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Unveiling the development principles and mechanistic understanding of controlled drug delivery strategies for chronic bone defects and diabetic wound management

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Hydrogel and ferrogel-based systems are leading the way in therapeutic approaches for treating diabetes-related complications, such as bone abnormalities and impaired wound healing. As a desirable multipurpose material, transition metal oxides (TMO) are receiving more interest in biological applications. The doping of TMOs inside the polymer network is the focus of the present review, which also covers the basic ideas and important capabilities of hydrogels and ferrogels. Notably, the use of DNA engineering and nanotechnology in hydrogel frameworks has greatly advanced their functioning by allowing for precise and regulated release mechanisms. This review highlights the significant influence of TMO-grafted hydrogels on regulating the immune system, reducing inflammation, promoting angiogenesis, and supporting osteogenic differentiation, all of which excellently aid in wound healing and bone repair in diabetic circumstances. The combination of these characteristics attributes how hydrogel drug-loading devices can revolutionize tissue repair and diabetic treatment approaches, and usher in a new age of improved, customized healthcare solutions. This review offers a thorough depiction of the diverse spectrum of projections over hydrogels to provide readers with a clear grasp of the most recent advancements, traits, history, and applications of hydrogels and ferrogels.

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1. Introduction

Diabetes mellitus is linked to several problems with bone health,[1,2] such as a higher risk of fractures, a slower rate of bone repair, and a decrease in the density of bone minerals. The accumulation of oxidative stress, chronic inflammation, and advanced glycation end products (AGEs) brought on by hyperglycemia all contribute to these problems by reducing the osteogenic capacity of cells that create bone and interfering with the bone remodelling process. Natural healing processes are insufficient to reinstate structural veracity and purpose when bone abnormalities are present, making the problem much more difficult. Several studies have provided insight into how diabetes affects bone curing and how to improve bone regeneration in diabetic individuals. Insulin is necessary for the treatment of type 1 diabetes mellitus (T1DM), whereas several hypoglycemic medications may be used as adjunct therapy for type 2 diabetes mellitus (T2DM).[3] For example, Metformin (Met) has been demonstrated to improve bone mass and strength by preventing the buildup of AGEs.[4] At the same time, its impact on fracture risk in people with type 2 diabetes varies, exhibiting either beneficial or insignificant effects.[5] By inhibiting bone formation and speeding up resorption, thiazolidinediones (TZDs) reduce blood glucose levels but negatively impact bone, resulting in reduced trabecular and cortical bone mass components.[6] By raising the risk of hypoglycaemia,[7] sulfonylurea drugs unintentionally upsurge the menace of falls and fractures while reducing the effects of hyperglycemia on osteoblasts.[6] This contradiction emphasizes the intricate connection between bone health and hypoglycemic therapies, underscoring the need for more research on the efficacy and safety of these drugs.[8] As a result, current studies have shifted their focus to finding more effective treatment approaches, like cutting-edge drug delivery methods such as reinforced hydrogel drug delivery systems.[9,10] These developments might revolutionize patient care for diabetes-associated bone diseases by providing more focused and efficient therapies for diabetic bone abnormalities.[11]

TMO-decorated hydrogels have become the perfect medium for the controlled administration of medications and bioactive compounds for bone abnormalities because of their swelling capacity, non-toxicity, and adjustable physical

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characteristics.[12–14] Numerous therapeutic substances, such as anti-inflammatory medications, antibiotics, growth factors, and cells, can be encapsulated in these three-dimensional networks and released gradually over time. Because it guarantees that therapeutic contents are reached at the site of damage without causing systemic adverse effects, this localized delivery technique is very beneficial for diabetic bone repair and wound healing.[15] First, TMO-decorated hydrogels can be designed for controlled delivery against the response to particular stimuli that are typical of diabetic wound settings, such as temperature, pH, or enzyme activity changes. Furthermore, hydrogels' porous nature facilitates osteogenic cell infiltration and delivers a scaffold for developing new bone tissue. Furthermore, TMO-decorated hydrogels can reduce the chronic tenderness linked to diabetes by directly delivering anti-inflammatory drugs to bone abnormalities, producing an environment more favourable to bone repair and foot ulcer healing (Fig. 1). Lastly, to deal with the complex character of poor bone regeneration in diabetes, TMO-decorated hydrogels can be created with different bioactive compounds.[16,17] To improve the consequence of diabetes bone defect regeneration, the ability of TMO-decorated hydrogel-based hybrids to promote bone regeneration in diabetic mice has been shown in several recent research. A further tactic to control hyperglycemia and encourage bone repair at the same time is the introduction of antidiabetic medications into TMO-decorated hydrogels.

Because of its numerous mechanisms that endorse bone repair, TMO-decorated hydrogel-based drug release devices are at the forefront of invention for addressing diabetes-associated bone and wound abnormalities. For example, these systems can efficiently stimulate bone repair by regulating the body's immunological response. To control the percentage of macrophages, IL-10 triggers the JAK-STAT pathway, particularly the production of signal transducers and activators of transcription 3 (STAT3) transcription factors. This controls the release of proinflammatory substances and enhances the immunological environment.[18] By inhibiting inflammatory mediators, pathways including the MEKK-3/IKK/IκB and ASK-1/MEK4/6/JNK/p38 MAPK/AP-1 pathways are deactivated, and factors like nuclear transcription factor-κB (NF-κB) and activator protein-1 (AP-1) are released less often, which promotes bone regeneration.[18,19] Additionally, certain TMO-decorated hydrogel systems enhance the milieu at the defect location by directly targeting inflammation. This improvement lowers the production of reactive oxygen species (ROS), stops ROS-induced inflammatory cascades, and greatly enhances mitochondrial dynamics. It also speeds up bone regeneration by reducing the production of the inflammasome and proinflammatory cytokines. Furthermore, because TMO-decorated hydrogel drug delivery methods encourage angiogenesis and osteogenic differentiation, they show a crucial role in bone healing. Agevgel, a DNA skeleton-based hydrogel developed by Ge Peng *et al.*, improved the trabecular structure and markedly sped up the regeneration of alveolar bone blemishes.[20] These various approaches demonstrate the great promise of TMO-decorated hydrogel drug delivery hybrids in treating bone and foot ulcer abnormalities in diabetics and offer guidance for future treatment approaches that combine medical innovation and materials science to improve patient outcomes.

The study on TMO-decorated hydrogel-based drug delivery systems is thoroughly reviewed in this paper, setting the groundwork for further studies on diabetic bone abnormalities and the creation of novel therapeutic approaches. Next, how diabetes and hypoglycemic treatment affect bone defects and categorize TMO-decorated hydrogel systems was examined. TMO-decorated hydrogel systems are outlined along with a drug-loading method, offering a promising approach for treating bone defects and diabetes-related foot ulcers. Additionally, these systems can promote wound healing and have demonstrated potential in the management of many ailments, such as arthritis and periodontitis. Despite these developments, more progress requires a better comprehension of the underlying mechanics. Furthermore, clarifying signalling pathways may help find new therapeutic targets, opening the door to the creation of more potent and successful treatment plans. This review provides a more comprehensive and mechanistically thorough description of TMO-decorated hydrogel and ferrogel

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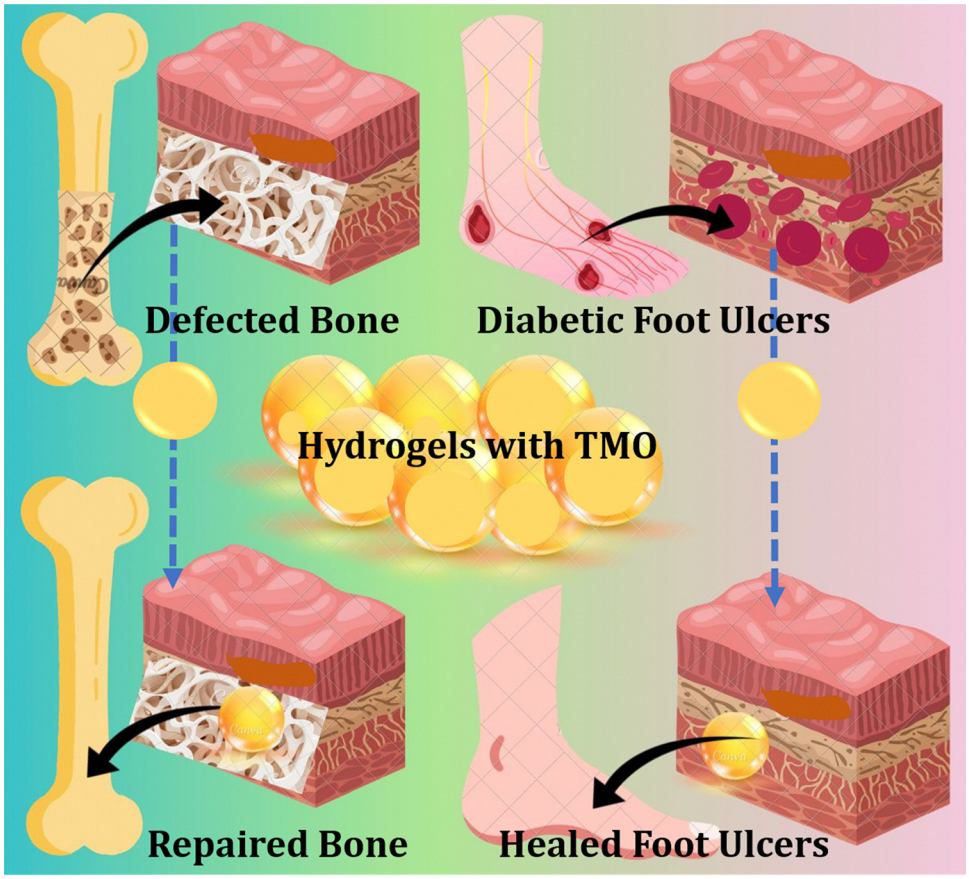

Fig. 1 Schematic representation of regeneration of diabetic foot defects and foot ulcer healing using transition metal oxide decorated hydrogels.

systems than earlier published reviews. It is especially designed for complicated diabetes situations that include persistent bone abnormalities and poor wound healing. The recent reviews mainly provide studies of smart hydrogel systems that emphasize adjustable drug delivery and stimulus-responsive release, but they don't concentrate on the immunomodulatory or regenerative effects of transition metal oxide integration. Also, the complementary benefits of ferrogels or TMO-induced bioactivity in reducing inflammation and wound healing were not examined in the current literature. In contrast, this study integrates cutting-edge hydrogel engineering techniques like DNA self-assembly and nanostructuring with the therapeutic potential of TMOs, including their ROS-scavenging capabilities, magnetic responsiveness, and catalytic activity. This makes it possible to get a multifaceted knowledge of how these systems affect angiogenesis, oxidative stress, and immunological responses, all of which are often disregarded in evaluations that are more material- or application-specific. Furthermore, by incorporating applications beyond conventional wound and bone healing, like diabetic foot ulcers, arthritis, and periodontitis, this work presents itself as a more comprehensive and forward-looking framework that not only summarizes recent research but also describes the translational and clinical potential of next-generation hydrogel-based treatments.

2. Approaches for designing drug-loading systems using hydrogel

2.1. Selection of TMO

In bone tissue engineering, nanostructured materials including rare-earth-based materials, transition metal oxide (TMO) nanoparticles, for example, iron oxide (Fe_3O_4), titania (TiO_2), zirconia (ZrO_2) *etc.*, are utilized to increase mechanical qualities, encourage cell proliferation, and improve material structure and bioactivity.[21–24] Because hydrogels and their inorganic components work in concert, there is a growing interest in TMO-hydrogel composite materials that incorporate an inorganic nanostructure.[25] A variety of such additives have been added to hydrogel to create composite materials with specific mechanical characteristics.[26–28] The scaffold can replicate the precise structure of a tissue because it contains nanoparticles trapped in a hydrogel matrix, which makes it a nanocomposite material. A new avenue in controlled drug delivery techniques has been made possible by the incorporation of TMOs into hydrogel systems, especially for the treatment of chronic and complicated diseases, including bone regeneration and diabetic wound healing. TMOs with special physicochemical characteristics, including magnetism, redox activity, photocatalysis, and high surface area, may be customized for multipurpose drug delivery applications.[29] The target tissue's compatibility, reactivity to physiological stimuli,

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interaction with hydrogel matrices, and contribution to therapeutic action all play a role in the choice of a suitable TMO. TMOs that maintain structural integrity, encourage osteogenesis, and allow for continuous medication release are ideal for treating chronic bone abnormalities. On the other hand, choosing TMOs with antibacterial, antioxidative, and pro-angiogenic qualities is crucial for diabetic wounds.[30]

Because of its magnetic responsiveness, biocompatibility, and potential for magnetically guided or triggered drug release, Fe_3O_4 (magnetite) is often employed in hydrogel composites. Because external magnetic fields may be used to guide the hydrogel-drug combination to the defect site and promote cell differentiation *via* mechanical signals, its potential in bone defect repair is very promising. Similar to this, Fe_3O_4-loaded hydrogels in wound care provide a multipurpose platform by enabling targeted medication administration and real-time magnetic resonance imaging (MRI).[31]

TiO_2 is another interesting TMO because of its photocatalytic activity, which may be used for antibacterial and light-triggered medication release. To improve its therapeutic efficiency, functionalization or doping is necessary due to its inertness in the biological environment. TiO_2 is a potential option for bone regeneration techniques due to its capacity to promote cell adhesion and proliferation, particularly when paired with bioactive ceramics.[32,33] Particularly important in the treatment of diabetic wounds are CuO and ZnO TMOs. Both have been shown to stimulate collagen deposition and angiogenesis and have inherent antibacterial qualities. ROS produced by ZnO nanoparticles prevent bacterial growth without impairing tissue repair. Furthermore, during skin regeneration, Zn^{2+} ions are crucial for enzymatic processes. These oxides enable regulated ion release in hydrogel systems, which works in concert with encapsulated medications to improve the effectiveness of healing.[34] Their possible cytotoxicity at high concentrations, however, calls for careful dose monitoring, which is possible in a hydrogel matrix.

