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Advanced materials and technologies for oral diseases

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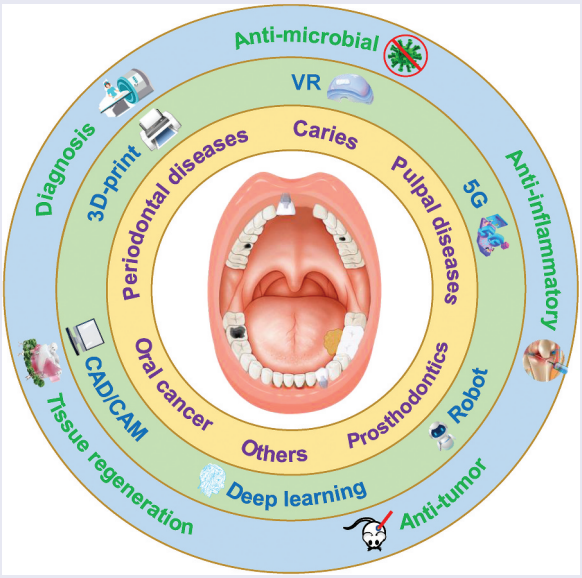
ABSTRACT

Oral disease, as a class of diseases with very high morbidity, brings great physical and mental damage to people worldwide. The increasing burden and strain on individuals and society make oral diseases an urgent global health problem. Since the treatment of almost all oral diseases relies on materials, the rapid development of advanced materials and technologies has also promoted innovations in the treatment methods and strategies of oral diseases. In this review, we systematically summarized the application strategies in advanced materials and technologies for oral diseases according to the etiology of the diseases and the comparison of new and old materials. Finally, the challenges and directions of future development for advanced materials and technologies in the treatment of oral diseases were refined. This review will guide the fundamental research and clinical translation of oral diseases for practitioners of oral medicine.



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1. Introduction

Oral disease is one of the preeminent reasons that endanger the physical and mental of the human body, with a tremendous burden and strain on individuals and society [1]. The available data suggest that the number of oral diseases in the population exceeds 3.5 billion, according to the latest definition of oral health organized by the World Health Organization (WHO) [2]. The treatment of most oral diseases relies on materials, such as filling materials for tooth defects, osteogenic materials for bone defects, implants for restoration of missing teeth, and so on. At present, the hazard of oral diseases and the importance of maintaining oral health are gradually being understood and valued by the public, especially in developing countries [3]. According to incomplete statistics, the global market sales of titanium dental implants alone had reached $6.3 billion in 2021. With the aging of the global population, oral diseases represented by periodontitis and tooth loss have further increased in incidence [4]. Therefore, there are huge space and social-economic benefits for the development of oral materials and technologies.

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Although oral materials have been developed for decades, there has been no significant improvement in the performance of clinically applied materials in the past 10 years [5]. Overall, traditional oral materials have a simple structure and function. For instance, the filling materials for tooth defects mainly consider properties regarding bonding and strength, with a lack of antibacterial and other functions. Since the introduction of nanomaterials in the 1970s, the exponential development of material science has promoted the iteration of the preclinical field for oral nanomaterials. Nanomaterials refer to materials with at least one dimension in the three-dimensional space at nanometer size or are composed of basic units [6]. Nanomaterials have been applied in various fields in daily life, such as nano-ceramics, nano-computers, nano-catalytic materials, nano-ceramic materials and so on. At present, the processing technology of nanomaterials is mainly based on physical and chemical methods. Different processing technology has certain influence on the size and mechanism of nanomaterials, and ultimately affect the function of nanomaterials. In the field of stomatology, these properties help scientists better develop the structure, composition, and function of oral materials, which make up for the shortcomings in the traditional treatment of oral diseases and change the concept of treatment for oral diseases [7]. In particular, scholars are more concerned with the interconnection between materials and biological organisms. For example, for the research and development of composite resins, people no longer deliberately pursue aesthetics and mechanical properties but pay more attention to the relationship between materials and oral microorganisms or soft and hard tissues in the oral cavity [8]. Besides, the nano drug delivery system can simulate the microenvironment of biological tissues, so as to accurately deliver various drugs into diseased tissues, thereby effectively improving the utilization of drugs [9].

In addition to the development of materials science, advanced technology, and manufacturing have also brought new opportunities for the therapeutics of oral diseases. With the emergence, development and maturity of 5th generation (5 G) mobile networks technology, it has also been widely used in medicine, including oral medicine [10]. 5 G is not only people-centered but also object-centered, realizing the connection between and within people and objects. At present, 5 G technology has been successfully applied in oral medicine. Such as, 5 G technology has dramatically improved the problem of slow and inefficient transmission and retrieval of imaging data, reduced the waiting time of oral patients, and improved the efficiency of doctors' treatment [11]; Wearable devices synergized with 5 G are used for the detection of ozostomia [12]; 5 G combined with virtual reality (VR) and surgical robots are used for remote diagnosis and treatment [13]. In addition to 5 G, artificial intelligence (AI) has been reported for the inspection of oral tumors according to oral photos [14]; 3D printing technology is used for the preparation of oral biomimetic materials [15]; Computer-aided design and computer-aided manufacturing (CAD/CAM) technology has realized the restoration of missing teeth for oral patients in a single visit [16]. Presently, the application of advanced technology and manufacture in oral diseases is just in its infancy, and further integration is needed to promote the reform of the therapeutics for oral diseases.

Herein, we review the recent progressions made in advanced materials and technologies for oral medicine, and summarize the application strategies of nanomaterials in oral diseases based on the etiology of the diseases and the comparison of new and old materials and technologies (Figure 1). At the end, we sum up the major challenges and essential issues that should be addressed, which are expected to promote the development of advanced materials and technologies for oral medicine.

2. Caries

Caries is a disease characterized by chronic progressive destruction of dental hard tissues caused mainly by bacteria. It is one of the most common oral diseases, which the WHO has listed as one of the three major human diseases to prevent and treat, alongside cancer and cardiovascular disease [29]. Although people have paid more attention to focus on oral health issues in recent years, along with the fact that dental filling materials have undergone certain development, the success rate of caries filling after 5 years is still only 50%, which is mainly due to the excessive focus on aesthetics and mechanical properties instead of biological properties in current filler material development [30]. In contrast, the new types of anti-caries materials are paid more attention to the relationship between the material and the oral microenvironment, especially the excellent antibacterial and remineralization potential of the dental hard tissue. This section focuses on the principles and strategies of several commonly used nanoparticles in anti-caries (Table 1).

2.1. Antibacteria

2.1.1. Ag+ and AgNPs

The antibacterial properties of silver ions (Ag+) come from the positive charge on the surface, which inhibits the synthesis of proteins and nucleic acids of microorganisms through electrostatic action, and finally causes the death of microorganisms [30]. The clinical use of Ag+ as a primary material in fluoride coating depends on its stable nature and broad-spectrum antibacterial ability. However, the clinical application of

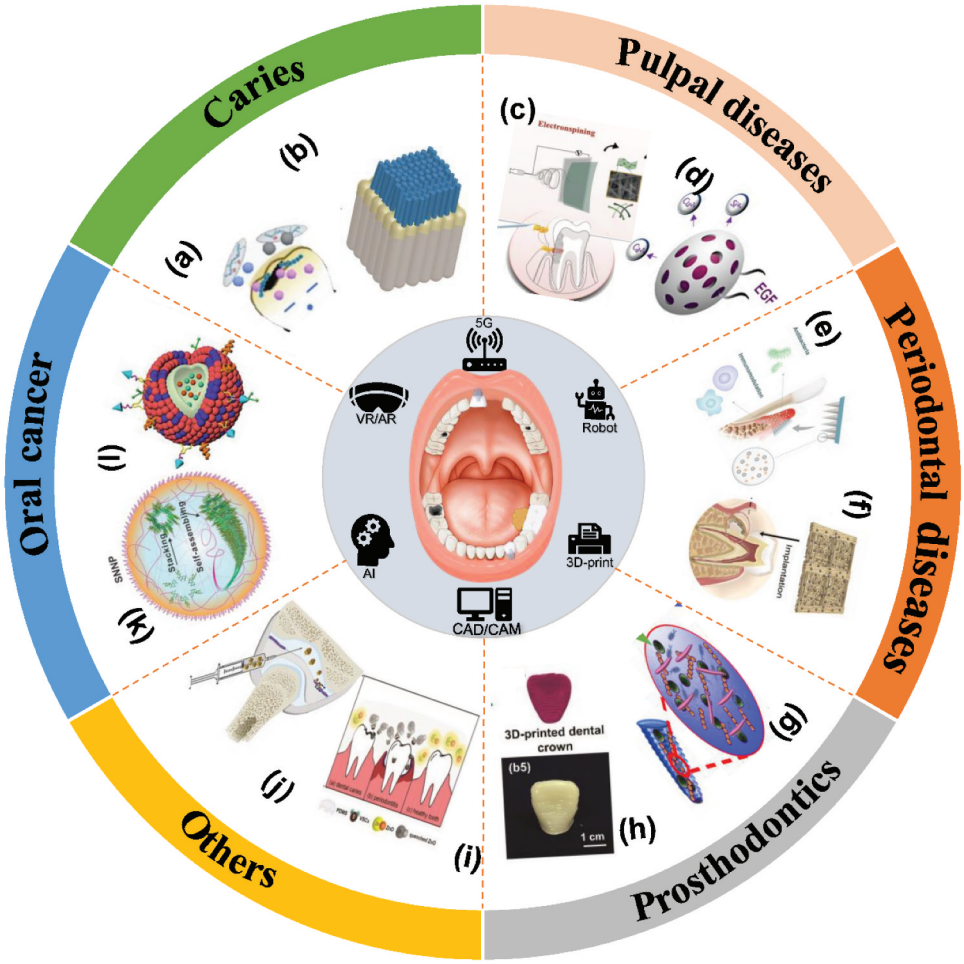

Figure 1. Advanced materials and technologies in oral diseases. (a) Nano anti-caries material. Reproduced by permission from [17], copyright 2020, Elsevier. (b) Dental enamel regeneration materials. Reproduced by permission from [18], copyright 2020, Wiley. (c) Anti-dentin-sensitive materials. Reproduced by permission from [19], copyright 2021, Dovepress. (d) Dental pulp regeneration materials. Reproduced by permission from [20], copyright 2020, Elsevier. (e) Periodontal drug delivery carriers. Reproduced by permission from [21], copyright 2022, Cell Press. (f) Scaffold materials for tissue engineering. Reproduced by permission from [22], copyright 2021, Wiley. (g) Nanorobot system for antibacterial implants. Reproduced by permission from [23], copyright 2022, American Chemical Society. (h) Nano Ceramic Crown. Reproduced by permission from [24], copyright 2021, Wiley. (i) Nanosensors for oral gas detection. Reproduced by permission from [25], copyright 2020, Wiley. (j) Temporomandibular joint cartilage regeneration material. Reproduced by permission from [26], copyright 2019, Wiley. (k) Chemotherapy drug delivery materials. Reproduced by permission from [27], copyright 2015, American Chemical Society. (l) Hybrid membrane bionanomaterials. Reproduced by permission from [28], copyright 2021, Springer Nature.

Ag+ will inevitably lead to pigmentation of the tooth surface due to oxidation and deposition of Ag+ on the enamel surface [31]. Moreover, a high concentration of Ag+ has certain toxic reactions which may lead to oral dysbiosis and systemic toxicity.

In contrast to translational Ag+ materials, silver nanoparticles (AgNPs) have a broader range of uses. On the one hand, AgNPs possess a larger surface area, which increases their ability to come into contact with bacteria. On the other hand, the smaller size of the particles penetrates more easily into the enamel or dentin, thus extending the antibacterial time [32]. This suggests that AgNPs can maintain excellent antibacterial properties at low concentrations. Surprisingly, it was also found in the study that no significant black plaque appeared on the tooth surface after applying AgNPs, which Santos attributed mainly to the fact that the AgNPs do not form oxides when in contact with oxygen in the oral environment [48,49].

As the research progresses, various strategies for applying AgNPs in caries treatment have been developed. For example, a stronger antibacterial function can be obtained without affecting the dentin bonding strength and biocompatibility by using dual antibacterial agents (MDPB+AgNPs) (Figure 2(a,b)) [33]. Reduced graphene can be used as a substrate to control the release of AgNPs, and this material can be used as an addition to glass ionomer cements (GIC) to effectively extend the antibacterial time without affecting the mechanical properties of the GIC [35]. Modifying AgNPs not only improves the antibacterial properties but also increases the material's mechanical properties through certain

Table 1. Application of nanomaterials in caries and pulp diseases.

Disease types	Application	Core materials/ nanomaterial	Key features	Ref
Caries	Antibacterial	AgNPs	Strong antibacterial power without causing hyperpigmentation.	[31,32]
		MDPB+AgNPs	Synergistic antibacterial ability without affecting bonding performance.	[33]
		AgBr/BHPVP	Controlling release of Ag+.	[34]
		R-GNs/Ag	Improving antibacterial activity of GIC.	[35]
		ZnNPs	Low toxicity and multi-mechanism antibacterial and significant effect on *Streptomyces mutants*.	[36,37]
		Ag+ZnNPs	Antibacterial multi-mechanisms	[38,39]
		ZnG	Graphene preventing bacterial adhesion.	[40]
		Cationic NPs	pH responsiveness for antibacterial drug delivery.	[41]
		Dex-NZM	pH responsiveness and antibacterial multi-mechanisms	[42]
	Remineralization	NHAP	Supplementary Ca^{2+}, PO_4^{3-}	[43,44]
		NHAP+Sr^{2+}	Improving biocompatibility.	[45]
		NTMP	Supplementary PO_4^{3-}	[46]
		$NCaF_2$	Reducing dentin permeability.	[47]
		NSF/NSDF	Antibacterial (actions) and remineralization.	[48,49]
		Synthetic peptides	Promoting regeneration of enamel.	[50]
		PTL/C-AMG	Promoting regeneration of enamel.	[18]
		Ca/PPILP	Promoting dentin bionic remineralization.	[51]
Dentine hypersensitivity	Sealing of dentin tubules	NHAP	Promoting dentin remineralization.	[52,53]
		ZnNPs	Accelerating the active remodeling of dentin and improving the maturation and mechanical properties of dentin.	[54]
		NBG	A Sol-gel system that can reduce electrical conductivity.	[55]
		Si/Ca/SrNPs	Acid resistance, antibacterial and low cytotoxicity as well as the ability to promote dentin bionic remineralization.	[19]
Pulp exposure	Capping Marrow	NHA	Promoting restorative dentin formation.	[56]
		NHA+FGF2	Further enhancing the formation of calcified tissue	[57]
		NHA/SB	SB increases the adhesion capacity of NHA.	[58]
		Zn-Si-CaNPs	ZnNPs can down-regulate the expression of M1-macrophages.	[59]
		nCur	Combined with aPDT produces a long-lasting anti-inflammatory effect.	[60]
Pulpitis or periradicular lesions	RCT	AgNPs	Antibacterial.	[61,62]
		Nano $Ca(OH)_2$	High penetration ability.	[63]
		MgONPsNano-ceramic	Stronger antibacterial effect against Enterococcus faecalis.	[64]
		Sealer	Good biocompatibility and low cytotoxicity.	[65]
		DMAHDM +AgNPs+NACP	Multifunctional root canal sealer.	[66]
	Pulp regeneration	PGA-α-MSH	Treatment of pulpal damage and promotion of fibroblast proliferation.	[67]
		SHEDs/SMS	Promotes regeneration of vascularized dental pulp-like tissue *in vivo*.	[68]
		EGF@Cu-BGn	Antibacterial, pro-angiogenic and odontogenic multiple therapeutic effects.	[20]

special treatments. For instance, the incorporation of 0.5 wt.% silanized nanofibers (SiO_2/Ag-0.5S) in the composite resin material resulted in adequate roughness and bending strength parameters in addition to the inhibition of *Streptococcus pyogenes* [69]. Although the effect of the concentration of AgNPs on the mechanical properties of the filling material still needs to be verified by many experiments, AgNPs are more suitable for the prevention and treatment of caries than Ag+.

2.1.2. Zn^{2+} and ZnNPs

In the late 20th century, zinc oxide (ZnO) was used as the primary filling material for dental caries because of its better biocompatibility and antibacterial properties. In the era of composite resins, the lack of mechanical strength and the fact that ZnO adhesives would disrupt the bonding reaction of the resin matrix led to their abandonment. However, it has been shown that adding Zn^{2+} to the total etching binder can inhibit the activity of matrix metalloproteinases (MMPs) and reduce the decomposition of dentin collagen bundles [70]. The advent of nanotechnology has brought back the popularity of ZnO in the form of ZnNPs, which have more powerful antibacterial properties than micron-sized Zn^{2+} and are consequently more suitable for developing dental filling materials and adhesives [71,72].

