REVIEW PAPER

Metal–organic frameworks in oral disease therapy: a review of antimicrobial, anti-inflammatory, and regenerative nanomedicine approaches

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ABSTRACT

Metal–organic frameworks (MOFs) have recently garnered considerable attention as versatile nanoplatforms for dental and oral biomedical applications due to their tunable structures, high porosity, and capacity for multifunctional drug delivery. Increasing evidence indicates that MOF-based systems can release antimicrobial metal ions and catalytic species capable of disrupting pathogenic oral biofilms, thereby contributing to the prevention and management of dental caries and periodontal infections. In periodontal disease, several studies also suggest that MOFs can modulate inflammatory pathways and mitigate tissue damage associated with chronic inflammation. Beyond their antimicrobial and anti-inflammatory functions, MOF-based platforms have shown promising potential in promoting osteogenic differentiation and supporting bone regeneration in periodontitis-related defects. In cariogenic environments, these materials can further serve as carriers for controlled and localized drug delivery, enhancing therapeutic efficacy while minimizing systemic exposure. More recently, MOF-assisted photodynamic and photothermal therapies have emerged as promising strategies for the management of oral squamous cell carcinoma (OSCC), enabling efficient photosensitizer delivery, enhanced reactive oxygen species generation, and targeted tumor cell destruction. Despite these encouraging findings, several challenges still limit the clinical translation of MOF-based technologies, including issues related to large-scale synthesis, long-term biocompatibility, stability in the oral environment, and regulatory approval. This review summarizes current advances in MOF-based strategies for oral disease therapy and highlights both the opportunities and the remaining challenges that must be addressed prior to successful clinical application.

Keywords*: Metal–organic frameworks; Antimicrobial; Periodontitis; Dental caries; Oral cancer therapy*

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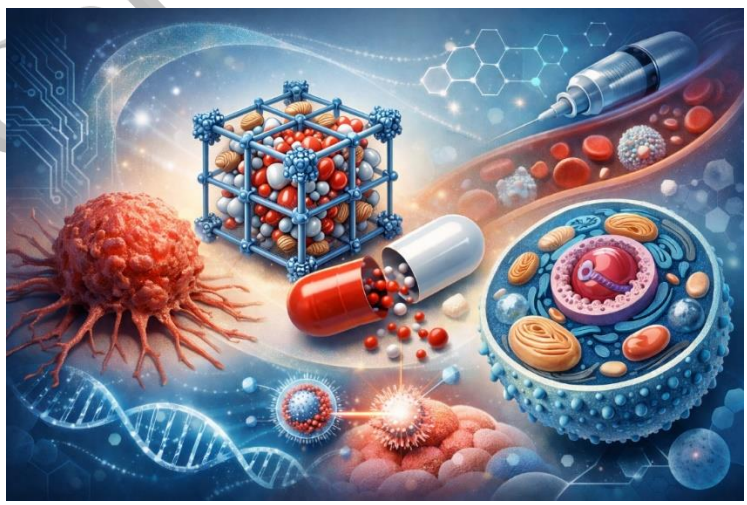
Abbreviations

MOF: Metal–Organic Frameworks; OSCC: Oral Squamous Cell Carcinoma; PDA: Polydopamine; PDT: Photodynamic Therapy; ROS: Reactive Oxygen Species

GRAPHICAL ABSTRACT



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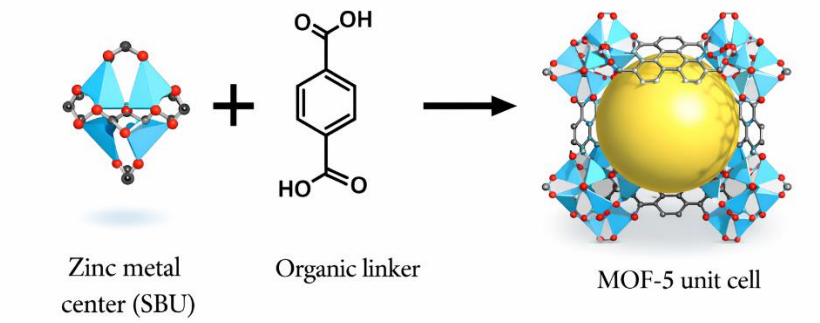

Fig. 1. Organic ligands coordinate with metal centers to form MOFs [15].

INTRODUCTION

Oral diseases—including dental caries, periodontitis, and oral squamous cell carcinoma (OSCC)—remain a major global health challenge. In 2016 alone, approximately 5.4 million new cases of severe periodontitis and 4.6 million cases of untreated caries were reported, ranking these conditions among the most prevalent diseases worldwide [1,2]. Their economic burden is also substantial, with global costs exceeding USD 540 billion in 2015 [3]. Beyond causing local tissue damage, these disorders have increasingly been associated with systemic complications, including respiratory diseases [4], cardiovascular diseases [5], and gastrointestinal malignancies [6]. Furthermore, growing evidence suggests that specific oral pathogens, such as Fusobacterium nucleatum and Porphyromonas gingivalis, may contribute to tumor initiation and progression [7–12].

Despite advances in clinical management, conventional treatment strategies—including broad-spectrum antimicrobials, mechanical debridement, surgery, radiotherapy, and chemotherapy—still face several important limitations. Many antimicrobial agents are associated with increasing bacterial resistance, rapid clearance from the oral environment, limited biocompatibility, and potential systemic toxicity [13,14]. Likewise, current oncologic therapies may lead to recurrence and unintended damage to surrounding healthy tissues. These challenges underscore the need for more selective and multifunctional therapeutic approaches.

MOFs have gained considerable attention as promising candidates for overcoming these limitations. Owing to their exceptionally high surface area, often exceeding 3000 m^2/g, tunable porosity, controllable degradation, and ability to simultaneously deliver metal ions, drugs, and catalytic or photosensitizing components, MOFs offer remarkable functional versatility (Figure 1) [15–20]. These properties make them a unique platform capable of integrating antimicrobial activity, immunomodulation, support for tissue regeneration, and imaging capabilities within a single system.

This review provides an overview of recent advances in MOF-based technologies for oral disease therapy, with a particular focus on four key areas: antimicrobial treatment, periodontitis management, targeted therapy for oral carcinoma, and strategies for the prevention of dental caries.

Antimicrobial agent

Due to their high porosity, large surface area, and chemically labile structures, MOFs are being considered promising antimicrobial tools in dental treatment. By selecting appropriate metal centers, such as Ag^+, Cu^{2+}, and Zn^{2+}, together with suitable organic ligands, MOFs can be tailored to deliver controlled doses of biocidal ions. Silver, copper, and zinc ions have demonstrated excellent antimicrobial efficacy. Their high redox potential enables them to interact rapidly with thiol groups present in bacterial proteases and other essential proteins. This interaction can inhibit enzymatic activity, disrupt vital cellular processes, and ultimately lead to bacterial cell death. These ions can also interfere with bacterial cell membranes and essential biochemical functions, thereby preventing bacterial replication. Moreover, following initial bacterial damage, sustained ion release from MOFs may continue to exert antimicrobial effects against residual bacteria, helping to reduce the overall pathogenic burden during a single treatment [21–24].

