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Recent advancements in oxygen-releasing materials for tissue regenerative medicine and wound healing

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ABSTRACT

Oxygen-releasing biomaterials have been used to resolve hypoxia-related challenges in tissue regeneration and wound healing process. This group of biomaterials has practical challenges, such as oxidative stress, biocompatibility, and high manufacturing costs. This review focuses on the role of oxygen in cellular metabolism, angiogenesis, collagen production, and immune response for chronic and ischemic wounds. Typical oxygen-releasing biomaterials, including peroxide-based compounds (e.g., calcium- and magnesium-based), metal-organic frameworks (MOFs), hemoglobin-based oxygen carriers (HBOCs), perfluorocarbons (PFCs), zeolites, and cyclodextrin-based nanosponges are described and discussed. Other mechanisms, such as hydrolysis, enzymatic activity, and stimuli-responsive release are reviewed, highlighting their applications in tissue regeneration and chronic wound care. Current challenges are also presented, along with an outline of future directions to the development of next-generation oxygen-releasing biomaterials for clinical translation.

1. Introduction

Oxygen is essential for regeneration and recovery of damaged tissues or wounds in the body system, a process that involves the stages of hemostasis, inflammation, proliferation, epithelialization, and remodeling [1–3]. The oxygen level in the tissues regulates energy production and cellular activity during wound healing through aerobic respiration [4]. The rate and yield of wound healing are proportional to the effective consumption of oxygen [5]. In addition, the oxygen radicals against pathogens helps the immune system combat and reduces the risk of infection [6]. The cells utilize oxygen to break down glucose in the mitochondria, resulting in the synthesis of ATP, which is the primary energy source for the cells [7,8]. Aerobic respiration, which depends on oxygen to produce ATP, generates more energy than anaerobic respiration, yielding up to 38 ATP molecules per glucose molecule, in

contrast to only 2 ATP molecules produced in anaerobic conditions [9, 10]. This efficiency stems from oxygen acting as the final electron acceptor in the aerobic respiration process, enabling the oxidation of nutrients [11]. Thus, organisms employing aerobic respiration are better adapted to environmental conditions, thus benefiting from an evolutionary advantage, such as photosynthesis [12]. These organisms convert carbon dioxide (CO₂) and water (H₂O) into glucose [13]. Oxygen also helps decomposing fungi and bacteria, while insects employ oxygen to break down organic material, releasing CO₂ back into the atmosphere [14]. Clinical studies have shown that the rate of bacterial infection in patients who were given air mixtures containing 80 % oxygen (compared to normal room air, which contains about 21 %) decreased by 50 % compared to the control group [15]. Oxygen undertakes the hydroxylation of proline and lysine residues for the collagen stability [16]. Many studies have shown that collagen synthesis decreased and

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matrix metalloproteinase-1 (MMP-1) synthesis increased under hypoxic conditions, indicating a delayed healing [17]. In addition, oxygen promotes angiogenesis through the release of molecules such as vascular endothelial growth factor (VEGF) into circulation [18]. Animal studies have shown that 100 % oxygen exposure increased angiogenesis, whereas angiogenesis decreased for 13 % oxygen exposure [19]. Oxygen helps the production of nitric oxide that regulates vascular tone, promotes angiogenesis, and contributes to new vessel formation by increasing the mobilization of endothelial progenitor cells (EPCs) [20].

Hypoxia yields collagen synthesis reduction, weakened wound strength, and a delayed healing process [21,22]. It negatively affects angiogenesis and disrupts the flow of blood and nutrients to the damaged region [23]. Prolonged hypoxia triggers apoptosis (programmed cell death) in cells involved in the healing process. For example, a decrease in mitochondrial membrane potential (MMP) and early apoptosis signs were observed in L929 and HUVEC cells under hypoxic conditions [24]. Prolonging inflammation through the increased production of pro-inflammatory cytokines (e.g., IL-6 and TNF- α) was also observed for hypoxia. For instance, in RAW264.7 cells, IL-6 and TNF- α levels increased over 24 h compared to the control group [24].

Prolonged hypoxia leads to the excessive activation of molecular signals such as hypoxia-inducible factor (HIF-1) [25]. Chronic hypoxia results in the excessive expression of these factors and an inhibitory effect on wound healing [22]. They block the processes of neo-vascularization and angiogenesis, thus weakening the impact of epithelialization processes [26]. An example of existing biomaterial groups for regenerative medicine is the family of polymer-bioactive glass nanocomposite that can significantly enhance the mechanical performance and degradation behavior of tissue scaffolds. Experimental evaluations on PLA/BG nanocomposites show that incorporating surface-treated nanoparticles leads to improved mechanical integrity and controlled biodegradability, both critical features for bone tissue regeneration [27].

This review aims to address the latest technological advancements, mechanisms, and clinical application potential of oxygen-releasing biomaterials, such as hydrogels, polymer microspheres, and 3D scaffolds. It provides innovative solutions to overcome the hypoxia-related healing barriers of chronic wounds and ischemic tissues are discussed by highlighting the persistent challenges, such as oxidative stress, biocompatibility limitations, and sustainable release kinetics, as well as the success of these materials in enhancing angiogenesis and cell

functions (Fig. 1).

2. Types of oxygen-releasing materials

An overview of oxygen-generative biomaterials is summarized in Table 1 based on their mechanisms and sources. They are explained in details in the following sections.

2.1. Peroxides and percarbonates

Calcium peroxide (CaO_2) is an inorganic peroxide compound, which consists of calcium and oxygen, commonly used as an oxygen-releasing agent not only in biomedical applications but also in various non-medical fields, including agriculture and environmental implementations. It appears as a white, water-insoluble powder that undergoes hydrolysis to produce hydrogen peroxide (H_2O_2) and subsequently decomposes into water and oxygen. This controlled oxygen release property makes CaO_2 particularly useful in wound healing and tissue regeneration applications, where oxygen deficiency (hypoxia) is a critical challenge (Fig. 2). CaO_2 undergoes a two-step decomposition process in aqueous environments according to the following chemical reaction (Reactions (1) and (2)):



The first reaction indicates the hydrolysis of CaO_2 to calcium hydroxide and H_2O_2 in the presence of water molecules, and the second reaction defines the catalytic decomposition reaction of H_2O_2 to water molecules and oxygen atoms. This reaction mechanism enables a sustained release of molecular oxygen to the target tissue or wound zone. Furthermore, the alkaline pH generated by Ca(OH)_2 and the release of reactive oxygen species (ROS) from H_2O_2 decomposition create an unsuitable environment for anaerobic pathogens such as Clostridium and Bacteroides [40]. Besides, controlled and maintained Ca^{2+} release induces calcium stress in bacterial cells, impairing metabolic functions and enhancing bactericidal activity. This dual antimicrobial action reduces infection risks without inducing antibiotic resistance and effectively prevents bacterial infection in the damaged area. Ca^{2+} ions activate calcium-sensing receptors such as PI3K/AKT and MEK/ERK signaling pathways, promoting fibroblast keratinocytes migration, proliferation, and extracellular matrix (ECM) deposition [41]. H_2O_2 acts as a signaling molecule at low concentrations ($<100 \mu\text{M}$), stimulating

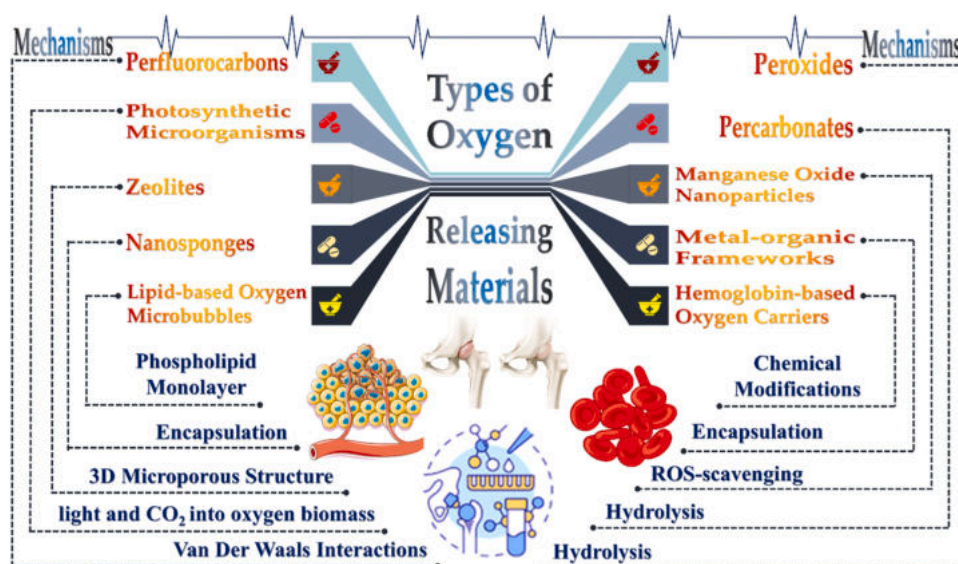


Fig. 1. Schematic of the main types of oxygen-releasing materials.

Table 1

Overall comparison of the materials used in oxygen-releasing biomaterials in bioengineering applications [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38].

Biomaterial Type	Oxygen Release Mechanism	Typical Release Kinetics	Common Fabrication Methods	Primary Target Tissue/Application Examples	Key Advantages	Key Challenges/Limitations	Representative application	Clinical Outcome
CaO ₂	Hydrolysis followed by H ₂ O ₂ decomposition	Sustained, Tunable	Incorporation into scaffolds, encapsulation, and surface coating	Bone, cartilage, pancreatic islets, and wound healing	High purity, cost-effective, controllable release	Potential for burst release, pH increase	Chronic / diabetic wounds; bone defects	Almost 100 % wound closure by day 14 compared to 70 % closure for control; Bone volume fraction 50 % vs 31 % for control sample at 8 weeks
Sodium Percarbonate	Direct decomposition to carbonate, H ₂ O ₂ , then oxygen	Fast initially, then slower	Incorporation into films, scaffolds	Wound healing, muscle injury, and skin flap survival	Rapid oxygen release can delay necrosis	Potential for rapid release, alkaline pH shift	Myocardial infarction; large bone defects	15 % increase in left-ventricular ejection fraction vs. untreated Myocardial infarction; Bone volume fraction 65 % vs. 39 % control
MgO ₂	Hydrolysis followed by H ₂ O ₂ decomposition	Very slow, Prolonged	Incorporation into scaffolds	Applications requiring very long-term oxygen release	Very slow release	Lower purity, slower reaction rate	Hypoxia-sensitive tissue constructs (preclinical)	Significantly improved cell viability and metabolic activity under hypoxia vs. non-oxygen scaffolds
MOFs	Oxygen release upon de-adsorption	Very slow, Prolonged	Incorporation into scaffolds	Applications requiring very long-term oxygen release	Very slow release	Potential cytotoxicity	Bone and wound scaffolds (small-animal models)	Enhanced angiogenesis and tissue regeneration vs. MOF-free controls;
HBOCs	Reversible binding and release of oxygen	Dependent on pO ₂	Encapsulation in liposomes, nanoparticles	Blood substitutes, tissue oxygenation	High oxygen-carrying capacity	Stability issues, potential toxicity, short duration	Local oxygen delivery	Improved tissue oxygen tension and short-term graft/cell survival; systemic use limited by oxidative toxicity
PFCs	The high solubility of oxygen, release is dependent on pO ₂	Dependent on pO ₂ , tunable	Emulsions, incorporation into hydrogels	Artificial blood substitutes enhance cell survival	High oxygen solubility, chemically inert	Poor control over release, short duration	Chronic wounds	3–4 fold increase of pO ₂ in local tissue
LOMs	Oxygen-laden core with surfactant shell	Short-term	Intravenous injection	Addressing acute hypoxemia	Can transport oxygen through the bloodstream	Short duration, potential hemodynamic effects	Acute hypoxemia	Rapid but transient oxygenation; suitable for acute use rather than sustained healing
Oxygen-Laden Dextran Nanosponges	Entrapment and release of oxygen	Tunable	Incorporation into various matrices	Enhancing cell viability under anoxic conditions	Sustained release possible	Relatively novel technology	Cell survival under hypoxia	Maintained cell viability for 24–48 h under hypoxia/anoxia vs. rapid loss in controls

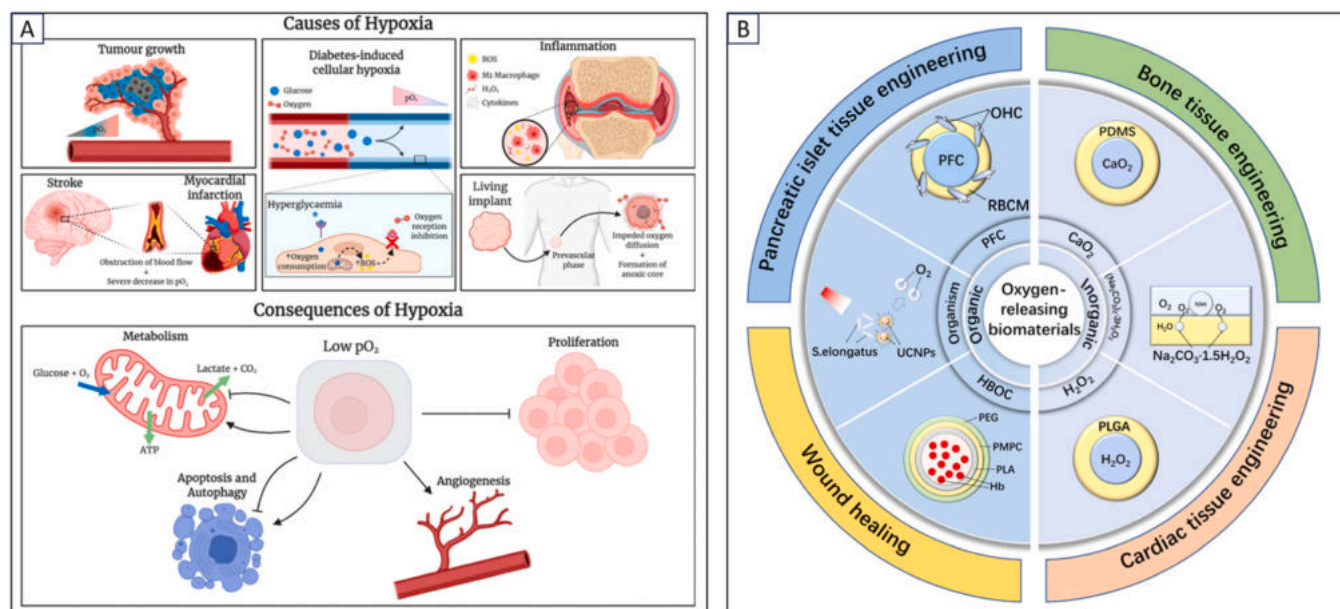


Fig. 2. (A) Incidents leading to hypoxia and the results on cellular metabolism and behavior [39], (B) Types of materials used for oxygen release in biomedical purposes [29].

angiogenesis and collagen deposition. This accelerates re-epithelialization and granulation tissue formation. In bone grafts, CaO₂ serves as an oxygen releaser, which supports osteoblast viability in avascular regions, and calcium ions are supplied to contribute to mineralized matrix deposition in the target area [42]. Mg²⁺ ions play critical roles in cellular metabolism, ATPase activation, and DNA repair. They modulate inflammatory responses by reducing pro-inflammatory cytokines (e.g., TNF- α , IL-6) and enhancing anti-inflammatory signaling [43]. MgO₂ is another inorganic compound consisting of magnesium cations (Mg²⁺) and peroxide anions (O₂²⁻). It is a white or grayish powder that decomposes to release oxygen (O₂) and magnesium hydroxide (Mg(OH)₂) in aqueous environments like CaO₂. It was demonstrated that Mg²⁺ ions play critical roles in cellular metabolism, ATPase activation, and DNA repair. They modulate inflammatory responses by reducing pro-inflammatory cytokines (e.g., TNF- α , IL-6) and enhancing anti-inflammatory signaling. Furthermore, Mg²⁺ ions promote keratinocyte proliferation and re-epithelialization by activating integrin and mitogen-activated protein kinases (MAPKs) pathways [44]. Mg²⁺ is also essential in bone tissue engineering for osteoblast differentiation and bone mineralization. MgO₂-doped scaffolds promote and enhance osteogenesis by providing oxygen to cells in avascular regions and releasing Mg²⁺ to stimulate runt-related transcription factor 2 (RUNX2) and osteocalcin expression [45]. In cartilage repair, MgO₂ mitigates hypoxia in deep tissue layers, supporting chondrocyte viability and glycosaminoglycan synthesis. The other characteristics and working pathway of peroxide-based materials act the same as CaO₂.

