

Perspective

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Functional hydrogels for dental disease treatment

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Abstract

Dental disease treatment has achieved significant progress, yet challenges remain due to limitations of conventional dental materials, including suboptimal biocompatibility and biodegradability. Functional hydrogels, as one kind of versatile biomaterial, have gained widespread attention in biomedical applications, offering notable advantages and promising potential for dental therapies. This paper summarizes the basic properties of functional hydrogels and recent advancements in treating various dental diseases. It emphasizes the working mechanisms and therapeutic effects. Lastly, the challenges and issues encountered by hydrogels in dental treatments are discussed, along with future development prospects. With ongoing advances in hydrogel design and fabrication, their performance is expected to improve further, expanding their role and potential in managing dental diseases, oral health, and related medical conditions.

Keywords: Functional hydrogels, dental disease treatment, tooth health

INTRODUCTION

Oral health is fundamental to overall human well-being, with dental health serving as a critical



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component^[1-3]. Due to variations in diet and lifestyle, individuals may encounter a range of dental issues, including tooth discoloration^[4-6], cavities^[7-9], pulp diseases^[10-13], and periapical/root canal diseases^[14-17]. If not treated in time, the tooth may need to be extracted and there is a risk of infection in the extraction socket^[18,19]. Among these, tooth discoloration and cavities are the most widespread oral concerns^[20,21]. Surveys indicate that nearly half of Chinese adults have experienced some degree of tooth discoloration^[20]; meanwhile, cavities rank alongside cardiovascular diseases and cancer as one of the three most common global health concerns^[22,23]. Maintaining dental health is vital, yet current oral biomaterials face safety and reliability challenges, which emphasizes the urgent need for more effective and safe dental materials^[24,25].

Functional hydrogels are emerging polymer materials that resemble natural soft tissues^[26-29], due to their flexibility and elasticity. Their three-dimensional network structure endows functional hydrogels with high water absorption and retention capacities^[30,31]. Importantly, they are highly biocompatible and biodegradable, meaning they can avoid immune rejection and gradually degrade within the body or the environment^[32-35]. These properties make hydrogels ideal for biomedical applications such as wound healing, hemostasis, disinfection, and drug delivery^[36-39]. Additionally, their adjustable wet adhesion, mechanical strength, and antifatigue properties make them suitable for the moist and dynamic environment of the oral cavity^[40,41]. For example, the excellent wet adhesion and drug release properties facilitate the application of hydrogels in the wound healing of tooth extraction sockets^[18,19], and the good injectability and temperature-sensitive properties make hydrogels suitable for root canal treatment and dental pulp regeneration^[42-44]. In recent years, continuous advancements in hydrogel performance have led to their widespread use in the treatment of dental diseases, particularly for addressing common oral issues [Figure 1], such as oral ulcers, oral cancer, periodontitis, *etc.*^[5,42,45-49].

This paper primarily discusses the research progress of functional hydrogels in the treatment of dental diseases, focusing on areas such as teeth whitening, caries treatment, post-extraction wound healing, and pulpitis treatment. It aims to analyze their mechanisms and therapeutic effects, while also discussing the challenges and opportunities associated with hydrogel-based dental therapies, and outlining future development trends.

RECENT PROGRESS IN FUNCTIONAL HYDROGELS FOR DENTAL DISEASE TREATMENT

With the growing emphasis on beauty in modern society, white, bright, and healthy teeth have become key beauty standards^[1,50]. Due to the limitations of current whitening technologies, various safe and effective methods have been developed, such as piezoelectric^[51,52], photodynamic^[4,53], and pyroelectric^[54] catalytic whitening. These techniques rely on the generation of reactive oxygen species (ROS), which break down organic pigments into colorless molecules, producing a whitening effect^[51,53].

Figure 2A illustrates the schematic diagram of photodynamic teeth whitening with an injectable hydrogel^[6], and this hydrogel consists of copper(I) oxide (Cu_2O) as an antibacterial agent and bismuth chloride ($\text{Bi}_{12}\text{O}_{17}\text{Cl}_2$) nanoparticles as a photosensitizer. $\text{Bi}_{12}\text{O}_{17}\text{Cl}_2$ can generate ROS under green light. This dual action not only whitens teeth by removing pigmentation but also eradicates bacteria and clears biofilms, preventing tooth decay. Figure 2B shows another novel whitening method using temperature fluctuations during oral movements^[54]. Barium titanate (BaTiO_3) nanoparticles with pyroelectric effects are incorporated into the hydrogel. The temperature fluctuations within the oral cavity will lead to changes in the polarization intensity of the barium titanate material, triggering the release or absorption of screening charges, which in turn promotes the formation of ROS. This ROS helps degrade large pigment molecules on the tooth surface, resulting in whitening. To demonstrate the whitening effect, the enamel of several stained isolated teeth was covered with pyroelectric hydrogel and subjected to 2,000 cold-hot thermal cycles, and

