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# Engineering next-generation smart delivery materials for dentistry

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ABSTRACT

Over the last two decades, the healthcare field has witnessed exponential growth in the applications of stimuli-responsive biomaterials for diverse therapeutic purposes. This has led to the development of numerous smart dental biomaterials tailored for the precise and on-demand delivery of therapeutic agents. By leveraging the specific exogenous and endogenous stimuli, these smart materials fine-tune their physicochemical properties to improve the clinical efficacy of the therapeutic agents and mitigate their side effects. This review systemically examines the design and objectives of the smart biomaterials platforms specifically for dental and associated soft tissue. Additionally, we comprehensively summarize various smart biomaterials-based delivery platforms, categorized by the nature of the stimuli, including pH, enzyme, temperature, light, ultrasound, electricity, and pressure. Furthermore, this review discusses several newly developed smart platforms utilized in different dental conditions, with a particular focus on those undergoing clinical trials. This review aims to provide an overview of the state-of-the-art smart drug delivery systems in dentistry and offer insights into developing next-generation platforms to address various clinical needs, such as infection eradication, inflammation modulation, tissue regeneration, and immunotherapy.

## 1. Introduction

The maintenance of dental tissue homeostasis is vital to oral health. According to the WHO Global Oral Health Status Report (2022), nearly 3.5 billion people worldwide are affected by oral disease, and more than 60 % of these patients are directly impacted by dental diseases [1]. These epidemiological findings highlight the urgent need for specific dental medications to restore oral homeostasis. Typically, dental pathological conditions, such as periodontitis, endodontitis, peri-implantitis, and caries, are caused by various microorganisms that disrupt the homeostasis of dental tissues [2–4]. Additionally, uncontrolled inflammation during these pathological conditions, coupled with defects arising from trauma, infection, tumors, and surgeries, worsens oral homeostasis and hinders the regeneration of damaged tissues.

To address dental infectious diseases such as endodontics, periodontics, mucositis, and peri-implantitis, traditional therapy often relies on administering antibiotic agents to the affected area [5]. However, effective management of those conditions necessitates the spatiotemporally controlled delivery of therapeutic agents to sequentially achieve infection eradication, inflammation control, tissue repair, and functional remodeling [6–8]. Most traditional dental biomaterials that have been used in clinical practice nowadays are not able to attain therapeutic outcomes without causing local or systemic adverse drug reactions. Moreover, most of those therapeutic strategies fail to provide potent and long-lasting disinfection, adaptable inflammation regulation, and targeted control of tissue regeneration. The administration of therapeutic agents without proper control can lead to unwanted complications. For example, the widely used disinfectant chlorhexidine can cause discoloration and taste abnormalities [9,10]. Additionally, calcium hydroxide, which is extensively used for remineralization, has been reported to cause chemical burns, permanent lung damage, and even blindness [11,12]. Moreover, many biomaterials have not yielded promising clinical outcomes due to their inherent physicochemical properties, such as surface topography, spatial configuration, and mechanical characteristics [13]. For instance, it is difficult for regenerative biomaterials to adequately recapitulate the spatial arrangement and mechanical properties of the ‘cementum-periodontium-alveolar bone’ complex in periodontitis patients [14,15]. Meanwhile, the degradation

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characteristic of the delivery platforms is also crucial as it directly impacts the release profile of the therapeutic agents [16,17]. For example, in the context of peri-implantitis, biomaterials lacking controllable degradation exhibit limited clinical efficacy because they are not able to sequentially accomplish microbial eradication, inflammation modulation, bone regeneration, and tissue remodeling [18,19].

With recent breakthroughs in the design of biomaterials at the molecular scale and more in-depth mechanistic understandings of dental diseases, significant advancements have been made in developing next-generation smart biomaterials for dentistry. Smart biomaterials, also referred to as stimuli-responsive biomaterials, are characterized by their ability to sense endogenous cues or exogenous stimuli and respond accordingly. This responsiveness can be leveraged to regulate various biochemical functions, offering substantial benefits for drug delivery applications through precise spatial, temporal, and dosage controls [20]. Furthermore, advancements in smart biomaterials open new avenues for improving the penetration of therapeutic agents into deep tissue, preventing local aggregation, and enhancing stability and spatiotemporal controllability [21]. Additionally, through biochemical conjugation, these materials enable precise targeting, multiple sequential drug delivery, with real-time on-site imaging [9,22].

Although various smart biomaterials have been developed to address different complex clinical problems, they are specifically designed for tackling dental diseases and remain limited. Indeed, many smart biomaterials proposed to be used in various dental conditions are not originally designed with a determined goal of dental application or a clear understanding of relevant dental diseases. More importantly, a critical literature review to introduce smart biomaterials from the perspective of dentistry is lacking. Therefore, we aim to comprehensively review the smart drug delivery platforms, especially those with the potential to be used in different dental scenarios. Firstly, we systematically address the complexity of dental tissue structure and discuss various physiological barriers that impede therapeutic delivery. Next, we provide an in-depth analysis of the design strategy for diverse smart delivery platforms categorized based on different responsiveness to either internal or external stimuli, which not only clarifies the design principles and mechanisms of responsive materials but also highlights their potential clinical translation in dentistry. We believe this categorization would more effectively target the challenges and opportunities of smart material design in clinical scenarios. Furthermore, we highlight recent breakthroughs in stimuli-responsive delivery platforms for various dental diseases and analyze the current clinical challenges and therapeutic obstacles that have hindered the translation of smart biomaterials from bench to bedside.

## 2. Special consideration for smart drug delivery platforms in dentistry

Dental tissues are highly complex organs composed of many associated soft and hard tissues with highly dynamic physicochemical

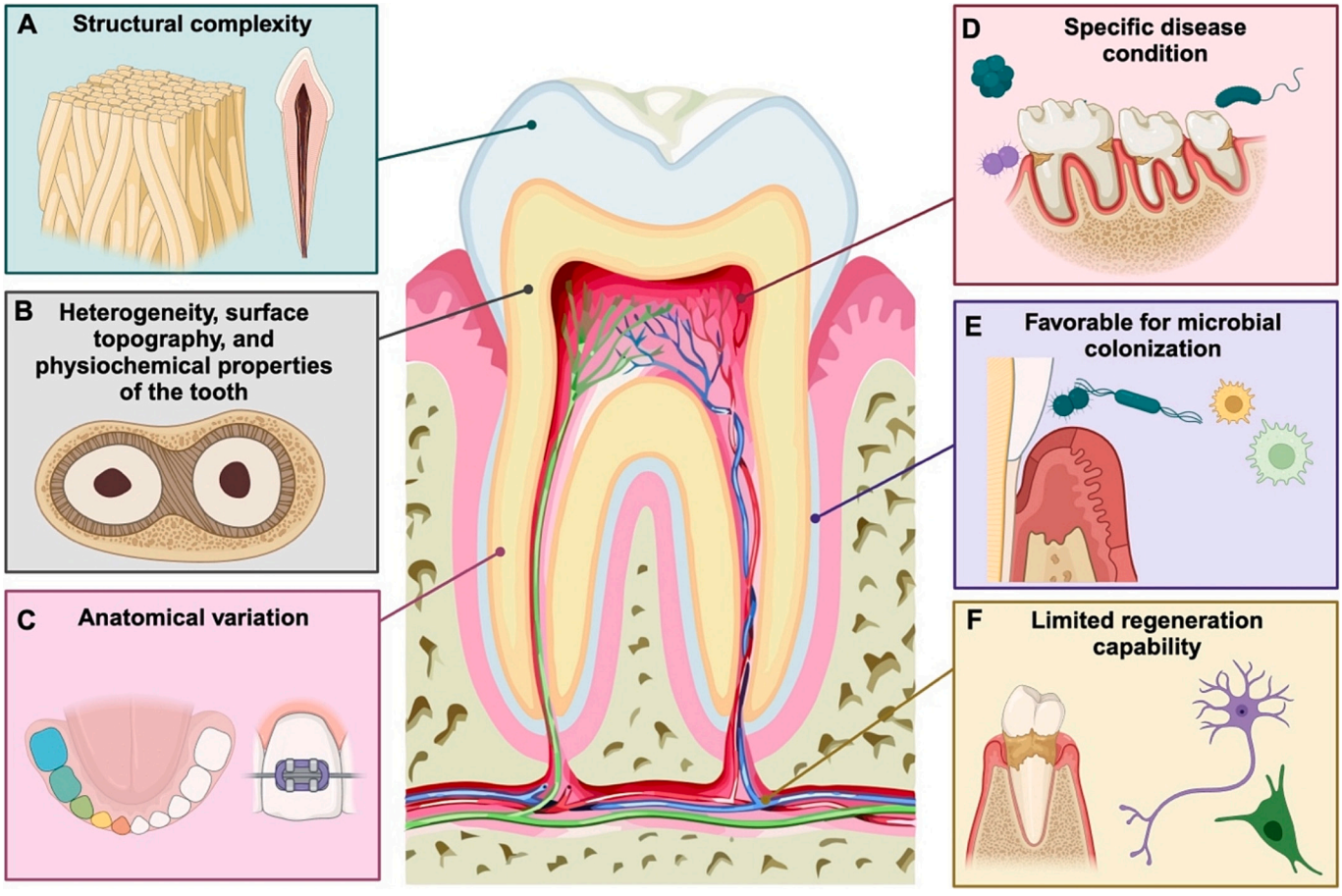


**Fig. 1.** Schematic illustration depicting the key challenges for the therapeutic delivery to dental and associated tissues. (A) Enamel comprises highly mineralized inorganic components with precisely organized micro- and nano-architectures; also, the tiny micro-channels in the pulp tissue pose challenges to delivering the therapeutic agents. (B) Diverse physicochemical and surface topography make effective biomaterial development critical. Local inflammatory conditions worsen the drug penetration and efficacy. (C) Variances in the anatomical structures and position significantly hamper the delivery of therapeutic molecules to their target. (D) Severe localized inflammation conditions in certain dental diseases present additional challenges for effective drug administration. (E) Due to the presence of micro-level cellular junctions and favourable nutrient flow, dental tissue is highly susceptible to microbial colonization, which can subsequently lead to the development of dental diseases. (F) The limited regenerative capacity of dental tissue makes functional restoration after disease recovery particularly difficult.

microenvironments [23,24]. The complexity of the oral cavity necessitates the development of advanced drug delivery systems to effectively address current treatment challenges. Thus, the delivery of therapeutic agents to the different regions of the oro-dental tissues requires precise strategies to ensure these agents can exert their biological activity and maintain oral homeostasis [25–27]. Recent advancements in bio-nanotechnology, material science, and additive manufacturing have introduced potential delivery platforms for various tissue-specific applications, including bone, cartilage, tendons, and neurons [28–30]. However, unlike other organs and tissues, drug delivery to the dental tissues presents multiple impediments due to a range of challenges, as illustrated in Fig. 1.

Firstly, the architectural complexity of dental tissue is remarkably diverse, with varying structural compositions across different regions [31]. For example, enamel is composed of highly mineralized inorganic components with a sophisticated micro- and nano-architecture [32]. Due to its densely packed structure, conventional delivery platforms encounter significant challenges in achieving site-specific therapeutic agent release and penetration [33]. Conversely, regenerating the interface between the dentin and pulp is also challenging, as it consists of a complex organic matrix interspersed with spatially arranged odontoblast cells [33]. Additionally, the odontogenic zone and pulp tissue are highly conducive to microbial colonization due to their highly confined spaces and nutrient-rich environments [34]. Therefore, delivering therapeutic payloads under the hard dental enamel or within confined tubules with such micro-level proximity is exceedingly difficult (Fig. 1A).

Secondly, different parts of dental tissues possess diverse physicochemical and surface characteristics (Fig. 1B**)**. For instance, the outer layer of the crown enamel is predominantly composed of inorganic materials with highly compacted crystals, whereas the pulp tissue is primarily composed of organic materials such as cells and extracellular matrix [33]. This variation in the inorganic-to-organic ratio affects the properties and physiological immunity of these tissues. Furthermore, the surface topography of specific parts of the tooth tissue is crucial, serves as the initial contact site between biomaterials and the tissue surface [32]. Therefore, the therapeutic delivery approach to these tissues necessitates the design of highly compatible platforms.

Thirdly, tooth structure and configuration are highly variable among individuals. Anatomical dental variances in morphology predominantly involve disparities in the length, breadth, height, area, or volume of the crown and root of dental tissue [35]. Conventional therapeutic strategies often lack the adaptability required to accommodate specific anatomical variations, such as dental cavities and root furcation areas. Therefore, it is imperative to adopt configurable smart delivery approaches to achieve site-specific, personalized oral care (Fig. 1C**)**.

Furthermore, the constant flow of salivary fluids containing various protease enzymes makes the oral environment extremely dynamic [26,36]. This dynamism significantly complicates the development of durable, sustained delivery platforms for oro-dental tissue. Traditional tissue-adhesive biomaterials have been developed to circumvent this issue. However, in the case of oral diseases, the buccal mucosa is far less permeable than the sublingual mucosa, reducing drug absorption and bioavailability. Moreover, the sublingual mucosa is not ideal for mucoadhesion since it is uneven, movable, and continuously salivated [26]. Therefore, to achieve sustained release kinetics of therapeutic agents, the delivery platforms need to be mucoadhesive for a longer period. More importantly, biodegradable materials for dental applications are frequently used in microenvironments susceptible to the influences of humoral regulation and immune responses (Fig. 1D, E). Under disease conditions, those biomaterials are exposed to crevicular fluid and saliva containing various inflammatory mediators, such as cytokines, enzymes, and peptidases [37,38]. The inflammatory microenvironment can directly impact the degradation of biomaterials by activating or inactivating certain catalysts typically needed for polymer breakdown [39], thereby altering the release kinetics of loaded drugs. Therefore, the design of biodegradable biomaterial-based delivery platforms should consider tuning the payload amount for specific disease severity and the host immune response.

Compared with many other tissues, the regeneration capability of dental tissues is more limited [40]. For example, enamel is completely acellular, making it completely non-regenerative (Fig. 1F**)** [33]. Moreover, the regeneration capability of dentin, periodontal ligament, or pulp tissue is also limited, which is associated with the insufficient supply of dental pulp stem cells (DPSCs) and periodontal ligament stem cells (PDLSCs) [41]. Therefore, smart delivery platforms for dental tissue regeneration should be able to recruit regenerative cells into pulp or periodontium, as well as support their proliferation and differentiation in the healing process [42,43].

Finally, active therapeutic agents may encounter different barriers at chemical, mucosal, and cellular levels when used in dental diseases (Fig. 2A). The presence of infection can even worsen the situation due to the formation of microbial biofilm (Fig. 2B). Host cells perceive microbial invasion and subsequently release different pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). These molecules later recruit several immune cells and polarized macrophages through the cytokine secretion within the periodontal tissues (Fig. 2C). However, under dysregulated conditions, these immune pathways may become severely impaired, compromising the host defense response. Taken together, the design of smart drug delivery systems for dental diseases should discreetly consider the unique characteristics of oral and dental tissues as well as the specific pathological conditions in these areas.