In recent years, MOFs have attracted significant attention for their potential in antimicrobial applications via multifunctional scaffolds. They have been successfully doped to target bacteria with excellent results. MOFs possess a unique combination of properties compared with conventional antimicrobial compounds: (a) Controlled release of antimicrobial metal ions: With

progressive degradation of MOFs, metal ions and organic ligands can be released in a controlled manner over time, thereby enhancing antimicrobial activity [25,26]. (b) Increased membrane permeability: Metal ions bound to organic ligands reduce overall polarity, facilitating better permeation of metal ions into bacterial cell membranes [27]. (c) Adjustable photocatalysis: Different metal ions and ligands can modulate band gaps, enabling ROS production under specific light wavelengths and generating potent antimicrobial photocatalysts [28,29]. Here, reactive oxygen species (ROS) refer to highly reactive molecules capable of inducing cellular damage, and photocatalysis denotes a light-driven process in which the material absorbs photonic energy to facilitate chemical reactions, including ROS generation. (d) Enzyme-mimetic catalysis: MOFs with coordination chemistry analogous to natural oxidases can catalyze reactions to produce ROS without additional energy inputs. (e) Enhanced antimicrobial loading capacity: MOFs with higher surface areas can simultaneously load larger quantities of antimicrobial compounds in a controlled manner [30–32]. Through these mechanisms, the combination of metal ion release, ROS generation, and targeted membrane disruption can substantially improve antimicrobial efficacy while reducing required doses [29,31,33,34]. As shown in Figure 2, MOF-based antimicrobial systems demonstrate clear advantages over conventional antimicrobial compounds and metal-ion–based nanomaterials. Their tunable porous structures enable controlled release of antimicrobial ions and bioactive species, supporting sustained antibacterial effects. In contrast, conventional antimicrobials and other antimicrobial nanomaterials may exhibit limited long-term efficacy due to resistance development and/or insufficient control over release kinetics.

MOFs also exhibit good biocompatibility in toxicity assessments, supporting their safe in vivo applications [35]. MOF-based systems derived from natural compounds have demonstrated antimicrobial efficacy, anti-inflammatory properties, and provide a novel strategy in antimicrobial therapy with proven effectiveness [36]. The release of metal ions from MOFs plays a critical role in antimicrobial activity by inhibiting common pathogens such as *Streptococcus mutans, Clostridium nucleatum, Porphyromonas gingivalis*, and *Streptococcus pyogenes*. For instance, ZIF-8 MOFs facilitate controlled zinc ion release, which can prevent S. *mutans* growth and exert additional antimicrobial effects [37]. Previously, MOFs incorporating antimicrobial metal ions demonstrated controlled release of Ag^+ ions, effectively killing pathogens including Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa [38]. Ag^+ ions disrupt bacterial cell membranes, leading to envelope loss and cell death through leakage of cytoplasmic contents [39].

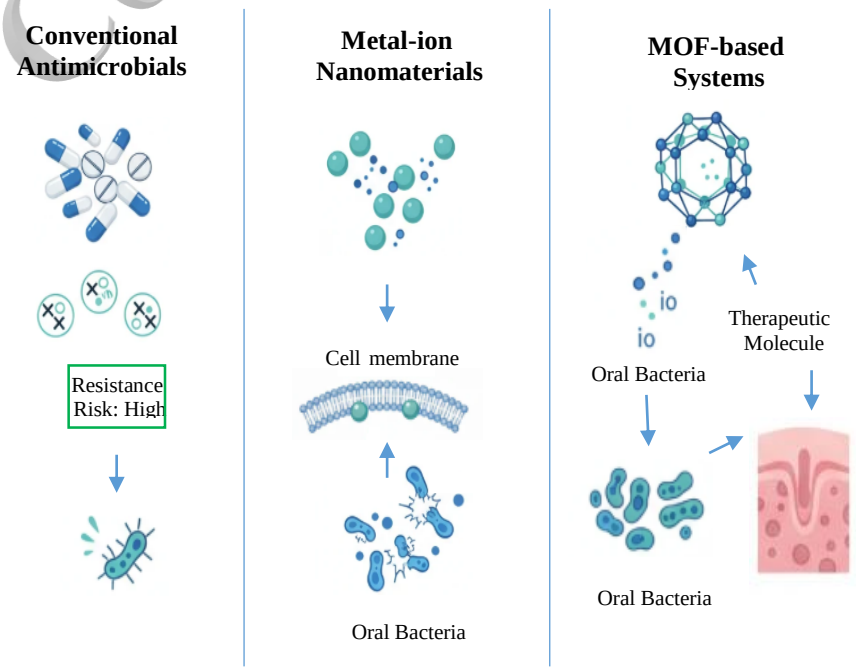

Fig. 2. Comparison of antimicrobial strategies in dental applications: conventional agents, metal-ion nanomaterials, and MOF-based systems.

Recently, manganese-based MOFs, particularly UoB-4, have shown potent antimicrobial activity, significantly inhibiting both Gram-positive and Gram-negative bacteria. These MOFs also interfere with bacterial cell wall synthesis and aminobenzoic acid production. Their high surface area and Mn^{2+} leachability enhance bacterial susceptibility by targeting membranes and disrupting key biochemical pathways [40]. Zeolite-like frameworks derived from imidazolate, such as ZIFs containing transition metal ions (Zn^{2+} or Co^{2+}), exhibit strong antimicrobial properties [41]. Motakef et al. described an eco-friendly and rapid method for synthesizing ZIF-8 nanostructures using pulsed laser ablation in liquids (PLAL). This approach involves pulsed laser ablation of zinc targets in a methanolic 2-methylimidazole solution, avoiding high-temperature solvothermal reactions. Their results demonstrated potent antimicrobial effects of laser-ablated ZIF-8 against E. coli and S. aureus. Agar disc diffusion tests with 1 mg/mL ZIF-8 discs showed inhibition zones exceeding 12 mm for E. coli and 10 mm for S. aureus, with larger zones observed at higher concentrations. The rapid bactericidal activity of ZIF-8 nanostructures is primarily attributed to the slow release of Zn^{2+} ions, which affect cell membranes and critical biochemical pathways, as well as membrane interactions facilitated by their high surface area [42].

For example, ZIF-8 nanocomposite layers have demonstrated strong inhibitory effects against Escherichia coli through ROS generation without the involvement of Ag or Cu species within the MOF structure [43]. Iron-containing MOF nanoparticles, including MIL-100(Fe), MIL-88B, and MOF-53(Fe), which consist of ferric centers and terephthalate ligands, have shown dose-dependent bactericidal activity against Staphylococcus aureus at concentrations ranging from 20 to 160 mg/mL [44]. Similarly, the Co-containing MOFs ZIF-67 and Co-SIM-1 achieved more than 50% inhibition of Pseudomonas putida and Escherichia coli at concentrations of 5–10 mg/mL [45]. Given the limited penetration of conventional antimicrobials across lipid bilayers and their inability to maintain sustained local concentrations, increasing attention has been directed toward MOF-based drug delivery systems [46]. Nanostructured MIL-100(Fe) has demonstrated the capacity to encapsulate tetracycline hydrochloride and doxycycline monohydrate, enabling controlled drug release in a controlled animal study [47]. Consistent with these findings, a tetracycline-loaded ZIF-8/hyaluronic acid nanohybrid exhibited potent antimicrobial activity in both in vitro and in vivo studies. Considering the substantial clinical burden of dental caries, MOF-based delivery systems represent promising platforms for both preventive and therapeutic applications. This is particularly relevant because dental caries affects approximately 2.5 billion people worldwide and accounts for a considerable proportion of productivity losses associated with oral diseases [3,48–52].