Percarbonates, most commonly as sodium percarbonate (Na₂CO₃·1.5H₂O₂), use the hydrolysis of H₂O₂ to release oxygen upon dissolution. A temporary source of oxygen is provided as the H₂O₂ is decomposed by catalase (CAT) or peroxidases in aqueous environments [46,47]. In comparison with peroxides, percarbonates possess higher stability and can be handled more easily in their crystalline form, making them more suitable for wound healing and tissue engineering systems. Although the challenge of percarbonates is the inconsistent release kinetics and the dependency on local enzyme activities, meanwhile, the risk of cytotoxicity is raised with H₂O₂ being the byproduct of the mechanism. Percarbonates are often incorporated in hydrogels and polymers to control the release kinetics [48].

2.2. Manganese dioxide nanoparticles

Manganese dioxide (MnO₂) is a versatile inorganic compound with diverse applications across different industrial areas, including energy storage, catalysis, and environmental remediation. The practical applications of MnO₂ in wound healing and tissue regeneration are less explored compared to other areas. MnO₂ also plays a crucial role in modulating the oxidative microenvironment, mitigating oxidative stress, and supplying oxygen to hypoxic tissues. In addition, its unique enzymatic mimetic activity allows it to function as a “nanozyme”, mimicking natural peroxidase, CAT, and superoxide dismutase (SOD) activities [49]. MnO₂ not only dissociates to manganese ions and H₂O₂ but also demonstrates ROS-scavenging properties, converting harmful superoxide radicals (O₂^{•-}) and H₂O₂ into less toxic molecules, which enable effective and swift decomposition of ROS molecules to release oxygen into the target area [50]. MnO₂ nanozymes also enhance the efficacy of photodynamic and photothermal therapies (PDT/PTT) for treating infected wounds by significantly accelerating wound healing by eliminating bacterial biofilms while maintaining a favorable oxidative balance [51]. Mn²⁺ ions stimulate osteogenesis by activating alkaline phosphatase (ALP) and osteocalcin expression that promotes mineralization. The catalytic degradation of H₂O₂ also reduces oxidative damage to osteoblasts in inflammatory bone defects. MnO₂-functionalized cardiac patches oxygenate ischemic myocardium, reducing infarct size and apoptosis [52]. Mn²⁺ ions also improve endothelial function by up-regulating nitric oxide synthase (eNOS), enhancing vasodilation and perfusion.

Beyond the qualitative description above, several studies have quantified the dual oxygen-releasing and ROS-regulating behavior of MnO₂ nanozymes. For example, Yu et al. designed a δ -MnO₂@graphene oxide SOD nanozyme that achieved a 95.5 % inhibition rate toward superoxide radicals, corresponding to a 222.6 % and 1605.4 % increase in SOD-like activity relative to graphene oxide and bare MnO₂ nanoparticles, respectively, confirming the high intrinsic ROS-scavenging efficiency of the MnO₂ active sites [53]. Gu et al. developed a tannic-acid-modified MnO₂ nanozyme (MnO₂@TA) with combined SOD- and CAT-like activity; in TGF β -stimulated cardiac fibroblasts, MnO₂@TA markedly reduced DCFH-DA ROS fluorescence and down-regulated α -SMA, collagen I, fibronectin, and periostin, while in a murine myocardial infarction model it significantly improved

left-ventricular ejection fraction and reduced fibrosis without detectable organ toxicity, demonstrating that MnO₂-based nanozymes can safely normalize pathological oxidative stress *in vivo* [54]. In the context of infected skin defects, Wen et al. incorporated a CN-MnO₂ nanozyme into a poly(L-lactic acid) dressing; the MnO₂ component catalytically decomposed endogenous H₂O₂ to generate O₂ while exerting GPx-like GSH-consumption activity. In a rat wound model co-infected with *S. aureus* and *P. aeruginosa*, this dressing achieved a wound healing rate exceeding 99 % and almost complete wound closure by day 14, compared with $\approx$ 86–88 % closure for blank and PLLA dressings and 94.4 % for CN/PLLA controls, and provided biofilm-resistance rates of 83 % and 62 % against *S. aureus* and *P. aeruginosa*, with an overall antibacterial rate of 99 % [55]. Consistently, Jiang et al. reported MnO₂-Au nanoflower-loaded hydrogels that rapidly cleaved H₂O₂ *in vitro*, markedly reduced DHE-detected ROS levels in diabetic wound tissue, and yielded the highest wound-closure percentages among treatment groups by day 14 in a diabetic rat model [56]. These quantitative data reveal that MnO₂ nanozymes can simultaneously catalyze H₂O₂ decomposition into O₂ and scavenge excess ROS via SOD/CAT/GPx-like activities, thereby alleviating hypoxia and normalizing the redox microenvironment in a synergistic manner that underpins the improved infection control, angiogenesis, and tissue regeneration.

2.3. Metal-organic frameworks

Metal-organic frameworks (MOFs) are a class of highly porous crystalline materials composed of metal ions coordinated with organic linkers. MOFs consist of two fundamental components: (i) ions of transition metals, including Zn²⁺, Cu²⁺, Fe³⁺, Co²⁺, and Zr⁴⁺, which serve as coordination centers for ligand attachment, and (ii) bridging organic ligands, which contain carboxylate (-COO⁻), amine (-NH₂), or imidazolate groups that coordinate to metal centers [57]. The most common organic linkers in MOFs include 1,4-benzenedicarboxylate (BDC, derived from terephthalic acid), 2-methylimidazole (HmIm, the linker in ZIF structures), 1,3,5-benzenetricarboxylate (BTC, derived from trimesic acid), and bipyridine derivatives (BPY). Due to their high surface area, tunable porosity, and excellent host-guest chemistry, MOFs have been widely explored for gas storage, catalysis, drug delivery, and other biomedical applications [58]. In wound healing and tissue regeneration, oxygen-releasing MOFs are utilized to supply molecular O₂ to hypoxic tissues, enhancing wound healing rates and regenerative capacity. Since MOFs have an exceptionally high specific surface area that can reach 14600 m²/g [59], they can store oxygen and release it controllably. Moreover, the tunable pore size facilitates gas diffusion and prolonged oxygen delivery at the wound site [60]. MOFs are mostly engineered to store and gradually release O₂ via encapsulation of oxygen-rich species such as H₂O₂ and CaO₂ or incorporating catalytic decomposition of oxygen donors, including Mn, Co, or Fe active sites, which catalyze H₂O₂ decomposition into O₂. Some of the MOFs, like ZIF-8 (zeolitic imidazolate framework), Fe-MOFs, and Cu-based MOFs, are classified as biodegradable as they gradually dissolve, releasing metal ions that can further promote angiogenesis and tissue remodeling in the damaged tissue area [61]. For instance, ZIF-8 decomposes into non-toxic zinc ions and organic ligands under physiological conditions [62]. MOFs can also be treated with various biomolecules such as chitosan, peptides, and hydrogels to enhance biocompatibility and reduce cytotoxicity [63]. Moreover, MOFs are usually incorporated into biopolymeric hydrogels, which are mostly alginate, chitosan, and gelatin, to establish moist and oxygenated wound microenvironments. Thus, these composite materials prevent tissue dehydration while ensuring a sustained release of oxygen, promoting faster healing [64]. MOFs can also co-deliver oxygen and therapeutic agents, including antibiotics and growth factors, to synergistically enhance healing [65]. In addition, their porous structure allows the integration of nanoparticles, particularly for antimicrobial activity, containing Ag or Zn, which prevents the infection while healing

the wound in the target area [66].

2.4. Hemoglobin-based oxygen carriers

Hemoglobin (Hb) is a tetrameric protein composed of two α and two β globin chains, each containing a heme group that binds O₂ [67]. The Hb molecules have a short plasma half-life (a few minutes) due to rapid clearance in the blood. Oxidative damage occurs due to Hb auto-oxidation to methemoglobin (MetHb), which cannot bind O₂. In order to overcome the limitations of free Hb, hemoglobin-based oxygen carriers (HBOCs) appear as an alternative implementation for O₂ release in the damaged tissues. HBOCs are engineered biomaterials designed to mimic the oxygen-transport function of red blood cells. These systems address hypoxia in chronic wounds and enhance tissue regeneration through controlled oxygen delivery. HBOCs are engineered using chemical modifications or encapsulation techniques, ensuring stability, prolonged circulation, and controlled O₂ release. HBOCs retain the ability of the heme group to bind and release oxygen reversibly. Modifications (e.g., polymerization, crosslinking) stabilize Hb tetramers, preventing dissociation into toxic dimers [68]. Oxygen affinity (P₅₀) is tunable to match physiological needs, ensuring optimal oxygen release in hypoxic tissues and exhibiting extended shelf life (>1 year) at room temperature, unlike sensitive red blood cells [69]. There are various types of HBOCs, including polymerized hemoglobin (PolyHb), which are chemically crosslinked with agents such as glutaraldehyde, maleimide, or dextran polymers [70]. Hb can be encapsulated within liposomes, polymeric nanoparticles, or hydrogels to form artificial oxygen carriers [71]. PEGylated hemoglobin (PEG-Hb) is another HBOC, comprising polyethylene glycol (PEG) chains that are conjugated to Hb, thus creating a hydrophilic shield that prevents immune clearance [72]. In hemoglobin-metal hybrid HBOCs, Hb molecules are immobilized on MOFs or nanoscale metal oxides, enhancing oxygen diffusion and stability [73].

2.5. Perfluorocarbons

Perfluorocarbons (PFCs) are synthetic, fluorinated hydrocarbons – whose hydrogen atoms are replaced by fluorine – with a superior ability to dissolve and transport gases, particularly oxygen, while possessing inert and non-polar characteristics. Their high oxygen solubility, biocompatibility, and chemical stability make them ideal candidates in wound healing and tissue engineering, where oxygen supply plays a critical role in cell proliferation, angiogenesis, and ECM formation. The capability of PFC's dissolving is 20–50 times more than water (up to 44 mM) and 4 times more than blood plasma, enabling efficient oxygen delivery to hypoxic tissues [74]. Their strong C–F bonds make them chemically and biologically inert, minimizing toxicity risks, improving tissue penetration, and reducing biofilm formation at wound sites. They can remain stable at room temperature for over a year, eliminating the need for cold-chain storage and making them more practical for clinical use. Since PFCs are immiscible in water, they require emulsification or encapsulation to be used in wound healing and tissue regeneration [75]. Therefore, stabilized nanoemulsions or polymer coatings are applied to the material to enhance its biocompatibility and dispersibility in biological fluids. PFCs dissolve oxygen via van der Waals interactions and release it along concentration gradients into hypoxic tissues. Therefore, they are often incorporated into chitosan-, alginate-, or gelatin-based hydrogel wound dressings to create a moist, oxygenated microenvironment [29]. Moreover, supersaturated oxygen emulsion systems are utilized to increase tissue oxygenation by up to 4-fold in hypoxic tissue to enhance accelerated granulation and angiogenesis of human keratinocytes [76]. Perfluorodecalin (PFD), Perfluorooctyl Bromide (PFOB), and Perfluorotributylamine (PFTBA) are the most employed PFC materials in wound healing and tissue regeneration. There are some commercially available PFC-based emulsions, such as Oxycyte® and Perfortan®, that are safe to be used at controlled doses for injured

individuals [77].

2.6. Photosynthetic Microorganisms

The incorporation of photosynthetic microorganisms such as microalgae and cyanobacteria into biomaterials has emerged as an innovative way of oxygen release, to solve the limited ways of the past studies. These microorganisms are capable of converting light and CO₂ into oxygen biomass, and unlike passive carriers, they provide sustained release of oxygen as long as a light source is provided. In the early works of Hopfner et al. [78], and Schenck et al. [79], biocompatible scaffolds were embedded by microalgae. The studies showed that the photosynthetic activity reduced hypoxia in co-cultured fibroblasts, and algae-containing scaffolds showed more survival and functionalities in mouse skin defects. Continuing this concept, Fu et al. [80], developed hydrogels incorporated with microalgae to produce dissolved oxygen concentrations of 6.13 mg/L, sustaining for 7 days under adequate illumination. Furthermore, in an oxygen-depleted environment, the system provided 60 days of oxygen, showing the remarkable potential of photosynthetic microorganisms. In addition, the study reported that the scaffold design not only provides a viable environment for microorganisms but also increases the oxygen-releasing capabilities, which is crucial in clinical biomaterials applications. These *in vivo* experiments showed evidence of the therapeutic potential of biologically driven oxygen-releasing microorganisms to be further studied and utilized in tissue repair and regenerative medicine.

2.7. Zeolites

Zeolites are porous, crystalline aluminosilicates with a highly ordered structure and exceptional ion exchange and gas adsorption capabilities. They have a 3D microporous framework of SiO₄ and AlO₄, providing a tunable porosity with high surface area (300–1000 m²/g), which facilitates high-capacity oxygen adsorption, allowing them to adsorb and release oxygen molecules in a controlled manner [81]. Their microporous structure (pore diameter ~0.5 – 2 nm) is capable of adsorbing oxygen via van der Waals forces, acting as reservoirs to then sustain oxygen release. Besides being extensively utilized in catalysis and adsorption, zeolites are also utilized in wound healing and tissue regeneration. Their bioactivity, antimicrobial properties, and ability to regulate the wound microenvironment make them highly promising candidates for advanced wound dressings and tissue scaffolds. Zeolites are resistant to thermal degradation and chemical corrosion, which maintains their structural integrity during wound healing [82]. Furthermore, the modification of zeolites with metal doping further enhances oxygen storage and catalytic oxygen generation. Zeolites can exchange Na⁺, Ca²⁺, K⁺, and Mg²⁺ ions, influencing cell adhesion, proliferation, and differentiation [83,84]. Moreover, specifically-modified zeolites with silicon and calcium-releasing capability stimulate osteogenesis and angiogenesis in both bone and soft tissue healing. Specifically, silicon ions upregulate BMP-2 and RUNX2 genes, driving stem cell differentiation into osteoblasts [85]. Zeolites remain stable under physiological conditions (pH 5–9, 37 °C), thus allowing long-term functionality in wound environments.

