

Review Article

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Nanotechnology interventions as a putative tool for the treatment of dental afflictions

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Abstract: Advancement in nanotechnology and its intervention into the medical field has led to significant development in the field of oral health. Also, the combination of nanomaterial science and biotechnology in dental nanorobotics has enthralled us by adding momentum to contemporary dental practices. The progressive nature of dental afflictions often requires an umbrella approach for their prevention, diagnosis, and complete treatment. Furthermore, the complex nature of dental diseases entails customized treatment modalities, which provides the development of various nanotechnology armamentariums. Furthermore, with the objective of controlled drug delivery, researchers have done a plethora of work to apply nanomaterials such as nanospheres, nanotubes, and nanocomposites for dental infections. However, the fundamental concern with nanotechnology is cost involvement and scaleup hurdles which limits its commercialization. Nevertheless, we hope that optimal utilization of the available nanotechnological interventions for modern dental practice will shortly improve oral health. Hence, this review primarily focuses on the types of nanotechnological interventions

explored for various dental afflictions. Also, the authors have attempted to enlighten the readers about the practical aspects of nanotherapeutics for dental disease, that is, a journey from laboratory to product commercialization.

Keywords: nanotechnology, nanotherapeutics, restorative dentistry, preventive dentistry, operative dentistry, periodontal therapy

1 Introduction

The past few years have witnessed a remarkable development in the clinical applications of nanobiomaterials in health care and dentistry. Nanotechnology appears as a valuable tool to the health care industry, and its applications have led to a significant improvement in modern medicine and dental practices. Currently, nanotechnology is driving the dental material industry at a high pace [1]. Applications of nanotechnology offer an impeccable and suitable solution in dentistry and seem to have answers to the problems of conventional dental practices. These novel nanobiomaterials can mimic the surface and interface properties of dental tissues [2]. In the past few decades, biotechnology and regenerative medicine have significantly impacted human lives. However, an advanced level of research is still required to overcome the drawbacks of conventional biomaterials. Although nanodentistry is still in its infancy, it has enormous potential to give innovative solutions for operative and preventive dentistry, tooth restoration, and periodontics (Figure 1). The use of nanoparticles in root end sealants and fillers provides more strength and luster.

Similarly, the incorporation of antimicrobial nanoparticles in restorative materials assures protection against caries forming bacteria and maintains the health of the oral environment. Also, a nanoparticle-based system is an attractive approach for localized drug delivery in periodontitis and oral squamous cell carcinomas [3,4]. Nanotechnology-based hydroxyapatite (HA) is well sufficient to treat osseous defects [5]. Neocis' Yomi is the only Food and Drug Administration (FDA)-approved robotic navigation

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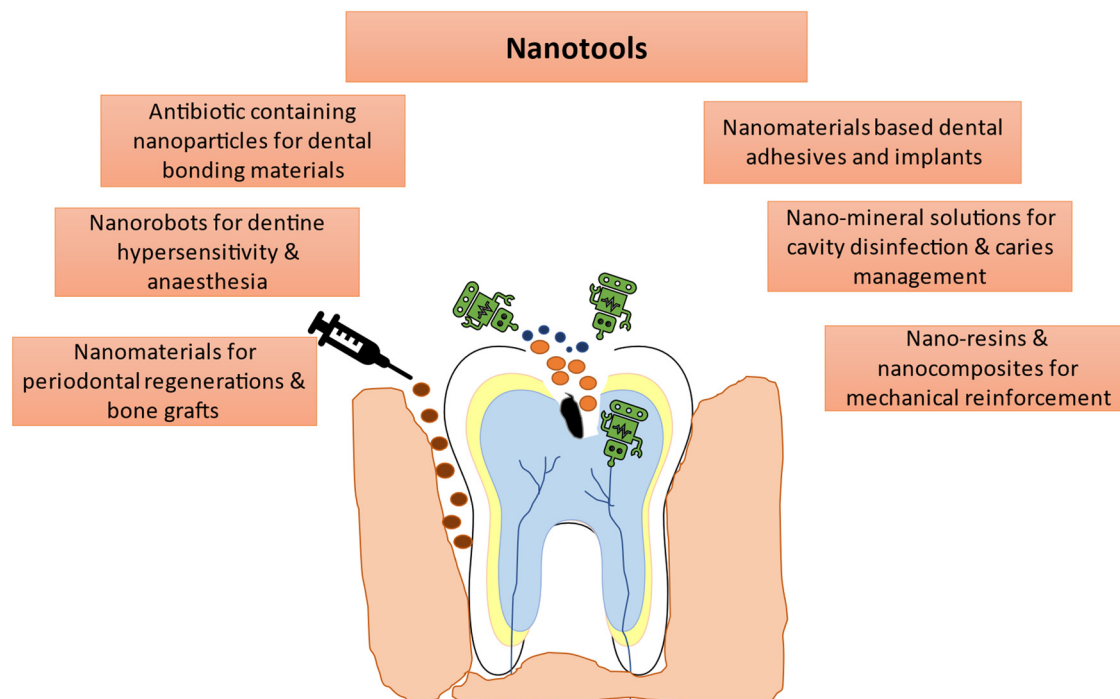