## 3. Smart drug delivery platforms in dentistry

### 3.1. Externally controlled drug delivery strategies

External stimuli-responsive delivery platforms are specialized therapeutic systems that can be triggered by external stimuli, such as light, electricity, and magnetic fields [44]. One of the significant advantages of these biomaterials is the precise control over the magnitude or degree of the response, which can be finely tuned by adjusting the intensity of the stimulus [45]. Moreover, due to their spatiotemporal tunability and rapid response capability, external stimuli responsive-based biomaterials hold great promise for drug delivery in dental tissues [45]. Despite the outstanding therapeutic effects achieved through the external stimuli-responsive drug delivery platforms, several limitations must be addressed. For instance, continuous exposure to external stimuli is required to be carefully optimized to ensure therapeutic efficacy while minimizing adverse effects associated with prolonged exposure [46]. In the following sections, we will delve into these specific concerns categorized by the type of stimulus.

#### 3.1.1. Light-responsive strategies

Light- or photo-sensitive biomaterial-based platforms are widely used stimuli-responsive strategies for delivering bioactive molecules to specific locations [47–49]. Generally, most light-responsive strategies can be classified into three subclasses depending on the nature of the source photon/wavelength: ultraviolet (UV), visible light, and near-infrared (NIR) stimulation [48,50,51]. Additionally, the molecular mechanisms of light-responsive strategies can be categorized into three broad classes: photochemical, photo-isomerization, and photothermal, based on the mechanisms of the photo-sensitive moieties (Fig. 3A) [52]. Activation of these photo-sensitive moieties produces ROS that can eliminate invading microorganisms and kill tumor cells through oxidative stress. Compared to other exogenous stimuli, controllable light-responsive strategies offer the advantages of precise local targeting, on-demand release, and less chemotoxicity.

Based on these advantages, photodynamic therapy (PDT) has recently been explored as a light-triggered therapeutic system. PDT offers several benefits over conventional antibiotics, such as inhibiting

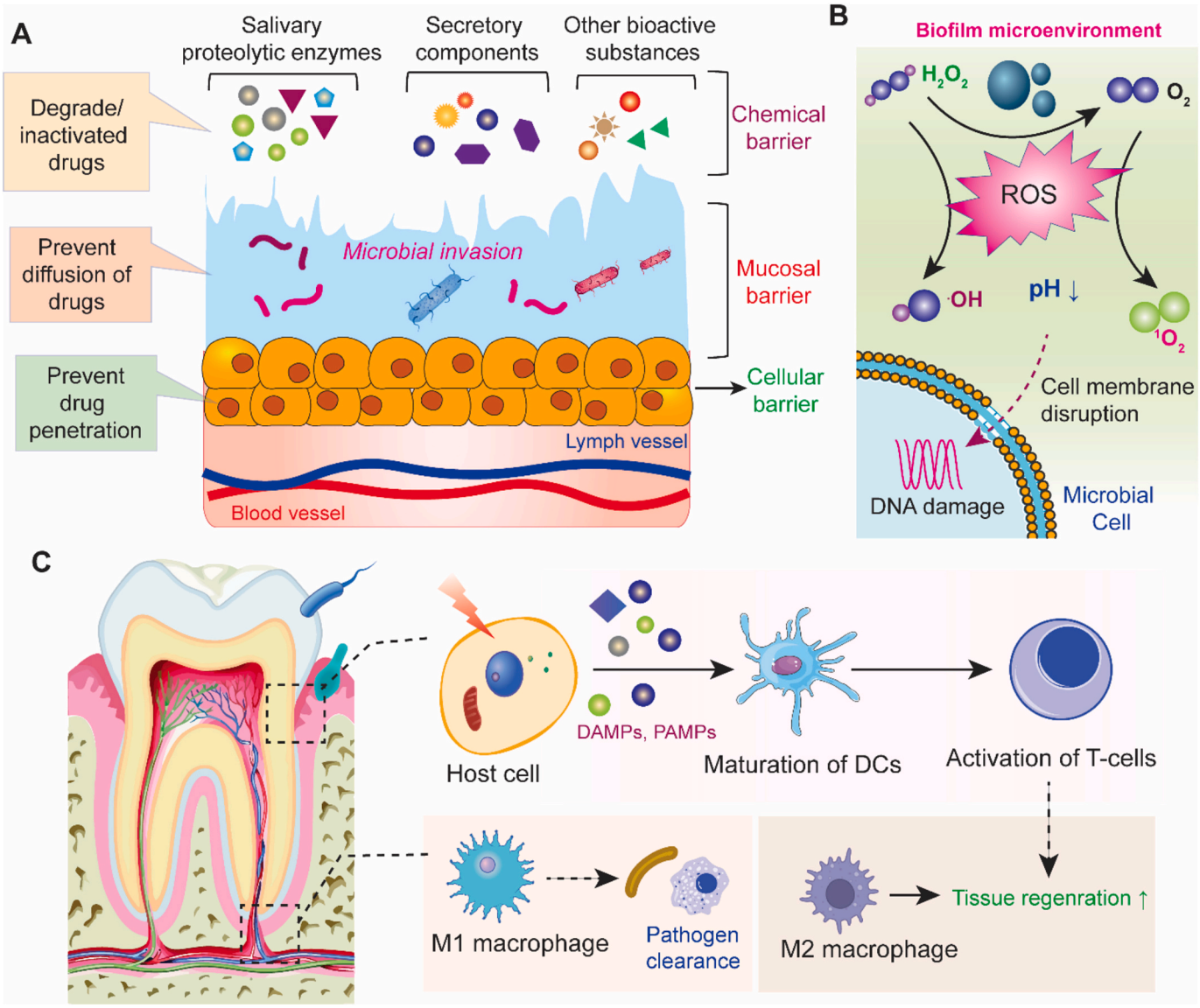


**Fig. 2.** (A) Schematics of different levels of the barriers for the delivery of therapeutic molecules in the dental tissue. (B) Strategy and mode of action of reactive oxygen species (ROS) mediated microbial elimination and killing by the various smart nanoparticles. (C) Schematic illustration of host cell response and macrophage repolarization following the microbial infection of periodontal tissues. The bioactive substances of the delivery systems directly affect the release of various stimulatory elements such as PAMPs and DAMPs, and modulate the release of inflammatory cytokines, resulting in inflammation modulation and host immunity.

bacterial biofilm growth without inducing bacterial resistance, owing to its deep biofilm penetration and potent persister cell killing ability [53,54]. For instance, Rose Bengal-based photodynamic adaptive NPs were developed by conjugating charge-converting polymyxin B (PMB) and gluconic acid (GA) in a layer-by-layer fashion to exhibit the pH-sensitive interaction with gram-negative bacterial cell-walls. Upon photo-activation, the charge conversion allows higher surface affinity and greater PDT-mediated ROS generation for better biofilm penetration and eradication [55]. Furthermore, photosensitive biomaterials have also been utilized for simultaneous tooth whitening with an antimicrobial effect. For instance, Li et al. [56] fabricated an injectable sodium alginate hydrogel doped with electron-hole pair-based photosensitive bismuth oxychloride ($Bi_{12}O_{17}Cl_2$) and cuprous oxide ($Cu_2O$) nanoparticles, which exhibit local tooth whitening and biofilm removal under green light activation (Fig. 3C). Zhang et al. [57] synthesized a Zwitterion-modified porphyrin (ZMP) based on the electron donor-acceptor approach (Fig. 3B, D). They demonstrated that ZMP stimulated by purple light can degrade chromogen to whiten the tooth surface while simultaneously disrupting the biofilm matrix [57].

Moreover, despite the significant contributions of various photosensitizers with the PDT effect to drug delivery and in situ antimicrobial killing, several challenges remain. Photosensitizers stimulated with lower wavelength light encounter challenges with lower tissue penetration, resulting in incomplete microbial elimination. Additionally, issues such as duration of exposure, photo intensity, and heat generation need to be addressed in future studies to avoid phototoxicity-mediated tissue damage [58]. Nevertheless, UV degradation, damage to biological molecules (e.g., DNA and proteins), and photo-dependent enzyme inhibition remain to be addressed in the future.

### 3.1.2. *Magnetic field-responsive strategies*

The magnetic field is extensively employed in stimuli-responsive drug delivery systems due to its ease of cell-membrane penetration, good biocompatibility, facile large-scale production, and immunomodulatory activity (Fig. 4A) [58,59]. Magnetic-responsive platforms have been tested in dental applications. For instance, Zaharia et al. demonstrated that reinforcement of multicore-shell with $Fe_3O_4$-$SiO_2$ magnetic nanoparticles can reduce the thickness of the adhesive layer by 30 %

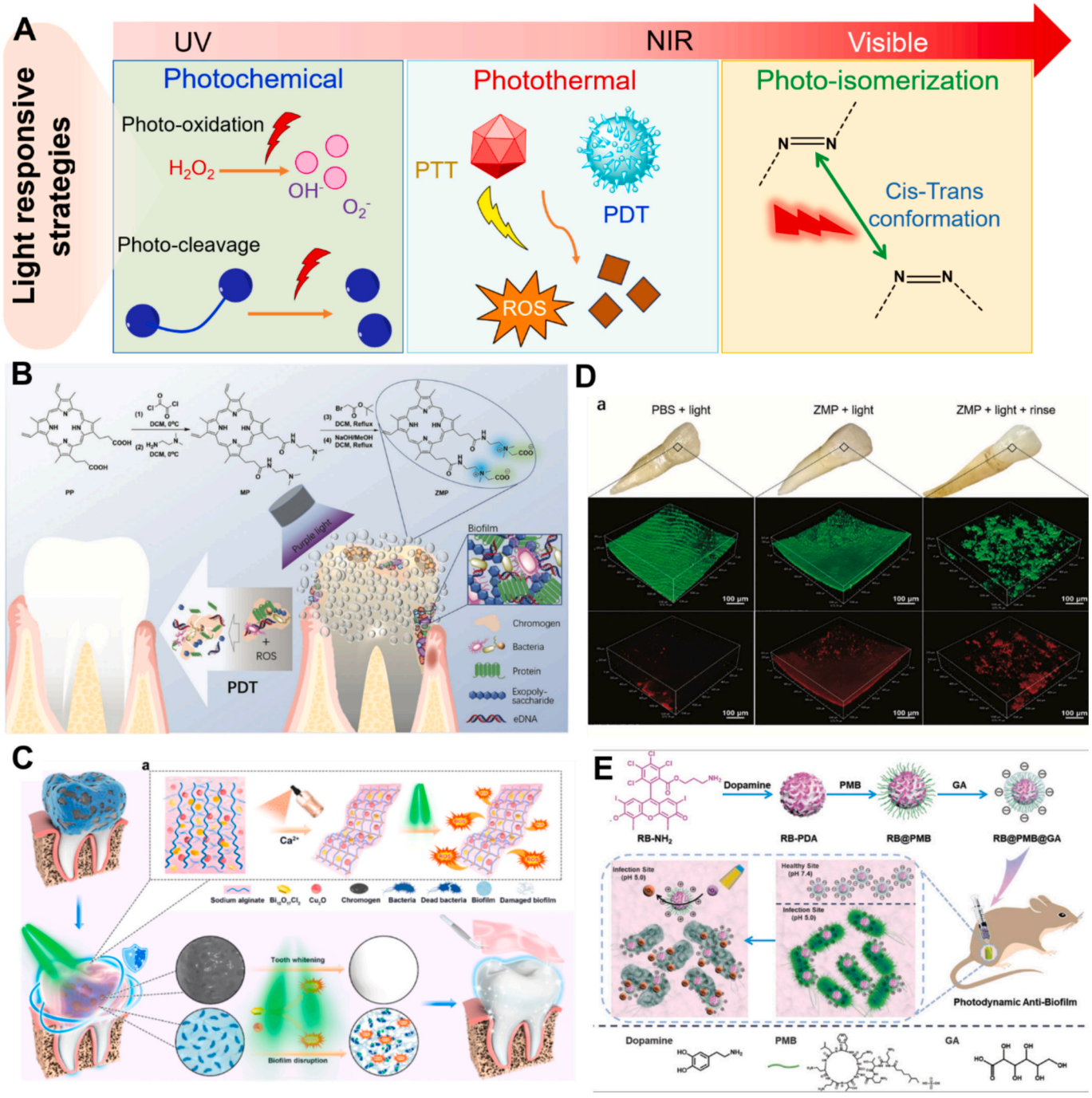


**Fig. 3.** Photo-sensitive drug delivery strategies. (A) Illustration of different light-responsive strategies and their mode of action to deliver the drug upon the stimulation of suitable photons. (B) Schematic illustration of ZMP-mediated photodynamic dental therapy (PDDT) for tooth whitening by oxidizing the chromogen. Adapted from [57]. (C) Illustration of the construction of BC-SA and the working principle. The solution of SA containing $Bi_{12}O_{17}Cl_2$ and $Cu_2O$ is cross-linked with $Ca^{2+}$. BC-SA produces ROS under GL for localized biofilm disruption and tooth whitening. Reprinted with permission from [56]. (D) Representative confocal images of biofilm killing ability of ZMP-mediated photodynamic dental therapy to eradicate the biofilm over ex vivo dental enamel. Adapted from [57]. (E) Illustration of the preparation process of photodynamic NPs for enhanced penetration and antibacterial efficiency in biofilms. Reprinted with permission from [57].

under an external magnetic field compared to conventional dental adhesives [60]. Similarly, Garcia et al. [61] showed improved adhesive bond strength in superparamagnetic iron oxide nanoparticles (SPIONs)-doped BisGMA dental resin on a tooth pulpal pressure model. They reported that under the guided magnetic field, the SPION-doped adhesive increased the bond strength through better hybridization from SPION motion against the pulpal pressure and reduced phase separation between resin monomers [61].

