinfection techniques during endodontic treatment [Shrestha A. et al., 2009], the failure to thoroughly disinfect the root canal system has been linked to the root canal system's anatomic complexity and dentin structure [Nair P. N. et al., 2005]. The therapy of an infected root canal includes chemomechanical root canal disinfection as well as medication between the appointments [Renugalakshmi et al., 2011]. Moreover, the traditional CaOH treatment may have an effect on mechanical dentin characteristics by reducing flexural strength over time [Sharan et al., 2017].

4.1.3. Periodontics

Periodontal treatment procedures are divided into three stages: nonsurgical (phase I), surgical (phase II), and supportive (phase III). Phase I therapy includes the patient's oral hygiene applications as well as the clinician's interventions, such as mechanical instrumentation on the tooth and root surfaces to eliminate microbial etiologic factors and the release of predisposing factors. The surgical phase of periodontal treatment, which includes resective and/or regenerative techniques, is known as phase II therapy. In order to maintain and improve the benefits of periodontal treatments, Phase III comprises patient recall visits at predetermined intervals. Moreover, achieving an effective local antibiotic concentration via parenteral delivery is challenging in the treatment of periodontal infections, where vascularity is impaired, direct distribution of an active antimicrobial agent to the infection site provides a feasible alternative therapy [Greenstein G. et al., 1998].

4.2. Novel nanotechnology-based strategies for treatment

4.2.1. Dentin Hypersensitivity

According to research, bioactive glass nanoparticles promote the production of apatite in dentin, suggesting that it might be utilized to treat dentin hypersensitivity. Dentin tubule occlusion may lessen or eliminate hypersensitivity by constraining the dentinal fluid flow. The higher surface area associated with nanoparticles translates to more successful ion release, thus, the procedure of remineralization of dentin tubes is faster when utilizing products with bioactive glass nanoparticles [Sharan et al., 2017]. Hypersensitivity treatments that can develop large quantities of mineral particles within dentin tubules are possibly helpful [Cherng A. M. et al., 2004]. The tubule apertures are tiny (about 5 µm in diameter) and are sometimes partly covered by a "smear layer," thus closing the tubule is difficult [Brännström M. et al., 1986]. The smear layer is a microcrystalline debris layer that is amorphous and generally smooth, with a featureless surface that cannot be seen with the naked human eye [Pashley D. H. et al., 1984]. Dentifrice, slurry, and sealants are examples of nanodrug delivery methods designed to treat dentinal hypersensitivity. Because the nano particles may penetrate the tubules, nanoCaF_2 can be utilized as a slurry for therapy [Sun L. et al., 2008]. However, the therapy is more successful when nano CaF_2 is coupled with calcium phosphate, which can create more F^-containing apatitic compounds that are more stable in the mouth under both ordinary and cariogenic circumstances [Wefel J. S. et al., 1984], [White D. J. et al., 1994] than calcium phosphate alone [Brännström M., 1986]. Using mesoporous silica as a nano carrier for CaO, a novel nanomaterial nanoCaO mesoporous silica (NCMS) with sizes smaller than 37µm has been created. When NCMS were combined with 30% phosphoric acid, it showed a significant reduction in dentin permeability in vitro. When NCMS and phosphoric acid were combined, a rapid dissolving response occured, resulting in the release of a substantial number of calcium ions. After passing through the dentinal tubules, the Ca^{2+} and $HPO_4{}^{2-}$ ions eventually produced $Ca^- HPO_4.2H_2O$ precipitates, which blocked the tubules owing to the increased pH [Chiang Y. C. et al., 2010]. To reduce dentin hypersensitivity, biomimetic CHA nanocrystals have been tested in the form of dentrifrice. The possible desensitizing action of CHA is attributed to the gradual closing of dentin tubular holes with plugs after a few minutes until the regeneration of a mineralized layer starts within a few hours [Orsini G. et al., 2010]. Lately, the transfer of nano-structured bioactive glass (BAG) particles with glycerol was seen to be effective in achieving an immediate reduction in dentin hypersensitivity and preserving it for at least a week, implying that the BAG's occluding layer is tenaciously bound to the dentin surface [Mitchell J. C. et al., 2011]. Silver staining was utilized to assist occlude the open tubules and minimize dentin sensitivity when GNPs were discovered to be easily deposited on the inner dentinal tubule walls. Laser irradiation enhanced the agglomeration of nanoparticles to occlude the uncovered tubules after brushing the opening tubules with highly concentrated GNPs [Liu M. H. et al., 2007]. Additionally, by selecting and accurately occluding the tubules in minutes utilizing biological materials, dental nanorobots provide a rapid and permanent treatment for dentin hypersensitivity [Freitas R. A. et al., 2000].

4.2.2. Endodontics

In an attempt to disinfect root canals, many nanoparticles, like zinc oxide and chitosan, have been added into root canal sealers, either alone or in combinations. They had no impact on the flow of the sealers, but they improved the antimicrobial activity, as evidenced by a substantial decrease in Enterococcus faecalis attached to treated dentin [Kishen A. et al., 2008]. Metal oxide nanoparticles, such as magnesium oxide nanoparticles, have shown promising antibacterial activity in both in vitro and ex vivo studies. Magnesium oxide nanoparticles (5 mg/L) shown a statistical significance in long-term impact in the removal of E. faecalis adhering to root canal dentin as compared to the standard NaOCl solution (5.25 %) [Monzavi A. et al., 2015]. Nanoparticles are being used to improve the disinfecting characteristics of root canals. The antibacterial characteristics of bioactive glasses are based on their ability to raise the pH of aqueous suspensions [Hench L. L. et al., 1984] due to the exchange of sodium ions and protons in an aqueous environment [Stoor P. et al., 1998]. Bioactive glass has been shown to have a broad range antibacterial action in various oral microbes, justifying its usage as an intracanal therapeutic in endodontic treatment [Waltimo T. et al., 2007]. The rise in specific surface area of bioactive glass nanoparticles enhances the area of active ion release, which improves the material's antibacterial capabilities. Nevertheless, in a direct contact model, particles of 20–50 nm bioactive glass enhanced the antibacterial activity against E. faecalis [Dong A. et al., 2011]. Silver nanoparticles have been used in a wide range of applications over the last decade, ranging from electronics to antibacterial/antifungal agents in biotechnology and bioengineering. Another method of root canal disinfecting being researched is nanoparticle-based antimicrobial photodynamic treatment. Using transmission electron microscopy (TEM), Pagonis et al. [Pagonis T. et al., 2010] investigated the in vitro effects of poly(lactic-co-glycolic acid) (PLGA) nanoparticles coated with the photosensitizer methylene blue (MB) and light against Enterococcus faecalis. They concluded that PLGA nanoparticles loaded with photoactive medicines might be a potential adjuvant in antibacterial endodontic treatment. The use of nanoparticles may increase the surface area between the dentin and the obturating substance, resulting in improved adaptation. One of the most recent nanoparticles utilized in endodontic treatment is bioactive glass 45S5. It contains amorphous nanoparticles ranging in size from 20 to 60 nm. Bioactive glass 45S5, like CaOH, has been utilized to heal damaged front teeth with an open apex. CaOH treatment may have an effect on mechanical dentin characteristics by lowering flexural strength over time. Marending et al. [Marending M. et al., 2009] utilized nano particle bioactive glass 45S5 suspensions as a dressing material in injured front teeth with open apices and compared it to CaOH. The results indicated a 35% reduction in dentin mean flexural strength values with CaOH and a 20% decrease with bioactive glass 45S5, indicating that the latter was better. After setting in an extracted tooth model, Chen et al. [Chen Z. L. et al., 2007] utilized a novel root canal filling sealer largely consisting of nanohydroxyapatite crystals in 279 nm in their investigation. When compared to two other materials, the sealer exhibited better antibacterial action and also negligible micro leakage. Saghiri et al. investigated the physiochemical characteristics of a nano-modified MTA. They came to the conclusion that increasing the surface area of powder by nanodispersion can shorten setting time and enhance micro hardness [Mehrvarzfar P. et al., 2011].