Periodontitis treatment

Periodontitis is a chronic inflammatory disease resulting from the accumulation of plaque beneath the gum line, which, if left untreated, can lead to gum recession, alveolar bone loss, and ultimately tooth loss. Advanced stages of periodontitis involve destruction of collagen fibers within the periodontal ligament and the formation of deep periodontal pockets, accelerating disease progression. Therefore, one of the primary goals in periodontitis management is to re-establish an adequate soft tissue seal around affected teeth [53]. Metal–organic frameworks (MOFs) offer a versatile, multifunctional approach to periodontitis therapy by integrating antimicrobial, anti-inflammatory, and regenerative activities within a single platform. Their high porosity and tunable composition allow for the loading and controlled release of bioactive metal ions, such as Mg^{2+}, Zn^{2+}, and Co^{2+}, as well as phenolic antioxidants, which collectively stabilize the periodontal microenvironment and promote bone regeneration [54,55]. In 2024, Luo et al. reported an injectable, self-repairing hydrogel incorporating a magnesium–gallic acid MOF (Mg-GA MOF), which responds to reactive oxygen species (ROS) and pH signals to degrade on demand within inflamed periodontal pockets. This process releases Mg^{2+} ions to enhance osteogenic activity and gallic acid to scavenge excessive ROS. In a rat model of periodontitis, treatment with the Mg-GA hydrogel resulted in significantly reduced inflammatory cytokines (TNF-α, IL-6) and enhanced alveolar bone regeneration compared to controls, demonstrating both immunomodulatory and osteogenic effects [54]. A similar trajectory of progress has been observed in bone tissue engineering, where 3D-printed PLGA/β-TCP scaffolds have exhibited significantly greater osteogenic potential than conventionally fabricated scaffolds, underscoring the critical role of scaffold design in alveolar bone regeneration [56]. Yang et al. designed an ATP-responsive bimetallic Mg/Zn MOF that disassembles in the presence of extracellular ATP, a danger signal associated with periodontitis. The released Mg^{2+} and Zn^{2+} ions cooperatively inhibit gasdermin D-mediated pyroptosis by suppressing both the NLRP3–caspase-1–GSDMD and caspase-

11–GSDMD pathways. Lin and coworkers developed a bimetallic Zn–Co MOF that modulates the oxidative microenvironment of periodontal tissues and accelerates bone healing. This material continuously releases Zn^{2+} and Co^{2+} ions to activate osteoblasts while catalyzing ROS decomposition, thereby protecting cells from oxidative stress. Local application of Zn/Co-MOF in a ligature-induced periodontitis model reduced alveolar bone loss and inflammatory markers, mainly due to the antioxidative and osteogenic properties of the material [57]. Taken together, these studies demonstrate that MOFs can be rationally engineered by tuning metal ions, ligands, and stimulus-responsive properties to enable localized delivery of ions and bioactive compounds at target sites. This minimally invasive strategy may help reduce inflammation, limit cell death, and ultimately promote periodontal tissue regeneration. MOFs have also been recognized as promising materials for local drug delivery in dental applications because of their high drug-loading capacity and reduced risk of premature release. For instance, ZIF-8 has been used to encapsulate ceftazidime, showing bactericidal activity against Escherichia coli through sustained release over one week [58]. In another approach, composite microspheres were fabricated using CDMOF nanocrystals and a polyacrylic acid scaffold loaded with ibuprofen and lansoprazole. These microspheres remained structurally stable, provided sustained drug release over time, and exhibited lower cytotoxicity [59]. Photodynamic therapy (PDT) has attracted increasing clinical interest because of its strong antibacterial activity and is being explored as a potential alternative or adjunct to conventional treatments for periodontitis [60]. Some MOFs exhibit photocatalytic activity, whereby irradiation induces structural changes that alter coordination environments and bond configurations [61–64]. Two-dimensional porphyrin-based MOFs are particularly promising for PDT applications. For example, dispersing ferric oxide-containing 2D MOF nanosheets within a PEG matrix can yield an ointment that, upon irradiation, generates ROS and releases ions, thereby extending antibacterial activity. This formulation can also reduce inflammation and stimulate angiogenesis, enhancing infection control against pathogens such as Porphyromonas gingivalis and Pseudomonas species [65]. Photocontrolled drug delivery is an emerging strategy that enables precise spatiotemporal regulation of therapeutic activity. Combining photosensitizers with MOFs may facilitate the development of light-controlled drug delivery systems. One notable recent example is AuNR@SiO_2@UiO-66, in which UiO-66 serves as the MOF framework. This system demonstrates dual drug-release behavior, including NIR-triggered release and slower passive release enhanced at higher drug loading levels, together with strong antibacterial activity against both Gram-positive and Gram-negative bacteria [66].

Overall, the complexity of the oral microbiome often necessitates the use of broad-spectrum antimicrobials as part of periodontal therapy. MOFs are well suited for local antibiotic delivery because even low doses of systemic antibiotics may cause adverse reactions and disrupt the microbial balance of the oral cavity. Therefore, MOF-based platforms represent a promising strategy for periodontal disease management by enabling site-specific and controllable therapeutic release, with the potential to reduce inflammation, prevent tissue damage, and support periodontal tissue regeneration.

Oral cancer treatment

Oral cancer represents a major global health burden and is ranked as the sixth most common malignancy by incidence, causing more than 50,000 deaths annually [8,67,68]. Despite advances in clinical management, conventional therapies, including chemotherapy, surgical resection, and/or radiotherapy, remain associated with substantial adverse effects as well as cosmetic and functional impairment, and have produced only limited improvements in five-year survival rates for patients with this malignancy [69–73]. In this context, the development of more effective drug delivery systems based on active or passive targeting has been widely discussed in the literature, highlighting the potential role of MOF nanocarriers in oral cancer therapy [13].

Recently, increasing attention has been directed toward local chemotherapeutic delivery systems for oral cancer. Such systems can maintain sustained drug concentrations at the tumor site for prolonged periods while achieving higher local drug levels, thereby reducing systemic toxicity [74,75]. Oral squamous cell carcinoma (OSCC), a common and highly aggressive malignancy of the maxillofacial region, frequently invades adjacent tissues and metastasizes, making surgery alone insufficient in many cases. As a therapeutic strategy, chemotherapy remains an important approach for eliminating cancer cells and inhibiting recurrence and metastasis [76,77]. However, one major limitation of current chemotherapy is the gradual accumulation of drugs in normal tissues, which can cause serious adverse effects and potentially compromise OSCC treatment outcomes.

Enhancing the tumor-targeting efficiency of chemotherapeutic agents therefore represents a promising strategy for overcoming these limitations [78–80].

MOFs have emerged as versatile technological platforms for OSCC targeting, enabling precise drug delivery, phototherapy, and imaging within a single system. Their high porosity, tunable pore chemistry, and facile surface modification allow chemotherapeutic agents, photosensitizers, and imaging probes to be integrated into multifunctional nanoplatforms optimized for OSCC targeting. However, achieving selective nanoparticle targeting of tumor cells remains a major challenge in OSCC treatment. Recent studies suggest that OSCC cells secrete CXCL8, a chemokine that acts as a guidance cue for cell migration and can recruit dental pulp mesenchymal stem cells (DPSCs) through activation of CXCR2 receptors. This CXCL8/CXCR2-mediated interaction supports the migration of DPSCs toward injured or tumor-associated sites. Based on this mechanism, MOF nanoparticles have been functionalized with membranes derived from DPSCs, yielding a novel formulation termed MOF@DPSCM. In vitro and in vivo assessments confirmed the tumor-specific affinity of MOF@DPSCM toward OSCC. Moreover, the doxorubicin-loaded variant, MOF-DOX@DPSCM, exhibited potent cytotoxicity against CAL27 cells in vitro and significantly suppressed CAL27 tumor progression in vivo. These findings suggest that MOF-DOX@DPSCM may represent a promising platform for targeted chemotherapy of OSCC in future clinical applications [81].