Figure 1: Various nanotools for dental afflictions.

system used in US dentistry and has performed more than 1,000 implants in 2019 [6]. Altogether, it is believed that, in the future, nanotechnology will yield precise and customized solutions in dentistry [7,8].

However, due to the submicron size, physical, chemical, and mechanical properties of any material change, it is a matter of investigation. And as FDA regulates pre-market authorization of drugs and biologics, nanomedicines are also pre-clinically and clinically validated by FDA. Therefore, the safety of nanomaterials is a paramount concern [9].

Henceforth, this review attempts to appraise the readers about the various available nanotherapeutic tools for operative dentistry, preventive dentistry, and periodontotherapy. Also, information on the granted patents, clinical trials, available products in the market, and the regulatory aspects of nanobiomaterials have been collected. It is hoped that this review will enlighten the readers about the practical aspects of nanotools for dental disease, that is, a journey from laboratory to product commercialization.

2 Nanotherapeutic tools for dental afflictions

Oral health has been majorly affected by the emergence of advanced nanomaterials, tissue engineering techniques,

and nanorobotics. The techniques, as mentioned earlier, aim to improvise dental therapy and reduce surgery-associated pain and phobia.

Nowadays, nano-anaesthesia during dental surgery is preferred to reduce pain. Oral nano-anaesthesia is the colloidal suspension of nanorobotic particles, which are analgesic in nature. When the anaesthesia is injected into the gingiva, it travels to the dentinal tubules, as directed by the dentist through the computerized navigation and desensitized the nerves, ensuring the analgesic effect. Once the surgical procedure is completed, nanorobots can be easily removed by the dentist. Excellent patient comfort, selectivity, and controllability are the significant advantages of nano-anaesthesia over conventional anaesthetics [10,11].

These days, caries is the most common teeth problem, which adversely affects an individual's daily life. Their progressive and infectious nature requires mechanical excavation and further filling with the resins or the restorative materials. Conventional filling materials such as HA, metals, and inorganic glues have the problem of microleakage: the discrepancy in physicochemical properties exists between them and the tooth [12]. Clinical studies showed that conventional filling materials lack anticaries properties, which could result in a high incidence of secondary caries. There is approximately 50% failure in filling restorations, thereby leading to wastage

of public health resources. In order to resolve the above issues, nanomaterial-based dental filling materials were introduced and they served as the major breakthrough in caries management. Various anticaries agents such as silver nanoparticles, nano-zinc and nano-zinc oxide, other metal nanoparticles, remineralized nano-anticaries materials, and biomimetic nanocatalysts were explored by the researchers to challenge the current problems of caries management [13]. In nutshell, we can say that with the availability of nanomaterial-based tooth repair materials, diagnosis and treatment of dental caries can be improved. Furthermore, applications of nanotools in various segments of dentistry are explained as follows.

2.1 Nanotools in preventive dentistry

Nanotools are gaining much attention in modern dentistry to prevent disease progression, where tooth decay prevention and treatment of carious lesions are of prime concern. Controlling the dentine hypersensitivity with the nanotools is an emerging field [14].