By breaking down endogenous hydrogen peroxide in diabetic wounds, which are usually hypoxic, MnO_2-based hydrogels provide the ability to generate oxygen. By fostering a more conducive healing environment, this reduces oxidative stress and enhances medication performance.[35] Because they may encourage mineralization, Mn-based oxides also hold potential for bone tissue engineering. CeO_2 resembles enzyme antioxidants such as catalase and superoxide dismutase and is recognized for its reversible redox behaviour (Ce^{3+}/Ce^{4+}). Because of this, ceria nanoparticles may be used to treat diabetic lesions with high levels of oxidative stress. CeO_2 allows for a long-lasting antioxidative impact when implanted in hydrogels, which lowers inflammation and encourages tissue healing.[36,37] Long-lasting action is provided by its regenerative redox cycle, which makes it an appropriate addition for long-term therapeutic uses. Another element that influences the choice of TMOs is how they interact with hydrogel networks. Because of their high-water content, biocompatibility, and adjustable porosity, hydrogels provide flexible platforms. The resultant composite's mechanical strength, rate of degradation, and drug release characteristics may be altered by physically mixing, covalently attaching, or synthesizing TMOs *in situ* inside the polymer matrix. Crucially, the chosen TMO must not compromise the hydrogel's structural integrity or swelling behaviour, both of which are essential for diffusion-controlled release mechanisms.

The physicochemical and biological characteristics of the TMO, the mechanical and functional needs of the hydrogel scaffold, and the therapeutic demands of the target tissue must all be balanced in order to create TMO-hydrogel systems for drug administration that make sense. The creation of hybrid TMOs, controlled doping, and intelligent hydrogel designs that react dynamically to disease-specific microenvironments needs to be the top priorities of future studies. By accomplishing this, TMO-decorated hydrogels may realize their potential as next-generation delivery systems that are site-specific, regulated, and long-lasting in the management of long-term bone and wound conditions linked to diabetes.

2.2. Assortment of TMO-decorated hydrogels

When building a hydrogel drug-loaded structure, the hydrogel material selection is crucial, and the mix of several materials can significantly affect the therapeutic efficacy. Methacrylic anhydride (MA) and gelatin are combined to create gelatin methacrylate (GelMA), the original and most popular solution. Excellent biocompatibility, biodegradability, and bioplasticity, along with the capacity to offer three-dimensional (3D) networks, are the primary drivers of this material's extensive use, along with its ability to promote cell development and differentiation with a specific level of strength by the processes of cross-linking or photopolymerization. Many hydrogel drug-carrying systems, including GelMA-*g*-GSH hydrogels,[38] POM gelatin hydrogels,[39] and PDGF-BB nanocomposite hydrogels,[40] employ this structure as an implant to treat diabetic bone and wound abnormalities. Furthermore, several investigations have given hydrogel drug delivery systems smart responsiveness by using more inventive hydrogel materials decorated with TMO. By combining fibrinogen with thrombin-conjugated with γ-Fe_2O_3, new magneto-responsive fibrin hydrogel composites were created. Additionally, the growth factor's covalent and physical conjugation to the magnetic nanoparticles stabilized basal fibroblast growth factor (bFGF). When compared to the same concentration, the γ-Fe_2O_3 nanoparticles dramatically improve the migration, proliferation, and differentiation of adult nasal olfactory mucosa cells placed within the fibrin scaffolds.[41] Itaconic acid graft copolymerization onto starch in the occurrence of Fe_3O_4 nanoparticles produced a pH-responsive magnetic hydrogel hybrid for the transport of guaifenesin (GFN) for wound healing. Only around 54.1% GFN was released after 24 hours for the free Fe_3O_4-nanocomposite (in pH 7.4), however, that was enhanced (90.4%) for the nanocomposite containing 0.83% Fe_3O_4 under the same conditions. This is because the introduction of an external magnetic field may greatly increase the drug release percentage. More significantly, the bioavailability of the released GFN was maintained. When combined, these hydrogel drug carriers offer both a dressing

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for wound healing and a viable platform for magnetically focused drug delivery.[42]

Furthermore, while selecting hydrogel materials, there are medication delivery methods using hydrogel that concentrate on the achievement of more accurate, regulated, and efficient drug delivery. For instance, PEG serves as a hydrogel scaffold in the polyethylene glycol (PEG)/DNA hydrogel drug-loaded structure.[43] More significantly, PEG contains many functional groups, and it is hydrophilic and biocompatible as a carrier. To completely realize the responsive and targeting features of DNA and accurately manage drug delivery, this advantage facilitates the connection of different DNA structures, including DNA aptamer linkers, DNA S1 and DNA S2, and hybrid DNA hydrogels, more quickly and easily. Furthermore, regulated drug delivery is shown by the MgO/HA nanocrystalline PGA-Cys hydrogel drug-loading composite.[44] In order to further support bone tissue growth and repair, magnesium and hydroxyapatite nanocrystalline ions are added. Additionally, γ-polyglutamic acid and magnesium ions chelate to provide prolonged delivery of magnesium ions, preventing potential negative consequences and extending the impact. Naturally, scientists are also trying to create hydrogel mediums with osteogenic qualities to use as hydrogel drug delivery system carriers. Using a range of materials, including graphene oxide (GO), chitosan (CS), β-glycerophosphate (β-GP) and hydroxyethyl cellulose (HEC), the CS/GO/HEC/β-GP hydrogel system (thermosensitive)[45] creates hydrogel scaffolds that fully utilize their significant osteogenesis-endorsing qualities and biocompatibility while also working in concert with piggybacked medications to repair bone defects. Damage from external sources, such as burns, cuts, incisions, and chemical injuries, is frequently foreseeable. The significance of creating hydrogel hybrids with nanoparticles (inorganic) that have antimicrobial qualities to cure diabetic wounds and speed up the skin renaissance progression is highlighted by antibiotic-resistant microorganisms at wound sites. A promising TiO_2–HAp@PF-127@CBM hydrogel hybrid with inorganic and organic integration was created in this work to address issues related to wound healing and bacterial resistance. The final product was achieved by coating the generated TiO_2–hydroxyapatite (HAp) with Pluronic F-127 polymer (FDA-approved) and combining it with a carbomer hydrogel (CBM). The TiO_2–HAp@PF-127@CBM group showed improved tissue regeneration and decreased inflammation, which points to a conducive environment for wound healing.[46]

A paradigm change in the design of drug delivery systems has been brought about by the decoration of hydrogels with transition metal oxides (TMOs). These hybrid materials provide hydrogels with a variety of multipurpose qualities, including externally induced drug release, imaging capabilities, catalytic activity, and magnetic responsiveness. The capabilities of traditional hydrogels, which mostly rely on passive release mechanisms like diffusion or ambient pH/temperature fluctuations, are far exceeded by these improvements. Fe_3O_4-decorated hydrogels, for instance, react to alternating magnetic fields by generating localized heating, allowing for regulated drug release, and perhaps improving MRI contrast at the same time. Similarly, Cu_2O/MXene composites release therapeutic ions selectively in acidic tumour settings, enabling both photothermal treatment (PTT) and chemodynamic therapy (CDT).[47] Using π–π stacking interactions, MoS_2-embedded hydrogels provide doxorubicin (DOX) carriers and provide dual photothermal and photodynamic effects, making them another attractive platform. These devices promise non-invasive cancer therapy approaches because they show light-triggered medication release, especially when exposed to near-infrared (NIR) light.[48]

TMO-decorated hydrogels exhibit strength over traditional systems. The ability of TMO-decorated hydrogels to respond to external stimuli is one of their main advantages. These systems may be designed to release their pharmacological payloads in response to certain stimuli, such as light irradiation (MoS_2), magnetic fields (Fe_3O_4), or changes in the pH and redox environments (CuO/MXene hybrids, for example). Because typical hydrogels rely on passive processes like diffusion, temperature, or pH changes in bulk, they are unable to provide precise spatial and temporal control of drug release.[47] TMO-based devices thus have great potential for targeted treatment with fewer systemic adverse effects. Moreover, the inclusion of TMOs significantly improves hydrogels' mechanical performance in addition to their functional responsiveness. Metal–ligand coordination, for example, is used in systems that include Fe^{3+} ions and catechol groups (as in DOPA–Fe(III)–MNP hydrogels) to build stronger, more robust networks that also enable reversible and adjustable drug release.[49] Biomedical applications needing long-term mechanical integrity need this degree of structural strengthening. Moreover, adding metal or oxide nanoparticles increases the hydrogel's flexibility, endurance, and response to outside stimuli. Traditional polymer hydrogels, which are fragile and prone to quick deterioration, often lack these qualities. Combining many treatment modalities on a single hydrogel substrate is made possible by TMO ornamentation. For example, MOF or MXene-based systems provide synergistic photodynamic, photothermal, and chemodynamic treatments, whereas Fe–DOPA hydrogels allow the combination of hyperthermia and chemotherapy (DOX release). These multimodal platforms are very appealing for complicated illnesses like cancer and chronic wounds since they have shown improved treatment success in preclinical models as compared to solo approaches.[50] The possibility for theranostics, simultaneous treatment and diagnostics, is another advantage of TMO-decorated hydrogels. Magnetic nanoparticles such as Fe_3O_4 enable MRI-guided administration, while oxides based on Au or Ag may help with plasmonic biosensing or computed tomography (CT) imaging.[51] Insights into treatment effectiveness and real-time monitoring of the drug delivery process are made possible by this multifunctionality, which is not possible with conventional hydrogels unless they are significantly altered. Precision medicine and patient-specific treatment plans are made possible by the combination of therapy and diagnostics on a single platform. These systems may potentially aid in overcoming medication

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resistance and enhancing treatment results by combining several modes of action.

The intricacy of their synthesis places limitations on TMO-hydrogel composites, despite their numerous benefits. Precise and often multistep production processes are necessary to achieve homogeneous dispersion of nanoparticles, manage particle size, and maintain constant surface chemistry. Particularly when scaling up for industrial or clinical purposes, these difficulties raise questions about reproducibility and batch-to-batch variability. Moreover, a major obstacle still exists regarding these hybrid systems' stability in physiological settings. For instance, transition metal oxides may aggregate, decreasing their functional effectiveness and jeopardizing system homogeneity, while metal–organic frameworks (MOFs) may deteriorate prematurely in acidic conditions. The biocompatibility of TMO-decorated hydrogels is another significant issue. Even though a lot of TMOs have therapeutic properties, if they are not properly managed or targeted, their breakdown products, including metal ions or ROS, may be harmful to healthy tissues. For example, oxidative stress in non-target cells has been linked to Cu^{2+} ion release during chemodynamic treatment.[52] Furthermore, thorough toxicological research is required since the long-term fate, biodistribution, and clearance of inorganic nanomaterials in the body are still little known. On the other hand, conventional hydrogels made of synthetic or natural biopolymers are already authorized for a number of therapeutic applications and are often regarded as safe.[53]

It is still technically challenging to achieve reliable, regulated drug release from TMO-decorated hydrogels. It is difficult to avoid unwanted burst release while maintaining timely medication availability, even though these systems are built for stimuli-responsive release. For instance, in acidic tumour microenvironments, hydrogels containing MOFs may degrade quickly, causing the medication to release prematurely before it reaches the therapeutic location.[54] Furthermore, the development of hydrogels with dynamic viscoelastic characteristics that might modify release kinetics after injection is still in its infancy. More study is required to fully realize this promise in therapeutic settings, even though encouraging advancements are being made, such as the use of dynamic crosslinking techniques to adjust release behaviour.