Resin material containing ZnNPs significantly affects *Streptomyces mutans* [36,37]. Similar to AgNPs, the antibacterial ability of ZnNPs also comes from Zn^{2+}. However, structural changes can also affect the antibacterial properties of the material. Elena Zanni et al. have designed zinc oxide nanorods-decorated graphene nanoplatelets and found that the primary antibacterial mechanism of ZnNPs stems from the associated mechanical damage to the cell surface of this dental pathogen rather than the production of reactive oxygen species (ROS) [40]. These results demonstrate the multiple antibacterial capabilities of ZnNPs. Based on this result, Wang et al. modified Ag+ into ZnO nanorods. They found that this material could cause severe physical damage to bacteria and achieve

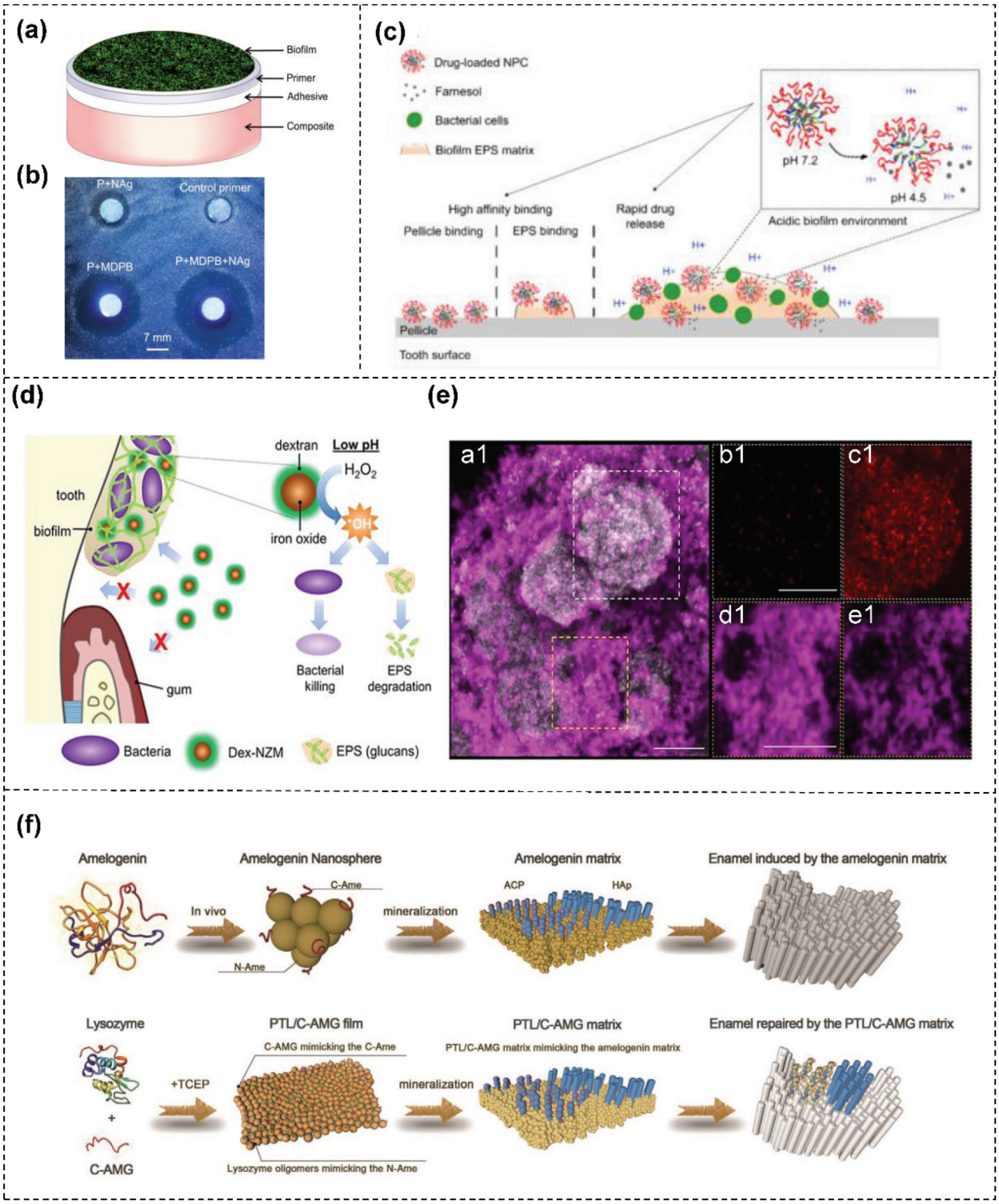

Figure 2. (a,b) Synergistic antibacterial mechanism of MDPB and AgNps. Reproduced by permission from [33], copyright 2013, Elsevier. (c) Proposed mode of action of pH-responsive nanoparticles. Reproduced by permission from [41], copyright 2015, American Chemical Society. (d) Patterns of pH-responsive dextran-coated iron oxide nanoparticles targeting bacterial biofilms. (e) Representative image of a Dex-NZM treated S. mutans biofilm (a1) before addition of H_2O_2; dashed white and yellow boxed indicate selected areas for localized antibiofilm effects of Dex-NZM. Close-up views of bacteria and exopolysaccharides before H_2O_2 exposure (panels b1 and c1, respectively) and 100 min after H_2O_2 exposure (panels d1 and e1). Reproduced by permission from [42], copyright 2019, American Chemical Society. (f) Schematic demonstration of amelogenin and the PTL/C-AMG matrix (mimicking the *N*-Ame and C-Ame) to mediate the transition from ACP to HAP on enamel for in situ remineralization. Reproduced by permission from [18], copyright 2018, Wiley.

multiple mechanisms of bactericidal effect through surface potential and oxidative stress reaction [38]. Recently, an antibacterial toothbrush has been prepared using AgNPs and ZnNPs to increase the effectiveness of removing plaque during brushing [39]. Nevertheless, due to the lack of long-term test results, it is not known whether the long-term application of this toothbrush will lead to the development of drug resistance in oral microorganisms. Therefore, avoiding oral flora dysbiosis in applying nanomaterials antibacterial strategies is a question worth considering.

2.1.3. pH-responsive antibacterial materials

In addition to the above two traditional anti-caries materials, some other metal ions have also been attempted in antibacterial strategies. The antibacterial mechanisms of these metal ions are predominantly the same, but due to their toxic nature, they are also difficult to add directly to the filling material. We will not go into too many details about these materials here.

Recently, considering that cariogenic biofilm is related to the acidification of extracellular polysaccharide matrix, the development of pH-responsive anti-caries materials can effectively increase the targeting of drugs. For example, A positively charged nanoparticles (consisting of hydroxyapatite (HAP), saliva-coated HA (sHA), and exopolysaccharides) were designed in 2015 (Figure 2(c)). This material targets bacterial biofilms through a positive surface charge. Then the structural stability of this nanomaterial will be destroyed in acidic environments, and the hydrophobic drug farnesol will be released to exert antibacterial effects [41].

Another pH-responsive material consists of dextran iron oxide nanozyme coating (DEX-NZM). Iron oxide nanozymes (NZM) can produce strong antibacterial effects by catalyzing hydrogen peroxide (H_2O_2) in acidic conditions, but their stability in solutions in physiological media is inferior, and they can cause some damage to healthy tissues. Studies have shown that coatings prepared by encapsulating iron oxide NZM with dextran can effectively solve these problems. This coating has a strong killing effect on bacterial biofilms. Histopathological analysis on gingival tissues revealed no visible signs of adverse effects, such as proliferative changes, inflammatory responses, or necrosis, of treatment with Dex-NZM, or H_2O_2 or the Dex-NZM/H_2O_2 (Figure 2(d,e)) [42].

These experimental results demonstrate the significance of understanding the interaction between materials and organisms for rational materials design. Nonetheless, the current research and development of antibacterial materials for caries focus on filling materials. As long as the design is reasonable, the clinical practice may witness the use of materials like coatings, adhesives, and even dental caries vaccines in the future.

2.2. Demineralization and remineralization

2.2.1. Ca^{2+}-based materials

Nowadays, various Ca^{2+}-based materials have been developed as remineralizing agents for clinical applications, such as HAP, amorphous calcium phosphate (ACP), calcium fluoride (CaF_2), calcium silicate ($CaSiO_4$) and so on. Among them, HAP, similar to the composition of the dentinal tissue, can promote remineralization of defective hard tissue by stimulating or inducing bone proliferation by releasing ions that are not harmful to the organism and participate in *in vivo* metabolism. However, the poor mechanical properties and porous structure of HAP are not suitable for direct processing into filling materials for caries filling [73].

Nano-hydroxyapatite (NHAP) improves the disadvantage of the poor mechanical properties of HAP itself to a certain extent [43]. In the early stage of caries, the hard tissues of teeth lose mineral ions due to the acid erosion produced by bacterial metabolism, but the collagen network is not affected. The porous NHAP can be used as both a direct replacement of the final mineral and a carrier of the lost ions in the caries attack, which can effectively promote the remineralization of the hard tissues of teeth and avoid the progress of caries [74]. Studies have been conducted to add NHAP to toothpaste to provide ions that reduce demineralization and improve remineralization, a strategy that can effectively penetrate tooth pores and create a protective layer on the tooth surface [75,76]. This demonstrates the unique potential of Ca^{2+}-based nanomaterials in remineralizing dental hard tissue.

2.2.2. Phosphate materials

Although PO_4^{3-} is mainly bound to Ca^{2+} to participate in the remineralization of tooth enamel, avoiding the loss of PO_4^{3-} is also a strategy to reduce the demineralization of dental tissues. When sodium trimetaphosphate (TMP) is adsorbed on the enamel surface, it reduces enamel, enhances enamel remineralization, decreases HAP solubility and mineral exchange, and changes the affinity between enamel surface and salivary proteins, thus reducing demineralization of dental tissue and avoiding caries progression [46]. For example, TMP is used as an additive in toothpaste formulations or chewing gum because this polyphosphate plays a vital role in reducing the dissolution of HAP [77,78]. One study showed that the addition of TMP to toothpaste with low fluoride concentration had *in vitro* anti-caries activity similar to or better than standard toothpaste containing F- at the concentration of 1100 ppm, and the addition of TMP

effectively reduced the concentration of fluoride [79]. This indicates that phosphate can play an anti-caries role independently of Ca^{2+} supplement.

Compared with TMP, nano-trimetaphosphate (NTMP) can play a remineralization function in the progressive area that can penetrate deep into caries. In a performance test comparison between NTMP and TMP, the results demonstrate that the remineralization ability of NTMP is significantly better than TMP when used independently. When used as an additive in toothpaste or resin-modified glass ionomer cement (RMGIC), NTMP is also easier to promote the release of fluoride [46,80].

2.2.3. Fluoride materials

Unlike Ca^{2+} and PO_4^{3-} direct replenishment strategies for demineralized tissues, F– can displace OH- in HAP and produce fluorapatite that is more resistant to the acidic environment produced by bacteria, thus avoiding demineralization of dental tissues. In the past few decades, adding fluoride to drinking water or toothpaste has proven its effectiveness in preventing caries. But too much fluoride intake often leads to dental fluorosis or bone fluorosis. The recent development of nano-fluoride has effectively solved these problems. One of the materials based on nano-calcium fluoride ($NCaF_2$) can be used as an unstable fluoride reservoir for more effective fluoride therapy. Meanwhile, as an agent for reducing dentin permeability, $NCaF_2$ also achieves the ability to promote tooth remineralization [47]. Due to the size effect, nano-scale fluoride is more suitable for use in coating materials, especially silver fluoride-based materials, which can achieve the remineralization of antibacterial agents simultaneously.

2.2.4. Biomimetic remineralization materials

HAP and fluoride-containing oral care products can effectively promote enamel remineralization but have no potential to promote the formation of organized apatite crystals. People have recently proposed a therapeutic concept of tooth hard tissue regeneration [81]. Biomimetic remineralization refers to forming HAP crystals mediated by the organic matrix through the interaction of proteins and inorganic materials [82]. For example, amelogenin can direct the formation of highly anisotropic and ordered apatite crystals during enamel development, and the development of amelogenin-based synthetic peptides can increase the remineralization of early enamel lesions [50].

In order to avoid the polypeptide being dissolved by saliva, Wang et al. combined the N-terminal amelogenin (N-Ame) with the central domain and the synthetic peptide (C-AMG) based on the C-terminal peptide (C-Ame) domain with phasetransited lysozyme (PTL) enzyme membrane bound. In the PTL/C-AMG matrix, C-AMG promotes the directional alignment of ACP nanoparticles and their conversion to ordered enamel-like HAp crystals, while PTL acts as a strong interfacial anchor to bind C-AMG peptide and PTL/C-AMG matrix was immobilized on the surface of the multifunctional matrix. After 7 days of culture in saliva, nascent HAP was evident on the enamel surface of this material but not on the fluoride surface (Figure 2(f)) [18]. This also demonstrates the difference between biomimetic enamel regeneration and fluoride-induced remineralization alone.

Due to structural differences, dentin biomimetic mineralization strategies differ from those of enamel. The reparative dentin formation starts from the pulp cavity, while the dentin formed by biomimetic remineralization is located in the lesion body. Remineralizing demineralized-dentin is important for improving dentin bond stability and controlling primary and secondary caries [83]. Biomimetic remineralization of demineralized dentin using calcium phosphate polymer-induced liquid precursors (Ca/PPILP) is a promising strategy based on non-classical crystallization pathway theory using ACP and non-collagen protein (NCP) analogs to backfill demineralized dentin. This dentin biomimetic remineralization material can improve the integrity of the bonding interface of remineralized artificial carious dentin lesions and significantly improve the bonding strength [51].

Both size effect and structure effect can significantly improve the antibacterial properties of caries prevention materials, but most of the current strategies focus on filling resin processing. If more effective caries prevention products such as mouthwash, toothbrush, toothpaste can be developed, the incidence of caries can be significantly reduced, but this process requires our attention to more things. As for the remineralization of tooth hard tissue, the current technology is separate in the mineralization or regeneration of tooth enamel and dentin. In the future, we may be able to induce the regeneration of tooth enamel and dentin at the same time through new technology. In addition, we might consider incorporating 3D printing technology to fully restore the structure and shape of the tooth.

3. Pulpal diseases

Pulpal diseases are a series of diseases that occur in the dental pulp tissue [84]. Traditional endodontic treatment methods include pulp capping or root canal treatment, depending on the condition of the pulp infection. Since the nerve blood vessels in the pulp cavity provide nutrition for the hard tissue of the tooth and guide the development of the tooth root, more and more people are beginning to realize the importance of preserving the living pulp [85]. Therefore, new technologies have emerged as time requires, such as pulp revascularization, apical induction, pulp

regeneration, and so on [68,86]. The basis for achieving these new technologies is the development of material science. In this section, pulp diseases are classified by analyzing the etiology and treatment methods of different pulp diseases. Combined with the characteristics of materials, the advantages and development strategies of some new materials for pulp diseases are summarized (Table 1).

3.1. Dentin hypersensitivity

Trauma, abrasion, and acid erosion often cause dentin tubules to be exposed in the mouth, and external stimuli can cause fluid flow in the dentin tubules, ultimately leading pulpal reactive pain [87]. Sealing the dentin tubules and avoiding the transmission of irritation are the keys to solving the problem of dentin hypersensitivity. In recent years, a number of desensitizers designed to seal dentin tubules have become available [88]. However, the dissolution of most materials in the oral cavity and poor penetration has resulted in the short-term efficacy of desensitization therapy. In contrast, considering that the average diameter of dentinal tubules is about 1–2.5 μm, nano-sized dental materials are more likely to play advantage in treating dentin hypersensitivity.

Desensitizing toothpaste is a solution to dentin allergy in daily life. In a double-blind clinical trial, Vano et al. demonstrated that toothpaste with a 2% concentration of NHAP [52]. Except for concentration, the particle size of NHAP is another factor that affects the ability of dentin to mineralize [53]. In addition to CaNPs, ZnNPs are thought to accelerate dentin active remodeling, thereby improving dentin's maturation and mechanical properties. When dentin was treated with ZnNPs, higher values of composite modulus were obtained at intertubular and peritubular dentin than those obtained after the application of CaNPs [54]. The application of nanostructured sol-gel bioactive glass (BG) effectively reduces the electrical conductivity of acidic solutions, thus reducing the symptoms of dentin hypersensitivity [55]. A multifunctional material based on the nano-Si /Ca(Sr) system has been developed. The ability of this material can achieve acid resistance, bacterial inhibition and low cytotoxicity as well as to promote dentin bionic remineralization, providing an option for the current development of multifunctional nanomaterials [19].

3.2. Pulp exposure

In treating of pulp exposure due to caries or trauma, direct pulp capping or root canal therapy can be performed depending on the size of the exposed pulp hole. To avoid infection of the pulp, direct capping is mainly used when the exposed pulp hole is less than 0.5 mm in order to preserve the living pulp. Calcium hydroxide ($Ca(OH)_2$) is the most commonly used capping agent, depending on its ability to induce the formation of new dentin from dental pulp stem cells (DPSCs) and antibacterial capacity in an alkaline environment. However, the failure rate of $Ca(OH)_2$ for direct pulp capping after 24 months of treatment has been clinically proven to be more than 30%, which is related to the irritating effect of $Ca(OH)_2$ on the pulp and the weak dentin formation ability [89,90]. Mineral trioxide aggregate (MTA), a universal dental restorative material, is considered the most clinically suitable material for capping the pulp. Still, it has been reported that MTA does not achieve adequate adhesion to the dentin, which may increase the risk of bacterial infiltration in the oral cavity after treatment [91]. Therefore, it is necessary to develop more suitable capping agents for clinical applications.

NHAP is significantly better than $Ca(OH)_2$ at promoting restorative dentin formation [56]. NHAP, as a scaffold material loading fibroblast growth factor-2 (FGF2), can efficiently enhance the formation of calcified tissue [57]. Considering that NHAP cannot have the ability to adhere, Yoshida et al. applied a dental adhesive super-bond in combination with NHAP for pulp capping and showed that dense restorative dentin was produced in the exposed areas of the pulp [58]. In addition to promoting restorative dentin formation, anti-inflammatory treatment is crucial to the success of pulp capping. Studies have shown that the adding Zn NPs-containing pulp capping agents to Si-Ca NPs-containing capping agents can downregulate the expression of M1 macrophages, thereby reducing inflammation [59]. In addition, the anti-inflammatory power of nano curcumin (nCur) combined with photodynamic therapy (PDT) allows for a long-term anti-inflammatory effect of capping agents [60].

3.3. Pulpitis or periradicular lesions

3.3.1. Root canal treatment

The conventional treatment of endodontic and periapical diseases is based on root canal treatment (RCT), the primary purpose of which is to remove the infected material from the root canal. Root canal disinfection is a method to quickly clean the infected material in the root canal. The commonly used drugs in clinical practice include $NaClO_4$, $Ca(OH)_2$, ethylene diamine tetraacetic acid (EDTA), etc., which mainly use the acidic or alkaline environment produced to kill the bacteria. However, these drugs have poor penetration ability to dentin, certain cytotoxicity to tissues, and poor antibacterial effect [92].

The antibacterial effect of AgNPs still applies in root canal disinfection [61,62]. In addition, *in vitro* tests showed that the penetration ability of nano

$Ca(OH)_2$ on dentin tubules was significantly better than that of conventional $Ca(OH)_2$, which indicates that the nano $Ca(OH)_2$ is more powerful in terms of antibacterial strength and the ability to promote dentin tubule mineralization [63]. Compared to $NaClO_4$, MgO NPs have significant advantages in removing *Enterococcus faecalis* with good biocompatibility and are hence more suitable for root canal irrigation [64].