Dental enamel being a calcified tissue is mainly consisting of calcium-deficient carbonate hydroxyapatite. On the nanoscale, they appeared as a crystalline nanorod-like structure where the calcium hydroxyapatite crystallites are arranged roughly parallel to each other. However, the dentine is a hydrated tissue and comprises minerals, collagenous and non-collagenous proteins, and fluids. And the dentinal matrix is mainly made up of type I collagen fibrils which form a three-dimensional scaffold and are supported by hydroxyapatite crystallites [15]. As biofilm deposition on the enamel surface leads to caries lesion due to acids from bacterial metabolism, frequent consumption of acidic foods and beverages may also cause demineralization and induce enamel erosion [16]. Various approaches for remineralization include fluoride treatment, casein phosphopeptide (CPP)-stabilized amorphous calcium phosphate (ACP) treatment, and biomimetic materials. Fluoride is a widely accepted agent for enamel remineralization [17]. CPP stabilizes calcium and phosphate ions by forming the amorphous nanocomplexes and ensures continuous availability of ions for biomineralization [18]. MI Paste, Recaldent, and GC Tooth Mousse are the marketed products containing CPP-ACP [19]. Amongst the biomimetic approaches to remineralization, biomimetic carbonate hydroxyapatite nanoparticles were used to repair the micrometre-sized tooth surface defects. These crystals have been incorporated into toothpastes or mouth rinses to promote enamel remineralization, and based upon their size, they are deposited onto the

dentinal surface (20 nm) or enamel surface (100 nm) [20]. BioRepair from Coswell Laboratory is a commercially available product that contains carbonate hydroxyapatite nanoparticles for enamel remineralization which have been proved to be effective in *in vitro* conditions after 10 min application [21]. Also, it has been shown that the nano-hydroxyapatite toothpaste with either spheroidal or needle-like particles was comparatively more effective than the sodium fluoride solution for remineralization of etched enamel [22]. However, due to the complex organic and inorganic structure of the dentine, remineralizing dentine into a functional state remains one of the most difficult challenges of dentistry.

If caries or enamel defects enlarge, they may lead to tissue damage which cannot be repaired by remineralization techniques. But with the help of the tissue engineering approach, treatment of damaged tissue is possible. Cells or drugs can be easily loaded into the nanoparticles or scaffolds and selectively targeted to particular tissue, thereby ensuring the sustained and controlled release. Scaffolds are designed in such a way that they can carry both signalling molecules for homing and therapeutic molecules for targeted delivery. Furthermore, for tissue engineering, three components are necessary: cell (mainly stem cell), bioactive signalling molecule (to assist tissue regeneration), and a polymeric scaffold. Researchers have exploited numerous nanomaterials to fabricate tissue engineering scaffolds. Differentiation and functionality are the prerequisite of scaffold material to act as an extracellular matrix for supporting tissue regeneration. Different techniques exist for nanofibrous polymeric scaffolds, and electrospinning is the most commonly used one [14,23].

2.2 Nanotools in operative dentistry

Operative dentistry is based on the diagnosis, treatment, and prognosis of complex tissue defects of the tooth with a prime focus on restoring the form, function, and aesthetic [24]. Superior alternatives were developed by incorporating nanoparticles, nanofibres, and nanoclusters in traditional composites. The ideal size of a nanocomposite should be 1–100 nm. Nanohybrid composites are resin matrices made up of nanoparticles and large filler particles, and their size may vary from 0.4 to 5.0 μm [25]. The incorporation of nanostructures assures significantly enhanced properties of dental composites due to the availability of larger surface areas and binding sites. These dental composites also elicit improved smoothness, high gloss finish, better translucency, and aesthetic look fortified with excellent wear resistance [7,26]. InfinixTM Universal composite, approved