Magnetic stimulus-based antimicrobial platforms have also been investigated as an anti-infection strategy in various dental disease conditions. Ji et al. demonstrated that the antimicrobial and biofilm eradication ability of iron (II, III) oxide ($Fe_3O_4$) MNPs makes them a potential root canal disinfectant [62]. Besides, $Fe_3O_4$ MNPs modified with an endogenous oxidoreductase enzyme, namely glucose oxidase (GOx), exhibited enhanced antibacterial and antifungal efficacy against *C. albicans* and *E. faecalis*. Subsequently, the biofilm eradication efficiency of the GOx-modified $Fe_3O_4$ MNPs was also improved due to the bio-catalyzed activity of $GO_x$, which oxidizes β-D-glucose into $H_2O_2$. This

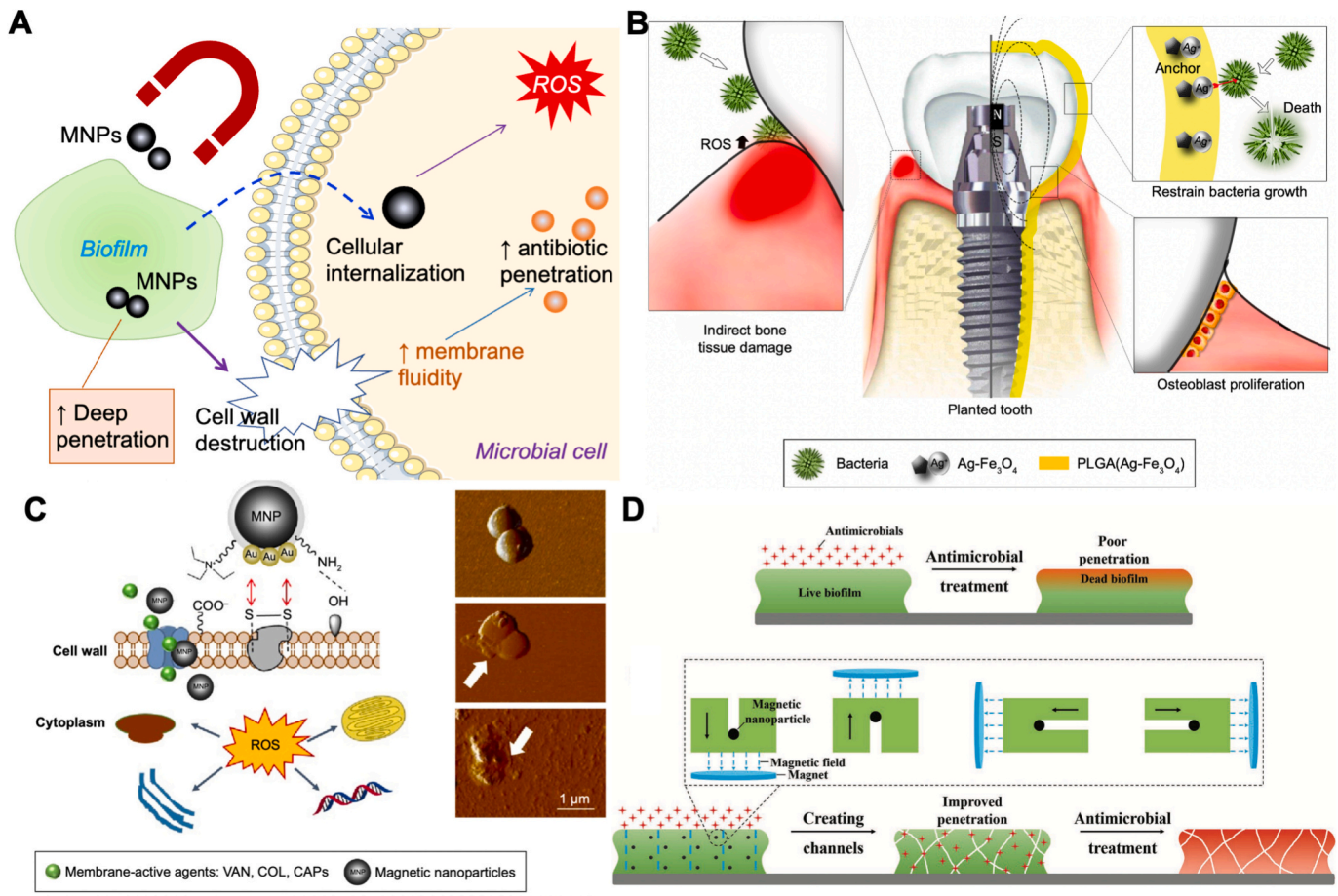


**Fig. 4.** Magnetic field-responsive strategies. (A) Schematic illustration of the multifaceted action of MNPs. MNPs interact with bacterial cell wall components and enhance membrane fluidity, followed by accelerating active agent penetration and/or uptake. Further, after internalization, MNPs exert oxidative stress, causing organelle damage to kill the pathogens. (B) PLGA(Ag-$Fe_3O_4$)-coated dental implants inhibit bacterial adherence and osteogenic inducement under a magnetic field. Reprinted with permission from [63]. (C) The combination of MNPs with conventional antimicrobial agents improves antimicrobial efficacy. Reprinted with permission from [67]. (D) Illustration of MNPs can be used to engineer artificial channels within biofilm to improve antimicrobial penetration and enhance bacterial eradication. Reprinted with permission from [66].

$H_2O_2$ is further catalyzed by bacterial peroxidases to disrupt the dense biofilm matrix, along with the toxic OH radicals generated by the MNPs [62]. The clinical efficiency of magnetic stimuli-based platforms has also been explored for dental implant-related complications. For instance, implant failure is predominantly caused by microbial accumulation at the peri-implant pockets. Yang et al. demonstrated that the combination of Silver (Ag)-modified $Fe_3O_4$ superparamagnetic nanoparticles coated with poly lactic-*co*-glycolic acid (PLGA) polymer exhibited superior antibacterial and cellular compatibility, significantly reducing *S. mutans* adhesion on the implant surface under external magnetic fields, compared to pure Ag and Ag-$Fe_3O_4$ combinations (Fig. 4B, C) [63].

The combination of traditional antibiotics or antimicrobial peptides (AMP) with MNPs could exhibit several advantages over pristine agents, such as enhanced bactericidal efficacy, reduced host cytotoxicity, and a lower risk of microbial resistance. MNPs interact with polar components of bacterial cell walls and enhance the permeation or cellular uptake of membrane-active antibiotics. After cellular internalization, MNPs exert oxidative stress, resulting in organelle damage. Niemirowicz et al. demonstrated that the immobilization of antimicrobial agents over core-shell MNPs composed of iron oxide and gold (Au) nanoparticles exhibits enhanced bactericidal activity against methicillin-resistant *Staphylococcus aureus* Xen 30 and *Pseudomonas aeruginosa* Xen 5 compared to using the drug alone. This effect was ascribed to increased internalizations of the drug caused by the magnetic field [64]. Similarly, Peng et al. reported a single-step synthesis procedure for superparamagnetic Ni colloidal nanocrystal clusters, which can bind to the gram-positive (*Bacillus subtilis*) and gram-negative (*Escherichia coli*) bacteria, as well as bacterial spores [65]. To address the challenges of bacterial biofilm for limiting the efficacy of antimicrobial drugs, Quan et al. recently reported that magnetic-iron-oxide nanoparticles (MIONPs) can create artificial channels within biofilms to enhance antimicrobial agent penetration and bacterial eradication (Fig. 4C) [66]. These micro-channels created by MIONPs significantly enhanced the efficacy of traditional antibiotics, like gentamycin, by 4- to 6-fold in an *S. aureus* biofilm model [66]. Moreover, conventional antibiotics combined with MNPs have been shown to increase the bacterial cell membrane fluidity, facilitating drug penetration, membrane permeabilization, and depolarization, which ultimately results in enhanced antimicrobial efficacy of the pristine drug molecules [67].

Additionally, magnetic stimulation has been utilized to generate magnetic traction forces that propel MNPs through dentin tubules. This technique facilitates the local delivery of therapeutic agents to reduce the inflammation in the injured pulp tissue and enhances the penetration of dental adhesives into the dentin (Fig. 4D) [67]. However, the clinical translation of MNPs-based therapeutics are hindered by several challenges, including the cytotoxicity of the metallic counterparts, the high magnetic field intensities required, and concerns for patients with implanted medical devices such as pacemakers or metallic implants. Additionally, precise control of magnetic fields, non-specific binding, limited tissue penetration, and complicated regulatory approval

processes are required to ensure the therapeutic efficacy of the magnetic field-based therapeutic delivery systems, which can be technically challenging and expensive [64,67].

### 3.1.3. Ultrasound-responsive strategies

Sono-dynamic therapy (SDT) is a class of non-invasive stimuli-responsive strategies in which acoustic or ultrasound waves act as a triggering signal to activate or deliver therapeutics from the corresponding platforms [17,68,69]. Both high-intensity focused ultrasound and low-intensity pulsed ultrasound (intensity ranging from 30 to 100 mW/cm$^2$) have been explored for therapeutic and diagnostic applications [70]. Generally, low-frequency ultrasound has been observed to be more effective for drug delivery, as it can form an aqueous bypath in the perturbed bilayer of the cells through cavitation effects [71]. Ultrasound waves with energies ranging from 20 kHz to 16 MHz effectively deliver therapeutic molecules through the sonoporation process. Although the exact molecular mechanism of the sonophoresis is not fully elucidated, several studies have demonstrated that the efficiency of this method can be influenced by physical characteristics, such as solubility, dissociation and ionization constants, as well as electrical properties (including conductivity, impedance, hydrophilicity) of the targeted molecules [72,73]. Furthermore, the sonoporation process can be optimized by tuning the duration of exposure and treatment cycles.

While ultrasound is quite well-established for diagnostic and tissue healing strategies in dentistry, ultrasound-mediated drug delivery platforms for dental therapeutics remain limited. Recently, Li et al. investigated an efficient strategy to release drugs upon ultrasound stimulation at an intensity of 0.67 W/cm$^2$ and a frequency of 42 kHz. This method specifically eradicated multidrug-resistant *Mycobacterium tuberculosis* (MTB) through BM2 aptamer-conjugated levofloxacin-loaded PLGA-PEG (poly-lactide-*co*-glycolide polyethylene glycol) nanoparticles [74]. Meanwhile, ultrasound waves have been used to enhance the antimicrobial efficacy of traditional agents. Hartmann et al. reported an increased antimicrobial efficacy of peracetic acid and EDTA with passive ultrasonic irrigation in an *Enterococcus faecalis* biofilm model [75]. While this method offers several advantages, such as non-invasiveness and localized delivery, there remain several disadvantages and challenges, including limited penetration depth, localized heating that can lead to tissue damage or necrosis, and cavitation effects from high-intensity ultrasound that can mechanically disrupt cells and tissues. Additionally, precise control of ultrasound parameters (e.g., frequency, intensity, duration), which is critical to both efficacy and safety, can be technically challenging [76]. Despite these limitations, ultrasound-stimulated drug delivery remains a promising strategy, especially in the delivery of therapeutic agents to dental tissues [74,76]. Further research and technological advancements are necessary to optimize this approach, ensuring its safe and effective application.

### 3.1.4. Electric stimulation-responsive strategies

Over the past decades, the effect of direct electrical stimulation on various tissues has garnered significant interest [77]. Direct electrical stimulation offers several advantages over other external stimuli, including rapid action, precise spatiotemporal controllability, and deeper penetration into biofilm through the iontophoresis process. The iontophoretic drug delivery system is widely explored as a non-invasive and safe method of delivering cationic or uncharged drug molecules across the cellular barrier under the application of a precise external electrical field [78,79]. In dentistry, the iontophoresis process has been used to enhance the drug permeation into the dentin, enamel, and other dental tissues [80]. Previous studies reported that iontophoresis-mediated delivery was improved by 10 to 2000 times compared with conventional forms of delivery [79]. Typically, the iontophoresis strategy was developed on the principle of electrophoresis, electro-osmosis, and electro-permeabilisation process [79]. In the electrophoresis process, the positively charged drug molecules are repelled from the anode electrode and vice versa under direct electrical stimulation. It has also been demonstrated that the use of alternating current exhibits superior performance compared to constant current stimulation [81]. The electro-osmosis process involves the delivery of ionic or neutral drug molecules, along with the bulk solvent flow generated from the impact of the electrical field, across biological membranes. In the electro-permeabilization process, the intrinsic properties of the biological membrane (e.g., tight junction space, membrane fluidity, and pore size) are altered to facilitate drug penetration under the electrical stimulation.

In dentistry, the iontophoretic drug delivery strategy was predominantly used to deliver non-steroidal anti-inflammatory drugs, local anesthetics, anti-bacterial drugs, and various ions of interest like fluoride, calcium, or potassium. For instance, Peng et al. reported the electric-stimulated system for enhanced transportation of $F^-$, $Ca^{2+}$, $K^+$, and $Na^+$ ions into the nanopores inside the dental enamel (Fig. 5A). They demonstrated that using 5 V/mm DC, the ions can penetrate the entire depth of the enamel layer (~1 mm)) through the electrokinetic flows [82]. In another work of the same group verified that, under the electrokinetic flow, molecules with sizes above a critical threshold can also penetrate the wet normal enamel pores without prior acid etching. Using an innovative microfluidics platform, they have demonstrated that Thoulet's solution with a high refractive index can penetrate 5 to 6-fold more volume under the electrokinetic flows (Fig. 5B) [83]. Furthermore, by leveraging the nano-dimensional size and the positive charged silver nanocomposites, iontophoresis has also been explored for deeper penetration of $Ag^{2+}$ into the dentinal tubules, reaching depths 10 times deeper than without current stimulation [84].

Besides delivering the specific cationic ions, iontophoretic delivery strategies were also explored for releasing antimicrobial agents. Gergova et al. reported that iontophoresis-mediated iodine and chlorhexidine delivery exhibited better antimicrobial efficacy than conventional platforms [85]. Similarly, metronidazole, salicylate, and naproxen were found to be delivered more effectively under the influence of iontophoresis compared to diffusion-based strategies [86]. Iontophoresis strategy has also been explored to treat dental hypersensitivity and pain management. For instance, Seeni et al. [87] developed an electro-conductive microneedle patch to deliver local anesthetic lidocaine for painless dental anesthesia (Fig. 5D). They have demonstrated that under a low-voltage current stimulation, an iontophoresis-mediated conductive microneedle patch could direct and accelerate the delivery of drug molecules to targeted teeth [87].

Additionally, electrical stimuli have also been explored for the simultaneous sensing and on-demand drug release application. Shi et al. developed a wearable and battery-free dental patch for monitoring in situ oral microbial dysbiosis and delivering drugs on demand (Fig. 5C) [88]. The device is integrated with an electrochemical potentiometric sensor, which can precisely sense the topical acidic environment variation caused by microbial metabolism and indicate the potential caries lesions. Simultaneously, using an advanced wireless electrical stimulation strategy using near-field communication technology, fluoride ions can be delivered for antibacterial action. Moreover, this study reported an electrical stimulation-based theranostic approach for intraoral biosensing and on-demand drug release [88].

