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Advances in hybridized nanoarchitectures for improved oro-dental health

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Abstract

On a global note, oral health plays a critical role in improving the overall human health. In this vein, dental-related issues with dentin exposure often facilitate the risk of developing various oral-related diseases in gums and teeth. Several oral-based ailments include gums-associated (gingivitis or periodontitis), tooth-based (dental caries, root infection, enamel erosion, and edentulous or total tooth loss), as well as miscellaneous diseases in the buccal or oral cavity (bad breath, mouth sores, and oral cancer). Although established conventional treatment modalities have been available to improve oral health, these therapeutic options suffer from several limitations, such as fail to eradicate bacterial biofilms, deprived regeneration of dental pulp cells, and poor remineralization of teeth, resulting in dental emergencies. To this end, the advent of nanotechnology has resulted in the development of various innovative nanoarchitectured composites from diverse sources. This review presents a comprehensive overview of different nanoarchitectured composites for improving overall oral health. Initially, we emphasize various oral-related diseases, providing detailed pathological circumstances and their effects on human health along with deficiencies of the conventional therapeutic modalities. Further, the importance of various nanostructured components is emphasized, highlighting their predominant actions in solving crucial dental issues, such as anti-bacterial, remineralization, and tissue regeneration abilities. In addition to an emphasis on the synthesis of different nanostructures, various nano-therapeutic solutions from diverse sources are discussed, including natural (plant, animal, and marine)-based components and other synthetic (organic- and inorganic-) architectures, as well as their composites for improving oral health. Finally, we summarize the article with an interesting outlook on overcoming the challenges of translating these innovative platforms to clinics.

Keywords Nanoarchitectures, Dental emergencies, Periodontitis, Hybridized composites, Oral cancer

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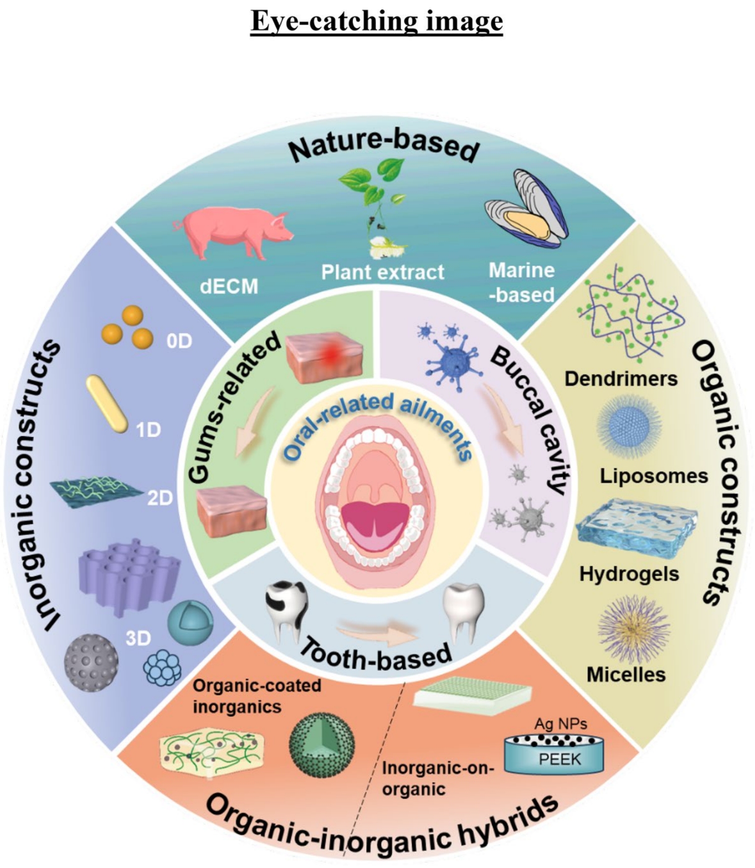
Graphical abstract



Introduction

Over the past few decades, it has been increasingly recognized that oral health always plays a crucial role in expediting the overall health of humans [1]. Although oral diseases are majorly preventable, several dental/oral-related diseases pose a major health burden in many countries, affecting lifestyle, discomfort, and even death [1]. According to World Health Organization (WHO) statistics, the Global Oral Health Status Report in 2022 stated that oral-related diseases have significantly affected approximately 3.5 billion people globally, accounting for 3 out of 4 people in middle-income countries [2]. Along this line, some of the most common diseases that impact oral health include cavities (tooth decay), gum-related (periodontal) diseases, and oral cancer [3]. In this context, tooth caries affected a total of 2 billion people of adults with permanent teeth and 0.5 billion of children with temporary teeth [4]. Considerably, the statistics indicated that over 40% of adults reported pain last year, and over 80% of people had at least a cavity by the age of 34 [5]. The predominant reasons for the increased rate of dental-related disorders could be untreated dental caries in permanent teeth because of expensive treatment, no health insurance coverage, and insufficient infrastructure in most low- and middle-income countries [6].

Typically, dental-related issues with dentin exposure often increase the risk of developing oral diseases [7]. Prior to exploring dental-related ailments and their treatments, it is imperative to understand the tooth hierarchical structure, including periodontal (superficial), orthodontic (bone-associated), and endodontic layers (dentin-pulp). Briefly, the superficial periodontal components of the tooth are predominantly made of the toughest enamel tissue with hierarchical layers. The middle orthodontic layer is composed of a bony layer offering physical support. The lower or deeper endodontic layer is composed of the dentin. The periodontitis or dental caries caused by a microbial infection on the top layers of the tooth may influence the dentin-pulp complex in the endodontic layer. In this framework, several dental-related disorders include gums-associated (gingivitis or periodontitis, and inflammation), tooth-based (dental caries, root infection, enamel erosion, tooth sensitivity, erosion, decay, and edentulous or total tooth loss), as well as overall buccal/oral-related ailments (dry mouth, bad breath, mouth sores, oral cancer, and miscellaneous bacterial infections) [8]. These highly painful oral-related disorders often result in toothaches and dental emergencies. Other prominent oral conditions include noma (pediatric gangrenous disease), oro-facial clefts, and oro-dental trauma [9]. These oral diseases, including dental caries (tooth decay), periodontal diseases, and oral cancers, are often caused by a range of modifiable risk factors [10], such as sugar intake, alcohol, and tobacco consumption, as well as poor hygiene, among others [11, 12]. The prevalence of oral-based ailments has been growing with urbanization and changes in the living conditions of the patients, such as inadequate exposure to fluoride, high sugar, alcohol intake, and insufficient access to health services.[13] Although general considerations are specified, the main reasons and available treatment options for dental problems are elucidated in the further sections (Sect. "Oral ailments").

Notably, dentists often prescribe various conventional formulations to improve oral health with preventable therapeutic outcomes in the early stages. Along this line, several established treatment modalities for multiple kinds of ailments include conventional dental care formulations, such as antibiotic solutions, mouthwashes, and calcium constructs, among others. Regarding early caries and bacterial infections, various antibiotic solutions and mouthwashes are widely used to deliver antimicrobial agents. Despite the availability, these established conventional treatment modalities suffer from several limitations. Predominantly, the biofilms created by the bacterial colonies and acquired antibiotic resistance as defense mechanisms result in poor therapeutic outcomes, leading to further progression of oral diseases towards the loss of teeth and damage of gums [14]. In terms of designing the mouthwashes, formulating these traditional dosage forms with conventional drug formulations is highly challenging due to the hydrophobicity of the antimicrobial agents. Regarding the mineralization of hard tissues, several irrigants are applied, such as sodium hypochlorite, ethylenediaminetetraacetic acid (EDTA) [15], and chlorhexidine (CHX), which can pose compatibility-associated risks due to the accidental extrusion [16]. Moreover, the eventual sealing agents filling the gaps between the filler and root dentine may pose to bacterial growth and result in the poor remineralization of the tooth, requiring the encapsulation of antimicrobial agents towards improved remineralization [17, 18]. Towards the reconstruction of damaged tissues, biomimetic conventional scaffolds have been applied, posing various limitations in terms of lack of regeneration abilities. Although various stem cells can be predominantly utilized, the lack of odontogenic potential results in the deprived regeneration of dental pulp cells, leading to recurrence and dental emergencies [14]. Considering these limitations, it is required to explore various innovative nanoarchitectures as proven constructs towards improved drug delivery, remineralization, and regeneration abilities. In addition to oro-dental conditions, several reports suggested that various oral diseases (for instance, tooth loss) were associated with psychological disorders, such as depression. The reasons could be past periodontal inflammation or autonomic nerve imbalance due to oral-related pain, stress, and discomfort, increasing symptoms of depression [19]. In addition, as stated in the cohort studies, poor oral hygiene, *i.e.,* oral microbiota, could be associated with systemic inflammation and bacteremia, resulting in the development of gastrointestinal cancers, such as oral, esophageal, gastric, and pancreatic, among other [20]. Moreover, the inflammation in the gums leads to various systemic diseases based on cardiovascular diseases, such as atherosclerosis [21]. Considering these attributes, every human being would be required to maintain healthy oro-dental conditions to have a fresh breath and boost confidence [22].

Since the advent of nanotechnology, several advancements have been evidenced toward generating various nanoarchitectures within the size range of 1–100 nm in one of the dimensions [23]. Specifically, these ultrafine structures offer various advantages, such as convenient synthesis, stability, ease of scale-up, and tailorable morphological (size, shape, and structure), as well as physicochemical (mechanical, electronic, optical, and magnetic) characteristics [24, 25]. These nanoarchitectures gained enormous interest from researchers due to their predominant advantages, such as high surface-to-volume ratio and abundant surface chemistry, facilitating the loading of diverse guest molecules either through encapsulation in the framework or immobilization on the surface [26]. In addition, these ultrafine structures encapsulated with guest species facilitate the ease of conveyance by not only crossing the typical biological barriers in the body but also enabling the responsive (ultrasound- [27], magnetic- [28], and photo-[29]) release towards improving the therapeutic efficacy in vitro and in vivo.[30] In addition to encapsulation and delivery abilities, the convenient tailorable surface substantially improves the intrinsic features of biocompatibility and thermal, as well as colloidal stabilities [31]. These ultrasmall-sized nanoarchitectures are often synthesized using diverse sources and precursors, including polymeric (chitosan, and alginate), gold (Au), silver (Ag), titanium, calcium phosphates (hydroxyapatite), zinc oxide (ZnO)-based quantum dots (QDs), MXenes, rhodium, silica (mesoporous silica and amorphous silica), and palladium-based nanoconstructs [32–34]. These nanoarchitectures with tunable advantages and multiple precursors are of particular interest in various fields of science and technology, including but not limited to adsorption, agriculture, engineering, energy, environment, and biomedicine-related fields [35–37]. Apart from the diverse sources, substantial technological advancements have changed medical care and integrated it with dentistry [38]. More importantly, developing innovative anti-microbial, evaluating genomics, and evolving robotics and artificial intelligence can transform the clinical care of dental-related diseases [39].

Despite several reviews on dental-related diseases and exploring various nanostructured components [40, 41], this review presents a comprehensive overview of different nanoarchitectured components and their hybridized composites for improving oro-dental health (Fig. 1). In this review, we first discuss various bothering dental-related diseases, highlighting detailed pathological circumstances and their effects on human health and deficiencies with the currently available conventional therapeutic modalities. Further, the importance of various nanostructured components and their predominant roles in addressing severe dental-related issues are emphasized, highlighting substantial anti-bacterial effects, remineralization, and tissue regeneration abilities. This section provides a discussion of how the materials act to improve oral health. In addition, a brief note on different synthesis approaches of nanostructured components and their hybridized composites is provided, exploring the impact of various synthesis conditions on their morphological and physicochemical properties. Further, various hybridized nanocomposites based on numerous precursors as therapeutic solutions are discussed, including nature-based (plant-, animal-, and marine-derived) and synthetic (organic- and inorganic-) precursors for improving oral health. Finally, we summarize the article with an interesting outlook, focusing on overcoming the challenges of translating these innovative platforms into clinics.

Oral ailments

The major cause of various dental-related disorders is the growth of microorganisms in the oral cavity [42]. The oral cavity acts as one of the predominant gateways for over 700 bacterial species, connecting the external environment with the gastrointestinal tract [43]. Notably, microbiome dysbiosis plays a crucial role in oral

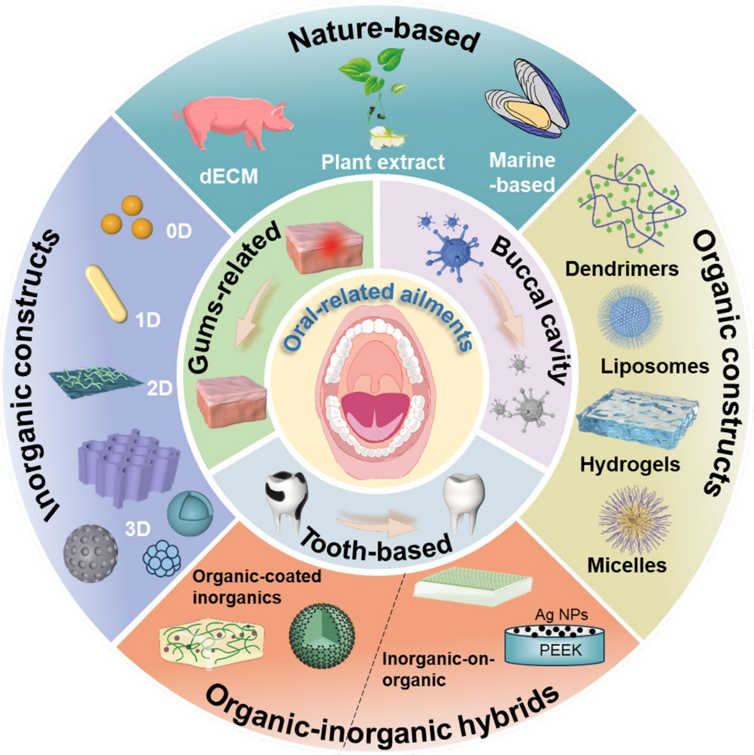


Fig. 1 Schematic displaying various dental-related (gum-/tooth-/oral or buccal-based) ailments and appropriate therapeutic solutions based on natural (plant/marine/animal-derived) and synthetic (organic–inorganic-/organic–inorganic-based) nanoarchitectures

hygiene, in which the imbalance leads to various oro-dental diseases. The sequential progression of dental health issues and eventual tooth loss can be explained in several stages [44, 45]. Initially, the microbial imbalance in the oral cavity results in the bacterial biofilm formation, leading to the formation of caries or plaques on the tooth surface [46, 47]. The untreated plaques lead to pulpitis and apical periodontitis, resulting in local inflammation [48, 49]. Further, the inflammatory responses throughout the oral cavity result in highly complex gum-related diseases, such as gingivitis, periodontitis (mild or advanced), and peri-implantitis [50]. In addition to dental issues, several reports indicated that microbial dysbiosis inducing systemic inflammation would result in other complex ailments such as diabetes, risk of cancer, and myocardial infarction [49]. Several other predominant direct reasons for the cause of these dental-related disorders include sugar intake [51], alcohol [52], and tobacco consumption [53], as well as poor hygiene, among others. Apart from direct reasons, other external factors may influence dental health. For instance, the patients subjected to radiation therapy for head and neck cancers result in long-term adverse effects of mouth dryness, swallowing dysfunction, and altered taste [54, 55]. Although it has a minor influence on dental health, research remains to explore patient compliance after head and neck cancer therapy [56].

Considering these complications, several dental-related disorders have been broadly categorized into three categories, including gums-related, teeth-related, and miscellaneous diseases in the buccal cavity (Fig. 2). The gums-associated conditions are predominantly encountered, including gingivitis or periodontitis, referring to inflammation in the gums. Tooth-based ailments include dental caries, enamel erosion, root infection, tooth sensitivity, erosion, decay, and edentulous (total tooth loss). Lastly, various miscellaneous diseases affecting the oral cavity, other than gums and teeth, include dry mouth, bad breath, mouth sores (canker, cold, and thrush), oral cancer, and miscellaneous bacterial infections, eventually distressing gums and teeth, resulting in toothaches and other oro-dental ailments. This section presents discussions relevant to these diseases, highlighting predominant causes, severity, and treatments available for these ailments.

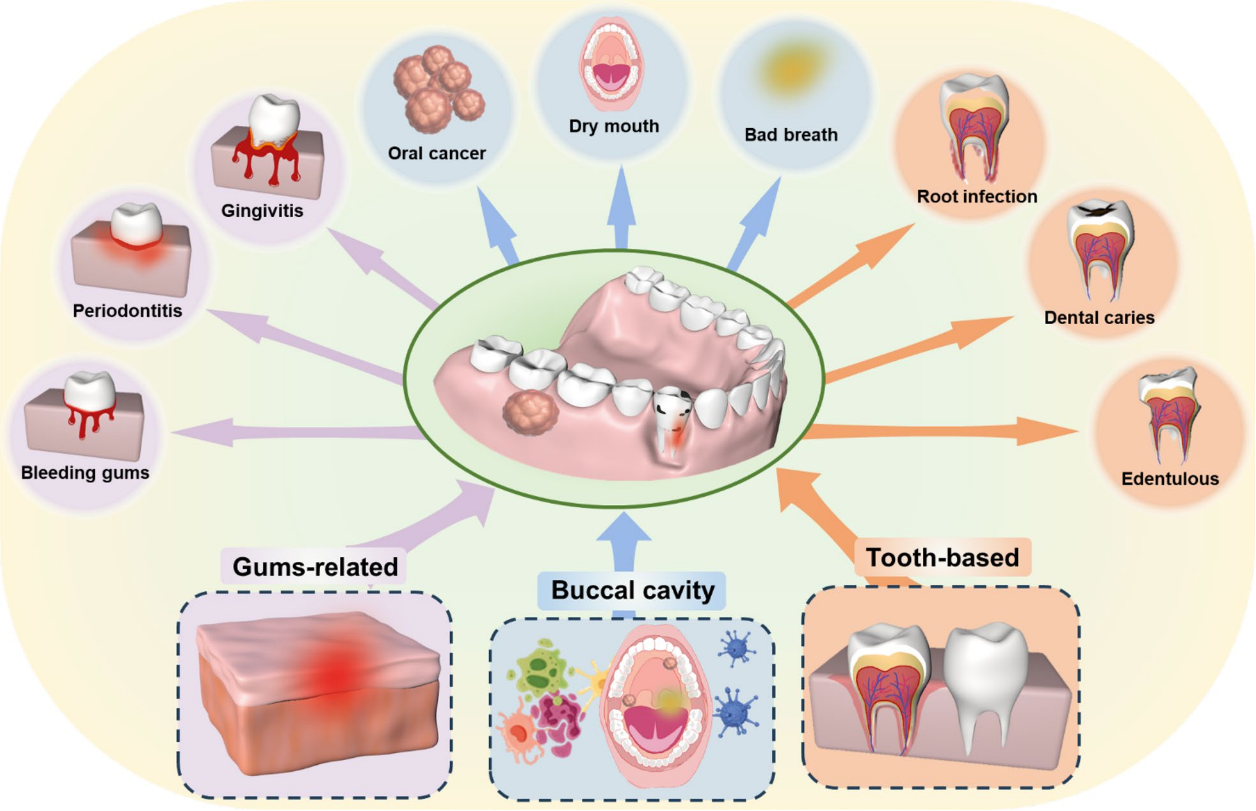


Fig. 2 Schematic illustrating various oral-related (gum-/tooth-/buccal-based) ailments

Gums-related disorders

Several gums-related ailments, referred to as periodontal (gum) diseases, are characterized by the systemic inflammation of the tissues surrounding teeth, such as gingiva, periodontal ligament, and alveolar bone [57]. Often, the symptoms of various periodontal diseases include bleeding or swollen gums (gingivitis), pain, and sometimes bad breath, even leading to tooth loss in several instances. The severity of periodontal diseases can be statistically estimated [58]. Overall, 1 billion cases have been recorded, accounting for 20% of the global population [59]. The predominant reasons include poor oral hygiene and extensive tobacco usage, causing periodontal diseases. Among various periodontal diseases, gingivitis is the early stage of gum-related ailments, often caused by bacterial infection [60–62]. This mild periodontal ailment is initially caused by bacterial film accumulated on the teeth surface adjacent to the gums, affecting the supporting structures of the teeth [63]. The common symptoms include redness, swelling, and bleeding gums. Different from gingivitis in terms of infection and affected structures, periodontitis is the advanced stage of gums-related diseases, involving the loss of the alveolar bone and leading to tooth loss [49]. More often, untreated gingivitis results in periodontitis, manifested by infected gum pockets and shrinking of gums, leading to the damage of bone and surrounding tissues [64]. The periodontitis condition can trigger inflammatory responses throughout the body, resulting in various metabolic disorders [65]. In addition to conventional inflammatory diseases in gums, receding gums can lead to other dental issues, exposing the delicate root of the tooth and making it susceptible to damage, requiring special care in terms of cleaning and brushing [66]. In addition to poor brushing, the other common reasons for various periodontal diseases include extensive tobacco usage, diabetes, and pregnancy [67]. Some common solutions for periodontal diseases include appropriate cleaning, regular brushing, and flossing. Notably, several invasive procedures that use dental materials for the restoration of caries or the placement of implants require incorporating anti-microbial agents to avoid undesirable gum damage.

Tooth-related illnesses

In addition to gums, tooth-related disorders have been evident due to microbial infection and subsequent undesirable effects on the surface of the tooth and root canal, such as dental caries, cracked teeth, enamel erosion, root infection, and edentulous (tooth loss). Among various dental-related ailments, the dental caries condition, often referred to as tooth decay, has emerged as the most prevalent tooth-related ailment [68]. Considering the etiology, the microbial imbalance in the oral cavity results in bacterial biofilm formation on the surface of the tooth, leading to dental caries [69]. Further, the formed plaques on the tooth surface convert the consumed sugars to acids, leading to tooth demineralization. In addition, the acids work on the soft dentin layer and permanently damage the enamel [70]. Simultaneously, the induced caries destroy the tooth progressively [71]. The symptoms of tooth decay include bad breath, spots on teeth, and unpleasant taste. Common sources of tooth decay include excessive sugar consumption, inadequate fluoride exposure, and unremoved plaque promptly. Further, these tooth decay conditions often cause extreme pain [72]. In some instances, excessive infection may lead to tooth loss. More often, the condition of dental caries is treated by filling restoration followed by dental implants to address the complete tooth decay [73]. Nevertheless, the lack of anti-caries properties of the fillers may result in secondary caries, requiring new anti-caries materials [74]. In addition, common suggestions from dentists include appropriate brushing, flossing, and scraping of plaques.

Several minor ailments are commonly seen, such as cracked teeth, bruxism, enamel erosion, and root infection. The broken or cracked teeth are obvious, manifested due to injuries and mouth piercings. These conditions can be treated with veneer, crowning, capping, or tooth-colored filling. Similarly, bruxism, called teeth grinding, often occurs in sleep, causing teeth damage and may lead to severe pain and headache [75]. Typically, bruxism is caused by sleeping disorders and other neurological conditions such as anxiety [76]. Further, enamel erosion happens due to the long-term high consumption of sugars and acidic beverages. Rarely, frequent brushing and often cleaning with pressure for a long time may result in the loss of enamel [77]. The erosion of enamel usually leads to sensitive teeth being more susceptible to cracks [78]. The major treatment options include the restoration of enamel and a significant reduction in damage by avoiding sugars and acidic foods. The root canal, i.e., the basement of the tooth, can be infected with bacteria, resulting in tooth cavities, damaging the nerves, and ultimately developing abscesses. The pathological manifestations include chronic toothache and a swollen face around the infection [79]. Typically, the root canal is applied to treat root infections due to minimal pain with the safe use of local anesthesia [80]. The major issue with these toot-related ailments is their sensitivity [81], hampering the food intake of extreme temperatures, such as hot and cold foods and drinks. The sensitivity increases in the case of dentin exposure due to the wearing of enamel. The sensitivity results in pain as the nerves in deeper dentin are exposed to the consumed substances. More often, tooth sensitivity can be caused by tooth decay, gum diseases, root infection, cracked tooth enamel erosion, and receding gums [82]. These aforementioned tooth-related ailments can be treated with specific strategies of tooth caring and remineralization, crowning, capping, and other approaches [83]. The condition of edentulous or total tooth loss is generally the eventual point of an oral disease. In this context, several dental caries, advanced periodontal diseases, and other diseases often result in edentulous conditions. As per statistics, the average prevalence of total tooth loss for people 60 years or older would be 23% [95] while for 20 years or older, it would be 7%. It should be noted that the edentulous conditions would be psychologically distressing and traumatic from social and functional points of view.

Miscellaneous diseases

In addition to specific tooth- and gums-based ailments, several other diseases in the buccal cavity influence oral hygiene, such as oral cancer, dry mouth, and bad breath. Oral cancers, the most dreadful oral ailments, are often evident in the buccal cavity and gums, such as cancer on the lips, oropharynx, and other mouth parts [84, 85]. These cancers are commonly seen in older adults and more dreadful in men than women, varying according to socio-economic status. Excessive usage of tobacco, alcohol, and betel quid are the leading sources of oral cancers in the buccal cavity [86]. In addition, human papillomavirus infections are crucial in young people affected with oral cancers in some areas, such as North America and Europe [87]. Surgical removal is the current initial choice of treatment. In addition, radiation therapy, molecularly-targeted chemotherapeutics (doxorubicin, adriamycin, and cisplatin, among others), and utilization of immune checkpoint inhibitors have been applied for advanced cancers [88, 89]. Several other commonly seen oral disorders include dry mouth and bad breath [90]. Although commonly seen in older people, any individual can be affected by dry mouth. Several reasons include various diseases, such as HIV/AIDs [91], nerve damage, salivary gland disease, and diabetes [92], as well as medications for cancer therapy [93]. The best choice over a dry mouth is consuming water frequently and avoiding alcohol, tobacco, caffeine, and high-sugar foods. To this end, one of the most common dental problems is bad breath from the oral cavity [94]. This highly distressing condition is caused by poor oral hygiene, dry mouth, certain spices (garlic and onion), and oral cancer [95]. Maintaining hygiene and reducing the intake of certain spices can improve the quality of breath.

Several other common ailments in the oral cavity are related to the tooth, gums, and oral cavity, and their effects are discussed. In this context, oral cavity ailments include oro-dental trauma, noma, and oro-facial clefts. Oro-dental trauma refers to damage to teeth, the mouth, and the oral cavity during injuries. Recent statistics estimated that over a billion people were affected by oro-dental trauma, with the prevalence of around 20% being children [96]. Traumatic conditions can be caused by many other factors, including injured teeth due to accidents [97] and inappropriate teeth alignment. The treatment options include filling restoration, capping, and teeth arrangement, which result in facial and psychological complications towards quality of life. Noma starts as a soft tissue lesion (a sore) of the gums, leading to acute necrotizing gingivitis and destroying all the soft tissues in the oral cavity initially and further the hard tissues on the face [98]. This gangrenous disease is prevalent in African countries and some parts of Asia and Latin America, often affecting children aged 2–6 years due to malnutrition, dreadful infections, poor hygiene, and feeble immune system [99]. This gangrenous disease is so terrifying that ~ 140,000 cases have been reported annually for 2 decades. The common sufferings of the infected individuals include difficulty while eating and swallowing and facial disfigurement, causing social stigma. If diagnosed at the early stage, specific treatment options include surgical removal, improved nutrition, application of antibiotics, and rehabilitation for treatment [100]. The oro-facial clefts, also called clefts on the lip and palate, are the most common craniofacial congenital disabilities, accounting for a global prevalence of over 1 in 1000 births [101]. As genetic disposition is a major cause, tobacco consumption, poor maternal nutrition, and high obesity during pregnancy influence oro-facial clefts. The surgical interventions along with complete rehabilitation are the possible treatment options.

Several common risk factors include tobacco and alcohol consumption, as well as a high-sugar diet. These factors with unhealthy diet lead to other diseases, such as CVDs, cancer, respiratory disorders, and diabetes [102]. More importantly, diabetes is reciprocally linked to the development of various periodontal diseases and dental caries [103]. The predominant options for maintaining oral health include public health interventions, following a healthy diet with well-balanced sugars rich in fruits and vegetables, reduced alcohol consumption, increased physical activities, and decreased risk of facial injuries. Apart from maintenance, oral health services and regular checks with the dentist play crucial roles. Notably, the unequal distribution of oral health professionals, including general dentists and surgeons, would facilitate access to services that are very low in many countries [104]. As dental equipment is quite sophisticated, oral health care costs are another major barrier for low-income countries. Conclusively, the response of the World Health

Organization (WHO) to improved oral health included a "Resolution on Oral Health" in 2021 at the 74th World Health Assembly. The resolution highlighted the preventive method rather than the traditional curative approaches by promoting oral health in schools, families, and work institutions [105]. Further, the World Health Assembly adopted a global health strategy with a vision of universal health coverage by 2030.

Importance of nanoarchitectured components

Prior to exploring the intrinsic features of these nanostructured components and their importance in dentistry, we briefly introduce the history of nanotechnology and its influence on science and, subsequently, in the field of dentistry. Although the advent happened to be in the mid-1950s, nanotechnology is currently being applied extensively in various fields of science and technology. The concept was first explained by Dr. Richard Feynman in 1959 [106]. The notable advancements include the concept of nanotubes in 1991 by Dr. Sumio Lijima [107]. Along this line, extensive research over the past three decades has evidenced the development of various nanostructured materials, including ultra-small sized dots (0D) to multi-dimensional nanocomposites, such as 1D nanotubes to 2D nanosheets and 3D mesoporous silicas [108]. As mentioned earlier, nanomaterials offer highly advantageous physicochemical properties and attractive morphological attributes due to their malleability, high surface-to-volume ratio, and tunable sizes, as well as shapes [109]. In dentistry, the integration of nanotechnology began in the early 2000s, and the term "nanodentistry" was coined by Dr. Freitas Jr [110]. The research progressed by Dr. Freitas Jr. resulted in the development of nanomaterials and nanorobots towards the regeneration of dentition and the development of dentifrobots, i.e., robots in dentifrices [111]. Although expressed as impossible in the early stages, it is now being researched extensively for the utilization of various nanostructured components in different modes to improve dental health [112]. This section provides an overview of various nanosized materials for these dental applications, highlighting their importance compared to conventional therapeutic choices. Although there seem to be some similarities with the final nanoarchitectures section, herein, we intend to demonstrate their impact, highlighting the roles of nanoarchitectures and their modifications.

Impact of nanostructures and their surfaces

Prior to exploring the importance of nanostructures in treating various dental ailments, it is quite crucial to understand the impact of designed nanoarchitectures and their modified surfaces on the improvement of therapeutic efficacy. As notified earlier, several efforts have been dedicated to synthesizing various nanostructured components from natural and synthetic sources in dentistry. These innovative biomaterials can treat diverse oral diseases along with their root causes in many ways, such as anti-microbial nanomaterials [113], remineralized nanoconstructs, regenerative composites, and tooth nano-whiteners [114]. Some of these notable nanomaterials with extensive ability for encapsulation of antimicrobial agents can eradicate biofilms [115]. Moreover, the anti-caries materials deposited with bioactive nanocomponents improve remineralization [116]. The encapsulated nanomaterials provide appropriate room and enable the growth of cells during tissue regeneration. Combining all their beneficial aspects, these nanoparticles will offer a new paradigm shift in the dentistry field (Fig. 3, Table 1) [117].