2.3. Choosing the appropriate drug for hydrogel systems and their loading strategies

To create a hydrogel drug-releasing structure to cure diabetic wounds and bone abnormalities, medications with osteogenic effects or a considerable reduction in inflammation can be chosen. These pharmaceuticals are not only conventional medications; they may also be growth factors like BMP-2 and SDF-1 that have the ability to promote osteoblast migration, proliferation, and differentiation. Furthermore, hydrogel drug delivery methods can contain cytokines. IL-10 is really the most often utilised cytokine and has strong anti-inflammatory properties. Lithium and magnesium ions, which typically have unexpected impacts on signalling pathways relevant to osteogenesis, are examples of therapeutic ions that can be added to drug-carrying systems microenvironment. Additionally, diabetes patients' pathological problems have been treated using antiglycemic medications like Met. MiRNA exosomes have been creatively used as medications because some studies have shown that miRNAs have a promoting influence on osteoblasts. Because of their unique characteristics and connections with the hydrogel network, the aforementioned materials have been included in hydrogel drug-loading systems (Table 1) to enhance the body's microenvironment or encourage osteogenesis.

System safety, therapeutic effectiveness, and drug release behaviour are all strongly impacted by the drug-loading method. Drug-loading mechanisms come in three varieties. The physical encapsulation approach is the first. By using the reticular structure of the hydrogel to regulate the drug's release, this technique mixes or disperses the medication straight into a hydrogel matrix. In particular, a monomer solution is combined with the drug, and as the monomer is cross-linked and polymerised, the medication is enclosed within the hydrogel. Photocrosslinking and thermal crosslinking are two popular crosslinking techniques. For instance, in the process of creating GM/M–Li hydrogels,[45] photoinitiators crosslink GelMA and M–Li to create a chemical connection between the drug and the hydrogel network, which allows for the precise and efficient release of lithium ions. Photocrosslinking is another method used to join GelMA to GSH in GelMA-*g*-GSH hydrogels.[28] The chemical bonding approach comes next. In order to induce a gradual release of the medicine, this approach uses chemical bonding to link the drug to the hydrogel matrix. Medication

Table 1 Drug assortment for drug delivery systems using hydrogel. Reproduced with permission from ref. 63. Copyright 2024 Elsevier

Drug loading system using hydrogel	Drug types	Name of the drug	Ref.
PVA gelatin	Growth factors and immunomodulators	IL-10 and BMP-2	64
The bioactive glass hydrogel is modified by lithium.	Ions	Lithium ions	65
PGA-Cys hydrogel nanocrystalline MgO/HA	Ions	Magnesium ions	44
A hybrid hydrogel of PEG and DNA	Exosomes of miRNA	miR-126-5p and miR-150-5p	43
PDGF-BB hydrogel nanocomposite	Growth factors produced from platelets	PDGF-BB	40
PPP-MM-S	Factors produced from stromal cells; hypoglycemic medications	SDF-1 and Met	66
GelMA-*g*-GSH hydrogel	Antioxidants	GSH	38
Thermosensitive hydrogel CS/GO/HEC/β-GP	Anti-inflammatory medications	Atstrin	45

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molecules can create chemical connections with the hydrogel's functional groups through certain chemical events, such as hydrolysis or enzymatic reactions, which will release the medication when needed. Although this method increases medication stability and controlled release, it could call for intricate settings and chemical reaction processes. The therapeutic agent and loading technique must be carefully chosen to match the target disease and physiological milieu in order for hydrogel-based drug delivery systems to be designed successfully. In contrast to conventional drug delivery methods like systemic injections or oral tablets, TMO-hydrogels provide enhanced bioavailability, site-specific administration, and adjustable release kinetics.[55] However, a thorough grasp of drug-hydrogel interactions, release processes, and physiological obstacles is necessary for improving these systems. From tiny hydrophobic medications to big biomacromolecules, including proteins, peptides, and nucleic acids, hydrogels provide a hydrophilic, porous network that may encapsulate a variety of medicinal compounds. Several loading procedures are used, depending on the drug's composition and the therapeutic setting: drug incorporation during gel formation is known as physical entrapment; post-gelation soaking in drug solutions is known as diffusion loading; and covalent drug bonding to the polymer matrix is known as chemical conjugation.[56] Novel strategies using stimulus-responsive hydrogels, which may change their shape in response to local stimuli, including pH, glucose, enzymes, and temperature, have been highlighted in recent research. This allows for regulated release in diabetic wounds or bone abnormalities. For example, a ROS-responsive hydrogel containing BMP-2 and deferoxamine for diabetic bone regeneration was described in recent studies, offering spatiotemporal modulation of osteogenic and angiogenic signals.[57,58]

Even with these developments, there are still a number of restrictions. First, because of possible denaturation or enzymatic degradation, medication stability in hydrogels may be jeopardized, especially for treatments based on proteins or peptides. Second, drug loading homogeneity and efficiency might differ, particularly in diffusion-based loading, where volumetric absorption is less important than surface adsorption.[59] Third, continuous delivery goals are undermined by burst release, which often occurs in physically confined systems. Furthermore, it is still difficult to achieve high loading for hydrophobic medications without the use of surfactants or chemical modification.[60] Furthermore, batch-to-batch variability and regulatory barriers related to degradation products and biocompatibility make it difficult to scale up these systems for clinical translation. Widespread implementation of hydrogel platforms is hampered by the advantages of known pharmacokinetics and patient compliance offered by less focused traditional techniques like intravenous injections or oral tablets.

In order to improve loading, stability, and targeting, emerging approaches involve incorporating nanocarriers (such as liposomes, micelles, and metal–organic frameworks) into hydrogel matrices. In contrast to traditional therapies, Wang *et al.* created a hybrid liposome-loaded alginate hydrogel for the co-delivery of antibiotics and anti-inflammatory drugs in diabetic wound care, greatly enhancing tissue remodelling and infection control.[61] Additionally, drug-hydrogel system design with machine learning support is becoming more popular as it enables *in silico* prediction of the best polymer–drug interactions and release patterns. These data-driven techniques speed up system optimization and material selection as compared to empirical trial-and-error methods. Hydrogel-based methods provide targeted, prolonged, and multi-modal distribution, which lowers systemic toxicity and dose frequency in contrast to conventional therapies.[62] However, hydrogels may not be as strong mechanically or integrate as well over time as other newer methods like microneedle patches or bioresorbable scaffolds. For next-generation applications, hybrid systems that combine hydrogels with electronics or structural supports, like smart wound dressings, are being investigated.

Thus, even though hydrogel-based drug delivery has several benefits over traditional methods, careful consideration of the drug kind, loading technique, and delivery context is essential. Current constraints are gradually being addressed by ongoing advancements in computational modelling, responsive materials, and hybrid systems, which are guiding hydrogel platforms toward greater clinical applicability.

3. Mechanism of TMO-grafted hydrogel drug delivery systems in wound dressing and bone defect repair

The potential of TMO-grafted hydrogel drug-loaded systems to repair diabetic bone and wounds is based on a variety of complex therapeutic processes. Numerous studies have classified these pathways into five main groups: oxidative stress reduction, immunological modulation, inflammation suppression, angiogenesis stimulation, and osteogenic differentiation augmentation. This categorization captures the all-encompassing technique these systems use to treat the intricate pathophysiology of diabetic bone abnormalities, utilizing a multifaceted approach to promote bone regeneration and repair.

3.1. Reduction of oxidative stress

It is vital to alter the implant's surface to provide it with antibacterial, anti-inflammatory, and other properties since bacterial infection is still one of the causes of orthopaedic implant surgery failures at this point. Ti and its alloys are thought to be the best materials for orthopaedic and dental implants because of their exceptional biocompatibility, mechanical strength, and chemical stability.[67–70] To create a drug delivery system with near-infrared light (NIR) stimulation response, black phosphorus quantum dots (BPQDs) were made using the liquid stripping method, mixed with a gel that can decompose ROS, and applied to arrays of TiO_2 nanotubes that were loaded with ibuprofen (IBU).[71] In addition to breaking the dynamic covalent bonds in the gel structure, which causes the gel to decompose and release IBU in an NIR-responsive manner, as well as speeding up the rate of IBU release, the ROS produced

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by the presence of BPQDs can also clearly have antibacterial properties.

Inflammation and bacterial infection prevent skin wounds from healing naturally and can lead to problems. The work designed by Liu *et al.*[72] created an antibacterial and antioxidant QT/PDA@ZnO/QCS/(PAM-PAMPS) hydrogel (QPQH) based on the previously stated factors. Using a dual network topology, the hydrogel dressing combines polydopamine-coated zinc oxide nanoparticles (PDA@ZnO NPs), quercetin (QT), and quaternary ammonium salt chitosan (QCS) into a polyacrylamide–poly(2-acrylamido-2-methyl-1-propanesulfonic acid) (PAM-*co*-AMPS) hydrogel. Good mechanical qualities, exceptional adhesive qualities, and the ability to stick firmly to the wound are all made possible by this design. PDA@ZnO NPs' moderate photothermal characteristics (>50 °C) and Zn^{2+} release capability can work in tandem with QCS's capacity to destroy bacterial cell membranes to achieve effective sterilization. The efficacy of this procedure against *Staphylococcus aureus* and *Escherichia coli* is more than 95% in both cases. Excellent antioxidant qualities are added to hydrogel by including QT, which helps to avoid inflammation and lessen oxidative stress in wounds (Fig. 2). Additionally, the hydrogel has good cell and blood compatibility, which aids in the remedial of bacterially infected ulcers and encourages the production of fresh blood vessels and collagen in the wound of the skin. In inference, there is a lot of promise for the therapeutic application of the QPQH dressing with antimicrobial and antioxidant features in the management of bacterially infected ulcers. A skin defect model infected with *Staphylococcus aureus* (methicillin-resistant) was created on the back of mice to assess QPQH's capacity to heal bacterially infected wounds. Histopathological examination was used to corroborate the findings. Three groups of mice were randomly assigned: one for QPQH, one for control, and one for QPQH (NIR+). Fig. 2A shows the hydrogel healing method for wounds with contaminated skin. The mice in individual assemblies had their wounds photographed during the 14-day treatment period to record the healing process. All groups showed a progressive decrease in wound area throughout the course of the treatment period. The comparative wound parts on the last day of the treatment period were 23.6%, 12.9%, and 0.7%, respectively (Fig. 2B). In contrast to the other groups, which had numerous bacterial colonies, the QPQH (NIR+) group had almost none, indicating that QPQH had a potent antibacterial impact *in vivo* by NIR irradiation. Following 14 days of curing, the QPQH (NIR+) group showed the most intact epithelial shape, the best wound healing, and the best-regenerated epidermis. New hair follicles, granulations, and additional skin attachments were also visible (granulations: red and hair follicles: blue), as shown in Fig. 2C. To assess how hydrogels affect the formation of collagen in wounds. The tissue from the mouse's wound was removed for histological examination and Masson staining following a 14-day treatment period (Fig. 2D). Red fluorescence is clearly visible in the QPQH (NIR+) group, as seen in Fig. 2E. The blank group, QPQH group, and QPQH (NIR+) group had relative capillary intensities of 5.3%, 17.6%, and 68.1%, respectively (Fig. 2G). Compared to the blank group (14.2%) and the QPQH group (20.7%), the value of the collagen fiber deposition rate was found to be considerably higher (Fig. 2F). It demonstrates that hydrogel may successfully encourage skin wound healing.

To enhance wound healing, a multifunctional transdermal substance was required that has strong remodelling and self-healing capabilities, antimicrobial and scavenging of radicals, and a good carrier with dual sensitivity. For this, gelatin (GLN) and oxidized cellulose (OC) were used to create a Schiff base hydrogel loaded with two drugs that incorporate iron nanoparticles (IONPS) to release insulin (INS) and metformin (MET) in a regulated and sustained manner, both of which worked in concert to promote wound healing.[73] For INS, the maximum encapsulation and medication loading efficacy was 93.20% and 98.8%, whereas for MET, the corresponding highs were 90.2% and 95.1%. Compared to the drug's pH-sensitive release (80.2% of MET and 83.5% of INS), the temperature-responsive drug delivery was much superior. Gram-negative bacteria's zone of inhibition values of 12 and 15 mm demonstrate the antibacterial action. The carrier's antioxidant activity protects the cells from reactive oxygen species and speeds up the healing process, as determined by the DPPH experiment. Using L929 cell lines in both diabetes and non-diabetic circumstances, the scratch assay verified the angiogenesis and cell proliferation, demonstrating the INS/MET-IONPS-OC/GLN hydrogel's capacity for healing.