In summary, electrical stimulation-based delivery strategies have been widely explored in dentistry for numerous applications to address the onset of caries. However, the currently available iontophoresis approach still needs improvement regarding the application procedure for electrical stimulation, which requires further modification to better function in the complex oral environment and to address the transient unwanted effect on the host cells. For instance, long-term application of iontophoretic devices in the highly humid oral cavity remains challenging due to factors like skin irritation, potential tissue damage, and the need for frequent treatments [88]. Lastly, the limited understanding of electrical properties of dental tissue (such as conductivity, resistance and threshold for current intensity), non-uniform electric field distribution that can result in uneven drug delivery, and the need for

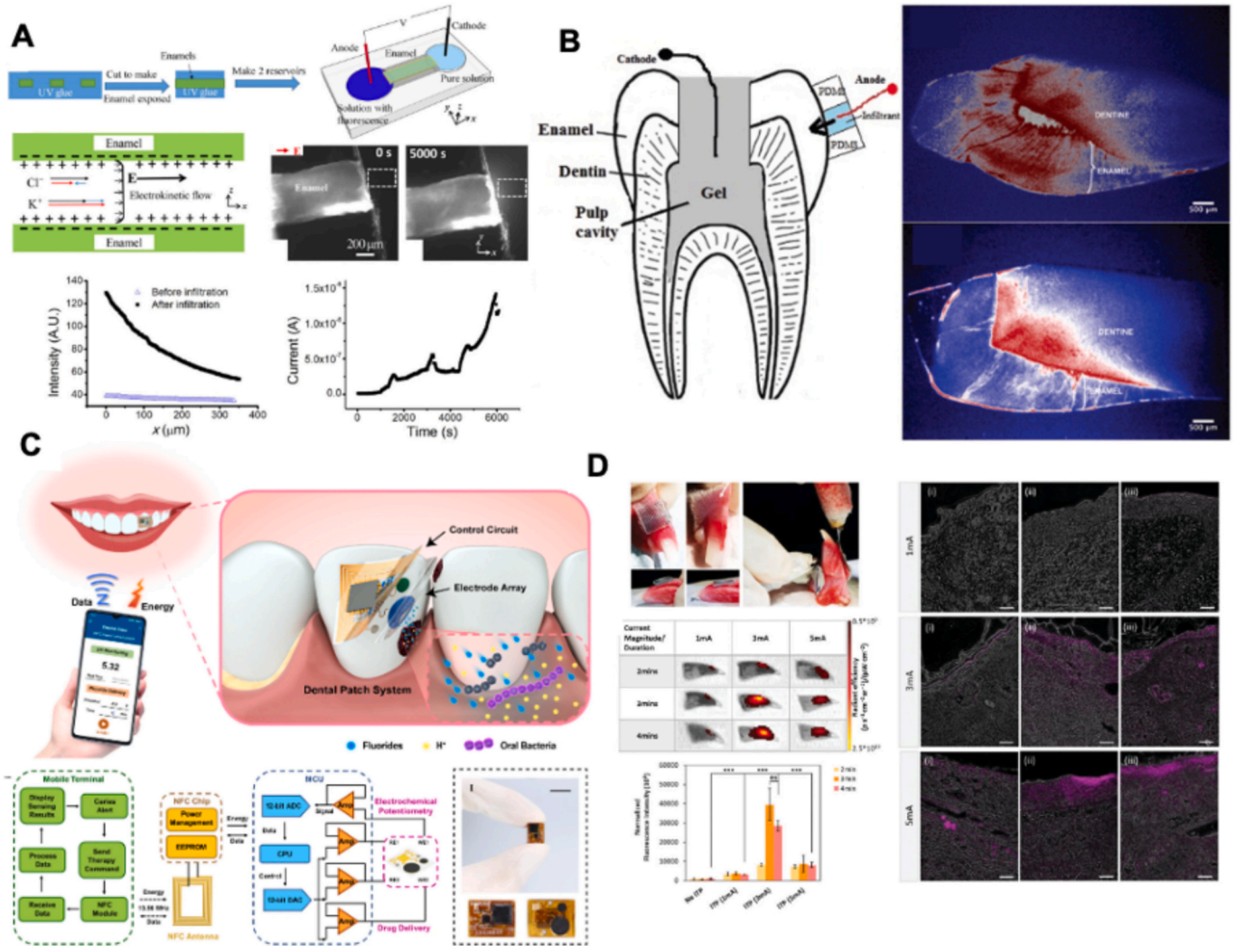


**Fig. 5.** External electrical stimulation-based delivery strategies. (A) Schematic of the microfluidic devices and iontophoretic delivery systems to deliver the $F^{-}$, $Ca^{2+}$, $K^{+}$, and $Na^{+}$ into the nanopores inside the dental enamel. Reprinted with permission from [82]. (B) Illustration of iontophoretic delivery procedure on dental crown and the fluorescence images showing the penetration of Thoulet's solution inside the enamel area under the influence of electro-kinetic flow. Reprinted with permission from [83]. (C) Illustration of wireless theranostic dental patch consisting of the control circuit and the electrode array for in situ oral microenvironment monitoring and on-demand drug delivery. Reprinted with permission from [88]. (D) Optical images showing the electroconductive microneedle-mediated delivery of local anesthetic lidocaine for pain management in the dental tissue. The fluorescence images indicated the deeper penetration of drug molecules inside the dental tissue under the influence of electrical stimulation. Reprinted with permission from [87].

specialized equipment and trained personnel also hinders the clinical translation of these devices [87,88].

### 3.2. *Internal microenvironment-responsive drug delivery strategies*

In addition to smart materials responding to external stimuli, there have been many smart materials responding to internal cues in the microenvironment, such as pH, pressure, temperature, hypoxia, enzymes, and specific genes [89]. Endogenous stimuli responsive materials possess many advantages, such as the ability to penetrate deep tissue, less dose dumping phenomenon, reduced adverse effects and toxicity than exogenous stimuli like ultrasounds or magnetisms [90,91]. Usually, tissue microenvironment undergoes a rapid physicochemical transition during the inflamed disease progression, which could be used to trigger the drug release from smart materials [92]. In this section, recent developments of internal microenvironment-responsive drug delivery platforms used in dental applications will be discussed.

#### 3.2.1. *ROS-responsive strategies*

Under certain infective and inflammatory conditions, such as oro-dental infection and dental pulp inflammation, ROS are produced depending on various circumstances as a metabolic byproduct [93]. Over the years, many ROS-responsive delivery materials have been developed to deliver antimicrobial agents. For example, Li et al. developed vancomycin-loaded surface-functionalized mesoporous silica nanoparticles (MSN) to eradicate *S. aureus* [94]. The amine-functionalized MSN is coated with a PEG-grafted via thioketal linkage, which gets cleaved in a high ROS environment and delivers the antimicrobial agent. In another work, a ROS-responsive hydrogel composed of sodium alginate with a ROS indicator RhB-Ac was developed for the delivery of mesenchymal stem cell-derived small extracellular vesicles to treat pulpitis [95]. Concomitantly, by leveraging the endogenous ROS, scavenging moieties incorporated with antibacterial agents are also employed for clearing intercellular pathogens [96].

Furthermore, tuning the ROS level has also been proven to modulate several immunological responses and exhibit antibacterial properties, which accelerates the tissue repair process [97]. For instance, Liu et al. reported a topical formulation of ferumoxytol nanoparticles, which disrupted intractable oral biofilms and prevented dental caries through its intrinsic peroxidase-like activity [98]. They demonstrated that

ferumoxytol nanoparticles can bind to the microscopic ultrastructure of the biofilms and generate ROS in the presence of a low concentration of $H_2O_2$, leading to in situ bacterial death via cell membrane disruption and EPS matrix degradation (Fig. 6A). On the similar line of investigation, when ferumoxytol is combined with stannous fluoride ($SnF_2$), markedly inhibiting both biofilm accumulation and enamel damage more effectively than either alone (Fig. 6B) [99]. In addition, Andrew et al. synthesized nitrogen-doped $TiO_2$ particles that can produce ROS under visible light exposure. They showed that the generated ROS significantly reduced bacterial counts and inhibited further biofilm formation without affecting the viability of host cells [100].

Besides the antimicrobial applications, ROS-responsive strategies have also been utilized to remove the smear layer produced during the use of dental instruments, such as reamers, files, and bars [101]. Taken together, ROS-responsive materials are promising in a variety of applications in dentistry. However, controlling the endogenous ROS level and minimizing the adverse effects of the ROS in the associated host cells need to be considered, as there is evidence showing that uncontrolled ROS generation, as a byproduct, causes uncontrolled cell activity, resulting in cell death and disease in the long run [102].

### 3.2.2. *pH-responsive strategy*

Among the internal microenvironment responsive drug delivery strategies, pH-based delivery strategies may be the most extensively studied because it is well-known that dental infections and tissue inflammation will contribute to an acidic environment [103,104]. The dental caries site generally has a pH under 4.5–5.5 because of the colonization of acid-producing bacteria. In contrast, the inflammatory site of the subgingival plaque has a pH of around 6.5 [105]. Nonetheless, it has also been reported that the peri-implant infection leads to a pH of around 5.5 on the implant surface. In inflamed dental tissues, a low pH microenvironment induces rapid exopolysaccharide (EPS) synthesis, where *S. mutans* and other cariogenic organisms thrive, which results in biofilm accumulation, acid-dissolution of tooth enamel, and, ultimately, the onset of carious lesions [106]. Thus, most pH-responsive smart delivery systems are designed to be triggered at pH levels lower than 7.4, which predominantly exists in the inflamed, infected conditions.

In most of the pH-responsive delivery platforms, the carrier polymers are modified with pH-sensitive linkers like tertiary amines or acid-labile bonds, which can be protonated/deprotonated or cleave specific chemical bonds and release the drugs during the change of pH [107]. Thus, based on the characteristics of the linkers, the pH-responsive hydrogels can further be classified into anionic hydrogels with pendant groups of carboxylic or sulfonic acid and cationic hydrogels with pendant groups of amines. However, the degree of swelling of these hydrogels depends on many factors such as concentrations, crosslinking

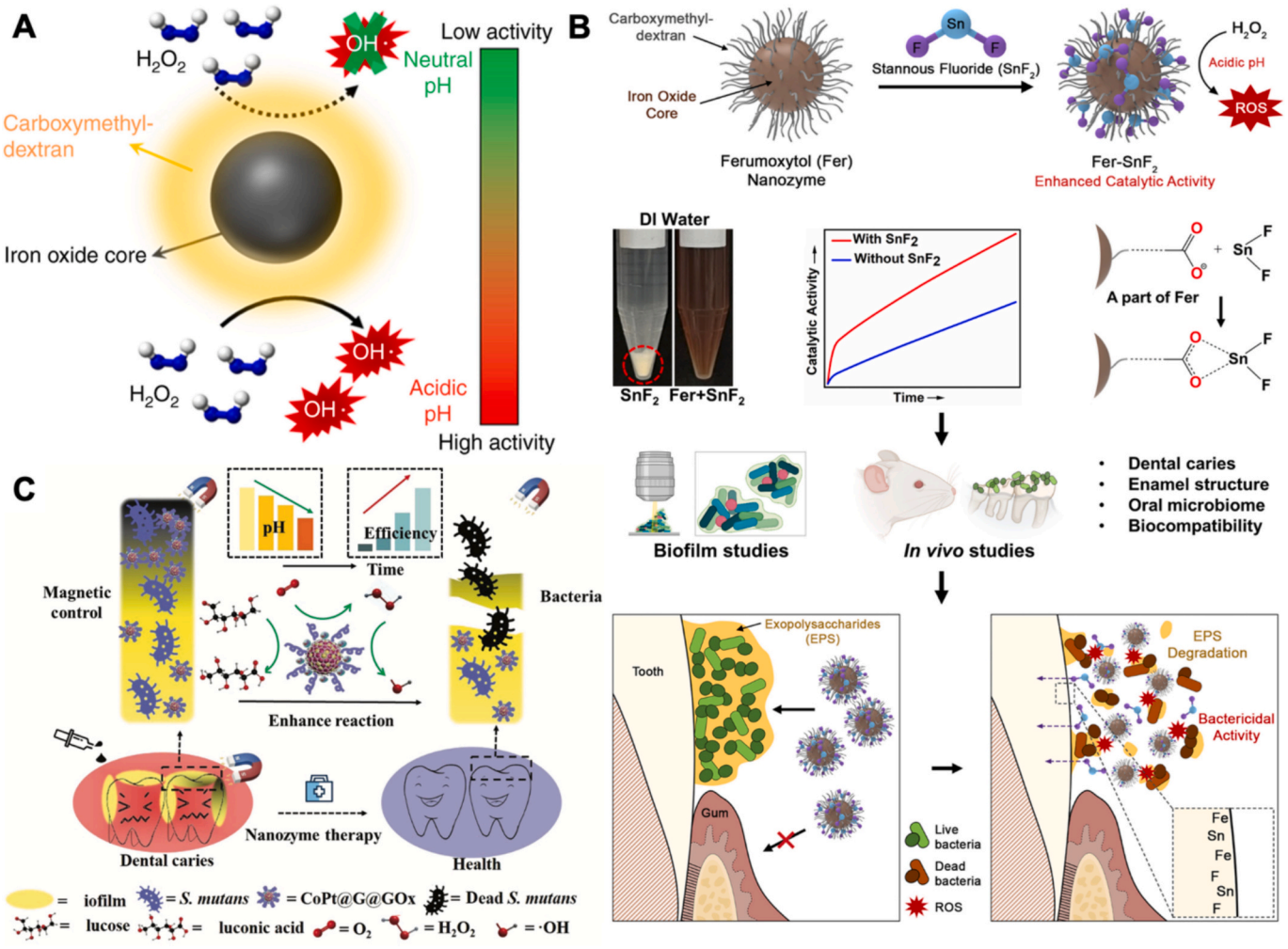


**Fig. 6.** (A) Schematic of pH-dependent catalytic activity of topical ferumoxytol nanoparticles disrupts biofilms and prevents tooth decay. (B) Chemical interactions and therapeutic activity of the combined treatment of Fer and $SnF_2$ to enhance stability in aqueous solution without any additives, while boosting catalytic activity. Reprinted with permission from [99]. (C) Design of an integrated enzyme, CoPt@graphene@glucose oxidase, which has cascade reaction activity with a two-step process. Hydrogen peroxide ($H_2O_2$) produced through glucose oxidation by GOx serves as the substrate for peroxidase-mimic CoPt@G to produce highly toxic hydroxyl radicals under an acidic environment for the treatment of *S. mutans* biofilms. Reprinted with permission from [116].

density, hydrophobicity or hydrophilicity, ionic charge, and degree of ionization [108,109].

Researchers have also developed various pH-responsive strategies based on the conformational changes of the active moieties to combat the pathogens responsible for dental caries. For example, Horev et al. [110] developed core-shell nanoparticles composed of cationic poly (dimethylaminoethyl methacrylate) (p(DMAEMA)) coronas with hydrophobic and pH-responsive cores. In the acidic environment of dental caries, the loaded Farnesol was released 2-fold faster than in the neutral environment due to the protonation of DMAEMA and propyl acrylic acid (PAA) residues within nanoparticle cores. As a result, this smart material contributed to significantly better biofilm removal compared to non-responsive nanoparticles or PBS-treated controls [110]. Similarly, Zhou et al. synthesized a Farnesol-loaded micelle using the same block polymer [111] and demonstrated that the drug release performance can be modulated by increasing the core molecular weight ratios. This micelle exhibits better physiological stability and enhanced drug release ability than those with lower core molecular weight ratios [111]. Additionally, a *'particle-in-particle'* approach has been reported, in which the carrier, composed of phosphonium-containing smaller therapeutic NPs, was wrapped in a pH-responsive layer of poly(styrene)-b-poly (*N*, *N*-dimethylaminoethyl methacrylate) [112]. These function-adaptive clustered NPs can eliminate the dense EPS of biofilm and significantly reduce the *S. mutans* viability in an ex vivo human teeth model.