Effective tumor control relies on sustained delivery of encapsulated chemotherapeutics combined with enhanced therapeutic efficacy. Localized oral cancer treatment using multi-drug regimens has shown considerable promise. A hybrid nanocomposite integrating MOFs with a thermosensitive hydrogel was developed as an injectable implant, in which doxorubicin and celecoxib were co-encapsulated (Dox/Cel/MOFs@Gel) for targeted oral cancer therapy. By leveraging celecoxib's anti-angiogenic activity together with the cytotoxic effects of doxorubicin, the system was extensively characterized in terms of particle size and morphology using SEM/TEM, formulation stability, encapsulation efficiency, and in vitro release kinetics. Enhanced cellular uptake and cytotoxicity against KB and SCC-9 cells were observed in vitro. In animal studies, the nanocomposite significantly inhibited tumor growth, increased apoptosis, and regulated angiogenesis through drug synergy, while reducing systemic toxicity and preserving the integrity of adjacent organs. Biosafety evaluations confirmed the acceptable biocompatibility of the MOF-based system, with no evidence of long-term in vivo toxicity. The Dox/Cel/MOFs@Gel platform provides pH-responsive drug release, potent antitumor effects, and excellent biocompatibility, highlighting its potential for future clinical application [7]. Zr-MOF nanocarriers, particularly PCN-224 and UiO-66 derivatives, have been employed to encapsulate doxorubicin (DOX) for targeted chemotherapy against OSCC. These MOFs are specifically designed to release DOX at the tumor site through pH-responsive linker cleavage in the acidic tumor microenvironment (pH ~6.5). This approach has achieved over 70% cytotoxicity against OSCC cell lines while sparing normal oral keratinocytes. Furthermore, surface modifications using folic acid or peptide ligands have been shown to enhance tumor targeting and cellular uptake, thereby reducing off-target toxicity in preclinical models [82]. Photodynamic and photothermal therapies using porphyrin-based MOFs, such as PCN-224, effectively combine intrinsic photosensitizing ligands with large surface areas to generate ROS under light irradiation in the 660–808 nm range. In OSCC spheroids, PCN-224-mediated therapy promoted efficient singlet oxygen generation, resulting in more than 90% tumor cell death within five minutes under near-infrared light exposure. Moreover, hybrid MOFs incorporating gold or copper nanoparticles achieved photothermal heating above 45°C together with ROS generation, producing synergistic antitumor effects in tumor-bearing mouse models with reduced systemic toxicity [83].

Theranostic imaging combined with lanthanide-doped MOFs, such as Gd-UiO-66 and Eu-MIL-101, provides a bifunctional platform that can enhance contrast in both MRI and CT imaging while simultaneously enabling drug delivery. In a study conducted by Zheng et al., a T1 relaxivity constant of 21 mM^{-1} s^{-1} was obtained for a Gd-UiO-66/DOX nanocomposite, which enabled pH-responsive DOX release. These MOF-based theranostic systems allow noninvasive monitoring of nanocomposite distribution and therapeutic performance [84].

Despite these encouraging preclinical findings, MOF-based oral cancer therapies still face challenges related to scalable production, long-term biosafety, and regulatory approval. To advance clinical translation, Zhang et al. emphasized the need for standardized procedures to evaluate MOF degradation products, immune responses, and pharmacokinetics. Future research should therefore focus on developing greener, water-based MOF synthesis methods and

comprehensive toxicity assessment protocols to facilitate clinical translation [85].

While current preclinical studies demonstrate substantial therapeutic efficacy and tumor-specific accumulation of MOF-based platforms, a notable limitation persists in the lack of quantitative biodistribution data and standardized uptake metrics. Most studies to date primarily report qualitative in vivo tumor suppression and imaging contrast, yet rigorous quantitative evaluation of pharmacokinetics, organ-specific accumulation, and precise cellular uptake percentages is essential. Future investigations should prioritize systematic analyses using techniques such as Inductively Coupled Plasma Mass Spectrometry (ICP-MS) or radiolabeling to generate concrete data on systemic circulation and clearance of MOF nanocarriers. Such quantitative evidence is critical for optimizing the therapeutic index, addressing long-term biosafety concerns, and bridging the gap between preclinical success and clinical translation.

Caries prevention

Dental caries is recognized as the most prevalent non-communicable disease worldwide and arises primarily from an imbalance in the dental microflora, leading to the overgrowth of acid-producing bacteria [86]. Central to caries pathogenesis is the formation of bacterial biofilms on tooth surfaces, which ferment dietary sugars into acidic compounds, lowering the local pH below 5.5 [87]. This acidic environment initiates demineralization of inorganic tooth components, including magnesium, calcium, and phosphate ions [88], and degrades the organic matrix, particularly collagen [89].

Current caries management typically involves the use of antibacterial agents in combination with synthetic restorative materials. However, conventional antimicrobial approaches may be insufficient to fully eliminate cariogenic pathogens such as *Streptococcus mutans*, *Streptococcus sobrinus*, and *Actinomyces viscosus* within the oral microenvironment. Overuse of broad-spectrum antimicrobials can disrupt the oral microbiota balance, potentially leading to adverse systemic effects. Furthermore, current dental restorative materials are prone to microleakage, which can trigger immune responses and contribute to recurrent caries [90–99].

Collectively, these findings highlight a critical need for an integrated therapeutic platform for caries control. Ideally, such a platform should be able to target cariogenic bacteria without disrupting the balance of the oral microflora, arrest and reverse caries progression driven by microbial dysbiosis and cariogenic acidity, reinforce and consolidate mineralized tooth structures, and activate the intrinsic self-repair capacity of teeth. Advances in site-specific and stimulus-responsive strategies offer promising opportunities to meet these requirements in a controlled manner. Innovative caries therapies exploit the acidic microenvironments generated by cariogenic bacteria to internally activate smart materials at caries sites. In this context, PMs@NaF-SAP, a pH-responsive multidrug carrier for caries treatment, has been developed [100]. Gallic acid, a natural compound derived from gallnuts, has also shown considerable potential for caries prevention because of its anti-inflammatory and antibacterial properties as well as its biocompatibility [101,102]. In parallel, MOFs have attracted attention for their ability to simultaneously suppress cariogenic biofilm formation and promote self-repair of tooth structures. Their intrinsic porosity and tunable chemistry enable controlled release of antimicrobial ions, sustained delivery of calcium and phosphate to support enamel remineralization, and acid-responsive cargo release for precision therapy [103]. MOFs have therefore emerged as promising nanoplatforms for precise drug delivery due to their well-organized, pH-sensitive structures, which can degrade in acidic environments [104,105]. By incorporating gallic acid into MOF matrices, the active compound can be released specifically in low-pH regions, such as cariogenic niches, maximizing therapeutic efficacy while minimizing potential adverse effects. This approach may offer a promising strategy for dental caries treatment. Light-driven external activation provides important advantages in dental therapy by enabling non-invasive and spatiotemporally controlled drug release [106,107]. However, UV and blue light sources may induce dermal oxidative stress [108] and photochemical damage to retinal tissue [109]. Consequently, antibacterial platforms have increasingly shifted toward photothermal therapy (PTT) using biocompatible near-infrared (NIR) irradiation. Polydopamine (PDA) is an effective photothermal agent that converts NIR light into heat and markedly improves bacterial eradication. Leveraging these properties, a dual-responsive nanocomposite was designed to address dental caries through both acidic pH and NIR stimuli. As illustrated in Fig. 3a, gallic acid-derived building blocks form a magnesium organic framework (Mg-MOF), which is subsequently coated with PDA and mineralized with calcium phosphate (CaP), yielding the multifunctional Mg-MOF@PDA@CaP composite (MPC) [110].