Oxidative stress, which is detrimental to cell development, may result from the release of ions from oxides. The therapeutic and bone-forming qualities of these ions can be improved by lowering oxidative stress. In order to release ions concurrently, Wang *et al.*[74] have created a unique titanium oxide and lithium oxide coating combination with gelatin/chitosan hydrogel. To deliver quercetin (QC), a naturally occurring antioxidant, hollow spherical titanium oxide particles were created. These particles were then added to a hydrogel made of gelatin and chitosan. The hydrogel was then further functionalized with carbon nanotubes, which enhanced its mechanical qualities and created conductivity. In contrast to a control group in which the drug was combined with hydrogel, it was observed that QC was released from the hydrogel gradually in drug release studies, highlighting the need of a secondary carrier. Furthermore, the cytotoxicity experiments showed how crucial it is to provide QC in conjunction with titanium and lithium ions since doing so decreased toxicity and increased bone-forming activity. Lastly, osteogenic differentiation tests demonstrated that the hydrogel containing drug-loaded hollow spherical particles may stimulate bone formation. Future non-load-bearing bone regeneration treatments may benefit from this novel strategy.

3.2. Immunological modulation

The immune system's condition is closely related to the regeneration of bone defects and wound healing in diabetic conditions, and a significant inequity between M2 and M1 macrophages is crucial in this regard.[75] M2 macrophages, which have anti-inflammatory qualities, are prevalent in the locations of bone

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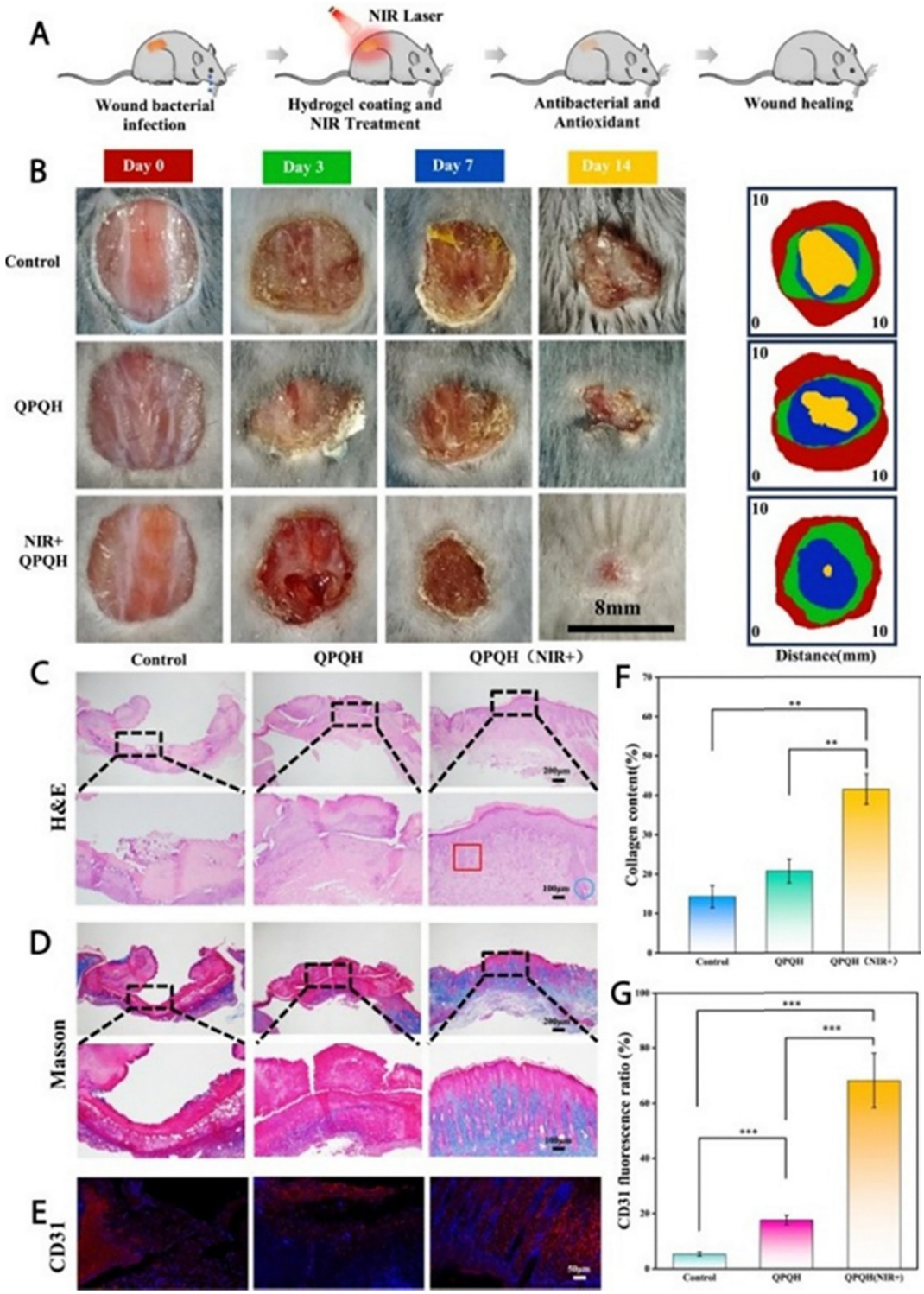

Fig. 2 By combining quaternary ammonium salt chitosan (QCS), quercetin (QT) and polydopamine-coated ZnO nanoparticles (PDA@ZnO NPs) into a polyacrylamide–poly(2-acrylamido-2-methyl-1-propanesulfonic acid) (PAM-*co*-AMPS), a QPQH hydrogel was formed, which lowers oxidative stress and promotes wound healing. In mice, QPQH facilitates the *in vivo* recovery of infected injuries. (A) Schematic showing how QPQH treats bacterially infected wounds using heat and moderate light. (B) After various treatment days, representative photos of the wound region and evidence of wound healing. (C) After 14 days of therapy, a histological picture of the wound region was stained with H&E (blue areas show hair follicles, red areas show granulations). (D) After 14 days of therapy, a histological picture of collagen deposition was stained with Masson's trichrome. (E) CD31 immunofluorescence picture following 14 days of therapy. (F) Rate of collagen deposition following 14 days of therapy. (G) CD31 fluorescence ratio following a 14-day course of therapy. Reproduced with permission from ref. 72. Copyright 2024 Elsevier.

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and wound defects in diabetics. Normal healing processes are interfered with by this imbalance, which delays tissue regeneration and the development of new blood vessels. At the same time, a small quantity of proinflammatory cytokines is released by the majority of M1 macrophages. These chemicals stimulate monocytes to develop into osteoclasts, cells linked to bone resorption, and encourage osteoblasts, essential cells for bone production, to undergo apoptosis.[76] Together, these events hinder the process of wound and bone defect repair, highlighting the intricate relationship between immune dysregulation brought on by diabetes and bone healing.[77,78]

To enhance *in situ* osteointegration, ideal titanium implants must actively contribute to bone healing. However, it is challenging to obtain both the active control and stability of bioactive ingredients over time using the conventional surface functionalization techniques for titanium implants. In this case, a new functionalized titanium that was coated in hydrogel and encumbered with thymosin β4 (Tβ4) was created and assessed by Li *et al.*[79] The surface topological structure and borate ester linkages worked to provide a durable adhesion between the titanium substrate and the coating. Furthermore, the hydrogel covering produced an *in vivo* adhesion between the implant and tissue by using hydrogen and borate bonding. Additionally, the implant can reduce the formation of fibrosis surrounding the implant interface and encourage osteointegration and vascularization of bone defects by regulating macrophage polarization and releasing Tβ4 in response to bone's immunological response repair (Fig. 3A). This is based on the ROS response property of borate bonds.

In the research work done by Li *et al.*,[80] a thermosensitive chitosan–glycerin–hydroxypropyl methylcellulose hydrogel (CGHH) was placed on top of TiO_2 nanotubes (NT) that had been loaded with simvastatin, a bioactive substance that stimulates osteogenesis. The presence of CGHH in a sol state at 37 °C, the standard human body temperature, allowed simvastatin (Sim) to be released under control to promote differentiation in MC3T3-E1 osteoblasts. According to research on *in vitro* cell culture, CGHH in a gel form would cause macrophages to polarize into the pro-inflammatory M1 phenotype. CGHH showed no antibacterial action in either the sol or gel forms when tested *in vitro* against *Escherichia coli* and *Staphylococcus aureus*. Nevertheless, the results of animal models of subcutaneous infections indicated that CGHH had outstanding *in vivo* antibacterial action. This may be explained by the fact that CGHH changed into a gel form and produced a significant quantity of glycerin at high temperatures brought on by an infection. An immediate inflammatory response and antibacterial activity were brought on by such a high glycerin intake. The recently developed simvastatin-loaded CGHH-embedded TiO_2 nanotubes are therefore interesting materials for use in orthopaedic implants because of their improved osteogenesis capabilities at room temperature and antimicrobial qualities when an infection is present. Macrophage culture was used to assess the immunoregulation properties of NT, Sim@NT, Sim@CGHH(sol), and Sim@CGHH(gel) extracts. Fig. 3B(a) displays the relevant cell-proliferation statistics. The cells in the various groups had comparable levels of proliferation after a day of culture. On day 4, however, the proliferation of cells grown in Sim@CGHH(gel) was noticeably greater than that of cells in other groups. The outcomes of macrophage live/dead staining cultivated for four days using various extracts are displayed in Fig. 3B(b). All groups' sample surfaces were covered with living cells, with very few dead cells; this suggests that the manufactured substances were in harmony with macrophages. The optical pictures of macrophages cultivated in various groups are displayed in Fig. 3B(c). The behaviour of macrophage polarization in response to various extracts was also assessed. The findings of stained with immunofluorescence for CD206 (M2 marker) and iNOS (M1 marker)[81] are shown in Fig. 3B(d), (e) and (f), respectively, show the corresponding quantitative values. CD86 and IL-6 expression are seen in Fig. 3B(g) and (i), respectively. The expression of TGF-β and CD163, two unique surface receptors of M2-phenotype macrophages and an anti-inflammatory cytokine, respectively, are shown in Fig. 3B(h) and (k). The findings presented here demonstrate that when macrophages moved from a sol to a gel, the hydrogel constituent in Sim@CGHH caused them to polarize into the M1 phenotype.

A healthy immune response is essential for biomaterial implantation to be effective. Since the microenvironment of the human anatomy is always changing, the necessary immune system should also adapt. To control the immunological response, a thermosensitive hydrogel made of hydroxypropyl methylcellulose (HMPC), glycerin (Gly) and chitosan (CS) was applied to the titanium surface (anodized).[82] The outcomes show that when the embedded hydrogel is in its sol state at body temperature, it has the potential to induce macrophages to adopt the M2 phenotype and facilitate tissue restoration; when the temperature rises due to microbial contamination, it will alter to a condition of gel and can induce the M1 phenotype will be the focus of macrophage polarization, endorse redness, and fulfil the criteria of variable immunity by achieving an intelligent detection and modulation of the physiological environment. To accomplish the goal of antibiosis or tissue repair, the thermosensitive hydrogel's temperature may be adjusted to induce the transition of macrophages M1 and M2, as well as the quick transfer of tissue from the inflammatory to the healing stages. It was confirmed that the different HMPC, CS, and Gly releases in the sol and gel stages were connected to the thermosensitive hydrogel's immunomodulatory function. The thermo-related gelation process of CGHH@NT materials is linked to their preferred immunoregulatory action. As seen in Fig. 3C, when bacteria infiltrate healthy tissues, the organism's innate immunity is triggered, and natural killer (NK) cells, neutrophils, and macrophages (examples of inflammatory cells) are collected around the infection site, causing local fever. The CGHH@NT will transition from a condition of sol to one of gel, causing the release of Gly, once the local temperature exceeds the lowest critical solution temperature (LCST) of the produced thermosensitive hydrogel. Gly is an inflammatory substance that causes macrophages to polarize to the M1 type and release