2.8. Nanosponges

Cyclodextrin-based nanosponges are highly porous, hyper-crosslinked polymer networks formed by reacting cyclodextrins and cyclic oligosaccharides with a hydrophobic cavity and hydrophilic exterior with crosslinkers, mostly by diphenyl carbonate or carbonyl diimidazole [86]. Specifically, these nanosponges consist of cross-linked β-cyclodextrin or γ-cyclodextrin units, resulting in a highly porous matrix. They are utilized to encapsulate and control the release of bioactive molecules, including oxygen-releasing agents, antimicrobial compounds, and growth factors [87]. Furthermore, the hydrophilic exterior

and hydrophobic cavities of these sponges allow them to encapsulate oxygen donors, including H₂O₂, PFCs, and sodium percarbonate [88]. Depending on the crosslinker utilized in the synthesis of cyclodextrin (e. g., diphenyl carbonate or diisocyanates) and polymer ratios in the blend, pore size can be tailored from 0.25 μm to 2.5 μm with a high surface area exceeding 500 m²/g, which facilitates precise oxygen-release over therapeutic delivery. Oxygen is physically adsorbed or chemically bonded via host-guest interactions within pores. This complex structure prevents premature oxygen degradation and ensures gradual oxygen diffusion, maintaining an oxygen-rich microenvironment that is essential for wound healing. Cyclodextrins are approved polysaccharides by the FDA because of their non-toxicity and biodegradability [89]. The release of oxygen can be tailored by adjusting the pH in the wound area, where oxygen releases faster in acidic wound microenvironments at a pH between 5 and 6.

2.9. Lipid-based oxygen microbubbles

Lipid-based oxygen microbubbles (LOMs) are vesicles in the size range of micron- or submicron- with a phospholipid monolayer encapsulating oxygen, being explored as therapeutic carriers of oxygen for disorders involving hypoxia and tissue engineering applications [90]. LOMs are protected by a biocompatible and mechanically stable lipid shell, while the core enables oxygen release upon diffusion and physical disruption. Moreover, an advantage of LOMs is the ability to release oxygen without producing any cytotoxic byproducts, making them a suitable candidate for tissue engineering. Passive diffusion and external triggers provide the driving force of the oxygen release in LOMs, and oxygen gradually diffuses out of the microbubble core, creating a localized oxygen gradient [91]. In addition, on-demand oxygen delivery could be potentially applied by using ultrasound exposure to induce cavitation, allowing the oxygen delivery with precision, utilized in cancer therapy [92]. Despite the advantageous properties, LOMs face an important challenge. Their short circulation half-life (typically minutes) prevents the long-term oxygen release, but to overcome this, studies have used strategies like PEGylation, incorporation of cholesterol, and conjugation of targeting ligands to prolong the stability and sustain the oxygen release [93].

2.10. Summary of the various options and selection criteria

From a translational standpoint, the long-term biocompatibility of oxygen-releasing systems is as critical as their oxygen-release kinetics. The main material families discussed in this review clearly differ markedly in degradation pathways, by-products, and potential for chronic tissue accumulation, which in turn shape their safety profiles *in vivo*. Inorganic peroxides such as CaO₂ and MgO₂ and percarbonate salts are considered attractive because they ultimately degrade to benign inorganic ions (Ca²⁺, Mg²⁺, carbonate) and water, without long-term persistence in organs [94]. Their decomposition unavoidably generates H₂O₂ and local pH shifts, so the therapeutic window is defined by a balance between alleviating hypoxia and avoiding ROS-mediated damage. Multiple *in vivo* studies in bone and chronic wound models show that when peroxides are embedded in hydrogels or polymeric microspheres and used at optimized loadings, they support tissue regeneration without chronic toxicity. For example, CaO₂- or sodium percarbonate-loaded hydrogels and microsphere systems have been reported to maintain elevated oxygen tension for days to weeks while yielding normal granulation tissue, minimal sustained inflammation, and improved closure in diabetic and ischemic wounds [95]. Similarly, CaO₂-containing scaffolds for bone repair improved bone volume and vascularization in long-term rodent and large-animal defect models without evidence of systemic organ damage, provided that burst release was controlled by encapsulation [96]. Collectively, these data suggest that peroxide/percarbonate donors have a favorable long-term safety profile when their release is moderated by appropriate matrices and

when local pH and ROS are kept within physiological adaptation limits.

MOF-based oxygen-releasing systems offer unparalleled tunability of porosity and co-delivery, but their chronic biocompatibility is more composition-dependent and less mature from a regulatory perspective. Systematic analyses of MOF biocompatibility show that frameworks based on endogenous or low-toxicity metals (e.g., Fe, Zr, Zn) and carboxylate/imidazolate linkers can be well tolerated *in vitro* and in small-animal models at dosages below defined thresholds, whereas Cu- and Co-based systems and high particle burdens are associated with greater risks of oxidative stress, inflammation, and organ retention [97]. Biodistribution and pharmacokinetic studies indicate that nanoscale MOFs often accumulate in the liver and spleen and are cleared only gradually, with partial dissolution into metal ions and ligands over weeks to months. Although several bio-MOFs have now demonstrated promotion of osteogenesis, angiogenesis, and antibacterial activity when used as coatings or hydrogel fillers, long-term (>3–6 months) toxicology and immunogenicity data remain limited compared with simple inorganic peroxides [98]. Consequently, MOF-based oxygen-releasing biomaterials should currently be regarded as highly promising but still “emerging” platforms, for which careful selection of metal–ligand chemistry, particle size, and degradability—as well as surface functionalization with biopolymers is essential to mitigate the risk of chronic metal overload and off-target accumulation.

PFC-based oxygen carriers have the longest and most extensive *in vivo* safety record among the systems covered in this review, owing to decades of development as blood substitutes and contrast media. PFCs are chemically and biologically inert, do not undergo metabolic transformation, and are eliminated predominantly via pulmonary exhalation after transient uptake by the reticuloendothelial system [99]. Clinical and preclinical data on emulsions such as Perftoran and dodecafluoropentane show that repeated dosing is generally well tolerated, with adverse events largely related to droplet size, surfactant formulation, and high intravenous doses (e.g., transient flu-like symptoms or complement activation), rather than to intrinsic PFC chemistry [100]. Importantly for regenerative medicine, several PFC-loaded hydrogels and dressings tested in chronic wound, cardiac, and neural injury models have demonstrated enhanced tissue oxygenation, angiogenesis, and functional recovery, accompanied by minimal local inflammation and no significant systemic toxicity, over follow-up periods of weeks to months. This combination of chemical inertness, well-characterized pharmacokinetics, and accumulating animal and early clinical data suggests that PFC-based constructs currently hold a comparative advantage for long-term systemic or repeated local oxygen delivery, provided that emulsion stability and droplet size are tightly controlled [101].

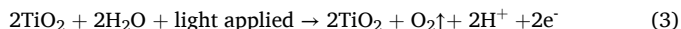
All in all, direct head-to-head and long-term *in vivo* studies that compare all three platform classes under identical conditions are still scarce; nevertheless, the existing literature allows some cautious, mechanism-based differentiation of their safety profiles. Peroxide/percarbonate donors are fully resorbable and do not accumulate in organs, but require precise control of loading and release to avoid ROS-mediated cytotoxicity and alkaline pH excursions. MOFs offer unmatched structural tunability and multifunctionality, yet their chronic safety is strongly dependent on metal identity and degradation behavior, and they currently have the least clinical experience. PFCs, by contrast, are chemically inert, have well-defined elimination pathways, and a substantial body of clinical and preclinical safety data. Their long residence time in the reticuloendothelial system mandates careful dosing and surfactant optimization. These comparative data support the conclusion that no single class is intrinsically “the safest” in all contexts; rather, the most appropriate oxygen-releasing platform for long-term *in vivo* use should be selected case-by-case, weighing the benefits of sustained oxygenation against the specific degradation products, accumulation behavior, and clinical maturity of each system. This perspective is now explicitly integrated into our discussion to guide rational material selection for future translational studies.

In addition to the classical oxygen-releasing materials and approaches, there are several innovative strategies that have emerged in the last few years that integrate oxygen delivery with advanced control over the wound microenvironment. These “next-generation” systems typically combine oxygen supply with immunomodulation, ROS scavenging, targeted cargo delivery or smart responsiveness to local biochemical cues [102]. One rapidly growing line of research is the use of oxygen nanobubbles and gas-filled nanocarriers. Hydrogels or in situ gels loaded with oxygen nanobubbles can markedly increase dissolved O_2 in the wound bed while avoiding caustic by-products. Carbopol-based ONB hydrogels have been shown to sustain elevated oxygen tension, accelerate re-epithelialization and granulation, and significantly shorten healing time in preclinical models [103]. In some designs, oxygen nanobubbles are combined with bioactive molecules (e.g. amino acids, antioxidants or antimicrobials), creating dual-action dressings that simultaneously improve oxygenation and modulate redox balance or bacterial burden. A second emerging strategy is the development of “living” photosynthetic and microalgae-based biomaterials that provide continuous, light-driven oxygen generation [104]. Early photosynthetic hydrogels embedding cyanobacteria or photosynthetic bacteria demonstrated robust O_2 production and protection of co-cultured fibroblasts in hypoxic wounds. More recently, programmed microalgae–gel systems have been engineered to couple sustained oxygen photosynthesis with antibiofilm activity and immunomodulation, yielding strong antibacterial effects, enhanced angiogenesis and accelerated closure in chronic and infected wound models [105]. These “bioactive living hydrogels” exemplify a fundamentally different paradigm from inert oxygen carriers, as long as illumination is available. A third area of innovation involves enzyme- and nanozyme-based oxygen-generating hydrogels. Beyond simple CaO_2 or H_2O_2 donors, cascade systems combining glucose oxidase (GOx), CAT, and redox-active nanozymes have been designed to regulate both oxygen and ROS levels *in situ*. Hydrogel dressings loaded with GOx/CAT-functionalized nanozymes or MOF-based nanozymes can consume excess glucose and H_2O_2 , generate molecular oxygen, and simultaneously scavenge pathogenic ROS, thereby normalizing the diabetic wound microenvironment while promoting revascularization and macrophage M2 polarization [106]. Recent “dynamic multistage” nanozyme hydrogels further integrate pH/ H_2O_2 -responsive behavior, enabling on-demand oxygenation coupled to mitochondrial protection and immune reprogramming [107]. Finally, hybrid exosome- and nanobubble-based oxygen dressings have attracted considerable attention. The OxOBand concept, for example, uses antioxidant polyurethane cryogels that slowly release oxygen while delivering adipose-derived stem cell exosomes; this platform significantly improved closure of diabetic and infected wounds, enhanced collagen deposition and angiogenesis, and reduced inflammatory cytokines *in vivo* [108]. More recent exosome-coated, oxygen–nanobubble-laden hydrogels show that combining biologically active vesicles with gas nanocarriers can further boost cell survival, neovascularization and immune regulation in difficult-to-heal ulcers [109]. Finally, these emerging oxygen-releasing strategies illustrate a shift from simple chemical oxygen donors toward multifunctional, microenvironment-responsive and biologically integrated systems. They complement traditional peroxides, MOFs and PFCs by offering finer spatiotemporal control over oxygen delivery, concurrent modulation of ROS and inflammation, and the possibility of combining oxygenation with advanced biologics (e.g. exosomes, stem cells or living photosynthetic cells). Highlighting these platforms underscores the rapid evolution of the field and delineates promising directions for next-generation oxygen-releasing biomaterials in tissue regeneration and chronic wound care.

3. Mechanisms of oxygen release in oxide-based systems

Peroxide-based materials release molecular oxygen, as mentioned in reactions (1) and (2). The decomposition of the materials results in the

generation of molecular oxygen, and the reaction takes place under aqueous and mild conditions, which can be applied to the wound area easily. Metal oxide-based materials release molecular oxygen in the very same manner when they contact water or CO₂ in the wound area, which is accelerated by a humid and warm zone [110]. In peroxide-based and metal oxide-based materials, the size of the nanoparticles plays a key role in oxygen release: smaller crystalline sizes promote faster O₂ release, whereas increasing the size slows it down due to increased diffusion barriers. In addition, some specifically-designed metal oxide materials can release molecular oxygen by the involvement of light or electrical stimuli (Fig. 3) [111]. For instance, titanium dioxide (TiO₂), as one of the inert metal oxide materials, is subjected to a photo-degradation reaction under a specific wavelength of the light to release oxygen as demonstrated in the following reaction (3) (Fig. 3):



The temperature is another important parameter in oxygen-releasing processes, in which higher temperatures increase the rate of decomposition reactions most of the time. For example, Arrhenius behavior significantly affects H₂O₂ decomposition in the wound area by doubling its efficiency with every 10 °C increase [113]. Excessive heat not only induces inflammation in the wound area but also may degrade the prepared material and cause premature or uncontrolled oxygen release, thus dramatically decreasing oxygen-releasing efficiency. The presence of a moist environment is another crucial parameter for oxygen-release reactions, particularly in making use of peroxides, as increased humidity significantly enhances the reaction rate of the hydrolysis of peroxide groups by providing the necessary hydroxyl groups [114]. In contrast, low humidity may slow down or completely prevent oxygen release in or from the material. Hydrophobic materials can inhibit water diffusion, which dramatically extends O₂ release to the target zone for up to weeks [115]. Hydrophilic characteristics cause rapid water contact with the material and ends up with oxygen burst release, which must be carefully controlled in order to prevent the generation of cytotoxic ROS that directly damage extracellular matrix, proteins, and DNA, delaying wound healing and tissue regeneration. The pH is considered another oxygen-releasing control parameter because the surrounding environment of the wound and the applied material firmly influences oxygen release by changing the solubility and reactivity of the material [39]. As an example, the oxygen-releasing systems that utilize metal oxides significantly benefit from an acidic environment in terms of oxygen-releasing efficiency, whereas an alkaline environment works in the opposite way. Lastly, the utilization of catalysts in the material development for wound healing and tissue regeneration processes substantially accelerates the oxygen release rate [28]. Therefore, MnO₂ is not merely used as an oxygen-releasing material; instead, it is also used

as a catalyst to improve the decomposition of peroxides or metal oxides. Fig. 4 provides an overview of these mechanisms, showing the effects of particle size, humidity, temperature, light, and pH.