Table 1: Nanomaterial-based dental products

Product name	Product category	Product component	Application of product	Ref.
Nanohybrid composite (brand: NHC SR Phonares®)	Prosthodontics	Silicon oxide	Denture teeth	[30]
Nanoresin-modified glass ionomer cement (GIC) (brand: Ketac™)	Restorations	Zirconia/silica	High shear (enamel) nanofillers and nanoclusters	[31]
Nano 3M ESPE)			Organically modified compressive nanofillers	[32,33]
Nanocomposite resins (brand: Ceram.x®, Mono™, Ceram.x®, Duo™, Dentsply)	Conservative	Ceramic/polysiloxane	Lower hardness and bond strength dentine	[34,35]
Nano-GIC (brand: GCP Glass Fill™ GCP Dental)	Conservative	Carbonized fluorapatite/HA nanoparticles		
Mineral solution (brand: NanoCare gold®, DNT™)	Cavity disinfectant	Silver nanoparticles	Antibacterial nanoparticles	[36]
Silicon-based sealer (brand: GuttaFlow™)	Endodontics	Nanosilver particles	Nanosized sealing agent	[37]
Bone grafts (brand: NanoBone®, Artoss GmbH®)	Periodontics	Nanocrystalline HA	Low cytotoxic and high biocompatible graft	[38]
Nano-implant coating (brand: NonoTite BIOMET 3i)	Implantology	Nano-HA	Biocompatible implant coating	[39]

by FDA in 2019, is based on Nobio's QASi composite technology and consists of quaternary ammonium silica dioxide [27,28]. Another composite 3M™ (Filtek™ Supreme Flowable) contains loosely bound 5–20 nm zirconia/silica particles [29]. Other nanomaterial-based marketed products are listed in Table 1.

The difference in the size of filler particles and HA crystals of tooth enamel results in poor bonding of the material with the tooth, thereby making it a little unstable. This issue was resolved by adding the nanoparticles to the composites, and promising results in smooth surface transition and interaction with tooth tissues were observed. Therefore, incorporated nanostructures improve the physico-mechanical and optical properties of the resin composites [40,41].

Longevity is the most desirable aspect of any dental restorative material; however, most of the restoration cannot meet the same due to the enzymatic activity of dental caries forming oral bacteria [42]. Orthodontic materials also suffer from a similar problem, that is to harbour the multiplication of caries-causing bacteria. These bacteria demineralize the enamel, which produces a white spot lesion in 50% of patients undergoing orthodontic treatments [43]. Recently, nanotechnology has become an important area of research with a prime focus on increasing the antimicrobial properties of dental restorative and orthodontic materials [44]. Among the various nanoparticles, silver nanoparticles were the most commonly exploited by researchers either alone [45] or in combination with others, such as nanoparticles of zinc oxide [45], HA nanowires [46], HA [47], silica nanoparticles [48], and quaternary ammonium dimethacrylate [49]. Titanium oxide nanoparticles are suitable candidates for dental bonding materials with additional antibacterial activity [44]. So, it can be concluded that nanoparticle-modified dental bonding materials offer a more significant antibacterial activity than conventional dental bonding materials.

In cases, when non-surgical approaches are contraindicated or fail, a surgical endodontic procedure is required to save the tooth. The basic steps are exposure of carious tooth, root-end resection, preparation, and filling of a root end sealing material [50]. Various nanomaterials have been explored for endodontic purposes such as sealants and irrigators for disinfection purposes.

EndoSequence BC sealer is a nanoparticle-based sealer having excellent dimensional stability and antimicrobial property with a setting time of 3–4 h. It consists of calcium hydroxide, calcium silicate, zirconia, thickening agent, and bioactive nanoparticles. After getting hydrated in the apical area of the tooth, it formed a nano-HA and calcium silicate and settled down over there [51].

Bioactive nanoparticles significantly improved the physical properties of the materials [52].

GuttaFlow sealer is another excellent root canal sealant with in-built resistance to bacterial penetration. It is made up of silicon-based material, silver nanoparticles, and dust of gutta-percha. This sealant is also dimensionally stable and has a setting time of 30 min [53].

Another sealant, nano-HA-modified gutta-percha, consists of nano-HA, bismuth oxide, hexamethylenetetramine, and bisphenol-A-diglycidylether as a liquid component [54].

The bioactive glass nanoparticles have proven their potential for root canal disinfection. Nanoparticles (20–90 nm) of bioactive glasses containing $\text{SiO}_2\text{CaOP}_2\text{O}_5$ were prepared, assessed for antimicrobial activity, and observed promising results [55]. With time-lapse, they release alkaline species in the biological environment, which are antibacterial [56]. Bioceramics are bioactive and biocompatible, and further release of alkaline antimicrobial species increases their suitability for root canal disinfection [57].