In another study, Fullriede et al. developed a pH-sensitive controlled drug delivery platform modifying nanoporous silica nanoparticles with poly(4-vinylpyridine) using a bismaleimide as a linker [113]. They showed that at physiological pH, the polymer chains in these modified nanoparticles prevent the release of chlorhexidine, whereas in the acidic environment, the polymer chains become protonated and straighten up due to electrostatic repulsion, leading to drug release [113]. Similarly, Dong et al. fabricated a pH-dependent AgNPs-releasing titanium nanotube arrays (TNT) implant for peri-implant infection control by chemically grafting AgNPs on the TNT implant surface via a low pH-sensitive acetal linker [114]. At pH 5.5, the AgNPs released from the TNT-AL-AgNPs implant increased significantly due to the cleavage of the acetal linker and enhanced antimicrobial activities against gram-positive and gram-negative bacteria compared with AgNPs released at pH 7.4 [114].

Nevertheless, Chang et al. [115] fabricated an in situ pH-responsive injectable hydrogel consisting of carboxymethyl hexanoyl chitosan, glycerol, and thermosensitive β-glycerol phosphate for the delivery of Naringin, a polyethoxylated flavonoid for periodontitis application. They observed the release of Naringin in a pH-dependent manner due to the protonation of the amine groups in chitosan in the acidic environment resulting from periodontitis [115]. However, the intrinsic pH-based delivery systems exhibit several limitations, including difficulty maintaining long-term stability due to particle aggregation, low transfection efficacy, and significant batch-to-batch variation. Additionally, anatomical variations, such as those arising from diet or disease state, influence their performance. Furthermore, pH-responsive systems are often constrained by a narrow operational pH range, which may not encompass all relevant physiological or pathological conditions [111,115]. Therefore, future studies should tackle these limitations with the appropriate biomaterial development with highly selective chemical moieties.

### 3.2.3. Enzyme-responsive strategy

Previous studies demonstrated that in oro-dental disease, certain types of enzymes, including cell-secreted matrix metalloproteinases (MMPs), cholesterol esterase, and glutathione, are upregulated due to the inflammatory microenvironments [117,118]. Moreover, over the years, various enzymes, including those produced by bacteria (e.g., esterase, phosphatase, phospholipase, β-lactamases), as well as salivary secreted lipase, protease, esterase, alpha-amylase, anhydrase and lysozyme have also been utilized to trigger moieties due to their high selectivity and good catalytic activity. Upon the hydrolysis, backbone cleavage, degradation, disassembly, phosphorylation, and dephosphorylation of the carriers induced by the enzymatic activity, the loaded active molecules get delivered to the specific sites responsively [119,120].

Prior studies have shown that traditional antimicrobial agents such as chlorhexidine can inhibit the proteolytic and glycoside enzyme activity in dental plaque bacteria [121]. Finer et al. showed that the bacterial-secreted enzyme-catalyzed hydrolysis of the resin composite by cleaving at the ester bonds of the methacrylate-based resin monomeric unit in a dose-dependent manner [122]. As it was previously reported that MMP-8 level in the gingival crevicular fluid was upregulated under the inflammatory condition of chronic periodontitis [123,124], these enzymes have been used to trigger drug release from smart materials. For instance, Guo et al. [125] fabricated a biodegradable MMP-8 responsive hydrogel using polyethylene glycol diacrylate and a cysteine-terminated peptide crosslinker via a Michael-type addition reaction. They also implemented the same platform to deliver minocycline, bovine serum albumin, and antibacterial peptides for periodontitis treatment [125]. Typically, cross-kingdom dual-species biofilm-like *C. albicans* and *Streptococcus mutans* are predominantly observed in dental caries, which is mediated through glucosyltransferases (GtfB) binding to mannans on the cell wall of *C. albicans* [126]. To circumvent this problem, Kim et al. demonstrate an enzymatic approach to disrupt the interaction between the mannans and GtfB using the three mannan-degrading enzymes, which are endoenzyme 1,4-β-mannanase and the two exoenzymes α- and β-mannosidase [126]. They observed that after the enzymatic treatment, there is a ~ 15-fold reduction in the binding force of GtFB to *C. albicans*.

Additionally, enzyme-responsive delivery strategies have also been explored for anti-adhesion and on-demand anti-infection activity in treating dental implant-associated infections. During the early microbial colonization over the implant surface, most gram-positive or negative bacteria secrete certain enzymes, such as bacterial collagenase or hyaluronidase, which can act as a triggering moiety [127]. For example, Titania nanotubes loaded into a hydrophilic, adhesive polymeric system composed of dopamine-modified hyaluronic acid and 3,4-dihydroxyhydrocinnamic acid-modified chitosan were used to modify Ti-implant coating for delivery of vancomycin [128]. Hyaluronidase-triggered vancomycin release from the coating not only elicited superior antimicrobial properties but also improved osseointegration through the upregulation of integrin αv and β3 genes [128]. However, the clinical translation of enzyme-responsive delivery platforms faces significant challenges, including variability in enzyme concentrations among individuals and the risk of dose-dumping effects. Moreover, enzymatic activity is influenced by the stage of disease progression and the age of the host, which emphasizes the need for personalized medicines.

### 3.2.4. Thermo-responsive strategies under body temperature

Temperature differences have been used to trigger the release of therapeutic molecules from biomaterials [129]. The injectable hydrogel emerges as one of the most extensively investigated thermo-responsive delivery systems in dentistry, as it allows the delivery of drugs in relatively small or deep spaces such as root canals, periodontal pockets, and decayed cavities [130]. These systems have the advantage of being administered in a '*sol* state' at room temperature and transforming into a '*gel* state' at body temperature [130]. The underlying principle of thermo-responsiveness relies on the temperature-dependent swelling behavior of these hydrogels. When the temperature exceeds the upper critical solution temperature, the hydrogel swells and releases the entrapped drug molecules [131,132]. Common thermo-responsive polymers, including methylcellulose, hydroxypropyl methylcellulose and poly-(N-isopropyl acrylamide) (NIPAM), have been explored in the development of smart drug delivery systems [131].

For example, Wang et al. formulated a novel polyisocyanopeptide (PIC)-based thermo-responsive hydrogel platform capable of releasing

Lipoxin A4 for periodontal tissue infection for over two weeks [133]. They reported that their hydrogel exhibits controlled-release characteristics owing to its stiff helical polyisocyanate backbone stabilized by the hydrogen-bonded diallyl groups, which form a semiflexible network in water and prevent the rapid drug dissolution from the gingival crevicular fluid [133]. Similarly, Raknam and colleagues reported another injectable gel utilizing a non-ionic surfactant Poloxomer 407 (also known as Pluronic F-127), for delivering the cell-free supernatant of *L. rhamnosus* SD11 to prevent dental caries [134]. However, considering the toxicity of Poloxomer 407 reported in rats [135], there is a great need to develop other biocompatible and non-ionic surfactant-based biopolymers for thermo-sensitive therapeutic agent delivery. Indeed, most of the current thermo-responsive delivery systems have notable limitations in terms of their biodegradability and biocompatibility.

### 3.3. Multi-responsive nano-platforms

Researchers have developed many multi-responsive delivery systems to facilitate therapeutic efficacy for better and faster therapeutic responses [6]. In general, in these delivery systems, the payloads were delivered by controlling multiple stimuli, ensuring clinical efficiency [136]. Recently, several researchers have explored the combination of intrinsic stimuli, like enzymes with various extrinsic stimuli to more precisely control the precise therapeutic activity [137]. In this regard, Dong and colleagues reported a multi-component, multi-stimuli responsive CoPt@graphene@glucose oxidase integrated nanosystem, which can produce $H_2O_2$ through the two-step cascade reaction (Fig. 6C) [116]. In this platform, GOx converts glucose into gluconic acid and $H_2O_2$, which is further transformed into the hydroxyl free radical through the peroxidase mimic CoPt@graphene counterparts [116]. Nevertheless, the magnetic property of the Co—Pt nanocrystals assists the whole nano-system to penetrate further inside the dense biofilm matrix. Another study by Carmen et al. [138] showed the feasibility of magnetically driven photoactive microrobots for biofilm eradication on dental implants. They have prepared a multi-responsive microrobot combining ferromagnetic $Fe_3O_4$ nanoparticles and photoactive $BiVO_4$ materials through polyethyleneimine micelles, in which the $Fe_3O_4$ serves as a propulsion force using a transversal rotating magnetic field. Simultaneously, $BiVO_4$ serves as the photoactive generator of ROS to eradicate the biofilm colonies under blue light exposure. Additionally, they tested the efficiency of these microrobots on a complex multispecies biofilm composed of gram-positive *Streptococcus gordonii, Actinomyces naeslundii, Veillonella parvula*, and gram-negative *F. nucleatum*. It was found that the multi-responsive microrobots contributed to a ~93 % reduction in biofilm, which is significantly more effective than an uncoated titanium implant [138]. Although multi-responsive drug delivery systems aim to achieve highly precise and controlled drug release, they come with several significant disadvantages despite their potential. Designing suitable materials that respond effectively to multiple stimuli while maintaining stability, biocompatibility, and sufficient drug-loading capacity is highly complex. Ensuring synergistic responsiveness, where the system reacts effectively to both internal and external stimuli without interference or unintended interactions, presents another challenge. Furthermore, the fabrication process for these dual-responsive systems is often more complicated and costly compared to single-responsive systems. Practically, premature activation can occur if the system responds to unintended stimuli in non-target areas, leading to early drug release and reduced efficacy. Conversely, incomplete release remains a risk if the system fails to respond adequately to the intended stimuli, resulting in suboptimal therapeutic outcomes. Regulatory hurdles are also heightened because these complex systems require a more rigorous and time-consuming approval process. Finally, a lack of long-term clinical data on safety and efficacy hinders widespread adoption. To overcome these limitations, next-generation targeted therapeutic strategies capable of performing tasks autonomously without off-target effects or toxicity concerns are being actively explored [138,139].

#### 3.3.1. Micro/nanorobots

In the past, micro/nanorobots have been explored for a variety of applications, including sensing, diagnosing, and imaging. They have also been developed as multipurpose delivery systems for precise, on-demand, off-target-controlled delivery and theragnostic strategies, outperforming other stimuli-responsive platforms (Fig. 7A) [139,140]. These micro/nanorobots are designed to mimic biological entities, such as cells or bacteria, in terms of behavior. For example, microbivores are engineered to emulate white blood cells capable of phagocytosing and digesting pathogenic infections in the bloodstream [141].

Typically, nanorobots are powered by external forces such as magnetic fields, electrical, US stimulation, or even chemical decomposition [142]. In the field of dentistry, micro/nanorobots are primarily employed to deliver antimicrobial agents to specific locations and enhancing drug permeation into deeper tissues or biofilms [143]. For example, Villa et al. reported a self-propelled, tubular-shaped $TiO_2$/Pt microrobot for dental biofilm disruption [144]. Only a 5-min treatment of the microrobots elicits >95 % eradication of biofilm due to the synergistic effects of simultaneous generation of hydroxyl radical through the $H_2O_2$ oxidation and microbubble formation on the surface of the biofilm [144]. In another work, Hwang and co-workers [145] designed vane-like and helicoid-shaped catalytic antimicrobial robots (Fig. 7B) based on the dual catalytic-magnetic functionality of iron-oxide nanoparticles and showed the “kill-degrade-and-remove” strategy to eradicate *S. aureus* biofilms from the highly confined anatomical surface of the teeth [145]. In a subsequent study, they developed magnetic-field driven surface topography-adaptive robotic superstructures named Surface Topography-Adaptive Robotic Superstructures (STARS) (Fig. 7C), which can eradicate microbial biofilm and disease sampling. Guided by precise magnetic fields, STARS can alter their shape, length, and stiffness to perform specific tasks. As a proof-of-concept, they demonstrated that varying the length of STARS can clear *S. mutans* and *C. albicans* biofilms grown on enamel substrates while simultaneously collecting microbial specimens on their bristles [146]. In conclusion, these studies revolutionize the application of microrobots in dentistry by enabling real-time mechanochemical biofilm removal and multi-kingdom pathogen detection. Nevertheless, future research should focus on developing biohybrid micro/nanorobots capable of performing such tasks autonomously and without toxicity concerns.

## 4. Tissue-specific applications in dentistry

Given the significant therapeutic benefits of smart drug delivery systems, they have been investigated for addressing a range of disease conditions. Therefore, in the next part of this review, we will provide a comprehensive overview of various dental applications of smart drug delivery platforms, categorized by specific tissues or diseases.

### 4.1. Smart therapeutic platforms for oral mucositis

Oral mucositis is a common but severe complication that affects immunosuppressed patients, including those who have severe infections (Human immunodeficiency virus, Epstein-Barr virus, *Mycobacterium tuberculosis*), serious systemic diseases, immunosuppressant medication, and chemotherapy or radiotherapy [147]. Oral mucositis can induce a range of clinical symptoms, such as oral pain, dysphagia, altered taste, inadequate oral intake, and secondary infection, which can complicate dental treatment, prolong hospitalization, and reduce the quality of life [148]. The pathophysiology of mucositis involves direct DNA damage, oxidative stress responses, and activation of the innate immune response. Consequently, numerous studies have focused on mitigating oxidative stress, reducing inflammatory responses, and promoting lesion healing [149].