3.1. Applications of oxygen-releasing biomaterials

Oxygen plays a crucial role in cellular metabolism, wound healing, and tissue regeneration; therefore considered a crucial element in biological endeavors. Moreover, the importance of oxygen in biological systems cannot be limited to those that are essential for aerobic respiration, energy production, and numerous metabolic processes. In many clinical scenarios, such as wound healing, tissue engineering, and transplantation, the ability to maintain adequate oxygen levels is crucial for a successful outcome. Hypoxia, characterized by an insufficient oxygen supply to a tissue or a target zone, represents a significant challenge in various pathological conditions, including chronic wounds, ischemic diseases, as well as in the development and application of tissue engineering materials [116]. The development of oxygen-releasing biomaterials has emerged as a promising strategy to address the mentioned challenges by providing controlled and sustained oxygen delivery to hypoxic tissues. These innovative materials combine biocompatible scaffolds with oxygen-generating components to create therapeutic systems capable of modulating the local oxygen microenvironment, which is designed to deliver oxygen in a controlled manner, thereby enhancing cell viability and promoting tissue regeneration in environments where oxygen scarcity can impede healing processes [39]. These biomaterials can be fabricated into various forms, such as microparticles, thin films, hydrogels, or 3D scaffolds, to meet specific application needs, to generate molecular oxygen through various chemical or enzymatic reactions, as explained in detail in the previous section. The integration of such oxygen-generating components within biocompatible matrices enables localized oxygen delivery while minimizing potential cytotoxicity and oxidative stress. The applications of oxygen-releasing biomaterials span multiple biomedical fields, from wound healing and tissue regeneration to cell therapy and 3D tissue culture systems. In chronic wound management, these materials can stimulate cellular proliferation, angiogenesis, and ECM synthesis, thereby accelerating the healing process. In tissue engineering, they can enhance cell survival and functionality within thick constructs, where oxygen diffusion limitations often present significant barriers. Additionally, in cell transplantation therapies, oxygen-releasing biomaterials can improve the viability and therapeutic efficacy of transplanted cells by providing a supportive microenvironment during the critical post-transplantation period. Fig. 5 summarizes the benefits of oxygen-releasing materials compared to traditional oxygen therapies, highlighting their improved wound-healing outcomes, practicality and

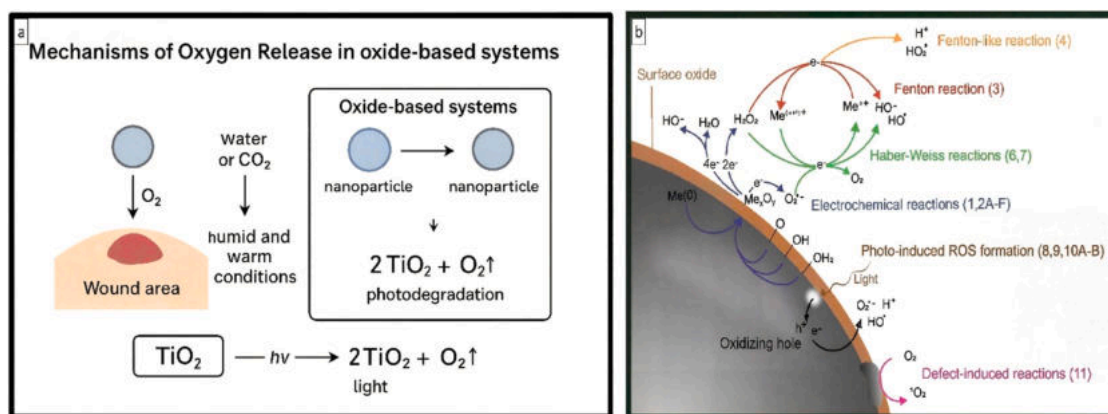


Fig. 3. (a) Peroxide- and metal oxide-based nanoparticles release O₂ under aqueous conditions, with kinetics influenced by particle size, in TiO₂, light-induced photodegradation also triggers oxygen generation., (b) different routes of oxygen generation on the surface of metal particles, with reactions taking place in proximity of the particle surface [112].

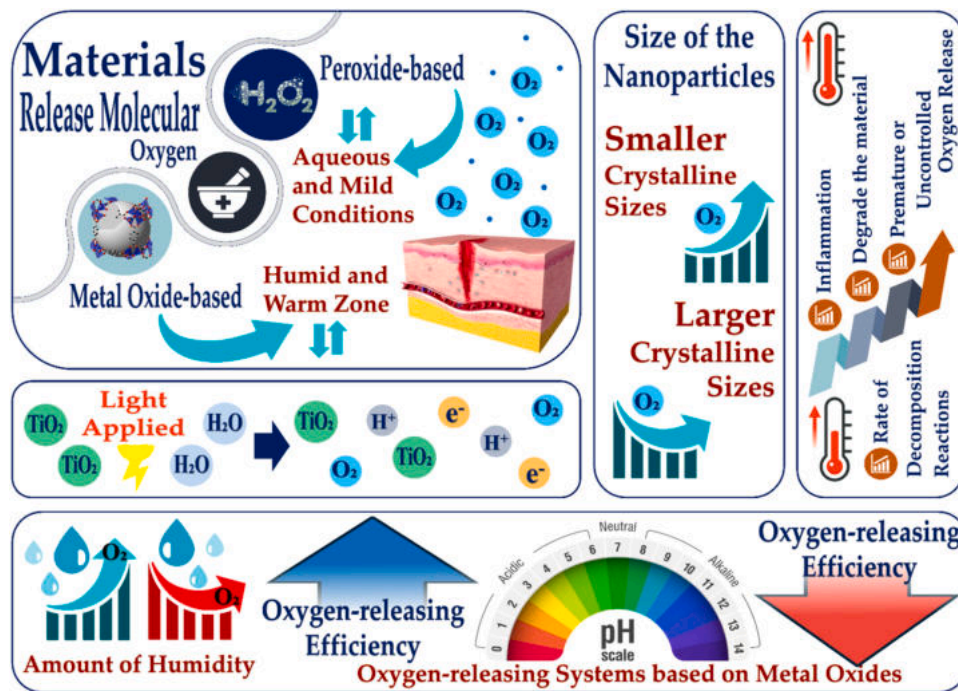


Fig. 4. An overview of the mechanisms of oxygen release in oxide-based systems.

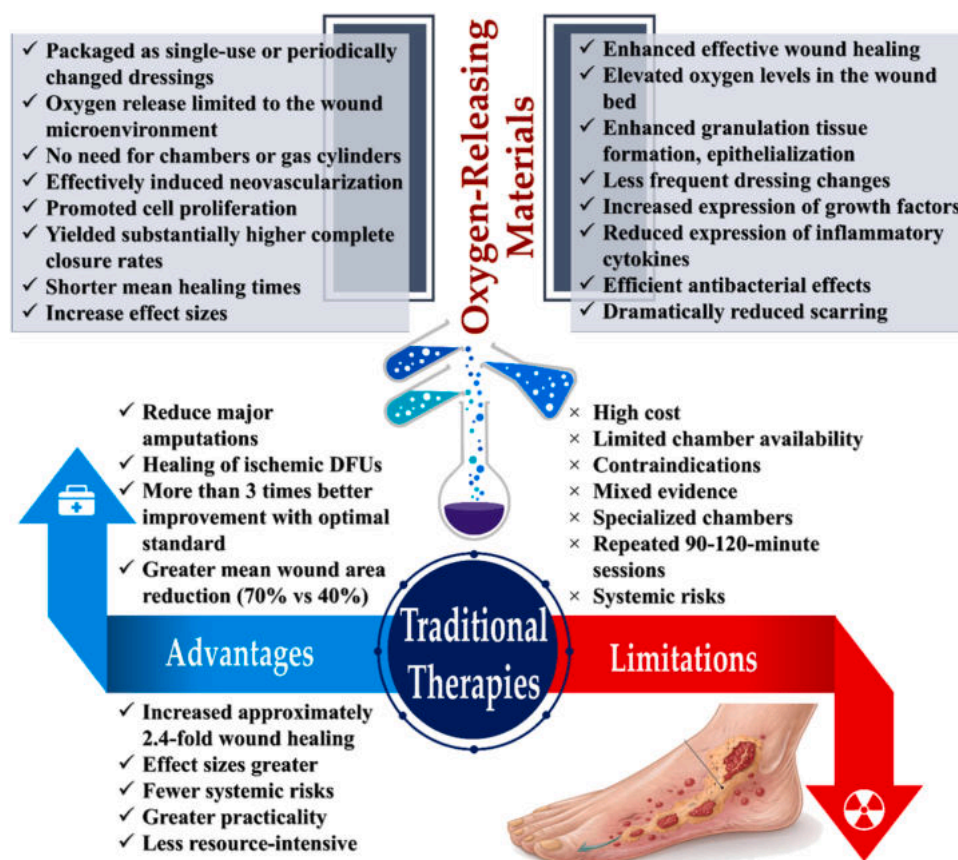


Fig. 5. Applications, advantages, and limitations of oxygen-releasing materials, compared to traditional therapies for wound healing.

remaining clinical limitations.

3.2. Tissue Engineering and Regeneration

3.2.1. Bone

Abdullah et al. [117] developed an oxygen-releasing antibacterial

fiber-based scaffold to address the scarcity of suitable bone auto/allografts, which are delaying surgical interventions. The group utilized electrospun composite scaffolds consisting of poly(glycerol sebacate) (PGS) and PCL via the ball-milling method to incorporate the desired amount of CaO_2 nanoparticles to obtain oxygen-releasing capability, as shown in Fig. 6 A. The percentage of CP was observed by using Alizarin red S staining, where the increasing concentration resulted in darkening of the scaffold color. The developed biomaterial enabled oxygen release for several days to a week in a sustained manner, as demonstrated in Fig. 6B, and dramatically enhanced cellular metabolic activity thanks to the alleviation of a hypoxic environment around primary bone-marrow-derived mesenchymal stem cells (BM-MSCs). Oh et al. [48] reported a CaO_2 -reinforced poly(lactic-co-glycolic acid) (PLGA) scaffolds provide a suitable environment for mesenchymal stem cells (MSCs). Their results demonstrated that the developed scaffold significantly enhanced MSC survival and osteogenic differentiation under hypoxic conditions. Besides, *in vivo* studies in critical-sized rat calvarial defects exhibited that these oxygen-releasing scaffolds improved bone mineral density and volume by approximately 45 % compared to control scaffolds after 12 weeks of implantation. This was due to sustained oxygen release that maintained cellular metabolism and promoted the expression of osteogenic markers, including alkaline phosphatase, osteocalcin, and runt-related transcription factor 2. Wang et al. [118] developed an oxygen-releasing hydrogel derived from a gelatin methacrylate (GelMA) enhanced with H_2O_2 -loaded microspheres. The system demonstrated controlled oxygen release for up to 14 days *in vitro* studies. Afterward, they combined this biomaterial with bone morphogenetic protein-2 (BMP-2) to gain enhanced bone regeneration in femoral defects in rabbits, which was verified by micro-CT analysis, revealing nearly complete defect healing after 8 weeks. Furthermore, histological assessments showed mature bone formation with organized collagen deposition and active mineralization at the defect sites.

3.2.2. Adipose

Pedraza et al. [119] reported oxygen-releasing hyaluronic acid (HA) hydrogels by incorporating CaO_2 nanoparticles for adipose tissue engineering. Their developed material system provided sustained oxygen

release for 7 days and significantly enhanced the viability and adipogenic differentiation of adipose-derived stem cells under hypoxic conditions *in vitro*. They also evaluated the biomaterial in a subcutaneous implantation model in mice and reported that the oxygen-releasing hydrogels promoted greater vascularization and adipose tissue formation compared to non-oxygen-releasing controls, with a 62 % increase in the volume of newly formed adipose tissue after 8 weeks.

3.2.3. Skeletal

In a study by Chen et al. [120] developed injectable oxygen-releasing microspheres based on methacrylated dextran material by integrating solid H_2O_2 for skeletal muscle regeneration. They utilized a mouse model of volumetric muscle loss to evaluate the effect of the biomaterial, which significantly enhanced the survival of transplanted myoblasts, promoted myofiber formation, and increased angiogenesis within the defect site. Functional assessments revealed a 40 % improvement in muscle contractile force in the oxygen-releasing microsphere group compared to standard treatments after 12 weeks of implantation.

3.2.4. Cardiac

Liu et al. [121] engineered a bioresorbable oxygen-releasing patch comprising sodium percarbonate embedded within a PCL/gelatin electrospun fibrous membrane. The developed patch could maintain oxygen release for approximately 4 h *in vitro*. They also used the biomaterial on infarcted rat hearts, which remarkably improved cardiomyocyte survival in the border zone of the infarct; specifically, echocardiographic assessments showed that treatment with the oxygen-releasing patch improved left ventricular ejection fraction by 15 % compared to untreated controls after 4 weeks, proving a preserved cardiac function. Zhang et al. [122] developed an enhanced dual-functional cardiac patch by incorporating both oxygen-releasing PFC nanocapsules and electrically conductive graphene oxide. The developed hybrid material provided both oxygen supplementation and electrical stimulation to encapsulated cardiomyocytes. The group utilized the biomaterial in a rat model of myocardial infarction, and the results showed that the oxygen-releasing conductive patches significantly enhanced cardiomyocyte survival, promoted angiogenesis, and reduced fibrosis in the

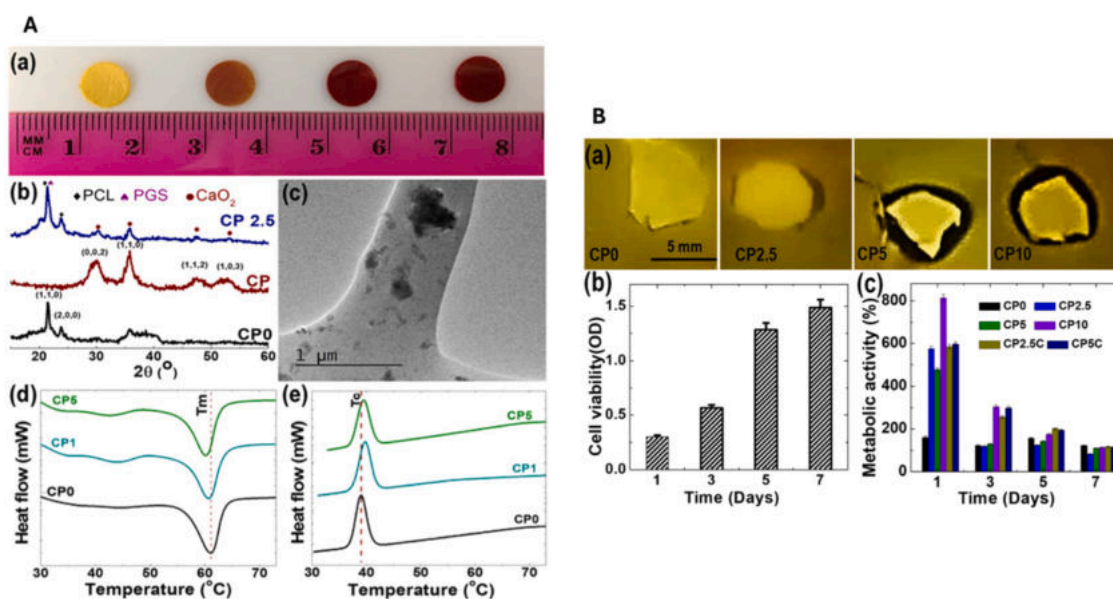


Fig. 6. (A) Increasing CP concentration darkens the scaffold color by Alizarin red S staining, confirming the incorporation of CP in the PGS/PCL scaffold (a). XRD spectra of bare CP nanoparticles, PCL/PGS hybrid scaffold, and CP-doped composite scaffold (b). TEM image of the nanofiber structure embedded with CP nanoparticles within the network of the fiber (c). DSC curve of PGS/PCL scaffold with different concentrations of CP nanoparticles when subjected to heating (d) and cooling (e). (B) The effectiveness of the scaffold in antibacterial activity against *S. aureus* is presented by the zone of inhibition of colonization (a). The results of cell viability in the scaffold-free 3D-printed ring (control), which was demonstrated in the optical density (OD) value for the MTT assays (b). Cellular metabolic activity of BM-MSCs in the scaffold (c) [117].

infarct region in rat models. Long-term studies demonstrated improved cardiac function with a 23 % increase in ejection fraction and reduced ventricular dilation after 12 weeks.