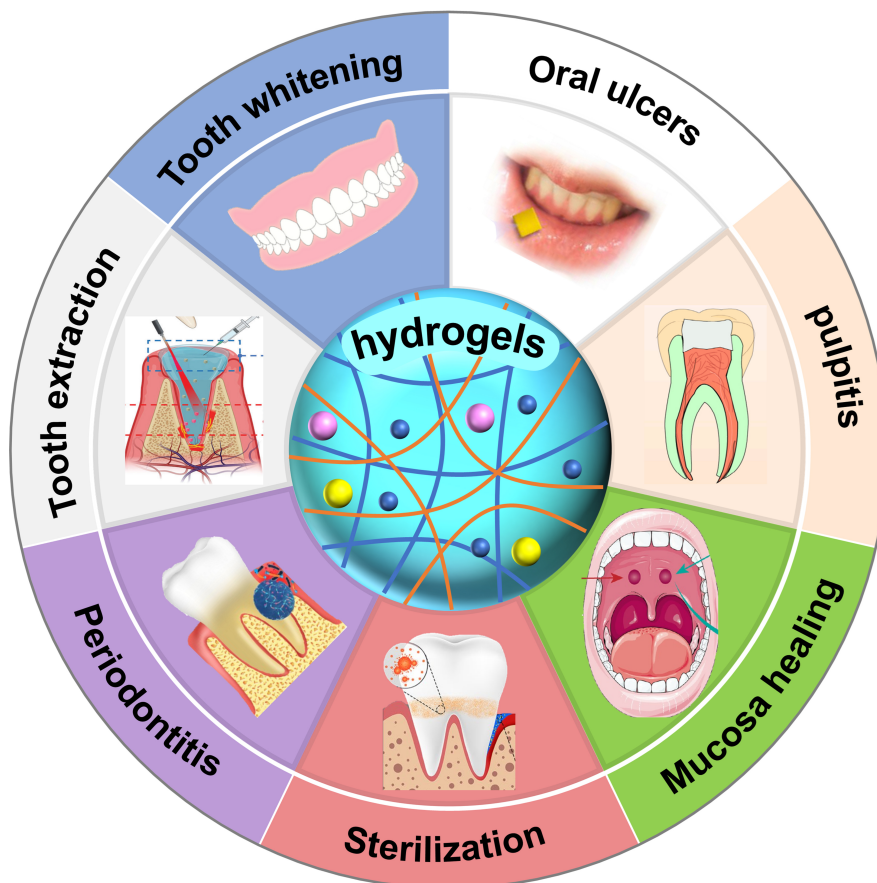


Figure 1. Functional hydrogels for treating different dental and oral diseases, including tooth whitening, pulpitis, mucosa healing, etc.^[5,42,45-49]. Reproduced with permission^[42]. Copyright©2021, American Chemical Society. Reproduced with permission^[5]. Copyright©2022, American Chemical Society. Reproduced with permission^[45]. Copyright©2023, Wiley-VCH. Reproduced with permission^[46]. Copyright©2023, American Chemical Society. Reproduced with permission^[47]. Copyright©2023, Elsevier. Reproduced with permission^[48]. Copyright©2023, MDPI. Reproduced with permission^[49]. Copyright©2022, Springer.

the surface of the stained enamel was significantly whitened^[54]. This method leverages the temperature changes in mouth, offering good biocompatibility and sustainability, though the whitening effect is slow.

Cavities are among the most common human diseases and, if left untreated, can progress to pulpitis and periodontitis^[55,56]. Biomimetic technology^[56-58], which facilitates the remineralization of dental hard tissues by releasing Ca^{2+} and PO_4^{3-} ions to convert amorphous calcium phosphate (ACP) into more stable forms, showing huge potential in caries treatment. Researchers have integrated ACP into amphoteric ion polycarboxylate betaine acrylamide (PCBAA), resulting in development of PCBAA/ACP nanocomposite material that exhibits both remineralization and antibiofilm properties^[9]. Due to strong electrostatic interactions, the negatively charged carboxyl ($-\text{COO}^-$) and positively charged quaternary ammonium ($-\text{R}_3\text{N}^+$) groups on the PCBAA molecular chain attract Ca^{2+} and PO_4^{3-} ions [Figure 3], significantly reducing the supersaturation of calcium phosphate and enhancing the crystallization barrier for ACP, thereby promoting enamel remineralization^[9].