Different from root canal irrigants, root canal sealers require long-term antibacterial properties and potentially to promote remineralization of tooth tissue. Not only that but the stability and biocompatibility of the root canal sealer is also necessary. Compared to epoxy resin-based sealers, Ca/Si-based nano-sealers are more biocompatible and less cytotoxic [65]. Baras et al. developed a multifunctional root canal sealer containing dimethylaminohexadecyl methacrylate (DMAHDM), AgNPs and NACP which can simultaneously exert antibacterial and promote the mineralization of the root canal side wall [66]. This type of sealer should also be a direction for the future of root canal sealer development.

3.3.2. Pulp regeneration

Permanent teeth with pulp necrosis inevitably lose the natural biological defenses inherent in the pulp and are prone to fracture over time, which seriously affects the survival rate of the teeth [93]. Pulp regeneration is one of the most desirable treatments for pulp infections, especially for young permanent teeth. The process of pulp regeneration is to promote the continuous development of teeth by promoting angiogenesis under the premise of ensuring antibacterial activity.

Human mesenchymal stem cells (MSCs) are highly accessible and expandable *in vitro* and are characterized by pluripotent differentiation [94]. DPSCs, as one of human MSCs, play a huge role in the tissue engineering of dental pulp regeneration. Studies have shown that human autologous deciduous tooth pulp stem cells can potentially promote dental pulp regeneration [95]. How to rationally activate the differentiation potential of DPSCs is a question worth considering.

In the early stage of research on dental pulp regeneration, most materials achieved a state of pulp regeneration by activating the angiogenesis of DPSCs [96]. However, due to the influence of angiogenesis efficiency, most materials cannot achieve pulp regeneration of the whole root. Based on this question, Li et al. utilized multifunctional gene carriers (including cell-penetrating peptides for enhanced cellular uptake, nuclear localization signal peptides to assist in the transfer of angiogenic genes to the nucleus, and fluorescent colorants for visualization and quantification of transfection efficiency) to transfect vascular

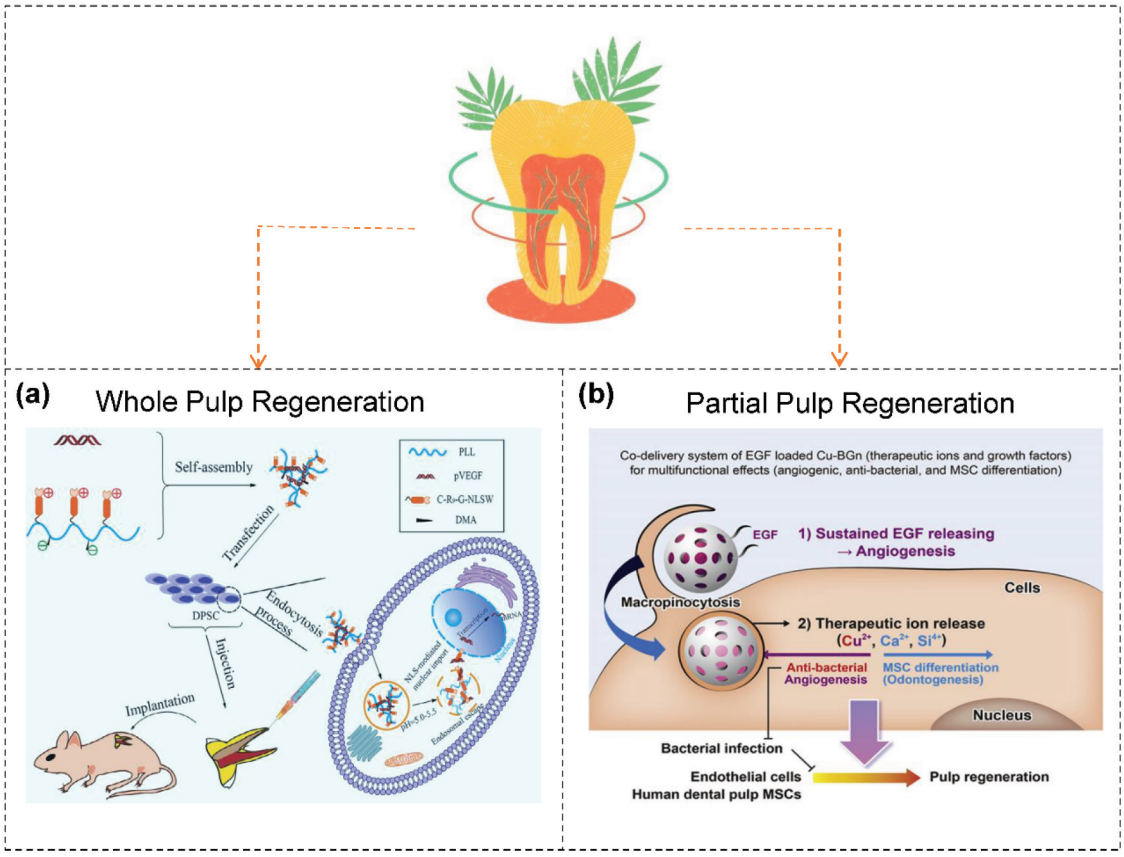

Figure 3. Different strategies in pulp regeneration. (a) the strategy of whole pulp regeneration. Reproduced by permission from [97], copyright 2021, Elsevier. (b) the strategy of partial pulp regeneration. Reproduced by permission from [20], copyright 2020, Elsevier.

endothelial growth factor (VEGF) into DPSCs. The expression of VEGF in DPSCs was up-regulated more than 8-fold. After 6 weeks of observation, DPSCs transfected with VEGF accelerated the formation of new blood vessels, and the regenerated pulp tissue occupied most of the full-length human root canal (Figure 3(a)) [97].

In addition to the direct processing of DPSCs, using composite nanoscaffold systems to promote dental pulp regeneration is still the mainstream research method. For example, an injectable simvastatin (SIM)-functionalized gelatin methacrylate (GelMA) cryogel microsphere (SMS) is loaded with stem cells from human exfoliated deciduous teeth (SHEDs) during injection; SMS with sustained SIM release promotes adhesion and proliferation, showing that cytoprotective properties during the injection process, while the sustained release of SIM can promote the adhesion and proliferation of SHEDs, which can effectively promote angiogenesis, highlighting the nanotherapeutic application of multifunctional nanoparticles in the regeneration of infected/damaged hard tissues [68].

Of course, strategies for pulp regeneration are not limited to pulpal necrotic teeth. In infected or degenerated pulp tissue, pulp can be regenerated utilizing endodontic repair. Unlike necrotic dental pulp, dental pulp repair does not require exogenous DPSCs. Therefore, the key to dental pulp repair is anti-inflammatory, antibacterial, and activation of the differentiation potential of DPSCs. Cu^{2+} enhances angiogenesis-related genes in a variety of cells by inducing a hypoxic microenvironment, which induces the expression of hypoxia-inducible factors and upregulates the expression of angiogenic genes, including vascular endothelial growth factor [98]. This property can be used in pulp regeneration.Recently, a mesoporous material has been developed to achieve multiple effects simultaneously through co-delivery. For example, the material can provide antibacterial potential and enhance VEGF expression by releasing Cu^{2+}. At the same time, the release of silicate and Ca^{2+} can effectively activate the osteogenic/odontogenic differentiation potential of MSCs to promote the repair of dental hard tissue (Figure 3(b)) [20]. This material highlights the potential of nanomaterials for drug delivery and provides more feasible options for pulp regeneration.

At present, the method of root canal treatment has changed from cold tooth filling to hot tooth filling. Although this method increases the degree of tightness between the root canal filling material and the tooth root, traditional root canal filling materials still lack long-term antibacterial properties. Therefore, the advantages of nanomaterials are still utilized to develop new root canal filling drugs that can repair the lateral wall of the root canal while achieving long-lasting antibacterial effect. Compared to pulp regeneration, this goal is relatively easy to achieve. Pulp regeneration technology has brought hope to patients with pulpitis, but there are still many limiting factors in clinical application, among which the most important is to strictly grasp the indications of the disease.

4. Periodontal diseases

The pathological characteristic of periodontitis is the destruction of teeth supporting tissues under the influence of pathogenic bacteria, such as *Porphyromonas gingivalis* (*P.g*) and *Actinobacillus concomitantus* (*A.a*) [99,100]. Progression of periodontitis can also trigger severe systemic diseases, including diabetes, cardiovascular disease, and even cancer [101,102]. Recent literature suggests more than 10% of adults are affected by severe periodontitis, which has posed challenges to the health of mankind [103]. For periodontitis therapy, the traditional perception is that destruction of periodontal tissue is irreversible and mainly limited to traditional materials. Fortunately, advanced nanomaterials have changed this stereotype. To highlight the crucial role of advanced nanomaterials in the periodontitis therapy, we discussed in detail their application in periodontal diagnosis (represented by advanced periodontal sensors), antibacterial therapy (including drug carriers suitable for periodontal antibacterial/anti-inflammatory drug delivery, antibacterial/anti-inflammatory materials suitable for photo-therapy) and tissue engineering (including scaffold materials and development strategies suitable for periodontal treatment). We also further summarized relative studies in Table 2.

4.1. Diagnosis

Currently, the gold standard to diagnose periodontitis is observing the degree of alveolar bone resorption by radiographs while disregarding disease activity, thereby limiting the capability to predict the risk of periodontitis progression and monitor periodontitis recovery during follow-up. Alternatively, evaluating periodontal tissue status by gingival crevicular fluid (GCF) is a reliable method [136,137]. For accurate analysis of GCF composition, an advanced sensor has been developed over recent years, consisting of magnetic nanoparticles functionalized with tertbutyl cuproaromatic. Thanks to magnetic nanoparticle films and ion carriers, such sensors can sense inorganic particles in different polymer matrices, thus assessing the status of periodontal tissue through analysis of the Na+ content in the gingival sulcus [138]. The advanced assessment strategy is more accurate and convenient for diagnosing periodontitis and allows for a comprehensive assessment of periodontitis. Nevertheless, limited by high-cost and

Table 2. Application of nanomaterials in periodontal diseases.

Denture Type	Applications	Core nanoparticles/ nanomaterial	Key features	Ref
Removable denture	Mechanical strength	ZrO_2 NPs	Effectively increasing the mechanical properties of PMMA.	[104–109]
		TiO_2 NPs		[110]
		SiO_2 NPs		[111]
		ZnNPs		[112]
		diamond NPs		[113]
		SiC NPs	Improving the thermal conductivity of PMMA.	[114]
	Antibacterial	AgNPs	Antibacterial effect by coating or filling	[115,116]
		Chitosan	Unique antibacterial ability against Candida.	[117]
		nGO	Increasing PMMA hydrophilicity to obtain antibacterial ability.	[118,119]
		TiO_2 NPs	Dual antibacterial power.	[120]
		SiO_2 NPs		
Implant restoration	Antibacterial	ZnNPs	Long-lasting antibacterial effect.	[121,122]
		CeO NPs	Stronger anti-inflammatory effects.	[123]
	Osseointegration	Nanopattern	Promotes osseointegration.	[124]
		nGO	Increasing the hydrophilic properties of the implant surface.	[125,126]
		SiNPs	Enhancing roughness and hydrophilic properties of the implant surface.	[127]
		NHA	Promoting osseointegration.	[128]
		nBG	Promoting osseointegration.	[129]
		CaNPs	Promoting osseointegration.	[130]
Fixed denture		Fe_3O_4+ $BiVO_4$	Antibacterial through dual mechanism of light and magnetism.	[23]
		Nano-ceramic resin	High bending strength, low abrasiveness, and easy polishability.	[131–133]
		ZnNPs	Increasing the antibacterial, mechanical and acid resistance of polycarboxylic acid binder.	[134]
		NACP	The bonding agent promotes the remineralization of dental tissue.	[135]

complicated synthesis processes, the development of such a strategy has been stalled in the laboratory phase, and the need to develop more convenient and economical sensors is still urgent.

4.2. Drug delivery system

Drug carriers, such as nanofibers, nanocapsules, and nanoparticles, provide multiple advantages for drug delivery, including protecting the drug from enzymatic damage, sustained release, reduced side-effect, improved targeted delivery, and so on [139]. Not only that, but it can also enhance tissue penetration and relieve pain in periodontal therapy [140]. Drug delivery system plays a huge role in periodontal antibacterial/anti-inflammatory therapy. Considering that most conventional drugs' antibacterial/anti-inflammatory potential has been clinically proven, this section

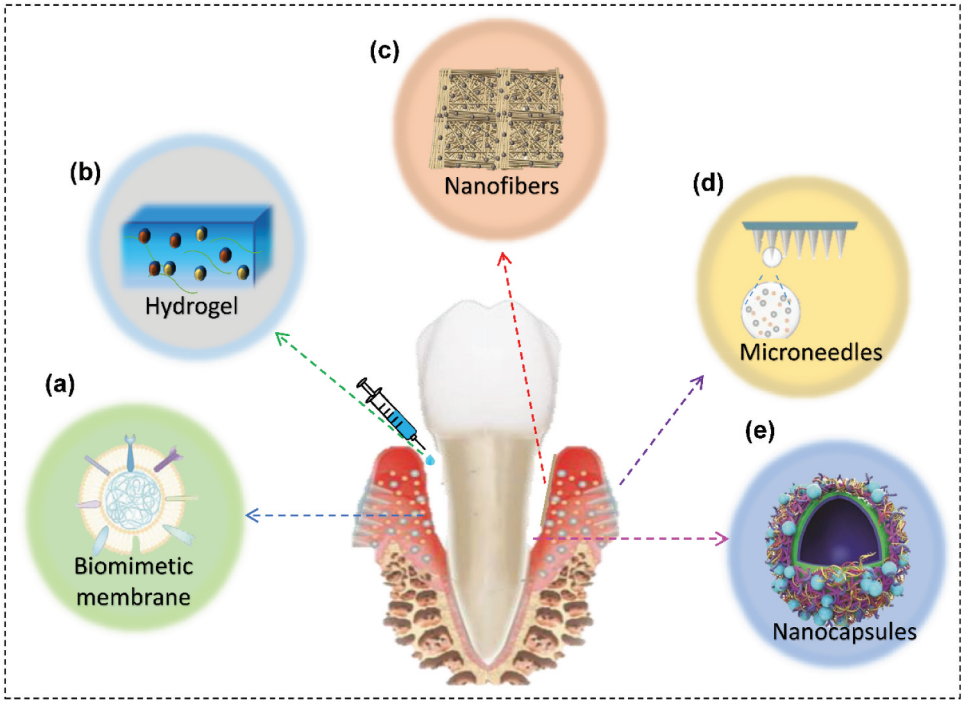

Figure 4. Drug carriers suitable for periodontal drug delivery. (a) Biomimetic cell membrane. Reproduced by permission from [141], copyright 2021, Elsevier. (b) Hydrogel. (c) Nanofibers. Reproduced by permission from [22], copyright 2022, Wiley. (d) MNs. Reproduced by permission from [21], copyright 2021, Elsevier. (e) Nanocapsules. Reproduced by permission from [142], copyright 2019, Wiley.

focuses on selecting several drug carriers suitable for oral clinical development (Figure 4).

4.2.1. Nanocapsules

Some antibacterial agents are effective in removing periodontal pathogenic bacteria, but they are often accompanied by side effects that limit their long-term clinical use. Nanocapsules can improve the efficacy of drugs and reduce side effects by controlling the ratio of encapsulating multiple nano drugs.

For example, the antibacterial ability of AgNPs against periodontal pathogens is undisputed [143]. However, using AgNPs alone for periodontal antibacterial purposes may produce unpredictable toxicity. The combination of AgNPs and antibiotics (azithromycin and clarithromycin) has a synergistic antibacterial effect on periodontal pathogenic microorganisms and can effectively reduce the toxicity of AgNPs [144]. Chlorhexidine (CHX), a commonly used oral rinse, has been clinically proven to be effective in inhibiting the production of oral bacteria. Still, CHX has been reported to have adverse effects such as tooth staining, hypersensitivity reactions, and poor bioavailability [145,146]. By nano-encapsulating baicalin with CHX in a 9:1 ratio, the resulting nanomaterial not only inherits the remarkable anti-inflammatory, antioxidant and immunomodulatory effects of baicalin but also minimizes the side effects of CHX [147,148].

4.2.2. Hydrogel

Hydrogel is a class of extremely hydrophilic, three-dimensional network structured gels, swells rapidly in water that retains them in the swollen state. Therefore, it is easy to achieve drug loading by mixture drug with a hydrogel in solution. More importantly, the porous structure gives hydrogel great drug loading capability compared to other nanoplatforms. Moreover, thanks to the viscidity, hydrogel readily attaches to the tissue surface, making it more suitable for periodontal treatment [149].

Studies in recent years have highlighted the unique role of hydrogel in this field. It has been shown that topical cur gel is more likely to improve the severity of gum disease compared to oral cur [150–152]. To the best of our knowledge, primarily in contrast to the difficult aggregation of free cur in the periodontal microenvironment, loaded cur into hydrogel prolongs its retention by sustained release. Secondly, except for cur, the composition of hydrogel, such as chitosan, may also have an the antibacterial effect, and can synergistically inhibit bacteria with cur. Furthermore, the porous structure of hydrogel is endowed with the capability to load multiple drugs without affecting their medicinal properties, thereby it is an outstanding carrier for co-delivery [153,154]. For example, using supramolecular hydrogel NapFFY to simultaneously load SDF-1/bone morphogenetic protein-2(BMP-2), these two bioactive factors can be released synchronously and continuously, effectively promoting the regeneration of alveolar bone [155]. What needs to be noted is that the biodegradation and irritation of hydrogel must be considered. Overly complex components will increase the risk of reduced biocompatibility of the hydrogel. Consequently, we believe drugs with self-assembly hydrogel, such as rhein hydrogel [156], are more favorable for periodontal antibacterial therapy. Despite the absence of a relative report, this is still an important development direction in the field.

4.2.3. Nanofibers

Nanofibers, the 1D nanomaterials produced by electrospinning, mortar grinding, cryogenic cutting, and ultrasonication, possess flexible structure and ultrahigh surface area, thereby with excellent drug loading capability similar to hydrogel [157]. Compared to hydrogel, nanofiber can also achieve sustained-drug release. Processing of polyethylene glycol blocks polycaprolactone, a biodegradable polymer with outstanding biocompatibility, into nanofibers by electrostatic spinning technique for loading mitogen-activated protein kinase inhibitors SP600125 and SB203580. Wang et al. proved the ability in long-term drug release of this nanofiber [158]. Compared to hydrogel, nanofibers are more prone to reach sequential release by establishing a barrier to limit the penetration of the drug. For example, a nanofibrous membrane with a shell-core structure (the polymer micelles of SP600125 are distributed in the shell layer, and BMP-2 is contained in the core) releases SP600124 and BMP-2 successively during a 4-week degradation period, thus achieving an antibacterial-osteogenic sequential periodontitis treatment, which reflects the excellent potential of nanofibers in drug controlled release [159]. Additionally, the great flexibility in material choice means the feasibility of preparing environmentally responsive nanofibers, especially to low pH and excessive glutathione microenvironment of bacterial infection [160], is more appropriate for periodontal antibacterial therapy.