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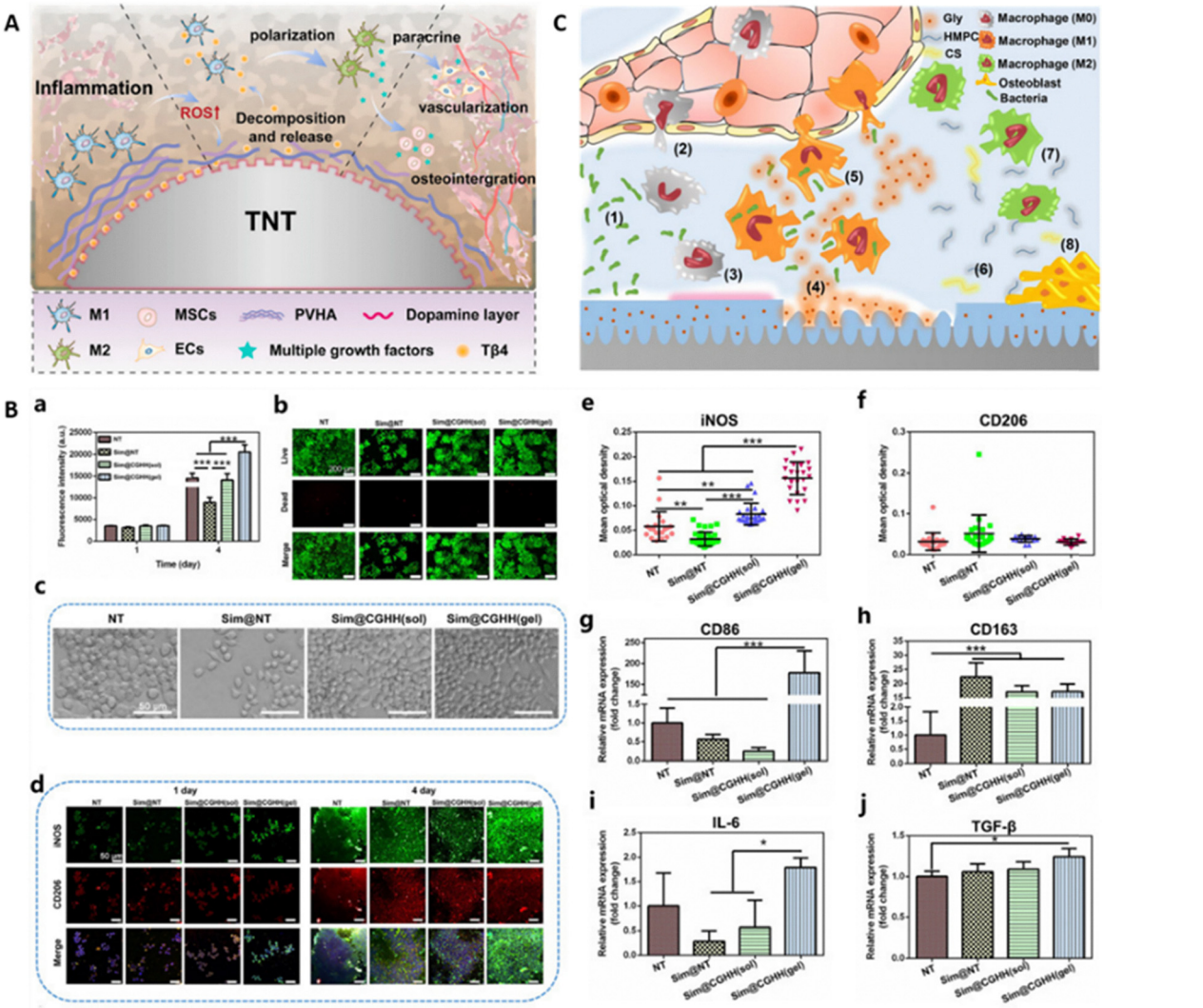

Fig. 3 (A) Diagrammatic representation of the study's immunomodulation-induced vascularization and osteointegration. Mesenchymal stem cells (MSCs), endothelial cells (ECs), polyvinyl hyaluronic acid (PVHA), thymosin β4 (Tβ4). Reproduced with permission from ref. 79. Copyright 2022 Elsevier. (B) Macrophages cultivated in different extracts were seen by proliferation (a), live/dead staining (b) and optical observation (c). Following one and four days of culture in different extracts, macrophages were immunofluorescence stained (d), and following one day of cultivation, the corresponding immunofluorescence density of the stained region was measured (e and f). The macrophages' RNA expression of CD86 (g), CD163 (h), IL-6 (i), and TGF-β (k) following four days of culture in different extracts. Reproduced with permission from ref. 80. Copyright 2021 Elsevier. (C) An example of the CGHH@NT samples' thermoresponsive immunoregulatory mechanism: (1) bacterial infection; (2) recruitment of macrophages; (3) local temperature increase; (4) phase transformation of CGHH@NT from sol state to gel state, resulting in the release of Gly; (5) polarization of macrophages toward M1 phenotype, which contributed to the killing of bacteria; (6) local temperature decrease, which resulted in the phase of CGHH@NT reverse transforming to a sol state and releasing HPMC and CS; (7) induction of macrophages to an M2 phenotype; and (8) promotion of tissue healing. Reproduced with permission from ref. 82. Copyright 2021 Elsevier.

cytokines that promote inflammation.[83] As a result, more inflammatory cells might be drawn to the affected location, increasing their ability to destroy germs. The inflammatory reaction will subside and the local temperature will drop once the bacteria have been eliminated, causing the CGHH@NT sample to return to its original condition. Thus, the release of CS and HPMC is stimulated whereas the release of Gly is blocked. According to several reports, HPMC and CS may suppress the inflammatory response, cause macrophages to adopt an M2 phenotype, and produce anti-inflammatory cytokines, all of which aid in tissue repair.[84–86] As a result, a clever transition between an anti-inflammatory and a pro-inflammatory milieu may be accomplished when local temperature changes occur.

By releasing ions or related cytokines, these examples demonstrate how hydrogel drug delivery systems that support the immune regulation-based regeneration of bone defects and wounds in diabetes essentially adjust the proportion of macrophages. This promotes the production of anti-inflammatory molecules and decreases the release of pro-inflammatory ones, enhancing the inflammatory milieu and several signalling pathways linked to osteogenesis, including the MEKK-3/IKK/IκB pathway, the Wnt pathway, the PI3K/AKT pathway.

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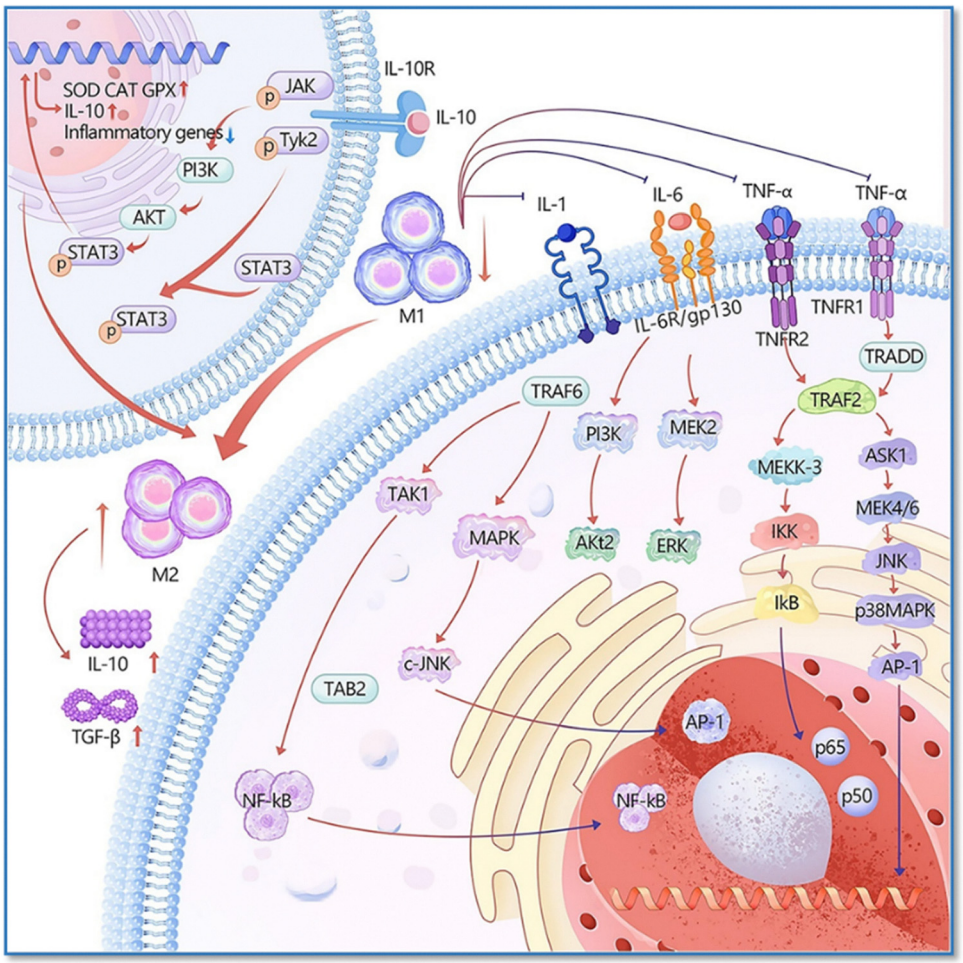

Fig. 4 By controlling several signalling pathways, immune modulation enhances the healing of bone defects. Following its binding to the receptor, the anti-inflammatory factor IL-10 controls the proportion of macrophages by activating the JAK/STAT signalling pathway. This results in a rise in M2 macrophages, which are favourable for the release of anti-inflammatory factors, including TGF-β and IL-10. ASK-1/MEK4/6/JNK/p38MAPK/AP-1 and MEKK-3/IKK/IκB are two examples of the signalling pathways that are inhibited when the proportion of M1 macrophages is downregulated. This effectively improves the inflammatory environment, increases the expression of genes related to osteogenesis, and promotes bone repair. Reproduced with permission from ref. 63. Copyright 2024 Elsevier.

Numerous signalling pathways may be stimulated or inhibited (Fig. 4) to greatly enhance the expression of genes linked to osteogenesis, hence facilitating bone repair.

3.3. Inflammation inhibition

By cleverly combining metformin with a supply of zinc ions, Lao and associates created a new hydrogel called Met@ZIF-8 that has both osteogenic and antioxidant properties.[87] This distinct composition affects macrophage polarization, increasing the production of cytokines that reduce inflammation, such as TNF-β and arginase-1 (Arg-1), while decreasing the delivery of pro-inflammatory markers like iNOS and IL-1β. This crucial hydrogel mechanism influences mitochondrial dynamics in addition to macrophage regulation.[88] Increased mitochondrial-associated membranes (MAMs) under high glucose settings cause increased mitochondrial fission and aberrant shape, which raises ROS levels and negatively impacts the microenvironment. By decreasing MAM,[89] GelMA/Met@ZIF-8 lessens these possessions by limiting mitochondrial fission and ROS generation,[90] which in turn reduces the inflammatory response. Moreover, the PI3K-AKT-mTOR pathway is modulated by this hydrogel system.[91,92] The autophagy indicators beclin-1 and microtubule-associated protein light chain 3-II/I (LC3-II/I) are upregulated when phosphorylated AKT is reduced because it reduces the strength of mTOR and TSC1/2 inhibition. This facilitates the removal of mitochondrial damage.[92] By these means, GelMA/Met@ZIF-8 inhibits excessive ROS production in addition to restoring mitochondrial function. By obstructing the TAK1/TAB2/NF-κB and MAPK/c-JNK/AP-1 signalling pathways, this improves the reduction of inflammation inside the osteogenic milieu and creates an atmosphere that is favourable for bone regeneration. It also reduces the expression of the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasomes and inflammatory cytokines like IL-1β and cysteinyl aspartate-specific proteinase (caspase-1). However, the production of Zn^{2+} also has a major impact.[93] Prior research has demonstrated that ZIF-8 may be absorbed by BMSCs and release

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zinc ions gradually. Following internalization, ZIF-8 triggers the cAMP-PKA and Gaq-PLC-IP_3 pathways and releases more zinc ions. Both cause cytoplasmic calcium ion events, which further activate the AKT and MAPK/ERK signalling pathways. Through a phosphorylation cascade event, downstream phosphorylated ERK is elevated by MAPK and transported to the nucleus, where it stimulates Runx2 and osterix, two downstream transcription factors, so encouraging osteoblast differentiation and proliferation. By cleverly using the synergistic impact of zinc ions and metformin, this hydrogel not only prevents inflammation but also further stimulates a number of signalling pathways linked to osteogenesis, hence accelerating bone repair (Fig. 5).