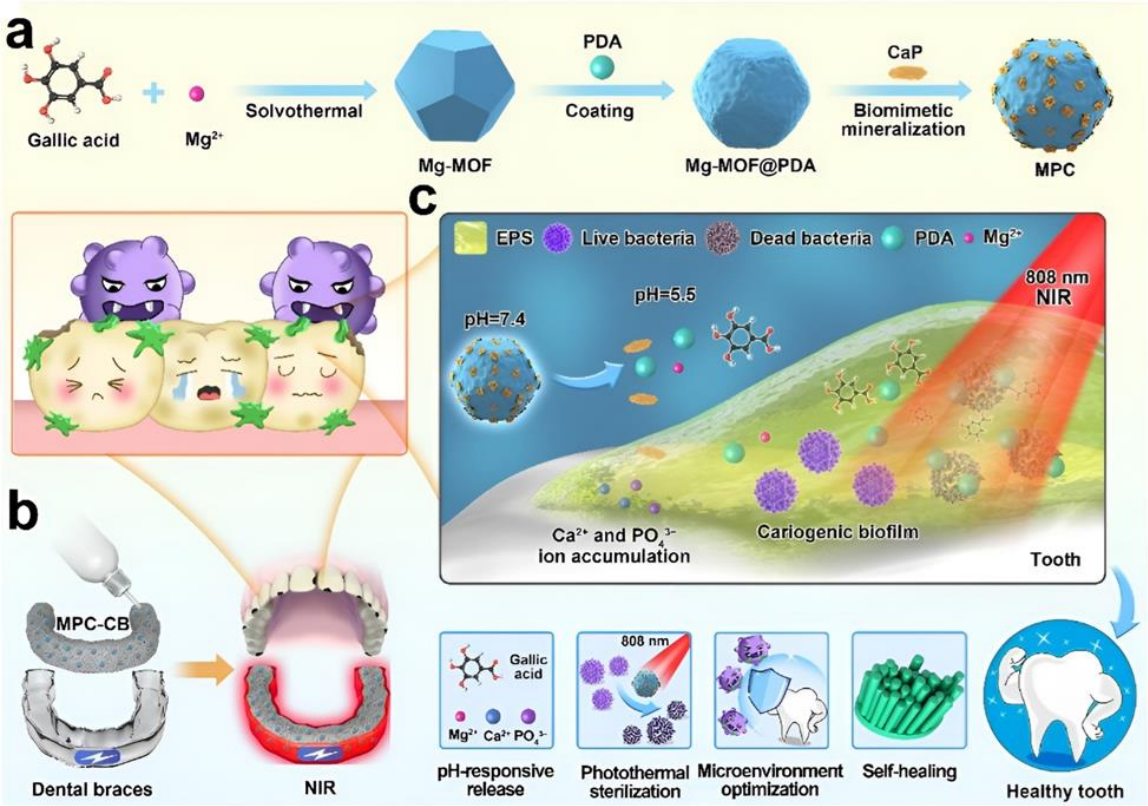

Fig. 3. Schematic illustration of the construction of the MPC and working principle. (a) The construction of the MPC. (b) The usage of MPC. (c) Photothermal and pH dual-responsive MPC for localized biofilm disruption, oral microenvironment optimization, and tooth hard tissue self-healing [110]. This figure is published under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International license (CC BY-NC-ND 4.0).

To enhance clinical applicability, foam-based braces incorporating MPC (MPC-CB) were fabricated using cocamidopropyl betaine as a foaming agent (Fig. 3b). Based on this design, the anticipated therapeutic sequence is as follows (Fig. 3c):

(i) acidic fluctuations within cariogenic microenvironments induce progressive dissolution of CaP and partial disassembly of the MOF, resulting in the release of Ca^{2+}, PO_4^{3-}, Mg^{2+}, and gallic acid;

(ii) upon NIR irradiation, MPC exerts a photothermal effect that disrupts cariogenic biofilms;

(iii) gradual degradation of the composite contributes to partial restoration of the local pH at the lesion site;

(iv) the released mineral ions (Ca^{2+}, PO_4^{3-}, Mg^{2+}) promote enamel remineralization and partial mechanical recovery, consistent with prior in vitro and in vivo observations [111–115]; and

(v) gallic acid and PDA exhibit strong binding affinity toward Ca^{2+}, PO_4^{3-}, and collagen, which may help stabilize demineralized tooth hard tissues [112,113].

In parallel, zinc- and silver-based MOFs, such as ZIF-8 and Ag-MOF, incorporating antimicrobial ions have been shown to inhibit Streptococcus mutans adhesion and acid production. In vitro studies demonstrated that Zn-MOF particles released Zn^{2+} ions at concentrations sufficient to reduce S. mutans viability by over 95% within 24 hours while maintaining low cytotoxicity toward human gingival fibroblasts [103]. Such sustained ion release interferes with early biofilm formation and can synergize with mechanical plaque control strategies. Furthermore, MOFs loaded with calcium and phosphate ions have been investigated as dynamic mineral reservoirs for enamel repair. Xu et al. reported that ZIF-8 co-loaded with Ca^{2+}/PO_4^{3-} precursors and chlorhexidine achieved biofilm eradication rates exceeding 90% and promoted in situ enamel crystallite growth. Scanning electron microscopy (SEM) revealed that demineralized enamel lesions recovered up to approximately 80% of their original mineral density within 14 days under simulated saliva flow conditions [111–115]. Enamel remineralization induced by MOF-based systems is typically assessed using a combination of mechanical, morphological, and crystallographic techniques. Surface and cross-sectional microhardness tests quantify the recovery of enamel mechanical strength, providing direct evidence of mineral reinforcement, while SEM visualizes morphological changes, including

formation of newly deposited mineral layers and restoration of prismatic structures within demineralized lesions. In addition, X-ray diffraction (XRD) analysis confirms hydroxyapatite recrystallization by revealing characteristic diffraction peaks and improved crystallinity following MOF-mediated mineral deposition. Collectively, these complementary measurements demonstrate both functional and structural restoration of enamel following MOF-based anti-caries treatment. Notably, certain MOFs possess acid-sensitive linkers that rapidly disassemble at pH ≤ 5.5, characteristic of cariogenic niches, enabling site-specific release of antimicrobial and remineralizing agents. Such targeted release strategies may reduce premature depletion of active components and limit adverse effects on surrounding healthy tissues [103]. While these findings support the potential of MOF-based systems in facilitating enamel remineralization, further quantitative validation—particularly under clinically relevant in vivo conditions—is required before definitive conclusions regarding enamel regeneration can be drawn.

Table 1 provides an overview of both in vitro bench studies and in vivo investigations of MOF-based approaches for oral health. The data highlight a broad biomedical scope, including the elimination of oral pathogens and disruption of biofilms, modulation of immune responses, promotion of bone healing in periodontitis, theranostic imaging and drug delivery in oral cancer, and caries prevention with enamel repair through remineralization. This concise overview compares different MOF formulations, experimental models, key findings, and assessment methods used to evaluate their potential translation into clinical dentistry.