4.2.4. Microneedles

Microneedles (MNs) were first introduced in 1998 to overcoming the skin barrier and have booming developed in recent years. According to the composition and structure, MNs can be classified into four types: solid MNs, hollow MNs, coated MNs and dissolvable MNs. Among them, solid MNs and hollow MNs are medical devices used to generate microchannels, which facilitate drug penetration. Conversely, coated MNs and dissolvable MNs possess the capability for drug delivery. For the coated MNs, the drug is dispersed on the surface of solid MNs, which will gradually release into interstitial fluid [161]. Considering the risk of non-degradable materials loss in the microchannels, the dissolvable MNs, with excellent

biodegradation, are more befitting for drug delivery. Zhang et al. are the first to use nano microneedle patch immunotherapy for local periodontitis. Including tetracycline-loaded poly (lactic-co-glycolic acid) nanoparticles for sustained release of antibiotics can effectively inhibit bacterial growth and the expression of pro-inflammatory factors. Cytokine-loaded silica microparticles were used to provide pro-regenerative signals and soft tissue healing. This material demonstrates the therapeutic potential of MN's local immunomodulatory capabilities for tissue regeneration [21].

4.2.5. Biomimetic cell membrane

As a microscopic drug carrier, the biomimetic cell membrane can not only modify the drug independently but also participate in the drug delivery of other nanoplatforms and play a unique role in the anti-inflammatory treatment of periodontitis. Although current nanoparticles for periodontitis therapy can acquire anti-inflammatory capabilities by modulating macrophage polarization, frequent high-dose administration is required to achieve desired efficacy [162]. In order to endow drugs with broad-spectrum immunomodulatory capabilities, Li et al. extracted Treg membranes for nano-drug delivery [141]. Since Treg cells retain intrinsic membrane proteins and functions, the coated nanoparticles can directly interact with multifaceted overactive immune cells, and this drug has demonstrated excellent performance in rat and animal models of beagle dog periodontitis. And this drug can achieve the desired effect through local anti-inflammatory ability administration, which is different from the active targeting strategy of biomimetic antitumor drugs for systemic administration in a certain sense.

4.3. Photo-therapy

The biomedical application of photosensitizers has attracted extensive attention over recent years and can be classified into photo-thermal therapy (PTT) and PDT by their different mechanisms [163]. For the PTT, photosensitizer convert light to thermal energy under the near-infrared radiation (NIR), causes hyperthermia and triggers necrosis and apoptosis [164], and is spatiotemporal-controlled because of the NIR-responsive characteristic [165]. And PTT has been widely applied in antitumor and antibacterial therapy. In particular, the lesions of periodontitis are relatively limited in scope, which can effectively avoid the disadvantage of weak tissue penetration ability of NIR light. Unfortunately, the high temperature could also damage the normal periodontal tissue, particularly to the temperature of antibacterial therapy needs to exceed 60°C. Thus the combination of PTT and other strategies, such as antibiotics, were used to improve the antibacterial effect of PTT at a lower temperature. By mild heat therapy (<50°C), the bacterial infection microenvironment has been changed, including activation of Na/KATPase, regulation of glutathione metabolism, and enhancement of local blood flow and oxygen tension, which provide benefit for the antibacterial effect of antibiotics [166,167]. Importantly, drug loading photosensitizers always possess NIR-responsive release capability, further enhancing antibiotics' antibacterial effect [168].

Different from PTT, PDT requires a photosensitizer to complete its antibacterial action. Photosensitizers undergo electronic transitions under radiation, from the ground state to the unstable excited state, and then rapidly transfer energy to the surrounding molecules through the cytotoxicity of ROS produced in this process to achieve the therapeutic purpose [169,170]. However, excessive GSH and hypoxia in the bacterial microenvironment decrease the antibacterial effect of PDT. Additionally, ROS accumulated after PDT can exacerbate the imbalance of oxidative/antioxidant activity in periodontal pockets, recruit inflammatory cells, and shift the polarization of macrophages to the M1 phenotype, which aggravates periodontal tissue destruction [171]. Except for the above, poor solubility, uncontrollable drug release, lack of targeting ability, and low extinction coefficient hinder the application of PDT in antibacterial therapy [172]. Functional metal nanocomposites as photosensitizers may help improve the antibacterial ability of PDT. By modified with targeting ligand, such photosensitizers will decrease internalization of normal cells but increase in bacteria, so as to enhance the antibacterial PDT and reduce side-effect. For example, sPDMA (star-shaped polycationic brush poly (2-(dimethylamino) ethyl methacrylate) can increase the bacterial targeting of indocyanine green (ICG) [173].

To address the behavior of excessive ROS to recruit inflammatory cells, a nanocomposite based on CeO_2 @Ce6 has been developed (Figure 5(a)). This CeO_2-containing nanocomposite not only inherits the photosensitive properties of the photosensitizer chlorin e6 (Ce6), but also possesses superoxide dismutase (SOD) and catalase (CAT)-mimicking activities, which will help scavenge excess ROS, depending on its ability to switch between Ce^{3+} to Ce^{4+} valence states (Figure 5(b)). After 4 days of treatment, it was found by comparison that this nanocomposite had the best antibacterial effect (Figure 5(c)). Finally, the analysis of the immune cell population in the periodontal pocket after treatment showed that this material could avoid the destruction of the periodontal tissue by pro-inflammatory cells by regulating the polarization of macrophages [174]. These results suggest that photo-therapy can be used as an adjunct to periodontal therapy, however a rational design is needed to address its side effects.

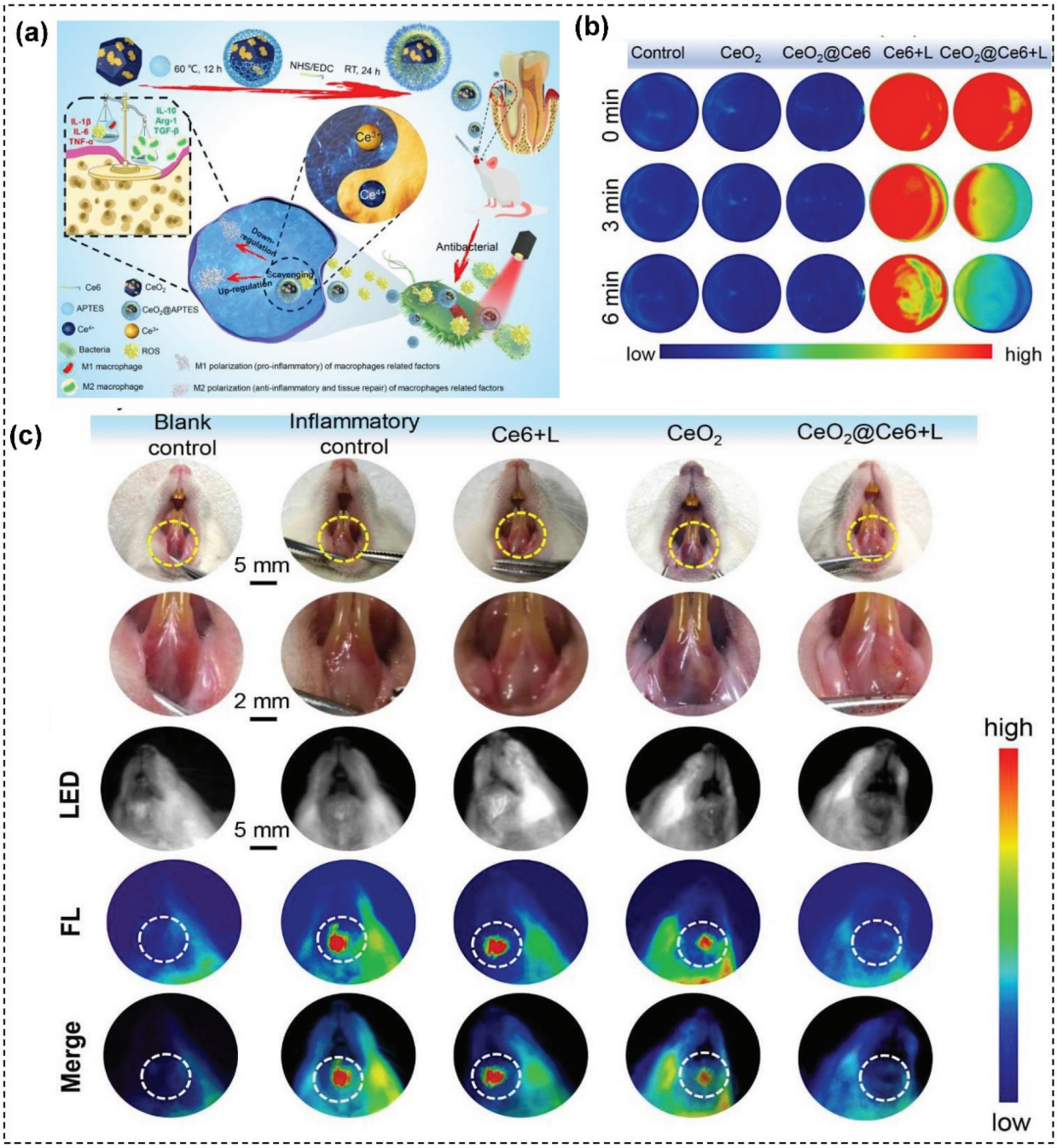

Figure 5. (a) Schematic illustration of CeO_2@Ce6 nanocomposite in synthesis, the antibacterial mechanism, and modulating the polarization of macrophages for the treatment of periodontitis. The enhanced antibacterial efficacy of CeO_2@Ce6 could rely on the generation of ROS by aPDT and the innate antibacterial activity of CeO_2. (b) *In vitro* fluorescence images of ROS generation via different nanoparticles by using an *in vitro* imaging system. The color change indicates that the combination of CeO2@ce6 with light can generate ROS resulting in antimicrobial effect and then remove the ROS to avoid damage to normal tissue. (c) the result of this study suggest that photo-therapy can be used as an adjunct to periodontal therapy, however, a rational design is needed to address its side effects. Reproduced by permission from [174], copyright 2020, Elsevier.

4.4. Tissue engineering

Replaced the damaged tissues with healthy is an essential process in periodontitis treatment. Tissue engineering, establishing a 3-dimensional spatial complex of cells and biomaterials, undoubtedly opens a new avenue for reconstructing the periodontal tissues. The applied cells in tissue engineering can secret extracellular matrix, which can be used to establish the tissue structure with great biological activity, to maintain the long-term stability and physiological function of regenerated tissue [175–177]. Periodontal embryonic stem cells are the most common cells in the tissue engineering of periodontitis treatment because of the ability to differentiate into osteoblasts, odontogenic osteocytes, fibroblasts and subsequently form the

corresponding periodontal tissues. In addition, growth factors, such as basic fibroblast growth factor (bFGF) [178], epidermal growth factor (EGF) [179], BMP [180], and VEGF [181], can promote the differentiation of seed cells, are also widely applied in the tissue engineering of periodontitis treatment. In this part, we will further introduce the types and design strategies of nanoscaffold for periodontal tissue engineering.

4.4.1. Inorganic nanoscaffold

NHAP is one of the most common inorganic scaffold materials with good biocompatibility and little inflammatory response after implantation into connective and bone tissues [182]. Different forms of NHAP affect the morphology of osteogenesis. For example, spherical NHAP is more likely to produce large bones *in vivo*, while rod-shaped NHAP produces small bones *in vivo* [183]. NHAP can be modified not only as an

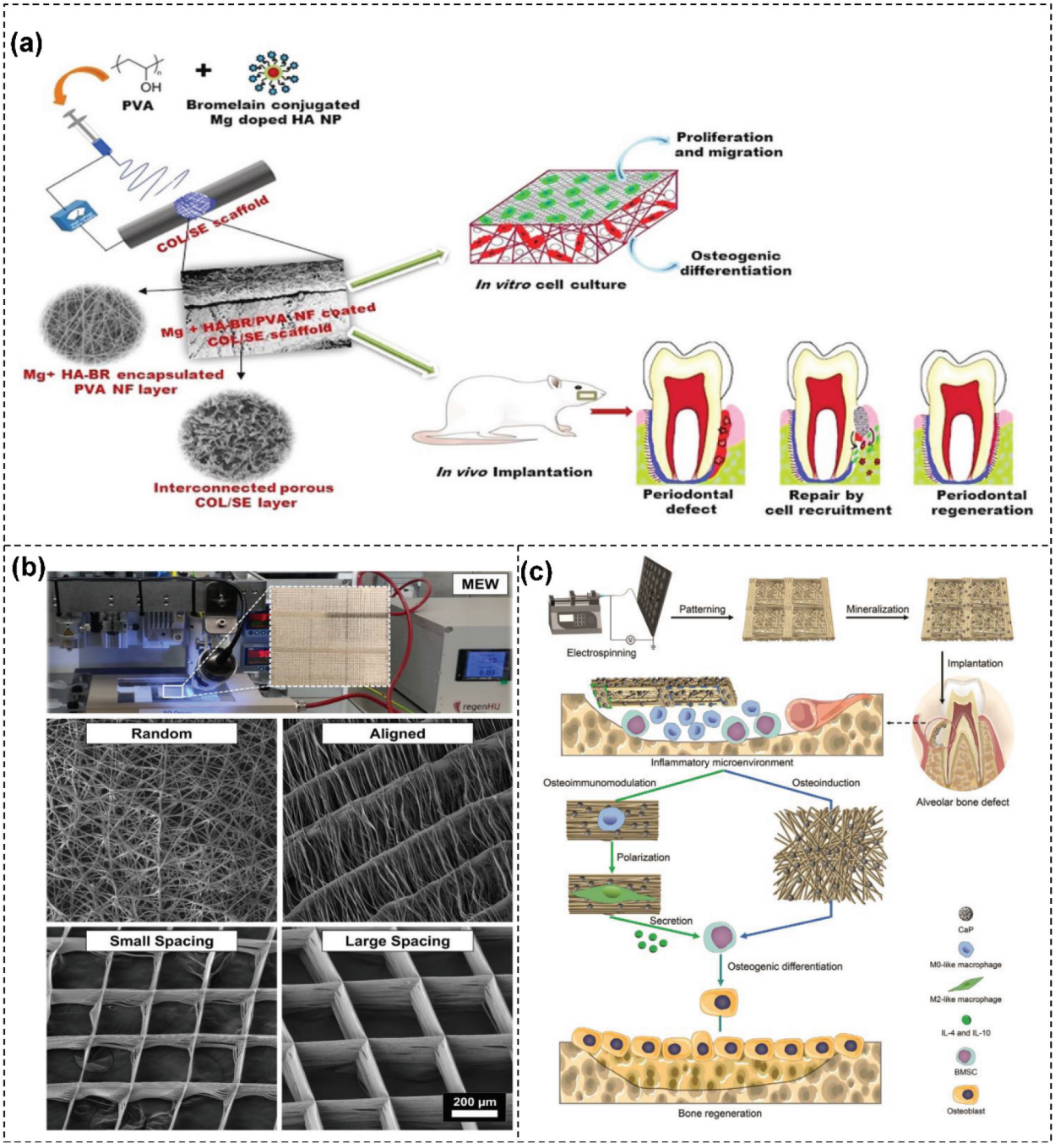

Figure 6. Different scaffold materials in periodontal tissue engineering. (a) Schematic diagram demonstrating the role of a double-layered scaffold for periodontal regeneration. Reproduced by permission from [185], copyright 2020, Elsevier. (b) MEW setup to fabricate fibrous scaffolds of distinct fiber configuration and highly-ordered architectures. Representative SEM images of the various MEW PCL scaffolds show melt electrowritten polymeric (i.e. poly(ε-caprolactone) scaffolds with tissue-specific attributes such as fiber morphology (random vs. aligned) and highly-ordered (0◦/90◦ crosshatch pattern) architecture with distinct strand spacings (small 250 μm and large 500 μm). Reproduced by permission from [186], copyright 2022, Elsevier. (c) Schematic illustration of hierarchical-structured mineralized nanofiber (HMF) scaffold for enhanced alveolar bone defect repair. Reproduced by permission from [22], copyright 2021, Wiley.

osteoinductive into other nanoscaffolds but also processed as a scaffold material to load seed cells or cytokines [182,184]. Functionalization of polymer scaffolds with pineapple protease and Mg-doped NHAP enhanced the mechanical, physicochemical, thermal, and biological properties of the scaffolds and provided the necessary bioactive cues to control cellular function, hemocompatibility and improve proliferation and migration *in vitro* by showing antibacterial potential (Figure 6(a)) [185].

The characteristics of NHAP stents vary from source to source, such as NHAP derived from eggshells. There is no risk of disease transfer, and the preparation process is environmentally friendly [187]. Hybrid scaffolds of NHAP derived from salmon scales have higher mechanical strength and Young's modulus [188]. In addition to NHAP, NBG [189] and nano calcium alginate (NCA) [190] can also be processed into scaffolds for tissue engineering applications.

4.4.2. Synthetic polymer scaffold

Synthetic polymers are biocompatible, biodegradable polyester materials widely used as tissue engineering scaffold materials due to their good mechanical properties, gradual absorption, non-toxicity, and ease of electrostatic spinning into nanofibers [191]. Promotion of protein uptake, cellular responses, activation of specific gene expression and intracellular signaling, and high surface area to volume ratio are important properties of synthetic polymeric nanofiber scaffolds [192]. Compared with macroporous sponge scaffolds, nanofiber scaffolds have a higher degree of cell adhesion and mineralization, and nanofiber scaffolds are more favorable for PDL cell differentiation and proliferation of MC3T3-E1-osteoblasts [193]. Melt ElectroWriting (MEW) has been introduced as an alternative additive manufacturing process that enables the production of fibrous scaffolds with well-defined macro- and microstructural features, such as porosity (i.e. strand spacing) and fiber alignment and diameter. Recently, Tissue-specific 3D fused electrowriting (i.e. poly-ε-caprolactone) scaffolds designed by the MEW process can be capable of directing tissue-specific (aligned fibers for PDL and highly-ordered 500 μm strand spacing fluorinated calcium phosphate [F/CaP]-coated fibers for alveolar bone) stem cell differentiation and macrophage polarization, which significantly promotes osteogenesis (Figure 6(b)) [186]. In addition, synthetic polymer scaffolds with hydrophobicity can also be used to guide tissue regeneration (GTR) by processing into membranes, which can act as a long-term barrier, thereby giving osteoblasts enough time to form new alveolar bone [194]. However, due to the non-degradability of such materials, patients often need to undergo secondary surgery.