As the only soft tissue within the tooth, when the dental pulp becomes inflamed, it will seriously endanger the safety of the tooth^[13,59]. Pulp regeneration offers an effective approach for treating pulpitis and restoring tooth vitality by replacing damaged pulp tissue^[60,61]. Injectable thermosensitive hydrogels, with excellent



Figure 2. (A) Photodynamic tooth whitening with injectable hydrogel. Reproduced with permission^[6]. Copyright©2022, American Chemical Society; (B) Pyroelectric catalytic effect for tooth whitening. Reproduced with permission^[54]. Copyright©2022, Springer Nature.

injectable molding capabilities, have emerged as ideal materials for biological scaffolds^[42-44]. Researchers have created a thermosensitive hydrogel (HPCH/CW/Exo) by incorporating exosomes (Exo) from human dental pulp stem cells (hDPSCs) into a hydrogel made of hydroxypropyl chitosan (HPCH) and chitosan whiskers (CW)^[62]. This hydrogel can easily penetrate irregular root canal spaces and solidify in place. When tested for dental tissue regeneration by injecting it into a human root model and implanting it in mice for 8 weeks, for the hDPSC-laden HPCH/CW/Exo hydrogel group, the pulp-like tissues with extracellular matrix and cells formed in the endodontic space, due to the exceptional delivery effect of the Exo that promotes odontogenesis and angiogenesis^[62]. However, the endodontic space almost remained empty in the comparative experiments, which confirms the good pulp regeneration ability of the hDPSC-laden HPCH/CW/Exo hydrogels. Furthermore, its flowability enables precise drug delivery and sustained antibacterial release for root canal disinfection^[63,64], and it demonstrates favorable biocompatibility with hDPSCs, highlighting its dual role in pulp regeneration and sterilization^[65-67].