A novel hydrogel dressing made of gelatin, Fe_3O_4, and celecoxib that combines the use of celecoxib medication with pulse electromagnetic field therapy to heal wounded tendons.[94] This gelatin/Fe_3O_4/celecoxib composite hydrogel system demonstrated coordinated release behaviours and functional properties in response to external environmental stimuli, according to the *in vitro* experiment. The *in vivo* assessment revealed that this synergistic approach produced a better repair than either celecoxib medication or single pulse electromagnetic, which not only successfully reduced the macrophage cells' inflammatory response while simultaneously assisting in the growth of M2 macrophages at the damage site. The authors have assessed the combination therapy by looking at the pathological damage and inflammatory infiltration of the tendon injury site. According to clinical research, inflammation occurred during the tendon damage repair process, and the healing of tendons was a protracted and intricate progression that included stages of inflammation, proliferation, and remodelling. Following the invasion of the fracture procedure, histopathologic damage and severe tendon inflammation were seen in the control group, according to the results of H&E staining. Gelatin/Fe_3O_4, gelatin/celecoxib, and gelatin/Fe_3O_4/celecoxib groups were able to decrease the inflammatory invasion following 3, 7, 14, and 28 days of treatment. These findings showed that in the procedure of repairing injury to the tendons, synergistic therapy can successfully lower the inflammatory response. Additionally, a

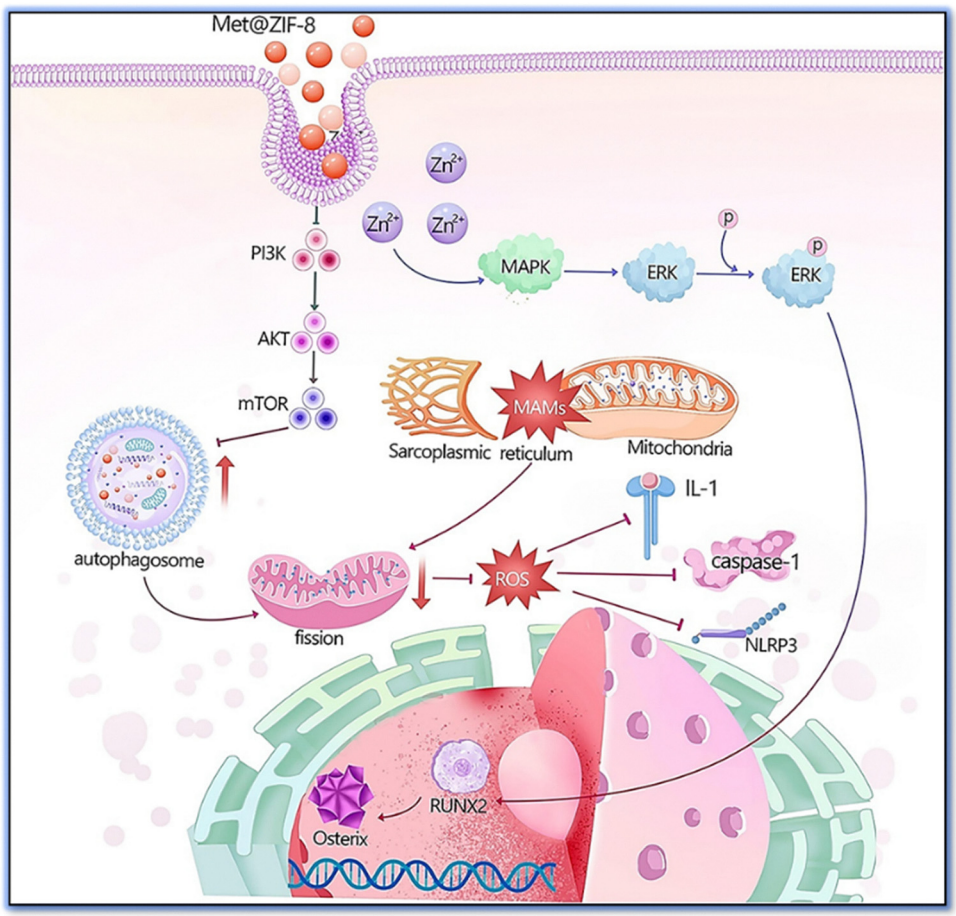

Fig. 5 Met at ZIF-8 reduce inflammation to aid in bone repair. (1) Met@ZIF-8 hydrogels improve mitochondrial dynamics and reduce ROS production, which in turn reduces the production of inflammatory factors and inflammatory bodies and effectively alleviates the inflammatory microenvironment of diabetes. They also increase autophagy expression by inhibiting the PI3K/AKT/mTOR pathway and reducing mitochondrial fission by inhibiting the production of MAMs. (2) ZIF-8 synergistically releases zinc ions to reduce inflammation. It phosphorylates downstream ERK and activates MAPK. Once within the nucleus, phosphorylated ERK dramatically increases the expression of genes linked to osteogenic factors. Reproduced with permission from ref. 63. Copyright 2024 Elsevier.

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gait study revealed that combined therapy was crucial and successful in the latter stages of tendon injury repair; that is, M2 macrophages were active throughout the production phase, and the healing of tendon injuries was strongly correlated with the polarization of M2-type macrophages. Consequently, this innovative kind of combination tendon repair therapy will lessen the patients' financial load and social strain, in addition to offering a useful theoretical foundation and treatment plan for clinical applications.

Recently, Li *et al.*[62] provided a collection of molecular design techniques aimed at improving semiconducting polymers' immunological compatibility. In particular, it was demonstrated that selenophene may reduce the foreign-body response (FBR) by inhibiting macrophage activation when it is integrated into the backbone. Furthermore, side-chain functionalization with immunomodulatory groups reduces the production of inflammatory biomarkers, which further lowers the FBR. According to the collagen density, the synthetic polymers collectively decrease the FBR by up to 68%. These immune-compatible designs continue to provide a high charge-carrier mobility of around 1 $cm^2\ V^{-1}\ s^{-1}$ in the interim. To suppress the FBR for implantable applications, it was expected that similar immune-compatible design principles may be applied to a range of conjugated polymers.

3.4. Encouragement of osteogenic differentiation and angiogenesis

Creating a 3D porous bone implant material as a means of delivering simvastatin and examining its impact on human osteoblasts from three donors was the objective of the study done by Pullisaar *et al.*[95] Highly porous scaffolds made of titanium dioxide (TiO_2) were immersed in an alginate solution containing simvastatin. Surface morphological examination of the scaffolds' microstructure showed that the TiO_2 scaffold struts' surface was covered with a uniformly distributed layer of alginate. Simvastatin was released gradually and continuously for up to 19 days. When compared to scaffolds lacking simvastatin, scaffolds with simvastatin did not exhibit any cytotoxic effects on osteoblasts. The expression of osteoblast markers, such as alkaline phosphatase, osteoprotegerin, bone morphogenetic protein 2, collagen type I alpha 1, osteocalcin, and vascular endothelial growth factor A, was assessed using real-time reverse transcriptase–polymerase chain reaction. Multiplex immunoassay (Luminex) was used to analyze the secretion of vascular endothelial growth factor A, osteoprotegerin and osteocalcin. After 21 days, cells grown on implants with simvastatin (10 μM) showed a substantial increase in the excretion of osteocalcin and relative appearance in comparison to implants devoid of simvastatin. Furthermore, at day 21, cells grown on scaffolds with simvastatin (both 10 nM and 10 μM) secreted considerably more vascular endothelial growth factor A than cells grown on scaffolds without simvastatin.

A distant, minimally invasive, and straightforward therapeutic approach is offered by the amalgamation of magnetic materials and static magnetic fields for bone tissue restoration.[96] Despite the widespread use of Fe_3O_4 nanoparticles (NPs) in bone tissue regeneration, their applications are limited by their high mobility and the oxidative stress caused by hydrogen peroxide (H_2O_2). Silk fibroin (SF) hydrogel was chosen for this work to limit the flowability of Fe_3O_4 NPs. SF is highly biocompatible and stimulates mesenchymal stem cells (MSCs) to differentiate into osteoblasts. The Fe_3O_4 NPs were modified using polyacrylic acid (PAA) to lessen the impact of oxidative stress. The findings showed that Fe_3O_4@PAA nanoparticles (Fe_3O_4@PAA NPs) decreased the production of hydroxyl radicals and removed almost 40% of H_2O_2 in three hours. According to intracellular research, SF hydrogel containing Fe_3O_4@PAA NPs enhanced cell activity by reducing intracellular ROS-induced damage. When a magnetic field was present, MSCs', mineralization capacity, collagen secretion level, and ALP activity were all higher than those of other groups on Fe_3O_4@PAA NPs loaded SF hydrogel.

Using the special capacity of SCAP-Exo exosomes to transfer miRNA, Jing Xuan and colleagues created an advanced PEG/DNA composite hydrogel loaded with SCAP-Exo for drug administration, therefore modifying the activity of target cells.[97] Their study demonstrates how SCAP-Exo exosomes upsurge the expression of miR-126-5p, which in turn triggers important signalling pathways such as the DLK1-NOTCH, PI3K-AKT, and thrombospondin 1 (THBS1) pathways (Fig. 6). By suppressing the expression of downstream TSC1/2 signalling molecules, the PI3K/AKT pathway raises mTOR expression. Mastermind-like transcriptional coactivator 1 (MAML1) and CSL signalling molecules are activated in the nucleus by DLK1-NOTCH activating downstream NOTCH intracellular domain (NICD) signalling molecules. Angiogenesis is promoted by this activation, which raises the production of angiogenic genes including VEGF and angiopoietin-1 (ANG-1).[98]

The recent research assessed the use of hydrogels containing chitosan, polyvinyl alcohol, graphene oxide, and nano titanium oxide (CS/PVA/GO/nano TiO_2) for the restoration of bone defects in dogs.[99] Dogs were given radius bones with circular bone defects (0.8 cm^2) in the mid-diaphyseal region. In the treatment group (n = 9), the hydrogel was used to implant bone defects, while the control group (n = 9) underwent spontaneous healing. At 15, 30, and 45 days after surgery, the dogs had clinical, radiographic, and scanning electron microscope (SEM) assessments. By the end of the third week after surgery, dogs in the treated group had no lameness, but dogs in the untreated group continued to show grade 1 lameness. At 30 and 45 days after surgery, respectively, the treated group's depth of bone defects (mm) dropped dramatically ($p < 0.05$) from the untreated group's (4.05 and 2.16) to 2.26 and 0.008. The radiographic density of the bone defects (px) in the treated group increased significantly ($p < 0.05$) during the course of the research (474) in comparison to the control group (619.6). The treated group's bone flaws were completely closed, according to the SEM data. Therefore, using the CS/PVA/GO/nano TiO_2 hydrogel to implant bone defects is a viable alternative to bone grafts for speeding up bone repair.

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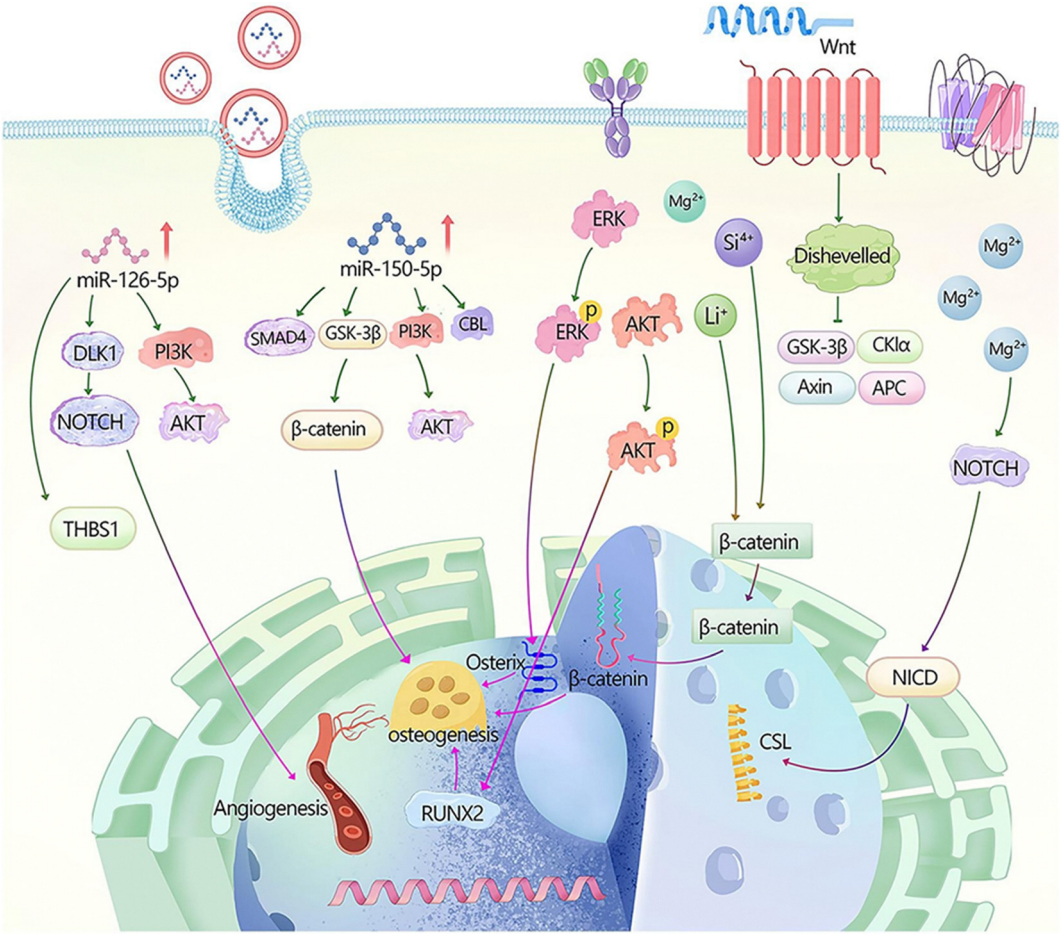

Fig. 6 Numerous signalling pathways that support osteogenic differentiation and angiogenesis are triggered. Angiogenesis and osteogenic differentiation are further promoted by the activation of many signalling pathways, including PI3K/AKT, Wnt, DLK1/NOTCH, ERK, and SMAD4. These include the stimulation of the Wnt pathway, which sends signals to the nucleus and activates important signalling molecules like β-catenin. Reproduced with permission from ref. 63. Copyright 2024 Elsevier.