4.4.3. Natural biodegradable polymer scaffold

The natural biodegradable polymers are polymeric degradable materials extracted from plant and animal tissues, including collagen, chitosan, gelatin, agar, dextran, and hyaluronic acid (HA). The characteristics of these materials are derived from the properties of the materials themselves. In tissue engineering, chitosan nanoparticles can promote the proliferation of periodontal embryonic stem cells and promote osteogenic differentiation [195]. Chitosan scaffold promotes oral soft tissue defects regeneration by loading trichloroacetic acid (TCA) and EGF [179]. The biodegradation efficiency of chitosan can be controlled by regulating its molecular weight and preparation process, thus reducing the risk of secondary surgery [139]. In addition, the processing process of the stent material will also affect the performance of the stent material, such as the higher proliferative/metabolic activity of chitosan nanoelectrospun collagen (CNC) membranes compared to pure chitosan membranes [196].

In essence, the application pattern of scaffold materials in tissue engineering is similar to drug carriers with antibacterial functions. But antibacterial therapeutics and tissue regeneration are two stages of the periodontal treatment process, especially since the scaffold material should coordinate its relationship with seed cells and periodontal tissue. Compared to the traditional scaffold, nanoscaffold materials offer higher mobility of drug-loaded particles in tissue engineering and effective *in vivo* responsiveness to nearby tissues. They can be used to label cells for continuous cell tracking and monitoring. The nanoscaffold has some osseointegration, osteoconductivity, and osteoinduction capabilities. Therefore, it is necessary to consider how to design a suitable scaffold in engineering tissue.

For example, single-layer scaffolds can be used in GTR. This type of scaffold generally only needs to balance the relationship between its degradation efficiency and tissue growth efficiency. The choice of which type of material depends on the development of the disease and the control of inflammation. The current mainstream direction of nanoscaffold research is based on multifunctional gradient scaffolds (Figure 6(c)) [22]. Such scaffold materials can also be combined with 3D printing technology to obtain more precise dimensions. Based on this, a relatively reasonable scaffold pattern is composed as follows: The upper layer of this scaffold (contact layer with epithelium) is generally made of synthetic polymer, whose excellent hydrophobic property can be used as a similar membrane material to isolate epithelial cells from attaching to the root surface, and the surface of the polymer can be modified with FGF to promote soft tissue regeneration or with antibacterial drugs to enhance antibacterial ability. The lower layer of the scaffold (the contact layer with the root) is mainly NHAP or chitosan, which can be used to induce bone regeneration. This multifunctional

gradient scaffold model is also a popular research direction at present [197–200].

Antibacterial and osteogenesis are therapeutic strategies for periodontal disease. However, due to the particularity of disease treatment, the design of periodontal antibacterial or osteoblast materials is different from that of dental diseases. In particular, periodontal antibacterial therapy is closely related to the oral microenvironment. In order to avoid the imbalance of oral flora, we need to improve the stability and local retention effect of periodontal antibacterial materials. Due to its viscoelasticity, hydrogel is a traditional drug carrier widely used for the injection of periodontal antibiotics, while the new carrier similar to the micronedle patch is more suitable for mucosal local immunotherapy of periodontal soft tissue. For periodontal tissue engineering, various forms of scaffolds have been developed one after another, and have demonstrated good bone formation ability. However, the research and development process of scaffolds still needs to consider the difficulty of clinical operation, and finally be applied in clinical practice.

5. Prosthodontics

Prosthodontics is a discipline most closely related to materials science and involves the restoration of missing teeth. Whether wearing a removable denture or a fixed denture, the precise restoration method can improve the patient's experience. Although some digital technologies such as CAD/CAM, 3D-printing technology, and implant robotic technology have greatly improved the accuracy of traditional restoration methods. However, it is worth noting that traditional restoration methods sometimes ignore the relationship between restorations and oral-jaw functions. For example, patients often choose restorations with high mechanical strength, which are much stronger than enamel and may increase abrasion on teeth as well as the incidence of biting disease with prolonged use. This shows the importance of balancing the various physicochemical properties of the restoration. Therefore, this section classifies commonly used restorations, focuses on the biological applications of new materials and technologies in different restorations, and summarizes them in Table 3.

Table 3. Application of nanomaterials in prosthodontics.

Application	Nanocarrier	Core nanoparticles	Key features	Ref
Drug delivery	Hydrogel	nCur	High bioavailability, suitable for topical application.	[150–152]
		CS+atorvastatin/ lovastatin	Anti-inflammatory and bone-enhancing effects.	[153]
		AgNPs	High bioavailability and lower toxicity.	[154]
	Nanofiber	PCL+Cip	Hydrophobic properties extending drug release time.	[201]
		mPEGPCL+Protein kinase inhibitors	Long-term stable antibacterial effect.	[158]
	Nano Microneedle	Tetracycline	Reduction of mucosal immunity and extended antibacterial time.	[21]
	Nanocapsules	AgNPs + antibiotics	Stronger antibacterial effect and lower toxicity.	[144]
		Nano-baicalin+CHX	Maintaining antibacterial and anti-inflammatory properties while reducing the side effects of CHX.	[147,148]
	Biomimetic cell membrane	Treg cell membrane	Endowing drugs with broad-spectrum immunomodulatory capabilities.	[141]
	PTT	GNC	Controlled drug release.	[168]
	PDT	sPDMA+ICG	Increasing the ability to target bacteria.	[173]
Tissue engineering	Inorganic nanoscaffold	NHAP	High osteoconductivity and biocompatibility.	[182]
		NHAP	Angiogenesis in early bone defect healing; Promotes osteogenesis	[181]
		NHAP+CG	Different morphologies have different effects on hiPSCs.	[183]
		NHAP+MgNPs	Improving antibacterial potential; Promotes cell proliferation; Migration and angiogenesis.	[185]
		NBG+AgNPs+CS	Enhanced antibacterial activity; Bioactivity; Controlled degradation; Non-toxic to cells	[189]
		NHAP	High osteoconductivity.	[202]
	Synthetic polymer scaffold	PLA	CS promotes the mechanical properties of PLA; PLA changes CS hydrophobic properties.	[195]
		PCL	Demonstrates both the antibacterial ability of MET and the osteogenic ability of NHAP.	[197]
		PLA	Improved mechanical properties and hydrophilicity.	[190]
		PCL	Good biocompatibility and good osteogenesis.	[199]
		PCL	Support materials that can be processed into specific structures by the MEW process	[185]
	Natural	CS+CC	Higher proliferative/metabolic activity.	[197]
	Biodegradable	CS	Promoting the regeneration of oral soft tissue defects.	[179]
	Polymer scaffold	CC+β-TCP	Improved compressive strength and cytocompatibility; Greatly enhanced periodontal tissue repair.	[203]
		CS	High load capacity enhancement; Excellent mechanical strengthening properties.	[198]

5.1. Removable denture

A removable denture is a self-retaining prosthesis that uses natural teeth or the alveolar ridge mucosa for retention. It consists of removable partial denture and complete denture. Denture base is one of the most critical components of the restoration, providing the framework for the entire removable denture and providing the largest area of contact with the mucosa. In clinical practice, the most used base material is polymethylmethacrylate（PMMA）, which is simple and cheap to make. However, its disadvantages are also obvious, such as poor mechanical strength, easy cause of bacterial accumulation and poor comfort [114]. To solve these problems, various nano-modification technologies for PMMA have been developed to improve the mechanical strength as well as the antibacterial ability of the denture base.

5.1.1. Mechanical strength

It has been proven in numerous tests that the use of nanoparticles can effectively improve the mechanical strength of PMMA. The product type, particle size and concentration of fillers will have different effects on the mechanical properties of PMMA. Zirconium oxide (ZrO_2) is a widely used metal oxide, one of the most commonly used materials for dental restorations due to its high mechanical strength, good surface properties, and good biocompatibility and biological properties. ZrO_2 NPs can be used as a filler for PMMA among them and be effective in increasing the mechanical properties of PMMA [104,105]. Studies have shown that adding 2.5% ZrO_2 NPs can be the best impact strength of PMMA [106]. 3.0% $ZirO_2$ NPs can obtain the best bonding properties [107], and 5.0% ZrO_2 NPs can improve the tensile strength of PMMA [108]. These experiments proved that the nanofiller has a specific concentration dependence. Also, silane-treated zirconia nanofillers can further improve the surface hardness and flexural strength of PMMA – zirconia nanocomposites [109]. Based on this, another study has been conducted to add alkylated ZnNPs as well as aluminum borate whiskers (ABWs) to PMMA at the same time, where the flexural strength of PMMA is significantly increased [204].

Of course, in addition to ZrO_2NPs, SiO_2NPs [111], TiO_2 NPs [110], ZnNPs [112], and diamond [113] have been shown to be effective in improving the mechanical strength of PMMA. Without affecting the strength and weight of PMMP, adding Al_2O_3 and SiCNPs can improve the thermal conductivity of PMMA and increase the comfort of use [114].

5.1.2. Antibacterial properties

Due to the porous and hydrophobic properties of PMMA, long-term denture wear, especially in the elderly population, often causes microbial accumulation, which can affect the oral mucosa or teeth of the wearer, and may cause denture stomatitis in severe cases. In contrast to the mechanical properties, adding nanoparticles with the antibacterial ability and improving the hydrophobicity of PMMA are two ways to improve the antibacterial ability of PMMA. The antibacterial properties of AgNPs have been utilized to achieve specific antibacterial effects by combining AgNPs with PMMA or attaching them to the PMMA surface in the form of a coating [115,116]. Adding chitosan nanoparticles to PMMA due to their unique antibacterial properties against Candida can effectively reduce the colonization of oral mucosa by fungi [117].

On the other hand, using nanomaterials to change the hydrophobic properties of PMMA to hydrophilic can effectively increase the scouring effect of saliva on the surface of the substrate, which is also an antibacterial idea. Studies have shown that adding graphene oxide nanoparticles (nGO) to PMMA can effectively increase its hydrophilic ability, demonstrate long-lasting antibacterial ability, and improve the mechanical strength of PMMA to a certain extent [118,119]. TiO_2 NPs and SiO_2 NPs have certain antibacterial abilities and can also increase the hydrophilic property of PMMA to a certain extent, achieving a dual antibacterial ability [205–207].

A more desirable material has recently been developed by adding 1% TiO_2 NPs as well as 1% poly(ether-ether-ketone) (PEEK) material to PMMA using 3D printing technology, which not only has superior mechanical and antibacterial properties but also exhibits a smooth surface and precise resolution [120]. Thus, it is evident that nanomaterials and technologies bring a more comfortable experience to patients who wear a denture for a long time.

5.2. Implant denture

For missing teeth, implant restoration is one of the most popular restoration methods. The main advantages are strong retention and no need for repeated removals. Achieving good initial stability and avoiding peri-implantitis are two critical factors for the success of implant restorations. Achieving this goal requires starting from the following two points. The first is to choose the right implant. Different implant designs differ significantly in osteogenesis and mechanical strength, such as choosing implants with antibacterial ability or implants with the pro-osteogenic ability [128,208]. Secondly, a large part of implant surgery's success depends on the doctor's proficiency. In addition, in order to further increase the success rate of the implant surgery, some new technologies such as 3D printing technology and human-robot collaborative dental implant system (HRCDIS) can effectively increase the accuracy of implantation and reduce the

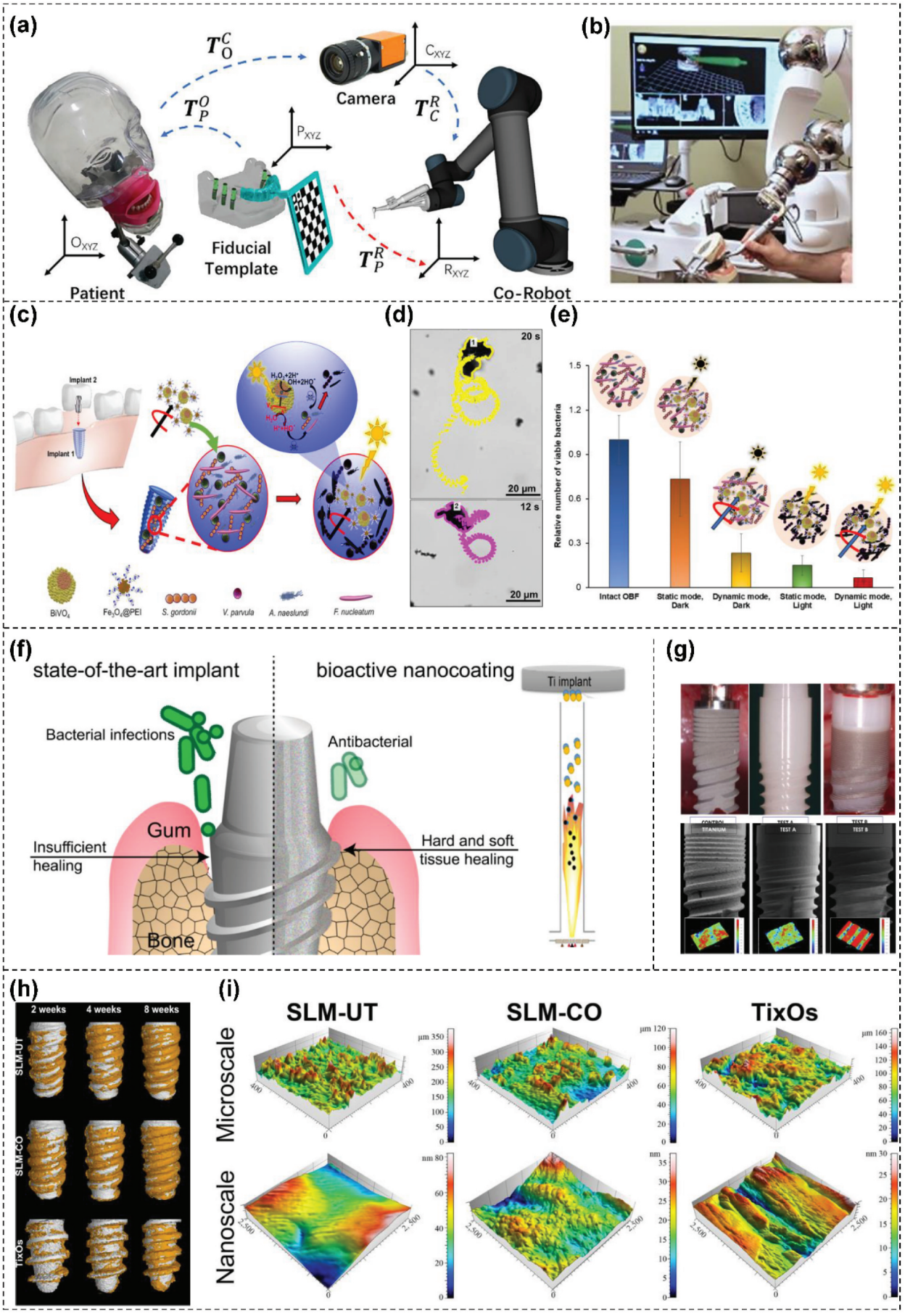

Figure 7. Advanced materials and technologies in dental implants. (a,b) Human-robot collaboration interaction of human-robot collaborative dental implant system (HRCDIS). Reproduced by permission from [209], copyright 2022, Wiley. (c – e) Schematic representation of oral antibiofilm activity of photoactive Fe_3O_4@PEI/$BiVO_4$ magnetic microrobots. Reproduced by permission from [23], copyright 2022, American Chemical Society. (f) One-step synthesis of versatile antimicrobial nano-architected implant coatings for hard and soft tissue healing. Reproduced by permission from [210], copyright 2021, American Chemical Society. (g) Optical and scanning electron microscopy (SEM) images of different implant types studied. Reproduced by permission from [211], copyright 2013, Wiley. (h,i) Application of nano-modification technology in the field of promoting osseointegration of implants. Reproduced by permission from [212], copyright 2020, Frontiers.

complications of long-term application of implants. HRCDIS is more precise regarding the direction of implant placement and the amount of force applied to the implant compared to a purely perceived operation (Figure 7(a,b)) [209,213]. This section introduces some new materials and technologies used in implant restoration.

5.2.1. Antibacterial properties

The primary material used for implants is titanium, a metal with good biocompatibility. It has the disadvantage of not having antibacterial properties, and bacteria tend to collect and adhere to its surface, leading to infection problems [214]. Peri-implantitis is often the leading cause of implant failure. The antibacterial ability of nanomaterials can also be applied in implants. One idea is to use materials or drugs with antibacterial ability to prepare a coating and modify it onto the implant surface to achieve an excellent antibacterial effect [215]. For example, ZnNPs were prepared as a coating and modified on the implant surface, and the results showed a significant reduction in the number of parthenogenic anaerobic bacteria and streptococci in the medium within 96 hours in an *in vitro* test compared to implants without the modified coating [121]. In addition, Wang et al. synthesized ZnO nanorods and ZnO nanorods using the hydrothermal method. Then ZnO nanorods were first covered with Ti surface, and finally, ZnNPs and ZnO nanorods were modified as the outermost layer. This coating can rapidly release ZnO nanorods, and the continuous release of ZnO nanorods can achieve a dual antibacterial effect [122]. In addition, the nanocerium oxide (CeO NPs) coating application was shown to reduce the average gene expression of tumor necrosis factor-α(TNF-α), interleukin-6 (IL-6), and interleukin-1b (IL-1b) in per titanium tissues, resulting in a powerful anti-inflammatory effect [123].