4.2.3. Periodontics

Due to its sufficient mechanical characteristics and composition resemblance to bone tissue, some authors have documented the use of hydroxyapatite as a drug carrier and propose that it might be utilized as a bone substitute material [Queiroz A. C. et al., 2003], [Rauschmann M. A. et al., 2005]. The chemical compositions, porosities, and surface areas of microspheres produced from hydroxyapatite nanocrystallites aggregated offered sufficient conditions for the prolonged release profile of amoxicillin, amoxicillin and clavulanic acid, and erythromycin. As a result, these microspheres might be viewed as a viable alternative method for carrying antibiotics and enhancing bone regeneration while treating periodontitis [Ferraz M. P. et al., 2007]. In periodontics, nanoparticles are currently being recognised as medication delivery platforms [Salvadori B. et al., 2006]. It is suggested that nanoparticles can be administered selectively to certain locations or cells. Localized administration of growth factors (GFs) to the periodontium is a new innovative therapeutic technique that has the ability to repair both the periodontium and the bone [Suh W. H. et al., 2009]. Several controlled release strategies are being investigated in order to retain GF bioactivity and regulate GF release, including the administration of GFs via micro- or nanoscale particles, prefabricated scaffolds, injectable gels, and composites. Nanoparticles in the periodontal pocket, according to Iijima and others, could be a drug-delivery system that lowers the dosing frequency while also allowing for effective active agent aggregation in the target areas over a long period of time while maintaining an effective rate of drug release [Iijima S. et al., 1991], [Reneker D. H., 2008]. Because of their biocompatibility, polymeric esters based on Poly(D,L-lactide) acid (PLA), poly(glycolic) acid, and poly(D,L-lactide-coglycolide) acid (PLGA) have been a major focus in the creation of nano/micro particles encapsulating medicinal therapeutics in controlled release applications [Hu H. et al., 2004]. Shi et al. [Shi X. et al., 2007] studied triclosan-loaded nanoparticles with a diameter of less than 500 nm to develop a new intrapocket delivery method for periodontal disease therapy, that has also been shown to be effective against a variety of bacteria that cause plaque. The antibacterial activity of PLGA nanoparticles and PLGA nanoparticles with polyethylene glycol (PEG) nanoparticles (PEGylated PLGA nanoparticles) that include minocycline [Kalbacova M. et al., 2007] was found to be higher than that of the free drug, presumably due to greater nanoparticle penetration into bacterial cells and better distribution of minocycline to the target site. Due to its capabilities of bone growth through osteoconduction and osteoinduction, bioactive glasses have been increasingly used in dentistry for the management of periodontal problems. Periodontal ligament cells in close contact with bioactive glass nanoparticles showed enhanced proliferating and cell survival, as well as an increase in alkaline phosphatase activity, according to recent research [Carvalho et al., 2013]. The bioactive glass nanoparticles have been shown to induce cell proliferation in periodontal ligament cells, particularly cementoblasts, demonstrating that they might be used to regenerate periodontal tissue. Researchers have created a bio membrane that promotes direct bone regeneration by electrospinning a suspension of poly (L-lactic acid), MWNT, and HA.

The membrane was shown to enhance desirable periodontal ligament cell (PDLC) adhesion and proliferation by 30% while reducing less desired epithelial cell proliferation [Mei F. et al., 2009], according to the researchers. Nano crystalline HA particles of Ostims, which are available on the market in a syringe as a paste (Heraeus Kutzer, Hanau, Germany), consist of 65 % water and 35% nanoscopic HA particles and have been utilized for augmenting operations in osseous deformities [Thorwarth M. et al., 2005]. Furthermore, the sustained release of oligonucleotides from chitosan nanoparticles might potentially be useful for locally treating periodontal disorders [Sharan et al., 2017].

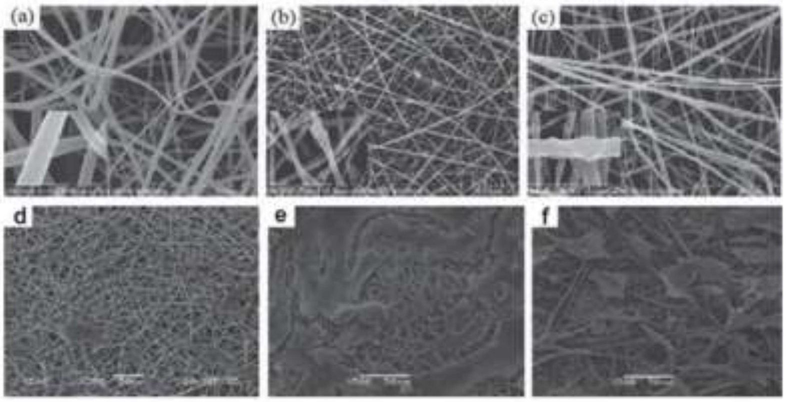

Figure 3. SEM pictures of PLLA, PLLA/HA, and PLLA/MWNTs/HA membranes for directed tissue regeneration (a, b, c). Human Periodontal Ligament cells (PDLc) growth and morphological responses during culture on (a) PLLA, (b) PLLA/HA, and (c) PLLA/MWNTs/HA, as shown by SEM. F. Mei et al., Biomacromolecules 8, 3729, reprinted with permission (2007). American Chemical Society, 2007.

4.2.4. Prosthodontics

Silver (Ag) is well-known for its antibacterial capabilities and has a long history of use in medicine, with a low toxicity profile and well-tolerated tissue response. When nanosized Ag^+ is integrated into the tissue conditioner or liner with prosthesis, it helps to reduce the microbial burden in the oral cavity while also ensuring the health of the tissues on which the prosthesis rest [Samuel U. et al., 2004]. Carbon/graphite fiber reinforced poly methyl methacrylate (PMMA) denture resin is a key application for meeting biomechanical criteria. To improve the flexural strength and fracture toughness of denture base materials, [Larson W. R. et al., 1991; Holston et al., 2007]

MWNT (0.1–1.0 wt %) has been added into PMMA. It strengthens the PMMA matrix prior to fracture initiation and stops/delays early crack development [Klapdohr S., 2005]. However, one significant clinical issue with carbon material infused items in oral use is their poor esthetics due to their black hue. To fulfill the necessary esthetic criteria, many researchers have proposed the use of additional inorganic additives such as sol–gel-based opalescent fillers or chromophoric xerogel coloring particles. Another possibility is to employ CNT/CNF-reinforced ceramic to increase fracture toughness. Silica nanoparticles (e.g., Aerosil (Degussa), HDK (Wacker), Cab–O–Sil (Cabot Corp.)) have been suggested as nanoscale fillers to improve dental resins throughout the previous decade [Nagano F. et al., 2009]. They can increase the end product's rheological behavior, scratch/abrasion tolerance, and surface hardness [Tran N. et al., 2009].