Several smart drug delivery strategies have been developed for

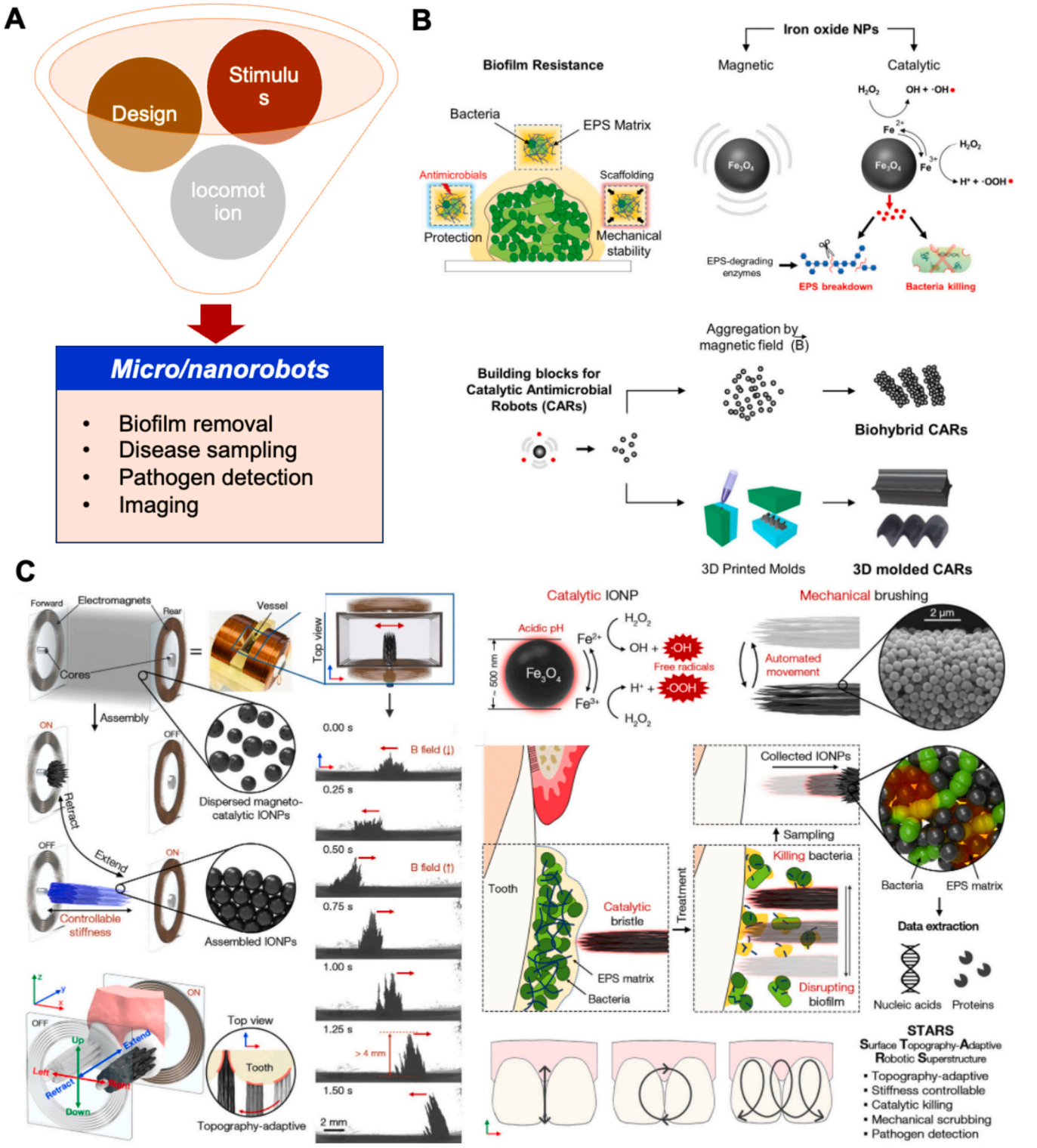


**Fig. 7. Micro/nanorobots explored for combating dental infections. (A)** Schematics of fundamental design criteria and applications of the micro/nano-robots in dentistry. **(B)** Magnetic iron oxide NPs as building blocks for small-scale robots designed for biofilm killing and removal. The magnetic-catalytic NPs and their bacterial killing and EPS degradation mechanisms via reactive free radicals generated from $H_2O_2$ via peroxidase-like activity. The EPS degrading activity was enhanced by the addition of mutanase/dextranase to digest extracellular glucans. Reprinted with permission from [145]. **(C)** Design, fabrication and working principle of Surface Topography-Adaptive Robotic Superstructures (STARS) for biofilm removal and pathogen detection on human teeth. The bristle motion of STARS is controlled to disrupt biofilms through mechanochemical action and retrieve biofilm contents (microbes, extracellular polysaccharides, biomolecules) for diagnostic sampling. Adapted from [146].

modulating local oxidative stress levels and improving the effectiveness of treatments for oral mucositis. Enzyme-responsive smart materials hold significant promise for addressing this condition due to the high levels of salivary enzymatic activity in the oral cavity. For example, Zhang et al. developed buccal tablets that can respond to salivary amylases through the incorporation of anti-inflammatory apremilast and starch controller in porous manganese-substituted Prussian blue nanocubes (PMPB NCs) [150]. These PMPB NCs effectively scavenge ROS and synergistically enhance the activity of apremilast to reduce inflammation. The starch controller is incorporated to react to SAs, enabling a continuous, sustained apremilast release at a pre-determined rate. The abundance of SAs and the α-amylase sensitivity of starch allow for the prolonged release of PMPB NCs and the cascade release of apremilast.

Similarly, water-responsive platforms have been investigated owing to the humid environment in the oral cavity. For example, core-shell PLGA NP was fabricated for inflammation management, and the mussel-inspired mucoadhesive film also presents a wet-adhesive manner. These platforms exhibit superior advantages for transporting drug molecules across the mucosal barrier with improved bioavailability (~3.5-fold greater than the direct oral delivery) and therapeutic efficacy in oral mucositis models (~6.0-fold improvement in wound closure within 5 days compared with no treatment) [151]. Apart from the mucoadhesive-based delivery, ROS scavenging strategies have also been investigated to modulate the therapeutic agent delivery and minimize the related toxicity. For instance, gold nanoparticles conjugated with polyvinylpyrrolidone were reported to exhibit increased therapeutic efficacy while reducing systemic toxicity [152].

Currently, only limited studies have investigated the use of smart drug delivery systems in oral mucositis treatment, most researchers have been focusing on modifying the physicochemical properties of biomaterials and employing nanomaterials to prolong the effectiveness of certain medications. Further studies are needed to improve the permeability of the epithelial layer and prevent mucositis. It is also important to note that future smart biomaterials are expected to address multiple challenges, including pain-relieving, anti-microbial properties, and anti-inflammatory effects sequentially to improve their clinical performance in treating mucosal lesions.

### 4.2. Smart therapeutic platforms for dental caries

Dental caries is an infectious condition that causes the deterioration of tooth structure and remains one of the most prevalent biofilm-dependent dental diseases [153]. It can lead to the loss of teeth, affecting functions such as chewing, aesthetics, and speech [154]. Since it is initiated by acidic by-products from cariogenic bacteria [155,156], pH-responsive and other stimulus-responsive functional biomaterials hold great potential in dental caries. These smart drug delivery platforms integrate antibacterial therapies, remineralization of decalcified tissue, and regulation of odontoblast cell activity [157], as summarized in Table 1.

Over the years, bioactive glasses (BGs) [158], modified resin [159], and mesoporous silica nanoparticles (MSN) [151] have been utilized as pH-responsive release platforms to facilitate the recalcification of teeth. Additionally, some ions with antibacterial effects, such as $F^-$ and $Ag^+$, are delivered to inhibit the acidogenic activity of cariogenic bacteria. Specifically, BGs exhibit the potential for pH-responsive dental tissue regeneration as they can stimulate mineralization and adjust pH levels [160]. Ion-releasing resins provide both ion-releasing and adhesive functions in dental practice, while pH-responsive resins have been developed to enhance their effectiveness [161]. Similarly, MSN was coated or chemically modified with various pH-sensitive linkers to serve as carriers for drug molecules [162].

For dental caries management, several attempts have been made to avoid mechanical removal of the damaged hard tissue. However, the clinical efficacy of non-mechanical approaches may be uncertain due to the caries environment. Most pH-responsive biomaterials only remain in

**Table 1**
Smart drug delivery platforms for dental caries.

| Mechanism | Stimuli | Application | Outcome | Ref. |
|---|---|---|---|---|
| $Ca^{2+}$-releasing | pH | ACP-based materials | Release supersaturated levels of $Ca^{2+}$ and $PO_4^{3-}$, with greater ion release at pH 4 | [173] |
| Ion-releasing | pH | Nano-scale ACP with calcium-based pastes to enhance their application effectiveness. | Higher surface area exhibited higher bioactive functions | [174] |
| Ion-releasing | pH | Nano-scale ACP incorporated as a filler in resin-based materials | Release of $Ca^{2+}$ at pH 4.0 | [175] |
| Ion-releasing | pH | NACP/ doxorubicin hydrochloride system | Release of $Ca^{2+}$ at pH 4–5 | [176] |
| Ion-releasing | pH | NaF-BGs with low sodium content can be added to dental resins for dental applications | Release of $F^-$ for dental tissues remineralization | [177] |
| Ion-releasing, anti-bacterial | pH | $Zn^{2+}$ releasing bioglass | Release higher levels of $Zn^{2+}$as the pH decreases and inhibit the growth of *S. mutans* in mildly acidic environments | [178] |
| pH-adjusting | pH | BGs release Na and K ions | Exchange with H ions in the solution, raising the pH value | [179] |
| pH-adjusting | pH | Moreover, Biomimetic resins such as Ariston pHc | Release a higher concentration of ions at low pH levels | [180,181] |
| Anti-bacterial | light | 3 % DMAEM to a DMAEM-modified resin adhesive | Effectively inhibit *S. mutans* in response to LED light | [182] |
| Anti-bacterial | Self-assembling | α-helical antimicrobial peptide (GH12) | Excellent antibacterial effects at pH 5.5 | [183] |
| Anti-bacterial | pH | antimicrobial agent Farnesal smart drug delivery system | Effectively eradicate cariogenic *S. mutans* in a rat model | [184] |
| Anti-bacterial | pH | CHX/nanoparticles | Penetrate dentinal tubules, releasing CHX within the dentin and exerting antibacterial effect | [185,186] [187–189] |
| De novo remineralization | pH | Adopt amelogenin-based peptide | Form the oriented buddle shape of crystal and promote the forming of hydroxyapatite | [190] |
| De novo remineralization | pH | Polyacrylic acid and dentin matrix dual loaded chitosan-based antibacterial drugs encapsulated hydrogel | Promote in situ regeneration of defective tooth | [191] |
| Functional remineralization | pH | PA-mediated assembly strategy | Induce fusion of the ACP particles on the enamel surface resulting in the formation of a crystalline-amorphous mineralization front with a continuous structure | [192–195] |
| Functional remineralization | pH | Self-assembly peptide P11–4 | Undergo self-assembly through intermolecular hydrogen bonding between peptide backbones, forming three-dimensional scaffolds within lesions | [196] |

the superficial region of the cavity, and this superficial remineralization can potentially promote the progression of untreated caries underneath. Therefore, in cases of hidden caries, more effort is needed to achieve de novo remineralization. This requires better delivery systems so the therapeutic agent can penetrate necrotic and contaminated areas to enhance mineralization in demineralized and translucent zones. For instance, pH-responsive peptides such as pHly-1 have been developed to penetrate deeper in liquid form and prevent further caries progression in hidden caries and early-stage caries [142]. A similar study by Zhang et al. showed that pHly-1 forms self-assembling nanoparticles and changes β-folded to helical conformation when the surrounding environment becomes acidic, which is common in cariogenic microenvironments [163]. Those pHly-1 in helical conformation can bind to the bacterial membrane, leading to the destruction of the bacterial cell membrane and subsequently the elimination of those cariogenic bacteria. Similar strategies have been developed as a more comprehensive approach to facilitate the fusion of amorphous precursors with crystals and establish a continuous growth boundary [164–166].

While de novo remineralization has made significant advancements, it is still challenging to functionally restore the damaged enamel, dentin, or cementum with hierarchical structures [167,168]. Long-term remineralization can be achieved through the regular cycles of the nucleation-mineralization process that guarantee crystal growth [167,168]. Amelogenin, collagenous fiber, and non-collagen protein serve as templates for crystal nucleation [65]. Thus, liquid forms of amorphous calcium phosphate (ACP) nano-precursor particles were developed as a filling for mineral-deficient areas, which is supported by non-collagenous protein scaffolds [169,170]. Calcium or silicon ions were adopted to form ion clusters that initiate the self-assembly of amphiphilic peptides for remineralization and promote the natural biomineralization process [171]. In another study, Li et al. engineered a dual-functional peptide that exhibited good affinity to collagen binding and absorbed free minerals [172]. These multi-functional stimuli-responsive peptides can penetrate subsurface lesions and later transform aggregates within the lesion, contributing to the formation of hydroxyapatite nanocrystals to restore dentin.

Taken together, the development of dental caries comprises a series of processes, including bacterial colonization, acid production, disruption of the balance between recalcification and decalcification, as well as cavity formation. Current strategies typically only focus on addressing one aspect of these processes, such as antibacterial, remineralization, or surface modification. However, those strategies are not sufficient to effectively address the issues present at different stages of caries development. Additionally, it is challenging to fully replicate the complicated and well-aligned apatite structure, even though recalcification can improve the hardness and strength of infected enamel [171]. Therefore, efforts should be made to develop multi-functional approaches to fulfil antibacterial, remineralization, and regeneration purposes.

### 4.3. Smart therapeutic platforms for endodontic diseases

Pulpal and periapical diseases are common reasons for dental visits worldwide, and the primary treatment options for endodontic diseases are vital pulp therapy (VPT), root canal treatment (RCT), or pulp regeneration [197]. However, distinct smart drug delivery systems are required to achieve specific therapeutic goals for different dental pulp diseases through VPT, RCT, or pulp regeneration. This section provides an overview of the various smart responsive materials used in different clinical scenarios, which are summarized in Table 2.

VPT, which includes techniques such as direct or indirect pulp capping, pulpectomy, and partial pulpotomy, is a less invasive treatment option for protecting and healing compromised pulp, since it does not require removing all the pulp tissue [198]. The use of bioactive materials during classic VPT can regenerate new hard tissue on vital dental pulp. Typically, these therapeutic agents possessed antibacterial, hemostatic, anti-inflammatory, and angiogenic properties, and were often combined with exogenous stimulus-responsive biomaterials [161] to controllably deliver drugs with corresponding functions [199]. For instance, mineral trioxide aggregate is a common capping material used for VPT owing to its antibacterial pH-responsive range that differs from that of caries remineralization. Moreover, inflammation is considered a critical part of the repair process, as it sets the stage for healing to occur [191]. However, excessive inflammation can also lead to compromised blood flow and even necrosis of the dental pulp in VPT [200–204]. Therefore, combating inflammatory exudates becomes particularly important to prevent these detrimental effects [200–204]. Thus, effective management of inflammation plays a key role in the treatment of endodontic diseases and the experience of the patients. Meanwhile, simultaneous use of bioactive agents, such as resolvin E1, epigallocatechin-3-gallate ester of resveratrol and simvastatin, acts as an adjunct for immunomodulation and enhanced remineralization [176].