AgNPs play key role in preventing peri-implantitis [216]. Considering the toxicity of silver ions, the modification of AgNPs alone on the implant surface may cause certain damage to bone tissue. AgNPs usually need to be processed before they can be better used in implant restoration. For example, using CS as a stabilizer and reducing agent, AgNPs were biosynthesized by a simple 'green' method, and a loaded carrier was constructed on an alkali-heat-treated titanium (Ti) substrate by a layer-by-layer (LbL) self-assembly technique. The CS heparin polyelectrolyte multilayer membrane (PEM) of AgNPs can be used to form a continuous antimicrobial coating [217]. Wang et al. found that the MBG – Ag coating can convert the hydrophobicity of the titanium implant surface into hydrophilicity, and this mesoporous structure can also prolong the antibacterial time by controlling the release of Ag. May help prevent and treat early implant failure and peri-implantitis [218]. These results suggest that nanosilver coating is a promising material with antibacterial properties for implant abutments and prostheses to prevent peri-implantitis.

Cu^{2+} are thought to favor soft tissue healing due to their angiogenic and antimicrobial functions, a property that makes them uniquely advantageous in implant restorations. Studies have shown that CuNPs have obvious killing effects on *Staphylococcus aureus* (Sa) and *Escherichia coli* (Ec) [219,220]. Doping CuNPs into bioglass and modifying its coating into TiO_2 by electrophoretic deposition can enhance endothelial cell migration and reduce bacterial growth [221]. Zhu et al. proposed a surface design strategy to fabricate specific microgrooves patterns on the titanium surface and then sequentially deposit a nanostructured copper -containing tantalum (TaCu) layer and a pure Ta cap layer, This structure significantly enhanced osteogenic differentiation in vitro, while the controlled local sustained release of Cu^{2+} also maintained efficient antimicrobial activity [222]. These results demonstrate that designing implants with a copper core is a viable approach.

Recently, a nanorobot using a magnetic field and light as power sources has been developed. The study shows that a dual mechanism can effectively remove biofilm on the implant surface (Figure 7(c)). This nanorobot modification to the implant surface is activated by a programmed magnetic field as well as a light source, which mechanically removes the biofilm from the implant surface and achieves long-term antibacterial stability (Figure 7(d,e)) [23]. These results indicate that new technology and materials have specific application prospects in antibacterial implants. However, high concentrations of antibacterial materials tend to produce some cytotoxicity, so attention should be paid to applying phase nanomaterial preparation when applying safety.

5.2.2. Osseointegration

Nanocoating technology can be used not only to enhance the antibacterial capacity of the implant but also to modify the implant to promote its osseointegration capacity. For example, a scalable liquid-feed flame spray pyrolysis (LF-FSP) technique was used to construct a one-step synthetic nanostructured tissue-specific coating (Figure 7(f)). The coating is composed of CeO NPs and BG, and the composition of the material can be adjusted to achieve different soft and hard tissue healing patterns, thus giving individualized implants to different patients [210]. In addition, modification of graphene nanoparticles to the rough surface of the implant increases the hydrophilic properties of the implant surface, and graphene has good biocompatibility. And it does not have specific effects on osteoblasts and osteogenic differentiation of bone marrow MSCs induced by nGO through the

FAK/P38 pathway [125,126]. Hydrophilic implants have been clinically shown to enhance the osseointegration of implants and shorten the osteogenic time [223]. Similarly, SiO_2 nanoparticle modification to the implant surface enhances the roughness as well as the hydrophilic properties of the implant surface [127]. In addition, modification of some materials that can induce osteoblast development, such as NHA [128], nBG [129], and CaNPs [130] in the nanoporous structure of the implant, can enhance the osteogenic capacity of the implant surface.

The roughness of the implant surface often affects the osseointegration capacity of the implant. Applying the sandblasting and acid etching technique increases the roughness of the titanium surface on a macroscopic level, which has been proved in clinic complications. The microgroove surface allows for more excellent osseointegration of the titanium and zirconia implants (Figure 7(g)). Compared to this technology, studies have shown that, the osseointegration strength produced by nanoscale titanium surface roughness is more significant than that of medium- and micron-sized titanium surfaces [224]. For example, Selective laser melting (SLM) builds nanostructures on the implant surface to create a hierarchical micro-nanomorphology that significantly promotes the osseointegration of the implant over an 8-week observation period (Figure 7(h–i)) [212]. To investigate the effect of different nanopatterns on the osseointegration of implants, Zhou et al. used microgrooves and nanotubes to prepare different morphological nanopatterns on the implant surface, and then found through the study that the groove pattern of 2 μm deep and 10 μm wide combined with nanotubes of 85 nm diameter is favorable for the attachment of osteoblasts, the groove structure of 3.6 μm deep and 10 μm wide covered by nanotubes of 55 nm is suitable for the attachment of fibroblasts, the 85 nm diameter nanotubes covered with a groove structure 2 μm deep and 5 μm wide are more favorable for epithelial cell attachment, and the 2 μm deep and 10 μm wide groove can produce greater inhibitory ability against *P.g.* Based on this conclusion, an optimal combination can be achieved by promoting epithelial cell attachment in the cervical part of the implant and osteoblast attachment in the root [124]. Thus, the use of nano-modification techniques can give implants specific properties according to clinical needs, thus increasing the success rate of implants.

5.3. Fixed denture

A fixed denture is a crown fixed to an implant or abutment tooth using screws or bonding agents. As various processing technologies have matured, the hardness and aesthetics of various crowns have improved dramatically. For example, CAD/CAM technology can be used to design dental implant crowns and greatly improve dental restorative procedures, which significantly shortens the time required to design and process restorations (Figure 8(a)) [225]. AI technology can be used to analyze occlusal morphology and thus automate the design of crown morphology (Figure 8(b)) [226]. Recently it was demonstrated that additive manufacturing technology can be used for designing and processing porcelain fused to metal (PFM) crowns. This study manufactured multilayer crowns with gradient colors and structures using a material jet printer. In the manufacturing process, different materials of different colors and properties were used and mixed in different ratios to achieve different desired designs (Figure 8(c,d)) [227].

In addition to applying new technologies in the design of restorations, the creation of several new materials has also contributed to the development of restorative dentistry. PEEK is a high-performance polymer with durability against corrosion and wear, and excellent tribological properties compared to alloys and ceramics. With the help of CAD/CAM technology, metal-free, lightweight prosthetic frames can be produced to replace structures made of traditional materials, especially for fixing sleeve crowns or implants (Figure 8(e)) [228]. In addition, nano-ceramic resin is a nanomaterial used for processing crowns. Although it is less hard than ZrO_2, its high flexural strength, low abrasiveness, and easy polishability make it more suitable for CAD/CAM chairside restorations. This material was first introduced by Lava Ultimate (3 M) and was shown in a 5-year clinical study to be indistinguishable from glass-ceramic when used [131]. In another comparison of materials for temporary crown restorations, nano-ceramic resin demonstrated superior marginal fit and comfort [132]. With the help of CAD/CAM technology, the custom-made cores fit the dentin more closely, and the material itself is the flexibility of the material itself can effectively reduce the appearance of root fractures [133]. 3D printing combined with a programming technique to assemble NHAP in a particular order, resulting in a denture with excellent mechanical properties and ideal bioactivity, especially suitable for chairside restorations (Figure 8(f)) [24].

Some known bonding agents in clinical practice have strong bonding power. However, these agents can have some toxic effects on gingival epithelial cells when they enter the gingival tissue, which makes them more complicated to operate in clinical practice. Similar to filling materials, adding some nanomaterials to bonding agents can give them some antibacterial ability and promote remineralization of dental hard tissues, which is the direction of new bonding agent development. For example, adding ZnNPs to zinc polycarboxylate cement showed that this approach increased their antimicrobial, mechanical, and acid resistance properties and maintained outstanding biocompatibility [134]. A new bioactive

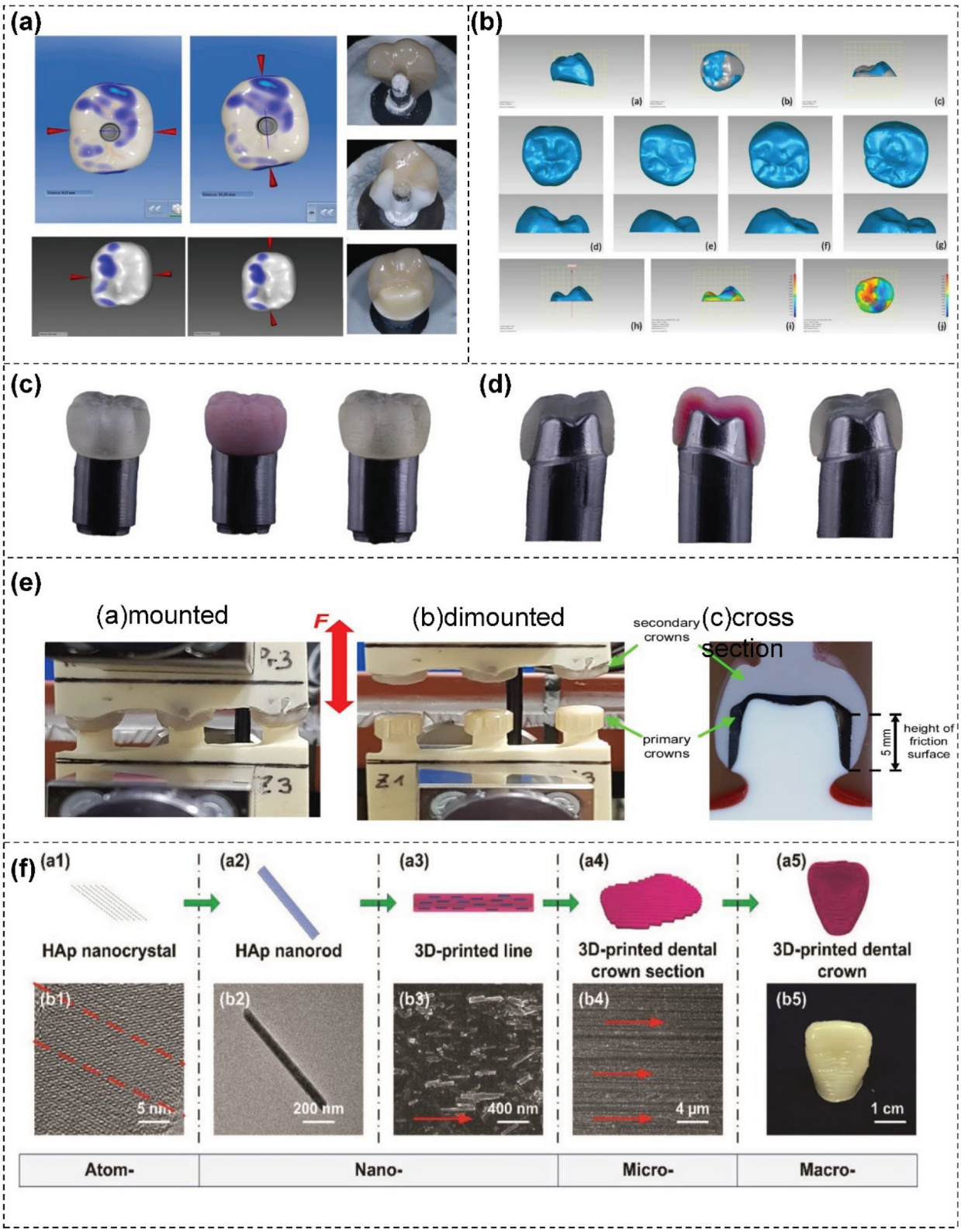

Figure 8. Advanced materials and technologies for dental crowns. (a) Application of CAD/CAM technology in the field of dental implant crown design. Reproduced by permission from [225], copyright 2021, Wiley. (b) Morphology and fracture behavior of lithium disilicate dental crowns designed by human and knowledge-based AI. Reproduced by permission from [226], copyright 2022, Elsevier. (c,d) Additive manufacturing technologies in the field crown design. Reproduced by permission from [227], copyright 2021, American College of Prosthodontists. (e) Design of PEEK based telescopic crowns. Reproduced by permission from [228], copyright 2021, Elsevier. (f) Construction process of the multi-scale highly aligned HAP nanorod structures. Reproduced by permission from [24], copyright 2021, Wiley.

crown cement combining DMAHDM and NACP, which is capable of long-lasting Ca^{2}+ and PO_4^{3-} particles, thus promoted remineralization of dental tissues [135]. Nevertheless, the new cement's

mechanical properties and bonding ability need to be further validated before they can be used in clinical practice.

Prosthodontics is one of the disciplines most closely related to materials and new technologies. With the maturity of digital technology and 3D printing technology, the precision of various restorations is gradually improving. At present, the processing of removable dentures and implants is mainly based on coating technology. This design concept depends on patients' oral conditions and economic conditions. As long as the toxic effects of materials are solved, it can be applied in clinical practice earlier. Considering that the mechanical strength of dental crowns in the market is too high, and considering the damage to the jaw teeth, perhaps the appearance of bionic dental crowns can better solve this problem, but the bond strength should also be an important factor to be considered when making dental crowns.

6. Oral cancer

Oral cancers are one of the common diseases of the oral cavity, among which squamous cell carcinoma (SCC) is the most common. Smoking, alcohol consumption, and chewing betel nut are considered major risk factors for oral squamous cell carcinoma (OSCC) [229,230]. To date, the 5-year survival rate for surgically expanded resection of oral malignancies is only 50%, and postoperative patients often experience changes in facial appearance and function [231]. Conventional radiotherapy is only available as an adjuvant treatment for oral malignancies and is accompanied by severe adverse effects [232]. Moreover, the response rate of OSCC to most immunotherapies is meager.

As mentioned above, each strategy of oral cancer treatment has certain disadvantages. The application of nanomaterials and new technologies can somewhat solve these problems. For example, nanomaterials can improve the clarity of tumor imaging, attenuate the side effects of chemotherapy drugs, and improve the targeting of antitumor drugs [233]. Although there is not much research on nanomaterials for oral cancer, these materials play an essential role in oral cancer. We summarized various new techniques or materials applied in diagnosing and treating oral cancer since 2006 (Figure 9).

6.1. Diagnosis of oral cancer

The aggressive nature of oral cancer makes it difficult to precisely identify tumor tissue demarcation lines, which often causes some difficulties for clinicians. Accurate imaging is of great importance in guiding surgical resection of tumors. In recent years, the enhanced permeability and retention (EPR) effect of nanomaterials has played a great role in tumor imaging. This section describes some diagnostic methods applied to oral cancers.

6.1.1. AI

AI is a technology that utilizes machines to mimic intelligent human behavior. Using AI technology to diagnose oral cancer is fast, efficient and economical. Unlike other methods, AI does not require any

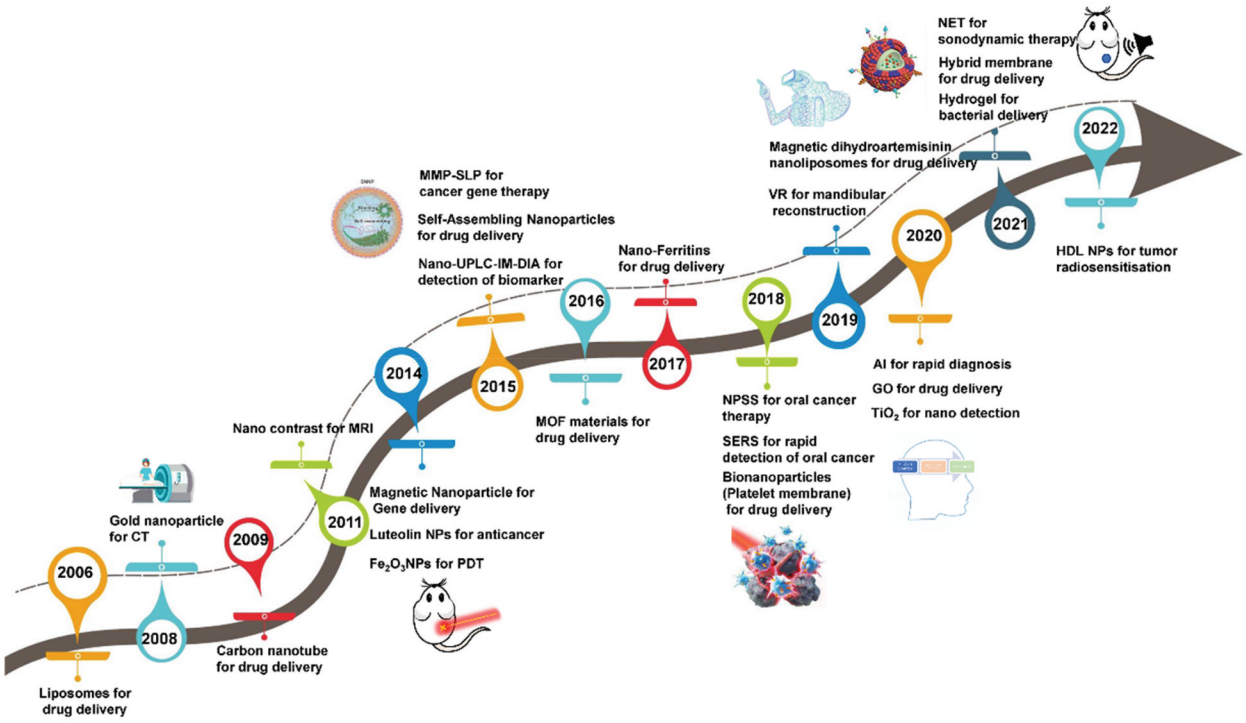

Figure 9. Development of materials and technologies in the treatment of oral cancer in 2006–2022.