Typically, the microenvironment of various native tissues is exceptionally organized with numerous nanofibrous elements, including but not limited to elastin, collagen, and other proteins. On the one end, these complex biomolecules significantly guide cell behavior. On the other hand, these ultra-small components offer a convenient way to alter the biochemical and mechanical cues in the biological microenvironment during the application of various delivery platforms. Notably, it is imperative to understand the importance of various nanoparticles and their interactions with the oral microenvironment towards improved delivery. Considerably, several attributes play crucial roles in the performance efficacy, such as the complex microenvironment and its components, as well as the morphological characteristics of the designed nanoparticles. Regarding the applicability of various nanoconstructs in oro-dental diseases, the interactions and interplay between nanoparticles and membranes of cells/bacteria. Considering these aspects, the designed nanoplatforms with alterable surfaces and immobilized organic linkers may improve the hydrophobicity, enhancing the interactions with the cell membrane and the biomolecules in the oral microenvironment. In this context, 1D (TiO_2 nanotubes) and 2D (nanosheets) architectures play crucial roles in offering better control over the degree of surface functionalization [36, 118, 119]. Contrarily, the reactive plasma treatments could extend the hydrophilic stability and wet storage on TiO_2 nanotube surfaces, resulting in the improved viability and compatibility attributes of cells [120]. Moreover, the surface treatment often affects the physicochemical properties of the designed nanoconstructs, leading to altered biological responses. In one instance, titanium discs were exposed to altered surface treatments and the adhesion of osteoblasts and bacteria [121]. These improved interactions and altered surface topology, including those coated on the dental implants, enhance the delivery efficacy of

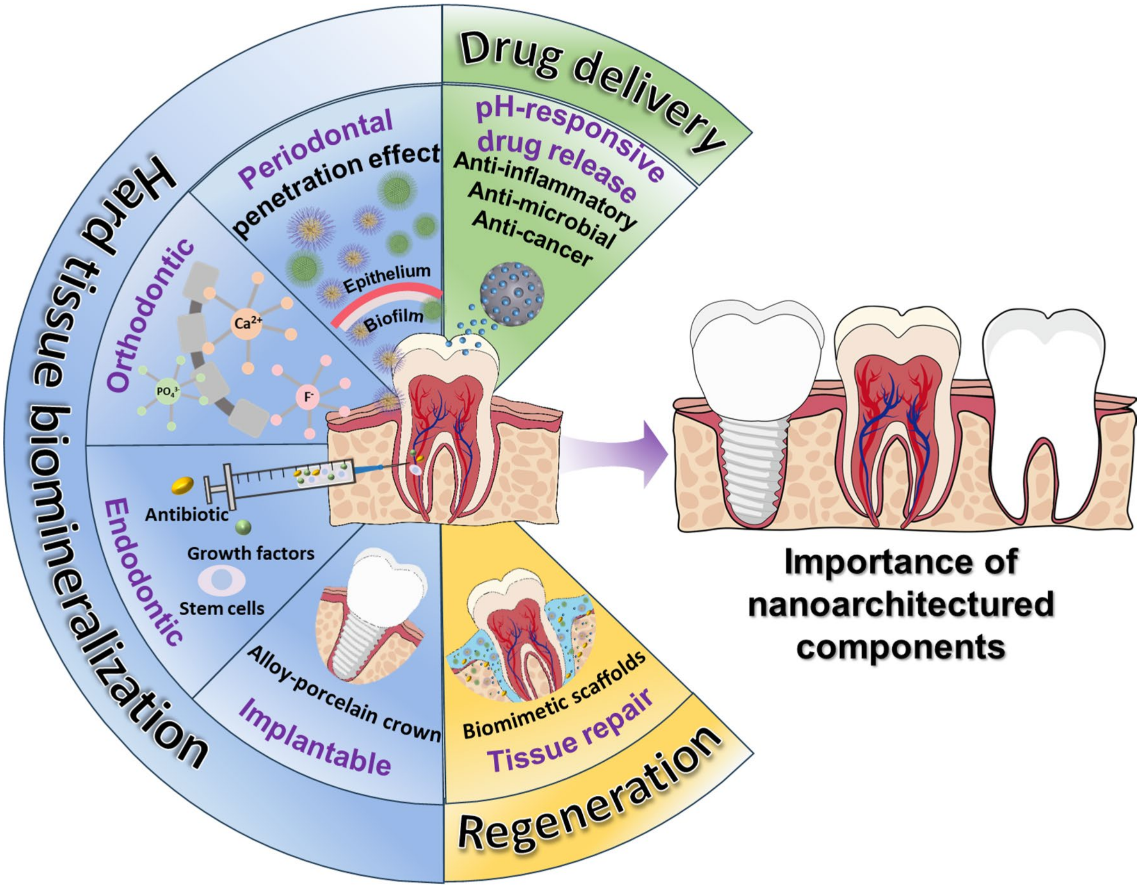


Fig. 3 Illustration presenting the diverse key functionalities of the designed nanoarchitectures for improved dental health, including drug (anti-microbial/anti-inflammatory/anti-cancer) delivery characteristics, hard-tissue remineralization, and regeneration of soft oral tissues

the therapeutic nanoplatforms, presenting enhanced antibacterial efficacy and osteo-inductive performance [118]. Moreover, the cells may respond to the 3D topology of encapsulated nanoparticles in the biomimetic scaffolds toward tissue regeneration. These attributes, along with tunable physicochemical characteristics, may provide substantial scope toward enhanced performance in the oro-dental applications.

Drug delivery

Several dental-related disorders often begin with the deposition of bacteria, such as gingivitis and dental caries, in the gaps of teeth and gums. In terms of exhibiting anti-microbial characteristics, several conventional anti-microbial solutions, such as mouthwashes and other formulations with various antibiotics, have been applied to ablate the deposited bacteria on the tooth and gums and cure different tooth- and gum-related diseases [122]. Although anti-microbial solutions work to execute the bacterial ablation effect, several traditional formulations suffer from notable disadvantages in terms of formulation and performance aspects. Predominantly, the formulation of various dosage forms often suffers a major limitation of the poor solubility of hydrophobic drugs, limiting their successful formulation [123]. In terms of performance, it is extremely challenging to eradicate formed biofilms, leading to increased anti-bacterial resistance and resulting in deprived therapeutic efficacy [124]. To this end, several advancements have been evidenced in designing various kinds of materials in the nano-sized range, which could ultimately act through multiple mechanisms by addressing the limitations of traditional anti-microbial formulations. Considering the formulation strategies, it is feasible to fabricate various anti-microbial nanoformulations either by encapsulating different antibiotics or generating anti-microbial materials. Owing to the high surface-to-volume ratio, several kinds of antibiotics can be encapsulated in their pores of the porous nanomaterials (for instance, mesoporous silica) [125] or on the surface through conjugation in the non-porous nanomaterials (polymeric constructs or 1D or 2D materials) [118, 126]. Specifically, 1D nanotubes

Table 1 Diverse nanostructured components with specific action against various dental-related ailments

Action	Precursor	Size	Ailments gum/tooth/ Buccal	Outcome	Refs.
Drug delivery (anti-microbial/anti-inflammatory/anti-cancer)	Ag-TIPS-Ti	50–100 nm	Dental implants	The silver ions were released continuously from the Ag-TIPS-Ti surface for 7 d, causing outstanding anti-bacterial activity over 12 h of culturing. However, they exhibited no severe cytotoxicity for fibroblast cells for up to 10 days	[130]
	Fe_3O_4-doped ZrO_2	35 nm	Dental implants	The inhibition zone of ~32 mm against bacillus bacteria was revealed, suggesting their potential use as dental filler	[240]
	UCNPs@TiO_2	39.7 nm	Periodontitis	These composites showed high biocompatibility, and when NIR triggered aPDT, it caused the ablation of plankton and eradication of biofilms	[272]
	PLGA-coated TiO_2	68 ± 2 nm	Dental implants	These polymeric-antibiotic-loaded coatings might be applied to prevent early infections, favoring multifunctional surfaces for intra- and trans-mucosal components of dental implants	[119]
	Chitosan-TiO_2 nanocomposites	–	Self-healing dental composites	These nanocomposites demonstrated high self-healing retention efficacy	[273]
	TiO_2 nanotubule	–	Dental implant	The Ag/CaP coatings displayed obvious anti-bacterial effects on *S. aureus* bacteria	[274]
	ZnO nanorods – nanospheres hierarchical structure (NRS)	–	Dental implants	These composites showed excellent anti-bacterial activities against both *Escherichia coli* and *Staphylococcus aureus* and low cellular cytotoxicity	[261]
	mPEG-b-PDPA	300 nm	Caries	These composites pH-responsively delivered hydrophobic anti-bacterial agents in bacteria in acidic environments and mature biofilm	[228]
	Nano ZnO	51.08 nm	Dental adhesive	The design showed lower metabolic activity and higher dead bacteria without impairing the physicochemical performance	[275]
	TiO_2 nanotubes loaded with sodium naproxen	–	Dental implants	The biocompatible TiO_2 with self-sustained diffusion offered exceptional delivery of anti-inflammatory drugs	[276]
	Nano-silver (NAg) particles	–	Fixed orthodontic	The colony-forming unit of tested microorganisms continuously decreased with increased NAg concentration	[277]
	ACC-MH@SiO_2	190 nm	Periodontitis	The nanoreactor achieved good inhibitory effects on three common periodontal ailments	[278]

Table 1 (continued)

Action	Precursor	Size	Ailments gum/tooth/ Buccal	Outcome	Refs.
	PMs@NaF-SAP	300 nm	Caries	These composites adhered to the tooth-identified cariogenic conditions and intelligently released drugs at acidic pH, thereby providing anti-bacterial adhesion and cariogenic biofilm resistance	[229]
	Dual-sensitive anti-bacterial peptide nanoparticles pHly-1 NPs	40 nm	Caries	The peptide underwent the coil-helix conformational transition upon binding to bacterial membranes in the acidic cariogenic biofilm microenvironment, thereby killing cariogenic bacteria	[279]
	GA-Ag NPs	4–26 nm	Caries	These composites inhibited bacterial adhesion and biofilm formation on the surface of the tooth enamel	[280]
	SiO_2-Ag-NPs	418 ~ 502 nm	Dental prosthesis	Superior dispersion was selected for the antibiofilm test, then with increased concentration, causing ablation of bacteria	[281]
	nZnO/MTC-Ti	50–100 nm	Dental implants	These composites possessed higher capability for enhancing bone regeneration, antibiosis, and osseointegration in vivo, accelerating osseointegration, inhibiting bacteria, and decreasing infection	[236]
	Au–Ag nanoparticles containing procyanidins AuAg-PC(IIIIII)	49, 79, 122 nm	Periodontitis	It showed a good anti-inflammatory effect, promoting tissue repair and assisting in photothermal immunotherapy	[230]
	CHX-S NPs	69 nm	Dental fillers	These components showed growth inhibition against bacteria in a concentration-dependent manner and reduced biofilm formation of *S. mutans* biofilm	[282]
Biomineralization	$nCaF_2$	58 nm	Enamel white spot lesions	These components offered greater enamel hardness than the commercial control group	[283]
	Low-shrinkage-stress nanocomposite	–	Caries	These composites reduced polymerization stress and protected enamel hardness	[284]
	NACP + DMAHDM	–	Caries	These composites demonstrated excellent remineralization effectiveness. The sample adhesive released a great number of Ca^{2+} and PO_4^{3-}	[285]
	Fluorine-containing cationic polymer, PHMB-F	–	Caries	It showed better antiseptic efficacy for S. mutans than just PHMB. Markedly lowered the ion concentrations in the microenvironment adjacent to hard dental tissues needed to maintain equilibrium	[286]

Table 1 (continued)

Action	Precursor	Size	Ailments gum/tooth/ Buccal	Outcome	Refs.
	Apatite-coating on the TiO_2 nanotubes	–	Dental implants	Mineralization experiments indicated that TiO_2 nanotubes after ALIM treatment promote natural apatite formation significantly in a simulated body fluid	[287]
	Mineralized ECM/dental pulp stem cell microspheres (MMCMs)	–	Periodontal tissue regeneration	These composites promoted functional periodontal regeneration through activation of the transforming growth factor signaling pathway. Inhibition of another signaling pathway significantly impaired the osteogenic potential and matrix secretion of MMCMs	[163]
	NACP	116 nm	Dental caries	These composites released abundant Ca and P ions, achieved acid neutralization, reduced lactic acid production, and lowered CFU count. Enamel treated with NACP adhesive demonstrated the best remineralization effectiveness, with a remineralization value of 52.29%	[288]
	Melatonin-doped polymeric nanoparticles (ML-NPs)	–	Reducing dentin permeability and facilitating dentin remineralization	ML-NPs promoted total occlusion of dentinal tubules and an almost complete reduction of fluid flow, exhibiting the highest sealing ability among groups	[257]
	Alkasite restorative material (CN)	20–30 µm	Crisis	This design showed an initial substantial increase in pH followed by a steady increase, with values higher than other groups. It released more calcium ions, resulting in an effective resistance to demineralization	[289]
	PCBAA/AC	50.67 nm	Dental fillers	After 3 days, the nanocomposite was still stable in solution. It exerted a significant inhibitory effect on the adhesion and biofilm formation of bactericidal, promoting the remineralization of demineralized enamel and the occlusion of exposed dentinal tubules	[242]
	ACP co-delivery hollow mesoporous silica (E/PA@HMS)	408.4 nm	Exposure of dentin	Effectively sealed the acid-resistant and wear-resistant stable dentin tubules, inhibited the formation of *S. mutans* biofilm, and induced the mineralization and demineralized dentin re-mineralization in collagen fibers	[7]
	Abalone nacre water-soluble organic matrix (WSM)	155 nm	Dental fillers	These composites showed a significantly increased protein yield from 7.60% to 9.60% and improved the polysaccharide yield from 2.59% to 3.34%, respectively, indicating the excellent extraction efficiency of WSM	[211]

Table 1 (continued)

Action	Precursor	Size	Ailments gum/tooth/ Buccal	Outcome	Refs.
	NACP + DMAHDM	–	Caries	These composites demonstrated excellent remineralization effectiveness. Adhesive released a great number of Ca^{2+} and PO_4^{3-} ions, increased pH to 5.81 via acid neutralization, decreased the production of lactic acid and reduced the amount of *S. mutans*	[290]
	$nCaF_2$	32 nm	Dental fillers	For all recharge cycles, ion release maintained similar levels, demonstrating that long-term ion release was possible. After the final recharge cycle, $nCaF_2$ nanocomposites provided continuous ion release for 42 days without further recharge	[231]
	ALONs-CaP	20–50 nm	Dental fillers	Providing a new collagen mineralization strategy promoted intrafibrillar mineralization	[291]
	Enamel protein amelotin (AMTN) based bio-nano complexes	–	Dental implant	The pretreatment of dentin with the bio-nano complexes before adhesive application significantly improved shear bond strength, accelerating the mineral formation and collagen mineralization of bio-nano complexes	[260]
	PAH-ACP-loaded silica/mesoporous titanium–zirconium (STZ) yolk-shell nanocomposite	–	Dentin hypersensitivity	These composites demonstrated outstanding acid and mechanical resistance, induced intrafibrillar mineralization of single-layer collagen fibrils, and remineralization of demineralized dentin matrix. They promoted the odontogenic differentiation of DPSCs by releasing ACP and silicon ions	[247]
	Propolis nanoparticles (NPro) and nano-curcumin-based PDT (NCur-PDT)-(NPro + NCur-PDT)	93.56 nm	Orthodontic treatments	The amount of microhardness significantly increased over time. NPro + NCur-PDT treatment remineralization in that group had improved considerably compared to other groups	[212]
	Bioactive calcium phosphate nanoparticles	–	Caries and erosion	These composites showed remineralizing ability by epitaxial growth of a layer showing the morphology and composition of human hydroxyapatite	[292]
	PAA-CMC-TDM	–	Regeneration of dentin/bone hard tissue	Hydrogel could promote the odontogenesis or osteogenic differentiation of mesenchymal stem cells, adapting to irregular hard tissue defects and promoting in situ regeneration of defective tooth and bone tissues	[219]

Table 1 (continued)

Action	Precursor	Size	Ailments gum/tooth/ Buccal	Outcome	Refs.
	Zn-Dex-NPs	100–200 nm	Dental implant	Dentin surfaces treated with Zn-Dex-NPs attained the lowest nano-roughness values, provoked the highest crystallinity, and produced the longest and shortest crystallite and grain size	[258]
	Sr-N-co-doped TiO_2 nanoparticles and nanohydroxyapatite (n-HA)	–	Dental implant	The resin exhibited excellent self-remineralization and showed significant inhibition effects	[259]
	Fluoride-doped calcium phosphates	–	Dental implants	VSG20F presented a prolonged release of fluoride ions into the storage media (45 d). At lower dilutions (1:10, 1:50, and 1:100), all specimens showed no significant toxicity to hDPSCs but an increase in cell proliferation	[293]
Tissue regeneration	CHI–HAp–collagen	15–30 nm	Bone regeneration	Exceptional biocompatibility and up-regulation in DPSCs on modified membranes were evident compared to unmodified membranes. The composites showed anti-microbial and antibiofilm effects against periopathogens	[294]
	Drug@HDPA NPs	87.8 nm	Tooth extraction fossa bone generation	The released drugs from the HPDA NPs promoted osteogenic differentiation and proliferation of rat bone marrow mesenchymal stem cells (rBMSCs)	[215]
	TGF-β1–loaded PLGA-PEG-PLGA	80–100 nm	Cartilage tissue engineering-DPSCs	The chondroblast differentiation in hDPSCs through the expression of chondrogenic genes was observed	[164]
	TiO_2 nanotubes and human bone morphogenetic protein-2 (rhBMP-2)	70–110 nm	Osseointegration	TiO_2 nanotube arrays could potentially be used as a reservoir for rhBMP-2 to reinforce osseointegration on the surface of dental implants	[295]
	GRGDS-immobilized TiO_2 nanotubes	–	osseointegration	GRGDS-immobilized TiO2 nanotubes might be effective in improving the osseointegration of dental implants	[296]
	SHEDs/SMS	14 µm	Dental pulp necrosis	These composites promoted vascularized tissue regeneration proliferation and exhibited cell protection properties	[216]
	Bioink	–	Oral soft tissue	The enhanced proliferation and viability of printed gingival fibroblasts further confirmed the growth factor bioavailability and enhanced angiogenic activity	[297]
	Zn-CaP distributed TiO_2 nanorod films	–	Osteogenic differentiation	Micro-/nanotopography and bioactive ion release on the surface would be promising ways to enhance osteogenic activity for orthopedic and dental implants	

Table 1 (continued)

Action	Precursor	Size	Ailments gum/tooth/ Buccal	Outcome	Refs.
	DMP1 or BMP2 plasmid DNA-carrying calcium phosphate nanoparticles	57 nm or 121 nm	Dentinogenesis-inducing factors (pBMP2/NPs or pDMP1/NPs)	Bacterial viability was time- and concentration-dependent. The selected one had the ideal treatment concentration and, when used in combination with the HTFD scaffold, maintained a high level of cell viability in vitro and caused no adverse reactions in vivo	[298]
	Calcium-based materials on hDPSCs	–	Regeneration of dentin-pulp complex	An upregulation in odontoblastic cell-related genes was demonstrated along with the treatment of pulp tissue with $CaCO_3$ and $Ca(OH)_2$, and even better with MTA, which seemed to be effective for dentinogenesis	[235]
	Metal ion-dependent-PDA-Ti	–	Dental implant	These composites inhibited bacterial attachment, but they also enhanced the biological properties of the implants	[299]
	TiO_2 nanotubule	–	Dental implant	The Ag/CaP coatings displayed obvious antibacterial effects on *S. aureus* bacteria and relatively excellent osteointegration	[274]
	Wnt3a-loaded hydroxyapatite nanowire @ mesoporous silica (Wnt3a-HANW@MpSi)	30–50 nm	Dental pulp exposure	These composites promoted the oxidative stress resistance of DPSCs, enhanced their migration and odontogenic differentiation, and exhibited superior properties of angiogenesis that were closely related to multiple biological processes and signaling pathways toward pulp/dentin regeneration	[300]
	L/D-Cys-AuNPs	45 nm	Periodontal tissue regeneration	L-Cys-AuNPs showed a better performance in cellular internalization, regulation of autophagy, cell osteogenic differentiation, and periodontal tissue regeneration	[301]
	N-BSA-CDP	790.87 nm	Alveolar bone regeneration	These composites accelerated hard tissue regeneration and sustained release could be achieved for > 12 weeks with all formulations	[217]
	OINC	15 nm	Periodontal bone regeneration	OINCs absorbed proinflammatory cytokines in inflamed periodontal tissue, then released IL-4 controlled by far-red irradiation. Boosted periodontal bone regeneration	[302]

(for instance, TiO_2) with extensive surfaces showcase exceptional topology with favorable antibacterial outcomes [119]. Regarding delivery, these innovative nanomaterials encapsulated with antibiotics substantially improve the solubility of the hydrophobic drugs, leading to their improved performance efficacy [127].

Typically, the nanomaterials encapsulated with antibiotics act through various mechanisms, depending on numerous factors in terms of types of nanoparticles and their delivery patterns. Several mechanisms at multiple levels include electrostatic interactions on the surface, metal ion hemostasis in the cytoplasm intracellularly, and genotoxicity and inhibition of signal transduction in the nucleus [127]. Establishing the electrostatic attractions is the most predominant way that anti-bacterial materials act through crosstalk between the material and the bacterial surface, starting at the cell wall doors. Considering the electrostatic interactions, the delivery efficacy and eventual anti-bacterial action of nanoparticles often depend on the surface charge as the positively-charged nanoparticles usually enable the attachment with the negatively-charged bacterial surface through the electrostatic attractions [128]. The successful interactions and subsequent accumulation at the cell wall doors would facilitate the successful internalization of the bacteria for the delivery of drugs [129]. In addition, the excessive accumulation would damage the cell wall framework, leading to cell membrane disruption and allowing intercellular content leakage and eventual ablation of bacteria [130]. Further, the binding of nanoparticles with mesosomes affects the respiration, division, and eventual replication processes, resulting in reduced bacterial infection. The metal ion homeostasis plays a crucial role in the anti-bacterial action of various metallic nanoparticles; the classic example is the silver nanoparticles (AgNPs) [131]. Typically, different intracellular metal ions often participate in various metabolic activities in microbes. The excess deposition of metallic nanoparticles intracellularly and further irreversible damage to the cell wall would disturb the intracellular metal ion hemostasis and metabolic functions [132]. In this context, AgNPs-coated titanium interfaces have been applied to treat the undesirable bacterial infection [133]. Moreover, the nanomaterials are capable of generating reactive oxygen species (ROS) and attacking cell membranes, causing disturbing respiration and decreased energy production. Some metal oxide-based nanoparticles result in the formation of ROS by actively participating in the redox cycling [134]. In addition, several protein-denaturing nanomaterials often act by the formation of carbonyls, catalyzing the oxidative process of the amino acid chain and leading to the protein denaturation [135]. In addition to surface and cytoplasm, the anti-bacterial nanomaterials act in the cellular core, *i.e.,* the nucleus [136]. Owing to their electrical properties, the internalized nanoparticles could interact with the nucleic acid molecules, resulting in an undesirable influence on the chromosomal replication towards inhibiting signal transduction. In addition, these nanoparticles intracellularly act through modulation of cell signaling by altering the phosphotyrosine profiling [137].

Hard tissue biomineralization

Oftentimes, the condition of dental caries affects the quality of teeth, damaging the enamel and teeth subsequently due to bacterial growth. The damaged teeth portions can be fulfilled by remineralizing the hard tissues using various adhesives or resins [138]. These adhesives or resins added with multiple biologically active nanomaterials act as remineralized anti-caries nanomaterials [74]. On the one hand, these nanomaterials remineralize the exposed collagen, preventing its degradation and improving bonding durability [139]. On the other hand, the encapsulated nanoparticles can facilitate the release of highly required calcium and phosphate ions to improve strength at low pH values, promoting the remineralization of the tooth [140]. Moreover, the strong anti-caries action would be facilitated by encapsulating some anti-microbial materials. Remineralization of hard tissues towards treating dental caries follows sequential steps of irrigation, intracanal medicament, and obturation (filling and sealing). The irrigation of the root canal, an initial physical cleaning process, involves the removal of damaged tissues and the introduction of chemicals for preparing the bulk filling process, including the explicit cleaning with anti-microbial agents, demineralization, tissue dissolution, bleaching, deodorizing, and hemorrhage control [141]. Several predominantly applied irrigants include sodium hypochlorite, ethylenediaminetetraacetic acid (EDTA) [15], and chlorhexidine (CHX) [16]. However, some of these irrigants pose compatibility-associated risks. For instance, sodium hypochlorite suffers from a major challenge of cytotoxicity due to the accidental extrusion beyond the apical foramen of the tooth [142]. Considering the limitations of traditional chemicals-based irrigants, several nanoformulations have been developed, possessing enhanced anti-biofilm efficacy and disabling bacterial endotoxins, such as chitosan nanoconstructs [143]. Comparatively, these nanoformulations would be safer in terms of compatibility compared to the sensible release of deadly ROS. Prior to filling the irrigated canal, the root canal is cleaned with the medication referred to as the interappointment intracanal medicaments, employing anti-inflammatory and anti-microbial agents [144]. A typical intracanal medicament applied is the calcium hydroxide paste, which acts as not only an anti-microbial but also a calcium supplement by initiating hydroxyl ions that increase pH and damage microbial DNA, cell membranes, and enzymes [145]. In some instances, other anti-microbial agents, such as AgNPs and chlorhexidine, are mixed with calcium hydroxide, showing enhanced anti-microbial action [146].

The final step of remineralization is referred to as obturation, which is the combination of filling and sealing after the intracanal medication of a canal [147]. Typically, the general bulk fillers, either in the form of solids or semi-solids, along with the sealers, are used to complete the obturation process [148]. The commonly used bulk fillers include silver points, Gutta-percha (GP), and Resilon [149]. The ideal properties of these bulk fillers include compatible, inert, and structurally stable. In recent times, several nanoparticles encapsulated with antibiotics, such as bioactive glass, have been incorporated into these fillers to provide additional benefits, including enhanced mechanical strength and anti-microbial properties [150]. Eventually, the sealing of the filled inert material with the endodontic substances is a crucial step in closing the root canal system, as some of the fillers with flow ability may lead to poor obturation [151]. Sealer is important in overcoming the appropriate deposition of filler and establishing an association with the root dentin. Accordingly, the sealer fills the gaps between the filler and root dentine, achieving the fluid-snug seal [152]. In several instances, anti-bacterial nanomaterials, such as chitosan and ZnO nanoparticles, are added to obturating sealers, facilitating an enhanced anti-microbial action for a long time and mechanical properties, leading to improved remineralization [17, 18].

Regeneration of oral tissues

Indeed, some dental-related ailments often result in the loss of tissues to a great extent, specifically during tooth loss and surgical removal. Indeed, the highly complex extracellular matrix (ECM) microenvironment of native tissues is well organized, guiding cell behavior. However, the regeneration ability of these removed or damaged tissues is quite poor [153]. In this vein, various biomimetic scaffolds for engineering tissues include self-assembled polymers and proteins for cell or drug delivery, as well as layer-by-layer supramolecular complexes. Nevertheless, the reconstruction of damaged tissues using these biomimetic conventional scaffolds may pose various limitations in terms of lack of regeneration abilities. Moreover, the surface coalition with the cells also leads to poor regeneration outcomes due to poor spatiotemporal attributes of the conventional macro-sized materials.

The integration of nanotechnology and encapsulation of several nanoconstructs in the biomimetic scaffolds have offered enormous potential for the functional improvement and structural restoration of tissues [154, 155]. Thus, the integrated nanoconstructs facilitate the host–guest cross-talks and improve regeneration ability [156]. From the host's point of view, the oral tissues could take control of the 3D topology of the designed innovative nanocomposites, improving intercellular communication [157]. From the guest species point of view, the inherent molecular properties of the encapsulated nanomaterials in the biomimetic scaffolds enable the alteration of the spatial rearrangement of their extracellular cues in the ECM. Moreover, these composites enable the improved crosstalk intercellular, enabling the regulation of mechanical signals in the ECM [158, 159]. In addition, the sufficiently high surface-to-volume ratio, abundant surface area, and active surface facilitate the encapsulation of various oro-protective drugs, including antibiotics [160]. Several examples include polymeric nanoconstructs (polylactic-co-glycolic acid, PLGA, polylactic acid, PLA) and inorganic structures (titanium dioxide, TiO_2, calcium fluoride, CaF, Ag, Au, iron oxide nanoparticles, IONPs, and mesoporous silica nanoparticles, MSNs) and their composites [24]. Notably, the particle characteristics (hydrophobicity, curvature, and radius), morphological attributes (size and shape), charge, and coated materials often command the eventual outcome. To a considerable extent, several modifications have been applied, such as immobilizing organic assemblies on the inorganic structures to establish interactions with the biological environment for improved performance [161].

In addition to typical tissue growth using various supplements altering the ECM environment in the oral cavity, stem cells have been employed for tissue regeneration applications. Along this line, human dental pulp stem cells (hDPSCs) can be employed for tissue restoration, in which these specific stem cells can be isolated from the dental pulp of permanent teeth or extracted wisdom teeth. Moreover, periodontal ligament stem cells (PDLSCs) can be harvested from this wisdom tooth to explore the guided periodontal tissue regeneration [154]. Although various sources of stem cells have been available for tissue establishment, in some instances, it is required to improve the odontogenic potential by enhancing their differentiation ability. In this context, some nanoconstructs with exceptional regeneration ability offer improved differentiation efficacy of hDPSc to odontoblastic-like cells, such as inorganic (calcium-based materials, ACP, silicon) and organic (dendrimers) [162–164]. These hDPSCs can be encapsulated in the scaffolds with the mineralized ECM-like components for their improvement of regeneration efficacy, inducing intrafibrillar mineralization of single-layer collagen fibrils [163]. In addition to regeneration potential expressing specific odontogenic/chondrogenic-related genes, these nanoparticles functionalized with peptides may result in the enhanced mineralization process and nerve regeneration of pulp to the neuronal differentiation potential of hDPSCs [162, 164].

Synthetic approaches

Over the decades of research, several approaches have been developed for the synthesis of various kinds of nanomaterials, depending on the physicochemical properties, solubility of the precursors, dimension, size, and applicability of the end products [165]. Despite various kinds of strategies, most of these synthesis methods have been broadly classified into two predominant strategies, *i.e.,* top-down and bottom-up approaches [166]. The top-down process refers to reducing the size of initial bulk materials to nano-sized constructs using externally controlled conditions, for instance, ball milling strategy [167]. The bottom-up approach reduces or miniaturizes the materials to the atomic level and subsequently assembles them into nanometer-sized constructs in an organized manner [168]. For instance, the self-assembly approach results in the colloidal dispersions. Comparatively, the bottom-up strategies are highly advantageous and applied more over the top-down methods due to various reasons, such as the formation of homogenous composition, ease of controlling ability by altering the synthesis conditions, better ordering of molecules, and formation of uniformly dispersed materials [169]. Notably, the selection of an appropriate method often depends on the requirements based on form, dimension, eventual particle size, and yield of the product. Several methods (physical- and chemical-based) have been applied for synthesizing various nanomaterials, such as hydrothermal/solvothermal, magnetron sputtering, ball milling, chemical vapor deposition, solid-state reaction, photoreduction, sol–gel, and spray pyrolysis techniques [170]. Although these methods have been employed extensively, they have limitations in terms of high-temperature requirements, time consumption, and energy prerequisites, requiring the appropriate selection and optimization of the conditions. In this article, we selected some commonly employed techniques, such as self-assembly, templating, phase separation, sonochemical, and miscellaneous (electrospinning, exfoliation, ball milling, and microwave-assisted irradiation) approaches (Fig. 4).

Self-assembly

Self-assembly has emerged as one of the important processes in synthesizing materials, in which the precursors or components are either arranged spontaneously or linked to each other, systematically forming the ordered aggregates without the influence of any external stimuli [171]. This intrinsic process is predominantly evident, including the building blocks in the human body, in which various components can be rearranged, ranging from small-sized (nanometric domains) molecules to large-sized (macroscopic) components that are visible to the naked eye. This process can be broadly classified into atomic [172], molecular [173], and colloidal self-assembly dispersions. The critical features of self-assembly include the appropriate favorable conditions and appropriate charge for establishing the interactions between the pre-existing components. Accordingly, this arrangement of molecules into supramolecular architectures often manifests through diverse mechanisms involving direct and indirect interactions in the solvent environment, such as inter-/intra-molecular forces and Hamaker interaction forces. The arrangement is favorable by minimizing Gibb's free energy, enhancing the attraction between them. These molecules with extended chemical bonds, along with weak interactions, could encompass the nanoscale building blocks at all length scales and dimensions ranging from 0 to 3D nanomaterials [174]. Other advantages include flexibility and ease of scalability [175]. However, the major challenge of self-assembly is that it is difficult to control the designed architectures at appropriate desirable sizes and challenging to predict the outcome.