4.2.5. Restorative Dentistry

When it comes to crystal size, nanoscale particles are more comparable to natural tooth. Furthermore, the nanoscopic particles' large surface area would allow for effective mechanical interaction with the polymeric matrix. In addition to smooth surface effects and volume effects, [Arcís R. W. et al., 2002] nano fillers provide excellent optical characteristics. Furthermore, as contrasted to minifilled composites, they have a greater contact surface with the organic phase, which improves material hardness [Mota E. G. et al., 2006]. A nanofilled resin-modified glass ionomer cement (GIC) was recently created by 3M ESPE Ketac N100 (KN) with particle size 100 nm compared to 30 µm in standard GIC. KN restorative improves appearance while also providing the benefits of glass ionomer chemistry, like fluoride release. In comparison to other commercially available dental materials, the use of nanofillers improves surface wear and shine [Bala O. et al., 2012]. Another nanofilled resin-modified glass ionomer composite (Equia system) with inorganic nanofillers was recently created. The fillers are made of silica powder with a mean particle size of 40 nm, and because they are uniformly distributed within the solution, the restoration has a greater degree of wear resistance. The nanofilled particles' penetration and dispersion protects the restoration and margins while increasing hardness and resistance to bending and wear. Additionally, because it prevents the breakdown and disintegration of the material's outermost layer, the nanofilled resin keeps the polished surface of the repair for a long time. The esthetic look has also been enhanced using nanofilled resins, which offer the filling the same radiance as a real tooth. Moshaverinia et al. [Moshaverinia A., 2008] produced nano-HA and FA and integrated them into commercial glass ionomer powder (Fuji II GC). CS, DTS, and BFS were all greater than the standard GIC. A commercial glass ionomer powder (Riva SC) containing YbF3/BaSO4 nanoparticles is available in various concentrations (1, 2, 5, 10, 15, and 25% (w/w)). The inclusion of these nanoparticles leads in a substantial reduction in the working and setting time of cements, indicating a strong engagement of the nanoparticles with the glass ionomer matrix [Prentice L. H. et al., 2006]. More efforts have been directed to dental nanocomposite during the last decade, with the expectation that modern nanocomposites with ceramic nanofillers will offer improved esthetics, strength, and longevity. A variety of calcium phosphates (CaPs) have been explored as fillers in mineral releasing dental composites, including hydroxyapatite phosphate (HAP), anhydrous calcium phosphate (ACP), tetra calcium phosphate (TTCP), and dicalcium phosphate anhydrous (DCPA). Skrtic et al [Skrtic D. et al., 1996] shown that hybridization of ACP fillers with agents such as tetraethoxysilane (TEOS) or $ZrOCl_2$ solution enhanced the mechanical characteristics of composites containing ACP fillers. To assist enhance the durability of composite restorations in the oral cavity, functionalized single walled nanotubes (SWNT) have been added to dental composite in order to boost its tensile strength and Young's modulus. The addition of functionalized SWNT substantially improved its flexural strength by taking in more stress [Zhang F. et al., 2008]. However, further effort in development of CNT-reinforced composite resin has been hampered because of its dark color primarily from CNT, being a major drawback for esthetic composite resin. Because of their remarkable regeneration capabilities in mineralized tissues, bioactive glass nanoparticles have been employed in research regarding the particular impacts of dentin remineralization for decades. The use of bioactive glass nanoparticles, because the nanoparticles' large specific surface area may aid in the dissolution of ions from the glass and therefore expedite dentin mineralization [Vollenweider M. et al., 2007]. Marelli et al. demonstrated that after 30 days of treatment with bioactive glass nanoparticles, there was a significant increase in the mineral content of the dentin samples [Marelli B. et al., 2011]. Furthermore, bioactive glass nanoparticles can be utilized in the preparation of teeth for less invasive cavity preparation. The remineralization of dentin tubes is accelerated when products containing bioactive glass nanoparticles are used, since the increased surface area associated with nanoscale particles results in more effective ion release. The incorporation of bioactive glass nanoparticles into a polymer matrix replicates the structure of real bone, which comprises nanoscaled-size HA crystallites [Sharan et al., 2017].

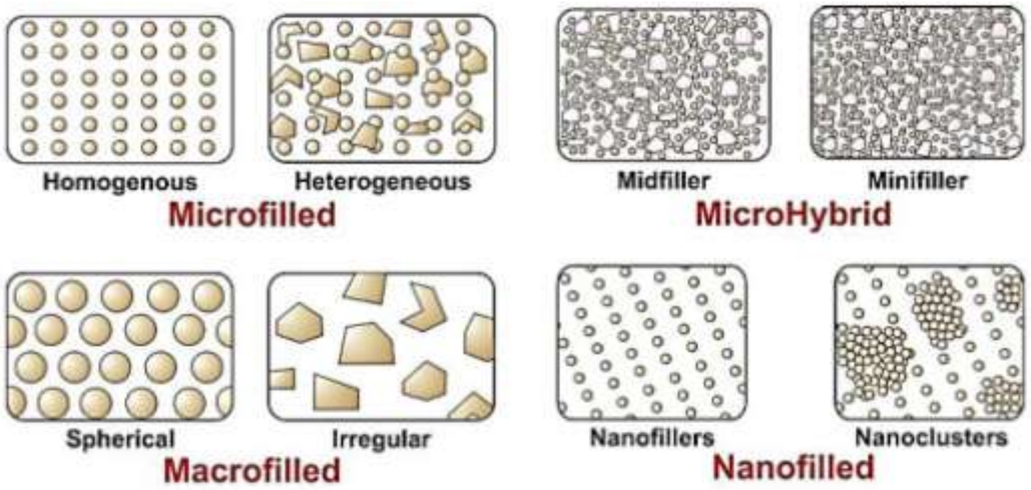

Figure 4. The particle size and structure are used to classify dental composites.