Though VPT can be used to address mild infections, RCT needs to be considered in instances of severe root canal infection, where the prospect of salvaging the pulp is minimal. RCT is critical for eliminating infections and maintaining an aseptic environment in the affected area

**Table 2**
Smart drug delivery platform for endodontic diseases.

| Therapy | Stimuli | Application | Outcome | Ref. |
|---|---|---|---|---|
| VPT | Photo | Photo-responsive hydrogel | Polymerizes the MMP-9, inhibits destructive effects on dental tissues | [167] |
| VPT | pH/light | $SrCuSi_4O_{10}$ /GelMA Composite Hydrogel | Eliminates *S. mutans* and *Lactobacillus casei* and inhibit biofilm formation under photothermal heating | [168] |
| VPT | ROS | Resolvin E1, epigallocatechin-3-gallate ester of resveratrol, simvastatin | Adjuncts for immunomodulation and enhanced remineralization | [167] |
| VPT | ROS | Epigallocatechin gallate (EGCG) | Increases SOD activity and reduce ROS expression under hypoxia | [175] |
| VPT | ROS | L-arginine (L-Arg) | L-Arg can release NO. NO can penetrate tissues more deeply to effectively eliminate deep-seated bacterial infections | [176] |
| RCT | pH | Egyptian propolis (ProE) encapsulated in polymeric nanoparticles | Promotes sealing ability in bacterial infections in dental pulp. | [77] |
| RCT | light/ion | DMAHDM and NACP functioned as a smart drug delivery system | Antibiofilm activity against *E. faecalis* and high Ca and P ion release for remineralization and sealing properties | [180] |
| Dentin-Pulp Complex Regeneration | Temperature | Chitosan/pNIPAAm hydrogel | Creates favourable microenvironment for proliferation and differentiation of DPSCs | [181] |
| Dentin-Pulp Complex Regeneration | Self-assembling | Dentinogenic peptide (Sled) | Self-assembles into β-sheet-based biodegradable nanofibers and support DPSCs | [182] |
| Pulp Revascularization | pH | VEGF-loaded dimethylmaleic anhydride (DMA) hydrogels | Accelerate angiogenesis | [214] |
| Pulp Revascularization | Light | Poly-N-isopropylacrylamide-*co*-butyl acrylate (PN) and extracellular matrix proteins | Promote the differentiation of DPSCs into neuronal cells | [215] |

[3,4,197,205]. However, it can lead to reduced strength, increased risk of fracture, and discoloration due to the complete removal of pulp tissues. To enhance tissue strength and potentially improve treatment effectiveness, external stimulus-responsive biomaterials carrying drugs with corresponding functions are often combined with root canal treatments (Table 3). Meanwhile, ROS-responsive drug delivery platforms have been developed to address inflammatory exudates, especially in diseases such as pulpitis and apical periodontitis [199]. ROS-responsive drug delivery platforms are potential due to the significant oxidative stress burden in these scenarios [172]. For example, Li et al. utilized epigallocatechin gallate (EGCG) to increase superoxide dismutase (SOD) activity and reduce ROS under hypoxia [192]. Similarly, Wang et al. utilized L-arginine (L-Arg), which can release nitric oxide (NO) by reacting with ROS and generate a driving force for deeper tissue penetration, to eliminate deep-seated bacterial infections [193]. Additionally, magnetically driven nanobots have been shown to penetrate dentinal tubules in radicular dentin and release specific antibiotics to sterilize and treat root canal infections [62,66,143]. However, this non-vital treatment compromises the blood supply and neuro-nutritive effects on dentin, resulting in increased brittleness of the tooth structure [158]. For these reasons, it is necessary to look for other treatments, such as pulp regeneration [206].

Pulp regeneration aims at preserving the vitality and function of teeth. Due to the unique anatomical structure of the root canal system, the biomaterials need to have good flowability to reach the pulp region to facilitate tissue regeneration. Moreover, the root canal system is protected by mineralized tissue, making it difficult to control the biomaterials externally. Therefore, it is important for the next-generation smart-drug delivery platform to effectively eradicate the infection, exhibit long-term antibacterial effects to prevent recontamination, and resolve the inflammation to relieve the symptoms [206]. Nevertheless, the success of pulp regeneration hinges on two critical challenges: pulp revascularization and reinnervation [207], as demonstrated in Table 2. Newly regenerated blood vessels contribute to a favourable regenerative niche, which provides necessary nutrition and resistance to external infections. The delivery of bioactive factors, such as platelet-rich plasma, inflammatory cytokines (e.g., TGF-β), and growth factors (e.g., PDGF and VEGF), has been utilized in vascular regeneration [208]. Thus, thermoresponsive hydrogel was adopted to deliver angiogenetic horn peptide [209]. Similarly, a pH-responsive polymer was used for controlled release of Simvastatin, a drug that has been proven to promote inflammation regulation and revascularization [210,211]. Reinnervation is also critical in pulp regeneration due to the important sensory, nutritional, and defensive functions of the nerves in pulp tissue [212]. Some light-cured hydrogels encapsulating dental stem cells have achieved full-length dental pulp regeneration with nerve reinnervation [213]. Additionally, there are abundant drug delivery materials with stimuli-responsiveness due to their altered degradation profile in distinct environments [210]. However, it is under debate whether these materials can be regarded as smart drug delivery systems for endodontic therapeutics as these platforms focus more on modifying degradation rates or mechanical properties rather than precisely controlled or enhanced theraputic outcomes.

### 4.4. Smart therapeutic platforms for periodontal diseases

Periodontitis is one of the most common chronic, destructive, inflammatory dental infections that occurs due to bacterial colonization, primarily involving anaerobic gram-negative bacteria such as *P. gingivalis, Aggregatibacter actinomycetemcomitans, and Tannerella Forsythia* [216–219]. Although periodontal treatment is imperative in dealing with periodontitis, traditional platforms used in clinical practice exhibit several limitations. Firstly, both topical and systemic antibacterial therapies can be less effective with the emergence of bacterial resistance or insufficient drug penetration, which may lead to unwanted adverse effects. Secondly, the management of periodontitis requires a sequential approach involving infection control, inflammation resolution, and tissue regeneration. Thirdly, the majority of platforms cannot fulfil all these expectations throughout the process of periodontitis management, as simple localized adjustments may be insufficient to effectively modulate the immune response [220].

Despite those challenges, several smart drug delivery systems have been proposed [221], as summarized in Table 3. To increase the effectiveness of smart drug delivery, thermo-responsive, pH-responsive, and light-responsive systems have been tested [220]. For example, aspirin/erythropoietin dual-loaded thermo-responsive hydrogel provided prolonged drug release for sustained anti-inflammatory effect [222]. Besides, Poloxamer 407/poly (acrylic acid)-based thermo-responsive hydrogel was used for prolonged Metronidazole release at endogenous pH and temperature [223,224]. In addition, the release of tetracycline was precisely controlled through gold nanocages, a light-responsive platform [225].

The application of smart materials with multiple drugs for sequentially managing the host immune response and promoting tissue regeneration has also been explored. For instance, N, N′-carbonyl diimidazole and hyaluronic acid were included in a multifunctional nanoparticle to create a platform for controlled release of curcumin and 4-hydroxybenzeneboronic acid, which have antibacterial and antioxidative stress properties, respectively. The drug release achieved by these materials induced various cellular pathways to mitigate the infection, regulate inflammation, prevent bone loss, and stimulate bone regeneration [226].

Moreover, some research focused on immunoregulation to strengthen the roles of immune cells in defending against microbial infection and limiting tissue damage [216,217]. The microenvironment of periodontitis infections causes inflammation, hypoxia, and the production of toxic end products from immune cells. Thus, some researchers attempted to treat periodontitis by modulating the polarization of macrophages and the balance of T-cell phenotypes [227], thereby eliminating the dysregulated neutrophil-mediated killing to prevent

**Table 3**
Smart drug delivery platform for periodontitis management.

| Function(s) | Agent(s) | Stimuli | Carrier | Outcomes | Ref. |
|---|---|---|---|---|---|
| Bacterial suppression | Moxifloxacin | Temperature | Polymer nanoparticle containing hydrogel | Prolonged drug release, enhanced efficacy, and improved nanoparticle retention | [231] |
| Periodontal tissue regeneration | Dental pulp stem cell-derived exosomes | Temperature | Exosomes incorporated polymeric nanoparticles | Converts macrophages to anti-inflammatory phenotype in periodontitis microenvironment. | [228] |
| Inflammation inhibition | Erythropoietin (ERY) and aspirin | Temperature | Polymer nanoparticle containing hydrogel | Restores alveolar bone height, alleviates inflammation | [222] |
| Immuno-modulation | Minocycline | Glucose | Metal-organic framework | Improves macrophage pyroptosis; reduces pro-inflammatory factors secretion; mitigates inflame-aging | [232] |
| Periodontal tissue regeneration | Dexamethasone | UV light | Nanocomposite-injectable hydrogel | Strong antibacterial properties; supports cell proliferation and osteogenesis | [233] |
| Multi-sequence management | Curcumin | ROS | N, N′-carbonyldiimidazole, Hyaluronic acid, 4-hydroxybenzeneboronic acid | Antibacterial and immunomodulatory effects | [226] |

periodontal tissue destruction [228]. For example, doxycycline/metformin dual-loaded to oxidized dextran/phenylboronic acid-functionalized poly-(ethylene imine) hydrogel was used to treat the infection by immunomodulation. This strategy manages periodontitis by sequentially enhancing anti-infection and anti-inflammatory properties through the release of different immunomodulatory drugs [229,230].

In addition to addressing periodontitis through targeted pathogenic mechanisms, smart drug delivery can also act on the systemic risk factors of periodontitis. For instance, since diabetes can complicate the treatment of periodontitis, glucose-responsive hydrogels were developed using glucose oxidase (GOx) and chitosan as crosslinkers to treat diabetic periodontitis. GOx oxidizes glucose to produce hydrogen ions, which protonate the amino groups of chitosan, raising osmotic pressure and enabling drug release. Similarly, Zheng et al. developed a glucose-responsive platform for managing periodontitis by protecting mitochondria from ROS, thereby inhibiting the activation of the NLRP3 inflammatory pathway and promoting the synthesis of ECM, which is essential for subsequent tissue regeneration [226].

### 4.5. Smart therapeutic platforms for peri-implantitis

Bacterial colonization and biofilm formation on the implant surface account for most implant failures and peri-implant diseases [234,235]. To circumvent implant-associated infections, most strategies focused on the eradication of biofilms and the development of fouling-resistant surfaces [63], and the removal of microbial cells [236,237]. Unfortunately, conventional methods turned out to be not quite successful, as it is difficult for drugs to reach the implant-bone interface and eliminate infection on the rough surface of a dental implant [238,239]. In this context, Fabio et al. tested chitosan-coated Ti implants with PDT capability and found that they can significantly improve antibacterial efficacy against bacteria such as *S. aureus*, *E. coli*, and *P. aeruginosa* [240]. Meanwhile, some other studies have tried SDT, which may address some drawbacks of PDT, such as light-mediated tissue damage [68,70,241]. Under ultrasound stimulation, SDT allows for greater cellular absorption of drugs through acoustic microstreaming and hydrodynamic shearing, thereby increasing the drug efficacy [242,243]. For instance, SDT achieved by PLGA nanoparticles loaded with methylene blue led to significant killing effects against *P. gingivalis* [80]. Additionally, Fenton-type catalytic reactions in chemo-dynamic treatment (CDT) can generate highly toxic •OH radicals, indicating its potent antibacterial properties as a new therapeutic strategy [244]. Those approaches developed and tested over time for the management of peri-implantitis are summarized in Table 4. PTT under NIR irradiation, SDT under ultrasound irradiation, and CDT under Fenton catalyst irradiation have all been shown to be more reliable, better controllable, and less invasive than conventional methods for antibacterial agent delivery [245]. Nowadays, the rapid progress of nanotechnology has enabled the development of multifunctional smart coatings for drug delivery (Table 5). However, most of these coatings were only tested in vitro under laboratory conditions

**Table 5**
Different types of smart coating on dental implants for drug delivery.

| Coating | Material(s) | Activity | Ref. |
|---|---|---|---|
| Polycation | Hydrophobic polycationic coating composed of *N*, *N*-dodecylmethyl-PEI | Prevents implant colonization with biofilm; promotes bone healing | [251] |
| AMP | TBP-1-GGG-hBD3 coated Ti | Better antibacterial activity against different Staphylococcus species | [247] |
| | GL13K coated Ti | Activity against *Porphyromonas gingivalis* | [240] |
| Biosurfactants | Rhamnolipid biosurfactant R89 physically adsorbed on titanium discs | Inhibited biofilm biomass and cell metabolic activity for *S. aureus*, and *S. epidermidis* | [252] |
| Antibiotics | Polysiloxane coating functionalized with chlorhexidine digluconate | Inactivation of microbial species after a 15min contact | [253] |
| | Vancomycin loaded PLGA electrospun fibers on Ti implant | Prevents adherence of methicillin-resistant *S. aureus* to a titanium implant in an in vivo rodent model | [254] |
| | Organic-inorganic Gentamycin loaded sol-gel coating on HA-coated titanium | Activity against *S. epidermidis* and *S. aureus; better osseointegration and bone healing.* | [255] |
| Bacteriophages (Phages) | Combination therapy using linezolid and bacteriophage impregnated in hydroxypropyl methylcellulose | 4 log reduction in bacterial adhesion | [256] |
| | Bacteriophages encapsulated Alginate-nano HA hydrogels. | Inhibited attachment and colonization of multidrug-resistant *E. faecalis*; excellent osteogenic and mineralization properties | [257] |
| Chitosan | Chitosan-coated Ti implants under laser light for 60 s | Synergistic antimicrobial effect on titanium-adherent biofilms of *S. aureus*, *E. coli*, and *P. aeruginosa* via PDT | [240] |

**Table 4**
Smart drug delivery platform for peri-implantitis management.

| Function(s) | Agent(s) | Stimuli | Carrier | Outcomes | Ref. |
|---|---|---|---|---|---|
| Antimicrobial | Human β-defensin-3 | Electrical charge | Three chimeric peptides with high-affinity Ti-binding capability | Inhibit initial colonizer adhesion and biofilm formation on Ti- dental implant surfaces | [247] |
| Antimicrobial | Zinc-phthalocyanine | NIR | Nanoparticles conjugated with photosensitizers | Generate singlet-oxygen and prevent premature release of photosensitizer. | [240] |
| Antimicrobial | Antibacterial peptide | MMP-8 | PEG hydrogels | On-demand intraoral localized drug delivery | [125] |
| Antimicrobial, biosealing and bone regeneration | Fluoride ions | NIR | Si/P/F doped $TiO_2$ matrix | The combination of heat and fluoride ions triggered by NIR irradiation exhibits antibacterial effect | [248] |
| Antimicrobial | Chlorhexidine | pH | Chitosan-Coated Titanium Silica Composite | Significant reduction in biofilm formation | [249] |
| Antimicrobial | Gatifloxacin with tannins | NIR/pH | Nanoparticles | Effectively kill methicillin-resistant and Gemifloxacin-resistant *S. aureus* | [245] |
| Antimicrobial | Hematoporphyrin monomethyl ether | Sound | Zeolitic imidazolate framework-8 | Reduces bone loss in bacterial-induced peri-implantitis. | [246] |
| Osseointegration | n–n heterojunction calcium titanate and defective titanium dioxide | NIR | Titanium implant | Accelerating bone-to-implant integration | [250] |

[246]. The lack of clinical trials to validate the therapeutic effects of these coatings, particularly for peri-implantitis treatment, can hinder their clinical translation and the future advancement of these technologies.