4. The benefits of drug-loaded hydrogel systems

4.1. Application in bone defects treatment

TMO-grafted hydrogels can closely resemble the cellular milieu because of their notable resemblance to the natural extracellular matrix (ECM). During bone repair processes, this property is essential for improving the effectiveness of embedded medications or ions in controlling osteoblast action and encouraging bone repair.[100,101] To resist the increased glucose and inflammatory situation brought on by diabetes and to advance the clinical effects of loading agents for the process of bone tissue regeneration and osteoblast regulation, studies have demonstrated that hydrogels may efficiently imitate ECM activities. The ability of certain hydrogels to react independently to changes in their surroundings, such as variations in glucose levels, pH, or temperature is one of their unique characteristics. These intelligent hydrogels can change their behaviour in reaction to outside inputs, giving precise control over the time and method of release of different medications. The effectiveness of treatment may be greatly increased by simulating the biological cascade procedure of bone regeneration and ensuring targeted medication therapy for bone abnormalities through the intelligent regulation of the drug release timing and sequence depending on changes in the external environment.[102] Furthermore, it is possible to create complicated drug release systems with programmable delivery patterns by incorporating numerous medicines into hydrogels.[103] This method makes it easier to distribute therapeutic medications one after the other, opening the door to more individualized and effective bone regeneration therapy plans.

Hydrogels are excellent at adjusting to the intricate geometry of bone defects in terms of biocompatibility and adaptability. They ensure a tight fit and speed up the healing process by forming a smooth link with the surrounding bone tissue.[104] The researchers created an injectable hydrogel based on polysaccharides that mimic mussels and have high adhesion qualities and a controlled form.[105] This versatility is also demonstrated by Li-modified bioactive glass (BG) hydrogels, which have superior adhesion and biocompatibility[106] and also get around the fixability and aggregation issues with mesoporous bioglass nanoparticles (MBNs). These hydrogels' therapeutic potential is

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further increased by the fact that they facilitate the prolonged release of lithium ions.[107] Hydrogels' hydrophilicity gives them special mechanical qualities including flexibility, resilience to stress, and moisture retention.[108] Wang *et al.*[109] created injectable programmable proanthocyanidin (PC)-added zinc-based composite hydrogels (ipPZCHs) by combining antibacterial PC-coordinated ZnO microspheres with sodium alginate grafted with thioether (TSA) and then crosslinking them with calcium chloride ($CaCl_2$). The hydrophilicity of TSA can be greatly enhanced in response to the high endogenous ROS milieu in diseased bone imperfections, which will cause the disintegration of ipPZCHs and the rapid release of PC-coordinated ZnOs. The significant antibacterial activity of ipPZCHs is ensured by this, as well as the readily dissociable PC–Zn^{2+} coordination that causes the quick delivery of Zn^{2+} with/without Ag^{+} from PC-coordinated zinc oxides. Simultaneously, ipPZCHs' breakdown or disintegration in response to ROS makes room for bone development. By scavenging excess ROS, the concurrently released powerful antioxidant PC improves Zn^{2+} immunomodulatory and osteoinductive properties. As a result, The previously described self-adaptive and programmable processes effectively promote the repair of infected bone. These characteristics contribute to the overall efficacy of TMO-encapsulated hydrogels in the restoration of diabetic bone deformities, underscoring the many advantages of hydrogels in promoting tissue engineering and therapeutic treatments.

4.2. Improved drug-delivery system of TMO decorated hydrogels

ZIF-8, which is a zeolite imidazolate framework-8 is a crucial nanomaterial for drug delivery systems based on hydrogel. Because of its pH-dependent reaction, which is well adapted to the acidic environment linked to diabetic inflammation,[87] the medication may be released on schedule. ZIF-8 is a great drug candidate for drug encapsulation because of its increased stability and notable porosity in aqueous settings.[110] Furthermore, by encouraging bone formation, stabilizing the mitochondrial structure, and lowering inflammation, zinc ions generated by ZIF-8 can work in concert to increase the drug's effectiveness.[111] Diabetic bone abnormalities can be effectively targeted by these features. LAPONITE® is now a unique nanomaterial thanks to the creation of PDGF@Gel-Lap hybrid hydrogels. The wide surface area and distinct charge distribution of LAPONITE®, a two-dimensional nanosilicate, facilitate effective drug adsorption. This characteristic creates a prolonged release profile by extending the period of medication release.[112] Another benefit of nanomaterials is their ability to control the mechanical characteristics and pace of deterioration of composites.[113] They can also produce a range of ions that greatly aid in immune response control and bone tissue repair.[114] Certain nanostructures, like the PDLLA-PEG-PDLLA-Met@MSN-SDF-1 system of hydrogel, can form barriers that allow medications to be released one after the other. Here, mesoporous silica nanoparticles that had been isolated from SDF-1 were loaded with metformin. This spacing enhances the therapeutic action and avoids simultaneous release, which is compatible with the normal bone healing cascade. Weon and co-workers[115] used a solvent-in-oil emulsion's sol–gel transition to create cellulose/Fe_3O_4 hydrogel microbeads using a variety of solvents that dissolve cellulose and surfactant-free soybean oil. In particular, cellulose was dissolved at ambient temperature by tetrabutylammonium hydroxide (40% TBAH) and tetrabutylphosphonium hydroxide (40% TBPH), which also efficiently disseminated Fe_3O_4 to generate cellulose/Fe_3O_4 microbeads (15 μm diameter). Because they can deliver medications to specific areas consistently over an extended period, stimulus-responsive microbeads hold great promise for biomedical applications. In particular, the progress of oral release systems for protein medicines heavily relies on pH-based release control mechanisms. For oral protein medication delivery, the authors investigated the possibility of using cellulose/silk/Fe_3O_4 hydrogel microbeads as a structure capable of releasing proteins *via* the pH differential between the small intestine and the gastrointestinal tract. In comparison to the microbeads of cellulose/silk/Fe_3O_4, the same hydrogel fabricated with TBPH established a significantly larger variance in the amount and degree of BSA delivered due to pH fluctuation. This is probably due to the fact that the cellulose/silk/Fe_3O_4 microbeads made with TBPH showed larger swelling ratios at neutral pH and had slightly coarser surfaces when compared to those made with TBAH.

Furthermore, DNA scaffolds advance drug delivery technology by enhancing accuracy and biocompatibility. DNA may react strongly to environmental factors such as temperature, pH, metal ions, voltage, and biological signals because of its various architectures, distinct sequences, and targeting capacities.[116] Drug release is adjusted to match the changing demands of the diseased microenvironment thanks to this responsiveness.[117] Apart from functional fitness, DNA's biocompatibility and inherent degradability reduce cytotoxicity, further integrating the delivery system with the body's natural milieu and promoting the growth of osteoblasts. To sum up, developments in DNA scaffolds and nanomaterials mark important breakthroughs in the creation of drug-releasing systems related to hydrogels. These technologies are anticipated to represent significant advancements in therapeutic applications by increasing their accuracy, effectiveness, and safety.

4.3. Diabetic foot ulcers healing

Because of the negative impact of ROS on the cellular microenvironment and decreased blood vessel development, diabetes makes wound healing more difficult.[118] These difficulties are comparable to those seen in bone abnormalities caused by diabetes.[119] Because of their superior hydrophilicity, biocompatibility, and injectability, hydrogels have become highly effective vehicles for cells and therapeutic substances used in wound care.[108] Hydrogels also aid in preventing bacterial development and decrease inflammation by absorbing and holding onto wound leachate.[120] Beyond only delivering the medicine, hydrogel drug-loading systems are effective because they encourage the hydrogel's long-term adhesion to the wound site.[121] Continuous drug release is made possible by this prolonged interaction, which promotes cell division and proliferation. As a

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result, these systems are essential for quickening the healing of wounds. Yang Jiayi and colleagues' creation of PF-127 thermosensitive hydrogels having exosomes produced from human umbilical cord mesenchymal stem cells (hUCMSCs) is a noteworthy achievement in this field.[122] This novel hydrogel system has been shown to increase the production of vascular endothelial growth factor (VEGF) and transforming growth factor-β1 (TGF-β1), as well as platelet endothelial cell adhesion molecule-1 (PECAM-1) and Ki67. In addition, the use of smart-responsive hydrogel dressings for wound healing is becoming more widespread.[123] By integrating a stimulus-responsive component with hydrogel support, they react to dynamic environmental deviations at the wound spot, including glucose, pH, temperature, light, and ROS. By improving drug release efficiency and compensating for standard hydrogels' incapacity to modify drug release in response to the disease environment, responsive hydrogels successfully aid in the control of wound healing. Hu *et al.*[124] created multifunctional hydrogels, which were crucial for addressing the main issues of chronic wounds, such as lowering oxidative stress, encouraging angiogenesis, enhancing the extracellular matrix's natural remodelling, and enhancing immunological control. For this purpose, sodium alginate (SA), manganese oxide (MnO_2) nanoparticles, recombinant humanized collagen III (RHC), and mesenchymal stem cells (MSCs) combine to form a composite hydrogel, SA@MnO_2/RHC/MSCs. High mechanical qualities and strong biocompatibility are attributes of the hydrogel. *In vitro*, SA@MnO_2/RHC/MSCs hydrogel had synergistic effects on cell migration and proliferation while also efficiently promoting the development of complex tubular structures and angiogenesis. *In vivo*, the SA@MnO_2/RHC/MSCs hydrogel promoted abundant wound angiogenesis, favourable collagen deposition, quick re-epithelization, and diabetic wound healing. These results showed that the synergistic actions of SA, MnO_2, RHC, and MSCs accelerated healing and decreased healing time. These observed healing benefits showed how this multifunctional hydrogel might revolutionize the treatment of chronic wounds and enhance patient outcomes (Fig. 7).

This investigation into TMO-embedded hydrogel drug-releasing structures for diabetic wound repair is a prime example of how biomaterials may be used to solve difficult medical problems. These systems provide a potential strategy to enhance treatment results for problems connected to diabetes by utilizing their special qualities.

4.4. Periodontitis treatment

With several benefits over traditional antibiotic treatments, hydrogel drug delivery devices provide an innovative method of treating periodontitis. These systems are skilled at maintaining medication efficacy, acclimating to the complex geometries of bone imperfections, and reacting on their own to environmental changes.[125–127] Hydrogels are a better option for treating periodontitis because of their capacity to modify their characteristics in response to particular requirements, which enhances their antibacterial activity.[128]

The creation of an antibacterial hydrogel (dual-action) by Xushu and associates has advanced this area. Chitosan (CS) is crosslinked with a derivative of polyethylene glycol (PEG) that has been altered with antimicrobial peptides (AMPs), and curcumin is added to create this hydrogel (CS–PA).[129] The CS–PA hydrogel stands out for its all-encompassing therapeutic benefits, which include strong antibacterial activity, antioxidant capacity, anti-inflammatory qualities, and immunological

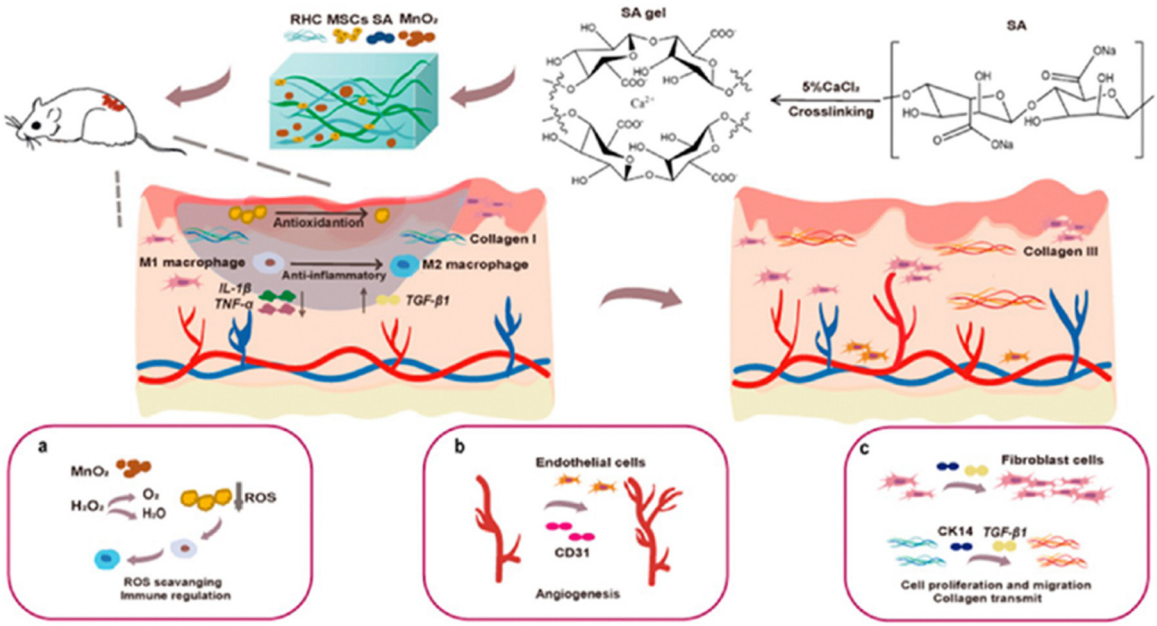

Fig. 7 SA@MnO_2/RHC/MSCs hydrogel's mechanism of action in the management of chronic diabetic wounds. For immunological modulation, (a) ROS scavenging lowers oxidative stress and encourages macrophage polarization. (b) Encourage angiogenesis in wounds. (c) Encourage tissue regeneration and collagen deposition. Reproduced with permission from ref. 124. Copyright 2024 American Chemical Society.