2.3 Nanotools in periodontal therapy

Periodontitis is a complex disease that destroys collagen and tooth-supporting materials. Its treatment is based on the delivery of antimicrobials along with the host modulatory agents [58,59]. From high-dose systemic antibiotics to localized drug delivery devices, nanotechnology has tremendously improved the treatment strategy.

In periodontics, nanoparticles such as nanospheres and nanocapsules have been extensively used as drug delivery carriers. Clinical data suggest that Atridox[®] (Collagenex Pharmaceuticals, Newtown, PA, USA), a biodegradable sustained release device containing doxycycline hyclate, is capable of reducing probing periodontal pocket depths after initial treatment of peri-implant lesions [60].

Also, promising results have been observed in a controlled phase 3 clinical trial wherein Arestin[®] (micro-spheres of minocycline) was administered as an adjunct to scaling and root planning (SRP) for the treatment of periodontitis. Adjunctive treatment reduces probing depth significantly more than the SRP alone [61].

Since periodontitis is a classic example of biofilm-based disease, and similar to other biofilm-mediated infections, it is unmanageable with alone antibiotics and host modulatory agents. Also, for complete amelioration, multiple placements of localized drug delivery systems are required, and this ultimately mounts the cost. The non-invasive perio-protect method tray was proposed as a solution for this problem. A period-tray with a customized sealing system delivers medication deep inside the periodontal

pockets and is the one and only FDA-approved medication delivery system for periodontitis. In clinical settings as well, promising results were observed with this system [62].

Apart from the killing of periodontopathic bacteria, regeneration of periodontium and bone is the prerequisite for the complete treatment of periodontal diseases. Localized delivery of growth factors (GFs) to the periodontal cavity is a new approach to the regeneration of periodontium. Various strategies such as micro-particles, nanoparticles, scaffolds, injectable gels, and composites are being explored to preserve the bioactivity of GF and control its release [51].

Bioactive glasses also promote bone formation by osteoinduction and osteoconduction, which has led to the use of bioactive glasses that have been widely applied in dentistry. It has been observed that the periodontal ligament cells, when placed adjacent to the bioactive glass nanoparticles, showed high growth and enhanced viability along with elevated alkaline phosphatase activity [63].

When multiwalled carbon nanotubes were immersed in calcium phosphate solution at 37°C for 2 weeks, they resulted in the formation of nanoscale HA, thus indicating the potential of carbon nanotubes for periodontal tissue regeneration [64]. Ostim (Heraeus Kutzer, Hanau, Germany), a ready-to-use paste consisting of 35% of nanocrystalline particles of HA and 65% the water, has been widely used for the treatment of osseous defects. Clinically, its application results in a marked reduction in periodontal pocket depth and, after therapy, attains clinical attachment in 6 months [65,66].

3 Patents and clinical trials

Based on the acceptable performance of nanomaterials for dental procedures, patents have been granted in various countries, and a few of the granted patents are listed in Table 2.

Although the nanomaterial-based dental products showed promising results in *in vitro* conditions, safety, and efficacy still need to be evaluated by clinical trials, few completed trials are listed in Table 3.

4 Regulatory aspect of nanotools or nano-based products for dentistry

The regulatory guidelines/aspects are defined as a range of scientific disciplines encompassing the quality, safety,