Phase separation

The phase separation process is the chemical segregation of a single homogeneous mixture into different forms while reducing the free energy. Phase separation-based techniques are classified based on phases, including liquid-phase- and gas-phase-based separations [176]. Among them, the liquid phase requires more attention as it involves an additional phase, resulting in agglomerated particles. This liquid-based approach involves the precipitation of nanoparticles in desired particle size and altered morphological distribution through diffusion or the Ostwald ripening methods [177]. However, it should be noted that the desired morphological attributes could be evident through the strict optimization of the substrate concentration and other conditions, such as the temperature of the reaction. Often, this process results in the extensive aggregation of the components, resulting in the aggregated products over micron-sized structures, limiting their applicability. To overcome this limitation, some additives can be applied while fabricating nanometric domains, such as surfactants [178] or electrolytes [179]. However, these may form contaminated interfaces. The formation of nanometric domains in the separation approach involves a series of steps, including the initial formation of the nucleus through a chemical reaction, subsequent aggregation of molecules, and coalescence

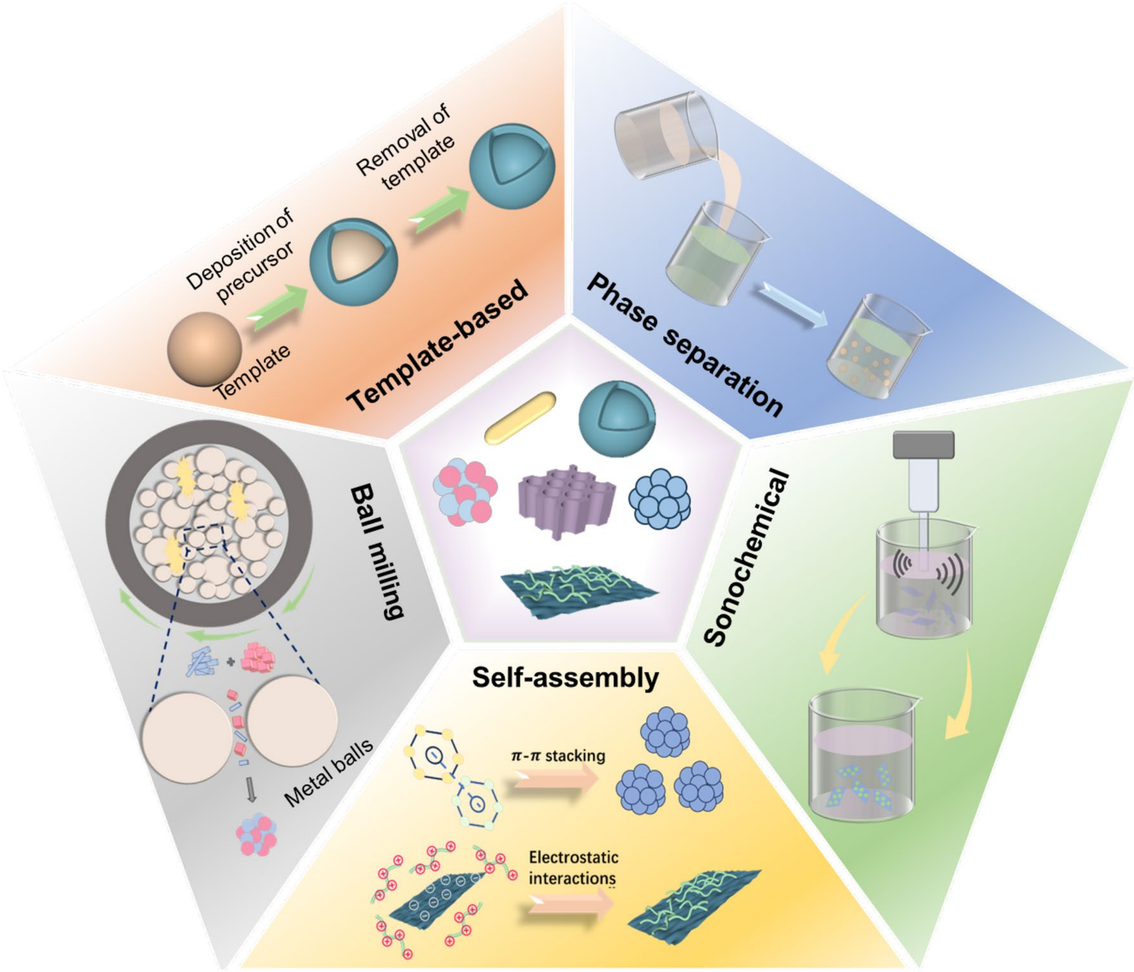


Fig. 4 Schematic illustrating various predominantly applied synthesis approaches (top-down and bottom-up) for generating multiple nanoconstructs in diverse dimensions (0–3D) of miscellaneous precursors

to nanostructures. The application of high temperatures may result in large-sized highly stable agglomerates, which can be separated and pulverized into uniform-sized small particles.

Template-based synthesis

The template-based synthesis approach is applied to fabricate various nanometric domains using the sacrificial templates [180]. including soft (amphiphilic surfactants and vesicles) [181] and hard templates (copper oxide) [182]. This approach is often used to fabricate porous and non-porous constructs, in which these sacrificial templates can be removed to form mesoporous to large-sized porous and hollow architectures. For instance, CTAB is used to generate MSNs [183] and copper oxide for hollow architectures. Initially, the templates are arranged in the required ways considering their physicochemical features, which are further utilized to deposit the precursor of the material of interest. Additionally, the sacrificial templates are removed, resulting in the desired porous architectures. These porous arrays can be employed to encapsulate the desired guest species. Several particle designing strategies include chemical vapor deposition [184], chemical polymerization [185], electrochemical deposition, and sol–gel approaches. This templating approach can be applied to synthesize various nano-sized domains of diverse materials, metals, semiconductors, and other solids in various dimensions, such as 1D (tubes/belts/rods) to 3D materials (hollow spheres) [186].

Sonochemical approach

The sonchemical process has garnered enormous interest from researchers in generating nanoparticles with desired morphological attributes [187]. This facile approach addresses a major limitation of energy requirement compared to other conventional techniques. The synthesis involves the application of ultrasound radiation at a frequency range of 20 kHz to 100 MHz and temperature for acoustic cavitation, in which the sound waves act as an energy source for the conversion of reactants to products [188]. The sound wave strikes the precursors and results in the formation of bubbles. After breaking the bubbles due to acoustic cavitation, the microenvironment surrounding the bubbles leads to high tension, raising the local temperature and forming a high-pressure region [189]. The sudden change in the temperature and pressure conditions activate precursors, forming nanomaterials due to the kinetic energy gained during the reaction kinetics [190]. This facile one-step approach with no additional heat treatment for crystallinity results in high surface area with limited agglomeration as the heat treatment increases crystallinity and reduces surface area [191]. Various inorganic nanoconstructs of ultrasmall-sized constructs, along with convenient fabrication of metal-doped composites and alloys, result in desired particle size distribution for various applications, including biomedicine [192].

Miscellaneous

In addition to various major synthetic strategies with defined principles of nanometric domain synthesis, several other methods have been discussed hereunder, highlighting their importance and shortcomings in synthesizing multiple kinds of nanoparticles. These specific approaches include ball milling, microwave-assisted irradiation, electrospinning, and exfoliation.

Ball milling is one of the most applied top-down processes, referred to as a mechanical operation often applied not only in the food industry for grinding powders but also for synthesizing various nanocomposite materials from their bulk counterparts [193]. This eco-friendly physical modification approach (no solvents required) offers different mechanical actions based on the balls made of stainless steel, ceramic, or rubber, increasing the mechanical reactivity and spatial distribution of precursor components. The formation is based on the principle of applying friction, shear, collision, and impingement of various forces, resulting in the microscopic structures of the bulk components [194]. These balls inside the grinding jar result in frictional forces due to their movement, in which the resulting kinetic energy sufficiently breaks the bonds between the components [195]. The substantial mass and energy transfer leads to the breakdown of the structure. These reduced sizes alter their morphology and functional properties, including dispersibility, heat stability, and retrodegradation. Several operating parameters include the speed of the rotating balls, ball-to-powder ratio, and grinding time, among others. This approach offers advantageous features, such as ensuring higher safety, being facile in nature, cost-effectiveness, and the absence of undesirable by-products. Nevertheless, this approach may result in the aggregation of non-homogenous products, hampering their applicability.

Exfoliation is one of the top-down approaches often used to synthesize single-layered sheets from the bulk sheets of their counterparts. Typically, the bulk sheets, which are composed of a stack of monolayer sheets, are exfoliated into single sheets [196]. This process results in the nanosheets exhibiting improved physicochemical, magnetic, electric, and optical properties [197]. The method of exfoliation can be performed using various strategies based on swelling and delamination, including liquid-phase exfoliation (urea and formamide), plasma-based separation, and dry delamination. More often, the exfoliation approach may result in defect structures, which could present improved physicochemical features. Although convenient and facile, this approach requires large amounts of chemicals and solvents, hampering their applicability. Moreover, the separation of single sheets is highly challenging to get in high yield.

Electrospinning is one of the traditional and widely applied techniques for developing fibrous architectures, such as nanofibers, which can be patterned using the co-axial spinnerets influencing the functional attributes [198]. The predominant advantages of electrospinning to counter the contemporary synthesis methods include one-step, facile in nature, safe, and cost-effective [199]. Moreover, this approach can be effectively applied to design desired nanoarchitectures by substantially optimizing various operating parameters, such as voltage, feeding rate, and tip-to-collector distance. The morphological features can be modified by altering these operational parameters. The major challenge is to generate ultrasmall-sized nanoarchitectures in defined forms except fibrous architectures. Microwave-assisted irradiation is the most applied technique in various chemical reactions due to the advantages of short reaction time (minutes instead of hours), non-utilization of solvents, and high yields [200]. This approach reduces the utilization of organic solvents in large amounts and saves energy consumption and cost. Considering these attributes, this approach has been applied recently for the synthesis of nanomaterials (for instance, graphene) due to the rapid reaction rates and homogenous heating of the precursor materials in the reaction system [201].

Nanotherapeutic solutions

As one of the exquisite innovations of humankind, nanotechnology has attracted enormous attention from researchers since its advent in the mid-1950s towards various innovative applications, including medicine [24]. However, these innovative nano-sized constructs have been applied recently as therapeutic solutions to treat and prevent various dental-related infections. In this framework, several advancements have been evidenced by the generation of diverse kinds of nanoparticles based on the source of precursors, including natural (plant-, animal, and marine-life) and synthetic (organic-, inorganic-, as well as organic–inorganic) nanocomposites. More often, these innovative ultrasmall-sized nanomaterials can be incorporated into various macro-sized constructs for improved applicability, such as resins, ceramics, and metals, among others. These composite mixtures can be applied to various locations of the teeth based on the relevance and type of ailment, such as prosthetics, endodontics, periodontal treatments, and comprehensive implantation. Moreover, the therapeutic effects, either by themselves or through encapsulating various drugs, can address various dental ailments, such as anti-inflammatory agents for addressing gingivitis for gum-related disorders, anti-microbial agents for treating periodontal and cariogenic bacteria and remineralizing nanocomposites, for curing dental-related diseases by reducing the hypersensitivity of the tooth. In this section, we discuss various kinds of nanoconstructs from natural (plant-, animal-, and marine-derived) and synthetic (organic/inorganic/organic–inorganic) sources, highlighting the oral applications towards improved dental health (Fig. 5, Table 2).

Nature-derived constructs

Indeed, nature has provided us with enormous opportunities in terms of therapeutic potential through various ways, such as drugs and sources for synthesizing materials. Although these therapeutic materials are synthesized in a facile way with mild synthesis conditions and ultrafacile precursors, the materials have emerged as highly complex architectures through evolution for millions of years. Considerably, these complex architectures offer exceptional mechanical properties, outperforming the synthetic components and their combined mixtures. In addition, these natural components exhibit large diversity with extensive sources of precursors with degradability attributes. In this regard, various small molecules from natural sources have been widely applied as anti-microbial agents and remineralization of enamel [202]. Several sources, such as plants, animals, and marine life, have been available for the fabrication of various nanocomposites. Although, in some instances, various nature-derived

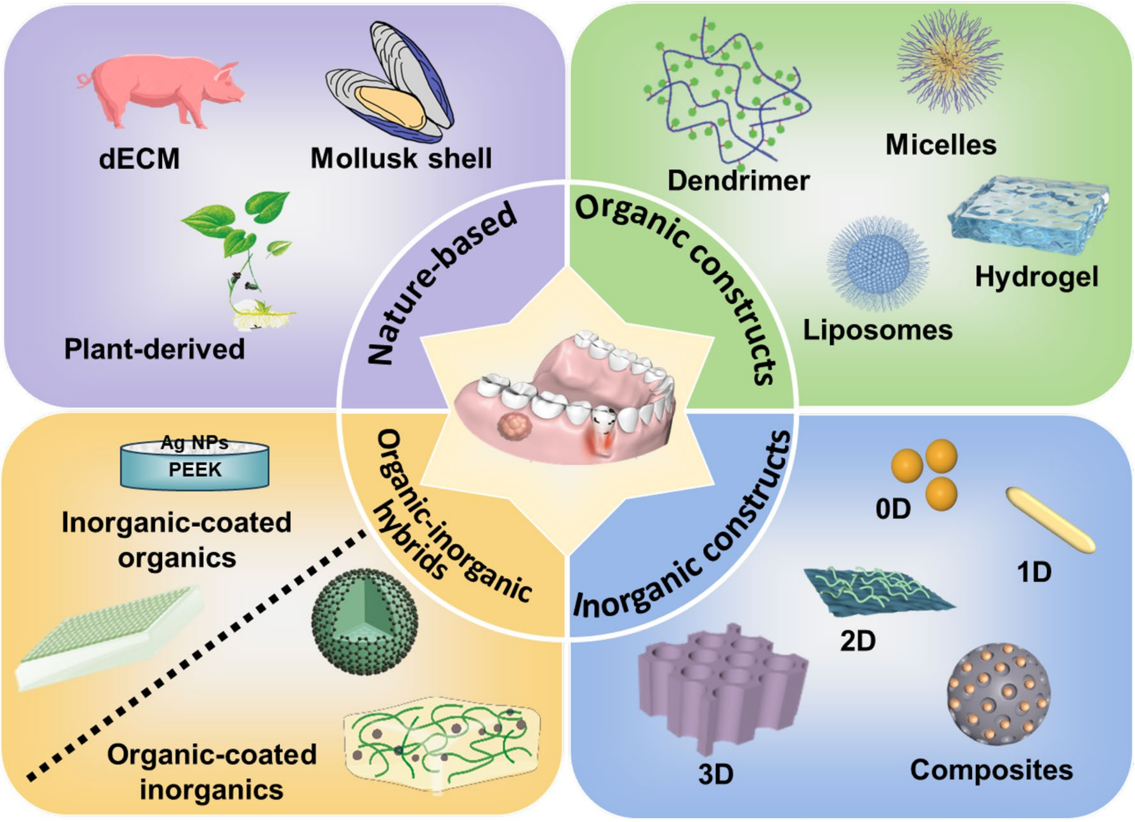


Fig. 5 A representation illustrating various predominantly applied nanoarchitectures based on natural (plant/animal/marine-derived) and synthetic (organic-/inorganic-/organic–inorganic-based) nanoconstructs of miscellaneous precursors

Table 2 A summary of various nanostructured components for various dental-related ailments

	Type	Precursor	Size	Drug	Ailments gum/tooth/oral	Outcome	Refs.
Nature-derived constructs	Plant-derived extracts	Proanthocyanidins (PA), myricetin, resveratrol, and kaempferol	–	–	Remineralization	Exhibited the efficacies of the four polyphenols in promoting dentin biomimetic remineralization and improving resin-dentin bond durability. The surface hardness of PA-pretreated dentin was the greatest. µTBS decreased significantly during aging	[202]
		Chlorhexidine gluconate	–	Melaleuca alternifolia	Oral anti-bacterial、anti-inflammatory	MEL nanoparticle domains have significantly lower mean Quigley & Hein plaque index on biofilm-free and biofilm-covered surfaces, presenting exceptional anti-inflammatory effects with better control over the biofilm	[204]
		Propolis nanoparticles (NPro) and nano-curcumin (NCur)	93.56 nm	NCur	Orthodontic treatments	The amount of micro-hardness significantly increased over time. NPro + NCur-PDT treatment remineralization in that group had improved considerably compared to other groups	[212]
	Animal-derived composites	Gelatin/dECM	–	–	Periodontal defects	These biomimetic scaffolds enhanced immunomodulatory effects, reduced proinflammatory factors released by M1 macrophages, decreased local inflammation, and improved the periodontium regeneration potential of hybrid periodontal tissues in rats	[210]

Table 2 (continued)

	Type	Precursor	Size	Drug	Ailments gum/tooth/oral	Outcome	Refs.
	Marine-derived components	Abalone nacre water-soluble organic matrix (WSM)	155 nm	–	Dental remineralization	WSM could induce the growth of enamel-like hydroxyapatite crystals to facilitate biomimetic remineralization of the demineralized enamel further and restore its continuous and smooth surface structure in vitro	[211]
Organic (synthetic) assemblies	Polymeric conjugates	Polymeric nanoparticles loaded with Zn NPs	225.9 nm	Zn NPs	Cariogenic biofilm	The combined anti-bacterial and demineralizing effects, when Zn-NPs were applied, reduced biofilm formation	[256]
		Melatonin-doped polymeric nanoparticles	–	Melatonin	Endodontic	Advanced functional dentin remineralization and higher crystallinity were achieved and preserved with the use of ML-NPs	[257]
		SHEDs/SMS	14 µm	Stem cells	Dental pulp necrosis	These composites promoted vascularized tissue regeneration proliferation and exhibited cell protection properties	[216]
		N-BSA-CDP	790.87 nm	PLGA nanoparticle	Alveolar bone regeneration	Accelerate hard tissue regeneration and sustained release could be achieved for > 12 weeks with all formulations	[217]
		HA hydrogels	342 nm	NanoGSK	Periodotitis	Overexpressed MMP-2 could release NanoGSK cargo in the gingival tissue of periodontitis, inhibiting inflammation-induced PERK and exhibiting exceptional alveolar bone repair capability	[218]

Table 2 (continued)

Type	Precursor	Size	Drug	Ailments gum/tooth/oral	Outcome	Refs.
	p(GEMA-*b*-FA)-I and p(GUA-*b*-FA)-I	184.3 nm-196.3 nm	Nanophotosensitizer	Treatment of biofilm-induced diseases	p(GF/GEF)-I immersed in the EPS matrix could produce ROS oxidized the polysaccharide matrix under light irradiation, destroying and degrading the biofilm	[213]
	PAA-CMC-TDM	–	Calcium phosphates (ACPs)	Regeneration of dentin/bone hard tissue	Hydrogel could promote the odontogenesis or osteogenic differentiation of mesenchymal stem cells, adapt to irregular hard tissue defects, and promote in situ regeneration of defective tooth and bone tissues	[219]
Dendrimers	PAMAM	–	αVβ3-specific, cyclic arginine-glycine-aspartic acid (RGD) peptides	Regeneration of dentin/bone hard tissue	Long-term G5-RGD treatment of dental pulp cells resulted in enhanced mineralization as examined via Von Kossa assay, suggesting that PAMAM dendrimers conjugated to cyclic RGD peptides can increase the odontogenic potential of these cells	[162]
Liposomes	1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC)	100 nm	ICG-rapamycin	Oral microenvironment-regulating	The encapsulated nanoparticles significantly altered the oral microenvironment. In addition to improved microbial-cellular interactions, these composites promoted macrophage M2 polarization, upregulating the anti-inflammatory effects and promoting phagocytosis	[225]

Table 2 (continued)

	Type	Precursor	Size	Drug	Ailments gum/tooth/oral	Outcome	Refs.
		Tris(tetra-n-butylammonium) hydrogen pyrophosphate-binding CHEMS-PEG2000-OH liposomes	200 nm	Magnolol and fluconazole	Dental caries	The nanoplatform overcame the hydrophobicity, improved the medicinal properties and antibacterial activity of both drugs against *C. albicans* and *S. mutans*, and effectively delivered the drugs to dental caries because of their high affinity for hydroxyapatite	[226]
	Micelles	mPEG-b-PDPA	300 nm	Bedaquiline	Dental caries	The hydrophilic micelles could deliver bedaquiline, a hydrophobic antibacterial agent on *S. mutans*, in acidic environments and mature biofilm. No cytotoxic effect on the periodontal cells was detected within 48 h	[228]
		MAL-PEG-b-PLL/PBA	–	TA, NAF, and DpSpSEEK (SAP)	Dental caries	The micelles could provide anti-bacterial adhesion and cariogenic biofilm resistance and restore the microarchitecture and mechanical properties of demineralized teeth	[229]
Inorganic (synthetic)	0D	Ag NPs	–	–	Dental fillers	The shear bond strength decreased after the incorporation of Ag NPs (0.3% (w/w)) but was still above the recommended SBS of 5.9–7.8 MPa. This was associated with significant anti-bacterial activity that did not change much after 30 days	[303]

Table 2 (continued)

	Type	Precursor	Size	Drug	Ailments gum/tooth/oral	Outcome	Refs.
		AgF	7–30 nm	–	Enamel	The AgF test presented long-term stability and superficial and in-depth demineralizing capacity with anti-microbial potential and biocompatibility and did not stain the enamel	[304]
		GA-Ag NPs	4–26 nm	–	Dental caries	The GA-Ag NPs 0.4 g inhibited *S. mutans* adhesion and biofilm formation on the surface of the tooth enamel	[280]
	1D	ZnO nanorods	50 nm	–	Periodontitis	Bdellovibrio triggered ZnO nanorods to produce ROS to enhance the removal of plaque biofilm	[233]
	2D	Boron nitride (BNNPs)	2 μm	–	Dental fillers	BNNP showed potential as a solution to the low-temperature degradation phenomenon, but there was no obvious toxicity	[234]
		Epoxy resin, $Ti_3C_2T_x$ MXene	300 nm	–	Dental fillers	The as-fabricated MXene/resin composite exhibited improved mechanical and abrasive results and displayed antibacterial activity due to the high photothermal efficiency of MXene	[305]
	3D	Zn-Dex-NPs	100–200 nm	Dexamethasone	Dental implants	Dentin surfaces treated with Zn-Dex-NPs attained the lowest nano-roughness values, provoked the highest crystallinity, and produced the longest and shortest crystallite and grain size	[258]

Table 2 (continued)

Type	Precursor	Size	Drug	Ailments gum/tooth/oral	Outcome	Refs.
	Drug@HDPA NPs	87.8 nm	Osteogenic drugs	Tooth extraction fossa bone generation	The drugs could effectively be released from the HPDA NPs, promoting osteogenic differentiation and proliferation of rat bone marrow mesenchymal stem cells (rBMSCs). The HPDA NPs effectively promoted bone regeneration in the defect of tooth extraction fossa	[215]
	Au–Ag nanoparticles containing procyanidins AuAg-PC(IIIIII)	49, 79, 122 nm	PC	Periodontitis	Ag^+ contributed to the preparation of a nanoparticle-branched structure that improved the photothermal efficiency and helped PTT achieve an excellent anti-bacterial effect and avoid periodontal tissue damage	[230]
	Fe_3O_4-doped ZrO_2	35 nm	–	Dental fillers	The inhibition zone of ~32 mm against bacillus bacteria was revealed, suggesting their potential use as dental filler. Relatively high microwave power results in volume shrinkage	[240]
	nZnO/MTC-Ti	–	ZnO	Osteogenesis, Antibiosis	The accelerated osseointegration, antibiosis, and improved anti-bacterial action of nZnO/MTC-Ti implants facilitated improved performance efficacy in SD rats in vivo after tooth extraction	[236]
	SiO_2-Ag-NPs	418–502 nm	Ag	Dental prosthesis	Superior dispersion was selected for the anti-biofilm test, then with increased concentration, causing ablation of bacteria	[281]

Table 2 (continued)

	Type	Precursor	Size	Drug	Ailments gum/tooth/oral	Outcome	Refs.
		CHX-SNPs	–	chlorhexidine (CHX)	Dental composites	CHX-SNPs exhibit desirable antimicrobial potential against the main bacteria related to oral biofilm formation and can act as fillers to assure satisfactory physicochemical properties of the nanomaterial,	[282]
		$nCaF_2$	32 nm	–	Dental materials	Nanocomposites with nCaF2 particles in the BisGMA-TEGDMA resin had an initial flexural strength of 1.5 folds of commercial control composite. They had fourfold greater strength results than the commercial resin-modified glass ionomer restorations	[231]
		FerIONP	–	Ferumoxytol	Antibiosis	FerIONP nanoparticles are bound preferentially to S mutans biofilms, generating free radicals in situ to kill bacteria effectively	[306]
Supramolecular (organic–inorganic) composites	Organic-coated inorganics	E/PA@HMS	408.4 nm	EGCG/PAH-ACP	Exposure of dentin tooth and caries	E/PA@HMS induced interfibrous mineralization and demineralized dentin remineralization of collagen fibers	[7]
		ZnO- Chitosan nanoparticles	< 25 nm	ZnO	Restorative dentistry	Chitosan-decorated ZnO nanoparticles had been effectively illustrated and in-specifically boosted by chitosan-capped ZnO nanoparticle-reinforced dental adhesive discs	[246]

Table 2 (continued)

Type	Precursor	Size	Drug	Ailments gum/tooth/oral	Outcome	Refs.
	PSTA PAH-ACP-loaded silica/mesoporous titanium–zirconium (STZ) yolk-shell nanocomposite (PSTZ)	–	Amorphous calcium phosphate (ACP)	Dentin hypersensitivity	The outstanding acid and mechanical resistance induced intrafibrillar mineralization of single-layer collagen fibrils and remineralization of demineralized dentin matrix and promoted the odontogenic differentiation of dental pulp stem cells by releasing ACP and silicon ions	[247]
	DAA hydrogels	29.10–40.23 nm	TA@PVP NPs	Oral Cancer Treatment	Ta@PVP-DAA hydrogels effectively inhibit tumor development under photothermal-assisted radiotherapy while avoiding the appearance of deformities and damage to surrounding normal tissues (oral mucosa, skin, and salivary glands)	[248]
	Piezoelectric nanoparticles ($BaTiO_3$) into dental resins	–	$BaTiO_3$	Dental composite	A significant reduction in biofilm growth and the formation of thick and dense layers of calcium phosphate minerals in piezoelectric composites compared to control groups were observed	[249]
	Triglycerol monostearate/2,6-di-tert-butyl-4-methylphenol	–	Copper tannic acid coordination nanosheets, CuTA NSs	Periodontitis	CuTA can further transform M1 macrophages to M2 macrophages through the regulation of the Nrf2/NF-κB pathway, thus reducing the pro-inflammatory factors as well as upregulating the anti-inflammatory factors and the expression of osteogenesis genes, further promoting periodontal tissue regeneration	[250]

Table 2 (continued)

Type	Precursor	Size	Drug	Ailments gum/tooth/oral	Outcome	Refs.
	PDA-HA-Gelatin @ Ti (PHG@Ti)	–	PDA	Dental implants	The PHG coating showed anti-bacterial activity against Streptococcus mutans, as well as anti-inflammatory effects, potentially via the regulation of macrophages	[252]
	PEI micelles	–	Fe_3O_4 and $BiVO_4$	Dental Implant Biofilm Eradication	The enclosed Fe_3O_4 materials could propel under a transversal rotating magnetic field, while the $BiVO_4$ produced excessive ROS to eradicate biofilm colonies by 90% in the oral microenvironment	[254]
	Sulfonated lignin-Pd (SLS-Pd)	4–8 nm	Pd NPs	Oral polymicrobial biofilm infection	These nanoparticles could be conducive to the reduction of O_2 on the surface, essentially generating the NIR-induced hyperthermia towards ablating S. mutans and Enterococcus Faecalis (E. faecalis) via its oxidase-like property, eradicating oral polymicrobial biofilm-associated infections	[255]
	Dual-sensitive anti-bacterial peptide nanoparticles pHly-1 NPs	40 nm	pHly-1 NPs	Dental caries	The peptide underwent the coil-helix conformational transition upon binding to bacterial membranes in the acidic cariogenic biofilm microenvironment, thereby killing cariogenic bacteria. Displayed reliable anti-bacterial activity against *bacteria*, mainly via cell membrane disruption	[279]

Table 2 (continued)

Type	Precursor	Size	Drug	Ailments gum/tooth/oral	Outcome	Refs.
	NACP + DMAHDM	–	NACP	Dental caries	Adhesive released a great number of Ca^{2+} and PO_4^{3-} ions, increased pH to 5.81 via acid neutralization, decreased production of lactic acid, and reduced amount count of S. mutans	[290]
	ALONs-CaP	20–50 nm	CaP	Mineralized collagen fibrils are the basic building blocks of bone, dentin, and cementum	Providing a new collagen mineralization strategy to promote intrafibrillar mineralization	[291]
	Enamel protein amelotin (AMTN) based bio-nano complexes	–	Enamel	Dental implant	The bio-nano complexes showed pretreatment of dentin with the bio-nano complexes before adhesive application significantly improved shear bond strength	[260]
	Sr-N-co-doped titanium dioxide (Sr-N-TiO_2) nanoparticles and nano-hydroxyapatite (n-HA)	–	–	Dental caries	The resin exhibited excellent self-remineralization and showed significant inhibition effects	[259]
	Chitosan–Nano-Hydroxyapatite	15–30 nm	Hydroxyapatite	Oral surgery for bone regeneration	There is no cytotoxicity in membranes decorated with CHI–HApNPs. An antimicrobial effect on the surrounding medium was demonstrated for the tested Gram-negative bacteria, *F. nucleatum*, and *P. gingivalis*	[294]
	DMP1 or BMP2 plasmid DNA-carrying calcium phosphate nanoparticles	57 nm or 121 nm	Dentinogenesis-inducing factors	Dentin scaffolds	Nanoparticles combined with HTFD scaffolds preserved high levels of cell viability in vitro and caused no adverse reactions in vivo, and the HTFD/NP constructs induced a rapid and pronounced odontogenic shift of the DPSCs,	[298]

Table 2 (continued)

	Type	Precursor	Size	Drug	Ailments gum/tooth/oral	Outcome	Refs.
		Wnt3a-HANW@MpSi core – shell nanocomposite	30–50 nm	Wnt3a and Si ions	Pulp exposure	The composites promoted the oxidative stress resistance of dental pulp stem cells (DPSCs), enhanced their migration and odontogenic differentiation, and exhibited superior properties of angiogenesis toward pulp/dentin regeneration	[300]
		$nCaF_2$ + DMAHDM	32 nm	CaF_2	Dental nanocomposite	The nCaF2 + DMAHDM composite had similarly potent biofilm reduction, with mechanical properties matching those of the commercial control composite	[307]
		Zn-NP (Polymeric nanospheres)	120 nm	Zn	Dental implants	The combined anti-bacterial and demineralizing effects, when Zn-NPs were applied, reduced biofilm formation, promoting a durable sealing ability	[308]
	Inorganic-coated organics	PCBAA/AC	50.67 nm	ACP	Dental fillers	The nanocomposite demonstrated superior effects in promoting the remineralization of demineralized enamel and the occlusion of exposed dentinal tubules	[242]

extracts are not in nanometric domains, it is worth discussing their efficacy in addressing oral ailments. In this section, we present a detailed view of various nature-derived components, highlighting their advantages and applicability against various oral diseases.