Table 1. In Vitro and In Vivo Evaluation of MOF-Based Strategies in Oral Applications

Study Type	MOF System / Formulation	Application / Target	Key Findings	References
In vitro	Ag^{+}, Cu^{2+}, Zn^{2+} MOFs	Oral pathogens, biofilms	Controlled ion release, biofilm disruption, and antibacterial activity	[21–24]
In vitro	Sustained-release MOFs	Broad bacterial strains	Extended bactericidal activity via gradual degradation	[25–27]
In vitro	Porphyrin-based MOFs	Oral bacteria	Light-triggered ROS generation, photocatalytic antibacterial effect	[28,29]
In vitro	Enzyme-mimicking MOFs	Oral pathogens	ROS production without external energy	[28,29]
In vitro / in vivo	ZIF-8/hyaluronic acid nanohybrid	Oral pathogens	Controlled tetracycline release, potent antibacterial efficacy	[3, 48–52]
In vivo	MOF-based delivery systems	Cariogenic bacteria	Caries prevention, enamel remineralization	[48–52]
In vivo (rat)	Mg–GA hydrogel	Periodontitis	↓ TNF-α, IL-6; bone regeneration; immunomodulatory + osteogenic effects	[54]
In vitro	ATP-responsive Mg/Zn-MOF	Macrophages, pyroptosis	Blocked NLRP3–Caspase pathways; reduced inflammation	[55]
In vivo (rat)	Zn/Co-MOF	Periodontitis	Reduced bone loss, antioxidative + osteogenic properties	[57]
In vitro / in vivo	ZIF-8 encapsulating ceftazidime	E. coli infection	Sustained antibiotic release, bactericidal effect	[58]
In vitro / in vivo	Porphyrin-based 2D MOFs	*P. gingivalis*	Light-triggered ROS, antibacterial activity, and angiogenesis promotion	[65]
In vitro / in vivo	MOF@DPSCM (DOX-loaded)	Oral cancer (OSCC)	Tumor-specific affinity, suppressed progression	[81]
In vitro / in vivo	Dox/Cel/MOFs@Gel	Oral cancer	Sustained dual-drug release, apoptosis ↑, and angiogenesis ↓	[7]
In vitro	Zr-MOF nanocarriers	OSCC cell lines	pH-responsive DOX release, selective cytotoxicity	[82]
In vitro / in vivo	Porphyrin-based MOFs + Au/Cu	OSCC models	Photodynamic ROS, >90% apoptosis, tumor ablation	[83]
In vitro / in vivo	Lanthanide-doped MOFs	OSCC models	Theranostic imaging + chemotherapy	[84]
In vitro	PMs@NaF-SAP carrier	Cariogenic biofilm	Acid-triggered release, biofilm eradication	[101–102]
In vitro	Gallic acid-loaded MOFs	Cariogenic niches	Controlled release, antibacterial + anti-inflammatory	[101–105]
In vitro / in vivo	Mg-MOF@PDA@CaP	Caries model	Sequential ion release, enamel remineralization	[110–115]
In vitro	Zn-MOF particles	*S. mutans*	Sustained Zn^{2+} release, >95% viability reduction	[103]
In vitro / in vivo	ZIF-8 + Ca^{2+}/PO_4^{3-} + chlorhexidine	Biofilm, enamel	>90% biofilm kill, ~80% mineral recovery	[103]

Mechanisms of drug delivery and release modulation by MOFs in oral therapy

MOFs employ a range of sophisticated strategies to achieve site-specific drug delivery within the oral cavity. Their porous architecture, stimulus-responsive behavior, and tunable physicochemical properties enable precise control over drug loading, release kinetics, and targeted delivery to the desired therapeutic site.

Key delivery mechanisms:

MOFs facilitate controlled drug release in oral therapy through their crystalline frameworks, high porosity, and tunable surface chemistry. These properties enable controlled ion release, stimuli-responsive degradation, and multifunctional therapeutic effects (Figure 4). Initially, MOFs undergo gradual degradation, providing sustained release of biologically active metal ions such as Ag^{+}, Zn^{2+}, Cu^{2+}, Mn^{2+}, Mg^{2+}, and Co^{2+}. These ions can exert antimicrobial and anti-inflammatory effects and support bone-healing processes within the oral environment [21–24,37–42]. Such sustained release helps maintain consistent therapeutic activity against oral microorganisms.

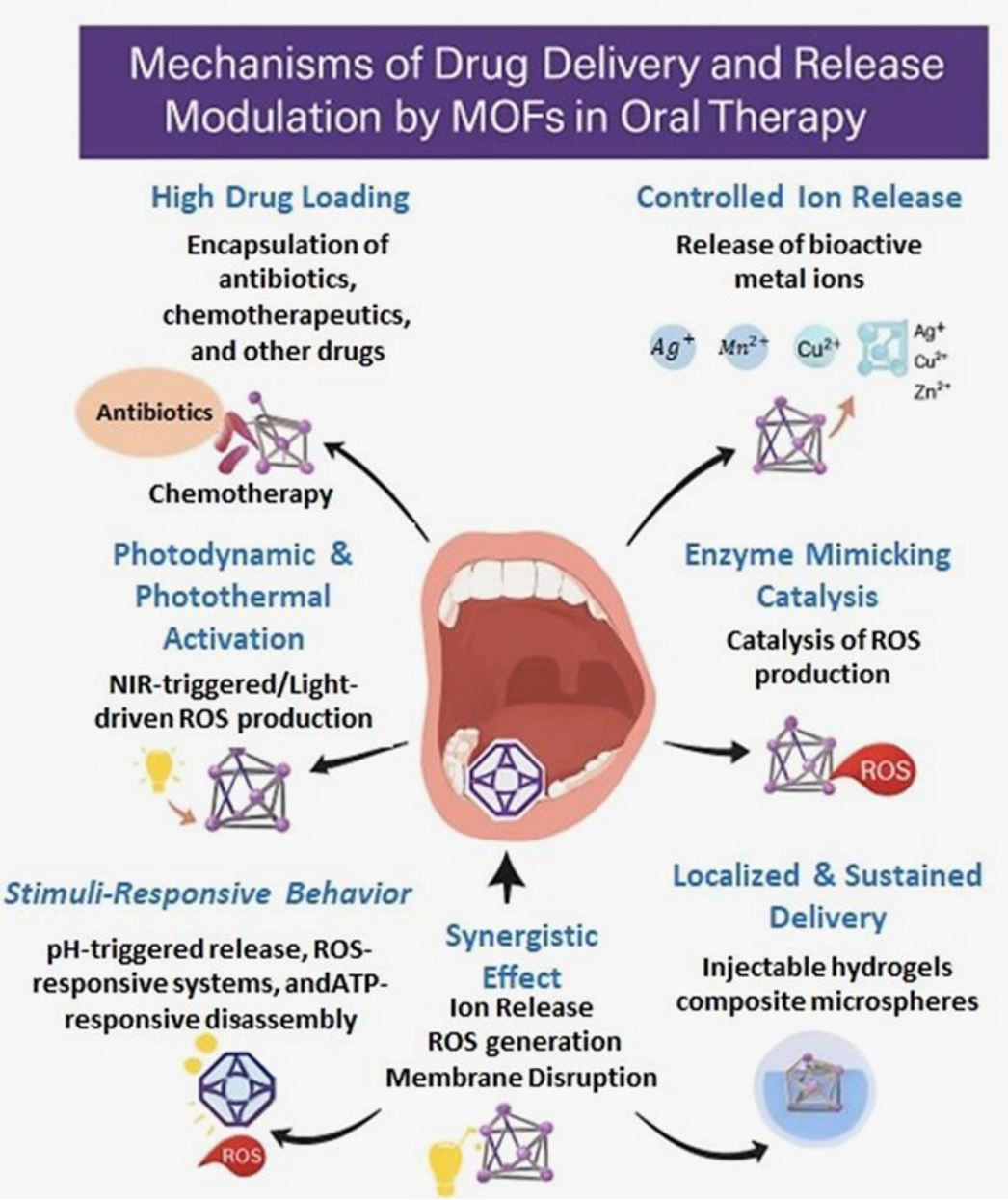

Fig. 4. Multifunctional Drug Delivery Strategies of MOFs in Oral Applications

Secondly, MOFs enable precise drug delivery through their stimulus-responsive behavior. Environmental triggers such as acidic conditions, oxidative stress via ROS, and elevated extracellular ATP levels induce degradation of the MOF system, facilitating targeted drug release in diseased regions, including carious lesions, inflamed periodontal pockets, and tumor tissues, where conventional therapies often demonstrate limited efficacy.