4.2.6. Oral Surgery

Nanotechnology is significant because it produces materials that resemble the inherent nanostructure of live human tissue. It is crucial to remember that bone is a natural nanostructured composite material consisting of tightly linked inorganic (bone apatite) and organic components (mainly collagen). Materials with nanoscale structures are obviously options for production of optimum bone implants and graft materials for osseous regeneration due to the hierarchical architecture of bone, with the lowest level of osseous materials in the nanoscale range. Manufactured bone scaffolds that imitate bone structural anatomy and can offer structures for new bone development have been examined. Authors discovered that nanocomposites containing ultrashort SWNT had greater compressive strength than poly(propylene fumarate) scaffold, showing that incorporating CNT into a highly porous polymer scaffold that resembles natural trabecular bone structure can strengthen it. Knitted composite has the potential to be utilized as a scaffold for bone replacement. Bioactive glasses are frequently utilized in bone repair. As a result, many researches on its applicability in oral and craniofacial surgery have been conducted. Bone tissue is a combination of organic and inorganic components arranged in a global architecture with dimension scales ranging from micro to nano. As a result, the use of glass nanoparticles in bone transplants has the dual goal of enhancing mechanical characteristics while also integrating nanotopographic qualities that imitate bone features. When evaluating bio ceramics for bone tissue engineering, it is critical to evaluate the materials' biodegradability (resorption) as well as mechanical strength. Porous hydroxyapatite (HA) and tricalcium phosphate (TCP), for instance, have been found to have high osteoconductive characteristics but low biodegradability [Edwards S. L. et al., 2009]. Nanotechnology has been proven to have a significant role in the creation of porous bioceramics with high mechanical strength as well as improved bioactivity and resorbability. Lately, the goal for tissue engineering applications has been to create nanosized HA with characteristics similar to those of real bone. Surface grain size, pore size, and wettability of nanophase HA can be adjusted for optimum osteoblast adhesion and long-term osteoconductivity [Kumta P. N. et al., 2005]. Angstrom Medica's NanOss bone void filler was the first nanotechnology medical device to be licensed by the US Food and Drug Administration in 2005. It is a novel structural biomaterial that is very osteoconductive and remodels into bone tissue over time, having applications in sports medicine, trauma, spine, and general orthopedics. It's the first material that mimics the architecture, content, and performance of human bone, according to the researchers. NanOss Bioactive Loadeds, a prefilled mixing syringe with NanOss mixed with a collagen-based biopolymer intended to be used in minimally invasive orthopedic surgical procedures, as well as NanOss Bioactive 3D bone graft that uses nanocrystalline HA suspended in porous gelatin-based foam to promote bone growth in the posterolateral region, are currently commercially available from Pioneer Surgical Technology Inc. [Aizenberg J. et al., 2005]. In addition to nano-HA preparations, some researchers have created nano-HA collagen composites (nano-HA/collagen) in an attempt to resemble real bone even more precisely [Chang M. C. et al., 2001; Zhang W. et al., 2003; Du C. et al., 2000]. In vitro investigations have demonstrated that this composite promotes osteoblastic cell proliferation and the production of new bone [Liao S. S. et al., 2004; Z. Chen et al., 2011]. The nano-HA/collagen-based scaffolds have now been utilized effectively in numerous clinical cases requiring various types of bone repair, with wound repair and no abnormalities discovered during long-term follow-up in local and systematic studies [Gkioni K. et al., 2010]. Because of hydrogels' natural capacity to expand in aqueous environments and allow the passage of enzymes and nutrients to and through various supporting ceramic scaffolds, there is growing interest in the use of hydrogels with ceramics in tissue engineering [Tamura H. et al., 2011; Chesnutt B. M. et al., 2009]. Chitosan, a linear polysaccharide made up of randomly dispersed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit), is frequently utilized in bone tissue regeneration [Tripathi A. et al., 2012]. Metallic nanoparticles such as copper and zinc have been used in the development of bone tissue engineering materials. The addition of nano copper and zinc to chitosan/nano-HA scaffolds has recently been demonstrated to dramatically enhance swelling, decrease breakdown, augment protein adsorption, and boost antibacterial activity [M. Peter et al., 2010]. These composites have been found to be non-toxic to osteoprogenitor cells and, as a result, may offer benefits over chitosan nano-HA scaffolds. A chitosan gelatin nano-bioactive glass ceramic composite, in particular, has been conceived and produced. It has been found to have several beneficial characteristics for usage in alveolar bone tissue repair [Sidqui M. et al., 1995]. Another very biocompatible substance with a lengthy clinical experience as a synthetic ceramic material is calcium sulfate (CS). One of the most basic synthetic bone-like grafts is the hemihydrate form of CS, often known as plaster of Paris. It is a strong osteoconductive scaffold that promotes bone repair [Bateman J. et al., 2005]. When treated with platelet-derived growth factor (PDGF-BB), CS has been found to absorb the growth factor and stimulate increased human osteoblastic cell proliferation in vitro [Park Y. B. et al., 2011]. Because it is biocompatible, hydrophilic, and biodegradable under normal physiological circumstances, alginate, a natural polysaccharide derived from brown sea algae, has been widely utilized in tissue engineering [Qi X. et al., 2009]. In the presence of certain divalent cations (e.g., Ca21) in low concentrations, it produces stable hydrogels [Allan I. et al., 2001]. Currently, a separate NanoCS product is available for clinical usage. This substance is commercialized and sold as NanoGens (Orthogen) and has received clinical approval in the United States [Sharan et al., 2017].

4.2.7. Oral cancers

GNPs were developed as a radiosensitizer in cancer radiation treatment, and they triggered cell death following gamma radiation. GNPs' radiosensitivity is proportional to their size [Zhang X. D. et al., 2012]. Nanodelivery platforms (e.g., naringenin-loaded nanoparticles in 7,12-dimethylbenz(a)anthracene) [Sulfikkarali N. et al., 2013] have been employed in cancer treatment to improve the stability and targeted and controlled delivery of chemotherapeutics. In photothermal therapy, which is accomplished using a plasmonic probe and NIR light, which has recently been proposed as a minimally invasive method for the treatment of deep tissue malignancies such as OSCC [Hannig M. et al., 2012]. GNPs were employed as a plasmonic nanoprobe in this treatment because of their increased NIR absorbance and capacity to transform absorbed light into heat energy. Because of its nanodimension, this probe is easily absorbed by targeted tissue, has little toxicity, and can be removed from the body after treatment. Coating the gold nanostructures with temperature and pH-responsive polymers, such as poly(N-isopropylacrylamide-co-acrylic acid), has been tried in order to improve their biocompatibility. RGD (arginine-glycine-aspartate) and NLS (nuclear localization sequence) peptide-conjugated nuclear targeting gold nanostructured materials can be easily caught by cancerous cells (eg, OSCC), disrupting their functions (DNA damage, induces cytokinesis arrest in cancer cells) and promoting cell apoptosis and necrosis [Kang B. et al., 2010]. The content and form of these nanostructures (for example, nanorods, [Hannig M. et al., 2012] nanospheres, and nanocages [Mackey M. A. et al., 2013] would boost their apoptotic action even more. Gold nanocages disrupted biological processes while also producing reactive oxygen species, which killed malignant cells

[Kang B. et al., 2010]. Iron-core–gold shell nanoparticles have been found to selectively suppress cancer cell proliferation via mitochondria-mediated autophagy [Wu Y. N. et al., 2011]. Nanotechnology has been extended to provide an effective treatment of the breakthrough pain associated with cancer, in addition to treating tumors. A nanodelivery transbuccal device was designed to deliver opioid analgesia to the target tissue quickly and efficiently with a constant and regulated diffusion. As a result, it reduces the danger of patients overdosing while also protecting them from needle placement. It also prevents the drug's enzymatic and spontaneous deterioration that occurs when it's taken orally [Sprintz M. et al., 2005].