Plant-derived extracts

The extracts of various plants with exceptional medicinal value have been employed for the treatment of different ailments, including oral diseases. Predominantly, these phytochemicals possess various bioactive components, including but not limited to flavonoids, phenolic acids, terpenoids, tannins, and alkaloids, among others. These medicinal components with improved pharmacological (anti-bacterial, anti-oxidant, anti-cancer, and anti-inflammatory) activities are of particular interest in various oral conditions of periodontitis, gingivitis, and other oral-related ailments [203]. Typically, these phytochemicals with aromatic features and anti-bacterial effects have been applied in traditional medicine as mouthwashes to act against various biofilms effectively. Along this line, several examples include *Salvia sclarea L., clary*, *Melaleuca alternifolia*, *Punica granatum L. fruits*, *Matricaria chamomilla L.*, *Rosmarinus officinalis*, *Punica granatum L. Lippia sidoides Cham.*, *Scutellaria baicalensis,* and *Camellia sinensis*, among others [203–206]. Notably, various biofilms are designed by the microbes as an ecological strategy for establishing multiple communities of various bacterial species. Furthermore, the formed biofilm is developed into a reservoir of chronic infections, resulting in the acquired resistance to the host immune system and anti-bacterial molecules. Importantly, caries and periodontitis are caused by several biofilms, resulting in the challenges of treating oral diseases. Considering the anti-bacterial resistance, the utilization of medicinal plants seems to be an affordable option for manipulating the acquired resistance by various bacterial communities in the biofilms. Moreover, these natural phytochemicals are better than chemotherapeutics in terms of no adverse effects. In an instance, Casarin and colleagues demonstrated the fabrication of *Melaleuca alternifolia*-based nanoparticles with 0.12% chlorhexidine gluconate against oral microorganisms in participants [204]. The designed nanoparticles were subjected to explore the anti-biofilm and anti-inflammatory effects on biofilm-free (BF) and biofilm-covered (BC) surfaces for comparison by assessing the Quigley & Hein plaque index (QHPI), gingival crevicular fluid (GCF) volume of the patients. Interestingly, the nanometric domains with significantly lower mean QHPI on BF and BC surfaces presented exceptional anti-inflammatory effects with better control over the biofilm. Although various plant extracts have been employed against oral infections, it is yet to explore the establishment of various nanotechnological solutions comprehensively using these exceptional medicinal plants. In addition, further clinical trials with different testing methods are required to explore their clinical applicability.

Considering the fabrication of nanoparticles, various physicochemical strategies have been developed over the past few decades, including chemical vapor deposition, lithography, laser ablation, electro-deposition, and sol–gel techniques [36]. However, these approaches suffer from various limitations, such as expensive and deprived biocompatibility and reproducibility challenges. Moreover, several methods are environmentally unfriendly due to the utilization of organic solvents, hampering their utility. In search of cheaper and eco-friendly sources, several reports demonstrated the utilization of nature-derived extracts from plants and microorganisms, which are subsequently applied for the fabrication of metallic nanoparticles. Among various sources, plant-based extracts (root, bark, leaf, and flowers) can be rapidly prepared for the synthesis of metallic nanoparticles in vitro using a single step, requiring no sophisticated purification methods [205]. These extracts containing various phytochemicals (e.g., terpenoids, alkaloids, and phenolic substituents) and secondary metabolites (amino acids, vitamins, proteins, polysaccharides, enzymes, and antioxidants) reduce to corresponding metallic nanoparticles. The classic example of plant-based reduction is the synthesis of AgNPs, which are synthesized by optimizing various formulations (pH, precursor concentration, and phytochemical composition) and processing parameters (reaction temperature). The conditions of basic pH and optimal temperature are often favorable for the synthesis of these spherical-shaped AgNPs. More often, these plant extracts act by enhancing the reduction efficacy of the metal precursors. Nevertheless, the synthesis of spherical-shaped AgNPs is usually favorable at high temperatures around 100 °C. To this end, the alternative route of AgNP synthesis using the mesophilic organisms utilizes ≤ 40 °C, resulting in smaller-sized AgNPs. Together, these plant-derived AgNPs can be fabricated at ambient temperatures ranging from 25 °C to 37 °C. These metallic nanoparticles can be highly effective for dental-related ailments, predominantly for the anti-microbial effects, attributing to several synthetic parameters, including but not limited to surface composition, charge, and size [207]. These green approach-based metallic nanoparticles with intrinsic features of stability and compatibility attributes could be substituted with chemically synthesized metallic nanoparticles due to various reasons, such as cost-effective and high performance efficacy against oral pathogens [208, 209]. Several plant sources include *Azadirachta indica* (*A. indica*), *Ficus bengalensis* (*F. bengalensis*), and

Salvadora persica (*S. persica*), which have been applied for the synthesis of AgNPs for dental-related ailments [203, 205]. Moreover, these biogenic nanoparticles eventually showed improved anti-microbial effects compared to chemically synthesized nanoparticles and traditional antibiotics. In addition, several antibiotics in combination with AgNPs from the leaf extract were highly effective against various microorganisms associated with dental caries and periodontal diseases, ablating *Escherichia coli (E. coli), Streptococcus mutans (S. mutans), Lactobacillus lactis (L. lactis), Lactobacillus acidophilus (L. acidophilus), Staphylococcus aureus (S. aureus), Bacillus subtilis (B. subtilis), Pseudomonas aeruginosa (P. aeruginosa), Micrococcus luteus (M. Luteus), and Candida albicans (C. albicans)* [205]. Owing to these aspects, these biogenic metallic nanoparticles can be added with different formulations, such as mouthwashes and toothpaste, offering anti-bacterial activity towards sustainable therapeutic effects against oral pathogens.

Animal-derived composites

The plentiful endowment of animal tissues offers a potential solution to address the desperate shortage of human tissues substantially. Considering the material affordability, several animal tissues can be grown into functional organs due to their structural and functional attributes. In the field of tissue engineering, repairing abnormal or damaged tissue remains a significant challenge for external scaffolds due to the lack of stimulation of the tissue microenvironment and supportive components for tissue growth. In this vein, decellularized ECM (dECM), an exquisite biomaterial from natural tissues, has garnered enormous attention from researchers due to their biocompatibility and malleability attributes, for instance, dECM based on porcine tissues. These advantages, along with various exceptional structural and morphological characteristics, facilitate natural cell infiltration, improving tissue regeneration. In addition, dECM possesses various proteins (collagen, proteoglycans, fibronectin, and glycoproteins) and exceptional growth factors simulating the tissue environment. These natural tissue-mimicking environments enable the transmission of appropriate signaling cues and facilitate the proliferation and differentiation of the deposited cells in the dECM matrices. Along this line, some efforts have been made to employ dECM-based scaffolds for improved oral health. Typically, the poor orientation of fibers and mismatched bone-ligament interface fusion may result in periodontal defects. In a case, Yang and coworkers addressed these defects by designing a 3D bioprinted periodontal module using the gelatin/dECM composite bioink (Fig. 6A) [210]. Considering the exceptional mechanical properties and biochemically conducive environment, these biomimetic scaffolds offered high-precision topographical cues, regulating encapsulated cell behavior. In addition, several important attributes included enhanced immunomodulatory effects, reduced proinflammatory factors released by M1 macrophages, and decreased local inflammation. Moreover, these scaffolds presented well-aligned periodontal fibers, the anchored structures of the bone–ligament interface, and highly mineralized alveolar bone, improving the periodontium regeneration potential of hybrid periodontal tissues in Sprague–Dawley (SD) rats. Considering the exceptional attributes, dECM from the other sources can be applied towards the development of personalized periodontium regeneration. Although it opens a new avenue for improving oral health, there is a long way to go as it requires numerous trials at different levels of animal and human for their applicability in clinics.

Marine-derived components

Marine life has provided us with enormous opportunities for dental health, such as seashells, bones, and corals, among others. These marine components offer exceptional biocompatibility and mechanical properties, which are of particular interest towards displaying various functional attributes of osteoconductive and osteogenic properties, as well as anti-thrombogenic and anti-microbial activities. Enamel, the outermost layer of hard tissue, is the hierarchical structure, which is an outermost surface that might be prone to damage during external stress or bacterial infection in caries. The controlled spatiotemporal order of this organic matrix is referred to as amelogenin, and the regulation of the ameloblasts plays a crucial role in the mineralization of hydroxyapatite. Nonetheless, the enamel loses its ability to regenerate due to the apoptosis of the ameloblasts and eventual degradation of amelogenin. In an attempt to reconstruct the enamel-like hydroxyapatite structures, Xing et al. isolated abalone nacre water-soluble organic matrix (average size of ~ 155 nm) using the ultrasonication-assisted extraction without disturbing the bioefficacy towards hard tissue mineralization (Fig. 6B, C) [211]. These components, inspired by the mineralization of mollusk nacre by nature, substantially improved the yields of the protein (7.60–9.60%) and polysaccharide (2.59–3.34%). These innovative structures coupled significantly induce the growth of enamel-like crystals to facilitate the biomimetic remineralization of the enamel towards forming a smooth tooth surface of a mineralized layer in vitro, enabling the elastic modulus and restoring the tooth permanently. In another instance, the propolis nanoparticles and curcumin from a plant source were applied to bovine tooth remineralization based on photodynamic therapy (PDT) [212]. For example, various natural polyphenols

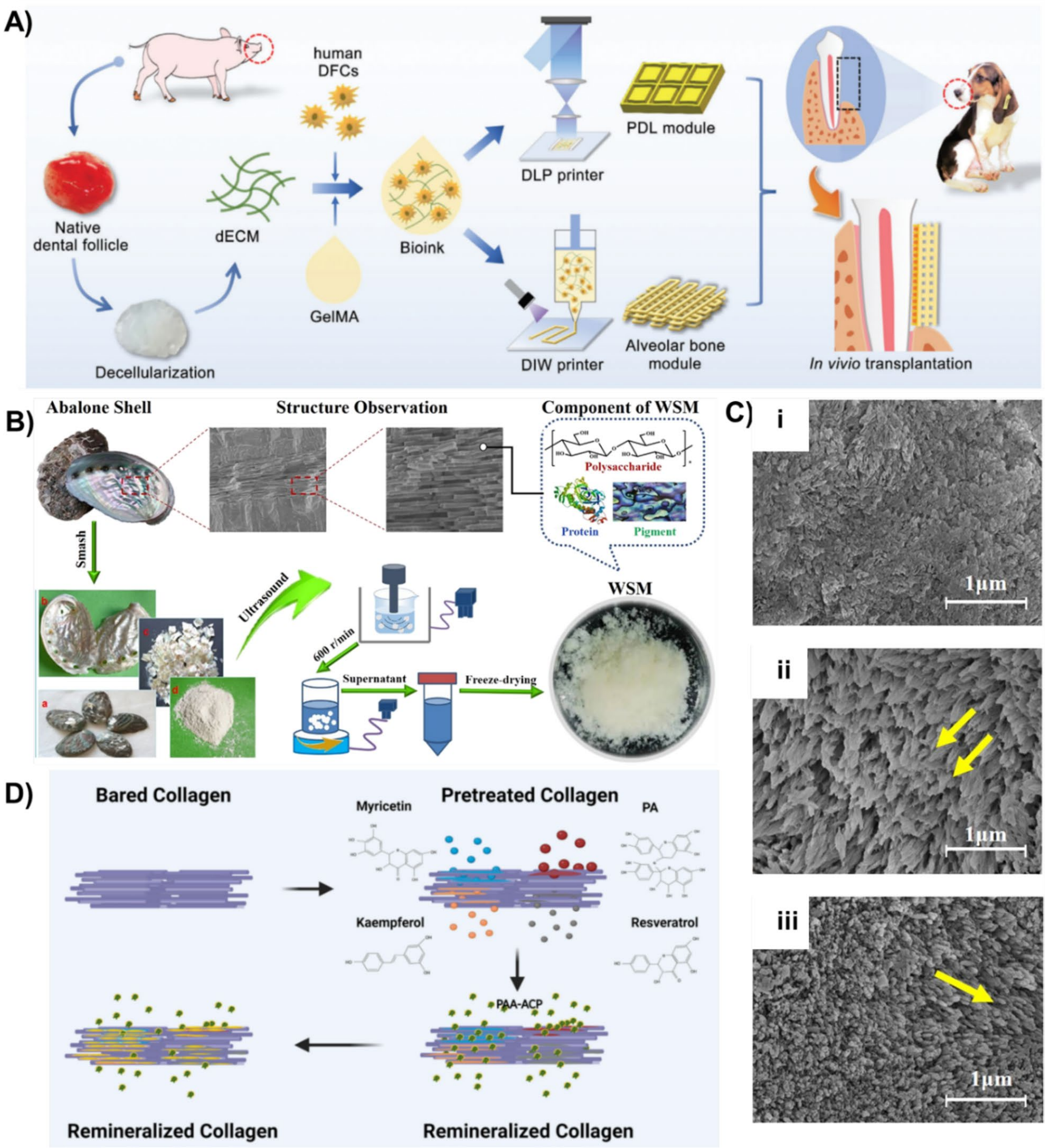


Fig. 6 **A** Schematic overview of the 3D bioprinting of periodontal modules with GelMA/dECM bioink encapsulating human DFCs for periodontal regeneration. Reproduced with permission from Ref. [210] Copyright 2023, John Wiley & Sons. **B** The preparation procedures for WSM extraction using the UAE strategy. FESEM images of an enamel-like HA layer grown on acid-etched enamel. **C** The remineralized enamel at different additions of WSM: (i) without addition, (ii) 0.025 wt%, and (iii) 0.075 wt%, respectively. (Yellow arrows show the re-mineralized layers). Reproduced with permission from Ref. [211] Copyright 2022, Elsevier. **D** Schematic illustrating the outline of various natural polyphenols (proanthocyanidins (PA), myricetin, resveratrol, and kaempferol) from plants on resin-dentin bonding performance towards remineralization. Reproduced with permission from Ref. [202] Copyright 2023, Dovepress

(proanthocyanidins (PA), myricetin, resveratrol, and kaempferol) from plants also showed improved resin-dentin bonding performance by inhibiting the matrix metalloproteinase (MMP) activity (Fig. 6D) [202]. In another instance, Yan and coworkers designed potential dental materials by comprehensively analyzing various natural mollusk shells (*Strombus gigas, Strombus latissimus, Lotoria lotoria, Cypraecassis rufa, Lambis lambis, Chicoreus torrefactus, Hippopus porcellanus, and Tridacna squamosa)*. Interestingly, the authors systematically demonstrated their feasibility by determining their aesthetic performance, mechanical and biomedical properties, as well as machinability. Among various species, the *Strombus latissimus* shell offered exceptional flexural strength and high fracture toughness, exhibiting highly stable crack extension over the commercially available 3Y-TZP dental materials. Considering the biocompatibility and antifungal attributes due to hydrophilicity and negative surface charge, these specified natural mollusk shells could offer a unique combination of natural teeth-like characteristics towards oro-dental applications. Although the in vitro findings demonstrated exceptional therapeutic abilities, it is further required to demonstrate their in vivo capabilities.

Organic (synthetic) constructs

Several organic-based nanoparticles have been synthesized for various biomedical applications, including the treatment of dental-related ailments. In this framework, different kinds of polymeric constructs with a carbon backbone include polymeric (PLGA, PLA, chitosan, and alginate), liposomal (DSPE and cholesterol), micellar/vesicular (surfactants), collagozomes, and dendrimer-based constructs. The arrangement of these polymers into nano-sized particles is often facilitated by their assembly based on various intermolecular interactions based on coordination, ionic, hydrophobic, and Van der Walls forces. Like inorganic species, these polymeric delivery systems can encapsulate different drugs (anti-inflammatory, anti-microbial, and anti-cancer drugs) and deliver them appropriately. In contrast to inorganic species, these organic species are preferred due to their facile synthesis, colloidal stability, biocompatibility, and degradability. In addition, these organic species with supramolecular structures could overcome the macrophage escape and are safer to use for biomedical applications compared to inorganic species. However, these constructs suffer from poor thermal stability and bioavailability issues, resulting in poor dosage-related risks. Accordingly, there exists a debate between the organic and inorganic-based materials regarding their properties and performance attributes.

Polymeric conjugates

Recently, several efforts have been dedicated to the application of various polymeric nanoparticles for the treatment of dental ailments. In this vein, different kinds of polymers employed for the fabrication of nanoplatforms for the delivery of antimicrobials and scaffolds for engineering tissues include PLGA, polyethylene glycol (PEG), PLA, chitosan, and alginate, among others. The predominant role of different polymeric constructs has been the protection of teeth and gums from bacterial infections. Although several delivery platforms for the release of antibiotics have been developed for teeth protection, the resultant high-protein biofilm formed for their defense is highly challenging in cracking down bacterial infection on the surface of teeth. In addition, these consequences substantially result in the development of resistance to antibiotics, limiting their bioavailability and reducing efficacy. To address the adequate penetration, targeting ability, and degradation of biofilms, several intelligent nano-delivery systems have been developed to improve biofilm permeability and increase their bioavailability. In an attempt to overcome the dreadful hypoxic biofilm, low pH, and nutritional deprivation microenvironment, Wang and colleagues demonstrated the Boron dipyrrolidyl iodide (BODIPY-I)-based phototherapy to eliminate pathogenic bacteria under laser irradiation (Figs. 7A, B) [213]. By decorating these nanophotosensitizers with guanidine and galactose and copolymerized perfluoropolyether through self-assembly, these formulations offered the oxygen self-sufficient capability, greatly limiting the oxygen-dependent PDT effects. In addition, the positively charged surfaces of the formulation enhanced biofilm permeability towards eradicating oral biofilms. These nanophotosensitizers with positively charged surfaces inhibited the recolonization of *S. mutans* with improved efficacy against dental biofilms, preventing secondary infections without harming the surrounding healthy tissue in the oral cavity. In addition to being antimicrobial, these polymeric conjugates can be employed for the ablation of oral carcinomas, specifically oral squamous cell carcinoma (OSCC). In a case, Zeng and colleagues fabricated the targeted drug delivery platform based on folic acid (FA)-modified PEG-PLA nanoparticles encapsulated with JQ1 [a small-molecule inhibitor of bromodomain-containing protein 4 (BRD4)] (Fig. 7C) [214]. These targeted nanoparticles could not only improve the formulation targeting tumor tissues but also prolong the half-life of the encapsulated drug. The internalized nanoparticles successfully inhibited carcinoma growth, inducing tumor apoptosis and preventing tumor angiogenesis, as well as the polarization of M2-type macrophages.

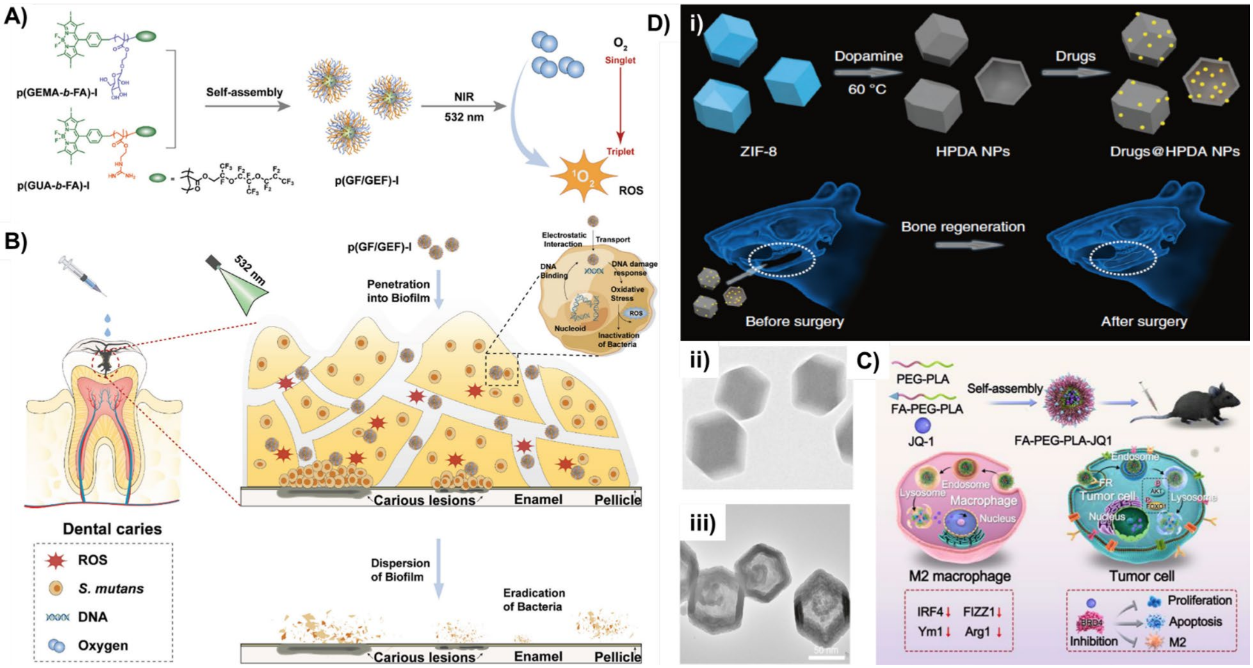


Fig. 7 **A** The principle of nanophotosensitizer, p(GF/GEF)-I, to eradicate caries-causing biofilm. **A** Schematic illustration of the construction of p(GF/GEF)-I. **B** Mechanism of effective removal of biofilm by p(GF/GEF)-I nanoparticle-mediated photodynamic therapy. The p(GF/GEF)-I species penetrate the biofilm, subsequently bind to pathogenic bacteria in the biofilm, and induce the quick generation of a high level of ROS that can damage cell membranes and kill bacteria. Self-oxygenated nanophotosensitizer improves PDT efficiency and ultimately significantly disperses biofilms. Reproduced with permission from Ref [213]. Copyright 2023, John Wiley & Sons. **C** Schematic representation of the formation of FA-PEG-PLA-JQ1. Reproduced with permission from Ref [214]. Copyright 2024, Elsevier. **D** (i) Schematic diagram of the construction of a drug sustainable release system and its application in bone regeneration. Physical characteristics of hollow polydopamine (HPDA) nanoparticles. (ii) TEM image of ZIF-8. (iii) TEM image of HPDA nanoparticles. Reproduced with permission from Ref. [215] Copyright 2021, Nature Publishing Group

In addition to drug delivery, several organic constructs have been applied as nano-delivery systems for bone regeneration [215] and vascularized pulp regeneration [216]. In a case, hollow polydopamine nanoparticles were developed based on the templating approach of ZIF-8 MOFs, which could efficiently encapsulate and deliver four types of osteogenic drugs (Fig. 7D) [215]. Moreover, these polydopamine nanoparticles with high biocompatibility could effectively promote the proliferation of rat bone marrow mesenchymal stem cells (rBMSCs) and their osteogenic differentiation in vitro. In another case, Ilhan and colleagues demonstrated the encapsulation of clindamycin phosphate and BMP-7 growth factor in the polymeric nanoparticles for alveolar bone regeneration [217]. Yuan and coworkers demonstrated the regeneration of vascularized pulp using the GelMA cryogel microspheres loaded with PLGA nanoparticles and stem cells from human exfoliated teeth [216]. The designed nano-in-micro constructs with controlled release ability showed exceptional promotion of vascularized tissue regeneration by subcutaneous implantation in mice. These biocompatible and biodegradable organic constructs possessed exceptional sustained release and differentiation abilities to treat bone defects in clinical practice and endodontic regenerative dentistry. Although these organic constructs offer precise compatibility and degradability attributes, several features of stability issues, and precise and sustained release of therapeutic cargo are required to be addressed for the treatment of dental ailments.

Although traditional polymers in solid forms have become exquisite alternatives to drug delivery and tissue regeneration, several drawbacks still may limit their applicability, such as poor stability, strong hydrophobicity, and adverse effects due to deprived colloidal stability. To this end, polymer-based hydrogels have been employed for localized drug delivery due to their exceptional hydrophilicity, tailorable shapes, mechanical characteristics, and malleability, which are of particular interest for oral-based ailments. Along this line, several exceptionally intelligent hydrogels with stimuli-responsive features have garnered enormous interest from researchers in delivering drugs (anti-microbial and anti-inflammatory agents). These smart hydrogel-based constructs encapsulated with drugs offer promising advantages, such as on-demand release, long action time, and low administration frequency, resulting in their improved bioavailability. Specifically, smart hydrogels can be designed with pH and enzyme-responsive stimuli. In terms of pH-responsiveness, biofilms contain low pH in the bacteria-rich environment, facilitating improved delivery in the affected area. In addition, several oral pathological conditions, such as dental plaques and periodontal diseases, express MMPs, specifically MMP-2, involved in connective tissue degradation. Thus, the designing of hydrogels with MMP-2 responsiveness could improve the localized delivery of various drugs while reducing the side effects. Nevertheless, the major limitation of hydrogels for designing formulations for oral-related ailments is the encapsulation of hydrophobic drugs, limiting their applicability. Considering the advantages of smart hydrogels, one of the most effective methods to encapsulate hydrophobic drugs into hydrogels is to load them in their nanometric domains. In this vein, the nano-sized drugs offer uniform distribution and high dispersibility, improving the loading efficiency into hydrogels and avoiding side effects. Moreover, these hydrogel building blocks are often engineered using various chemical reactions for crosslinking during the fabrication in situ towards improved encapsulation of biological moieties, modulating hydrogel properties, and tailoring mechanical properties. In a case, collagenase-responsive HA hydrogels were designed for periodontitis to deliver nano GSK (GSK2606414) to inhibit the inflammation-induced expression of PERK in PDLSCs [218]. Initially, NanoGSK was encapsulated into hydrogels based on the Michael addition reaction between an MMP-2-cleaved peptide cross-linker (MMPc) and acrylated HA. Further, the in vitro and in vivo evaluation studies demonstrated that the overexpressed MMP-2 could release NanoGSK cargo in the gingival tissue of periodontitis, inhibiting inflammation-induced PERK and exhibiting exceptional alveolar bone repair capability. Considerably, these hydrogels with advantageous attributes present themselves similar to an ECM-like environment, facilitating the hydrophilic environment towards tissue growth. In another instance, Wen and colleagues fabricated mineralized hydrogel composites based on amorphous calcium phosphate (ACP) encapsulated polyacrylic acid (PAA)-carboxymethyl chitosan (CMC)-dentin matrix (TDM) [219]. The established dynamic network based on calcium and carboxylate ions loaded with TDM exhibited exceptional self-repair ability and improved injectability, promoting odontogenesis or osteogenic differentiation of mesenchymal stem cells. Despite the advantages, it is necessary to focus on exploring the colloidal stability of these polymeric constructs.

Dendrimers

Among various organic constructs, the class of dendrimers, coined from the Greek term dendron referring to "branching tree", has emerged as highly ordered synthetic macromolecules manifested by a combination of compact molecular structures and diverse functional groups. These highly defined supramolecular architectures at a size of 1–15 nm are fabricated by sequential arrangement of various polymeric monomers into symmetric three-dimensional (3D) morphological structures. The defined shape and sphericity of dendrimers are attained by organized synthesis as branches of trees on a tiny core symmetrically. Although they belong to a family of polymers, these hyperbranched globular nanostructures are worth discussing separately, considering their spatiotemporal 3D arrangement of highly active functional groups rather than irregular assembly of traditional polymers. Unlike polymers that are synthesized by the polymerization reaction, these globular dendrimer structures are fabricated through a step-by-step process of altered functional groups successively into highly functionalized repetitive architectures, enabling the control over the eventual structure, for instance, polyamidoamine (PAMAM) dendrimers. Since the first dendrimers were fabricated, several efforts have been dedicated to exploring the generation of various 3D architectures involving the encapsulation of small molecules into nano-sized constructs. Considering these attributes, dendrimers have been explored in nanomedicine research for the delivery of drugs, including anti-cancer, antimicrobial, and anti-inflammatory, among others, for oral-based ailments [220].

Along this line, several dendrimers have been employed, including PAMAM [220], methyl methacrylate, and poly(epsilon-lysine) for oral applications, specifically drug delivery and in situ mineralization towards odontogenic potential, differentiation of osteoblastic cells, dentine restoration, and coating the implants [162, 220, 221]. Specifically, these dendrimers with various modifications with chemical functionalities like OH, –COOH, and –NH_2 terminal groups induce the regeneration of HA crystals, subsequently improving the remineralization and hardening of the acid-etched enamel, similar to the natural tooth. Owing to enhanced solubility and stability of small molecules, these dendrimers are entrapped with such moieties for improved bioavailability. In a case, Gardiner and colleagues enclosed triclosan in PAMAM dendrimers to enhance its solubility [220]. In addition, Tao and colleagues reported the generation of galardin-loaded PAMAM dendrimers, in which galardin inhibited MMPs to prevent collagen fibril breakdown, while NGV peptide improved collagen stabilization [222]. These dendrimers with dual collagen protection effects improve dentin remineralization, showcasing the efficacy of the anti-dentin caries in vivo. In another instance, Kim and colleagues presented PAMAM dendrimers functionalized with αVβ3-specific, cyclic arginine-glycine-aspartic acid (RGD) peptides to increase the odontogenic potential of dental pulp cells, resulting in the enhanced mineralization [162]. Moreover, these dendrimers could act as restorative vital substitutes in hard tissues, mimicking the non-collagenous proteins to promote mineralization. These features of improved performance in the oral cavity could be due to the enhanced mucoadhesive property and hyperbranched structure of dendrimers, enabling their comprehensive potential as a superior biomaterial for dental restorations and treatment of periodontal ailments.

Liposomes

Liposomes have become one of the versatile nanoplatforms that have been approved for clinical use. These lipid bilayer nanometric domains in the vesicular forms comprise amphiphilic precursors with a hydrophilic head and a lipophilic tail. These amphiphilic precursors are arranged in bilayers such that the lipophilic tails and hydrophilic heads are organized to form the inner aqueous core [223]. Interestingly, these bilayers can encapsulate hydrophilic components in the inner core and hydrophobic guests in the surrounding layer. These liposomal architectures offer several advantages, such as tailorable size and composition, modulating biodistribution towards controlling the drug delivery profiles. Considerably, these architectures stabilize the encapsulated therapeutic moieties by overcoming various challenges of minimizing systematic toxicity and improving cellular internalization at the cellular levels. Owing to their non-toxic nature and biodegradability, these liposomal-based therapeutic designs have been approved for the delivery of various drugs by the US-FDA, such as Doxil® (doxorubicin), DaunoXome® (daunorubicin), and Ambisome® (amphotericin B), among others [224]. Considering these attributes, liposomal formulations have been designed to explore their therapeutic efficacy in improving oral health. In a case, a liposomal formulation was developed by encapsulating indocyanine green (ICG) and rapamycin composite nanoparticles into the 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) constructs for regulating the oral microenvironment [225]. These encapsulated nanoparticles significantly altered the oral microenvironment by producing excessive ROS and temperature towards hyperthermia, leading to eradicating the growth of two strains of bacteria (Fig. 8A) [225]. In addition, these composites prevent bacterial adhesion and biofilm growth, aiding the prevention of recurrence towards anti-microbial treatments. In addition to improved microbial-cellular interactions, these composites promoted macrophage M2 polarization, upregulating the anti-inflammatory effects promoting phagocytosis. Furthermore, these mechanisms were systematically demonstrated in an in vivo mouse model infected with *S. oralis*. Interestingly, the liposomal formulations presented exceptional bioavailability of the encapsulated ICG and rapamycin composite nanoparticles. Despite exploring the drug delivery and corresponding mechanistic views, it is imperative to examine synergistic actions towards improving oral health, such as drug delivery for anti-microbial characteristics and increased biomineralization. In an instance, the hydrophobic drugs (magnolol and fluconazole) were encapsulated in the Tris(tetra-n-butylammonium) hydrogen pyrophosphate-binding CHEMS-PEG$_{2000}$-OH liposomes to over their hydrophobicity, achieving dual anti-bacterial activity against *C. albicans* and *S. mutans* [226]. In addition, these liposomal architectures offered exceptional hydroxyapatite binding ability, inhabiting acid resistance and biofilm formation towards treating dental caries.

In addition to conventional drugs and their composites, several essential natural molecules can be delivered directly into the oral matrix using liposomal formulations. Along this line, one of the MMPs critical for controlling the collagen in the oral ECM is collagenase, which can play a crucial role in the tissue remodeling process. This MMP is clinically approved for digesting abnormal thickening of tissues. To prevent undesirable

(See figure on next page.)