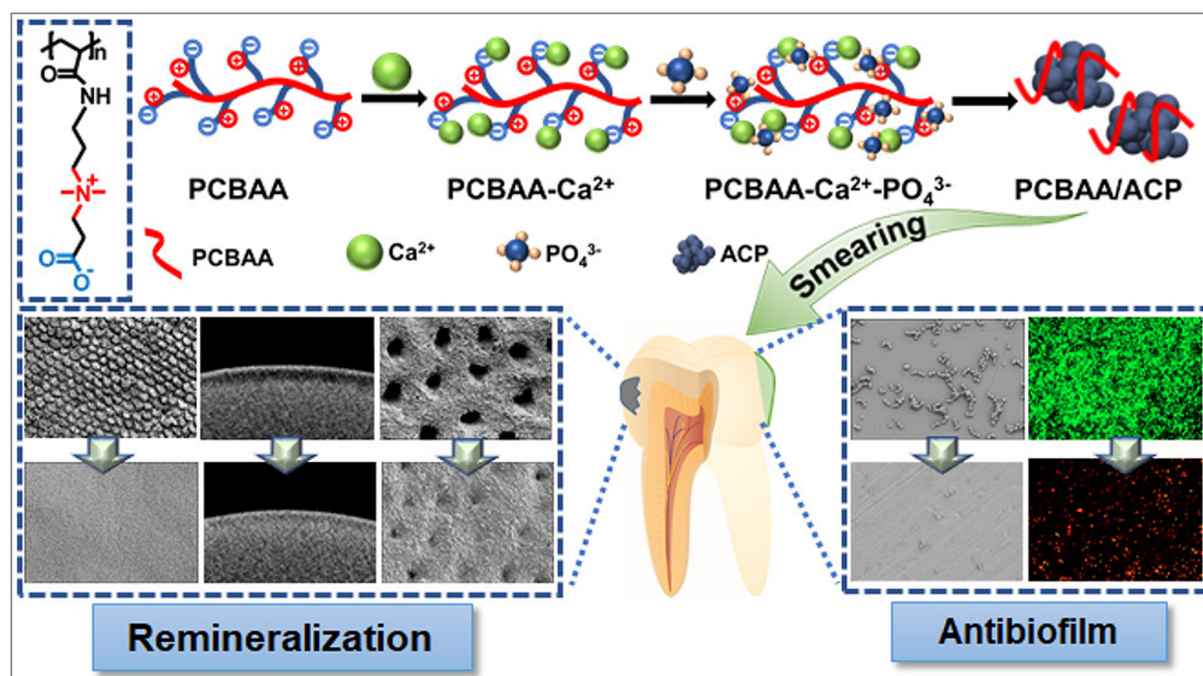


Figure 3. PCBAAC/ACP polyzwitterion hydrogel with remineralization and antibiofilm functions for dental demineralization. Reproduced with permission^[9]. Copyright©2022, American Chemical Society. PCBAAC: Polycarboxylate betaine acrylamide; ACP: amorphous calcium phosphate.

When a tooth is damaged to the extent that extraction is necessary, the healing of the extraction socket becomes critically important as well^[37,39]. Injectable and moldable hydrogels, with their excellent wet adhesion capabilities, are ideal materials for promoting tooth-extraction socket healing. By loading drugs, hydrogels can further achieve antibacterial, disinfectant, and hemostatic effects^[68,69]. Researchers developed a polyethylene glycol diacrylate (PEGDA) hydrogel containing chitosan-modified palladium nano-cube and glucose oxidase (GOx)- Fe^{2+} through step-by-step assembly^[45]. This hydrogel can promote healing of tooth-extraction wounds [Figure 4A]. The hydrogel combines GOx and Fe^{2+} , which generate toxic hydroxyl radicals ($\cdot\text{OH}$) to enhance enzyme activity [Figure 4B]. Under 808 nm light, combined with photothermal effect from the palladium nano-cubes, the hydrogel's photothermal effect and cascade reaction system help fight *Streptococcus mutans* that can cause infection [Figure 4C]. The $\cdot\text{OH}$ radicals also trigger the gelation of PEGDA monomers, creating a moist and sterile environment for healing. The hydrogel is biodegradable, ensuring it degrades as tissue regenerates for effective wound healing.

SUMMARY AND OUTLOOK

This paper concludes the basic properties, advantages, and future prospects of functional hydrogels in dental disease treatment, highlighting the working mechanisms and corresponding therapeutic effects. For instance, hydrogels loaded with photosensitive or pyroelectric materials can generate ROS induced by light or temperature stimulation, enabling teeth whitening and bacterial disinfection. As drug carriers, hydrogels can release Ca^{2+} and PO_4^{3-} ions to promote enamel remineralization, effectively treating cavities. Their injectability, moldability, and wet adhesion also make them suitable for pulp regeneration, post-extraction disinfection, and healing.

Hydrogels show great potential in dental disease treatment, but they still face several challenges. The most important factor is biocompatibility, which ensures the safety and reliability of dental treatments. However,