3.2.5. Neural

In a study, oxygen-releasing fibrous scaffolds based on electrospun PCL fibers incorporating PFTBA were designed, an oxygen carrier with high oxygen solubility [30]. These scaffolds maintained elevated oxygen levels in the microenvironment for up to 10 days *in vitro* and significantly enhanced the survival and neurite outgrowth of primary neurons under hypoxic conditions. In a rat model of spinal cord injury, the oxygen-releasing scaffolds promoted axonal regeneration across the lesion site and improved functional recovery as assessed by the Basso, Beattie, and Bresnahan (BBB) locomotor scale. Politrón-Zepeda et al. [123] developed a more complex system consisting of oxygen-releasing hyaluronic acid/chitosan hydrogels reinforced with CaO₂ nanoparticles and neural growth factors for brain tissue engineering. In the study, an *in vitro* model of cerebral ischemia was used as the model, and the hydrogels significantly enhanced neural stem cell survival and differentiation under oxygen-glucose deprivation conditions. Moreover, the group utilized the biomaterial *in vivo* studies as a stroke model, demonstrated reduced infarct volume, and the biomaterial demonstrated improved neurological function in animals treated with the oxygen-releasing hydrogels.

3.2.6. Angiogenesis and Vascularization

Jeong et al. [124] reported a novel oxygenating colloidal bioink designed for 3D bioprinting applications. The research group aimed to emphasize the need for sustained oxygen release in biofabricated tissue constructs. The designed and developed bioink was used to integrate perfluorocarbon-based oxygen carriers, which facilitate oxygen diffusion within engineered tissues, significantly improving cell survival and differentiation. Wang et al. [125] reported a dual-delivery system consisting of oxygen-releasing microspheres and VEGF within a gelatin-based hydrogel system. The oxygen-releasing component, as the oxygen supplier, maintained elevated oxygen levels for 14 days, while VEGF provided pro-angiogenic signaling in the tissue. The biomaterial was evaluated in a hindlimb ischemia model, which showed a significant enhancement in neovascularization. Doppler imaging investigation demonstrated that there was a 3-fold increase in blood perfusion compared to the control groups after 28 days. Mehrotra et al. [126] developed a bioprinted biomaterial consisting of vessel-like channels lined with endothelial cells, where the oxygen-releasing microparticles are embedded within the surrounding matrix. The proposed biomaterial maintained endothelial cell viability and functionality *in vitro*, while the oxygen-releasing component promoted vessel maturation through enhanced pericyte recruitment and basement membrane deposition. When implanted subcutaneously in mice as in the *in vivo* model, the biomaterial demonstrated rapid anastomosis with host vasculature and improved survival of the embedded tissue-specific cells.

3.3. Dental applications

Periodontal disease can be defined by inflammation and destruction of tooth-supporting structures that create a complex microenvironment often compromised by hypoxic conditions that impair healing. Oxygen-releasing biomaterials have been proposed in such dental applications for supplying oxygen to the hypoxic microenvironment that usually appears because of oral pathologies, thereby enhancing the regenerative outcomes in dental procedures [30,127]. Carmagnola et al. [128] investigated CaO₂-containing PLGA microspheres embedded in chitosan scaffolds for periodontal tissue engineering. The initial *in vitro* studies demonstrated that there was sustained oxygen release for up to 10 days, significantly improving and accelerating the proliferation and osteogenic differentiation of periodontal ligament stem cells under hypoxic conditions. In addition, the scaffold promoted the expression of RUNX2,

alkaline phosphatase, and osteocalcin, indicating enhanced osteogenic potential. Zou and colleagues reported an oxygen-releasing injectable hydrogel composed of gelatin methacrylate incorporating CaO₂ nanoparticles for periodontal regeneration [129]. They utilized a dog model with experimentally induced periodontal defects, and the oxygen-releasing hydrogels demonstrated superior periodontal regeneration compared to conventional hydrogels as the control group, with significant increases in new cementum formation (1.8-fold increase), periodontal ligament formation (1.5-fold increase), and alveolar bone regeneration (2.1-fold increase). Histomorphometric analysis revealed enhanced angiogenesis in the oxygen-releasing group, suggesting that the improvement created a more favorable regenerative microenvironment. Wang et al. [130] investigated the efficacy of oxygen-releasing collagen membranes, which were incorporated with H₂O₂-loaded microspheres for guided tissue regeneration in 45 patients with intrabony defects in a randomized controlled clinical trial. They observed that the sites treated with oxygen-releasing membranes demonstrated significantly greater clinical attachment level gain (5.2 ± 1.1 mm vs. 3.8 ± 0.9 mm) and radiographic bone fill (72.4 % vs. 58.9 %) compared to the standard collagen membranes, which served as the control group, after 12 months. The results showed that enhanced cellular metabolism and angiogenesis were attributed to sustained oxygen release.

Some dental implementations for an advanced treatment, particularly in regenerative endodontic procedures, require restoring the function of pulp-dentin complexes by inducing the regeneration of pulp-like tissues, which significantly depends on creating a conducive microenvironment that shall be supporting dental pulp stem cell (DPSC) survival and function in the application area. Müller-Heupt et al. [131] developed a HA-based oxygen-releasing biomaterial for periodontal tissue engineering, particularly for a supporting treatment for periodontitis. They designed an oxygen-releasing HA-based biomaterial by combining CaO₂ and sodium hyaluronate in specific amounts and ratios to obtain the best formulation in terms of controlled oxygen release in the desired biodegradation rate. The performed studies *in vitro* revealed that the oxygen-releasing HA was not cytotoxic towards human primary fibroblasts, osteoblasts, and HUVECs, as demonstrated by a CAM assay shown in Fig. 7. In addition, the developed biomaterial system demonstrated antibacterial activity against *P. gingivalis* when the calcium oxide concentration was above 256 mg/L in the formulations.

Liang et al. [132] developed a hydrogel system by using PFD as an oxygen carrier for pulp revitalization. *In vitro* studies demonstrated that PFD-loaded hydrogels maintained elevated oxygen levels for up to 7 days and significantly enhanced the survival and odontogenic differentiation of DPSCs under hypoxic conditions compared to the control group. Gene expression analyses revealed the upregulation of dentin sialophosphoprotein (DSPP) and dentin matrix protein 1 (DMP1) in DPSCs cultured with oxygen-releasing hydrogels, indicating enhanced odontogenic potential. Zou et al. [133] reported an injectable, oxygen-releasing hydrogel composed of HA reinforced with CaO₂ nanoparticles for pulp regeneration in a dog model of pulpectomy. They prepared the hydrogel material by seeding it with autologous DPSCs and injected it into root canals after complete pulp removal by surgical operation. The histological analysis revealed that there was significantly greater pulp-like tissue formation (65.3 % vs. 38.7 % of canal space), dentinal bridge formation, and vascularization in the oxygen-releasing hydrogel group compared to conventional hydrogels after 3 months. Furthermore, immunohistochemical analyses demonstrated higher expression of angiogenic markers (CD31, VEGF) and odontogenic markers (DSPP, DMP1) in the regenerated tissues of the oxygen-releasing group. By using the same biomaterial design, Glynis et al. [134] carried out a pilot clinical study to evaluate an oxygen-releasing hydrogel system for regenerative endodontic procedures in 20 immature permanent teeth with necrotic pulps in the path of the clinical translation from the fundamental implementations. The designed biomaterial was applied to the groups, and teeth treated with the oxygen-releasing material showed superior root development,

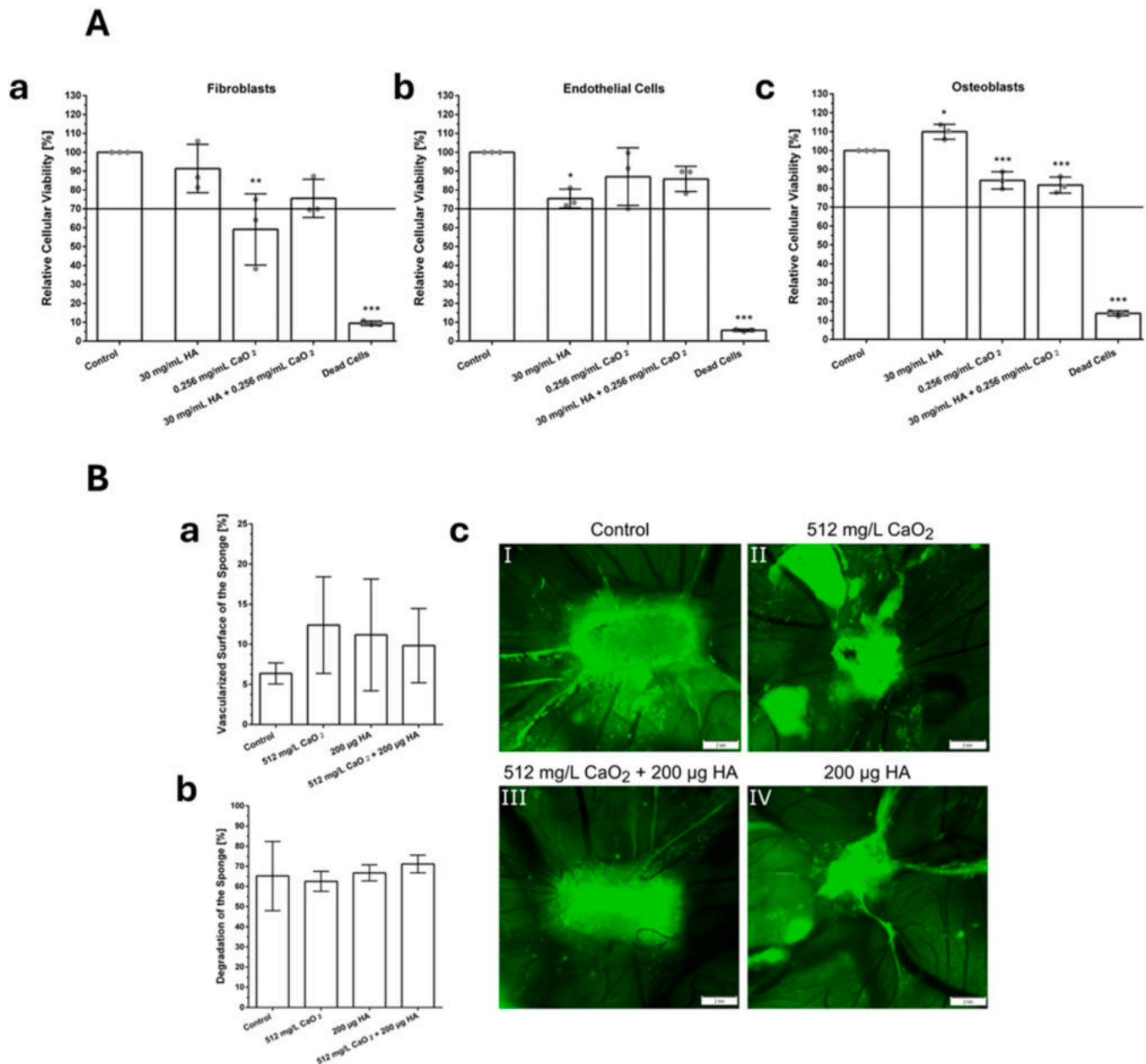


Fig. 7. (A) The positive effect of oxygen-releasing HA-based material on cellular viability of human primary fibroblasts (a), endothelial cells (b), and human primary osteoblast cells (c) with pristine HA, pristine calcium oxide, and the combination of both materials. (B) The generation of angiogenesis in HA, calcium oxide, and the combination of both materials (a). Cytotoxicity of the bare and combined materials investigated on the CAM (b). The degradation rates of the sponge when the different substances were mixed with the material, which was insignificantly different from the degradation of an empty sponge (c). Fluorescent microscopic images of the CAM tissue treated with control sponge only (I), 512 mg/L calcium oxide (II), 512 mg/L calcium oxide + 200 µg HA (III), and 200 µg HA only (IV) [131].

including increased length and width and apical closure compared to conventional blood clot-based regenerative endodontic procedures. Moreover, the group receiving the oxygen-releasing biomaterial showed higher rates of positive response to pulp sensibility tests (70 % vs. 40 %), thus yielding enhanced pulp-like tissue regeneration.

Oseointegration is one of the most important dental applications, which is specifically crucial for the long-term success of dental implants. It is a known fact that the inadequate oxygen supply to peri-implant tissues can drastically prevent the regeneration process, particularly in patients with insufficient wound healing capabilities because of chronic wounds. Khorshidi et al. [135] developed a novel oxygen-releasing titanium surface modified by the incorporation of CaO₂ nanoparticles within a nanoporous titanium oxide layer. The surface of the modified biomaterial enabled sustained oxygen release for up to 2 weeks and

remarkably enhanced the osteogenic differentiation of MSCs *in vitro*. They further examined the efficiency of the material by utilizing minipig models of dental implantation, where the oxygen-releasing implants demonstrated accelerated osseointegration with significantly higher bone-to-implant contact (68.7 % vs. 55.3 %) and peri-implant bone density after 4 weeks compared to conventional implants

Oral mucositis is a common dental complaint that can be characterized by painful inflammation and ulceration of the oral mucosa, which is a common side effect of radiation therapy and chemotherapy in patients undergoing cancer treatment. Oxygen-releasing biomaterials have been utilized in this field since it has a promising capability in accelerating oral mucosal healing and reducing the severity of mucositis. Senarat et al. [136] developed an oxygen-releasing buccal film based on hydroxypropyl methylcellulose incorporating H₂O₂-loaded

microspheres targeting post-surgical oral wound healing. They performed a randomized clinical study involving 60 patients who underwent third molar extraction. The application of the oxygen-releasing film yielded a reduced healing time by approximately 35 % and significantly decreased post-operative pain and swelling compared to standard therapy. Wound fluid analysis revealed that levels of growth factors increased, while levels of inflammatory cytokines were reduced in the group receiving oxygen-releasing biomaterials, indicating a shift toward a more regenerative microenvironment.