Table 2: Patents on nanotherapeutic tools for dental intervention

S.no	Grant no.	Study objective	Description
1	US20070043142A1	Dental compositions based on nanofibre reinforcement	The present invention describes the dental composition based on nanofibres
2	US9545295B2	Nanobubble generator for cleaning root canal of tooth and dental apparatus comprising the same	The present invention describes a nanobubble generator for root canal irrigation purposes
3	WO2001030307A1	Dental materials with nanosized silica particles	The present invention describes the composition of dental materials for sealant, prosthesis, and filler purpose
4	US8298329B2	Nanocrystalline dental ceramics	The present invention describes the composition of nanocrystalline dental ceramic
5	EP2495356A1	Dental implant with nanostructured surface and process for obtaining it	The present invention describes the method of production of nanotubes of titanium dioxide as a coating for dental implants
6	WO2014087412A1	Nanosurface-modified metallic titanium implants for orthopaedic or dental applications and methods of manufacturing thereof	The present invention describes the method of production of metallic implant
7	EP2409682A1	HA-binding nano- and microparticles for caries prophylaxis and reduction of dental hypersensitivity	The present invention describes the application of oligopeptide functionalized nanoparticles or microparticles for caries prevention
8	US8357732B2	Method for production of biocompatible nanoparticles containing dental adhesive	The present invention describes the process of production of HA nanorods containing dental adhesive
9	WO2017149474A1	Process for the production of antimicrobial dental adhesives including graphene and relative product thereof	The present invention describes the process of production of dental adhesive with antibacterial and antibiofilm activity
10	US20130108708A1	Dental composites comprising nanoparticles of amorphous calcium phosphate	The present invention describes the antibacterial agent containing dental composite
11	US20130017236A1	Toothpaste or tooth gel containing silver nanoparticles coated with silver oxide	The present invention describes the composition of silver nanoparticle-containing toothpaste
12	US9795543B1	Nanocomplexes for enamel remineralization	The present invention describes the preparation and composition of nanocomplexes
13	US20070213460A1	Antimicrobial nano-silver additive for polymerizable dental materials	The present invention describes the polymerizable dental material that can be used as dental filling material
14	US8641418B2	Titanium nanoscale etching on an implant surface	The present invention describes the process of roughening of implant surface for fixing dental prostheses thereon
15	CN103690376B	Dental pulp root canal filling paste	The present invention describes the preparation of paste for filling into the root pulp
16	US20100035214A1	Radio-opaque dental prosthetic member	The present invention describes the nanoparticle-containing radio-opaque material for dental prosthetics
17	US6890968B2	Pre-polymerized filler in dental restorative composite	The present invention describes the filler for a dental composite that can be used in stress-bearing restorations and cosmetic restorations
18	US9192545B2	Dental root canal filling material having improved thermal conductive characteristics	The present invention describes the dental root canal filling material with improved thermal property dental composite of high strength
19	WO2002092022A2	The dental composite containing discrete nanoparticles	The present invention describes the dental composite of high strength
20	US20100047224A1	Biosilica-adhesive protein nanocomposite materials: synthesis and application in dentistry	The present invention describes the application of silicate in-silk fibroin fusion proteins in dentistry to formulate silica-containing nanocomposite materials for nanocomposite as filling material

Table 3: Clinical trials on nanotherapeutic tools for dental intervention

S. no	Clinical trial no.	Study title	Condition	Intervention
1	NCT03186261	Antibacterial effect of nano-silver fluoride versus chlorhexidine on occlusal carious molars treated with partial caries removal technique	Dental caries	Nanosilver fluoride solution was compared with cavity cleanser
2	NCT02093091	Clinical evaluation of nano-ionomer filling in primary teeth	Dental caries	Ketac Nano was compared with a conventional filling material; vitremer
3	NCT02936830	Effectiveness of nano-hydroxyapatite paste on reducing dentin hypersensitivity	Dentin hypersensitivity	15% Nano-hydroxyapatite paste was compared with Glycerol and 5% sodium fluoride varnish
4	NCT03980847	Evaluation and the histomorphometric study of nanocrystalline HA (nanobone) with alendronate in the preservation of the tooth socket	Bone resorption	Alendronate 20 mg was combined with nanocrystal HA
5	NCT04213716	Comparison of the efficacy of calcium hydroxide with silver nanoparticle and conventional calcium hydroxide intra-canal medications on post-operative pain in symptomatic root canal treatment failure cases	Retreatment Root canal retreatment Non-surgical retreatment	Combination product of silver nano-particulate solution mixed with calcium hydroxide powder was compared with alone combination product and alone conventional calcium hydroxide
6	NCT03792178	Evaluation of postoperative sensitivity of bulk-fill resin composite versus the nano-resin composite	Sensitivity	Bulk fill composite was compared with nano-resin composite
7	NCT02895321	Nano-HA with potassium nitrate in the therapy of the dental sensitivity	Dentin sensitivity	Cavex bite and white ExSense was compared with Colgate protection caries and placebo gel
8	NCT03193606	Radiographic assessment of glass ionomer restorations with and without prior application of nano-silver fluoride in occlusal carious molars treated with partial caries removal technique	Partial dentin caries removal	Nanosilver fluoride solution was applied to carious dentin
9	NCT02918617	Clinical efficacy in relieving dentin hypersensitivity of nano-HA-containing toothpastes and cream	Dentin sensitivity	Control toothpaste containing Novamin technology compared with control toothpaste containing 1500 ppm fluoride as sodium monofluorophosphate and test toothpaste containing a high concentration of nano-hydroxyapatite Charisma-Diamond was compared with Filtek-Z550
10	NCT02893735	Clinical comparison of two resin composites on diastema closure and reshaping at four years	Diastema	Adhesive: OptiBond XTR; composite: Herculite Ultra in Arm 1 was compared with
11	NCT01464996	Clinical evaluation of a new two-component self-etch universal adhesive	Composite restorations of tooth lesions	Adhesive: OptiBond FL; Composite: Herculite Ultra in Arm 2
12	NCT04643288	Nanocrystalline HA bone substitute for treating periodontal intrabony defects	Chronic periodontitis	Open flap debridement procedure was performed in control group while nano-HA bone graft along with open flap debridement was given to intervention group
13	NCT02018783	Single application of desensitizing pastes as dentin sensitivity treatment	Dentine hypersensitivity	Colgate Sensodyne Nano P; and Cocorico were compared among themselves
14	NCT04059250	Nobio clinical study – demineralization prevention with a new antibacterial restorative composite	Dental caries, denture, partial, removable	Nobio composite was compared with traditional composite