Fig. 8 **A** Schematic diagram of the synthesis and effect mechanisms of indocyanine green (ICG)-Rapamycin: 1,2-dipalmitoyl-sn-glycero-3 -phosphocholine (DPPC) lipid bilayers encapsulate ICG and rapamycin to form nanoparticles. ICG-rapamycinmodulates microbial-cellular environments to perform the effects, which consist of elevating the ROS levels under an 808 nm laser excitation to achieve anti-bacterial effects, inhibiting bacterial adhesion from exerting anti-biofilm effects and promoting macrophage M2 polarization and bacterial phagocytosis to exert anti-inflammatory effects. In the mouse models of implant-associated infection and periodontitis, ICG-rapamycin performs treatment and prevention effects of the diseases by the modulation of microbial-cellular mechanisms. Reproduced with permission from Ref. [225] Copyright 2023, John Wiley & Sons. **B** Proposed concept of the bacteria-responsive micellar multidrug delivery system (PMs@NaF-SAP) targeting cariogenic biofilm. (i) Illustration of formulation and the bacteria-responsive activity of PMs@NaF. (ii) The modification of SAP and the formulation of PMs@ NaF-SAP. (iii) Schematic illustration of topical application of PMs@NaF-SAP on dental plaque biofilm and proposed mechanism for caries prevention and enamel restoration. Reproduced with permission from Ref. [229] Copyright 2023, Elsevier

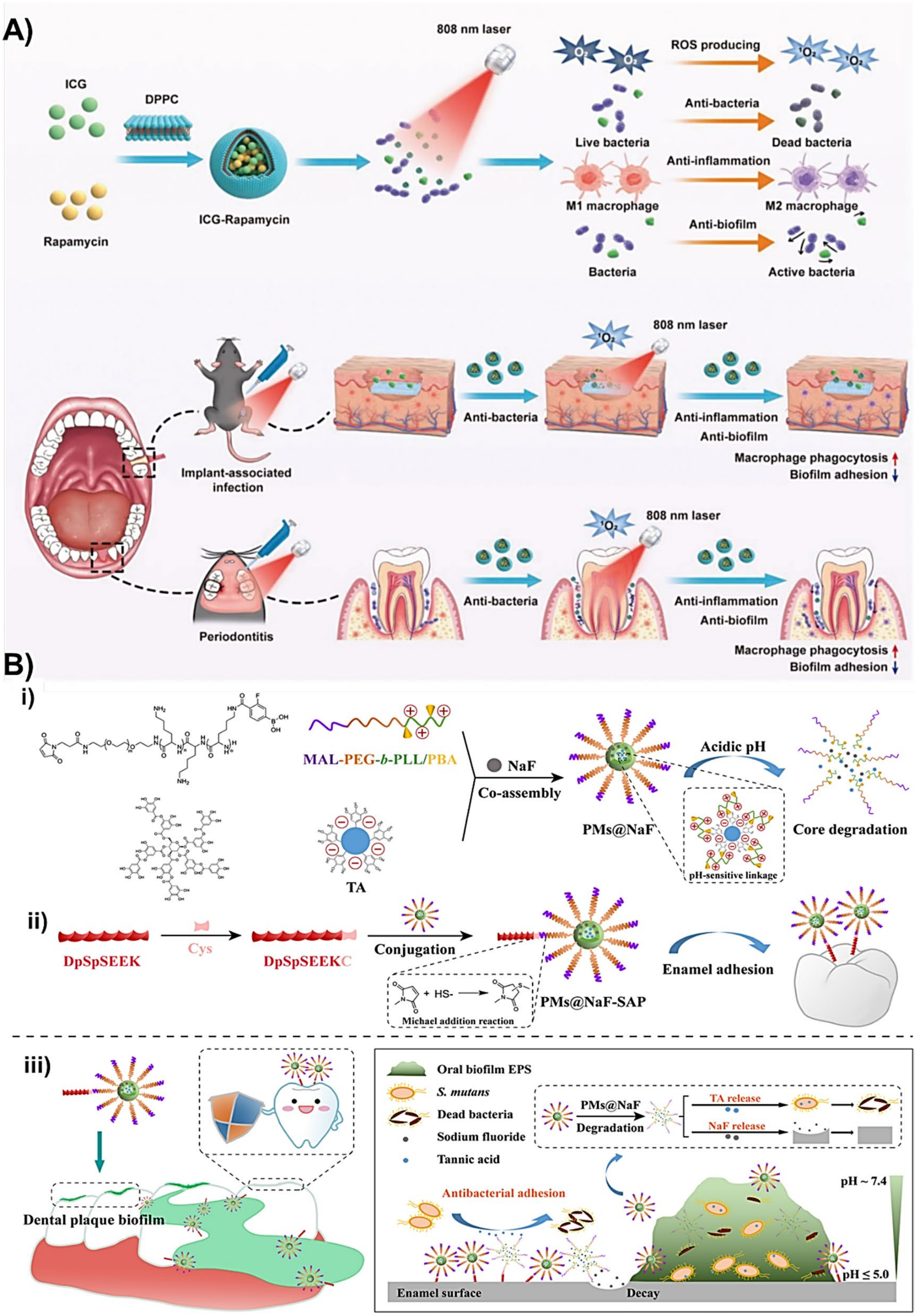


Fig. 8 (See legend on previous page.)

damage, spatial control over the enzyme to act against the collagen-containing tissues is necessary. In a case, Zinger and coworkers designed proteolytic nanoparticles based on the collagenase type-I-encapsulated liposomal architectures as surgical tools for controllable remodeling of oral connective tissues [227]. The designed liposomal nanoparticles loaded with collagenase in a deactivated form were released orally and activated by calcium in the oral environment for periodontal remodeling. The remodeling process was recorded owing to the enzymatic cleavage of the supracrustal collagen fibers connecting teeth and underlying bone.

Micelles

Structurally, the micelles are spherical-arranged amphiphilic assemblies similar to the liposomal architectures in tens to hundreds comprising of hydrophobic core and hydrophilic shell. However, these architectures differ in their arrangement, as liposomes are arranged in a bilayer, while the micelles are in a single layer with hydrophobic groups in the core. Interestingly, the hydrophilic shell improves the water solubility of these architectures for biomedical applications. Specifically, hydrophobic drugs entrapped in the hydrophobic core are administered intravenously. Considering the spatiotemporal arrangement, these micelles can also be arranged in other shapes, such as cylinders, bilayers, and ellipsoids, among others. Owing to these interesting attributes, several micellar architectures have been designed for drug delivery for various diseases, including oral ailments. Indeed, dental caries often develop from tooth demineralization due to the acid production of bacteria plaques. Although several treatment options have been applied for reducing plaques and restoration of defects, it remains a challenge to identify and precisely interrupt the development of caries. In a case, Zhang and colleagues developed pH-responsive core–shell nano-sized micelles based on mPEG-b-PDPA to deliver bedaquiline, an anti-bacterial agent within an acidic biofilm microenvironment [228]. These biocompatible polymeric nanoparticles to the periodontal cells showcased exceptional bactericidal effects on mature *S. mutans* biofilm. Inspired by the dental plaque, Xu and colleagues demonstrated the fabrication of versatile bacteria-responsive micellar-based nanosystems (Fig. 8B) [229]. The spherical-shaped core–shell structures of micelles based on 3-maleimidopropionic acid-poly(ethylene glycol)-block-poly(L-lysine)/phenylboronic acid (MAL-PEG-b-PLL/PBA) were loaded with drugs (TA in NaF) for antibacterial and tooth restoration effects. The delivery system based on PMs@NaF-SAP was self-assembled by conjugating with salivary-acquired peptide DpSpSEEK (SAP), endowing the designed nanoparticles with strong adhesion to enamel and identifying cariogenic conditions to release drugs in acidic pH for antibacterial activity against *S. mutans*. Together, the topical treatment of designed composites in the rodent cariogenic model subsequently eradicated the onset and severity of caries without significant impact on oral microbe diversity. Despite the success, there exist some concerns on these delivery platforms in terms of colloidal stability while storage and administration, similar to liposomes and soft polymeric nano-sized hydrogels. Although the synthesis is based on critical chemistry, the designs predominantly dependent on the self-assembly approach, resulting in the uncontrollable size and lack of reproducibility.

Inorganic (synthetic) nanoassemblies

Owing to the exceptional physicochemical features and tunable morphological attributes, various inorganic nanoconstructs have garnered enormous interest from researchers due to their remarkable electronic architecture. Several capable examples of inorganic nanoparticles include semiconductors (ZnO and zinc sulfide, ZnS-based quantum dots, QDs), metallic nanoparticles (silver, gold, aluminum, copper, and platinum), magnetic and paramagnetic substances (iron and iron oxide, cobalt, and nickel composites) and miscellaneous constructs. Considering the tunable morphologies and based on various synthetic strategies, these inorganic constructs can be fabricated into multi-dimensional architectures ranging from 0D (semiconductors QDs, metallic nanoparticles), 1D (rods and wires), 2D (sheets), 3D (spheres and hollow, and cubes), as well as their nanoarchitectured composites. Due to their extensive surface-to-volume ratio and abundant surface chemistry, these inorganic composites in various architectural forms, specifically 0D, 1D, 2D, and 3D materials, can be utilized to encapsulate and deliver different anti-microbial drugs for improved antibacterial efficacy. Considering these attributes and enormous precursors, in this section, we present discussions related to inorganic-based synthetic nanoassemblies into architectural forms, highlighting their importance in delivering drugs and tissue remineralization abilities. Considering these attributes of exceptional physicochemical features and drug delivery efficacy, these inorganic-based nanoarchitectures have been applied for various dental-related ailments. While addressing various dental-related ailments, the inorganic materials, for instance, 0D and 1D-based materials, often act by themselves or by delivering different small molecular or supramolecular drugs for anti-microbial and remineralization efficacies. Usually, these 2D and 3D-based materials with remarkable encapsulation ability have been immobilized with various antibiotics and dispersed in the mouthwashes for anti-microbial characteristics. These anti-microbial features enable the treatment of various dental ailments, such as dental caries. In addition, several anti-inflammatory drugs (indomethacin and diclofenac) and chemotherapeutics (cisplatin and doxorubicin) can be delivered for treating oral ailments (specifically, gingivitis and periodontitis), as well as oral tumors in the buccal cavity, respectively.

0D quantum dots

Typically, 0D materials are referred to as nanodots with no critical dimension at an average size of less than 10 nm. Interestingly, these ultra-small-sized nanoparticles with innovative electronic architecture and surface-to-volume ratio outperform various dimensional structures towards specific applications, such as stimuli-responsive biomedical applications. However, some nanodots are toxic, hampering their utilization. Considering the dose-dependent toxicity, some classes of nanodots have been explored in various biomedical applications. Along this line, several kinds of nanodots have been employed for oral health, such as AgNPs. As one of the classic examples, these AgNPs act as anti-microbial agents by providing silver ions, enabling cellular death through various mechanistic ways [230]. In addition to delivering encapsulated small-molecular drugs, the specific electronic architecture of inorganic matrices with optical properties facilitates the light excitation ability towards photo-related bioefficacy, such as PTT and PDT. Often, these photo-activated materials activated by light act by increased temperature or free radical generation, resulting in improved anti-microbial efficacy. In an instance, Wang and colleagues demonstrated the generation of the inorganic-based alloy mixture of Au–Ag complexes coated with procyanidins for precision antibacterial and synergistic immunotherapy for periodontitis (Fig. 9A) [230]. The released silver ions contribute to

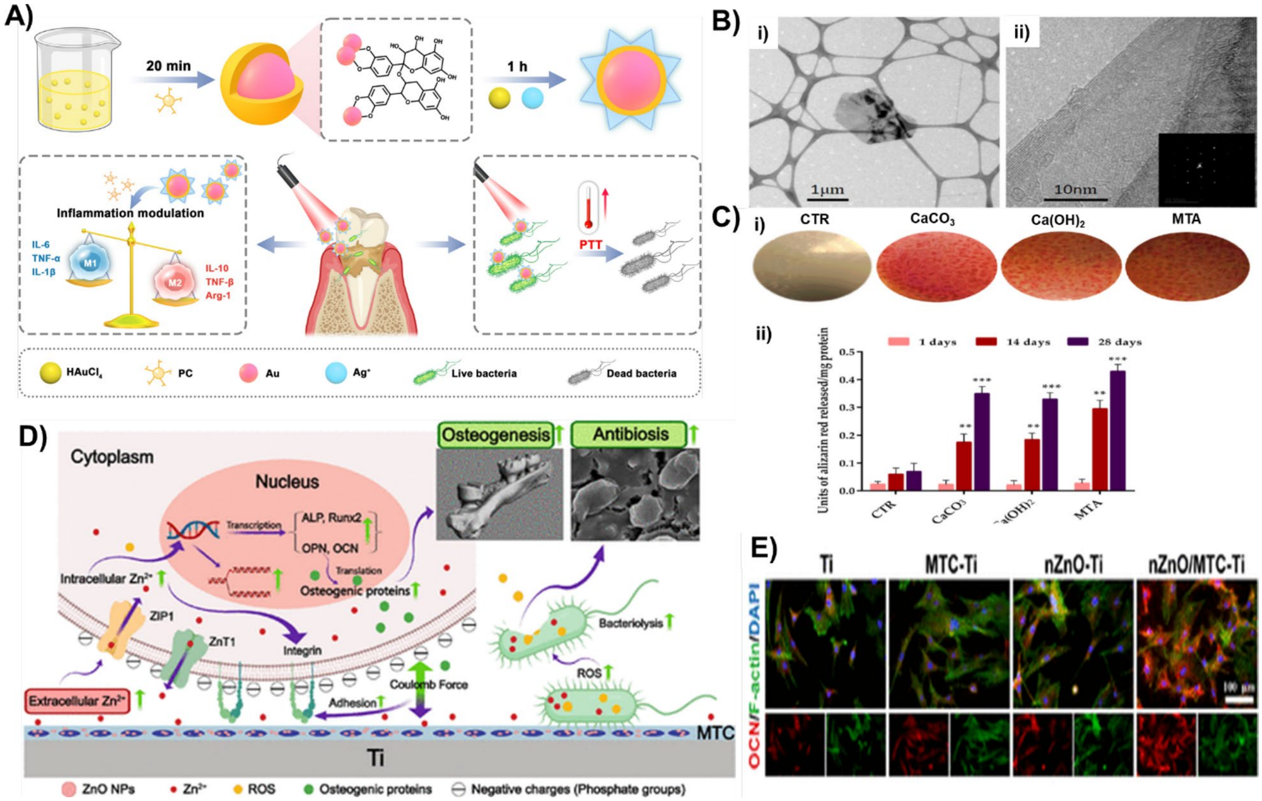


Fig. 9 **A** Schematic illustration of AuAg-PC NPs in the principle of synthesis and therapeutic mechanism in the treatment of periodontitis. Reproduced with permission from Ref [230]. Copyright 2023, Royal Society of Chemistry. **B** TEM analysis of BNNP fabricated by a hydroxyl-assisted ball-milling process: (**a**) Low-magnification image to determine the lateral size, (**b**) High-magnification image of BNNP edge to confirm the number of layers. Reproduced with permission from Ref [234]. Copyright 2020, Elsevier. **C** Effects of calcium-based materials on hDPSCs mineralization. Photographs of mineral nodules formed after 28 days of culture. Representative pictures of Alizarin Red S-stained assessed with transmitted light microscopy at 20× magnification are shown (i). Quantification of Alizarin red staining (ii). The result was representative of three different experiments. ** indicates $P < 0.01$, and *** represents $P < 0.005$ versus CTL. Reproduced with permission from Ref. [235] Copyright 2023, Elsevier. **D** Simplified schematic diagram of nZnO/MTC-Ti regulating Zn^{2+} release, osteogenesis, and antibiosis. **E** Osteogenic differentiation of BMSCs cultured on various Ti substrates: fluorescent staining images of OCN in the cytoplasm of BMSCs on various samples. Reproduced with permission from Ref. [236]. Copyright 2023, American Chemical Society

PTT effects, achieving an excellent anti-bacterial effect and avoiding periodontal tissue damage towards synergistic anti-bacterial and anti-inflammatory immunotherapy. In addition to anti-microbial efficacy, some of these innovative architectures (silica-based and TiO_2) have been employed to act as remineralization products by delivering the necessary ions for the remineralization or regeneration of tissues. A classic example of these actions was the CaF-based nanoparticles (nCaF_2), which could provide Ca and F ions that were important for dental health in terms of mineralizing and restoring the tooth structure. Nonetheless, the release of ion release persistently remains highly challenging [231]. Although several antimicrobials are available, it is necessary to address their growth right from the formation of microbial colonization in the oral cavities and subsequent biofilm formation. In recent times, Liu and colleagues generated copper-doped nanodots to improve the infiltration of biofilms in the oral cavity [232]. These dots with catalytic (peroxidase- and catalase-like) activities of copper species in the oral environment substantially inhibited the adhesion and growth of bacteria (*S. mutans*) towards eradicating the initial stages of biofilm formation. In terms of inhibiting the proliferation of Gram-positive and Gram-negative bacteria (*S. aureus* and *E coli*), these composites not only improved wound oozing infection and promoted rapid wound healing but also enhanced the performance in terms of whitening, addressing the negligible enamel and dentin destruction.

1D structures

Owing to a high aspect ratio, the fabrication of 1D nanostructures offers exceptional synergistic functionalities in terms of thermal, morphological, and optical, among other physicochemical properties. Moreover, these architectures with high aspect areas offer an elongated surface that facilitates improved adhesion to the biological surfaces towards enhanced penetration. The peculiar kinds of 1D nanostructures include nanorods and nanotubes, offering improved delivery of drugs towards enhanced therapeutic efficacy [118]. Specifically, the nanotube topography as a surface could lead to improved antibacterial properties, which, however, showed contrary findings in some other instances [118]. In one case, Kunrath and colleagues demonstrated the fabrication of a nanotextured surface (TiO_2 nanotubes) from pure Ti, which was then coated with PLGA and loaded with rifampicin [119]. These innovative architectures at an arbitrary range (macro to nano-sized constructs) could be applied for coating the dental implant platforms towards improved antibacterial efficacy. Several molecular and microbiological assays were performed to demonstrate and compare biological properties among these developed surfaces among various size ranges. Importantly, the hydrophilic surfaces presented optimal properties for intra-osseous surfaces, resulting in the potential characteristics to act against early contamination in the mucosal region. To a considerable extent, it would be nevertheless challenging to internalize the biofilm due to highly proteinaceous architectures. Considering these aspects, Tang and coworkers designed an innovative therapeutic platform, *i.e.,* a material-assistant micro-organism (MAMO) strategy, as a countermeasure based on ZnO nanorods-engineered *Bdellovibrio* to remove plaque biofilm in the oral cavity [233]. These ZnO nanorods with piezoelectric material could produce ROS by sensing mechanical pressure. *Bdellovibrio* adhered with ZnO nanorods, which could collide, realizing the generation of ROS during the predation process and removing the biofilm effectively. In addition, these composites could substantially alleviate inflammation and inhibit bone resorption in rats and rabbit periodontitis models.

2D nanoplates

The 2D materials are plate-like thin structures that possess a larger transverse area, offering enormous contact surface area with improved encapsulation efficacy of guest species compared to the low-dimensional materials, such as 0D and 1D materials. After the discovery of a classic example of graphene nanosheets, several efforts have been dedicated to fabricating various 2D materials, including transition metal-based dichalcogenides (TMDCs), MXenes, and layered double hydroxides (LDHs), among others [33, 34, 237]. Although coprecipitation and hydrothermal methods have been applied for the synthesis of 2D materials, the exfoliation-based top-down approach has emerged as one of the classic techniques to generate various 2D sheets with thickness, including mono-layered paper-like constructs. In an instance, Lee and colleagues fabricated boron nitride (BN) nanoplatelets by exfoliation h-BN using high-energy ball-milling and dispersion on a zirconia matrix (Fig. 9B) [234]. Several mechanical properties in terms of fracture toughness (~ 27.3%), flexural strength (~ 37.5%), and wear resistance were explored. This mild-temperature-assisted degradation of nanoplatelets showed exceptional biocompatibility, which could possess potential as reinforcement materials for dental ceramics. In another instance, Aati and colleagues fabricated graphene-based nanoplatelets and encapsulated at different concentrations [0.0, 0.025, 0.05, 0.1%, and 0.25% (w/w)] into acrylate-based resin to generate 3D printed resin-based composites for improved oral health [238]. These composites at a GNP concentration of 0.25 wt% enhanced printed nanocomposite hardness and elasticity. In addition to the biocompatibility attribute with oral fibroblasts, these composites showcased antimicrobial activities against *C. albicans.* Similarly, Hu and colleagues employed the recently emerged 2D MXene ($Ti_3C_2T_x$) nanosheets into the epoxy resin at altered mass ratios using the solution blending approach for practical dental applications. Interestingly, these as-fabricated MXenes in resin composites improved the mechanical properties compared to pure resin. In addition, these biocompatible nanocomposites against normal cells presented exceptional antibacterial activity after irradiation with natural light owing to their photothermal efficiency.

Although some studies have demonstrated the efficiency of 2D materials, it is imperative to explore the sole performance efficacy rather than a support material in resins. Nevertheless, some of the resin surfaces would result in secondary caries around the restoration of the oral cavities, requiring promising antibacterial material. To address this aspect, Li and colleagues fabricated ZnO nanorods-decorated graphene oxide composites for their application in dental resins [239]. These composites were fabricated using a facile hydrothermal method by changing the amount of seeded GO. The designed GO_3@ZnO-filled composites resulted in not only exceptional flexural strength and modulus but also resulted in the inhibition of *S mutans* compared to unmodified resin. These functional composites with promising physical–mechanical performance could be employed in dental fillers.

3D architectures

Compared to various low-dimensional (0–2D) architectures, the 3D nanostructures in the sub-micron range (10–1000 nm) have garnered enormous interest owing to their exceptional physicochemical and morphological attributes. Specifically, these nanoconstructs with porous architectures can be of particular interest in the encapsulation of various guest species (drugs, proteins, and genes). In addition, several inorganic precursors, such as silica and ZrO_2-based, can be applied to fabricate various porous architectures (hollow and core–shell) for encapsulating the inorganic components for antimicrobial effects [240, 241]. In this case, zirconia (ZrO_2)-based spherical composites were fabricated as dental fillers using microwave-assisted synthesis and doped with the Fe_3O_4 nanoparticles [240]. The authors demonstrated that the microwave energy dissipation resulted in the volume shrinkage of nanocomposites, which showcased the exceptional anti-bacterial effect of the doped Fe_3O_4 against *Bacillus* species towards acting as potential dental fillers with anti-microbial efficacy. In another instance, carbon dots-embedded silica nanoparticles were employed as non-destructive teeth-whitening agents [241]. These composites facilitated the passage of energy through the intersystem crossing (ISC) approach, thus encompassing the half-life of ROS towards thoroughly whitening teeth by reducing stains on the enamel.

In addition to improved anti-microbial efficacy and whitening, the tissue regeneration ability of the designed inorganic nanocomposites has been demonstrated using diverse precursors. Although the regeneration ability of polymers is profoundly explained, it is scarce in the case of inorganic composites due to toxicity issues and challenges in the fabrication of scaffolding constructs suitable for tissue growth. However, these inorganic components can offer specific physicochemical functionalities that can potentiate growth by improving the biochemical and mechanical cues. Nevertheless, the regeneration ability of various Ti-based/Ca-based implants has been explored in recent times. In an instance, Spagnuolo and coworkers demonstrated the ability of calcium-based materials ($CaCO_3$, $Ca(OH)_2$, and mineral trioxide aggregate (MTA)) in differentiating hDPSCs to odontoblastic-like cells by expressing specific odontogenic-related genes (Fig. 9C) [235]. These calcium supplements, specifically MTA, better than $CaCO_3$, $Ca(OH)_2$, resulted in the increased ALP activity and differentiation marker, matrix extracellular phosphoglycoprotein (MEPE), towards regenerative purposes. Nevertheless, dental implants as fillers or for regeneration lack biological effectiveness, increasing the cases of peri-implantitis. In a case, Wen and colleagues fabricated zinc oxide (ZnO) nanoparticles loaded on mesoporous TiO_2 coatings using the evaporation-induced self-assembly (EISA) approach (Fig. 9D) [236]. These composites, with sustained release of Zn^{2+} ions and subsequent transport through modulation of zinc transporters (ZIP1 and ZnT1), enabled their superior anti-microbial activity. Regulating the release of Zn^{2+} ions through proper channels substantially addressed their biocompatibility, promoting the osteogenic efficacy of BMSCs (Fig. 9E). Moreover, the accelerated osseointegration, antibiosis, and improved anti-bacterial action of nZnO/MTC-Ti implants facilitated improved performance efficacy in SD rats in vivo after tooth extraction.

Despite the success in the development of these innovative and highly stable architectures, most of these designs have been restricted to being applied as implants due to a lack of bioefficacy, leading to a risk of peri-implantitis. Further efforts are required to explore different alternative composites with improved anti-microbial effects and address their compatibility issues. Moreover, it should be noted that not all the inorganic constituents are stable, as ACP often suffers from instability issues, limiting its clinical application [242]. It is suggested that some composites be prepared that can improve their ability to release ions towards hard tissue mineralization. Along this line, several critical limitations of these inorganic assemblies include the risk of poor degradability-associated compatibility, hampering their clinical application. Although these constructs are feasible for the fabrication of remineralized products and dental implants in edentulous conditions, they are strictly required to address other dental-related ailments, specifically, providing the anti-microbial characteristics and regeneration of soft tissues in oral-based diseases.

Supramolecular (organic–inorganic) composites

Typically, the designed organic and inorganic-based constructs solely suffer from various individual limitations. For instance, organic materials pose stability issues from the colloidal point of view. Contrarily, the colloidally stable inorganic-based assemblies suffer from degradability issues. Considering these limitations of inorganic and organic species solely, several efforts have been dedicated to fabricating hybridized materials based on supramolecular organic–inorganic composites, either organic moieties-coated inorganics or inorganic-deposited organics, for treating oral ailments, such as secondary caries. These supramolecular assemblies of organic and inorganic constructs accommodatingly support each other in addressing their limitations [243, 244]. In this section, we further discuss the diverse arrangement of various organic and inorganic constructs for different dental ailments. For a better understanding, we present the discussions on these organic and inorganic-based composite constructs in terms of various size ranges, for instance, small-sized or sub-micron-ranged organic-coated inorganic nanoparticles or vice versa, for drug delivery and large-sized (micron-ranged) constructs coated with one over the other, or vice versa for synergistic implantable dental applications towards tissue regeneration.

Organic-coated over inorganics

Considering the flexibility and convenience of synthesis, it is feasible to coat organic layers on the rigid inorganic species extensively. Specifically, inorganic-based materials (Ag, Zn, barium titanate, $BaTiO_3$, and Ti) offer anti-microbial effects, and some possess remineralization (Ca and PO_4^{3-}) effects. The organic moieties are encapsulated with various inorganics, including chitosan, poly(carboxybetaine acrylamide) (PCBAA), PDA, polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), and poly(allylamine hydrochloride) (PAH), among others [7, 243, 245]. Accordingly, fabricating these precursors into diverse composites has garnered specific interest from researchers, in which metal ions are either doped in polymers or their nanoparticles coated with organic polymers. In a case, Javed and coworkers fabricated chitosan-coated ZnO nanocomposites (average size of 30 nm), presenting exceptional mechanical properties and remarkable reduction in the growth of *S. mutans* and *L. acidophillus* strains [246]. In another instance, Yi and colleagues fabricated yolk-shell architectures based on the silica-coated mesoporous titanium–zirconium nanocarrier, which was then coated with the PAH-stabilized ACPs (Fig. 10A) [247]. These composites improved the dentinal tubule occlusion, inducing the remineralization of demineralized dentin matrix and intrafibrillar mineralization of single-layer collagen fibrils. Similarly, Yu and colleagues fabricated a hybrid nanoplatform based on encapsulating epigallocatechin-3-gallate (EGCG) and PAH-ACP co-delivery using hollow mesoporous silicas (E/PA@HMS). These abrasion-resistant nanovehicles effectively occluded dentinal tubules and inhibited the biofilm of *S. mutans* (Fig. 10B) [7]. In addition, the surgical removal of OSCC often results in facial deformities and impaired oral function. Although radiotherapy has been predominantly applied as a primary non-invasive therapy to avoid surgical-based limitations, the lack of specificity hampers its applicability due to deprived radiation tolerance of normal tissues in the oral microenvironment and hypoxia-induced low radiosensitivity of tumors. In a case, Gu and coworkers fabricated mussel-inspired tantalum nanocomposites for OSCC treatment (Fig. 10C) [248]. Initially, the tantalum nanoparticles were encapsulated in PVP and deposited in dopamine acrylate (DAA) hydrogels. PVP encapsulation substantially augmented the X-ray deposition ability towards improved oxidative stress and improved hypoxia for tumor radiosensitivity. These hydrogels with catechol and bioadhesive features improved the precision radiotherapy of the composites in vivo (Fig. 10D–F).

Despite the development of various successful formulations in addressing these dental ailments, most of them fail to achieve clinical status due to multiple factors, such as poor performance efficacy, as well as resultant deprived physicochemical and mechanical features. The predominant reason is that the bacterial infection forms biofilm, results in the demineralization of the hard tissue, and damages the composite and eventual tissue architecture. To address these issues together, $BaTiO_3$-based piezoelectric nanoparticles were developed as a multifunctional bioactive filler in dental resin composites, offering subsequent anti-bacterial and remineralization efficiencies. These dental piezoelectric resin composites improved the physicochemical properties of resin and inhibited 90% of biofilm growth, forming the calcium phosphate minerals in piezoelectric composites. Interestingly, these large-sized composites validated the bond strength of dentin-adhesive-composite interfaces, providing long-lasting, non-rechargeable anti-bacterial/remineralization properties [249]. Xu and colleagues demonstrated the fabrication of oral microenvironment responsive release of metal-phenolic (copper tannic acid coordination

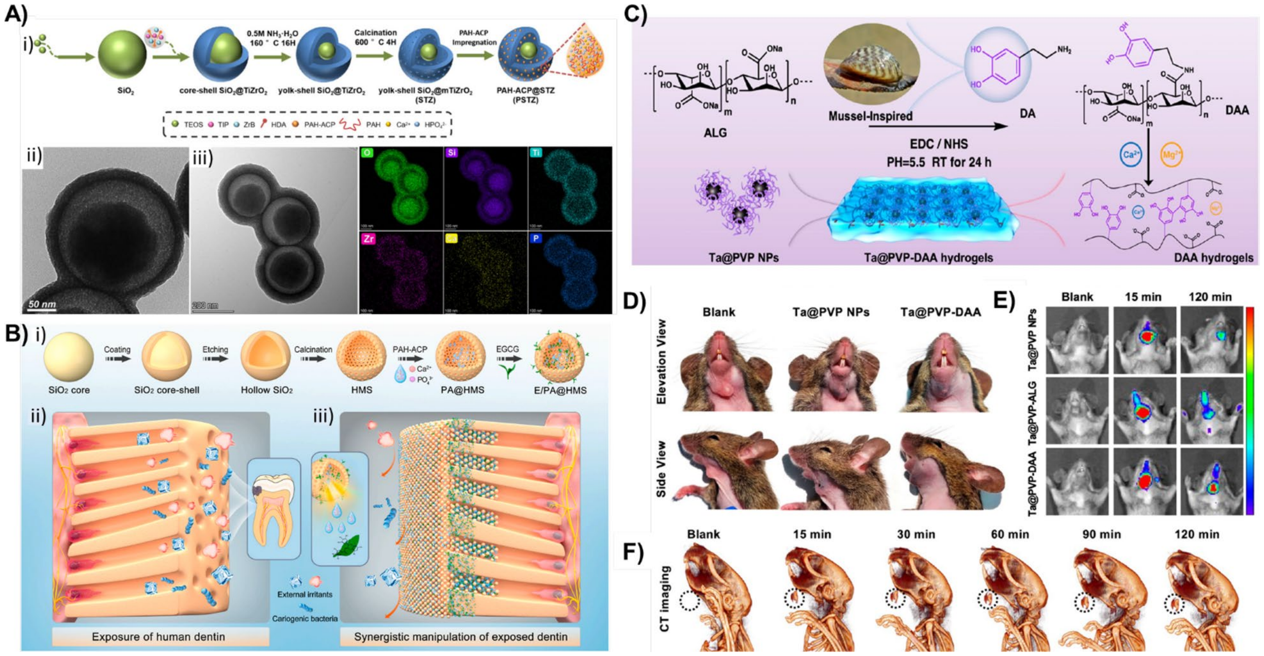


Fig. 10 **A** (i) Schematic illustration of the synthesis process of STZ and PSTZ. (ii) TEM microphotographs and corresponding elemental mapping of STZ and (iii) PSTZ. Reproduced with permission from Ref [247]. Copyright 2023, Royal Society of Chemistry. **B** (i) Schematic illustration of EGCG and PAH-ACP co-delivery hollow mesoporous silica (E/PA@HMS) nanosystem for synergistic management of exposed dentin. (ii) The exposure of dentinal tubules is susceptible to external stimuli and cariogenic bacterial attack, thereby leading to dentin hypersensitivity, caries, and pulp inflammation. (iii) The application of E/PA@HMS can durably occlude the dentinal tubules with acid-/abrasion-resistant stability and remineralization effects. Reproduced with permission from Ref. [7] Copyright 2023, KeAi Publishers. **C** Design thought of DAA hydrogels and Ta@PVP-DAA hydrogels. **D** Digital images of Ta@PVP NPs and Ta@PVP-DAA hydrogels in OSCC. **E** Fluorescence images of Ta@PVP NPs, Ta@PVP-ALG hydrogels, and Ta@PVP-DAA hydrogels in OSCC. The above-used Ta@PVP constructs are marked with Cy5. **F** CT images of Ta@PVP-DAA hydrogels in OSCC. Reproduced with permission from Ref [248]. Copyright 2023, American Chemical Society

nanosheets, CuTA NSs) components encapsulated in the hydrogel network based on triglycerol monostearate/2,6-di-*tert*-butyl-4-methylphenol (Fig. 11A) [250]. This innovative design offered improved resident time of enzyme, reduced dosage, and on-demand release of hydrophobic drugs, as well as favorable compatibility. In addition to reducing the oral anti-microbial effects, these innovative constructs improved the anti-inflammatory effects by regulating the Nrf2/NF-κB pathway and transforming M1 macrophages to M2 macrophages. Moreover, the expression of osteogenesis genes enunciated the accelerated regeneration of periodontal tissues towards the synergistic treatment of periodontitis (Figs. 11B–D). In another case, cobalt-ferrocene MOFs with strong Fenton reactivity were fabricated to act against OSCC with MDR (Fig. 11E) [251]. These MOFs were encapsulated with hydroxychloroquine and subsequently coated with the oral cancer cell membranes extracted from the CAL-27 cell line. The experimental results demonstrated exceptional tumor targeting effects, biosafety, and augmented therapeutic effects. Interestingly, these composites presented local autophagy ROS boosting towards ablating OSCC cells. In addition, a multifunctional coating using gelatin and /hydroxyapatite nanoparticles on Ti foils

(See figure on next page.)