4.2.8. Orthodontics

Nanomaterials and nanorobots have begun to be used in a variety of disciplines, including healthcare. It is certain that nanotechnology applications will improve rapidly in various fields of dentistry [Oh et al., 2014], such as orthodontics, which is one of the most significant elements of dentistry. With the use of nanotechnology, nanoorthodontics is delivering not only new solutions, such as improved instruments for diagnosis and management of orthodontic issues, but also better techniques. The following are the several types of nano-orthodontic structures and systems [Maheshwari et al., 2014 ; Subramani et al., 2013]:

a. Orthodontic nanocomposites

Nanocomposites and nanoionomers are biomaterials that have been created using nanoparticle technology. In composite matrix and glass ionomer cements, nanosized filler particles have been incorporated. Nanofillers may be made using nanoparticle technology techniques such as flame pyrolysis, flame spray pyrolysis, and sol gel procedures [Maheshwari et al., 2014]. The use of nanofillers into orthodontic composites clearly alters the mechanical characteristics of the materials. Bond failure caused by regular actions like as chewing or biting is one of the most serious difficulties for orthodontic mechanics. Bond failure results in more time spent in the chair and, of course, more money being spent. To overcome the issues described above or antibacterial problems, certain nanotechnological items like silver nanoparticles are now incorporated to orthodontic composites. To increase the antibacterial efficacy of orthodontic composites, nano-zincoxide and nano-chitosan particles are added. The efficacy of these composites is evaluated at various particle levels. In clinical settings, the presence of orthodontic mechanisms in the mouth increases the risk of cavities due to the difficulties of maintaining appropriate oral hygiene and changes in microbiota, particularly white spot lesions surrounding the brackets. As a result, nanocomposites with antibacterial properties are favored for reducing the risk of cavities during orthodontic treatment [Mirhashemi et al., 2013].

b. Nanoadhesives in orthodontics

One of the most common causes of orthodontic treatment delays and emergencies is bracket and tube debonding. Nanoparticles can also be found in composite materials and glass ionomer cement, which are used as adhesive agents in orthodontics to secure orthodontic brackets and bands to the surface of teeth. Improved mechanical characteristics and fluoride release, as well as prevention of bacterial adhesion and cavities during orthodontic therapy, are the goals of these novel materials [Subramani et al., 2013].

c. Nanocoated orthodontic archwire

Metal nanoparticles are coated on the archwire surface as a result of nanotechnological advancements. The coating of the archwire surface with Ni film lowers friction on the archwire surface. Inorganic fullerene-like tungsten disulfide nanoparticles can be coated on orthodontic wires. These nanoparticles have a dry lubricatory impact on the surface of the archwire and can minimize friction forces in orthodontic mechanics [Redlich et al., 2008; Sivaramakrishnan and Neelakantan, 2014]. Sandvik nanoflex is a newly designed stainless steel archwire that uses nanotechnology in dentistry. This archwire is stronger than ordinary wires and has improved characteristics such as deformability, corrosion resistance, and surface texture [Patel et al., 2014; Robert and Freitas et al., 2010; Dalai et al., 2014]. To treat orthodontic malocclusions, several methods are employed and various mechanical solutions are examined. Friction is an essential element at both the beginning of the treatment on the leveling and alignment phase and the conclusion of the treatment on the space closure phase, thus the degree of friction force has a direct impact on the therapeutic efficacy. Lower friction force allows for a faster treatment procedure, which saves money and time. Reduced friction can also assist to minimize undesirable side effects of orthodontic therapy, such as anchoring loss and root resorption. In low-friction situations, light force can be employed [Sivaramakrishnan and Neelakantan, 2014; Bhat et al., 2013].

d. Shape-memory nanocomposite polymer for orthodontic wires

Esthetic orthodontic wires built of shape-memory nanocomposite polymer could be a future application of nanotechnology in orthodontics. These materials should be able to revert to their previous state when exposed to particular stimuli (heat or light), which could alter tooth mobility [Subramani et al., 2013].

e. Nanocoatings for friction reduction

Nanoparticles can be used to create coatings for orthodontic archwires in order to reduce friction caused by orthodontic movement [Abiodun-Solanke et al., 2014].

f. Nanotechnologic orthodontic brackets

When hard alumina nanoparticles are combined with polysulfane, the result is a product with high strength, low friction, and excellent biocompatibility. Orthodontic brackets are a critical component of orthodontic mechanics because they convey the archwire forces to the teeth during orthodontic therapy. They also have appropriate tip and torque settings. As a result, their design is critical to the outcome of orthodontic therapy. Brackets are utilized from the start through the finish of active orthodontic treatment. That is, their strength, friction, biocompatibility, and corrosion resistance are all critical elements to consider.

g. Orthodontic nanorobots and furtherance

Nanorobots are the most significant topic in nanotechnology, and they will revolutionize the way diverse applications, such as orthodontic treatment, are done. Nanorobots have diameters ranging from 0.5 to 3 μm and component sizes ranging from 1 to 100 nm [Dalai et al., 2014]. A nanorobot is made up of two basic components: A robot arm with a biocompatible glycocalyx-coated diamondoid material with molecular sorting rotors. A camera, payload, capacitor, and a swimming tail are among the other components. Because of their functional specialization, additional elements such as sulfur, hydrogen, nitrogen, oxygen, fluoride, and other lightweight elements can be introduced to nanorobots [Dalai et al., 2014; Bhat et al., 2013; Kumar et al., 2011]. Nanorobots can be powered with either local glucose and oxygen or external sonic energy. Computers can communicate with nanorobots via broadcast-type acoustic signals, or the nanorobot can be controlled by an onboard preprogrammed nanocomputer [Boomi and Prabu, 2013]. These tiny robots can locate the proper cells by examining their antigens [Dalai et al., 2014; Babel and Mathur, 2011]. These nanotechnologic nanorobots, called orthodontic nanorobots" in the future, will be employed in orthodontic therapy. Nanorobots can be added to mouthwash or toothpastes to clean the surface of the teeth of undesirable bacteria during the day, perhaps lowering the risk of cavities [Ozak and Ozkan, 2013]. When examining the primary functional parameter, it is important to remember that the main medication for orthodontic treatment is the force that creates the tooth. Nanotechnology in dentistry can cause movement and, in certain cases, bone abnormalities. These processes involve very complicated biological activity generated by many bodily systems such as the immune, circulatory, skeletal, and muscular systems. Orthodontic nanorobots may be designed to manipulate periodontal tissues such as the periodontal ligament, cementum, alveolar bone, and gingiva, allowing for quicker and more pleasant orthodontic motions [Patel et al., 2014; Chandki et al., 2012; Freitas Jr., 2000; Jan et al., 2014]. The form and size of orthodontic bones and cartilages, such as the maxillary bone and temporomandibular condyle cartilage, can also be altered by these nanorobots. They can also alter the size and form of soft tissues such as lips and connected gingiva [Kohli and Martin, 2003]. Nanomaterials can also be used as skeletal tissues by nanorobots [Bozec and Horton, 2006]. It is apparent that these future plans can be readily improved. Orthodontic nanorobots will fix all sorts of orthodontic discrepancies in minutes or hours [Sivaramakrishnan and Neelakantan, 2014].

h. *Biomems for maxillary expansion and orthodontic tooth movement*

Biological microelectomechanical system (BioMEMS) are microcircuits that contain electric motors and generators for applying linear or rotational movement to a biological substrate. BioMEMS can mimic them at the nanoscale, implying that electrical circuits might be utilized to aid orthodontic movement. Electrical stimulation has been shown to hasten bone remodeling in animals, according to research. BioMEMS might enable enzymatic movement with the use of a microbattery if implanted in the gingiva near to the alveolar bone. This method should be noninvasive and not incorporated into the bone structure, relying on organic supplies such as glucose. These devices, especially those with high electrical conductivity, can be constructed using nanostructures. Nanostructures are able to improve enzymatic activities due to their large surface area [Subramani et al., 2013].

i. *Nanorobots for orthodontic movement*

Orthodontic motions will be possible in the future thanks to nanorobots that can control periodontal tissue. Because of the time necessary for orthodontic motions and the considerable adaption period required from the surrounding tissues, this notion now looks futuristic [Subramani et al., 2013].

j. *Nanotechnology and temporary anchorage devices*

Nanotechnology will be used to alter the surfaces of temporary anchoring devices (TADs) to improve their retention while yet allowing them to be removed when no longer necessary [Subramani et al., 2013].

k. *Nano-ultrasound device*

During orthodontic movement, nanofabricated ultrasonic devices could be employed to increase mandibular development and reduce root resorption [Subramani et al., 2013].