Third, MOFs can be engineered to incorporate phototoxic compounds. Porphyrin-based MOFs generate ROS upon light activation, while hybrid MOFs containing gold and/or copper nanoparticles exploit both photothermal effects and ROS production, enabling synergistic antimicrobial and anticancer therapeutic outcomes [28].

Furthermore, MOFs exhibit high drug-loading capacity owing to their large surface area and tunable pore structures. Accordingly, they can encapsulate antibiotics, chemotherapeutic agents, and antioxidants in a controlled manner. Representative examples include MIL-100(Fe) composites loaded with tetracycline or doxycycline, ZIF-8/hyaluronic acid nanohybrids, and microspheres containing ibuprofen and lansoprazole [30–32,47,48,58,59]. Another important advantage is their ability to integrate multiple therapeutic mechanisms within a single platform. MOFs can simultaneously provide ion release, ROS generation, and cell membrane disruption, thereby enhancing therapeutic efficacy while reducing dosing requirements. In addition, some MOFs possess oxidase-like active sites that enable direct ROS generation without requiring an external energy source [28,29].

Lastly, localized and sustained drug delivery can be achieved using injectable hydrogels and microspheres composed of MOFs, which maintain consistent drug concentrations at sites of infection or inflammation, thereby minimizing systemic toxicity [58,59]. Collectively, these mechanisms illustrate how MOFs have emerged as advanced biomaterials for oral therapy, offering controlled, responsive, and multifunctional drug delivery systems that surpass the capabilities of conventional therapeutic approaches.

Comparison of drug release kinetics: MOFs versus traditional oral delivery methods

Conventional oral drug carriers, including mouth rinses, gels, varnishes, and polymer-based systems, typically exhibit rapid clearance in the oral cavity due to high saliva flow and often display pronounced burst drug release, resulting in limited penetration into biofilms or periodontal pockets [91–93]. In contrast, MOFs offer several unique advantages, notably high pore accessibility, large surface areas, and tunable degradation rates, enabling more controlled and sustained drug delivery (Figure 5).

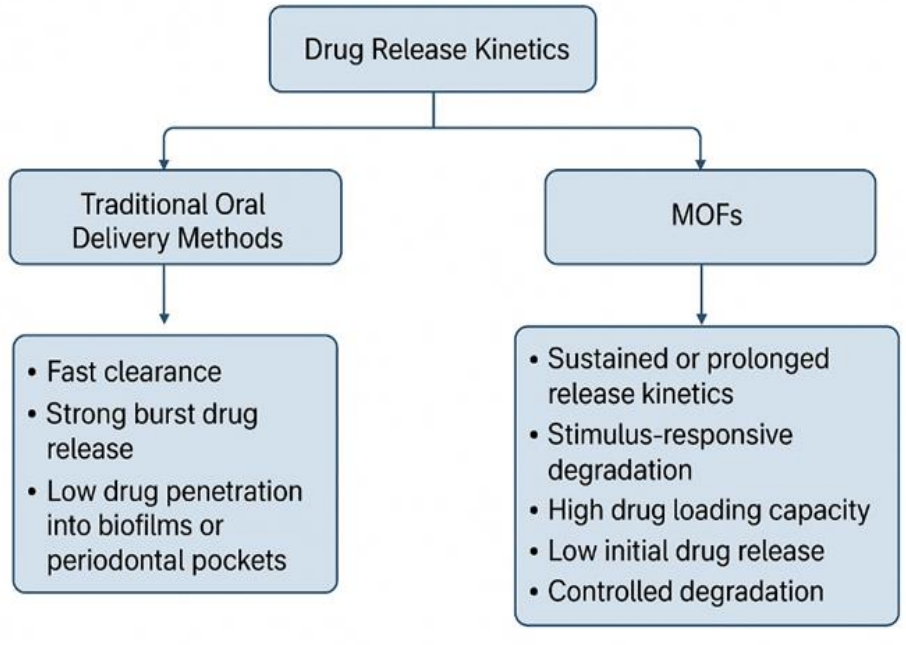

Fig. 5. Flowchart of Drug Release Behavior: MOF-Based Systems vs Conventional Carriers

First, a distinctive feature of MOFs is their sustained release kinetics, facilitated by gradual degradation and continuous liberation of therapeutic ions or drugs. Examples include MIL-100(Fe) enabling controlled release of tetracycline or doxycycline [48] and ZIF-8 carriers delivering multiple drugs over several days [58]. Second, many MOFs studied in oral applications exhibit stimulus-responsive properties, degrading rapidly in acidic, ROS-rich, or ATP-abundant environments, such as those present in caries, infections, or oral cancers. Specifically, pH-sensitive ZIF-8 degrades in cariogenic acidic niches [103], ROS-sensitive Mg-GA hydrogels disassemble within infected periodontal pockets [55], and ATP-responsive Mg-Zn-MOFs release drugs in a site-specific, inflammation-driven manner [56]. Third, MOFs provide remarkably high drug-loading capacity due to their extensive surface areas, often exceeding 3000 m^2/g, combined with controllable pore sizes, allowing incorporation of antibiotics, ions, and photosensitizer molecules [18,20]. Fourth, the ordered pore channels in MOFs minimize initial burst release, thereby enhancing biocompatibility relative to polymeric gels or varnishes [31,36]. Finally, the controlled degradation of MOFs within pathological microenvironments facilitates targeted drug delivery to sites such as periodontal pockets, carious lesions, or tumor tissues, improving therapeutic efficacy while reducing off-target effects [32,54,81].

Altogether, these properties indicate that MOFs can achieve more sustained, selective, and biologically relevant drug release profiles than conventional oral drug-delivery carriers. This advantage has increasingly positioned MOFs as promising next-generation platforms for controlled drug delivery in oral therapy.

Biocompatibility of MOFs in oral applications

Biocompatibility is one of the most critical considerations in translating MOFs from basic research to clinical dental applications. Several studies have shown that MOFs exhibit low cytotoxicity and favorable biological compatibility, supporting their potential as biocompatible materials with minimal adverse effects. For example, Ag-based, Zn-based, and Zn/Co-based metal–organic frameworks have demonstrated strong antimicrobial activity with low cytotoxicity [36–39], whereas magnesium–gallic acid (Mg-GA) hydrogels enhanced alveolar bone regeneration while reducing inflammatory cytokine levels [54]. In addition, Zn/Co-based MOFs exhibited antioxidative and osteogenic effects in ligature-induced periodontitis models, further supporting their dual therapeutic potential and biocompatibility [57]. In oral cancer applications, Zr-MOF-based nanocarriers, including UiO-66 derivatives, and hybrid MOFs encapsulating chemotherapeutic agents such as doxorubicin have shown acceptable biocompatibility, with no evidence of systemic toxicity in animal studies [7,83,84]. Moreover, Dox/Cel/MOFs@Gel composite implants demonstrated effective antitumor activity while preserving the integrity of adjacent organs, further confirming their biosafety [7].