Fig. 11 **(A)** TM/BHT/CuTA hydrogel was used to self-assemble the CuTA nanozyme, TM, and BHT to treat periodontitis. **(B, C)** The negatively charged TM/BHT/CuTA exhibited long-term retention at the inflammation sites with a positive charge through electrostatic adsorption. **(D)** The released CuTA nanozyme exhibited antibacterial effects on bacteria associated with periodontitis. Reproduced with permission from Ref [250]. Copyright 2023, American Chemical Society. **E)** Conceptual schematic diagram of the preparation process and intracellular mechanism of CM@Co-Fc@HCQ nanoparticles. Reproduced with permission from Ref [251]. Copyright 2023, John Wiley & Sons. **F)** Schematic illustration of the PCBAA/ACP nanocomposite with dual antibiofilm and remineralization functions, and evaluation of the effect of the PCBAA/ACP nanocomposite on inhibiting cariogenic bacterial adhesion and biofilm formation on the enamel surface and promoting enamel remineralization (including surface and subsurface lesions) and DT occlusion. Reproduced with permission from Ref. [242] Copyright 2022, American Chemical Society

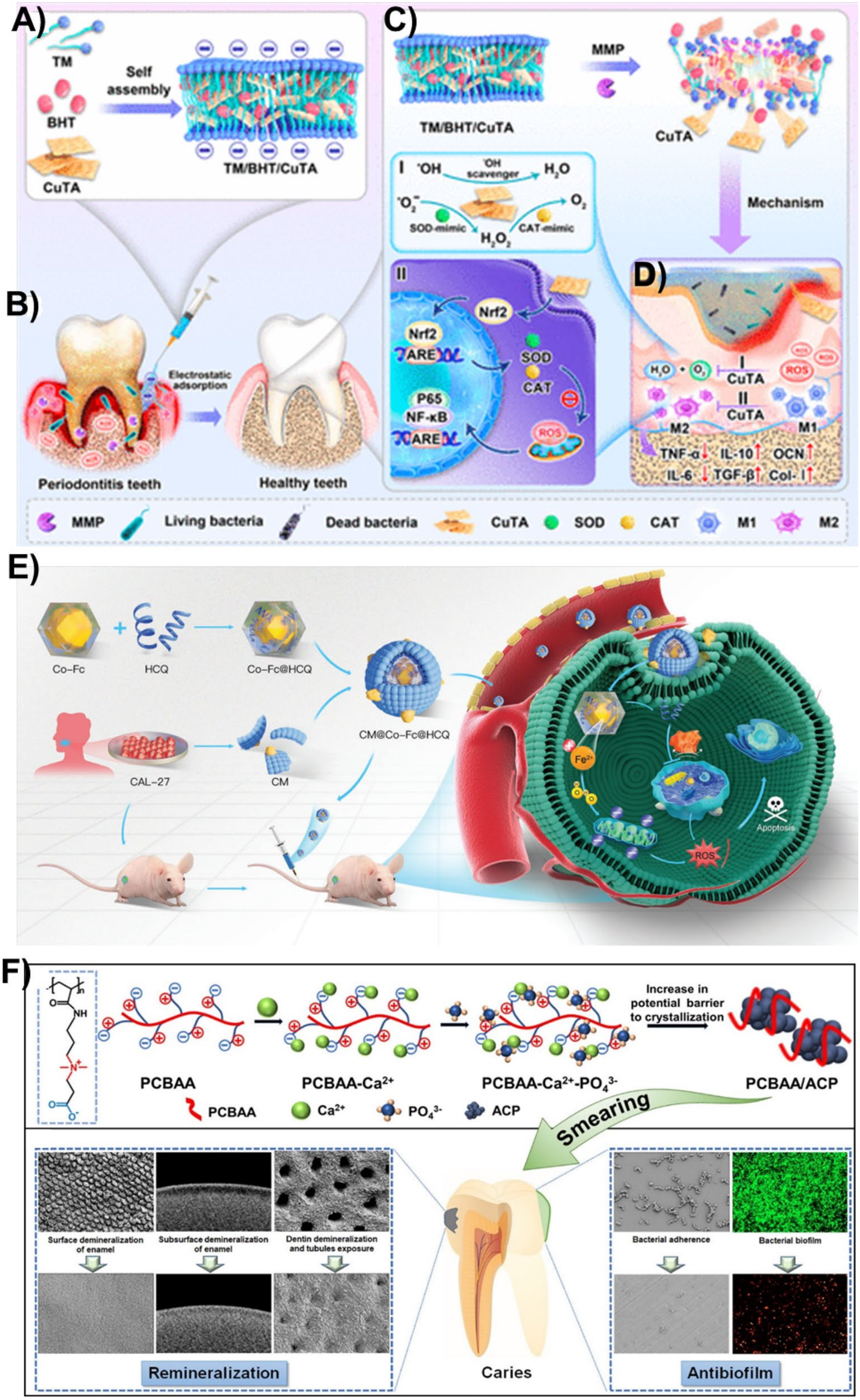


Fig. 11 (See legend on previous page.)

was performed, and the effects on cell adhesion, proliferation, and anti-bacterial effects were studied [252]. As anticipated, the cells deposited on these films showcased improved anti-bacterial effects against *S. mutans*, as well as cell attachment and osteogenic differentiation effects of the PHG-coated surfaces.

Inorganic-coated over organics

Owing to exceptional physicochemical attributes, various inorganic species have been coated on the organic constructs to fulfill the anti-microbial and tissue regeneration applications. Although it is quite challenging to fabricate inorganics on organic species, several researchers have explored the applicability of rigid inorganic nanodots on flexible organic macromolecular constructs for dental applications. In a case, Liu and colleagues fabricated thermoplastic poly-merpolyetheretherketone (PEEK) discs coated with nanosilver at varied thicknesses (3, 6, 9, and 12 nm) magnetron sputtering technology [253]. These nano-silver-coated compatible architectures not only improved the bacterial adhesion efficacy but also offered antibacterial efficacy against *S. mutans* and *S. aureus*. In addition to anti-microbial effects, remineralization approaches have been used to supply various essential ions, such as Ca^{2+} and PO_4^{3-} through amorphous calcium phosphate (ACP) constructs. In most instances, the ACP constructs suffer from instability, limiting their clinical application due to the lack of undesirable biofilm formation. For instance, He and coworkers fabricated the zwitterionic composites based on PCBAA and ACP to execute remineralization and antibiofilm properties (Fig. 11F) [242]. These composites also exhibited exceptional inhibitory effects on the biofilm formation of *S. mutans* under acidic conditions. In comparison to fluoride formulation, the designed dual-functional composites presented superior remineralization effects of demineralized enamel. Similarly, Dai and coworkers demonstrate the fabrication of an amorphous calcium phosphate nanocomposite with epigallocatechin gallate to interrupt the cariogenic biofilm formation during remineralization. These synthesized nanocomposites were highly compatible with L929 and human gingival fibroblasts, indicating their biosafety attribute. The sustained release of ACP from the designed EGCG-ACP composites exhibited substantial anti-bacterial effects and restored the demineralized enamel with improved microstructure and mechanical properties. Accordingly, these composites provided a theoretical basis in caries risk applications.

As mentioned earlier, the conventional precursors from organic and inorganic sources are assembled by coating one over the other, considering the performance and delivery applications. Although several kinds of hybrids have been fabricated systematically, in some instances, the combination of multiple components has been designed to improve the applicability of the single components. In an instance, Mayorga-Martinez and colleagues fabricated magnetic photoactive microrobots based on ferromagnetic (Fe_3O_4) and photoactive ($BiVO_4$) materials self-assembled using the PEI micelles to eradicate biofilm growth on a dental implant towards improving the subsequent formation of gingivitis and implant loss [254]. Initially, PEI-coated Fe_3O_4 composites were encapsulated with $BiVO_4$ through the self-assembly process. The enclosed Fe_3O_4 materials could propel under a transversal rotating magnetic field, while the $BiVO_4$ produced excessive ROS to eradicate biofilm colonies by 90% in the oral microenvironment. Interestingly, these actively driven ferromagnetic species enable the homogenous distribution of oxidative species by $BiVO_4$. Notably, these magnetically powered microrobots could precisely navigate toward biofilm destruction on titanium alloy-based implants. In another instance, Chen and colleagues fabricated a multi-component system based on the metal-phenolic networks with Pd nanoparticle nodes (MPN-Pd) for eradicating oral microbial biofilm-associated infections [255]. These Pd nanoconstructs stabilized in a polyphenol network through coordination linkages were reduced to nanoconstructs to inhibit their aggregation. These nanoparticles could be conducive to the reduction of O_2 on the surface, essentially generating the near-infrared (NIR)-induced hyperthermia towards ablating *S. mutans* and *Enterococcus Faecalis* (*E. faecalis*) via its oxidase-like property, eradicating oral polymicrobial biofilm-associated infections. Although the design sounds interesting, it is necessary to explore the optimization of various inorganic components to avoid severe aggregation. In addition, comprehensive biosafety investigations must be performed to investigate their further translation.

In some instances, these exquisite nanoparticles would act on reducing the bacterial infection, limiting the protection to resin-dentin bonded interface in terms of persistent apical periodontitis and lacking remineralization. In an attempt to protect the resin-dentin bonded interface, Toledano and colleagues fabricated PolymP-n Active (2-hydroxyethyl methacrylate, a cross-linker, ethylene glycol dimethacrylate, and a functional monomer, methacrylic acid) nanoparticles encapsulated with zinc and doxycycline [256]. The authors applied disks, which were exposed to a cariogenic biofilm challenge in a drip-flow reactor, for 72 h and 7 d. The Zn-doped polymeric nanoparticles resulted in exceptional anti-microbial efficacy, inhibiting the biofilm formation and the highest mineralization degree in accordance with the phosphate levels. Although the actions are limited by the pristine organic constructs, the combination of Zn and polymers resulted in synergistic anti-bacterial and remineralizing effects against cariogenic biofilm in vitro. In addition, the doxycycline-loaded PolymP-n Active nanoparticles resulted in the scaffolding of collagen but not remineralization. Similarly, they demonstrated the fabrication of melatonin-doped PolymP-n Active nanoparticles to decrease dentin permeability and ease dentin remineralization after endodontic treatment [257]. These melatonin-doped nanoparticles presented higher functional remineralization than the undoped nanoparticles. In another instance, the authors loaded dexamethasone and zinc-loaded nanoparticles to reinforce and remineralize the coronal dentin [258].

Dental implants

Typically, various dental-related ailments eventually result in the edentulous pathological condition, referred to as tooth loss, resulting in the further destruction of the oral cavity. To improve oro-dental conditions, various dental ailments, such as cracked teeth and complete tooth loss, can be treated by replacing voids surgically with certain dental implants, which can look and function like real teeth [240, 259]. Moreover, the surgical procedures are employed for establishing dental implants towards building the bridgework for tooth replacements. Nevertheless, dental implants must be considered based on the condition of the jawbone and the type of oro-dental condition. These implants offer solid support for the new teeth, requiring the bone to heal around the implants. Moreover, it facilitates the treatment of damaged tooth removal, jawbone preparation, bone growth, and eventual healing of the injured sites. Although these dental implants are way too large and fall outside of the scope, it is worth noting that they require some surface modification using various nanoengineering strategies for improved osseointegration purposes.

Several kinds of dental implants include titanium, porcelain, ceramics, and zirconium-based materials. Among them, porcelain titanium has emerged as one of the most common dental implants due to its ease of implantation in the jawbone. Moreover, the implantation of dental matrices often poses various challenges of inappropriate fixation and infection at the implantation site, as well as undesirable injuries, leading to nerve damage and sinus problems, among others. In addition to expert views and critical examination prior to implantation, the medical treatment plan should be appropriately planned using implants with improved performance. Considering these challenges of undesirable infections and abridged osseointegration, several surface treatments based on plasma and chemical-etching treatment approaches have been employed to modify their surfaces, altering their morphology, roughness, wettability, and compatibility, among other attributes. These treatments often involve atomic scale modifying the surfaces of the implant materials, improving the cell adhesion towards regeneration and osseointegration of implants. In this context, Ti, Ag, silica, and aluminum oxide (Al_2O_3) nanoparticles have been deposited using the acid-etching approach on the implant surfaces [130, 236, 240, 260]. In most instances, the coating of metallic nanocomposites improved the antibacterial efficacy of the dental implants [130, 261]. In a case, silver ions were released continuously from the Ag-TIPS-Ti surface for 7 d, causing remarkable antibacterial activity over 12 h of culturing [130]. However, these composites exhibited no severe cytotoxicity against fibroblast cells for up to 10 days, indicating their biocompatibility. In addition to anti-bacterial efficacy, some studies explored the importance of pretreatment towards improving osseointegration. In another case, the pretreatment of dentin with bio-nano complexes based on the enamel protein amelotin (AMTN) before adhesive application significantly improved shear bond strength, accelerating the mineral formation and collagen mineralization of bio-nano complexes [260]. Despite the improved performance of the implants, these strategies suffer from various limitations. Predominantly, nanocasting of various metallic layers over the traditional implants requires additional sophisticated processing. In addition, the osseointegration without any signs of cytotoxicity is merely challenging as some elements may pose accumulation-induced toxicity risks, requiring extensive comprehensive investigations. Finally, the long-term behavior of these nano-casting surfaces remains unexplored extensively against biomedical applications.

Challenges

In the past decade, the exploration of nanotechnology and related biomaterials has become exceptionally crucial in various areas of the biomedical field, including dentistry. Although extensive research has demonstrated the exploration of treating various oro-dental ailments (periodontitis and oral tissue engineering) using various nanotechnologies, it is quite challenging to translate these innovative nanoarchitectures to the commercial market [262]. There exist numerous reasons concerning the challenges of developing nanomaterial-based drug delivery systems, such as the requirement for innovative approaches to several biomaterials. Although the research and preclinical outcomes are satisfactory, various features of the developmental stage pose predominant challenges, including synthesis, analysis, safety, sterilization, and storage requirements [263]. In this chapter, we discuss the challenges faced by these innovative technologies and their products.

Typically, the demand for the rapid exploration of various strategies has pushed researchers toward the development of various innovative nanotechnologies for drug delivery and engineered dental implants. The predominant innovative explorations include the generation of nano-sized ultrasmall constructs for delivering drugs towards improving solubility and the integration of such nanotechnological products with conventional biomaterials for therapeutic achievements at the molecular levels [264]. Typically, the challenges concerning the synthesis of these nanomaterials include various aspects of preparation, equipment requirement, reproducibility, and cost and time constraints. The fabrication of nanomaterials is quite complex and diverse, requiring the facile and commonly applied synthesis method. Although several chemical-based facile approaches are quite convenient for synthesizing different innovative structures, most of the synthesis methods require enormous amounts of solvents, damaging the environment [36]. Accordingly, it is essential to develop eco-friendly techniques, such as supercritical fluid technology. Moreover, some of the precursors for the generation of nanoparticles are highly expensive, requiring the development of cheaper sources to reduce the cost of production on a large scale. Concomitantly, the generation of nanostructures is challenging to produce uniform-sized architectures with reproducibility, quite dissimilar to traditional drug delivery systems. Moreover, the encapsulation of various small molecules (antibiotics/anti-cancer/anti-inflammatory) are another challenging to reproduce the similar loading efficacy during the fabrication of nanoparticle-based delivery systems consistently. Considering these critical aspects, it is quite difficult to reproduce nanoparticle-based biomaterials for oro-dental ailments. In addition to typical nanoparticles, several metallic nanoparticles have been integrated with the dental implants, which can be employed for the anti-bacterial application for biofilm eradication and killing resistance bacteria in periodontal conditions and subsequent tissue regeneration successfully through osseointegration. The classic examples include coating Ag on Ti implants and metallic constructs (Ag, Sr, and Au) encapsulated with polymeric (hydroxyapatite and chitosan) constructs [264]. Along this line, various physicochemical approaches, such as laser vaporization, chemical vapor deposition, and spray-drying, among others, have been applied to fabricate these metallic nanoparticle-integrated implants [265, 266]. Nevertheless, the performance efficacy of such innovative nanocomposites on a large scale remains unexplored, requiring comprehensive investigations.

Further, the immediate step after synthesis is the evaluation of the designed innovative nanoarchitectures concerning their responses at the cellular level from the biological point of view. Although the research explorations have been demonstrated in most instances using in vitro and in vivo models, several reports indicated that these findings could fail to replicate the biological responses of these innovative biological materials due to the complexity of oral bone and periodontal tissues in human and large animals, such as osteoporosis and periodontitis, among others [267]. Along this line, several tissue models mimicking the 3D microenvironments and stem cell engineering have been employed to simulate the physiology of organs and tissues of the oral tissues [268]. In this regard, several investigations are required to be explored, along with the reproducibility of multiple species prior to clinical trials and their translation. Despite no complete replication between humans and animals in terms of absorption and metabolism, these studies applying larger animals and comparing them with small-sized animals can be no distant from human physiology [269]. Similar to bioefficacy, the biosafety of any nanoparticle-based delivery system is important, and it plays a major role in their approval and subsequent applicability in terms of patient compliance. Although the biosafety investigations ranging from cytocompatibility in 2D cultures in vitro and hemocompatibility in blood or tissue compatibility by various staining techniques, the altered tissue organization and their responses, as well as genotoxicity at the molecular levels, must be explored comprehensively. In addition to safety and efficacy attributes, degradability, which goes hand-in-hand with safety and excretion attributes, of any nanoparticle is extremely important to consider, requiring investigations in terms of exploring the degradation kinetics [270]. These comprehensive evaluations eventually influence the final bioefficacy and subsequent clinical translation of the delivery platforms.

Finally, the sterilization and preservation attributes of the designed dosage forms are quite equally important as their optimization/synthesis or bioefficacy/biosafety attributes of any delivery platform [264]. Several sterilization approaches are available to prevent contamination that might influence the findings in the cells and animal models [271]. Nevertheless, no detailed information is available on the sterilization of these biomaterials, requiring the comprehensive exploration of these investigations and their patent reports. Importantly, the applicability of various metallic or organic-based composites often requires altered sterilization conditions to avoid critical damage. Accordingly, the lack of detailed protocols and standard procedures usually leads to confusion among researchers or R&D personnel while determining the protocols. These attributes often require the dearth of information to overcome the massive gap in translating these innovative biomaterials for oro-dental applications [264]. After sterilization, the packing and durability should be considered, as the packed materials might influence the product, resulting in abridged therapeutic outcomes. Typically, the packing materials must not be prone to oxidation with enhanced shelf-life, increasing their protection with the coating materials till their application in the market.

Outlook and prospects

In summary, this article has provided a comprehensive overview of different nanoarchitectured composites for dental ailments. Initially, we presented various bothering dental-related diseases, such as gums-, tooth-, and oral-related ailments, highlighting detailed pathological circumstances and their effects on human health and deficiencies with the currently available conventional therapeutic modalities. Further, various nanostructured components are important in addressing severe dental-related issues. In addition, a brief note on different syntheses was provided, exploring the effects of multiple parameters on morphological and physicochemical features. Finally, various nanoarchitectured composites as therapeutic solutions are discussed, including natural components and other organic- and inorganic precursor-based constructs for improving dental health by providing substantial anti-bacterial, remineralization, and tissue regeneration abilities.

In terms of various nanoarchitectured composites used for dental ailments, the predominant nanostructures include multiple carriers for the delivery of anti-microbial/anti-inflammatory/anti-cancer therapeutics. Notably, most dental-related illnesses initially start with bacterial infections and successive biofilm formation, eventually leading to a critical dental ailment. Applying various antibiotics to treat such bacterial infections has resulted in global concerns about developing antibiotic resistance. Owing to these aspects, it is suggestible to use anti-bacterial materials based on external stimuli in terms of drugless or drug-like carriers for augmented anti-microbial therapeutics. However, strict optimization of various synthesis parameters is required to be explored, followed by comprehensive evaluations of substantial compatibility and toxicity attributes toward long-term effects. Considering the development of various anticaries and regenerative materials, most of the attributes remain to be explored towards their clinical translation. In most instances, researchers have exploited the development of different innovative constructs addressing the anti-microbial actions and their subsequent remineralization effects. Nevertheless, understanding the interactions between the composites or implants and the infections is inevitable to address them comprehensively. Although some materials have shown exceptional differentiation and successive regeneration ability, the comprehensive mechanistic explorations at the molecular levels are yet to be investigated in terms of utilizing various inorganics and organics, as well as their composites. Together, we believe that exploring these prospects will substantially pronounce their usage to demonstrate the full potential of these nanoarchitectured components for dental health.

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Author contributions

Jun Guo: Conceptualization, Data curation, and Writing- Original draft preparation. Pei Wang: Conceptualization, Figure arrangement, Software, and Writing- Original draft preparation. Yuyao Li: Software, Validation, Writing- Original draft preparation. Yifan Liu: Software, Table formatting, and Writing- Original draft preparation. Yingtong Ye: Software, Table formatting, and Writing- Original draft preparation. Yi Chen: Validation, Project administration, Supervision, and Writing- Reviewing and Editing. Ranjith Kumar Kankala: Conceptualization, Funding acquisition, Resources, Supervision, and Writing- Reviewing and Editing. Fei Tong: Conceptualization, Validation, Project administration, Supervision, and Writing- Reviewing and Editing. All authors reviewed the manuscript.

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Availability of data and materials

No datasets were generated or analysed as it is a review manuscript.

Declarations

Ethics approval and consent to participate

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Consent for publication

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Competing interests

We clarify that this publication has no such conflicts of interest from either of the authors.

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References

1. Peres MA, Macpherson LMD, Weyant RJ, Daly B, Venturelli R, Mathur MR, Listl S, Celeste RK, Guarnizo-Herreño CC, Kearns C, et al. Oral diseases: a global public health challenge. The Lancet. 2019;394:249–60.

2. Benzian H, Watt R, Makino Y, Stauf N, Varenne B. WHO calls to end the global crisis of oral health. The Lancet. 2022;400:1909–10.
3. Estevinho F, Gouveia M, Costa M, Moura S, Neves JS, Paulo-Subtil D, Marinho J, Leite-Moreira J. Early detection of oral cancer in Portugal: the experience of UMEMD. J Clin Oncol. 2017;35:e13039–e13039.
4. Cherian JM, Kurian N, Varghese KG, Thomas HA. World Health Organization's global oral health status report: paediatric dentistry in the spotlight. J Paediatr Child Health.
5. Nyorobi JM, Carneiro LC, Kabulwa MN. Knowledge and practices on periodontal health among adults, Misungwi, Tanzania. Int J Dentis. 2018;2018:7189402.
6. Bridge G, Martel A-S, Lomazzi M. Silver diamine fluoride: transforming community dental caries program. Int Dent J. 2021;71:458–61.
7. Yu J, Bian H, Zhao Y, Guo J, Yao C, Liu H, Shen Y, Yang H, Huang C. Epigallocatechin-3-gallate/mineralization precursors co-delivery hollow mesoporous nanosystem for synergistic manipulation of dentin exposure. Bioactive Mater. 2023;23:394–408.
8. Torpy JM, Burke AE, Glass RM. Periodontal disease. JAMA. 2008;299:598–598.
9. Tahmasebi E, Keshvad A, Alam M, Abbasi K, Rahimi S, Nouri F, Yazdanian M, Tebyaniyan H, Heboyan A, Fernandes GVO. Current infections of the orofacial region: treatment, diagnosis, and epidemiology. Life (Basel). 2023;13:269.
10. Dietrich T, Webb I, Stenhouse L, Pattni A, Ready D, Wanyonyi KL, White S, Gallagher JE. Evidence summary: the relationship between oral and cardiovascular disease. Br Dent J. 2017;222:381–5.
11. Kidane YS, Ziegler S, Keck V, Benson-Martin J, Jahn A, Gebresilassie T, Beiersmann C. Eritrean Refugees' and Asylum-Seekers' attitude towards and access to oral healthcare in Heidelberg, Germany: a qualitative study. Int J Environ Res Public Health. 2021;18:11559.
12. Northridge ME, Kumar A, Kaur R. Disparities in access to oral health care. Annu Rev Public Health. 2020;41:513–35.
13. Mosaddad SA, Talebi S, Hemmat M, Karimi M, Jahangirnia A, Alam M, Abbasi K, Yazadaniyan M, Hussain A, Tebyaniyan H, Abdollahi Namanloo R. Oral complications associated with the piercing of oral and perioral tissues and the corresponding degree of awareness among public and professionals: a systematic review. Diagnostics (Basel). 2023;13:3371.
14. Das D, Menon I, Gupta R, Arora V, Ashraf A, Ahsan I. Oral health literacy: a practical strategy towards better oral health status among adult population of Ghaziabad district. J Family Med Primary Care. 2020;9:764.
15. Johal S, Baumgartner JC, Marshall JG. Comparison of the antimicrobial efficacy of 1.3% NaOCl/BioPure MTAD to 5.25% NaOCl/15% EDTA for root canal irrigation. J Endodont. 2007;33:48–51.
16. Hülsmann M, Heckendorff M, Lennon Á. Chelating agents in root canal treatment: mode of action and indications for their use. Int Endod J. 2003;36:810–30.
17. Hussein H, Kishen A. Antibiofilm and immune response of engineered bioactive nanoparticles for endodontic disinfection. J Clin Med. 2020;9:930.
18. Lal A, Alam MK, Ahmed N, Maqsood A, Al-Qaisi RK, Shrivastava D, Alkhalaf ZA, Alanazi AM, Alshubrmi HR, Sghaireen MG, Srivastava KC. Nano drug delivery platforms for dental application: infection control and TMJ management—a review. Polymers (Basel). 2021;13:4175.
19. Matsuyama Y, Jürges H, Dewey M, Listl S. Causal effect of tooth loss on depression: evidence from a population-wide natural experiment in the USA. Epidemiol Psychiatr Sci. 2021;30: e38.
20. Lo C-H, Kwon S, Wang L, Polychronidis G, Knudsen MD, Zhong R, Cao Y, Wu K, Ogino S, Giovannucci EL, et al. Periodontal disease, tooth loss, and risk of oesophageal and gastric adenocarcinoma: a prospective study. Gut. 2021;70:620–1.
21. Bui FQ, Almeida-da-Silva CLC, Huynh B, Trinh A, Liu J, Woodward J, Asadi H, Ojcius DM. Association between periodontal pathogens and systemic disease. Biomed J. 2019;42:27–35.
22. Hampelska K, Jaworska MM, Babalska Z, Karpiński TM. The role of oral microbiota in intra-oral halitosis. J Clin Med. 2020;9:2484.
23. Kankala RK, Han Y-H, Na J, Lee C-H, Sun Z, Wang S-B, Kimura T, Ok YS, Yamauchi Y, Chen A-Z, Wu KC-W. Nanoarchitectured structure and surface biofunctionality of mesoporous silica nanoparticles. Adv Mater. 2020;32:1907035.
24. Kankala RK, Han Y-H, Xia H-Y, Wang S-B, Chen A-Z. Nanoarchitectured prototypes of mesoporous silica nanoparticles for innovative biomedical applications. J Nanobiotechnol. 2022;20:126.
25. Kumar S, Shukla MK, Sharma AK, Jayaprakash GK, Tonk RK, Chellappan DK, Singh SK, Dua K, Ahmed F, Bhattacharyya S, Kumar D. Metal-based nanomaterials and nanocomposites as promising frontier in cancer chemotherapy. MedComm. 2023;4: e253.
26. Riehemann K, Schneider SW, Luger TA, Godin B, Ferrari M, Fuchs H. Nanomedicine–challenge and perspectives. Angew Chem Int Ed. 2009;48:872–97.
27. Paris JL, Cabanas MV, Manzano M, Vallet-Regi M. Polymer-grafted mesoporous silica nanoparticles as ultrasound-responsive drug carriers. ACS Nano. 2015;9:11023–33.
28. Shao D, Li J, Zheng X, Pan Y, Wang Z, Zhang M, Chen Q-X, Dong W-F, Chen L. Janus "nano-bullets" for magnetic targeting liver cancer chemotherapy. Biomaterials. 2016;100:118–33.
29. Zhang L, Chen Y, Li Z, Li L, Saint-Cricq P, Li C, Lin J, Wang C, Su Z, Zink JI. Tailored synthesis of octopus-type Janus nanoparticles for synergistic actively-targeted and chemo-photothermal therapy. Angew Chem Int Ed. 2016;55:2118–21.
30. Chen Y, Chen H, Shi J. In vivo bio-safety evaluations and diagnostic/therapeutic applications of chemically designed mesoporous silica nanoparticles. Adv Mater. 2013;25:3144–76.
31. Duan C, Yu M, Xu J, Li B-Y, Zhao Y, Kankala RK. Overcoming cancer multi-drug resistance (MDR): reasons, mechanisms, nanotherapeutic solutions, and challenges. Biomed Pharmacother. 2023;162: 114643.
32. Ma Y, Huang J, Song S, Chen H, Zhang Z. Cancer-targeted nanotheranostics: recent advances and perspectives. Small. 2016;12:4936–54.
33. Kankala RK. Nanoarchitectured two-dimensional layered double hydroxides-based nanocomposites for biomedical applications. Adv Drug Deliv Rev. 2022;186: 114270.
34. Meng R-Y, Zhao Y, Xia H-Y, Wang S-B, Chen A-Z, Kankala RK. 2D architectures-transformed conformational nanoarchitectonics for light-augmented nanocatalytic chemodynamic and photothermal/photodynamic-based trimodal therapies. ACS Mater Lett. 2024;6:1160–77.
35. Wan ACA, Ying JY. Nanomaterials for in situ cell delivery and tissue regeneration. Adv Drug Deliv Rev. 2010;62:731–40.
36. Kankala RK, Zhu K, Sun X-N, Liu C-G, Wang S-B, Chen A-Z. Cardiac tissue engineering on the nanoscale. ACS Biomater Sci Eng. 2018;4:800–18.
37. Sun B, Luo C, Yu H, Zhang X, Chen Q, Yang W, Wang M, Kan Q, Zhang H, Wang Y, et al. Disulfide bond-driven oxidation- and reduction-responsive prodrug nanoassemblies for cancer therapy. Nano Lett. 2018;18:3643–50.
38. Hung KF, Yeung AWK, Bornstein MM, Schwendicke F. Personalized dental medicine, artificial intelligence, and their relevance for dentomaxillofacial imaging. Dentomaxillofac Radiol. 2023;52:20220335.
39. Nayyar N, Ojcius DM, Dugoni AA. The role of medicine and technology in shaping the future of oral health. J Calif Dent Assoc. 2020;48:127–30.
40. Mantri SS, Mantri SP. The nano era in dentistry. J Nat Sci Biol Med. 2013;4:39–44.
41. Paul M, Pramanik SD, Sahoo RN, Dey YN, Nayak AK. Dental delivery systems of antimicrobial drugs using chitosan, alginate, dextran, cellulose and other polysaccharides: a review. Int J Biol Macromol. 2023;247: 125808.
42. Silvestre ALP, Di Filippo LD, Besegato JF, de Annunzio SR, Furquim A, de Camargo B, de Melo PBG, Rastelli ANdS, Fontana CR, Chorilli M. Current applications of drug delivery nanosystems associated with antimicrobial photodynamic therapy for oral infections. Int J Pharmaceut. 2021;592: 120078.
43. Mashimo PA, Yamamoto Y, Slots J, Evans RT, Genco RJ. In vitro evaluation of antibiotics in the treatment of periodontal disease. Pharmacol Ther Dent. 1981;6:45–56.
44. Mohammed H, Varoni EM, Cochis A, Cordaro M, Gallenzi P, Patini R, Staderini E, Lajolo C, Rimondini L, Rocchetti V. Oral dysbiosis in pancreatic cancer and liver cirrhosis: a review of the literature. Biomedicines. 2018;6:115.
45. Idir F, Van Ginneken S, Coppola GA, Grenier D, Steenackers HP, Bendali F. Origanum vulgare ethanolic extracts as a promising source of compounds with antimicrobial, anti-biofilm, and anti-virulence activity against dental plaque bacteria. Front Microbiol. 2022;13:999839.