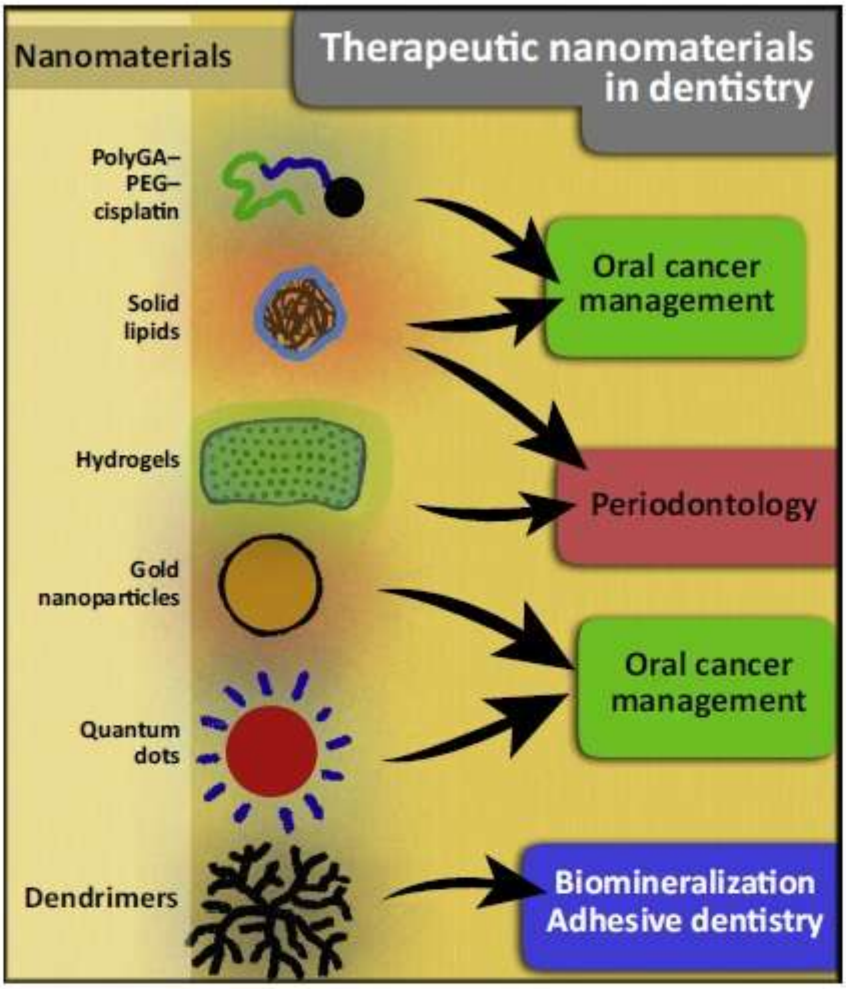

Figure 4. A Schematic Illustration of the Current and Future Applications of Nanomaterials in Therapeutic Dentistry. Solid polymeric nanoparticles, dendrimer nanoparticles, and hydrogels can be made by chemically and physically manipulating synthetic and biological polymers.

5. Oral Cavity diseases and prevention

5.1. Conventional methods for prevention

If the balance of the equilibrium swings toward demineralization over an extended length of time, carious lesions form [Shashikala and Sheela, 2011]. The detection of early enamel carious lesions is still a complicated matter for dentists all over the world. In the prevention and control of dental caries and dentine hypersensitivity utilizing minimally invasive treatment, the assessment and monitoring of mineralization of tooth hard tissues is critical. Fluoride has been found to minimize cavities in both primary and permanent dentition when applied in various formulations and ways over the years. Efforts to include fluoride into toothpastes were attempted earlier in the 1960s, and this became one of the most frequent and successful means of distribution of topical fluoride when applied to the surface of the tooth for the prevention of carious lesions globally [Queiroz et al., 2008]. Fluoride, which is widely accessible, is utilized as fluoridated dentifrices of varying strengths to achieve remineralization of the carious lesion, and it can also be delivered directly to the teeth. Fluoride functions as a catalyst, influencing reaction rates with dissolution and the conversion of tooth HA to fluorapatite, which resists demineralization and inhibits glycolysis of bacteria in plaque [Queiroz et al., 2008]. Clinically, visual approaches for identifying caries on undamaged occlusal surfaces have been proven to be somewhat insensitive. Fluoride administration has been approved since its discovery in the early twentieth century, and it has been utilized as a method of decreasing enamel sensitivity to decalcification. White spot lesions (primary carious lesions with the look of white chalky patches on enamel) to open cavities in the dentin are examples of these lesions. As a result, because dental plaque is the primary causal component, prevention of dental caries has historically been concentrated on mechanical or nonspecific control of dental plaque. Fluoride has been used successfully to reduce and control dental caries [Fontana et al., 2010]. Fluoride has the ability to both prevent demineralization and stimulate remineralization of hard tooth structures. Nonetheless, fluoride's poor penetration in dental plaque may limit its positive inhibitory effects in remaining plaque deposits that persist in inaccessible stagnation areas [Watson et al., 2005]. As a result, dental caries research continues to encounter problems in the prevention and management of caries lesions at proximal surfaces (regions where the side of one tooth meets the surface of another) and around fillings [Malterud et al., 2012].

5.2. Novel nanotechnology-based strategies for prevention

The objective of modern dentistry is to avoid biofilm-dependent oral diseases, such as dental caries, endodontic and periodontal problems, instead of curing them.

Nanotechnology has the potential to revolutionize oral disease prevention, notably in the areas of dental caries and periodontitis.

5.2.1 Dental caries

Dental caries is one of the most common and damaging illnesses that harm tooth structures. Bacteria such as Streptococcus mutans, Streptococcus sobrinus, and Lactobacillus spp. can cause it. These bacteria are frequently found in oral biofilms or dental plaques, which are clumps of bacteria adhering to one other and to tooth surfaces. They generate acids that induce demineralization, or the loss of calcium (Ca) and phosphate (PO_4), in tooth structures. Inhibiting bacterial activity, reversing the demineralization process, and encouraging remineralization are all ways to control dental caries. It has also been attempted to develop a vaccine for caries in this regard.