and efficacy assessments of health products (medicinal products and medical devices). These guidelines provide informed regulatory decision-making throughout the life-cycle of a health product ranging from drug development, licensing, registration, manufacturing, and marketing. They are cumulatively derived from the diverse fields of basic medical science, applied medicinal science, and social sciences [67]. The regulatory standards and tools often vary in different countries and for different products as well. Examples of major regulatory authorities are FDA, USA; Therapeutic Goods Administration, Australia; and Central Drug Standard Control Organization, India and European Medicines Agency. The international organizations to mandate such rules and regulations are World Health Organization, Pan American Health Organization, World Trade Organization, International Conference on Harmonization, and World Intellectual Property Organization [68]. The category of health products is broadly divided into two main heads, namely, medicinal products and medical devices [69]. The medical devices are subdivided into the categories of invasive (either surgical or not) and non-invasive (coming into direct contact with the skin) medical devices. Examples of invasive medical devices in dentistry are dental fillers, composites, and crowns [70]. Nanomaterials are classified as natural or formulated materials containing unbound/aggregate (strongly bound)/agglomerate (weakly bound) particles in a size range of 1–100 nm. The health and medicinal products encompassing nanomaterials can be termed nanotools and nanomedicines or nanoproducts, respectively. The medical devices fortified with nanotechnology are known as nanomedical devices [71]. The outline of a regulatory guideline for nanotechnology-based health products is all risks (physical/chemical/environmental) must be evaluated and reduced as far as possible; material toxicity, compatibility, contaminants, residues, and leachates must be checked before processing and minimized risk of injury in context with physical features and external dimensions [72]. To determine the possible health effects of nanomaterials (free/fixed/embedded) used in medical devices, the guidelines have two norms, one is for the cases where the nanomaterial might inadvertently be released into the human body, and second, are the cases where the nanomaterial is intended to be released into the human body. The assessment of nanomaterials used in medical devices is necessary to ensure consumer safety, to examine the emerging/newly identified health and environmental risks [73]. The regulation norms for nanomaterials involve material characterization, that is, either natural based or synthetic or a combination. Physicochemical characterizations include an evaluation of