The antibacterial properties of biomaterials are also important in dental applications to prevent infection during the healing process. Oxygen-releasing biomaterials with antibacterial features mostly rely on the incorporation of ROS generated during the decomposition of

peroxide-based materials, which have been employed for various dental applications, particularly for caries prevention and endodontic disinfection. Chen et al. [137] developed a novel glass ionomer cement supported by CaO_2 nanoparticles for sustained oxygen release and antibacterial activity. The oxygen-releasing blocks of cement demonstrated strong antibacterial effects against *Streptococcus mutans* biofilms, where the reduction of bacterial presence was over 99 % after 24 h of contact. Moreover, the blocks of cement maintained their mechanical properties within the acceptable range for dental restorations without showing decomposition and transformation, which also showed biocompatibility with dental pulp cells. They utilized a rat model of recurrent caries for further verification of the effectiveness of the biomaterial, which resulted in remarkable restoration and significantly

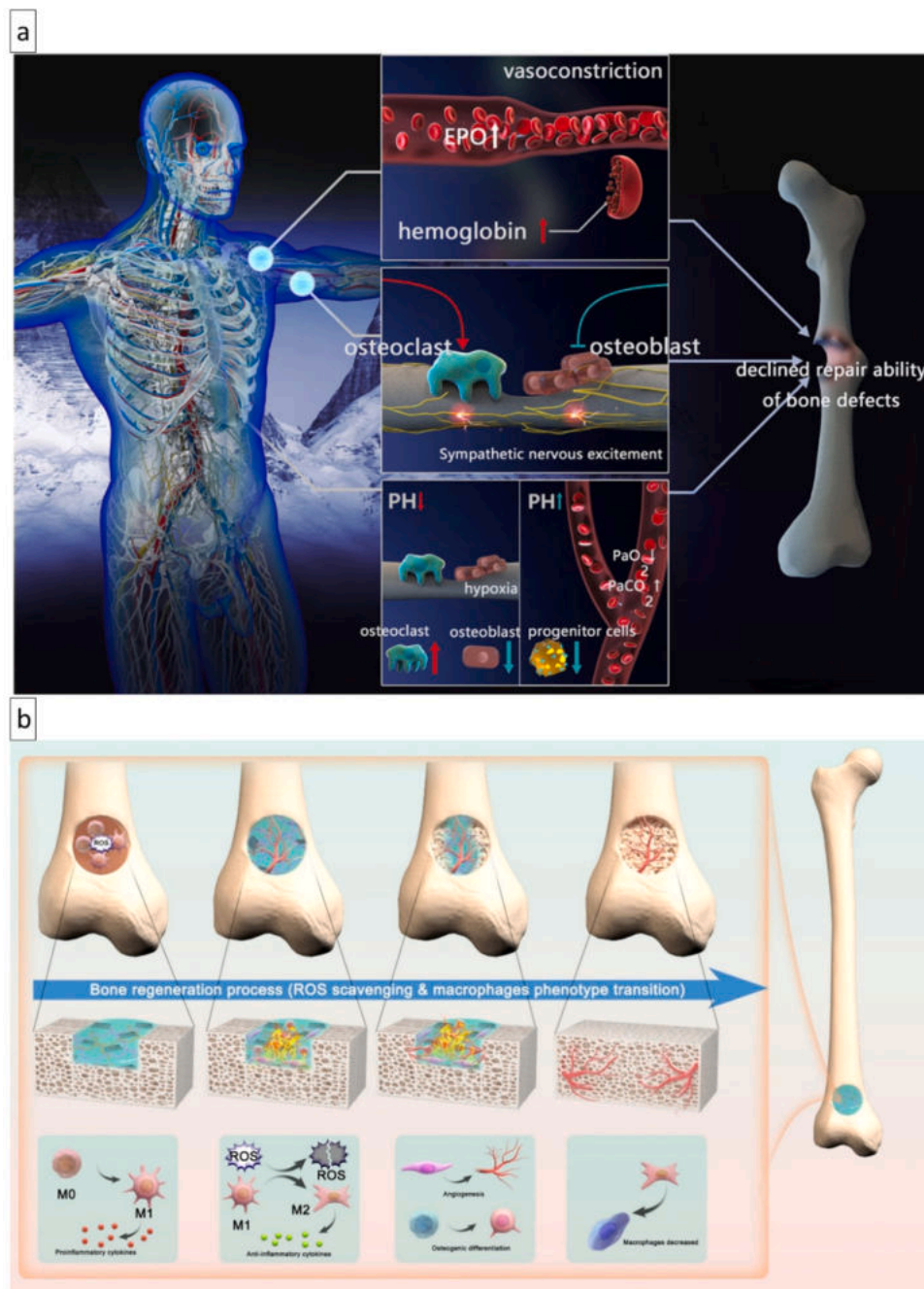


Fig. 8. (a) Hypoxia influences the bone defect repairability by blood compensation, osteoblast activity inhibition, and increased pH, inhibiting the bone marrow cell proliferation [145], (b) Schematic illustration of the mechanism of photocurable hydrogel composite promoting the healing of osteoporotic bone defect through ROS release [146].

reduced secondary caries formation compared to conventional blocks of cement after 12 weeks of application. Song et al. [138] reported an oxygen-releasing root canal irrigant composed of H_2O_2 -loaded chitosan nanoparticles in the context of endodontic disinfection treatment. The obtained results demonstrated that oxygen-releasing irrigant was superior in terms of antibacterial activity against endodontic pathogens that are *Enterococcus faecalis* biofilms compared to conventional sodium hypochlorite irrigation. Furthermore, a human tooth was extracted for evaluation as an *ex vivo* model, which was subjected to the oxygen-releasing irrigant that achieved a significantly greater reduction of bacterial biofilms within dentinal tubules (92.7 % vs. 76.3 % reduction) compared to the conventional cement blocks. Ersahan et al. [139] developed an advanced material as an oxygen-releasing root canal sealer consisting of epoxy resin that was doped with CaO_2 microparticles. They conducted a randomized clinical trial involving 80 patients with apical periodontitis. The teeth of the patients were obturated with the oxygen-releasing sealer, which exhibited significantly higher healing rates (92.5 % vs. 77.5 %) compared to conventional sealers after 12 months of implementation. The effects of the sealer were further examined by cone-beam computed tomography analysis, which revealed a greater reduction in periapical lesion size in the patients receiving oxygen-releasing sealer material compared to the control group, showing enhanced periapical healing.

3.4. Orthopedic applications

The application of oxygen-releasing biomaterials in bone repair has demonstrated significant potential in enhancing osteogenesis and angiogenesis in the damaged or wounded area. Hypoxia is considered a major challenge, particularly in large bone defects in the core regions of scaffolds, where diffusion is limited (Fig. 8). Oxygen-releasing biomaterials are utilized to overcome this limitation by providing an internal oxygen source rather than external supplementation, supporting cell survival and function throughout the scaffold. Bone healing represents a complex and challenging process that is highly dependent on oxygen availability [140]. Hypoxic conditions can significantly impair fracture healing, particularly in compromised patients with conditions such as diabetes or vascular insufficiency. Oxygen-releasing biomaterials have emerged as promising strategies to enhance bone regeneration by providing localized and sustained oxygen delivery. For instance, Zhao et al. [141] reported a study on the development of CaO_2 -incorporated hydrogels to maintain higher oxygen levels in 3D cell cultures, which resulted in enhanced osteogenic differentiation of MSCs. Wang et al. [142] developed CaO_2 and poly(propylene fumarate) (PPF) hybrid scaffolds for bone regeneration applications. The developed scaffolds demonstrated sustained oxygen release for up to 10 days and significantly enhanced the proliferation and osteogenic differentiation of human MSCs under hypoxic conditions *in vitro*. Further analysis revealed that the oxygen-releasing scaffolds maintained higher ATP levels in cells and promoted the expression of key osteogenic markers, e. g., RUNX2, osteocalcin, and osteopontin. The group further evaluated the efficiency of the biomaterial by utilizing a rat model of calvarial defect, which resulted in remarkably enhanced bone formation compared to non-oxygen-releasing control groups after 8 weeks of implantation (52 % vs. 31 % bone volume fraction). Liu et al. [143] investigated the synergistic effects of oxygen-releasing microspheres doped with bone morphogenetic protein-2 (BMP-2) in a critical-sized femoral defect model in rats. The developed composite scaffolds consisting of CaO_2 microparticles and BMP-2 exhibited significantly greater bone regeneration capability compared to scaffolds with either component alone (non-synergistic effect). Further analysis was performed by utilizing micro-CT analysis, which showed an achievement of 78 % defect bridging in the dual-delivery system compared to 45 % for BMP-2 alone and 32 % for oxygen-releasing scaffolds alone after 12 weeks of implementation. In addition, histological analysis verified the mature bone formation with well-organized osteons and active remodeling in

the dual-delivery group. Fernández et al. [144] investigated the translational potential of these biomaterials by conducting a study in a clinically relevant large animal model. They reported injectable oxygen-releasing hydrogels composed of HA and sodium percarbonate microparticles for the treatment of large bone defects in sheep models. The oxygen-releasing hydrogels maintained elevated oxygen levels in the defect site for up to 2 weeks of implementation, which was confirmed by *in situ* oxygen monitoring. The oxygen-releasing hydrogels demonstrated enhanced bone regeneration compared to the control group receiving standard care in the critical-sized iliac defects, after 24 weeks (65.3 % vs. 38.7 % bone volume fraction). Moreover, biomechanical testing was performed to evaluate the strength of the biomaterial, which revealed that the regenerated bone in the oxygen-releasing group achieved 78 % of the strength of native bone, whereas the control group was only 45 %.

Articular cartilage has a limited intrinsic healing capacity because of its structure and environment [147]. Besides, its avascular nature creates a naturally hypoxic environment, resulting in unique challenges for tissue engineering strategies for tissue or bone regeneration and wound healing. Although chondrocytes are adapted to function under hypoxic conditions, the regenerative process may be accelerated by controlled oxygen delivery, particularly during the early stages of repair. Almeida et al. [148] developed fibrin hydrogel microspheres containing CaO_2 as the oxygen carrier and chondrocyte cells. The oxygen-releasing hydrogels maintained oxygen concentrations in the cartilage site in the physiological range of about 5–10 % O_2 for up to one week, while preventing and avoiding both hypoxic and hyperoxic conditions by balancing the oxygen concentration. The same research group also utilized an *in vitro* model of cartilage formation, and then the biomaterial was applied to the system: as a result, it significantly enhanced glycosaminoglycan and collagen type II synthesis in the cartilage by the encapsulated chondrocytes compared to the control group. Gene expression analysis also revealed upregulation of SOX9 and enhanced expression ratio of collagen type II to type I, indicating improved chondrogenic phenotype maintenance. In a similar approach, Dong et al. [149] developed a gradient oxygen-releasing scaffold consisting of CaO_2 particles in the chondral and osseous regions to mimic the oxygen tension gradient in native osteochondral tissue. The proposed biphasic biomaterial scaffold created a gradient of oxygen release that intrinsically matched the physiological environment of the natural system. The effectiveness of the system was verified in a rabbit osteochondral defect model, in which the gradient scaffolds demonstrated higher cartilage regeneration with improved integration to surrounding tissue compared to uniform oxygen-releasing scaffolds or the control group after 12 weeks. Histological assessment, utilizing the modified O'Driscoll scoring system, revealed higher scores for the gradient scaffolds (18.3 ± 2.1) compared to uniform oxygen-releasing scaffolds (14.7 ± 1.8) or controls (10.2 ± 2.3).

Tendon and ligament injuries represent significant clinical challenges due to the limited vascularization and consequent hypoxic nature of these tissues, which are mostly encountered in sports and high-movement activities [150]. Therefore, oxygen-releasing biomaterials have been investigated as strategies to enhance tendon and ligament healing by improving the oxygen microenvironment during the repair process. Iorio et al. [151] reported a biomaterial system composed of electrospun PCL scaffolds incorporating H_2O_2 -loaded poly (glycerol sebacate) microspheres for the regeneration of tendon tissue. The proposed scaffolds enabled sustained oxygen release for up to 2 weeks and significantly enhanced the proliferation and tenogenic differentiation of tendon stem/progenitor cells (TSPCs) under hypoxic conditions *in vitro*. The effectiveness of the biomaterial was further evaluated in a rat model of Achilles tendon injury, in which the developed scaffolds demonstrated accelerated tendon healing, with not only improved collagen synthesis and organization but also increased mechanical properties compared to control scaffolds after 2 months of implementation. Further biomechanical analysis revealed that tendons treated with the

biomaterial achieved 82 % of the strength of native tendons, compared to 61 % for standard scaffolds.

3.5. Chronic wound healing

The formation of chronic wounds due to diabetic ulcers, pressure ulcers, and venous leg ulcers causes a significant clinical challenge, such as persistent inflammation, impaired angiogenesis, and bacterial colonization. Tissue hypoxia is considered a central factor in the pathophysiology of these chronic wounds, which makes oxygen-releasing biomaterials particularly promising for this application [152]. Choi et al. [153] developed an oxygen-delivering biomaterial composed of H₂O₂ and PLGA microspheres embedded into the alginate sponges for wound healing, shown in Fig. 9. They evaluated the developed biomaterials both *in vitro* and *in vivo*. While *in vitro* studies were carried out on scratch models (Fig. 9), *in vivo* studies were performed on male rats. The obtained results showed that the proposed biomaterial, which released oxygen, effectively induced neovascularization and promoted cell proliferation, resulting in enhanced effective wound healing.

Ullah et al. [154] developed a topical oxygen-releasing patch consisting of CaO₂ embedded within a chitosan/poly(vinyl alcohol) hydrogel system. Preliminary studies demonstrated that the patch maintained elevated oxygen levels in the wound bed for up to 12 h after a single application to the area. The study was further expanded by utilizing a diabetic mouse as a wound model, in which daily application of the biomaterial patch remarkably accelerated and improved wound closure, until complete closure was achieved at day 15 in the biomaterial and by day 22 in the controls. Moreover, the application area revealed enhanced granulation tissue formation, epithelialization, and angiogenesis. Immunohistochemical analysis demonstrated that CD31 and VEGF expression were dramatically increased in the oxygen-releasing group, indicating enhanced angiogenesis. Zhang et al. [155] developed an advanced oxygen-releasing dressing patch, composed of CaO₂ nanoparticles within a chitosan/alginate hydrogel matrix with controlled moisture transmission properties. The proposed material enabled sustained oxygen release for up to one week, providing a powerful alternative with the potential for less frequent dressing changes. Results in a diabetic mouse model showed that the biomaterial significantly accelerated wound closure with complete epithelialization by day 18, whereas 28 days were required with standard dressings. Molecular analysis indicated that the expression of growth factors (PDGF, EGF) was increased, and the expression of inflammatory cytokines (TNF- α , IL-1 β) was reduced dramatically in the wound bed. In addition, the oxygen-releasing dressings demonstrated efficient antibacterial effects against common wound pathogens, including *Staphylococcus aureus* and *Pseudomonas aeruginosa*, because of the presence of both peroxides and natural antibacterial properties of chitosan, contributing to improved wound healing capabilities and efficiencies. Additionally, a novel spray-applied oxygen-releasing hydrogel consisting of sodium percarbonate microparticles for treating diabetic foot ulcers (DFUs) was also developed [156]. A clinical study was conducted involving 45 patients with Wagner grade 1–2 DFUs: those treated with the oxygen-releasing hydrogel showed significantly higher healing rates (78 % vs. 46 % complete wound closure) and reduced mean healing time (6.2 weeks vs. 9.8 weeks) compared to standard hydrogel dressings over the 12-week treatment. Further analysis was performed on the wound bed by biopsies, which revealed increased granulation tissue formation, enhanced angiogenesis, and reduced bacterial load in the novel biomaterial receiving group.