5.2.2. Dental caries vaccine

Stimulation of the oral mucosal immune system via the nasal route would be an effective means of protecting the host against dental caries. Mucosal vaccination has several advantages, including good patient compliance, simplicity of delivery, and induction of mucosal and also systemic immunity [Moyle P. M. et al., 2004]. Anti-caries DNA vaccination trials have shown encouraging results [Guo J. H. et al., 2004], but mucosal delivery of "naked" DNA has had limited success due to a lack of effective targeting to the action site and the instability of antigen in the gastrointestinal system. The plasmid (pGJA-P) was encapsulated into CS nanoparticles to improve the inadequate immune reaction to naked anti-caries DNA mucosal vaccine. Chitosan (poly [1,4],-β-D-glucopyranosamine) is a naturally occurring biopolymer made from the deacylation of chitin, which is present in crustaceans' exoskeletons [Shrestha A. et al., 2009]. On mice, it has been proven to be an effective vaccine carrier system both in vitro and in vivo. The polymer is a useful excipient for oral drug or protein delivery systems due to its biocompatibility, biodegradability, low cost, and ability to open intercellular tight connections. The increased transfection efficiency of CS-pGJA-P nanoparticles may be due to the improved immune response. However, further human clinical studies are required before this caries prevention method may be implemented on a regular basis [Renugalakshmi et al., 2011].

5.2.3. Biomimetic remineralization - reversing the evolution of caries

Calcium carbonate (CC) nanoparticles have high stability on oral surfaces due to their colloidal particle size and capability for calcium ion delivery. They serve as a carrier for the gradual, continuous release of large concentrations of calcium ions into the oral fluids (saliva and dental plaque). CC nanoparticles have the capacity to raise the pH of the surrounding fluid. As a result, when added into an experimental tooth dentifrice, CC nanoparticles were efficient in remineralizing emerging enamel lesions [Nakashima S. et al., 2009]. When compared to its macro analog, nanosized calcium fluoride (CaF_2) has been found to be extremely soluble and reactive with dicalcium phosphate dihydrate as a labile reservoir for fluoride (F). Because of its high solubility, the reaction with dicalcium phosphate dihydrate might consume a large quantity of CaF_2, resulting in a significant degree of F incorporation into the stable reaction product (apatite). As a result, a mouth rinse including nanosized CaF_2 deposited more F (2.2 ± 0.3 g/cm^2) than a traditional sodium fluoride (NaF) rinse (0.31 ± 0.06 g/cm^2). By raising the F- content in oral fluids and therefore promoting tooth remineralization, the CaF_2 rinse might possibly be utilized as an anticaries agent.

5.2.4. Biomimetic remineralization – secondary caries

Because Ca^{2+} and PO_4^3 are required for remineralization, various Ca^{2+}- and PO_4^3-releasing dental nanocomposites have been created for their remineralizing activity; they therefore aid in the prevention of secondary decay near or under restorations Ca and PO_4 emission is influenced by the degradability and volume percentage of the CaP form [Xu H. H. et al., 2007]. Because these nanoparticles are combined with additional fillers, such as whiskers merged with nanosized silica, these nanocomposites might still be utilized for high-stress bearing applications, regardless of Ca and PO_4 release. Ca^{2+} and PO_4^3 can also be released on need, i.e. when the pH is decreased from neutral to cariogenic, and the rate of release increases substantially with acidic pH [Xu H. H. et al., 2009]. These nanoparticles connect to damaged enamel and dentin, producing a protective covering, and then reverse the action of acid or bacterial assault due to the chemical binding capacity of nanocalcium phosphate fillers, such as carbonate hydroxyapatite [Roveri N. et al., 2008].

5.2.5. Antibacterial nanotherapy

Many nanoparticles (such as zinc oxide, [Gu H. et al., 2012], [Xie Y. et al., 2011] silver [Allaker R. P. et al., 2010], and polyethylenimine [Shvero D. K. et al., 2010]) have been added into dental composites [Kasraei, S. et al., 2014] and dental adhesives [Chen, C. et al., 2014] to suppress growth of bacteria via a variety of methods. In an in vitro model, these nanoparticles were efficient in decreasing S. mutans and Lactobacillus acidophilus biofilms [das Neves P. B. et al., 2014], [Li, F. et al., 2014]. Antibacterial nanocoating was shown to be efficient in killing bacteria, preventing bacterial adherence, and maintaining tooth surface integrity in the presence of biological fluids (saliva) [Besinis A. et al., 2014]. The antibacterial activity of these nanoparticles was found to be size dependent [Lu Z. et al., 2013].

5.2.6. Orthodontics

a. *Nanotechnologic enamel-remineralizing agents*

Nanotechnology breakthroughs have resulted in the development of enamel-remineralizing agents such as nano-HA. The usage of calcium nanophosphate crystals improves the qualities of remineralizing agents [Maheshwari et al., 2014]. During orthodontic treatment, the enamel surface of the teeth can be seen demineralized. The risk of caries is reduced and undesirable side effects are avoided when the enamel surface is successfully remineralized.

b. *Nanocoatings to prevent enamel decalcification*

Brackets coated with a thin layer of nitrogen-doped titanium oxide exhibit strong antimicrobial and antibacterial adhesive properties against common oral pathogenic bacteria. This could be a strategy for orthodontic patients to avoid caries formation and gingivitis [Abiodun-Solanke et al., 2014].

c. *Nanoparticles released by orthodontic elastomeric ligatures*

Elastomeric ligature ties, which were formerly utilized to retain wire in the bracket, can now be used as a carrier scaffold for anticariogenic, anti-inflammatory, and antibacterial nanoparticles. Enamel decalcification and white spot lesions could be decreased in this method [Subramani et al., 2013].

d. *Nanomechanical sensors for orthodontic forces measurement*

To minimize excessive stresses and periodontal damage, nanomechanical sensors on brackets could quantify the forces and moment applied to teeth in real time [Subramani et al., 2013].

5.2.7. *Types of nanoparticles with antibacterial properties in caries prevention*

Mentioned below are some types of nanoparticles used in prevention of caries because of their antibacterial properties.

Silver Nanoparticles (AgNPs)

Silver-based nanomaterials are efficient against biofilms [de Lima R. et al., 2012], [Durán N. et al., 2011] because they may attack numerous locations within the cell at low concentrations (0.5–1.0 %) to inhibit bacterial development. Proteoglycans found inside bacteria cells and on their membranes appear to function as binding sites for AgNPs and silver ions in the antibacterial action of silver nanoparticles [Chaloupka K. et al., 2010]. Furthermore, silver ions can bind with sulfuryl groups during protein synthesis, impeding bacterial DNA replication [Radzig, M. A. et al., 2013]. Crucial aspects of dentistry must be considered while producing AgNPs, such as: firstly nanoparticle diffusion into a plaque biofilm has an inverse connection between size and efficacy, with nanoparticles bigger than 50 nm being unable to penetrate the biofilm [Peulen, T. O. et al., 2011]; and secondly negatively charged nanoparticles have a hard time diffusing through biofilms, which might be owing to the presence of carboxyl and phosphoryl groups on the bacterium surface, which make the cell wall electronegative [Abu-Lail N. I. et al., 2003].