### 4.6. Smart therapeutic platforms for oral cancer therapy

The quality of life and overall health conditions can be significantly impacted by malignant tumors that affect the oral and maxillofacial region, which include epithelial tissue-derived cancers such as oral carcinoma, mesenchymal tissue-derived sarcomas, and hematopoietic system-derived malignant lymphomas [258,259]. Chemotherapy is not only an adjuvant therapy for cancer but also the primary treatment for malignant tumors such as lymphomas and sarcomas. Unfortunately, conventional chemotherapy drugs (e.g., cisplatin, carboplatin, docetaxel, and indomethacin) have potent side effects on normal cells [260]. Meanwhile, monoclonal antibodies such as Cetuximab, pembrolizumab, tremelimumab, and nivolumab can also exhibit unwanted effects on other cells regulated by the same pathway [261]. For example, PD-1 inhibitors used in oral cancer can block the interaction between T lymphocytes and body cells by binding to PD-1, resulting in severe pneumonia [262]. The adverse effects caused by these therapies can increase patient suffering, compromise the treatment outcome, and even lead to treatment-related leukemia [263].

To overcome those issues mentioned above, PDT was introduced to cancer therapy due to its better selective effect on cancer cells (Table 6). PDT for oral cancer involves the administration of photosensitizers directly into the tumor tissue, followed by the application of targeted light wavelengths to induce ROS production [264]. Some photosensitizers, such as Verteprofin [265], can selectively attack abnormal blood vessels with laser irradiation, causing endothelial cell damage and vascular dysfunction [266]. The application of photosensitizers in PDT for the treatment of oral cancer has been comprehensively reviewed by Liang et al. [267]. Similarly, a mucoadhesive liquid crystal precursor platform for a long-lasting targeted tumor-killing effect was reported by Balian et al. [268]. Moreover, a thermosensitive and mucoadhesive polymer based on PEG and PDLLA-PEG-PDLLA (PLEL) was reported for the buccal delivery of gambogic acid in the treatment of oral squamous cell carcinoma [269]. The development of smart delivery systems has enabled improved targeted tumor killing and reduced side effects caused by systemic administration of drugs [270].

To address the compromised effectiveness of anti-tumor therapy due to the limited penetration of drugs into the tumor microenvironment and the complicated metabolic milieu of tumors, some multi-modal delivery systems similar to a “motor” have been developed to improve the efficacy of chemotherapy drugs. For instance, Li et al. developed a multi-responsive smart platform called NPF@DOX for the targeted delivery of doxorubicin (DOX) [271]. Another platform utilized fibroblast activation protein (FAP) targeting tumor-associated fibroblasts to increase its specificity to tumor tissue where GO was adopted to achieve photochemotherapy [272]. The synergistic chemo-photothermal treatment of NPF@DOX resulted in a stronger response and concomitant release of DOX from the NPF carriers in a pH-responsive manner, thereby enhancing anti-tumor effects. Through these synergistic effects, the targeted DOX release was achieved [273]. Moreover, a personalized 3D-printed plasmonic laser-responsive GO@cisplatin coated implant has been developed to prevent post-surgical relapse of oral cancer. The implant can be activated by laser to release the drug for 28 days and achieve local hyperthermia, leading to the destruction of cisplatin-resistant cancer cells [274]. In summary, smart drug delivery systems exhibit superior therapeutic effects on oral cancer. Moreover, through precise targeting, such as radio-sensitive nanoparticles, these systems can promote higher precision and reduce systemic adverse reactions associated with high drug doses, thereby improving treatment efficiency and patient comfort [275]. Furthermore, biomimetic nanocarriers for precision cancer therapy have also attracted great attention in recent years, as they can evade recognition by immune cells and prevent themselves from being eliminated as foreign substances by the immune system. A more comprehensive review of these kinds of systems can be found elsewhere [276–278].

## 5. Future horizons in the development of next-generation drug delivery platforms for dentistry

The maintenance of dental tissue homeostasis in the dynamic oral environment is challenging, particularly in the context of microbial infection and tissue injury. In Table 7, we have listed ongoing/completed clinical trials on combating oro-dental infections by using different classes of smart biomaterial platforms. Since the development of smart materials-based drug delivery platforms is crucial for addressing this issue. In addition to on-site and on-demand delivery of therapeutic agents to combat microbial infection, more efforts should be put into leveraging the internal defense mechanisms of our body through immunomodulation. Next-generation biomaterials could be engineered to activate immune cell infiltration or stimulate various defensive pathways simultaneously. For instance, some therapeutic strategies

**Table 6**
Advancement of different drug delivery platforms for oral cancer applications.

| Agent(s) | Carrier | Stimuli | Outcome | Mechanism | Ref. |
|---|---|---|---|---|---|
| Methylene blue (MB) | Mucoadhesive liquid crystal precursor | Light (PDT) | Increased the antitumoral activity of MB after 20 min of irradiation at 660 nm | ROS-related toxic effects on cancer cells | [268] |
| Gambogic acid (GA) | PDLLA-PEG-PDLLA (PLEL) micelle | Temperature | Facilitated sustained local delivery and reduce the toxicity GA release | GA-MIC-GEL down-regulated the expression of PD-1, therefore increasing cytotoxic T cell frequency | [269] |
| Paclitaxel | β-cyclodextrin (β-CD), PF127, PEO segments | Temperature | Improves the in vitro release and cytotoxic effect of paclitaxel | Undergo sol–gel transition and impart mucoadhesive property | [279] |
| Cetuximab, Cisplatin and 5 Fluorouracil | PEG-PLA-PEG-PEG | Water | Control-released in both systemic and local administration | Strong hydrogen bonding resulted in controlled release | [280] |
| Tocilizumab | Cationic chitosan/ hydrophobic PLGA | Water | Excellent muco-penetrating sustained release | Penetration through the mucosa was improved effectively by neutral particles | [281] |
| Doxorubicin (DOX) | Fibroblast activation protein (FAP); PEGylated nano-graphene oxide | pH/ Photothermal | Combined treatment with chemical and photothermal therapy improve antitumor outcomes against OSCC | NPF@DOX thermogenic effect promotes local release of DOX and apoptosis | [272,273] |
| Ultrasmall nitrogen-doped quantum dots | Carbon spheres | NIR | Heat-generating nanospheres showed a thermal ablation effect in oral cancer cells under 980 nm laser | Carbon spheres absorb longer wavelength radiation, transfer the absorbed optical energy into heat | [282] |
| Cisplatin | Laser-responsive graphene | NIR/ pH | Photothermolysis of cisplatin-resistant cancer cells under the combined influence of sustained cisplatin release | Laser-induced hyperthermia events from graphene in 3D-printed implant | [274] |

**Table 7**
A list of ongoing/completed clinical trials on combating oro-dental infections (Retrieved from www.clinicaltrials.gov and https://trialsearch.who.int/).

| Clinical Trial ID | Intervention | Application | Location | Phase |
|---|---|---|---|---|
| NCT05475444 | PLGA NPs encapsuated Ciprofloxacin | *E. feacalis* Infections in Endodontics | Mona Gamal Mohamed Afifi Arafa, British University, Egypt | Not applicable |
| NCT01950546 | Nanosilver Fluoride | For controlling the growth of *S. mutans* present in dental plaque of children | Priscila Lima de Luna Freire, University of Pernambuco | 1 |
| NCT05255913 | Nano-silver Fluoride and Silver Diamine Fluoride | For arresting early childhood caries (a Randomized Clinical Trial) | Maryam Quritum, Alexandria University | Not applicable |
| NCT05816512 | Biogenic gold nanoparticles from *pelargonium graveolens* leaves extract | Antibacterial efficacy of mouthwash against *Streptococcus mutans* and *Candida Albicans* | Ahmed Yousif Mahdi, University of Baghdad | Not applicable |
| CTRI/2023/07/055249 | Combination of Silver nanoparticles and proton pump inhibitors to traditional photodynamic therapy | Eradication of bacteria from root canals using nanoparticle-based photo-disinfection | Department of conservative dentistry and endodontics, St joseph dental college, Duggirala, Eluru 534,003 | Not applicable |
| ChiCTR2100045706 | Synergistic antibacterial efficiency of ZnO NPs and Polymorphonuclear Neutrophils | Elimination of endodontic microflora | Shanghai Sixth People's Hospital, 600 Yishan Road, Xuhui District, Shanghai | Not applicable |
| NCT00659204 | Compare the antimicrobial efficacy of silver nanoparticle gel to a commercialized alcohol-based hand gel | On bacterial counts isolated from the hands of 40 volunteers seeded with *Serratia marcescens* | Madigan Army Medical Center | Completed |
| NCT06016894 | Comparative Study between Hydroxyapetite Nanoparticles and Tricalcium Phosphate Nanoparticles Loaded on Platelet Rich Fibrin Membranes | Treatment of Gingival Recession | Enas Elgendy, October 6 University | Completed |
| NCT06070571 | Yarrow Moringa herbal combinations in buccal adhesive films | Treatment for gingivitis | Deraya University | Completed |
| NCT06089720 | ZnO NPs coated stainless steel orthodontic molar tube with | Antimicrobial effect | Ahmed Kamil Jawad, University of Baghdad | Not applicable |
| NCT00299598 | Alkylated PEI NPs with hybrid composite resin disks embedded in a palatal removable appliance | To evaluate antibacterial potency for contact mucositis | Hadassah Medical Organization | 2 |
| NCT06110494 | Commercially available iron oxide nanoparticle formulation Ferumoxytol/$H_2O_2$ treatments | Root canal biofilms disinfection | Bekir Karabucak, University of Pennsylvania | 4 |
| NCT04431440 | AgNPs | Bactericidal effect against Methicillin Resistant *Staph. aureus* (MRSA) and Vancomycin resistant *Staph aureus* (VRSA) isolated from critically ill patients | Rasha Hamed, Assiut University | Completed |
| NCT04930458 | Nanosilver Fluoride with Casein Phosphopeptides-amorphous Calcium Phosphate | Remineralization of dentine caries | Duaa Jawad, University of Baghdad | Completed |
| ChiCTR2000041192 | Silver nanoparticles: 0.5–2 μg/ml | Antimicrobial activity of the innate immune system by inhibiting neutrophil phagocytosis and ROS production | Shanghai Jiaotong University Affiliated Sixth People's Hospital, 600 Yishan Road, Xuhui District, Shanghai | Not applicable |
| CTRI/2022/02/040656 | Iron oxide magnetic nanoparticles | Pulpotomy medicament in primary teeth | King George medical college, Paediatric and preventive dentistry, Lucknow, India | 4 |
| IRCT20210305050580N1 | Coating thermoplastic retainers with $TiO_2$ nanoparticles | On the counting of *Strepococcus mutans*: a split mouth randomized clinical trial | Hamadan University of Medical Sciences, Shahid Fahmideh, Hamedan, Iran | Not applicable |

based on smart materials responding to exogenous or endogenous stimuli have been developed to control periodontal infections and mitigate tissue damage by eradicating causative microorganisms and alleviating inflammation [283,284]. Additionally, future antimicrobial therapy should also target multiple processes of infection, including biofilm formation, EPS production and quorum sensing. The development of smart, responsive material-based therapy will also contribute to the growing concern of antibiotic resistance. Another interesting application of these smart drug delivery systems would be the selective eradication of specific groups of microbial species without disrupting the host oral microbiota [285]. Furthermore, the development of smart material platforms that mimic native extracellular environments would greatly facilitate the functional regeneration of heterogeneous, structured dental tissues [286,287].

To date, most of the multifunctional strategies for dental diseases have been developed by combining multiple components, each with different functionalities. However, this approach leads to complex fabrication techniques that are not scalable and have limited clinical translation potential. Therefore, future strategies should focus on a single component with multifunctional characteristics [288]. For instance, there is great potential to develop an '*all-in-one*' solution that possesses potent antimicrobial, ROS scavenging, and pro-regenerative properties [289,290]. Additionally, theranostic-based stimuli-responsive materials hold significant promise for the dental field in the coming decades. The integration of precise therapeutic agents with diagnostic tools facilitates accurate disease diagnosis, early treatment, and improved prognosis [88,291].

Similarly, lab-on-chip-based microfluidics devices have been employed to mimic various physiological and pathological processes [292]. These devices also offer rapid screenings and real-life therapeutic outcomes for the biomaterials. Prior work has been reportedly developed to recapitulate various dental tissues such as dental pulp, gingival, and periodontal tissues [292,293]. They can be used to evaluate the therapeutic efficacy of different stimuli-responsive materials in specific disease conditions, such as periodontitis or pulpitis. Thus, the development of smart drug delivery material for various clinical scenarios can be significantly accelerated. Moreover, by using this in vitro method for screening of new smart materials, the need for in vivo experiments can be significantly reduced. Recently, artificial intelligence (AI) and machine learning (ML) have been employed for the development of new

metamaterials such as auxetics (i.e., materials with negative Poisson's ratio) as well as high-throughput screenings (HTS) for specific ligands or chemical motifs to target specific cells, intracellular protein/m-RNA delivery, or even cell-internalize pathogen killing [294–297]. Therefore, the application of AI-ML tools in the design of new smart materials has the potential to revolutionize dental materials. Taken together, the advancement of novel technologies has opened many potential avenues for the design, development, and application of next-generation smart materials for dentistry.

## 6. Conclusion

The development of stimuli-responsive materials for dental applications has sparked substantial interest in recent years. Given unique anatomical structures and the physiological characteristics of oro-dental tissues, as well as the highly dynamic microenvironment of the oral cavity, smart materials tailored based on the features of dental diseases are in demand. In this review, we introduced the special consideration for the design of smart materials for application in dentistry and critically summarized those external and internal stimulus-responsive materials developed for dental applications. We also discussed how those smart drug delivery platforms enhance therapeutic outcomes in different dental diseases and address the challenging dental conditions to provide a more clinically driven, forward-looking perspective regarding the design of smart drug delivery systems. Overall, we anticipate that this review will offer valuable insights into the design of next-generation stimuli-responsive materials tailored for diverse clinical scenarios, thereby inspiring the evolution of future dental treatment.

## CRediT authorship contribution statement

**Sumanta Ghosh:** Writing – original draft. **Chao Liang:** Writing – original draft. **Sang Jin Lee:** Writing – review & editing, Supervision, Funding acquisition. **Wei Qiao:** Writing – review & editing, Supervision, Funding acquisition.

## Declaration of competing interest

The authors declare no competing financial interest.

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## Data availability

No data was used for the research described in this article.

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