46. Sims KR Jr, Maceren JP, Liu Y, Rocha GR, Koo H, Benoit DSW. Dual antibacterial drug-loaded nanoparticles synergistically improve treatment of Streptococcus mutans biofilms. Acta Biomater. 2020;115:418–31.
47. Marsh PD, Zaura E. Dental biofilm: ecological interactions in health and disease. J Clin Periodontol. 2017;44:S12–22.
48. Fan Y, Lyu P, Bi R, Cui C, Xu R, Rosen CJ, Yuan Q, Zhou C. Creating an atlas of the bone microenvironment during oral inflammatory-related bone disease using single-cell profiling. Elife. 2023;12:e82537.
49. Yu J, Ploner A, Chen MS, Zhang J, Sandborgh-Englund G, Ye W. Poor dental health and risk of pancreatic cancer: a nationwide registry-based cohort study in Sweden, 2009–2016. Br J Cancer. 2022;127:2133–40.
50. He X, Hu W, Kaplan CW, Guo L, Shi W, Lux R. Adherence to streptococci facilitates Fusobacterium nucleatum integration into an oral microbial community. Microb Ecol. 2012;63:532–42.
51. Touger-Decker R, van Loveren C. Sugars and dental caries23. Am J Clin Nutr. 2003;78:881S-892S.
52. Jansson L. Association between alcohol consumption and dental health. J Clin Periodontol. 2008;35:379–84.
53. Chaffee BW, Lauten K, Sharma E, Everard CD, Duffy K, Park-Lee E, Taylor E, Tolliver E, Watkins-Bryant T, Iafolla T, et al. Oral health in the population assessment of tobacco and health study. J Dent Res. 2022;101:1046–54.
54. Guan Z, Zhang J, Jiang N, Tian M, Wang H, Liang B. Efficacy of mesenchymal stem cell therapy in rodent models of radiation-induced xerostomia and oral mucositis: a systematic review. Stem Cell Res Ther. 2023;14:82.
55. Jham BC, da Silva Freire AR. Oral complications of radiotherapy in the head and neck. Braz J Otorhinolaryngol. 2006;72:704–8.
56. Moore C, Donnelly M, Semple C, O'Neill C, McKenna G. Compliance with oral hygiene and dietary advice for the prevention of post-radiotherapy dental disease among head and neck cancer patients—a qualitative study. J Dent. 2023;138: 104720.
57. Chen IDS, Yang CM, Chen MJ, Chen MC, Weng RM, Yeh CH. Deep learning-based recognition of periodontitis and dental caries in dental X-ray images. Bioengineering (Basel). 2023;10:911.
58. Broomhead T, Gibson B, Parkinson CR, Vettore MV, Baker SR. Gum health and quality of life-subjective experiences from across the gum health-disease continuum in adults. BMC Oral Health. 2022;22:512.
59. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJL, Marcenes W. Global burden of untreated caries: a systematic review and metaregression. J Dent Res. 2015;94:650–8.
60. Könönen E, Gursoy M, Gursoy UK. Periodontitis: a multifaceted disease of tooth-supporting tissues. J Clin Med. 2019;8:1135.
61. Gumber HK, Louyakis AS, Sarma T, Fabijanic KI, Paul R, Mellenbruch K, Kilpatrick-Liverman L. Effect of a stannous fluoride dentifrice on biofilm composition. Gene expression and biomechanical properties. Microorganisms. 2022;10:1691.
62. Alzammam N, Almalki A. Knowledge and awareness of periodontal diseases among Jordanian University students: a cross-sectional study. J Indian Soc Periodontol. 2019;23:574–9.
63. Barzegar PEF, Ranjbar R, Yazdanian M, Tahmasebi E, Alam M, Abbasi K, Tebyaniyan H, Esmaeili Fard Barzegar K. The current natural/chemical materials and innovative technologies in periodontal diseases therapy and regeneration: a narrative review. Mater Today Commun. 2022;32:104099.
64. Abusleme L, Hoare A, Hong B-Y, Diaz PI. Microbial signatures of health, gingivitis, and periodontitis. Periodontol. 2000;2021(86):57–78.
65. Prayitno SW, Addy M, Wade WG. Does gingivitis lead to periodontitis in young adults? The Lancet. 1993;342:471–2.
66. Schaefer AS. Genetics of periodontitis: discovery, biology, and clinical impact. Periodontol. 2000;2018(78):162–73.
67. Wang RP-H, Ho Y-S, Leung WK, Goto T, Chang RC-C. Systemic inflammation linking chronic periodontitis to cognitive decline. Brain Behav Immunity. 2019;81:63–73.
68. Tebyaniyan H, Hussain A, Vivian M. Current antibacterial agents in dental bonding systems: a comprehensive overview. Future Microbiol. 2023;18:825–44.
69. Selwitz RH, Ismail AI, Pitts NB. Dental caries. The Lancet. 2007;369:51–9.
70. Forbes S, Latimer J, Sreenivasan PK, McBain AJ. Simultaneous assessment of acidogenesis-mitigation and specific bacterial growth-inhibition by dentifrices. PLoS ONE. 2016;11: e0149390.
71. Lemos JA, Burne RA. A model of efficiency: stress tolerance by Streptococcus mutans. Microbiology. 2008;154:3247–55.
72. Kumar H, Behura SS, Ramachandra S, Nishat R, Dash KC, Mohiddin G. Oral health knowledge, attitude, and practices among dental and medical students in eastern India—a comparative study. J Int Soc Prev Community Dent. 2017;7:58–63.
73. Pratap B, Gupta RK, Bhardwaj B, Nag M. Resin based restorative dental materials: characteristics and future perspectives. Jpn Dent Sci Rev. 2019;55:126–38.
74. Chen H, Gu L, Liao B, Zhou X, Cheng L, Ren B. Advances of anti-caries nanomaterials. Molecules. 2020;25:5047.
75. Biondi M, Picardi A. Temporomandibular joint pain-dysfunction syndrome and bruxism: etiopathogenesis and treatment from a psychosomatic integrative viewpoint. Psychother Psychosom. 2010;59:84–98.
76. Berlin R, Dessner L. Bruxism and chronic headache. The Lancet. 1960;276:289–91.
77. Penoni DC, Gomes Miranda M, Sader F, Vettore MV, Leão ATT. Factors associated with noncarious cervical lesions in different age ranges: a cross-sectional study. Eur J Dent. 2021;15:325–31.
78. Forbes-Haley C, Jones SB, Davies M, West NX. Establishing the effect of brushing and a day's diet on tooth tissue loss in vitro. Dent J (Basel). 2016;4:25.
79. Huang J, Wong HL, Zhou Y, Wu XY, Grad H, Komorowski R, Friedman S. In vitro studies and modeling of a controlled-release device for root canal therapy. J Control Release. 2000;67:293–307.
80. Strock MS. Clinical endodontics: a manual of scientific endodontics. JAMA. 1962;180:990–990.
81. Bernal L, Sotelo-Hitschfeld P, König C, Sinica V, Wyatt A, Winter Z, Hein A, Touska F, Reinhardt S, Tragl A, et al. Odontoblast TRPC5 channels signal cold pain in teeth. Sci Adv. 2021;7:eabf5567.
82. Ling W, Wang Y, Lu B, Shang X, Wu Z, Chen Z, Li X, Zou C, Yan J, Zhou Y, et al. Continuously quantifying oral chemicals based on flexible hybrid electronics for clinical diagnosis and pathogenetic study. Research. 2022;2022:9810129.
83. Vaquette C, Pilipchuk SP, Bartold PM, Hutmacher DW, Giannobile WV, Ivanovski S. Tissue engineered constructs for periodontal regeneration: current status and future perspectives. Adv Healthcare Mater. 2018;7:1800457.
84. Kaur J, Srivastava R, Borse V. Recent advances in point-of-care diagnostics for oral cancer. Biosens Bioelectron. 2021;178: 112995.
85. Ren Z-H, Hu C-Y, He H-R, Li Y-J, Lyu J. Global and regional burdens of oral cancer from 1990 to 2017: results from the global burden of disease study. Cancer Commun. 2020;40:81–92.
86. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49.
87. Scully C, Bedi R. Ethnicity and oral cancer. Lancet Oncol. 2000;1:37–42.
88. Xu Y, Wen N, Sonis ST, Villa A. Oral side effects of immune checkpoint inhibitor therapy (ICIT): an analysis of 4683 patients receiving ICIT for malignancies at Massachusetts General Hospital, Brigham & Women's Hospital, and the Dana-Farber Cancer Institute, 2011 to 2019. Cancer. 2021;127:1796–804.
89. Patil VM, Noronha V, Joshi A, Abhyankar A, Menon N, Dhumal S, Prabhash K. Beyond conventional chemotherapy, targeted therapy and immunotherapy in squamous cell cancer of the oral cavity. Oral Oncol. 2020;105: 104673.
90. Taubert M, Davies EMR, Back I. Dry mouth. BMJ. 2007;334:534–534.
91. Schiødt M, Greenspan D, Daniels TE, Nelson J, Leggott PJ, Wara DW, Greenspan JS. Parotid gland enlargement and xerostomia associated with labial sialadenitis in HIV-infected patients. J Autoimmun. 1989;2:415–25.
92. Wade WG. Resilience of the oral microbiome. Periodontol. 2000;2021(86):113–22.
93. Curtis C, Nicotera A, Griseri C, Roddam H. 1110P—patient reports of mouth symptoms after radiotherapy treatment for head and neck cancer: an international survey. Ann Oncol. 2018;29:394.
94. De Geest S, Laleman I, Teughels W, Dekeyser C, Quirynen M. Periodontal diseases as a source of halitosis: a review of the evidence and treatment approaches for dentists and dental hygienists. Periodontol. 2000;2016(71):213–27.

95. Izidoro C, Botelho J, Machado V, Reis AM, Proença L, Alves RC, Mendes JJ. Revisiting standard and novel therapeutic approaches in halitosis: a review. Int J Environ Res Public Health. 2022;19:11303.
96. Kumar M, Prakash S, Radha, Lorenzo JM, Chandran D, Dhumal S, Dey A, Senapathy M, Rais N, Singh S, et al. Apitherapy and periodontal disease: insights into in vitro, in vivo, and clinical studies. Antioxidants (Basel) 2022; 11.
97. Bilder L, Librov S, Gutmacher Z, Pasternak I, Shavit I. Adverse events during sedation for oro-dental trauma in an Israeli paediatric emergency department. Dent Traumatol. 2022;38:156–9.
98. Khammissa RAG, Lemmer J, Feller L. Noma staging: a review. Trop Med Health. 2022;50:40.
99. Georgiadou SP, Makaritsis KP, Dalekos GN. Leishmaniasis revisited: current aspects on epidemiology, diagnosis and treatment. J Transl Int Med. 2015;3:43–50.
100. Sykes LM, Essop RM. Combination intraoral and extraoral prosthesis used for rehabilitation of a patient treated for Cancrum oris: a clinical report. J Prosthet Dent. 2000;83:613–6.
101. Topolski F, Souza RBd, Franco A, Cuoghi OA, Assunção LRdS, Fernandes Â. Dental development of children and adolescents with cleft lip and palate. Brazil J Oral Sci. 2014; 13.
102. Bogdan C, Pop A, Iurian SM, Benedec D, Moldovan ML. Research advances in the use of bioactive compounds from Vitis vinifera by-products in oral care. Antioxidants (Basel). 2020;9:502.
103. Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. Nat Rev Endocrinol. 2011;7:738–48.
104. Hu Z, Yan X, Song Y, Ma S, Ma J, Zhu G. Trends of dental caries in permanent teeth among 12-year-old Chinese children: evidence from five consecutive national surveys between 1995 and 2014. BMC Oral Health. 2021;21:467.
105. Winkelmann J, Gómez Rossi J, Schwendicke F, Dimova A, Atanasova E, Habicht T, Kasekamp K, Gandré C, Or Z, McAuliffe Ú, et al. Exploring variation of coverage and access to dental care for adults in 11 European countries: a vignette approach. BMC Oral Health. 2022;22:65.
106. Bayda S, Adeel M, Tuccinardi T, Cordani M, Rizzolio F. The history of nanoscience and nanotechnology: from chemical-physical applications to nanomedicine. Molecules. 2020;25:112.
107. Khurshid Z, Zafar M, Qasim S, Shahab S, Naseem M, AbuReqaiba A. Advances in nanotechnology for restorative dentistry. Materials. 2015;8:717–31.
108. Guan QF, Han ZM, Luo TT, Yang HB, Liang HW, Chen SM, Wang GS, Yu SH. A general aerosol-assisted biosynthesis of functional bulk nanocomposites. Natl Sci Rev. 2019;6:64–73.
109. Navya PN, Daima HK. Rational engineering of physicochemical properties of nanomaterials for biomedical applications with nanotoxicological perspectives. Nano Converg. 2016;3:1.
110. Freitas RA. Nanodentistry. J Am Dent Assoc. 2000;131:1559–65.
111. Özdemir O, Kopac T. Recent progress on the applications of nanomaterials and nano-characterization techniques in endodontics: a review. Materials (Basel). 2022;15:5109.
112. Ozak ST, Ozkan P. Nanotechnology and dentistry. Eur J Dent. 2013;7:145–51.
113. Chen Z, Chu Z, Jiang Y, Xu L, Qian H, Wang Y, Wang W. Recent advances on nanomaterials for antibacterial treatment of oral diseases. Mater Today Bio. 2023;20: 100635.
114. Sharan J, Singh S, Lale SV, Mishra M, Koul V, Kharbanda P. Applications of nanomaterials in dental science: a review. J Nanosci Nanotechnol. 2017;17:2235–55.
115. Gupta A, Landis RF, Li CH, Schnurr M, Das R, Lee YW, Yazdani M, Liu Y, Kozlova A, Rotello VM. Engineered polymer nanoparticles with unprecedented antimicrobial efficacy and therapeutic indices against multidrug-resistant bacteria and biofilms. J Am Chem Soc. 2018;140:12137–43.
116. Cui H, You Y, Cheng GW, Lan Z, Zou KL, Mai QY, Han YH, Chen H, Zhao YY, Yu GT. Advanced materials and technologies for oral diseases. Sci Technol Adv Mater. 2023;24:2156257.
117. Raura N, Garg A, Arora A, Roma M. Nanoparticle technology and its implications in endodontics: a review. Biomater Res. 2020;24:21.
118. Kunrath MF, Farina G, Sturmer LBS, Teixeira ER. TiO_2 nanotubes as an antibacterial nanotextured surface for dental implants: systematic review and meta-analysis. Dent Mater. 2024;40:907–20.
119. Kunrath MF, Rubensam G, Rodrigues FVF, Marinowic DR, Sesterheim P, de Oliveira SD, Teixeira ER, Hubler R. Nano-scaled surfaces and sustainable-antibiotic-release from polymeric coating for application on intra-osseous implants and trans-mucosal abutments. Colloids Surf B. 2023;228: 113417.
120. Kunrath MF, Vargas ALM, Sesterheim P, Teixeira ER, Hubler R. Extension of hydrophilicity stability by reactive plasma treatment and wet storage on TiO(2) nanotube surfaces for biomedical implant applications. J R Soc Interface. 2020;17:20200650.
121. Kunrath MF, Dos Santos RP, de Oliveira SD, Hubler R, Sesterheim P, Teixeira ER. Osteoblastic cell behavior and early bacterial adhesion on macro-, micro-, and nanostructured titanium surfaces for biomedical implant applications. Int J Oral Maxillofac Implants. 2020;35:773–81.
122. Gugoasa AI, Racovita S, Vasiliu S, Popa M. Grafted microparticles based on glycidyl methacrylate, hydroxyethyl methacrylate and sodium hyaluronate: synthesis, characterization, adsorption and release studies of metronidazole. Polymers (Basel). 2022;14:4151.
123. Taha M, Alhakamy NA, Md S, Ahmad MZ, Rizwanullah M, Fatima S, Ahmed N, Alyazedi FM, Karim S, Ahmad J. Nanogels as potential delivery vehicles in improving the therapeutic efficacy of phytopharmaceuticals. Polymers (Basel). 2022;14:4141.
124. Mahmoud MY, Steinbach-Rankins JM, Demuth DR. Functional assessment of peptide-modified PLGA nanoparticles against oral biofilms in a murine model of periodontitis. J Control Release. 2019;297:3–13.
125. Xu W, He W, Du Z, Zhu L, Huang K, Lu Y, Luo Y. Functional nucleic acid nanomaterials: development, properties, and applications. Angew Chem Int Ed Engl. 2021;60:6890–918.
126. Shen S, Wu Y, Liu Y, Wu D. High drug-loading nanomedicines: progress, current status, and prospects. Int J Nanomed. 2017;12:4085–109.
127. Cao J, Gao M, Wang J, Liu Y, Zhang X, Ping Y, Liu J, Chen G, Xu D, Huang X, Liu G. Construction of nano slow-release systems for antibacterial active substances and its applications: a comprehensive review. Front Nutr. 2023;10:1109204.
128. Ramakrishnan R, Singh AK, Singh S, Chakravortty D, Das D. Enzymatic dispersion of biofilms: an emerging biocatalytic avenue to combat biofilm-mediated microbial infections. J Biol Chem. 2022;298: 102352.
129. Mao JY, Miscevic D, Unnikrishnan B, Chu HW, Chou CP, Chang L, Lin HJ, Huang CC. Carbon nanogels exert multipronged attack on resistant bacteria and strongly constrain resistance evolution. J Colloid Interface Sci. 2022;608:1813–26.
130. Kim S, Park C, Cheon K-H, Jung H-D, Song J, Kim H-E, Jang T-S. Antibacterial and bioactive properties of stabilized silver on titanium with a nanostructured surface for dental applications. Appl Surf Sci. 2018;451:232–40.
131. Buszewski B, Rogowska A, Railean-Plugaru V, Złoch M, Walczak-Skierska J, Pomastowski P. The influence of different forms of silver on selected pathogenic bacteria. Materials (Basel). 2020;13:2403.
132. León-Buitimea A, Garza-Cárdenas CR, Román-García MF, Ramírez-Díaz CA, Ulloa-Ramírez M, Morones-Ramírez JR. Nanomaterials-based combinatorial therapy as a strategy to combat antibiotic resistance. Antibiotics (Basel). 2022;11:794.
133. Lin L, Chi J, Yan Y, Luo R, Feng X, Zheng Y, Xian D, Li X, Quan G, Liu D, et al. Membrane-disruptive peptides/peptidomimetics-based therapeutics: promising systems to combat bacteria and cancer in the drug-resistant era. Acta Pharm Sin B. 2021;11:2609–44.
134. Mohammapdour R, Ghandehari H. Mechanisms of immune response to inorganic nanoparticles and their degradation products. Adv Drug Deliv Rev. 2022;180: 114022.
135. Butterfield DA. Ubiquitin carboxyl-terminal hydrolase L-1 in brain: focus on its oxidative/nitrosative modification and role in brains of subjects with Alzheimer disease and mild cognitive impairment. Free Radic Biol Med. 2021;177:278–86.
136. Macdonald TJ, Wu K, Sehmi SK, Noimark S, Peveler WJ, du Toit H, Voelcker NH, Allan E, MacRobert AJ, Gavriilidis A, Parkin IP. Thiol-capped gold nanoparticles swell-encapsulated into polyurethane as powerful antibacterial surfaces under dark and light conditions. Sci Rep. 2016;6:39272.
137. Panpaliya NP, Dahake PT, Kale YJ, Dadpe MV, Kendre SB, Siddiqi AG, Maggavi UR. In vitro evaluation of antimicrobial property of silver nanoparticles and chlorhexidine against five different oral pathogenic bacteria. Saudi Dent J. 2019;31:76–83.

138. Nizami MZI, Yin IX, Lung CYK, Niu JY, Mei ML, Chu CH. In vitro studies of graphene for management of dental caries and periodontal disease: a concise review. Pharmaceutics. 1997;2022:14.
139. Wu L, Shao H, Tao Y, Wu J, Wang X, Nian Q, Zheng S, Cao CY, Zhao Y, Zhou Z, et al. Oxidized dopamine acrylamide primer to achieve durable resin-dentin bonding. Research (Wash D C). 2023;6:0101.
140. Yang SY, Choi JW, Kim KM, Kwon JS. Prevention of secondary caries using resin-based pit and fissure sealants containing hydrated calcium silicate. Polymers (Basel). 2020;12:1200.
141. Neelakantan P, Romero M, Vera J, Daood U, Khan AU, Yan A, Cheung GSP. Biofilms in endodontics-current status and future directions. Int J Mol Sci. 2017;18:1748.
142. Witton R, Henthorn K, Ethunandan M, Harmer S, Brennan PA. Neurological complications following extrusion of sodium hypochlorite solution during root canal treatment. Int Endod J. 2005;38:843–8.
143. Khezri A, Karimi A, Yazdian F, Jokar M, Mofradnia SR, Rashedi H, Tavakoli Z. Molecular dynamic of curcumin/chitosan interaction using a computational molecular approach: emphasis on biofilm reduction. Int J Biol Macromol. 2018;114:972–8.
144. Sinha DJ, Sinha AA. Natural medicaments in dentistry. Ayu. 2014;35:113–8.
145. Ardeshna SM, Qualtrough AJE, Worthington HV. An in vitro comparison of pH changes in root dentine following canal dressing with calcium hydroxide points and a conventional calcium hydroxide paste. Int Endod J. 2002;35:239–44.
146. Ghabraei S, Bolhari B, Sabbagh MM, Afshar MS. Comparison of antimicrobial effects of triple antibiotic paste and calcium hydroxide mixed with 2% chlorhexidine as intracanal medicaments against Enterococcus faecalis biofilm. J Dent (Tehran). 2018;15:151–60.
147. Pontoriero DIK, Grandini S, Spagnuolo G, Discepoli N, Benedicenti S, Maccagnola V, Mosca A, Ferrari Cagidiaco E, Ferrari M. Clinical outcomes of endodontic treatments and restorations with and without posts up to 18 years. J Clin Med. 2021;10:908.
148. Machado R, da Silva I, Comparin D, de Mattos BAM, Alberton LR, da Silva Neto UX. Smear layer removal by passive ultrasonic irrigation and 2 new mechanical methods for activation of the chelating solution. Restor Dent Endod. 2021;46: e11.
149. Teoh YY, Athanassiadis B, Walsh LJ. Sealing ability of alkaline endodontic cements versus resin cements. Materials (Basel). 2017;10:1228.
150. Wang N, Fuh JYH, Dheen ST, Senthil Kumar A. Functions and applications of metallic and metallic oxide nanoparticles in orthopedic implants and scaffolds. J Biomed Mater Res B Appl Biomater. 2021;109:160–79.
151. Jerri Al-Bakhsh BA, Shafiei F, Hashemian A, Shekofteh K, Bolhari B, Behroozibakhsh M. In-vitro bioactivity evaluation and physical properties of an epoxy-based dental sealer reinforced with synthesized fluorine-substituted hydroxyapatite, hydroxyapatite and bioactive glass nanofillers. Bioact Mater. 2019;4:322–33.
152. Jin HR, Jang YE, Kim Y. Comparison of obturation quality between calcium silicate-based sealers and resin-based sealers for endodontic re-treatment. Materials (Basel). 2021;15:72.
153. Xu XY, Li X, Wang J, He XT, Sun HH, Chen FM. Concise review: periodontal tissue regeneration using stem cells: strategies and translational considerations. Stem Cells Transl Med. 2019;8:392–403.
154. Tafazoli Moghadam E, Yazdanian M, Alam M, Tebyanian H, Tafazoli A, Tahmasebi E, Ranjbar R, Yazdanian A, Seifalian A. Current natural bioactive materials in bone and tooth regeneration in dentistry: a comprehensive overview. J Market Res. 2021;13:2078–114.
155. Yazdanian M, Rahmani A, Tahmasebi E, Tebyanian H, Yazdanian A, Mosaddad SA. Current and advanced nanomaterials in dentistry as regeneration agents: an update. Mini Rev Med Chem. 2021;21:899–918.
156. Zarrintaj P, Khodadadi Yazdi M, Youssefi Azarfam M, Zare M, Ramsey JD, Seidi F, Reza Saeb M, Ramakrishna S, Mozafari M. Injectable cell-laden hydrogels for tissue engineering: recent advances and future opportunities. Tissue Eng Part A. 2021;27:821–43.
157. Gaitán-Salvatella I, González-Alva P, Montesinos JJ, Alvarez-Perez MA. In vitro bone differentiation of 3D microsphere from dental pulp-mesenchymal stem cells. Bioengineering (Basel). 2023;10:571.
158. Tang M, Tiwari SK, Agrawal K, Tan M, Dang J, Tam T, Tian J, Wan X, Schimelman J, You S, et al. Rapid 3D bioprinting of glioblastoma model mimicking native biophysical heterogeneity. Small. 2021;17: e2006050.
159. Wong SW, Lenzini S, Giovanni R, Knowles K, Shin JW. Matrix biophysical cues direct mesenchymal stromal cell functions in immunity. Acta Biomater. 2021;133:126–38.
160. Mikušová V, Mikuš P. Advances in chitosan-based nanoparticles for drug delivery. Int J Mol Sci. 2021;22:9652.
161. Venditti I. Nanostructured materials based on noble metals for advanced biological applications. Nanomaterials (Basel). 2019;9:1593.
162. Kim JK, Shukla R, Casagrande L, Sedgley C, Nör JE, Baker JR, Hill EE. Differentiating dental pulp cells via RGD-dendrimer conjugates. J Dent Res. 2010;89:1433–8.
163. Cui S-J, Fu Y, Yu M, Zhang L, Zhao W-Y, Zhang T, Qiu L-X, Gu Y, Zhou Y-H, Liu Y. Functional periodontal regeneration using biomineralized extracellular matrix/stem cell microspheroids. Chem Eng J. 2022;431: 133220.
164. Ghandforoushan P, Hanaee J, Aghazadeh Z, Samiei M, Navali AM, Khatibi A, Davaran S. Enhancing the function of PLGA-collagen scaffold by incorporating TGF-β1-loaded PLGA-PEG-PLGA nanoparticles for cartilage tissue engineering using human dental pulp stem cells. Drug Deliv Transl Res. 2022;12:2960–78.
165. Rizvi SAA, Saleh AM. Applications of nanoparticle systems in drug delivery technology. Saudi Pharmaceut J. 2018;26:64–70.
166. Soleimani Zohr Shiri M, Henderson W, Mucalo MR. A review of the lesser-studied microemulsion-based synthesis methodologies used for preparing nanoparticle systems of the noble metals, Os, Re, Ir and Rh. Materials (Basel). 2019;12:1896.
167. Zhou J, Yang T, Chen J, Wang C, Zhang H, Shao Y. Two-dimensional nanomaterial-based plasmonic sensing applications: advances and challenges. Coord Chem Rev. 2020;410: 213218.
168. Ji X, Kong N, Wang J, Li W, Xiao Y, Gan ST, Zhang Y, Li Y, Song X, Xiong Q, et al. A novel top-down synthesis of ultrathin 2d boron nanosheets for multimodal imaging-guided cancer therapy. Adv Mater. 2018;30:1803031.
169. Naik K, Chaudhary S, Ye L, Parmar AS. A strategic review on carbon quantum dots for cancer-diagnostics and treatment. Front Bioeng Biotechnol. 2022;10: 882100.
170. Xie J, Li H, Zhang T, Song B, Wang X, Gu Z. Recent advances in ZnO nanomaterial-mediated biological applications and action mechanisms. Nanomaterials (Basel). 2023;13:1500.
171. Krajina BA, Proctor AC, Schoen AP, Spakowitz AJ, Heilshorn SC. Biotemplated synthesis of inorganic materials: an emerging paradigm for nanomaterial synthesis inspired by nature. Prog Mater Sci. 2018;91:1–23.
172. Kang X, Zhu M. Tailoring the photoluminescence of atomically precise nanoclusters. Chem Soc Rev. 2019;48:2422–57.
173. Liao Q, Li Q, Li Z. The key role of molecular packing in luminescence property: from adjacent molecules to molecular aggregates. Adv Mater. 2023;2023:2306617.
174. Berbezier I, De Crescenzi M. Self-assembly of nanostructures and nanomaterials. Beilstein J Nanotechnol. 2015;6:1397–8.
175. Wu P, Fang Z, Zhang A, Zhang X, Tang Y, Zhou Y, Yu G. Chemically binding scaffolded anodes with 3D graphene architectures realizing fast and stable lithium storage. Research (Wash D C). 2019;2019:8393085.
176. Lee K-WD, Chan PK, Feng X. Morphology development and characterization of the phase-separated structure resulting from the thermal-induced phase separation phenomenon in polymer solutions under a temperature gradient. Chem Eng Sci. 2004;59:1491–504.
177. Bhandari S, Carneiro T, Lorenz H, Seidel-Morgenstern A. Shortcut model for batch preferential crystallization coupled with racemization for conglomerate-forming chiral systems. Cryst Growth Des. 2022;22:4094–104.
178. Ridi F, Meazzini I, Castroflorio B, Bonini M, Berti D, Baglioni P. Functional calcium phosphate composites in nanomedicine. Adv Coll Interface Sci. 2017;244:281–95.
179. Li X, Li S, Qi H, Han D, Chen N, Zhan Q, Li Z, Zhao J, Hou X, Yuan X, Yang X. Early healing of alveolar bone promoted by microRNA-21-loaded nanoparticles combined with Bio-Oss particles. Chem Eng J. 2020;401: 126026.
180. Gu D, Schüth F. Synthesis of non-siliceous mesoporous oxides. Chem Soc Rev. 2014;43:313–44.