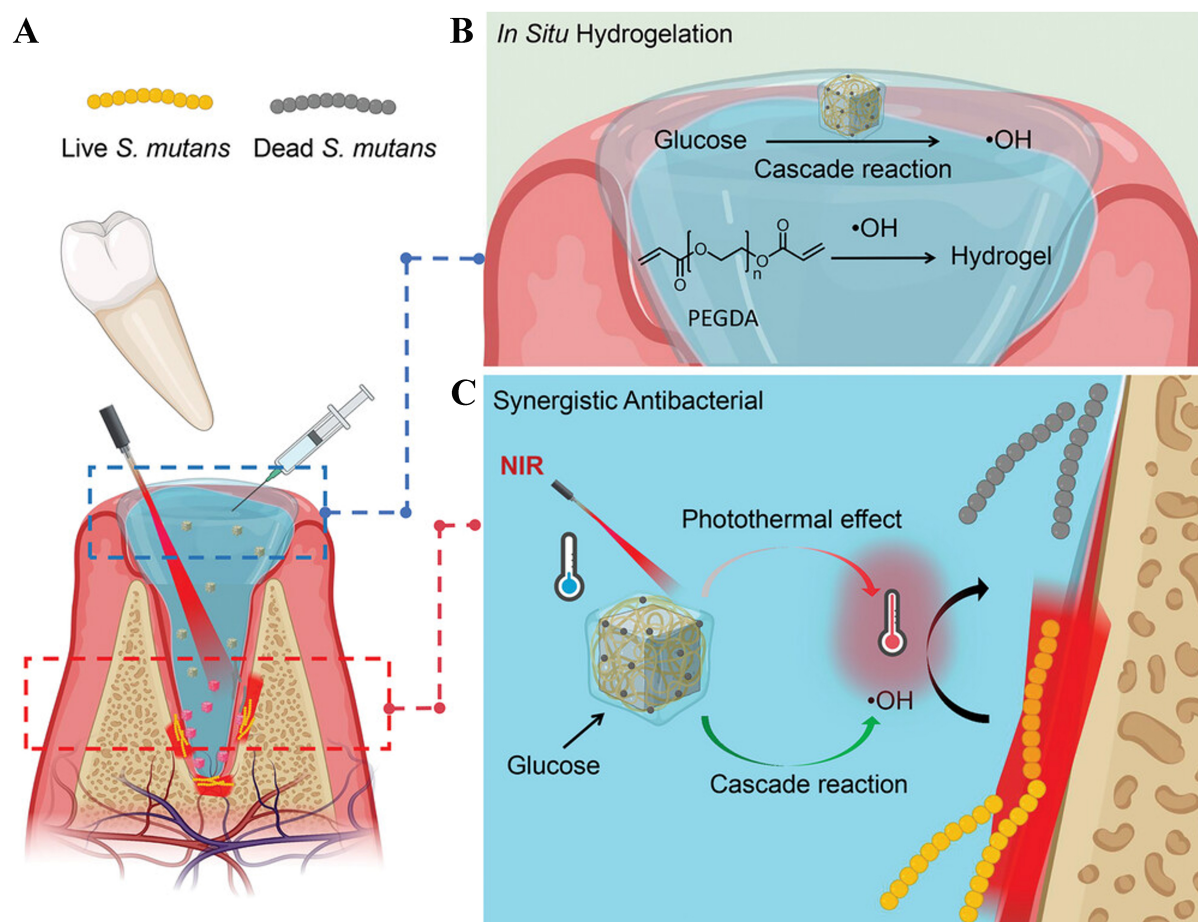


Figure 4. (A) Schematic illustration of PEGDA-based hydrogel for bacteria-induced tooth-extraction healing; (B) The hydroxyl radicals induce *in situ* hydrogelation of PEGDA; (C) Photothermal effect and chemodynamic cascade reaction for eradicating bacteria. Reproduced with permission^[45]. Copyright©2023, Wiley-VCH. PEGDA: Polyethylene glycol diacrylate.

prioritizing biocompatibility can reduce the mechanical strength of hydrogels. The mechanical properties can be improved by adding metal ions or nanoparticles, but this may reduce biocompatibility. For the hydrogels containing nanoparticles (e.g., Cu_2O , BaTiO_3), there is a lack of in-depth research and analysis on their degradation kinetics and degradation products, thus making it impossible to assess whether their long-term safety meets the standards set by the US Food and Drug Administration (FDA) and International Organization for Standardization (ISO). Additionally, the moist and dynamic nature of the oral environment presents challenges for hydrogels in clinical application, and the wet adhesive property can weaken due to tooth occlusion, saliva secretion, and swallowing over time. In future clinical applications, it is also necessary to consider the time cost of hydrogel preparation and preservation, as well as the chairside preparation work and patient compliance for light/temperature-activated systems. Based on all these considerations, the clinical application of safe, reliable and efficient hydrogels in treating dental diseases still has a long way to go.

Despite certain challenges, hydrogels offer significant advantages due to their simple preparation processes, low cost, and large-scale production. The diverse strategies for structural regulation and performance optimization also allow for the creation of functional hydrogels tailored to meet the specific requirements of disease treatment. Moreover, the rapidly developing artificial intelligence (AI) technology may be utilized to

assess and optimize the properties of functional hydrogels, while providing feedback on the drug loading and release characteristics of these hydrogels. Overall, functional hydrogels still hold vast potential and significant advantages for future applications in the dental and oral field.

DECLARATIONS

Authors' contributions

Literature review, the outline of the manuscript structure, and writing of manuscript draft: Li, H. (Huixu Li); Xu, X.

Revised the manuscript: Li, H. (Huixu Li); Xu, X.; Zhang, D.

Supervision, writing - review and editing: Zhang, D.; Li, H. (Haihui Li); Bao, P.

All authors have read the manuscript and approved the final version.

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate.

Not applicable.

Consent for publication

Not applicable.

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