Despite these encouraging results, the review emphasizes the need to establish standardized protocols for evaluating MOF degradation products, immune responses, and pharmacokinetic properties [84]. Long-term biosafety studies and scalable synthetic routes will remain crucial for ensuring the safe use of these materials in clinical applications. Overall, the existing literature suggests that MOFs may be considered biocompatible carriers for oral drug delivery.

Nevertheless, the long-term biocompatibility and potential systemic toxicity of MOF-based systems remain critical considerations for clinical translation. Following administration, partial degradation of MOFs may result in the release of metal ions or organic ligands, which could accumulate in systemic circulation or in organs such as the liver and kidneys. Although most current studies report minimal acute toxicity in animal models, comprehensive long-term evaluations—including chronic toxicity, biodistribution, clearance pathways, and potential immune responses—are still limited. Therefore, future research should incorporate extended in vivo assessments and standardized toxicological analyses to fully elucidate the long-term biosafety profile of MOF-based materials in oral and dental applications.

Challenges and future directions of MOF-based therapeutics in oral disease treatment

Despite their promising therapeutic potential, several challenges and limitations remain regarding the clinical translation of MOFs in oral disease management. First, scalability of synthesis is a major concern: most current MOF fabrication methods rely on complex solvothermal or high-energy procedures, limiting scale-up potential and increasing production costs. The development of green, aqueous-phase, and energy-efficient synthesis techniques is therefore essential to render MOFs clinically viable [42,46,85]. Second, stability in the oral environment remains a moving target, as fluctuations in pH, enzymatic activity, and saliva exposure can accelerate MOF degradation or

alter controlled-release profiles, reducing efficacy. Surface modifications and polymer coatings have been investigated to enhance MOF stability and prolong carrier functionality [54,57]. Third, long-term biocompatibility and toxicity represent a significant research gap. Although many MOFs exhibit low toxicity in vitro and appear safe in short-term animal studies [35,7], thorough in vivo evaluations—including degradation products, immune responses, and pharmacokinetics—are still limited [85]. Fourth, achieving precise stimulation-triggered drug release in the complex oral environment remains challenging. While pH-, ROS-, and ATP-responsive MOFs have demonstrated potential, their reproducibility and predictability require further improvement [54,57]. Finally, regulatory and translational obstacles impede clinical progress, as a lack of standardized safety protocols complicates approval processes. Addressing these issues will require coordinated efforts among scientists, clinicians, and regulatory authorities to ensure safe and effective translation of MOF-based oral therapies [85].

Moving forward, two primary directions can be identified in MOF research for oral therapies: first, the development of greener synthesis methods to reduce cost and environmental impact [85]; and second, the enhancement of surface modification and hybridization with polymers or biologically relevant molecules to improve stability and minimize toxicity [7,83]. Supramolecular engineering of MOFs to respond to oral environmental cues—such as pH, ROS, and ATP—is essential for the design of controlled drug delivery systems [54,55,103]. Platforms that integrate multifunctional capabilities, including antimicrobial, regenerative, and phototherapeutic functions, may offer a comprehensive treatment strategy within a single device [54,7,110]. Further in vivo studies using advanced animal models will be necessary to facilitate thorough translation of these approaches into clinical settings [81,83,85] (Figure 6).

CONCLUSION

Oral health remains a global concern, driving increasing interest in innovative therapeutic strategies that can improve patient outcomes. In this literature review, the versatile role of MOFs in dentistry and their potential to address major clinical challenges have been discussed in detail. MOFs incorporating antimicrobial metals such as silver, zinc, and copper have demonstrated controlled release of biocidal ions and catalyzed ROS generation, making them effective in disrupting pathogenic oral biofilms. Injectable self-healing MOF hydrogels and ATP-responsive bimetallic MOFs have emerged as minimally invasive platforms for targeted periodontitis therapy, with beneficial effects on inflammation, pyroptosis, and alveolar bone regeneration. In oral malignancies, MOF nanoplatforms have enabled combination strategies involving pH-responsive chemotherapy, photodynamic therapy, and photothermal therapy.

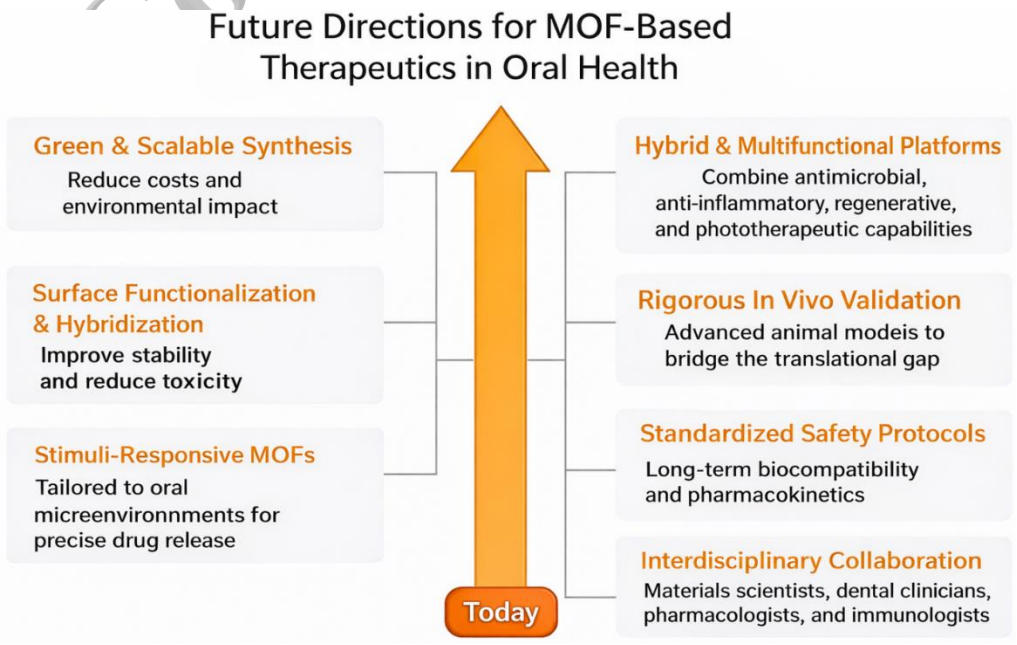

Fig. 6. Strategic Roadmap of Future Directions for MOF-Based Oral Disease Treatment

Meanwhile, lanthanide-doped MOFs show diagnostic potential in theranostic imaging by enabling real-time tracking. Dual-responsive MOF composites have also been developed for caries prevention through controlled delivery of antimicrobial ions, calcium, and phosphate ions, together with photothermal effects against cariogenic bacteria. Despite this considerable promise, several obstacles must be overcome before clinical translation. Scalable and environmentally friendly synthesis methods are needed, along with comprehensive long-term investigations of biocompatibility and immune responses. Improving responsiveness to multiple stimuli and developing hybrid MOFs capable of providing analgesic, antimicrobial, and regenerative effects within a single platform will also be essential. In conclusion, MOF-based materials are at the forefront of preventive, therapeutic, and restorative dentistry. By integrating nanotechnology with dental science, MOF-based strategies have strong potential to transform dental healthcare toward greater precision, minimal invasiveness, and personalization.

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TND; project administration, conceptualization, supervision, writing–review & editing; **ATD**; investigation, writing–original draft preparation

CONFLICTS OF INTEREST

There are no conflicts to declare.

AI STATEMENT

The authors acknowledge that AI-assisted tools were used to improve the clarity of the manuscript and to generate some schematic figures. All scientific content, interpretations, and conclusions were developed and verified by the authors, who take full responsibility for the accuracy of the work.

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