The injuries caused by burning represent a unique challenge characterized by extensive tissue damage, impaired vascularization, and high susceptibility to infection in the wound area. In this context, oxygen-releasing biomaterials have gained remarkable attention in enhancing burn wound healing through multiple mechanisms, such as the support of cellular metabolism, promotion of angiogenesis, and bacterial control. Bircă et al. [157] reported an oxygen-releasing foam

dressing composed of CaO₂ nanoparticles for the treatment of deep partial-thickness burns. The group utilized a burnt porcine skin model *in vitro*, in which the oxygen-releasing dressings remarkably accelerated the healing rate with complete re-epithelialization by day 15 compared to day 23 for standard silicone foam dressings. Furthermore, the biomaterial dressings dramatically reduced scarring, as assessed using the Vancouver Scar Scale after 60 days, showing lower scores for pigmentation, vascularity, pliability, and scar height. Gene expression analysis indicated that the oxygen-releasing biomaterial provided the modulation of the expression of transforming growth factor- β 1 (TGF- β 1), MMPs, which are key genes involved in scar formation, and tissue inhibitors of metalloproteinases (TIMPs), enabling a mechanism for the observed improvements in scarring conditions. Critical limb ischemia is defined as a severe manifestation of peripheral arterial disease specified by inadequate blood flow and tissue oxygenation, often leading to amputation of the affected area if it is not effectively treated. Oxygen-releasing biomaterials have been investigated as adjunctive treatments to enhance tissue salvage in these hard-to-rehabilitate clinical scenarios.

Classic randomized controlled trials (RCTs) generally show higher proportions of healed ulcers and/or fewer major amputations when HBOT is added to standard care in moderate-to-severe DFUs [158]. A 2021 meta-analysis pooling RCTs reported that HBOT significantly increased complete DFU healing (pooled OR $\approx$ 0.29 in favour of HBOT) and reduced major amputation risk by $\sim$ 40 % compared with standard care alone, albeit with heterogeneity and moderate evidence quality [159]. An updated 2024 systematic review overview focused on Wagner-graded DFUs reaches similar conclusions: HBOT improves healing and may reduce major amputations, but the certainty of evidence remains modest, and results across trials are not entirely consistent [160]. Importantly, national and international guidelines now characterize HBOT as a selective adjunct since it may be considered in carefully chosen ischemic DFUs that fail standard care, but is not recommended for routine use in all chronic wounds because of cost, limited chamber availability, contraindications, and the mixed evidence base [161]. The robust data on topical oxygen therapy (TOT) and continuous diffusion of oxygen (CDO) devices, which deliver oxygen locally at the wound surface including the topical wound oxygen (TWO2) RCT, showed that adjunctive cyclical pressurized TWO2 in hard-to-heal DFUs more than tripled the likelihood of complete healing at 12 weeks compared with sham treatment plus optimal standard care ($\approx$ 41–42 % vs $\approx$ 14 % healed), with benefits persisting at 12-month follow-up [162]. In a multicentre open RCT of continuous topical oxygen therapy, addition of TOT to guideline-based DFU care resulted in greater mean wound area reduction (70 % vs 40 %) and a higher proportion of completely closed ulcers over 12 weeks compared with standard care alone [163]. Several double-blind RCTs of CDO devices similarly demonstrate significantly higher healing rates and faster closure in chronic DFUs relative to sham or placebo oxygen delivery [164]. A 2021 meta-analysis focused on topical oxygen in DFUs found that TOT approximately doubled to a 2.4-fold increased likelihood of ulcer healing compared with controls (RR $\approx$ 2.37), although data on amputation and cost-effectiveness remain limited [165]. More recent systematic reviews converge on the conclusion that topical oxygen is an effective adjunct for chronic wounds, particularly DFUs with vascular compromise, with effect sizes broadly similar to or greater than those reported for HBOT, but with fewer systemic risks and greater practicality [165].

While most oxygen-releasing hydrogels and nanofiber dressings (e. g., CaO₂- or SPC-loaded constructs, OxOBand, PCL-SPC nanofibers) have been evaluated in diabetic rodent models with impressive acceleration of closure and angiogenesis, clinical data are beginning to emerge [166]. In a sprayable sodium-percarbonate-based oxygen-releasing hydrogel for DFU (clinical cohort $\sim$ 45 patients, Wagner grade 1–2), adjunctive use yielded substantially higher complete closure rates ($\sim$ 78 % vs $\sim$ 46 %) and shorter mean healing times ($\sim$ 6.2 vs 9.8 weeks) compared with standard hydrogel dressings over 12 weeks, effect sizes that are at

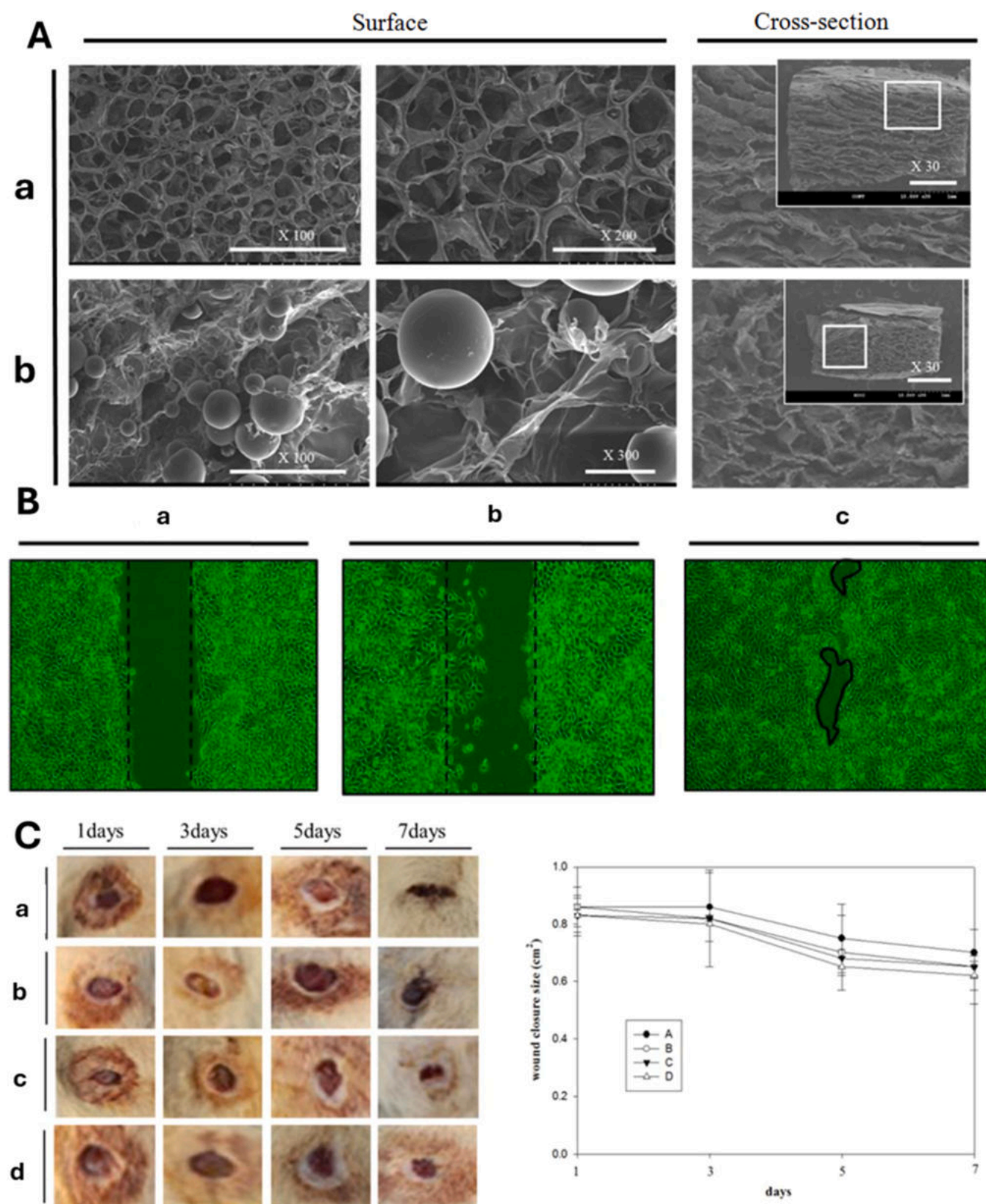


Fig. 9. (A) Field emission scanning electron microscope (FE-SEM) images of bare alginate hydrogel (a) and oxygen-releasing hydrogel sponge (b). The oxygen-releasing hydrogel sponge demonstrates smaller porosity compared to the control. (B) Scratch wound closure model exhibited by HaCaT cells as cells only (a) treated by alginate hydrogel (b), and oxygen-releasing hydrogel sponge treated (c). The recovery of the wound was dramatically more effective in the composite biomaterial group by increasing epithelial keratinocyte cell migration. (C) The observed morphology of opened wounds at different time intervals (right) and the closure of the wounds on 1st, 3rd, 5th, and 7th days (left) as full-thickness skin defect group without treatment, (b) gauze treated group, (c) alginate treated group, and (d) oxygen-releasing hydrogel sponge treated group [153].

least comparable to those reported for HBOT and topical oxygen devices, albeit in a smaller, single-study cohort. Commercial oxygen-releasing hydrogel dressings such as Oxyzyme/Iodozyme, which generate oxygen enzymatically *in situ*, have been used in chronic DFUs and venous leg ulcers. Case series and prospective cohorts report high rates of complete closure and pain reduction in long-standing ulcers, though the absence of randomized controls limits definitive conclusions. Multiple state-of-the-art dressings, such as exosome-laden oxygen-releasing cryogels (OxOBand), nanosponge- or nanobubble-based hydrogels, and sodium percarbonate-loaded nanofibers, consistently demonstrate in diabetic models as sustained oxygen release for 4–10 days, enhanced angiogenesis and collagen deposition, and near-complete wound closure within 14–21 days, compared to delayed or incomplete healing in controls [167]. When expressed as relative benefit vs control, the magnitude of improvement in healing rate and time-to-closure with oxygen-releasing biomaterials in preclinical DFU models (often 1.5–3-fold acceleration) is similar to that reported for HBOT and topical oxygen in clinical DFU RCTs [168]. HBOT requires specialized chambers, repeated 90–120-minute sessions, and carries systemic risks (e.g., barotrauma, oxygen toxicity, claustrophobia), whereas topical oxygen devices are less resource-intensive but still depend on powered equipment and consumables. In contrast, oxygen-releasing biomaterials can be packaged as single-use or periodically changed dressings (hydrogels, patches, nanofiber mats) applied in outpatient or even home settings, with oxygen release limited to the wound microenvironment and no need for chambers or gas cylinders. Positioning in the therapeutic landscape, the updated IWGDF guidelines acknowledge HBOT and topical oxygen as possible adjuncts in selected DFUs but do not yet address oxygen-releasing biomaterials, highlighting both the novelty of these platforms and the imperative for well-designed clinical trials. Therefore, the oxygen-releasing biomaterials should presently be regarded as promising, mechanistically rational heirs to HBOT/TOT for local oxygen delivery, with the realistic caveat that their clinical evidence base is still emerging.

4. Properties and characteristics of oxygen-releasing biomaterials

4.1. Mechanical properties

The mechanical strength of biomaterials is a key parameter in medical applications, particularly in bone regeneration and wound care, which ensures the scaffold or implant can withstand *in vivo* stresses without structural failure. It is also a crucial property that directly influences the effectiveness and durability of biomaterials, ensuring their ability to support tissue healing and integrate with the surrounding biological environment.

Bone regeneration-based applications require adequate compressive strength to support the load-bearing functions of the skeletal system while also maintaining the space for new bone tissue to form [169]. Materials with high mechanical strength can resist deformation and provide a stable environment for osteogenic cells, which is particularly important in load-bearing regions where mechanical stress is high. The human skeletal system is exposed to compressive forces ranging from 4 to 12 MPa in load-bearing bones, requiring biomaterials with

comparable compressive strength to provide temporary mechanical support during the regeneration process [170]. [170]. The elastic modulus of natural bone can change depending on the bone structure, i. e., cortical bones (12–20 GPa) and cancellous bone (0.1–0.5 GPa), as reported in Table 2. Therefore, materials such as hydroxyapatite, β -tricalcium phosphate (β -TCP), and polymer/ceramic composites are frequently utilized as components of bone biomaterials because of their ability to mimic the compressive strength of natural bone tissue. Flexibility is another important parameter in bone regeneration studies that ensures scaffolds conform to irregular bone defects, enabling efficient integration with the host tissue. The designed composite materials benefit from polymers like PCL and ceramics to achieve a balance between strength and flexibility [171]. Stress distribution is considered the third important mechanical parameter in the development of biomaterials in bone regeneration applications, which must distribute mechanical stress equally to the applied area to prevent localized damage or failure. The design of these biomaterials mostly takes advantage of nanomaterials and nano-architecture since they demonstrate a high surface area-to-volume ratio [172]. The studies performed in the bone regeneration field have demonstrated that oxygen-releasing scaffolds possess adequate mechanical strength. They not only provide structural support but also enhance cellular adhesion and proliferation, thereby accelerating the regenerative process since they more effectively mimic original bone tissue, which the local cell lines are adapted to. Strength and flexibility are individually critical. The optimal performance of oxygen-releasing biomaterials is heavily dependent on achieving a balance between these properties to ensure the material becomes neither too brittle (lacking flexibility) nor too soft (lacking strength), enabling it to meet the required challenging demands of bone regeneration applications [173].

Mechanical strength in wound dressings is also an essential parameter in order to maintain the structural integrity of the dressing during handling, the application process, and throughout the healing process [185]. Therefore, the biomaterial demonstrates load-bearing capability by maintaining its structural integrity under physical capability enables the sustaining of physical stresses imposed by patient movement or wound exudate without deforming, thus protecting the underlying damaged tissue. In addition, chronic wounds, such as diabetic ulcers or pressure sores, often require long-term care, which creates a challenge for the biomaterial to be resistant to deformation over time, ensuring consistent performance throughout the healing process. This requires materials with high tensile strength to be durable [186]. Moreover, the biomaterial should resist collapsing during tissue stresses, which guarantees the preserved microenvironment, facilitating cell migration and angiogenesis. As a result, it leads to enhanced cellular activity in terms of cell adhesion, proliferation, and migration by protecting the microenvironment and providing a biologically stable substrate for cell attachment. Mechanical properties are crucial, especially in chronic wounds, since tissue regeneration is compromised and heavily prone to infection if the injured area is exposed to the outside. Flexibility, is the second important parameter in soft tissue applications because it allows the dressing to conform to the wound bed and adjacent tissues, allowing the dressing to adapt to complex wound geometries, including irregular wound surfaces, and eliminates air gaps that may harbor bacteria [187]. Moreover, the designed soft and flexible biomaterial dress reduces

Table 2
Mechanical properties of cortical and cancellous bones versus the most utilized metal-based materials in orthopedic applications.