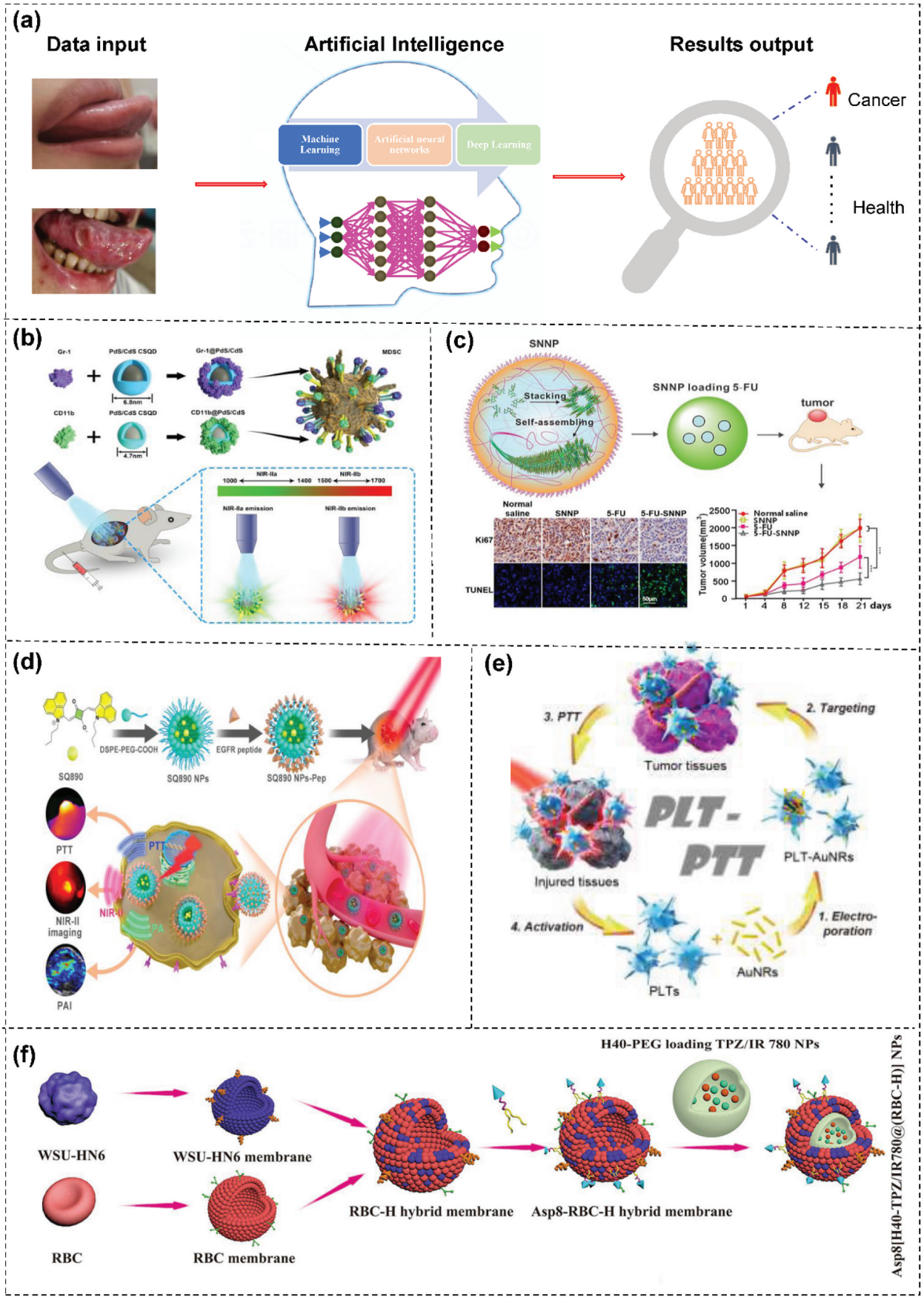

Figure 10. Advanced materials and technologies in oral cancer. (a) Application of AI technology in rapid diagnosis of oral cancer. (b) Application of NIR-II window-based nanoprobes in monitoring of the immune cell population *in vivo* to effectively assess the tumor progression. Reproduced by permission from [234], copyright 2019, American Chemical Society. (c) Self-loading nanoparticles for chemotherapy drug delivery. Reproduced by permission from [235], copyright 2015, American Chemical Society. (d) Schematic illustration of the NIR-II dye SQ890 and the EGFR-targeting nanoparticle SQ890 NPs-Pep for photoacoustic/nir-II fluorescence dual-modality imaging-guided PTT of oral cancer. Reproduced by permission from [236], copyright 2022, Springer. (e) Platelet-facilitated photothermal tumor therapy (PLT-PTT). Reproduced by permission from [237], copyright 2018, Wiley. (f) Application of hybridized membrane technology for drug delivery. Reproduced by permission from [28], copyright 2021, BMC.

materials, complex equipment, or even a dentist to diagnose oral cancer. Fu et al. developed an algorithm system by deep learning of many OSCC and normal oral tissue pictures. The final comparison with the clinical-pathological results shows that the accuracy rate has exceeded 90% (Figure 10(a)) [14]. This technology is only the prototype of AI technology and has certain limitations in clinical application [238]. However, with the development of AI technology, diagnosing OSCC will be more convenient, and patients can be reminded to seek medical treatment in the early stage of the disease, thereby reducing the difficulty of surgery and complications.

6.1.2. MRI

Magnetic resonance imaging (MRI) is one of the most commonly used imaging methods in clinical practice to evaluate primary tumors and bone invasion [239]. The traditional contrast agent enters the circulation after intravenous injection, typically has a metabolism time of 1–1.5 hours, and does not accumulate specifically in the tumor. The interpretation of such imaging results depends entirely on the clinician's experience.

Nanocontrast agents can identify unique cell surface markers and extend the half-life of blood circulation, allowing for shorter imaging times and increased imaging accuracy in clinical applications [240]. Shanavas et al. developed a contrast agent containing folic acid, chitosan and magnetic poly (lactic acid-glycolic acid) (PLGA) nanoparticles, which shortened the overall T2 relaxation time and significantly improved the imaging contrast [241]. Another novel magnetic nanocontrast agent is based on Gd^{3+}-doped amorphous TiO_2 for T1-weighted MRI, where folic acid-coupled nanoparticles specifically aggregate on the surface of folic acid receptor-positive oral cancer KB cells to produce precise imaging results [242].

6.1.3. Optical imaging

Optical imaging systems have been intensively studied for cancer diagnosis, respectively. Gastrin-releasing peptide receptor (GRPR) is an important target for OSCC imaging and therapy [243]. Li et al. successfully prepared gastrin-releasing peptide receptor-specific nGO nanoprobes for near-infrared fluorescence imaging of OSCC. The probe has the characteristics of large surface area, good water dispersibility, good biocompatibility, easy surface modification, and low manufacturing cost. Furthermore, it has a high binding affinity and specificity to GRPR-positive HSC-3 cells, which enhances the imaging effect [244]. In our previous experiments, we used the quantum dot (QD)-based overlap-free emission nanoprobes in a second NIR window (NIR-II, 1000) for analyzing the dynamic expression of MDSCs in the tumor microenvironment (TME) (Figure 10(b)). The result shows that NIR-II fluorescent nanoprobes with molecular targeting capability can be used as a real-time monitor for changes in the in vivo immune cell population to assess tumor progression [234]. These experimental results demonstrate the considerable potential of optical imaging systems for diagnosing oral cancer.

6.1.4. Surface-enhanced raman spectroscopy

Raman spectroscopy is a near-field effect with a low penetration depth, and its clinical application is limited by the weak Raman signal intensity and slow spectrum acquisition speed [245]. The ability of metal nanoparticles to enhance Raman signals has been widely used in various biological fields, especially in cancer. The labeled surface-enhanced Raman scattering (SERS) method is helpful for the diagnosis of oral cancer. Girish Chundayil Madathil et al. designed and demonstrated a SERS catheter device using TiO_2 nanostructures and 30 nm-sized AgNPs decorations. Upon contact with the tissue, the sensor part of the device formed by nano-leafy TiO_2 substrate decorated with Ag nanoparticles enhances the Raman signatures from the tissues. Then using PCA-DA to analyze the spectral changes associated with pathological changes can quickly and effectively identify the degree of differentiation of OSCC [246,247].

6.1.5. Detection of biomarkers

In addition to the above methods, using tumor biomarkers to detect oral cancer is feasible. However, single cancer biomarkers generally do not provide high sensitivity and specificity for reliable clinical cancer diagnosis [248]. Nassar et al. developed the nano-UPLC-IM-DIA bioassay as a viable method for identifying and quantifying proteins in complex samples without the need for stable isotope labeling [249]. This method can effectively detect the expression of interleukin-6 (IL-6), IL-8, VEGF-A, and VEGF-C which are useful in the diagnosis of oral cancer [250]. These results have important implications for rapid tumor diagnosis and prediction by monitoring proteins associated with cancer development and progression.

6.2. Drug delivery in oral cancers

6.2.1. Chemotherapy drugs

Chemotherapeutic agents commonly used in oral malignancies include platinum drugs, 5-fluorouracil (5-FU), paclitaxel (PTX) and doxorubicin (Dox). The application of conventional chemotherapy drugs often brings many side effects, such as nausea, vomiting, hair loss, liver and kidney function damage, drug resistance, etc [232]. Loading chemotherapeutic drugs through nano-delivery systems is a feasible way to enhance the targeting of chemotherapeutic drugs and reduce side effects.

For example, a self-assembled nucleoside nanoparticle (SNNP) was designed to deliver 5-FU in 2015. Unlike free 5-FU, SNNP loaded with 5-fluorouracil (5-FU-SNNP) significantly delayed tumor growth. The results of HE staining showed that the drug did not cause damage to related tissues and organs after two weeks of intraperitoneal administration. This indicates that SNNP effectively reduces the side effects of 5-FU. Finally, by comparing the drug concentration and metabolism distribution of 5-FU in various organs and tumors, it can be found that SNNP plays a slow-release and passive targeting role (Figure 10(c)). This suggests that SNNP is an effective chemotherapeutic drug carrier [235].

In addition to passive targeting, with the development of drug delivery systems, some drug carriers with active targeting capabilities have also been developed. For example, utilizing the ability of folic acid to target OSCC, the development of folic acid NPs loaded with PTX can effectively reduce the adverse drug reactions and have obvious tumor-suppressive effects *in vivo* [251]. Not only the targeting ability of the drug carrier itself, other properties of the drug carrier are also worthy of attention. For example, the controllable degradability and stability of the drug carrier and the anti-tumor effect of the carrier. A current study uses nanoparticles assembled with resveratrol glycosides (Polydatin) and PLGA, which have strong antioxidant activity, can reduce tissue lipid peroxidation, relieve the effect of exogenous metabolic enzymes, and assist chemotherapy drugs to achieve inhibition tumor purpose [27]. Chemotherapy drugs have been confirmed to kill tumor cells in the clinic, and rationally designed drug carriers will bring hope to OSCC patients.

6.2.2. Photosensitizers

Due to the limitation of light penetration in the tissue, PTT is more suitable for superficial malignancies such as oral squamous carcinoma and skin cancer. In most cases, PTT can be used as a switch for nano-pharmacotherapy to target the activation of drugs or materials with photothermal counterparts, often achieving unexpected results. However, the problems of single heavy state oxygen ($^1O_2$) quantum yield and long-term phototoxicity are inevitable in applying conventional photosensitizers. Therefore, it is necessary to process conventional photosensitizers or develop new ones.

Sulfur-doped carbon dots (S-CDs) as a novel nano-photosensitizer which can automatically enter TME and triggers cancer cell death potently under light exposure. By detecting the expression of apoptotic proteins, the study also observed that S-CDs-treated UM1 cells expressed higher levels of apoptotic proteins at the same concentration compared to UM1 cells treated with the classical photosensitizer 5-ALA [252]. In addition, the second-generation photosensitizer aluminum phthalocyanine (AlClPc) has a limited clinical application due to its tendency to aggregate in water. Some studies can effectively solve these problems by coating this material with liposomes [253]. This suggests that different drug carriers can act in multiple ways.

In addition to conventional photosensitizers, some nano-photothermal platforms with high photothermal conversion efficiency have been developed. Zhang et al. developed a co-assembled nano-photothermal platform, CPCI-NP, with superior photothermal conversion efficiency, efficient encapsulation and controlled release of cytotoxic molecules and immunomodulators. CPCI-NP, by loading adriamycin, proved to be an efficient combined photothermal/chemotherapy nanoplatforms for the treatment of in situ osc3 oral cancer xenograft models [254]. Another photothermal platform (CS- TPP-(shMTHFD1 L-ALA)- pdt) can inhibit OSCC cell proliferation and induce apoptosis by downregulating MTHFD1 L expression while mediating photodynamic effects and can also induce mitochondrial dysfunction by promoting ROS accumulation in OSCC cells, demonstrating unique antitumor effects [255].

Of course, most of the current photothermal conversion agents (PTAs) for oral cancer treatment are NIR-I region materials. As processed PTAs, NIR-II region photosensitizers have been developed one after another. These materials have high photothermal conversion efficiency, high photothermal stability and high penetration. Recently, the NIR-II dye SQ890 has been developed for tumor imaging and PTT of oral cancer. By assembling into nanoparticles and modifying with the epithelial growth factor receptor (EGFR)-targeting peptide GE11, SQ890 NPs-Pep can be specifically accumulated at the tumor site by active targeting, enabling photoacoustic/NIR-II fluorescence dual-mode imaging to guide PTT of oral cancer (Figure 10(d)) [236]. The results of these photothermal nanoplatforms also suggest that PTT has broad application prospects in oral cancers.

6.2.3. Bionanoparticles

Although nano drug delivery systems have demonstrated excellent effects in oral malignancies, low targeting ability and inefficient cycle times limit the clinical application of nano drug carriers due to the peculiarities of the human immune system [256]. The use of composite cell membranes to camouflage nanoparticles is the current approach to solve this problem. The synthesized bionanoparticles retain the physicochemical properties of synthetic nanoparticles while inheriting the biological functions of the source cells.

For example, Rao et al. wrapped gold nanorods with platelet membranes, combining the ability of platelet membranes to accumulate in the tumor and the photothermal properties of gold nanorods to

achieve a controlled treatment method for oral cancer in 2018 (Figure 10(e)) [257]. Specific cell membranes can be selected when targeting different tumors to increase targeting ability. Cheng et al. processed WSU-HN6 cell and red blood cell (RBC) hybrids into composite membranes wrapped with H40-PEG nanoparticles, a material that not only inherits RBC immune escape capability but also possesses WSU-HN6 cell-mediated bone targeting capability, an effective multi-targeted drug delivery platform for precise anti-cancer during bone invasion in OSCC treatment (Figure 10(f)) [28]. In addition, With the understanding of various immune cells or tumor cells, more and more cell membranes or extracellular vesicles will be extracted for drug delivery, thus effectively solving the problems faced by current drug carriers.

6.2.4. Other drugs

In addition to chemotherapeutic drugs, some non-cancerous chemotherapeutic drugs, as well as metal ions, genes, proteins and peptides, etc, can achieve the ability to specifically activate the immune system or directly and specifically kill tumor cells after being processed by nano-drug delivery systems [258]. These materials can play a role in the treatment of tumors in three different ways: by targeting cancer cells, TME, or the peripheral immune system [259].

Atipine (QC), an anti-malarial drug, was found to produce anticancer effects by acting as a DNA inserter and topoisomerase inhibitor. Some scholars processed gold nanoparticles with QC and showed that the synthesized hybrid nanoparticles could significantly inhibit cell proliferation, cause apoptosis, and disrupt angiogenesis and tumor regression *in vitro* [260]. miR-214 has been identified as a promoter of OSCC invasion and metastasis [261]. Using the excellent physicochemical properties and strong adsorption of graphene nanomaterials to process miR-214 inhibitors, the results demonstrate that this inhibitor can effectively inhibit intracellular miR-214, reduce OSCC cell invasion and migration by targeting PTEN and p53, and increase cell apoptosis [262,263].

Many studies have shown that microorganisms in the oral cavity and digestive tract correlate with tumor cells [264]. A recent interesting study found that *Streptococcus peptostreptococcus* had some inhibitory effect on oral squamous carcinoma cells and that this bacterium could escape the antibacterial power of AgNPs. On this basis, Zheng et al. developed an AgNPs-containing hydrogel system that combined the antibacterial properties of the broad-spectrum of Ag+. They used the silver nanoparticle-containing hydrogel in a tumor model to enhance the targeting ability of *Streptococcus gastricus* to OSCC by inhibiting other oral microorganisms from making *Streptococcus gastricus* the dominant oral microorganism, thus achieving an inhibitory method of tumor suppression [265].

6.3. Digitization technology in oral cancer

Digitization technology refers to a computer, communication engineering, etc., to express, transmit and process information technology. In recent years, the development of digital technology in the medical field has been evident to all. In January 2019, the Stomatological Hospital of Wuhan University used AR technology combined with MR imaging technology to successfully and accurately reconstruct the jaw shape after mandibular tumor resection. In August 2020, Wuhan University Stomatological Hospital used 5G technology and 3D navigation technology to remotely complete an operation for a cleft lip and palate patient in another city. After the resection of oral cancer, the use of PEEK material for jaw reconstruction can not only effectively reduce the damage caused by font bone graft, but also accurately restore jaw shape combined with 3D printing technology [266]. These cases show that digital technology has great application prospects in the field of oral and maxillofacial surgery. Previous reports have shown that using VR technology can effectively relieve anxiety during treatment in oral patients [267]. With the development of imaging systems, VR technology can perfectly replicate the patient's disease model, which is conducive to preoperative communication between doctors and patients and formulating treatment plans. Secondly, the addition of 5G communication technology can solve the unbalanced development of medical resources. Digital technology can improve the efficiency and accuracy of dental treatment in the field of oral treatment and is a technology worthy of future development in the medical field.

The innovation of materials undoubtedly enables clinicians to more clearly understand the location, morphology and scope of invasion of oral tumors, which has guiding significance for clinical surgery. At present, research on the diagnosis of oral cancer mainly needs to consider two issues, one is about the metabolism of the material itself in the body, and the other is about the charge of the diagnostic method. However, the current research on tumor therapy should focus on how to improve the efficacy of immunosuppressive drugs or traditional chemotherapy drugs, which largely depends on the design of drug carriers. Although most current studies are based on photodynamic therapy, and photodynamic materials have gradually changed from NIR I to NIR II, after all, the penetration effect of photodynamic in tissues is relatively poor. Perhaps with the development of acoustic dynamic, magnetic dynamic and microwave dynamic therapy, the targeted release of tumor drugs can be better promoted. The development of new technology can quickly solve the current clinical problems, including improving the precision of surgery, easing the fear of patients, and solving the imbalance

of medical resources. However, our understanding and application of new technology are far from enough, and a lot of research is still needed before it can be maturely applied in clinical practice.