Zinc Oxide-Based Nanoparticles (ZnONPs)

Zinc has also been utilized as a key filler component in dental cements for many years. Zinc ions have potent antibacterial action, which is enhanced when zinc oxide nanoparticles are present. The ability of ZnONPs to interact with the cell membrane of different species of bacteria may explain their bactericidal action. Zn strongly binds to lipids and proteins, altering the osmotic equilibrium and enhancing membrane permeability [Hajipour M. J. et al., 2012; Huh A. J. et al., 2011; Huang Z. et al., 2008]. Furthermore, because of their capacity to produce Zn^{2+} and reactive oxygen species, ZnONPs enhance oxidative stress within the bacterial cell, which can limit planktonic bacteria development.

Titanium Dioxide-Based Nanoparticles (TiO_2NPs)

When exposed to near-UV and UVA light, TiO_2 NPs photocatalyze, creating reactive oxygen species (ROS: mostly H_2O_2 and OH^-) that change the osmotic balance of bacteria. Moreover, TiO_2 NPs can affect phosphorylation, resulting in oxidative cell death [Blecher K. et al., 2011].

Copper-Based Nanoparticles (CuNPs)

CuNPs' mode of action, like that of other nanoparticles, is unknown. However, one probable reason is that Cu can bind to amine and carboxylic groups on the surface of microorganisms, causing changes to their cell membranes [Huh A. J. et al., 2011], [Blecher K. et al., 2011].

Chitosan Nanoparticles

Chitosan, a long polymer chain with N-acetyl-glucosamine and glucosamine residues that are randomly organized, has just been presented as a possible antibacterial agent in dentistry [Friedman A. J. et al., 2013]. The presence of deacetylated C_2

aminogroups, which become protonated and positively charged at pH 6.5, is thought to be responsible for chitosan's antibacterial properties. Consequently, chitosan attaches to the membrane of bacteria, causing I a rise in membrane permeability with a corresponding increase in the outward flow of ions and proteins from the microbial cell; and (ii) suppression of mRNA replication and alteration of protein translation due to chitosan binding to the DNA of several microbes [Blecher K. et al., 2011], [Friedman A. J. et al., 2013]. The antibacterial activity of nanoparticles appears to be significantly linked to the molecular weight of chitosan [Huh A. J. et al., 2011], [Fernandes J. C. et al., 2010].

Nanomaterials and Quaternary Ammonium Compounds (QACs)

Nanomaterials having lower concentrations (1%) of QACs have recently been utilized in dentistry due to their antibacterial properties against a variety of microorganisms, including S. mutans and Lactobacillus casei [Beyth N., 2010], [Zhang K. et al., 2013], [Gong S. Q. et al., 2014]. The antibacterial function of QACs has yet to be fully understood. QAC salts are thought to operate as extremely active cationic agents, causing positively charged polymers to adsorb on the bacterial cell wall. Such interactions would result in considerable alterations in membrane permeability, eventually leading to total lysis of the bacterium cell membrane [Padovani et al., 2015].

6. Discussion / Future Perspectives and Challenges

When it comes to healing or rebuilding damaged tissues at the molecular level, the nanoscale size of NPs has a significant impact. Recent advances in NPs and nanotubes in operative dentistry, endodontics, and periodontics will play an important role in dentistry. They can be employed in dental applications due to their low toxicity, antibacterial characteristics, and improved protein–surface interactions. The inclusion of NPs into different composite resins and adhesive systems, for instance, enhances the mechanical characteristics of restorative and adhesive materials. Because microleakage is eliminated and the connection between dentin and the adhesive substance is strengthened, the risk of secondary caries is reduced. Certain NPs have also been shown to have the ability to remineralize early carious lesions. NP-based irrigates can be a new technique for canal space irrigation in endodontics, with the added benefit of reaching the lateral canals for pulp debris removal. NPs have also been found to be effective against root canal-infective microorganisms, as well as reducing microleakage in canal spaces, avoiding infection relapse. NPs added to tissue conditioner polymers reduce the risk of denture stomatitis in replacement prostheses. They also make the denture base more resistant to breakage. Because of their antibacterial properties, NP coatings on titanium surfaces reduce peri-implant infection in implant dentistry. Due to their biocompatibility, they can also serve as osteogenic agents. NPs may activate periodontal ligament cells and play a key role in the regeneration of lost periodontal tissue for periodontal reasons. Organic NPs, when combined with regulated drug delivery methods, induce tumor cells to apoptosis, halting their spread. Given that many of these biomaterials’ applications are based on in vitro research, more in vivo and in situ experiments are needed to prove these advantages and overcome biocompatibility issues. Because the regeneration ability of dental tissues is restricted, NPs can help damaged tissues recover faster. Due to their enlarged and improved surface volume, biocompatibility, bioactivity, and better mechanical characteristics, novel injectable mixes (single or composites) of various NPs can be employed at the site of dental defects. Another strategy for periodontal disorders is to use exogenous stimuli to coordinate cellular components from gingiva in tissue regeneration [Bartold P. M. et al., 2000]. Recent advances in nanomaterials and nanotechnology may hold promise for practical applications of nanoparticles in the ‘true' regeneration of periodontal tissues, including dentine, cementum, periodontal ligaments, and bone. Scaffolds loaded with NPs and tissue engineering triads can act as an extracellular matrix, allowing host tissues to develop. These NPs can be employed for a variety of dental applications due to their low toxicity, antibacterial characteristics, and improved protein–surface interactions. Their potential involvement in the development of better biomaterials in various forms is a significant advancement in dentistry. A possible method to improve dental care is to combine continuous refinements in traditional treatment techniques with developments in clinical nanotechnology applications [Bapat et al., 2018].

7. Conclusion

To preserve human health, biomedical scientists and doctors all around the globe are focusing to prevention and early treatment. Nanotechnology is expected to have a significant influence on dental research and treatment techniques in the near future, resulting in better oral health care. Nanomaterials will be utilized much more widely and will have superior characteristics; when coupled with biotechnology, laser and digital guided surgery will offer great dental treatment. Using nanodiagnostics, smarter preventive approaches and earlier treatments to avoid craniofacial abnormalities appear to be a possibility. Nanotechnology research will undoubtedly pave the way for the creation of instruments that will help physicians to identify and treat oral cancers at an early stage. Biomimetics and nanotechnology have enabled us to bioengineer missing teeth and remineralize carious lesions. This is one topic that has piqued the curiosity of dentistry and nanotechnology researchers. Salivary glands can serve as a portal into the body for the administration of precise molecular treatments using nanoparticle-based drug delivery systems that have fewer adverse effects. Predictive technologies, such as "lab-on-a-chip," can use saliva as a medium to identify dental and other physical abnormalities in the human body. The cosmetic, physical, and mechanical characteristics of dental composite materials have been enhanced using nanofillers. Nanobots (nanoscale robots) have been proposed as a future treatment for carious lesions, dentin hypersensitivity, inducing dental anesthesia, and tooth repositioning (use in orthodontics, allowing painless movement). Dentifrobots (nanorobots in dentifrices) supplied by mouthwash or toothpaste might monitor supra- and subgingival surfaces of teeth, continuously removing plaque/calculus and metabolizing trapped organic matter into benign and odorless vapor. These concepts may appear to be outlandish, yet innovations have always been the result of outlandish scientific theories [Sharan et al., 2017].

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