Material/ Properties	Tensile Strength (MPa)	Compressive Strength (MPa)	Young's Modulus (GPa)	Strain to Failure (%)	Shear Strength (MPa)	Shear Modulus (GPa)	References
Cortical Bone	50–150	130–230	7–30	1–3	53–70	3	[174]
Cancellous Bone	10–100	2–12	0.02–0.5	5–7	-	-	[174]
Mg Alloy	87–280	20–246	41–45	13	145	16	[175]
Ti Alloy	240–1800	170–1060	110–117	10–25	550	45	[176–178]
Stainless Steel	490–1350	200–700	189–205	10–40	400	74	[179–181]
Co-Cr Alloy	900–1800	500–1500	230	10–50	570	23	[182–184]

discomfort during movement and dressing change, thus significantly improving the comfort of the patients. The flexibility of the material also supports the natural movement of the wound margins, enabling stimulation of cell mechanotransduction pathways, which is key in promoting angiogenesis and accelerating tissue regeneration.

4.2. Biocompatibility and biodegradability

The biodegradation kinetics of oxygen-releasing biomaterials refer to the rate and mechanism by which these materials undergo degradation in the biological environment, which is crucial for sustaining oxygen release while minimizing adverse effects. The biodegradation of oxygen-releasing biomaterials may occur through different mechanisms or operate simultaneously, but at different rates. In addition, the composition and structure of the material, including the type of material or composite used, the crystallinity rate, and the presence of labile groups, dramatically affect the intrinsic degradation rate of the biomaterial [188], [189]. For instance, more amorphous regions of a material are generally more prone to hydrolysis compared to crystalline regions. Moreover, the higher molecular weight of used polymers or the density of the utilized material generally results in slower degradation due to the longer chains of polymers or dense structure of the material, which shows resistance to enzymatic and hydrolytic attack [188]. Environmental conditions such as pH, temperature, and local enzyme concentration in the biomaterial-applied tissue microenvironment directly impact the degradation process of the material. Scaffold geometry and the rate of porosity of the material emerge as another determining parameter in biodegradation. For instance, increasing the surface area and porosity of the biomaterial improves water penetration through the architecture, thereby accelerating the degradation rate and process, while denser matrices show slower degradation [190]. Consequently, the biodegradation of the biomaterial occurs mainly in three pathways, which are hydrolytic degradation, enzymatic degradation, and oxidative degradation. Hydrolytic degradation is defined as the cleavage of chemical bonds through reactions with water molecules [191]. The reaction precisely occurs in polyester-based materials such as PLGA and PCL, where ester bonds undergo hydrolysis in aqueous environments. Hydrolytic degradation-based biodegradation depends on water accessibility, polymer crystallinity, and the presence of catalytic elements. Enzymatic degradation refers to the presence of specific enzymes in the tissues that catalyze the breakdown of biomaterial components [192]. It emerges as the primary biodegradation factor in natural polymers like collagen, gelatin, and hyaluronic acids, which are degraded by their specific enzymes as collagenases, gelatinases, and hyaluronidases, respectively. The specificity of enzyme-substrate interactions makes this mechanism highly specific to the local biological environment and varies considerably between implantation sites. Oxidative degradation becomes especially relevant for oxygen-releasing biomaterials due to the presence of ROS generated during oxygen release [193]. For instance, peroxide-based oxygen-releasing compounds like CaO_2 or sodium percarbonate not only deliver oxygen but also produce H_2O_2 , which can accelerate the oxidative degradation of polymer chains through radical-mediated processes. Multiple factors actively influence the biodegradation kinetics of oxygen-releasing biomaterials, which are considered through the design and development of the biomaterial. The chemical composition and structure of the material fundamentally determine susceptibility to various degradation mechanisms [194]. For example, higher glycolide content (i.e., PLGA) in a designed biomaterial dramatically increases hydrolytic degradation rates, while a greater crystallinity rate of the biomaterial usually slows degradation. The interaction of the biomaterial with biological components, including proteins, cells, and ECM components, also affects the biodegradation rate by adsorbing onto biomaterial surfaces, forming a complex interface that can either accelerate or inhibit degradation processes [195]. For instance, protein adsorption generally protects the materials from enzymatic degradation reactions, while cellular activity, including

phagocytosis and foreign body giant cell formation, dramatically accelerates material breakdown.

5. Challenges and limitations

5.1. Cost and manufacturing

The journey toward the production of high-quality oxygen-releasing biomaterials is fraught with numerous challenges that can impede their acceptance and utilization in clinical environments. The manufacturing processes typically employed are often intricate and require advanced technologies, such as electrospinning, 3D printing, or solvent casting [196]. These techniques can significantly elevate production costs, making it difficult for healthcare providers to access these innovative materials. Furthermore, achieving uniformity in the quality and performance of these biomaterials across different production lots is critical. Variability in manufacturing can result in inconsistencies in oxygen release rates, mechanical properties, and overall biocompatibility [197]. Such discrepancies can complicate the clinical application of these materials, as healthcare professionals require reliable and predictable performance to ensure patient safety and treatment efficacy. Consequently, manufacturers must invest heavily in quality assurance processes, which can further increase costs and delay the time to market.

5.2. Safety and toxicity

Safety is a paramount concern when it comes to the application of oxygen-releasing biomaterials in medical scenarios [198]. While oxygen is a vital component for cellular metabolism and tissue regeneration, an unregulated release of oxygen can lead to oxidative stress, which can damage cellular structures and disrupt normal physiological functions [199]. This oxidative stress can trigger inflammatory responses, leading to complications that may hinder the healing process [200]. In addition to oxidative stress, the potential cytotoxic effects of certain oxygen-releasing agents need thorough investigation. Some materials may elicit adverse reactions in surrounding tissues, leading to necrosis or impaired healing. Therefore, it is essential to conduct extensive pre-clinical evaluations to assess the biocompatibility of these biomaterials. Researchers must explore the interactions between oxygen-releasing agents and various cell types to better understand the mechanisms by which these materials may cause harm, thus ensuring the development of safer alternatives.

5.3. Regulatory and clinical hurdles

The regulatory landscape governing medical devices, particularly those incorporating innovative materials like oxygen-releasing biomaterials, can be complex and challenging to navigate. Regulatory agencies, such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), mandate rigorous testing to evaluate the safety and efficacy of these materials before they can be approved for clinical use [201,202]. This often involves a series of preclinical studies followed by multi-phase clinical trials, each designed to address specific safety and efficacy issues. The extensive time and resources required for these regulatory processes can create significant barriers to market entry for new biomaterials. Moreover, the evolving nature of regulations regarding novel materials and technologies can introduce uncertainty for researchers and manufacturers [203]. To overcome these hurdles, collaboration among researchers, industry stakeholders, and regulatory bodies is essential. Such partnerships can help streamline the approval process, facilitate knowledge sharing, and ultimately expedite the translation of oxygen-releasing biomaterials from the laboratory to clinical practice.

6. Future directions

6.1. New materials and innovations

The field of oxygen-releasing biomaterials is on the cusp of exciting advancements, particularly in the development of new materials that enhance their functionality and applicability in clinical settings. Recent innovations in nanotechnology have led to the creation of advanced oxygen-releasing agents, including nanoparticles and hydrogel composites [204–206]. These novel materials can be engineered to provide controlled and sustained oxygen release, addressing some of the limitations associated with traditional biomaterials. For instance, nanoparticles can be designed to respond to specific environmental stimuli, such as changes in pH or temperature, enabling them to deliver oxygen precisely when and where it is needed [207]. Hydrogel composites can be loaded by oxygen-releasing agents within a 3D matrix, allowing for improved integration with surrounding tissues [208]. This design not only facilitates cellular infiltration and proliferation but also enhances the overall biocompatibility and functionality of the materials. Additionally, research is exploring the use of biodegradable materials that can gradually release oxygen while being metabolized by the body. This approach minimizes the need for surgical removal after the healing process is complete and reduces the risk of long-term complications associated with permanent implants.

In parallel with the development of new oxygen carriers, intelligent regulation of the oxygen-releasing process is rapidly becoming a central design principle. Apart from the passive peroxides or MOFs, recent programmable and stimuli-responsive hydrogels can adjust oxygen output in response to pH, ROS level, enzymatic activity, temperature, or external triggers such as light and magnetic fields, enabling spatiotemporally controlled release that better matches dynamic tissue oxygen demand. For example, cascade systems that couple metal-peroxide particles or H_2O_2 donors with CAT, nanozymes, or redox-active MOFs function as self-regulating oxygen generators, consuming excess H_2O_2 and ROS while generating O_2 in proportion to local oxidant levels, thereby simultaneously correcting hypoxia and limiting oxidative damage [209]. In addition, emerging hydrogel-based wearable platforms integrate flexible electronics and sensors for real-time monitoring of wound pH, temperature, and perfusion; these systems conceptually allow closed-loop control where optical, electrical, or thermal cues can be used to trigger or modulate oxygen release on demand. Such approaches shift oxygen-releasing biomaterials from static dressings toward adaptive, feedback-regulated therapeutic systems. At the same time, oxygen-releasing biomaterials are expanding well beyond chronic skin wounds and bone defects into multiple clinical domains. In oncology, oxygen-generating hydrogels and metal-peroxide platforms are being exploited to alleviate tumor hypoxia and thereby enhance photodynamic therapy, radiotherapy, and chemotherapy, illustrating how local oxygen modulation can potentiate anti-cancer efficacy [210]. In cardiovascular medicine, CaO_2 -loaded polymer scaffolds and microparticle-based hydrogels provide sustained oxygenation to ischemic myocardium and engineered cardiac tissues over weeks, supporting cell survival and contractile function after infarction [211]. Other studies demonstrate oxygen-releasing constructs for cartilage repair (including 3D-bioprinted oxygen-releasing bioinks), neural tissue and spinal cord regeneration, pancreatic islet transplantation, and skeletal muscle repair, highlighting a broad cross-tissue applicability wherever hypoxia limits regeneration. Therefore, these trends indicate that next-generation oxygen-releasing biomaterials will not only be defined by their chemistry but also by their ability to sense and respond to the local microenvironment, operate within intelligent or wearable systems, and be tailored to diverse ischemic and hypoxic conditions across different organs.

6.2. Combination therapies

The exploration of combination therapies represents a promising direction for enhancing the therapeutic efficacy of oxygen-releasing biomaterials. By synergistically integrating these biomaterials with other therapeutic agents, such as growth factors, antimicrobial agents, or other bioactive molecules, researchers can create multifaceted treatment strategies that address various aspects of tissue healing and regeneration [212]. For example, combining oxygen-releasing biomaterials with growth factors like VEGF can significantly promote angiogenesis, thereby improving blood supply to the healing tissue [213]. This is particularly important in chronic wounds, where inadequate blood flow can impede healing. Similarly, incorporating antimicrobial agents into oxygen-releasing matrices can help reduce the risk of infection, a common wound healing issue, following bone or dental implant placement, which can delay recovery and lead to further complications [205]. Moreover, the combination of oxygen-releasing biomaterials with stem cells or other cell-based therapies may enhance tissue regeneration. By providing both the necessary oxygen and cellular components, such therapies could create a conducive environment for healing and tissue repair, ultimately leading to improved clinical outcomes.

6.3. Personalized medicine and targeted delivery

As the field of personalized medicine continues to evolve, the potential for tailoring oxygen-releasing biomaterials to meet specific patient needs or conditions becomes increasingly viable. The ability to customize oxygen release rates based on individual patient profiles can optimize therapeutic effects and minimize potential side effects. For instance, patients with different wound types or healing capacities may benefit from varying rates of oxygen delivery [214]. Emerging technologies, such as smart biomaterials and advanced drug delivery systems, can facilitate this personalized approach. Materials that respond dynamically to physiological cues, such as inflammation or hypoxia, can adjust their oxygen release accordingly, providing targeted therapy precisely when and where it is needed most [214]. This level of customization not only enhances treatment efficacy but also aligns with the growing emphasis on patient-centered care in modern medicine. Additionally, the integration of real-time monitoring technologies, such as biosensors, into oxygen-releasing biomaterials could provide valuable feedback on the healing process. By continuously assessing the local environment within a wound, healthcare providers could make informed decisions about treatment adjustments, further enhancing the effectiveness of oxygen-releasing therapies [215]. That is, while significant challenges and limitations persist in the development and application of oxygen-releasing biomaterials, ongoing research and innovations hold great promise for their future use in tissue regeneration and wound healing. By addressing these challenges and exploring new avenues for development, we can pave the way for more effective, safer, and personalized therapeutic options that can greatly benefit patients. The continued collaboration between researchers, clinicians, and industry stakeholders will be essential in realizing the full potential of these advanced biomaterials in clinical practice.

7. Conclusions

Hypoxia persists as an ever-fundamental issue that inhibits the success of regenerative therapies in engaging with the ecosystem of angiogenesis and ECM formation of ischemic tissues with low perfusion. Oxygen-releasing biomaterials represent an unprecedented approach that offers the potential of sustained oxygenation of these tissues according to spatial designs that cannot easily succeed with conventional delivery systems. Various oxygen-releasing materials encompassing peroxide and percarbonate salts of metal oxides, metal-organic structures, HBG-based oxygen-releasing carriers, perfluorocarbon emulsions,

zeolites, cyclodextrin nanosponges, lipid-based micro-bubbles and photosynthetic micro-organism-based oxygen-releasing biomaterial designs have emerged. Indeed, these technologies include different oxygen release mechanisms that allow the development of specific therapeutic strategies applicable according to the target condition of ischemia. The biomaterial designs possess multifunctional properties that underpin the enhancement of angiogenesis, regulation of the inflammatory reaction, repression of microbial growth, and mechanical reinforcement according to the clinical application. Satisfactory preclinical potential has been demonstrated toward the treatment of bone and cartilage, repair of skeletal/heart muscle, regeneration of central tissues, periodontal and endodontic therapies, bone implants, chronic/burn wound management, and ischemic conditions. Despite the progress made in these fields, target angiogenesis, matrixogenesis, cytogenesis and reinforcement of tissues with poor perfusion still remain critical issues that push the need for the careful design of new biomaterial architectures that directly target specific requirements toward tissue repair with precise control of oxygen release rate and reactive oxygen release. Indeed, the requirements for the development of reproducible technologies are of utmost priority. Future innovation should target the development of adaptive and stimulus-reactive materials that could control oxygen release based on local biochemical/physical stimuli like pH levels, enzyme activity, or external light and magnetic fields. Advanced materials fabrication technologies, like 3D bioprinting and nanoscale structuring, will also deserve to be considered. By integrating these materials with advanced computational modeling and individualized medicine technology, the problem of optimizing oxygen delivery could finally be overcome. Once these scientific and technological hurdles are overcome, oxygen-releasing biomaterials can move out of the laboratories and enter the hospitals as potential therapies for the treatment of complex wounds and the regeneration of highly demanding tissues.

CRediT authorship contribution statement

Amirhossein Moghanian: Writing – original draft, Supervision, Investigation, Conceptualization. **Sirus Safaee:** Writing – review & editing, Investigation. **Kizilkurtlu Ahmet Akif:** Writing – review & editing, Investigation. **Francesco Baino:** Writing – review & editing, Validation, Investigation. **Seyed Hesamedin Hosseini:** Writing – original draft, Investigation. **Amir K. Miri:** Writing – review & editing, Investigation. **Ramin Farmani:** Writing – review & editing, Investigation. **Majid Vaseghi:** Writing – review & editing, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

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

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