181. Hadden M, Martinez-Martin D, Yong KT, Ramaswamy Y, Singh G. Recent advancements in the fabrication of functional nanoporous materials and their biomedical applications. Materials (Basel). 2022;15:2111.
182. Liang S, Liao G, Zhu W, Zhang L. Manganese-based hollow nanoplatforms for MR imaging-guided cancer therapies. Biomater Res. 2022;26:32.
183. Pal N, Lee JH, Cho EB. Recent trends in morphology-controlled synthesis and application of mesoporous silica nanoparticles. Nanomaterials (Basel). 2020;10:2122.
184. Capasso A, Rodrigues J, Moschetta M, Buonocore F, Faggio G, Messina G, Kim MJ, Kwon J, Placidi E, Benfenati F, et al. Interactions between primary neurons and graphene films with different structure and electrical conductivity. Adv Func Mater. 2021;31:2005300.
185. Liu K, Nasrallah J, Chen L, Huang L, Ni Y, Lin S, Wang H. A facile template approach to preparing stable NFC/Ag/polyaniline nanocomposites for imparting multifunctionality to paper. Carbohyd Polym. 2018;194:97–102.
186. Doktycz MJ, Simpson ML. Nano-enabled synthetic biology. Mol Syst Biol. 2007;3:125.
187. Li Z, Dong J, Zhang H, Zhang Y, Wang H, Cui X, Wang Z. Sonochemical catalysis as a unique strategy for the fabrication of nano-/micro-structured inorganics. Nanoscale Adv. 2021;3:41–72.
188. Yadav VK, Ali D, Khan SH, Gnanamoorthy G, Choudhary N, Yadav KK, Thai VN, Hussain SA, Manhrdas S. Synthesis and characterization of amorphous iron oxide nanoparticles by the sonochemical method and their application for the remediation of heavy metals from wastewater. Nanomaterials (Basel). 2020;10:1551.
189. Thakur N, Manna P, Das J. Synthesis and biomedical applications of nanoceria, a redox active nanoparticle. J Nanobiotechnol. 2019;17:84.
190. He S, Wu L, Li X, Sun H, Xiong T, Liu J, Huang C, Xu H, Sun H, Chen W, et al. Metal-organic frameworks for advanced drug delivery. Acta Pharm Sin B. 2021;11:2362–95.
191. Stubbing J, Brown J, Price GJ. Sonochemical production of nanoparticle metal oxides for potential use in dentistry. Ultrason Sonochem. 2017;35:646–54.
192. Eshed M, Lellouche J, Banin E, Gedanken A. MgF2 nanoparticle-coated teeth inhibit Streptococcus mutans biofilm formation on a tooth model. J Mater Chem B. 2013;1:3985–91.
193. Belenguer AM, Lampronti GI, Cruz-Cabeza AJ, Hunter CA, Sanders JKM. Solvation and surface effects on polymorph stabilities at the nanoscale. Chem Sci. 2016;7:6617–27.
194. Garg P, Ghatmale P, Tarwadi K, Chavan S. Influence of nanotechnology and the role of nanostructures in biomimetic studies and their potential applications. Biomimetics (Basel). 2017;2:7.
195. He S, Qin Y, Walid E, Li L, Cui J, Ma Y. Effect of ball-milling on the physicochemical properties of maize starch. Biotechnol Rep (Amst). 2014;3:54–9.
196. Vasyukova IA, Zakharova OV, Kuznetsov DV, Gusev AA. Synthesis, toxicity assessment, environmental and biomedical applications of MXenes: a review. Nanomaterials (Basel). 2022;12:1797.
197. Lu D, Zhao H, Zhang X, Chen Y, Feng L. New horizons for MXenes in biosensing applications. Biosensors (Basel). 2022;12:820.
198. Xing J, Zhang M, Liu X, Wang C, Xu N, Xing D. Multi-material electrospinning: from methods to biomedical applications. Mater Today Bio. 2023;21: 100710.
199. Geethalakshmi R, Sarada DV. Gold and silver nanoparticles from Trianthema decandra: synthesis, characterization, and antimicrobial properties. Int J Nanomed. 2012;7:5375–84.
200. Thongsuksaengcharoen S, Samosorn S, Songsrirote K. A facile synthesis of self-catalytic hydrogel films and their application as a wound dressing material coupled with natural active compounds. ACS Omega. 2020;5:25973–83.
201. Negrescu AM, Killian MS, Raghu SNV, Schmuki P, Mazare A, Cimpean A. Metal oxide nanoparticles: review of synthesis, characterization and biological effects. J Funct Biomater. 2022;13:274.
202. Wang B, Han F, You R, Chen C, Xie H. Polyphenols can improve resin-dentin bond durability by promoting amorphous calcium phosphate nanoparticles to backfill the dentin matrix. Int J Nanomed. 2023;18:1491–505.
203. Huang Z, Yu Y, Lin X-L, Zhang T, Huang J-L, Xiao L, Liang M, Wang Y-F, Qi J. Efficacy confirmation of Scutellaria baicalensis Georgi in the treatment of periodontitis via topical administration and active ingredients screening. J Ethnopharmacol. 2023;300: 115699.
204. Casarin MP, Oliveira LM, Souza ME, Santos R, Zanatta FB. Anti-biofilm and anti-inflammatory effect of a herbal nanoparticle mouthwash: a randomized crossover trial. Braz Oral Res. 2019;33:e062.
205. Furquim dos SantosCardoso V, Amaral Roppa RH, Antunes C, Silva Moraes AN, Santi L, Konrath EL. Efficacy of medicinal plant extracts as dental and periodontal antibiofilm agents: a systematic review of randomized clinical trials. J Ethnopharmacol. 2021;281:114541.
206. Kostić M, Kitić D, Petrović MB, Jevtović-Stoimenov T, Jović M, Petrović A, Živanović S. Anti-inflammatory effect of the *Salvia sclarea* L. ethanolic extract on lipopolysaccharide-induced periodontitis in rats. J Ethnopharmacol. 2017;199:52–9.
207. Yazdanian M, Rostamzadeh P, Alam M, Abbasi K, Tahmasebi E, Tebyaniyan H, Ranjbar R, Seifalian A, Moghaddam MM, Kahnamoei MB. Evaluation of antimicrobial and cytotoxic effects of Echinacea and Arctium extracts and Zataria essential oil. AMB Express. 2022;12:75.
208. Yazdanian M, Rostamzadeh P, Rahbar M, Alam M, Abbasi K, Tahmasebi E, Tebyaniyan H, Ranjbar R, Seifalian A, Yazdanian A. The potential application of green-synthesized metal nanoparticles in dentistry: a comprehensive review. Bioinorg Chem Appl. 2022;2022:2311910.
209. Mosaddad SA, Hussain A, Tebyaniyan H. Green alternatives as antimicrobial agents in mitigating periodontal diseases: a narrative review. Microorganisms. 2023;11:1269.
210. Yang X, Ma Y, Wang X, Yuan S, Huo F, Yi G, Zhang J, Yang B, Tian W. A 3D-bioprinted functional module based on decellularized extracellular matrix bioink for periodontal regeneration. Adv Sci. 2023;10:2205041.
211. Xing H, Yang F, Sun S, Pan P, Wang H, Wang Y, Chen J. Green efficient ultrasonic-assisted extraction of abalone nacre water-soluble organic matrix for bioinspired enamel remineralization. Colloids Surf B. 2022;212: 112336.
212. Zaleh A-A, Salehi-Vaziri A, Pourhajibagher M, Bahador A. The synergistic effect of Nano-propolis and curcumin-based photodynamic therapy on remineralization of white spot lesions: an ex vivo study. Photodiagn Photodyn Ther. 2022;38: 102789.
213. Wang W, Hu Y, Chen Z, Yu L, Huang S, Zhang Y, Li J, Xue Y, Li A, Wang Y, et al. Guanidine and galactose decorated nanophotosensitizer with oxygen self-sufficient capability for the localized ablation of oral biofilm. Adv Func Mater. 2023;33:2300474.
214. Zeng D, Ma Z, Zan X, Luo T, Wang X, Gao X, Fu X. A folic acid-decorated nanoparticles loaded JQ1 for oral squamous cell carcinoma therapy. Chin Chem Lett. 2024;35: 108433.
215. Wang L, Liu S, Ren C, Xiang S, Li D, Hao X, Ni S, Chen Y, Zhang K, Sun H. Construction of hollow polydopamine nanoparticle based drug sustainable release system and its application in bone regeneration. Int J Oral Sci. 2021;13:27.
216. Yuan X, Yuan Z, Wang Y, Wan Z, Wang X, Yu S, Han J, Huang J, Xiong C, Ge L, et al. Vascularized pulp regeneration via injecting simvastatin functionalized GelMA cryogel microspheres loaded with stem cells from human exfoliated deciduous teeth. Mater Today Bio. 2022;13: 100209.
217. Ilhan M, Kilicarslan M, Alcigir ME, Bagis N, Ekim O, Orhan K. Clindamycin phosphate and bone morphogenetic protein-7 loaded combined nanoparticle-graft and nanoparticle-film formulations for alveolar bone regeneration—an in vitro and in vivo evaluation. Int J Pharm. 2023;636: 122826.
218. Zhou Y, Liu J, Xue P, Zhang J. Collagenase-responsive hydrogel loaded with GSK2606414 nanoparticles for periodontitis treatment through inhibiting inflammation-induced expression of PERK of periodontal ligament stem cells. Pharmaceutics. 2023;15:2503.
219. Wen B, Dai Y, Han X, Huo F, Xie L, Yu M, Wang Y, An N, Li Z, Guo W. Biomineralization-inspired mineralized hydrogel promotes the repair and regeneration of dentin/bone hard tissue. NPJ Regen Med. 2023;8:11.
220. Gardiner J, Freeman S, Leach M, Green A, Alcock J, D'Emanuele A. PAMAM dendrimers for the delivery of the antibacterial Triclosan. J Enzyme Inhib Med Chem. 2008;23:623–8.
221. Bengazi F, Lang NP, Canciani E, Viganò P, Velez JU, Botticelli D. Osseointegration of implants with dendrimers surface characteristics installed conventionally or with Piezosurgery®. A comparative study in the dog. Clin Oral Implants Res. 2014;25:10–5.

222. Tao S, Yang J, Su Z, Zhou F, Wang Z, Yang Y, Sun L, Deng Y, Liang K, Li J. A dentin biomimetic remineralization material with an ability to stabilize collagen. Small. 2022;18:2203644.
223. Guimarães D, Cavaco-Paulo A, Nogueira E. Design of liposomes as drug delivery system for therapeutic applications. Int J Pharm. 2021;601: 120571.
224. Li T, Cipolla D, Rades T, Boyd BJ. Drug nanocrystallisation within liposomes. J Control Release. 2018;288:96–110.
225. Xiao L, Feng M, Chen C, Xiao Q, Cui Y, Zhang Y. Microenvironment-regulating drug delivery nanoparticles for treating and preventing typical biofilm-induced oral diseases. Adv Mater. 2304982.
226. Luo Z, Lin Y, Zhou X, Yang L, Zhang Z, Liu Z, Zhou M, Jiang J, Wu J, Liu Z, et al. Biomineral-binding liposomes with dual antibacterial effects for preventing and treating dental caries. Biomater Sci. 2023;11:5984–6000.
227. Zinger A, Adir O, Alper M, Simon A, Poley M, Tzror C, Yaari Z, Krayem M, Kasten S, Nawy G, et al. Proteolytic nanoparticles replace a surgical blade by controllably remodeling the oral connective tissue. ACS Nano. 2018;12:1482–90.
228. Zhang M, Yu Z, Lo ECM. A new pH-responsive nano micelle for enhancing the effect of a hydrophobic bactericidal agent on mature Streptococcus mutans biofilm. Front Microbiol. 2021;12:761583.
229. Xu Y, You Y, Yi L, Wu X, Zhao Y, Yu J, Liu H, Shen Y, Guo J, Huang C. Dental plaque-inspired versatile nanosystem for caries prevention and tooth restoration. Bioactive Mater. 2023;20:418–33.
230. Wang H, Wang D, Huangfu H, Chen S, Qin Q, Ren S, Zhang Y, Fu L, Zhou Y. Highly efficient photothermal branched Au–Ag nanoparticles containing procyanidins for synergistic antibacterial and anti-inflammatory immunotherapy. Biomater Sci. 2023;11:1335–49.
231. Mitwalli H, AlSahafi R, Alhussein A, Oates TW, Melo MAS, Xu HHK, Weir MD. Novel rechargeable calcium fluoride dental nanocomposites. Dent Mater. 2022;38:397–408.
232. Liu M, Huang L, Xu X, Wei X, Yang X, Li X, Wang B, Xu Y, Li L, Yang Z. Copper doped carbon dots for addressing bacterial biofilm formation, wound infection, and tooth staining. ACS Nano. 2022;16:9479–97.
233. Tang Y, Huang Q-X, Zheng D-W, Chen Y, Ma L, Huang C, Zhang X-Z. Engineered Bdellovibrio bacteriovorus: a countermeasure for biofilm-induced periodontitis. Mater Today. 2022;53:71–83.
234. Lee B, Kwon J-S, Khalid MW, Kim K-M, Kim J, Lim KM, Hong SH. Boron nitride nanoplatelets as reinforcement material for dental ceramics. Dent Mater. 2020;36:744–54.
235. Spagnuolo G, De Luca I, Iaculli F, Barbato E, Valletta A, Calarco A, Valentino A, Riccitiello F. Regeneration of dentin-pulp complex: effect of calcium-based materials on hDPSCs differentiation and gene expression. Dent Mater. 2023;39:485–91.
236. Wen Z, Shi X, Li X, Liu W, Liu Y, Zhang R, Yu Y, Su J. Mesoporous TiO_2 coatings regulate ZnO nanoparticle loading and Zn_{2+} release on titanium dental implants for sustained osteogenic and antibacterial activity. ACS Appl Mater Interfaces. 2023;15:15235–49.
237. Xia H-Y, Li B-Y, Ye Y-T, Wang S-B, Chen A-Z, Kankala RK. Transition metal oxide-decorated MXenes as drugless nanoarchitectonics for enriched nanocatalytic chemodynamic treatment. Adv Healthc Mater. 2023;13:2303582.
238. Aati S, Chauhan A, Shrestha B, Rajan SM, Aati H, Fawzy A. Development of 3D printed dental resin nanocomposite with graphene nanoplatelets enhanced mechanical properties and induced drug-free antimicrobial activity. Dent Mater. 2022;38:1921–33.
239. Li Z, Wang J, Chen H, Wang R, Zhu M. Synthesis of ZnO nanorod-decorated graphene oxide for application in dental resin composites. ACS Biomater Sci Eng. 2023;9:2706–15.
240. Imran M, Riaz S, Sanaullah I, Khan U, Sabri AN, Naseem S. Microwave assisted synthesis and antimicrobial activity of Fe_3O_4-doped ZrO_2 nanoparticles. Ceram Int. 2019;45:10106–13.
241. Liu H, Chen Y, Mo L, Long F, Wang Y, Guo Z, Chen H, Hu C, Liu Z. "Afterglow" photodynamic therapy based on carbon dots embedded silica nanoparticles for nondestructive teeth whitening. ACS Nano. 2023;17:21195–205.
242. He J, Yang J, Li M, Li Y, Pang Y, Deng J, Zhang X, Liu W. Polyzwitterion manipulates remineralization and antibiofilm functions against dental demineralization. ACS Nano. 2022;16:3119–34.
243. Tong F, Wang P, Chen Z, Liu Y, Wang L, Guo J, Li Z, Cai H, Wei J. Combined ferromagnetic nanoparticles for effective periodontal biofilm eradication in rat model. Int J Nanomed. 2023;18:2371–88.
244. Wang P, Wang L, Zhan Y, Liu Y, Chen Z, Xu J, Guo J, Luo J, Wei J, Tong F, Li Z. Versatile hybrid nanoplatforms for treating periodontitis with chemical/photothermal therapy and reactive oxygen species scavenging. Chem Eng J. 2023;463: 142293.
245. Hu S, Wang L, Li J, Li D, Zeng H, Chen T, Li L, Xiang X. Catechol-modified and MnO2-nanozyme-reinforced hydrogel with improved antioxidant and antibacterial capacity for periodontitis treatment. ACS Biomater Sci Eng. 2023;9:5332–46.
246. Javed R, Rais F, Fatima H, Haq Iu, Kaleem M, Naz SS, Ao Q. Chitosan encapsulated ZnO nanocomposites: fabrication, characterization, and functionalization of bio-dental approaches. Mater Sci Eng C. 2020;116:111184.
247. Yi L, Wu H, Xu Y, Yu J, Zhao Y, Yang H, Huang C. Biomineralization-inspired sandwich dentin desensitization strategy based on multifunctional nanocomposite with yolk–shell structure. Nanoscale. 2023;15:127–43.
248. Zhao M, Ji C, Dai H, Wang C, Liu R, Xie J, Wang Y, Gu Z. Mussel-inspired tantalum nanocomposite hydrogels for in situ oral cancer treatment. ACS Appl Mater Interfaces. 2023;15:4984–95.
249. Montoya C, Jain A, Londoño JJ, Correa S, Lelkes PI, Melo MA, Orrego S. Multifunctional dental composite with piezoelectric nanofillers for combined antibacterial and mineralization effects. ACS Appl Mater Interfaces. 2021;13:43868–79.
250. Xu Y, Luo Y, Weng Z, Xu H, Zhang W, Li Q, Liu H, Liu L, Wang Y, Liu X, et al. Microenvironment-responsive metal-phenolic nanozyme release platform with antibacterial, ROS scavenging, and osteogenesis for periodontitis. ACS Nano. 2023;17:18732–46.
251. Chen J, Zhu Z, Pan Q, Bai Y, Yu M, Zhou Y. Targeted therapy of oral squamous cell carcinoma with cancer cell membrane coated Co-Fc nanoparticles via autophagy inhibition. Adv Func Mater. 2023;33:2300235.
252. Su T, Zheng A, Cao L, Peng L, Wang X, Wang J, Xin X, Jiang X. Adhesion-enhancing coating embedded with osteogenesis-promoting PDA/HA nanoparticles for peri-implant soft tissue sealing and osseointegration. Bio-Design Manuf. 2022;5:233–48.
253. Liu X, Gan K, Liu H, Song X, Chen T, Liu C. Antibacterial properties of nano-silver coated PEEK prepared through magnetron sputtering. Dent Mater. 2017;33:e348–60.
254. Mayorga-Martinez CC, Zelenka J, Klima K, Mayorga-Burrezo P, Hoang L, Ruml T, Pumera M. Swarming magnetic photoactive microrobots for dental implant biofilm eradication. ACS Nano. 2022;16:8694–703.
255. Chen L, Peng M, Li H, Zhou J, He W, Hu R, Ye F, Li Y, Shi L, Liu Y. Metal-phenolic network with Pd nanoparticle nodes synergizes oxidase-like and photothermal properties to eradicate oral polymicrobial biofilm-associated infections. Adv Mater. 2024;36: e2306376.
256. Toledano-Osorio M, Osorio R, Aguilera FS, Medina-Castillo AL, Toledano M, Osorio E, Acosta S, Chen R, Aparicio C. Polymeric nanoparticles protect the resin-dentin bonded interface from cariogenic biofilm degradation. Acta Biomater. 2020;111:316–26.
257. Toledano M, Aguilera FS, Osorio E, Toledano-Osorio M, Escames G, Medina-Castillo AL, Toledano R, Lynch CD, Osorio R. Melatonin-doped polymeric nanoparticles reinforce and remineralize radicular dentin: morpho-histological, chemical and biomechanical studies. Dent Mater. 2021;37:1107–20.
258. Toledano M, Osorio E, Aguilera FS, Osorio MT, Toledano R, López-López MT, Lynch CD, Osorio R. Dexamethasone and zinc loaded polymeric nanoparticles reinforce and remineralize coronal dentin. A morpho-histological and dynamic-biomechanical study. Dent Mater. 2023;39:41–56.
259. Zhao Y, Zhang H, Hong L, Zou X, Song J, Han R, Chen J, Yu Y, Liu X, Zhao H, Zhang Z. A multifunctional dental resin composite with Sr-N-doped TiO_2 and n-HA fillers for Antibacterial and mineralization effects. Int J Mol Sci. 2023;24:1274.
260. Neshatian M, Holcroft J, Kishen A, De Souza G, Ganss B. Promoting mineralization at biological interfaces Ex vivo with novel amelotin-based bio-nano complexes. Mater Today Bio. 2022;14: 100255.
261. Wang X, Fan H, Zhang F, Zhao S, Liu Y, Xu Y, Wu R, Li D, Yang Y, Liao L, et al. Antibacterial properties of bilayer biomimetic Nano-ZnO for dental implants. ACS Biomater Sci Eng. 2020;6:1880–6.

262. Omar O, Elgali I, Dahlin C, Thomsen P. Barrier membranes: more than the barrier effect? J Clin Periodontol. 2019;46:103–23.
263. Taylor DP, Yoshida M, Fuller K, Giannobile WV, Sfeir CS, Wagner WR, Kohn DH. Translating dental, oral, and craniofacial regenerative medicine innovations to the clinic through interdisciplinary commercial translation architecture. J Dent Res. 2021;100:1039–46.
264. Kunrath MF, Shah FA, Dahlin C. Bench-to-bedside: feasibility of nano-engineered and drug-delivery biomaterials for bone-anchored implants and periodontal applications. Mater Today Bio. 2023;18: 100540.
265. Kunrath MF, Correia A, Teixeira ER, Hubler R, Dahlin C. Superhydrophilic nanotextured surfaces for dental implants: influence of early saliva contamination and wet storage. Nanomaterials. 2022;12:2603.
266. Bapat RA, Joshi CP, Bapat P, Chaubal TV, Pandurangappa R, Jnanendrappa N, Gorain B, Khurana S, Kesharwani P. The use of nanoparticles as biomaterials in dentistry. Drug Discov Today. 2019;24:85–98.
267. Kantarci A, Hasturk H, Van Dyke TE. Animal models for periodontal regeneration and peri-implant responses. Periodontol. 2000;2015(68):66–82.
268. Franca CM, Balbinot GDS, Cunha D, Saboia VDPA, Ferracane J, Bertassoni LE. In-vitro models of biocompatibility testing for restorative dental materials: from 2D cultures to organs on-a-chip. Acta Biomater. 2022;150:58–66.
269. Ribitsch I, Baptista PM, Lange-Consiglio A, Melotti L, Patruno M, Jenner F, Schnabl-Feichter E, Dutton LC, Connolly DJ, van Steenbeek FG, et al. Large animal models in regenerative medicine and tissue engineering: to do or not to do. Front Bioeng Biotechnol. 2020;8:972.
270. Valic MS, Zheng G. Research tools for extrapolating the disposition and pharmacokinetics of nanomaterials from preclinical animals to humans. Theranostics. 2019;9:3365–87.
271. Baldin EKK, Malfatti CF, Rodói V, Brandalise RN. Effect of sterilization on the properties of a bioactive hybrid coating containing hydroxyapatite. Adv Mater Sci Eng. 2019;2019:8593193.
272. Qi M, Li X, Sun X, Li C, Tay FR, Weir MD, Dong B, Zhou Y, Wang L, Xu HHK. Novel nanotechnology and near-infrared photodynamic therapy to kill periodontitis-related biofilm pathogens and protect the periodontium. Dent Mater. 2019;35:1665–81.
273. Ravandi R, Zeinali Heris S, Hemmati S, Aghazadeh M, Davaran S, Abdyazdani N. Effects of chitosan and TiO$_2$ nanoparticles on the antibacterial property and ability to self-healing of cracks and retrieve mechanical characteristics of dental composites. Heliyon. 2024;10: e27734.
274. Li M, Liu Q, Jia ZJ, Xu XC, Shi YY, Cheng Y, Zheng YF. Polydopamine-induced nanocomposite Ag/CaP coatings on the surface of titania nanotubes for antibacterial and osteointegration functions. J Mater Chem B. 2015;3:8796–805.
275. Garcia IM, Balhaddad AA, Ibrahim MS, Weir MD, Xu HHK, Collares FM, Melo MAS. Antibacterial response of oral microcosm biofilm to nano-zinc oxide in adhesive resin. Dent Mater. 2021;37:e182–93.
276. Shokuhfar T, Sinha-Ray S, Sukotjo C, Yarin AL. Intercalation of anti-inflammatory drug molecules within TiO$_2$ nanotubes. RSC Adv. 2013;3:17380–6.
277. Mirhashemi A, Bahador A, Sodagar A, Pourhajibagher M, Amiri A, Gholamrezayi E. Evaluation of antimicrobial properties of nano-silver particles used in orthodontics fixed retainer composites: an experimental in-vitro study. J Dent Res Dent Clin Dent Prospects. 2021;15:87–93.
278. Xu L, Chen S, Feng Y, Chen M, Liu Y, Ma X, Jing J, Meng S, Yao Y, Sun W, Chen H. Persistent and enhanced elimination of bacteria-induced periodontitis using a local drug delivery nanoreactor. Adv Therapeut. 2023;6:2200230.
279. Zhang P, Wu S, Li J, Bu X, Dong X, Chen N, Li F, Zhu J, Sang L, Zeng Y, et al. Dual-sensitive antibacterial peptide nanoparticles prevent dental caries. Theranostics. 2022;12:4818–33.
280. Ahmed O, Sibuyi NRS, Fadaka AO, Madiehe AM, Maboza E, Olivier A, Meyer M, Geerts G. Antimicrobial effects of gum arabic-silver nanoparticles against oral pathogens. Bioinorg Chem Appl. 2022;2022:9602325.
281. Rossi NR, de Menezes BRC, Sampaio AdG, da Silva DM, Koga-Ito CY, Thim GP, Paes-Junior TJdA. Silver-coated silica nanoparticles modified with MPS: potential antimicrobial biomaterials applied in glaze and soft reliner. Polymers. 2022;14:4306.
282. Larissa P, Gambrill B, de Carvalho RDP, Picolo MZD, Cavalli V, Boaro LCC, Prokopovich P, Cogo-Müller K. Development, characterization and antimicrobial activity of multilayer silica nanoparticles with chlorhexidine incorporated into dental composites. Dent Mater. 2023;39:469–77.
283. Yi J, Dai Q, Weir MD, Melo MAS, Lynch CD, Oates TW, Zhang K, Zhao Z, Xu HHK. A nano-CaF2-containing orthodontic cement with antibacterial and remineralization capabilities to combat enamel white spot lesions. J Dent. 2019;89: 103172.
284. Bhadila G, Wang X, Zhou W, Menon D, Melo MAS, Montaner S, Oates TW, Weir MD, Sun J, Xu HHK. Novel low-shrinkage-stress nanocomposite with remineralization and antibacterial abilities to protect marginal enamel under biofilm. J Dent. 2020;99: 103406.
285. Tao S, Su Z, Xiang Z, Xu HHK, Weir MD, Fan M, Yu Z, Zhou X, Liang K, Li J. Nano-calcium phosphate and dimethylaminohexadecyl methacrylate adhesive for dentin remineralization in a biofilm-challenged environment. Dent Mater. 2020;36:e316–28.
286. Chen YD, Shu C, Duan ZH, Xu JJ, Li XJ, Chen F, Luo QJ, Li XD. Synthesis and characterization of an anti-caries and remineralizing fluorine-containing cationic polymer PHMB-F. Biomater Sci. 2021;9:2009–19.
287. Yu J, Xiao XF, Liang JH, Liu RF, Wang CY, Mao D. Filling TiO$_2$ nanotubes with biological apatite by alternative loop immersion method. J Inorg Mater. 2011;26:78–84.
288. Fan M, Yang J, Xu HHK, Weir MD, Tao S, Yu Z, Liu Y, Li M, Zhou X, Liang K, Li J. Remineralization effectiveness of adhesive containing amorphous calcium phosphate nanoparticles on artificial initial enamel caries in a biofilm-challenged environment. Clin Oral Invest. 2021;25:5375–90.
289. Kim M-J, Lee M-J, Kim K-M, Yang S-Y, Seo J-Y, Choi S-H, Kwon J-S. Enamel demineralization resistance and remineralization by various fluoride-releasing dental restorative materials. Materials. 2021;14:4554.
290. Fan M, Li M, Yang Y, Weir MD, Liu Y, Zhou X, Liang K, Li J, Xu HHK. Dual-functional adhesive containing amorphous calcium phosphate nanoparticles and dimethylaminohexadecyl methacrylate promoted enamel remineralization in a biofilm-challenged environment. Dent Mater. 2022;38:1518–31.
291. Guo M, Zhou Q, Wang Z, Li Q, Cao CY. Amyloid-like oligomeric nanospheres modify type I collagen to promote intrafibrillar mineralization. Mater Today Adv. 2022;14: 100246.
292. Ionescu AC, Degli Esposti L, Iafisco M, Brambilla E. Dental tissue remineralization by bioactive calcium phosphate nanoparticles formulations. Sci Rep. 2022;12:5994.
293. Sauro S, Spagnuolo G, Del Giudice C, Neto DMA, Fechine PBA, Chen X, Rengo S, Chen X, Feitosa VP. Chemical, structural and cytotoxicity characterisation of experimental fluoride-doped calcium phosphates as promising remineralising materials for dental applications. Dent Mater. 2023;39:391–401.
294. Lazarevic M, Petrovic S, Pierfelice TV, Ignjatovic N, Piattelli A, Vlajic Tovilovic T, Radunovic M. Antimicrobial and osteogenic effects of collagen membrane decorated with chitosan–nano-hydroxyapatite. Biomolecules. 2023;13:579.
295. Lee JK, Choi DS, Jang I, Choi WY. Improved osseointegration of dental titanium implants by TiO$_2$ nanotube arrays with recombinant human bone morphogenetic protein-2: a pilot in vivo study. Int J Nanomed. 2015;10:1145–54.
296. Kim GH, Kim IS, Park SW, Lee K, Yun KD, Kim HS, Oh GJ, Ji MK, Lim HP. Evaluation of osteoblast-like cell viability and differentiation on the Gly-Arg-Gly-Asp-Ser peptide immobilized titanium dioxide nanotube via chemical grafting. J Nanosci Nanotechnol. 2016;16:1396–9.
297. Yi K, Li Q, Lian X, Wang Y, Tang Z. Utilizing 3D bioprinted platelet-rich fibrin-based materials to promote the regeneration of oral soft tissue. Regenerat Biomater. 2022;9:rbac021.
298. Machla F, Sokolova V, Platania V, Prymak O, Kostka K, Kruse B, Agrymakis M, Pasadaki S, Kritis A, Alpantaki K, et al. Tissue engineering at the dentin-pulp interface using human treated dentin scaffolds conditioned with DMP1 or BMP2 plasmid DNA-carrying calcium phosphate nanoparticles. Acta Biomater. 2023;159:156–72.
299. Kao H, Chen C-C, Huang Y-R, Chu Y-H, Csík A, Ding S-J. Metal ion-dependent tailored antibacterial activity and biological properties of polydopamine-coated titanium implants. Surf Coat Technol. 2019;378: 124998.
300. Luo N, Deng Y-W, Wen J, Xu X-C, Jiang R-X, Zhan J-Y, Zhang Y, Lu B-Q, Chen F, Chen X. Wnt3a-loaded hydroxyapatite Nanowire@Mesoporous

silica core−shell nanocomposite promotes the regeneration of dentin−pulp complex via angiogenesis, oxidative stress resistance, and odontogenic induction of stem cells. Adv Healthcare Mater. 2023;12:2300229.
301. Zhang S, Zhou H, Kong N, Wang Z, Fu H, Zhang Y, Xiao Y, Yang W, Yan F. l-cysteine-modified chiral gold nanoparticles promote periodontal tissue regeneration. Bioactive Mater. 2021;6:3288–99.
302. Wang C, Zhao Q, Chen C, Li J, Zhang J, Qu S, Tang H, Zeng H, Zhang Y. CD301b+ macrophage: the new booster for activating bone regeneration in periodontitis treatment. Int J Oral Sci. 2023;15:19.
303. Eslamian L, Borzabadi-Farahani A, Karimi S, Saadat S, Badiee MR. Evaluation of the shear bond strength and antibacterial activity of orthodontic adhesive containing silver nanoparticle, an in-vitro study. Nanomaterials. 2020;10:1466.
304. Favaro JC, Detomini TR, Maia LP, Poli RC, Guiraldo RD, Lopes MB, Berger SB. Anticaries agent based on silver nanoparticles and fluoride: characterization and biological and remineralizing effects—an in vitro study. Int J Dentis. 2022;2022:9483589.
305. Hu Y, Xu Z, Pu J, Hu L, Zi Y, Wang M, Feng X, Huang W. 2D MXene Ti3C2Tx nanosheets in the development of a mechanically enhanced and efficient antibacterial dental resin composite. Front Chem. 2022;10:1090905.
306. Liu Y, Huang Y, Kim D, Ren Z, Oh MJ, Cormode DP, Hara AT, Zero DT, Koo H. Ferumoxytol nanoparticles target biofilms causing tooth decay in the human mouth. Nano Lett. 2021;21:9442–9.
307. Mitwalli H, Balhaddad AA, AlSahafi R, Oates TW, Melo MAS, Xu HHK, Weir MD. Novel CaF2 nanocomposites with antibacterial function and fluoride and calcium ion release to inhibit oral biofilm and protect teeth. J Funct Biomater. 2020;11:56.
308. Toledano M, Vallecillo-Rivas M, Aguilera FS, Osorio MT, Osorio E, Osorio R. Polymeric zinc-doped nanoparticles for high performance in restorative dentistry. J Dent. 2021;107: 103616.

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