various parameters such as chemical composition; particle size; particle/mass concentration; specific surface area; surface chemistry; surface charge; redox potential; solubility and partition properties; pH; viscosity; density and pore density; dustiness; chemical reactivity, catalytic and photocatalytic activities [74]. The nanomaterials used in dentistry tools and other medical devices are categorized in terms of low, medium, and high exposures and include various testing parameters such as toxicokinetic, cytotoxicity, acute toxicity, irritation, delayed-type hypersensitivity, genotoxicity, haemocompatibility, repeated-dose toxicity, implantation, chronic toxicity/carcinogenicity, reproductive, and developmental toxicity. For invasive dental products, a few additional studies include immunotoxicity, persistence, accumulation, and adsorption, distribution, metabolism, excretion (ADME) [75,76]. The risk evaluation of nanomaterials is based on release potential/kinetics; distribution and maintenance at the location site; and toxicity tests. The various aspects for evaluating the biocompatibility of nanomaterials used in dental and other medical devices are harmonized standards; assessment and testing in the risk management process; animal welfare requirements; toxicity studies; interactions with blood; implantation; irritation; and skin sensitization [77]. International Organization for Standardization (ISO) 10993 series describes considerations for the biocompatibility assessment or biological evaluation of nanomaterials based on dental and other medical devices. The additional considerations of the above series are surface nanostructures; nanomaterials incorporated within a medical device without intention to be released; nanomaterials bound on the surface of or within a medical device to be released; nanomaterials released from a medical device as degradation product, wear, or from mechanical treatment processes [78]. The general considerations of ISO 10993 include the assessment of release kinetics (rate and quantity), contact duration, potential cellular or tissue effects (beneficial or adverse), physicochemical characterization, and toxicokinetic (ADME)/tissue distribution of the nanomaterials [79]. The three prerequisites for the biological evaluation of dental nanomaterials are physical morphology, chemical composition, and extrinsic properties (interaction ability with the surrounding environment) [80]. The extrinsic properties cumulate protein–cellular interaction, cellular uptake (cross cellular and intracellular), interruption activity (DNA synthesis, oxidative stress, and other cellular functions), and translocation at the site of administration. Additionally, other studies such as evaluation of dose metrics, different properties to bulk form, mass/number concentration, surface area, aggregation, electric charge, and optical properties are also taken into consideration [81–83]. The significant toxicity studies

include genotoxicity, carcinogenicity, reproductive toxicity, immunotoxicity, and systemic toxicity. The *in vitro* toxicity analysis demonstrates exposure to the cell nucleus, and *in vivo* analysis ensures nanomaterials reach the target organ. The ability of nanoparticles to initiate an immune response or immunotoxicity results in their irritation and sensitization potential. The additional toxicity study includes haemocompatibility which is based on nanomaterial's ability to translocate from device to systemic and to induce prothrombotic effects, platelet activation, and inflammatory and hypersensitivity reactions [59,61,67].

5 Conclusion and future perspective

This up-to-date snapshot clearly explains the impact of nanotechnology on dentistry and how it has revolutionized the dental practice worldwide. Various nanotechnology-based products such as nanoresin modified-GIC, nanohybrid composite, nanocomposite resins, and nano-GIC are there on the market to restore the size, shape, and aesthetic of teeth. Also, nanotechnology-driven approaches have now improvised the diagnosis and treatment of dental caries too. Nano-based products such as Atridox and Arestin have gained much attention from clinicians to reduce the bacterial load of the periodontal cavity. However, due to the unpredictable nature of existing tissue engineering techniques, regeneration of the periodontal tissue still remains a challenge to clinicians across the world. But, delivery of GFs to the periodontal cavity along with nanocarriers and scaffolds can be considered for this purpose. Also, bone grafts and implants have shown promising results in periodontology. With the help of nano-anaesthesia and nanorobotics, dental surgeries are no more dreadful for patients. Although the communion of nanotechnology and dentistry is still in its infancy yet, its continuous progression has shown a greater impact on overall research and commercial translation. Due to their promising results in *in vitro* conditions, a large number of patents have been granted to dental nanoproducts across the world. However, to assure safety and efficacy, several clinical trials have been conducted, and many of them are now completed. The small size of these nanoproducts associates itself with nanotoxicity outcomes and hence is particularly subjected to FDA approval before marketing and patient usage and needs to pass the set criteria and pre-defined standards. In conclusion, it can be said that the nanotechnology-driven approaches have imparted an edge to the various dental procedures and serve as a valuable tool

for dental science. However, concerted efforts are required to address the various issues which could be pertinent to bridge the gap between its translation from the bench side to the clinical settings and also to have a substantial effect on major tooth repair using nanodentistry.

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