7. Other oral diseases

7.1. Orthodontic

The accumulation of food debris, the loss of orthodontic attachments, and the appearance of chalky plaque due to enamel demineralization after bracket removal are often problems that occur during orthodontic treatment, which often lead to gingivitis, caries, and unsightly teeth. To solve these problems, researchers have also gradually focused on the nanomodification of orthodontic bonding agents. Shear bond strength (SBS) and adhesive remnant index (ARI) are considered two indicators that can evaluate the quality of orthodontic bonding agents. It was shown that 5 wt% nGO could be used as an orthodontic adhesive additive to reduce microbial population and biofilm with no adverse effects on SBS and ARI [268]. However, this bonding agent does not address the enamel demineralization problem. On this basis, Liu et al. found that PND adhesives with 5% MAE-DB and 40% NACP had antibacterial and remineralization abilities and the bond strength was not altered [269]. In addition, the broad-spectrum antibacterial ability of AgNPs and the remineralization ability of CaF_2 were gradually applied in developing orthodontic adhesives, and significant results were also achieved [270,271].

Nanomodification of the orthodontic attachment itself is another focus of research. In the same way as implants, the antibacterial capacity of nanocoating technology can be applied to orthodontic treatment as well. A novel ZnNPs-nTi nanocoating has been demonstrated to endow orthodontic attachments with antibacterial and anticorrosive functions in orthodontics [272]. In addition, to address the problem of strength of the orthodontic wire itself and food accumulation caused by it, Lin et al. developed a double-layer grid sandblasted plasma polymerized (GB-PP) superhydrophobic coating by changing the micro-and nanostructured surface morphology of the AISI 304 stainless steel substrate. This material showed good superhydrophobicity and durability *in vitro* wear tests, which helped reduce food accumulation, bacterial overgrowth, and caries occurrence [273].

7.2. Halitosis

The essence of halitosis is the release of sulfide gases by microorganisms in the oral cavity. By analyzing these sulfides, different markers can be found to diagnose different diseases [274]. One of the markers of halitosis, H_2S, can be analyzed for effective monitoring of early oral diseases such as caries or periodontitis. Thanks to the advent of nanotechnology, such technology makes detection methods for oral gases more convenient and improves the sensitivity and specificity of detection [275,276]. $Ba_{0.5}Sr_{0.5}TiO_3$ (BST) films have been prepared, and the voltage induced by the gas in the presence of electrical changes can instantly display the results of the detection of the gas [277]. However, this method also has some limitations. For example, it does not effectively display the actual concentration of hydrogen sulfide in the gas. Another detection idea is to add a dye indicator to the sensor made through nanotechnology. When the oral gas is collected, the concentration of hydrogen sulfide can be effectively calculated by using gas chromatography analysis [278,279]. Li et al. developed a wearable fluorescent mouthguard composed of zinc oxide-polydimethylsiloxane (ZnO-PDMS)

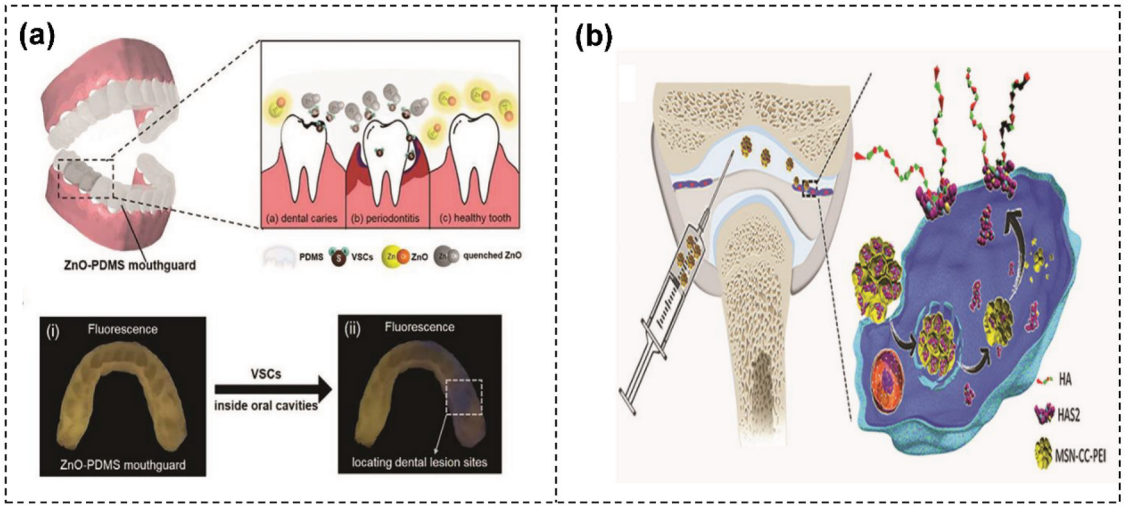

Figure 11. (a) Schematic diagram of a ZnO-PDMS mouthguard. Reproduced by permission from [25], copyright 2020, Wiley. (b) an illustration of the cellular delivery of HAS2 to synoviocytes using nanoparticles. Reproduced by permission from [280], copyright 2019, Wiley.

nanocomposites, which can pinpoint the site of tooth damage by detecting the local release of VSCs (Figure 11) [25]. Compared with the previous method, this method is also more intuitive. Supposing this nanosensor is applied to the mouthpiece, it can enable people to instantly know their oral condition to perform early intervention that can effectively prevent oral diseases.

7.3. Temporomandibular joint disorders (TMJD)

The temporomandibular joint disc is an important part of the temporomandibular joint that serves as a lubricant and cushion. Injury to the joint disc can lead to symptoms such as joint popping and difficulty opening the mouth. Disorders of the joint disc often require surgical treatment, but surgery in the TMJ area is often complex and can result in complications [281]. It has been shown that fibrochondrocytes can be used as seed cells to promote the repair of articular discs. Ronald et al. found that TiO_2 can enhance the behavior of fibrochondrocytes, and they developed TiO_2 nanofilm bilayers using layer-by-layer (LbL) nanoassembly technology, demonstrating that this nanomaterial can effectively repair damaged articular discs by loading fibrocartilage cells [282].

HA, a natural component of normal joint lubrication, is rapidly depleted during the progressive phase of osteoarthritis (OA), resulting in pain in the joint area and limited mouth opening [283]. Intra-articular injections of exogenous HA are a standard treatment, but exogenous HA degrades rapidly, increasing the number and cost of patient visits. Increasing the amount/activity of HAS2 in synovial cells under OA conditions provides a new strategy to promote endogenous HA production and restore normal synovial fluid function. Li et al. used mesoporous silica nanoparticles (MSN) encapsulated with hyaluronan synthase type 2 (HAS2), and after its intra-articular injection, found that HAS2-loaded MSN-CC-PEI could be endocytosed by synovial cells through internalization, escaping the nuclear endosome/lysosome and releasing HAS2 into the cytoplasm to participate in cellular functions [26]. The results of HE and MircoCT indicated that MSN-CC-PEI exhibited the best anti-inflammatory and bone regeneration effects after one week of treatment. Compared with the exogenous injection of HA alone, this approach can continuously promote HA de novo and thus reduce the associated symptoms in patients (Figure 11(b)).

8. Summary and outlook

8.1. Materials from “old” to “new”

In the process of material development, ‘new’ materials often replace ‘old’ materials, mainly depending on clinical needs. However, most new materials are modified from old materials by different processing techniques, which means that the same material can play different functions under different processing methods. First, compared with Ag+, the stability of AgNPs is enhanced and the toxicity is reduced, which indicates the influence of material size on material properties [32]. The way that the needle-like ZnNPs function in antibacterial is mainly mechanical friction, which indicates the influence of material structure on performance [40]. The osteogenic effect of HAP has been demonstrated, but mixing it in an injectable hydrogel can prolong its residence time in the periodontal tissue and thus enhance the osteogenic effect, indicating the effect of the state of the material on the material properties [73]. When two or more materials are mixed, there will be a certain synergistic effect, which shows the influence of the proportion of materials on the performance of materials. Of course, new materials are not only for the processing of old materials, but also include some that have been used in other disciplines and have not been used in the field of stomatology. For example, graphene can modify the surface of implants to make them hydrophilic to enhance their osseointegration. MOF materials have excellent biological properties and excellent drug loading capacity [284–286]. These materials are designed to cater to the needs of oral disease diagnosis and treatment. They are often more widely used and have more potent efficacy. Nevertheless, safety is the most crucial issue for such materials. Compared to the modification of traditional materials, which have a single function, developing and manufacturing non-traditional oral materials may be a more promising research direction in the future.

8.2. Function from “single” to “multiple”

Due to technical limitations, the development of traditional oral materials in the past was often based on solving the problem of oral diseases, leading to simplifying material functions. With further understanding of the etiology of oral diseases, a single functional material can no longer be satisfied in the therapeutics of most oral diseases. Fortunately, in recent years, some multifunctional nanocomposites have been reported for oral diseases one after another. For example, dental filling materials have both effects of antibacterial and promote tooth remineralization [20]; nano-scaffold materials have antibacterial and osteopromoting properties at the same time [287]; and nano-drug carriers include tumor active targeting and immune evasion ability [28]. It is worth noting that the functions of such materials often come from mixing multiple materials. Moreover, the relationship between material and material or between material and oral tissue has not been elucidated in most

literature. Whether these complex structures generate new questions requires a more rational experimental design. Even so, the research and development of these materials are undoubtedly more suitable for diagnosing and treating oral diseases at present. Furthermore, it is also an essential avenue for future research and the development of oral materials.

8.3. Diagnosis from "visible" to "precise"

The inability to clearly and precisely display the extent of the lesion is one of the primary reasons for the failure of oral disease treatment. In the past, root canal treatment often failed because the complex root canal system, such as collateral root canals, could not be displayed on the X-ray film of the lessons tooth, resulting in incomplete filling of the root canal and failure of the treatment [288]. For oral tumors, preoperative imaging data cannot accurately display the invasive margin of the lesion, which often results in residual tumor tissue and tumor recurrence. An important new route is the exploration of high-resolution photos for lesions of oral diseases utilizing nano technologies. For example, the high resolution of nano-CT can improve the understanding of the root canal system and evaluate the morphology of dental nanocomposites [289]. Various nano-contrast agents and photosensitizers have also been developed for tumor imaging, which helps physicians to more accurately determine the extent of lesions and complete tumor resection, reducing tumor recurrence [240,249]. Besides, nanorobots with autonomous locomotion capability have been developed for cancer diagnosis. Although this technology is currently in its infancy, the field is progressing rapidly through the scientific outcomes of numerous research groups. We believe that shortly we will see an application of nanorobots for diagnosing oral diseases.

8.4. Therapy from "recovery" to "balance"

Innovations in materials and technologies are gradually changing the concept of traditional therapy for oral diseases. Although oral disease can be controlled and recovered using traditional materials and techniques, while varying side effects often accompany therapy. For instance, Root canal treatment is the most definitive endodontic treatment, but it can lead to the insufficient mechanical strength of the tooth hard tissue [290]. Dental antibacterial products such as mouthwash and toothpaste can reduce the occurrence of caries or periodontal disease, but the long-term application will lead to dysbiosis of oral flora [291]. Oral cancer requires surgical resection, but large-scale excision will lead to the disorder of oral and jaw function. We can see that these treatments achieve the effect of curing the diseases but ignore a 'balance' problem. Herein, the 'balance' refers to a healthy, harmonious, and homeostatic oral state. Herein, the 'balance' refers to a healthy, harmonious and homeostasis oral state. We believe that the balance between cure and side effects is a major concern in developing oral materials and technologies in the future. We think this issue can be approached from the following two aspects. Firstly, it's necessary to increase the correlation between the material and the disease while avoiding the impact of the material on the non-disease area tissue. For example, mironeedles only work on the attached gum tissue and do not affect the soft and hard tissues in other mouth areas [21]. The application of biomimetic nanoparticles increases the accumulation of the drug within the tumor and reduces the systemic response [28]. Secondly, tissue engineering technology can also balance the side effects of some oral diseases after treatment by rebuilding the soft and hard tissues of the oral cavity, such as pulp regeneration [292], and alveolar bone regeneration [293], gingival regeneration [294] and so on. Moreover, the development of tissue engineering and materials will promote the maturity of regenerative medicine.

8.5. Technology from "traditional" to "intelligent"

With the rapid development of science and technology, some advanced technologies have been gradually applied to diagnosing and treating oral diseases. The emergence of 5 G technology has promoted the rapid development of telemedicine, making it a reality for experts to carry out remote diagnosis and treatment [295]. This technology also alleviates uneven distribution of medical resources to a certain extent. VR technology plays a dual role in diagnosing and treating oral diseases. Patients can use VR to understand the diagnosis and treatment process or video entertainment experience to relieve anxiety during the treatment process. Doctors can better understand real-time information such as imaging of lesions, help the treatment process of diseases, and reduce medical accidents through VR technology [296]. In the context of the era of big data, AI combined with algorithms has also emerged in the diagnosis of oral diseases. For example, a deep learning algorithm for detecting oral cavity squamous cell carcinoma from photographic images [14]. Smart wearable devices are widely used in the field of biomedicine [297]. However, the application of smart wearable devices in oral diseases has not been reported, especially for wearable devices with EMG monitoring for diagnosing bruxism, TMJ, and so on. Development in intelligent technology will bring benefits to all oral diseases.

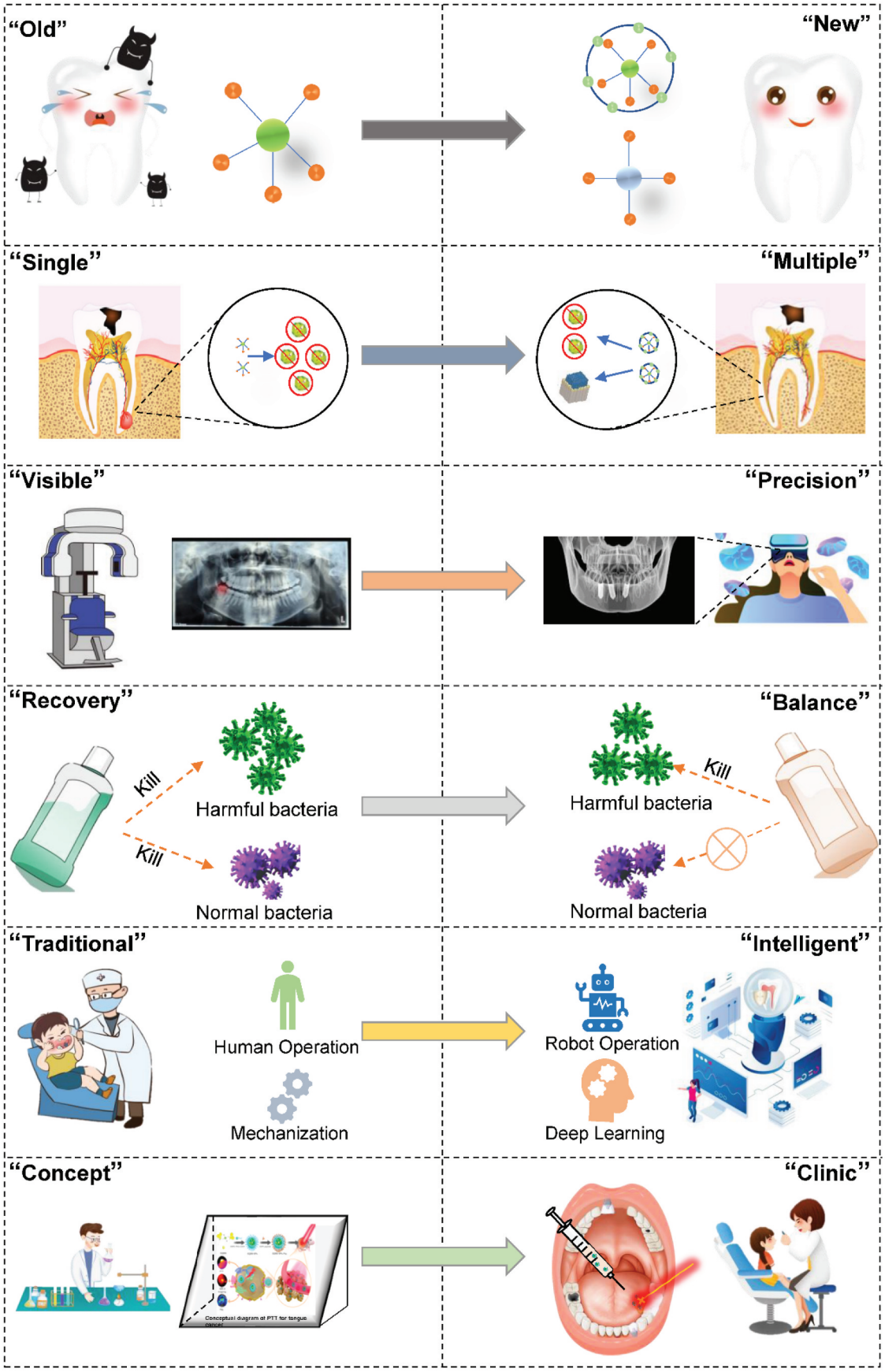

Figure 12. The development of materials and technologies from 'past' to 'future'.

8.6. Products from "concept" to "clinic"

The development of advanced materials and technologies stems from clinical problems, and the ultimate goal is to solve these clinical problems. Although preclinical research has developed rapidly in recent years, this is only a small step in the clinical translation process. Several vital

concerns remain to be taken into account during the translation process. First, biosecurity is paramount for clinical applications. The components of the materials should be long-term stable and have good biocompatibility without acute and chronic toxicity. Second, given the high incidence of oral diseases, the cost of materials is another aspect that hinders clinical translation. Doctors and patients cannot accept high-priced equivalent products of the same kind. This is also why we have used titanium implants, filling resins, etc., clinically for many years, but no new substitutes have emerged. Therefore, in the view of clinical translation, the cost of large-scale preparation should be considered in developing new materials, especially nanomaterials. Last but not least, in order to reduce the cycle time of clinical translation, we should return to the most essential issue, that is, we should consider whether and how our research can be clinically translatable when we initially design the material or develop the technology, which requires us to be willing to try and face various problems and solve them.

The road ahead will be long, and our climb will be steep (Figure 12). With interdisciplinary coordination (such as clinicians, bioengineers, computer programmers and pharmacologists) to drive clinical trials, we firmly believe that new, multifunctional, intelligent and biocompatible oral materials and technologies will bring an amazing revolution to oral medicine.

Disclosure statement

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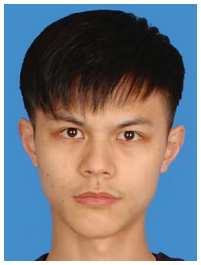

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