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modulation. This comprehensive technique for treating periodontitis not only fights periodontal bacteria but also promotes tissue repair and regeneration. A major advancement in dental medicine has been made with the use of hydrogel medication delivery systems in periodontal therapy. Researchers and medical professionals may create more efficient, focused, and patient-friendly therapies for periodontitis by utilizing the special qualities of hydrogels, which will promote better dental health results.

By addressing bacterial infection, oxidative stress, inflammation, and bone regeneration all at once, multifunctional hydrogels containing transition metal oxides have shown encouraging outcomes in recent 2025 trials for the treatment of periodontitis. ROS-responsive, on-demand release was shown *via* a novel injectable system that included Fe-quercetin nanoparticles and the antibacterial minocycline in a hyaluronic acid/PVA hydrogel. In animal studies, this HP-PVA@MH/Fe-Que hydrogel dramatically decreased alveolar bone loss, scavenged ROS, and regulated the Nrf2/NF-κB pathway to induce M2 macrophage polarization.[130] With *in vivo* evidence of improved periodontal regeneration, a thermosensitive chitosan hydrogel modified with ZIF-8 nanoparticles allowed for the sequential delivery of PDGF-BB and CMT-3 (a tetracycline derivative), which first reduced inflammation by eliminating ROS and then supported osteogenesis in diabetic periodontitis.[131]

In addition to iron and zinc, calcium peroxide (CaO_2)-infused alginate hydrogels are another metal-oxide strategy that releases oxygen to reduce inflammation, inhibit anaerobic bacteria, and promote bone healing. Zinc-ion cross-linked self-healing hydrogels, which are not technically metal oxides, have also surfaced. Because of their Zn^{2+} coordination and dynamic Schiff-based networks, these hydrogels have shown broad-spectrum antibacterial and osteogenic properties.[132] These research together show a distinct trend: designing metal-based hydrogels that are sensitive and target the complex pathophysiology of periodontitis in a less invasive way.

4.5. Treatment of arthritis by TMO-encapsulated hydrogels

TMO-based hydrogel drug release methods are becoming progressively essential in osteoarthritis therapy with bioactive properties such as anti-inflammation, mechanical lubrication, and tissue repair to ameliorate arthritis.[133] Together, the many qualities improve therapy efficacy and handle the complex issues raised by osteoarthritis. The creation of a thermosensitive hydrogel loaded with dexamethasone (DLTH) by Wang Qishan *et al.*[134] is a noteworthy accomplishment in this field. This technique greatly increases the effectiveness of dexamethasone by encapsulating it in a chitosan–glycerol–borax matrix. The hydrogel guarantees focused drug delivery to inflammatory areas, lowering systemic toxicity and prolonging drug release duration in comparison to administering dexamethasone alone.[135] This method successfully lessens the negative consequences of using dexamethasone.

The DLTH-treated group showed significant decreases in joint tenderness in the experimental models. Suppressing proinflammatory cytokines and nerve growth factors (IL-1β, IL-6, IL-17, TNF-α as cytokines, and NGF, respectively) in synovial tissues produced this result. The hydrogel's anti-inflammatory properties were further enhanced by its inhibition of the NF-κB signalling pathway and promotion of IκBα, IKKα, and IKKβ expression. Ren Shujing and associates developed a hydrogel (acupoint nanocomposite CCPA-Gel) to expand the range of hydrogel applications. This novel formulation targets inflammatory areas by combining cyclic citrullinated peptide (CCP)[136] with TP-human serum protein nanoparticles (TP@HSNPs). The CCPA-Gel is unique in that it improves the safety and efficacy of treating arthritis by tackling the problems of tripyrate's (TP) high toxicity and limited solubility. Rong *et al.*[137] created a unique multifunctional scaffold by using glycidyl methacrylate-modified hyaluronic acid (GMHA), which was photopolymerized as the matrix in the presence of hollow porous magnetic microspheres based on hydroxyapatite. The findings of *in vivo* subchondral bone repair show that the scaffold's careful design offers the best qualities for subchondral bone repair. The scaffold's inorganic particles' porous nature makes it easier for loaded exogenous vascular endothelial growth factor (VEGF) to be transported efficiently. The microsphere-assembled Fe_3O_4 nanoparticles speed up the formation of new bone by encouraging the mesenchymal stem cells' osteogenic development in bone marrow. These characteristics allow the scaffold to achieve good cartilage repair scores and demonstrate advantageous subchondral bone healing qualities. The outcomes of the therapy demonstrate how the subchondral bone support has a significant impact on the process of upper cartilage healing (Fig. 8). Additionally, Fe_3O_4 nanoparticles, which are progressively replaced by new bone during osteochondral defect healing, enable a non-invasive and radiation-free evaluation to follow the newborn bone during the osteoarthritis repair process, as shown by magnetic resonance imaging monitoring. In the treatment of osteoarthritis, the composite hydrogel scaffold (CHS) offers a flexible platform for biomedical applications.

In a noteworthy 2025 research, Xu *et al.*[138] propose an injectable microsphere system (DIC/Mg-PDA@HM) in which hyaluronic acid hydrogels are implanted with polydopamine (PDA) nanoparticles that chelate magnesium ions (Mg^{2+}). This construct sustainably releases Mg^{2+} upon intra-articular injection in rat models of osteoarthritis (OA), which induces chondrogenic differentiation of stem cells and changes the phenotype of macrophages from M1 to M2. PDA and diclofenac (DIC) both have anti-inflammatory and antioxidant properties at the same time. According to MRI and histology, the result was a considerable decrease in inflammation and repair of cartilage. Adding manganese dioxide nanoparticles to chondroitin sulfate hydrogels is another new tactic. By scavenging reactive oxygen species (ROS) and shielding chondrocytes from deterioration, these nanoparticles imitate the catalase and superoxide dismutase (SOD) enzymes, therefore addressing oxidative stress in OA.[139,140] More generally, different transition metal oxides, like Co nanowires, Mg-based phosphate glass fibers, or Fe oxides, have been embedded in organic–inorganic composite hydrogels to improve mechanical strength, mimic

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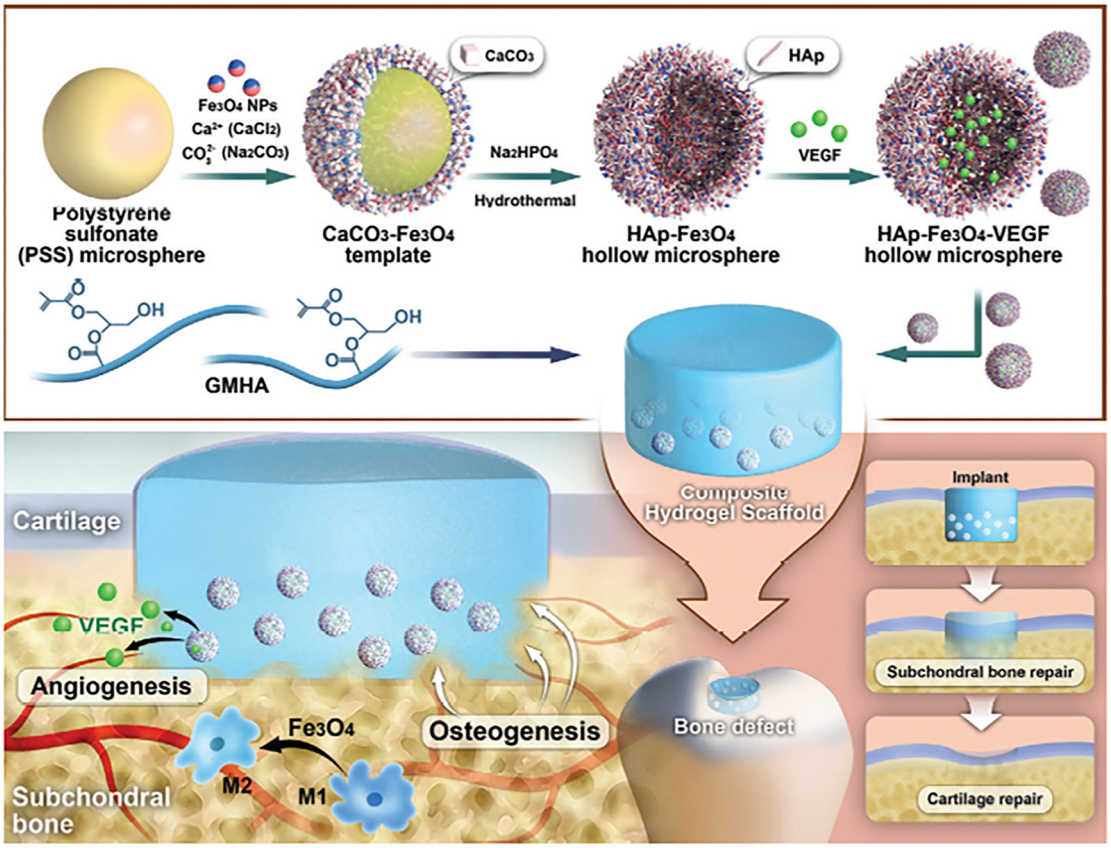

Fig. 8 The hydrogel composite scaffold's design and construction as a theranostic platform for osteogenesis regeneration. Reproduced with permission from ref. 137. Copyright 2024 Wiley.

hypoxic conditions for cartilage formation, and maintain the release of therapeutic ions. These hydrogels promote osteochondral regeneration and enhance the synthesis of extracellular matrix. By stabilizing and modifying joint environments *via* prolonged ion/drug release, ROS neutralization, and mechanical support, these investigations highlight the therapeutic synergy of transition metal oxide grafted hydrogels, opening the door for more sophisticated OA and RA therapies in recent years.

These progresses highlight how hydrogel drug delivery methods have the potential to revolutionize arthritis treatment. TMO-based hydrogels are establishing new standards for therapeutic interventions by emphasizing targeted release and reducing systemic side effects, promising more efficient and patient-friendly arthritis therapies.

5. Conclusions

TMO-encapsulated hydrogel drug-loading devices provide a potential and versatile therapy option for diabetes-related conditions such as bone abnormalities, poor wound healing, periodontitis, and arthritis. By using hydrogels' biocompatibility, structural flexibility, and stimuli-responsive qualities, these platforms allow for the localized and sustained administration of medicines. By facilitating regulated release and encouraging tissue regeneration, advancements made possible by the use of DNA scaffolds and functional nanomaterials have further increased accuracy and therapeutic effectiveness. Antibacterial and thermosensitive dual-purpose hydrogels have shown promising results in reducing inflammation and hastening the healing process.

Important obstacles still exist despite these developments. Depending on their concentration and oxidation state, certain TMOs may be cytotoxic, and the long-term biocompatibility and degradation behaviour of TMO-hydrogel composites *in vivo* are not well characterized. Additionally, universal application is limited by variations in treatment efficacy across patient profiles and illness stages. Clinical translation is further hampered by challenges with production scale, batch-to-batch uniformity, and regulatory compliance.

Future studies should concentrate on filling in these gaps by clarifying the fundamental mechanisms of TMO–tissue interactions in diabetic settings, improving composite formulations to attain adjustable drug release kinetics, and creating standardized *in vivo* models that faithfully replicate long-term diabetic complications. The development of smart hydrogels that dynamically adjust to local physiological circumstances and the incorporation of biosensors for real-time feedback-responsive medication delivery have the potential to greatly improve therapeutic results. To help these innovations go from

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the laboratory to the bedside, efforts must also be made toward scalable, good manufacturing practice-compliant manufacture and strong preclinical validation. It will need a concentrated effort to get over these scientific and translational obstacles to fully unlock the therapeutic potential of TMO-based hydrogel systems, which will eventually enhance treatment results and quality of life for patients with diabetes-related complications.

Conflicts of interest

The author declares no conflict of interest.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

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