



# Metal-organic framework-based nanomaterials for bone tissue engineering and wound healing



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## ABSTRACT

Over the past decade, tremendous growth has been witnessed in the synthesis of scaffolds fabricated by natural or synthetic, composite, or hybrid biomaterials to enhance wound healing, repair of bone fractures, and pathological loss of bones. However, the current limitations of using these scaffolds in tissue engineering are impaired cellular proliferation, poor differentiation, low mechanical stability, and bioactivity. Recent advances in the fabrication of nanoscale metal-organic framework (nano-MOF) scaffolds have provided golden opportunities to enhance the properties of scaffolds in bone and wound tissue engineering. In the past few years, studies have shown that incorporating nano-MOFs into scaffolds can be highly favorable in the regeneration of imperfect tissues owing to their unique properties such as high internal surface areas, high porosity, good mechanical stability, biocompatibility, and tunability. Moreover, the nanoscale structural and topological properties of nano-MOFs enhance the physicochemical properties of scaffolds, enrich them with drug-loading and ion-releasing capacity, and regulate stem cell attachment, proliferation, and differentiation after transplantation. This review initially introduces the various nano-MOFs incorporated into scaffolds for tissue engineering. Recent applications of nanoMOFs for bone and wound healing are comprehensively discussed. The unique properties of nano-MOFs for improving osteoconductivity, osteoinductivity, and wound healing, such as high antibacterial activity, high drug loading capacity (i.e., bioactive molecules and growth factors), and controlled drug release, are discussed. Finally, challenges, clinical barriers, and considerations for implementing these nanomaterials in different scaffolds, tissue-like structures, implants, fillers, and dressers in the orthopedic and wound clinics are comprised.

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## 1. Introduction

Bone tissue engineering and wound healing medicine are highly demanded areas in regenerative medicine that can be advanced by implementing innovative technologies, such as stem cell technology [1], biomaterials [2,3], nanotechnology [4], and polymer sciences [5]. These approaches can help tissue engineering researchers to speed the healing process of bone fractures and

wounds. In terms of nanotechnology and biomaterials, the nano-sized metal-organic frameworks (nano-MOFs), known as a class of crystalline porous nanomaterials consisting of endless lattices including metal ions and organic ligands, have attracted much attention in regenerative medicine [6,7]. These nanostructures can be implemented as scaffolds to augment healing steps in bone regeneration and wound healing.

In recent years, there has been a rapid rise in the use of MOF-based nanomaterials in biosensing [8], bioimaging [9], drug delivery [10], gene delivery [11], gas storage [12], and photodynamic therapy [13] owing to their exceptional properties such as tunable

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porosity, drug encapsulation, surface, biocompatibility, and intrinsic biodegradability. In addition, nano-MOFs have received much attention among the scientific community in regenerative medicine and tissue engineering [7,14–21]. Studies also have demonstrated nano-MOFs provide stem cells with guidance cues for enhancing their attachment, proliferation, and differentiation toward the desired cell types [22]. Modification of biomaterials with MOFs and nano-MOFs leads to altering physicochemical properties of scaffolds, including roughness, functional groups, porous structure, and hydrophilicity, which perhaps are the main reasons for promoting cell adhesion and responses [23–25]. In addition, nano-MOFs can be used as carriers with polymer scaffolds for loading growth factors necessary for cell differentiation and antibiotics for inhibiting infection [26]. The incorporation of nano-MOFs with scaffolds leads to higher drug-loading capacity than polymer scaffold alone owing to the high surface area and excellent porosity of nano-MOFs [27,28].

Many factors should be considered to design and synthesize appropriate MOFs for tissue engineering, including the architecture and properties of injured tissue, implementing safe fabrication methods, and choosing suitable metallic ions, ligands, and functional groups to regenerate tissue [29]. For instance, in terms of implementing nano-MOFs as drug carriers, the possibility of varying the porous size leads to changing the loading capacity, which can be tuned by altering the multimodal organic ligands [30,31]. Moreover, the stimuli-responsive properties of nano-MOFs enable controlled drug release through various stimulations, including pH, temperature, magnetic, ions, humidity, light, redox, pressure, and ions that are highly beneficial in tissue engineering [32–34]. Among different MOF-based stimuli-responsive systems, pH-responsive nano-MOFs have attracted much attention in regenerative medicine because they can release drugs, genes, small molecules, and ions in the target environment, especially in the bacterially infected tissues with acidic environments [35].

Bone tissue engineering aims to assist surgeons in repairing bone fractures or anomalies that cannot heal independently [36]. The mimicking of the complicated strategies and nanostructures is involved in natural bone healing, opening a new area in the fabrication of high-efficacy osteo-like structures [37]. Incorporating nano-MOFs into polymer scaffolds with safe concentration results in higher mechanical properties and stability of scaffolds [38]. Besides, various biomolecules, cytokines, growth factors, drugs, genes, and antibacterial agents that play significant roles in different phases of bone regeneration can be loaded into these nanostructures to increase angiogenesis, osteoinductivity, and osteoconductivity [19,39–41]. Moreover, various approaches have been proposed to use nano-MOFs in scaffolds and implants for inhibiting cancer reoccurrence after removing osteotumors [42].

Wound healing is also one of the most challenging issues in regenerative medicine [43]. Direct contact of the wound with the homeostasis system, immunity, external environment, and infectious agents around the wound can provide a suitable substrate for the formation of chronic infections and non-wound healing in patients with diabetes or patients with mobility impairments [43]. To overcome this issue, nano-MOFs have been applied in the fabrication of scaffolds, antibacterial shields, and wound dresses in the wound healing process owing to their high antibacterial properties [44]. On the other hand, the high loading capacity of nano-MOFs assists the physiological induction of the wound healing process by delivering various drugs, vitamins, antioxidants, and other anti-inflammatory and growth stimulants [45,46].

This review presents a comprehensive report on state of the art and applications of nano-MOFs for bone tissue engineering and wound healing. This review is organized into three main parts. The first section gives a brief overview of different nano-MOFs and their

specific properties for tissue engineering applications. The second section summarizes the physiology of bone and wound healing and the role of nano-MOFs in the process of bone and wound regeneration. In the third section, the current progress in implementing nano-MOFs to regenerate bones and wounds is discussed (graphical abstract). Finally, the fabrication challenges, preclinical, and clinical barriers for implementing these nanomaterials in scaffolds are discussed in the following sections.

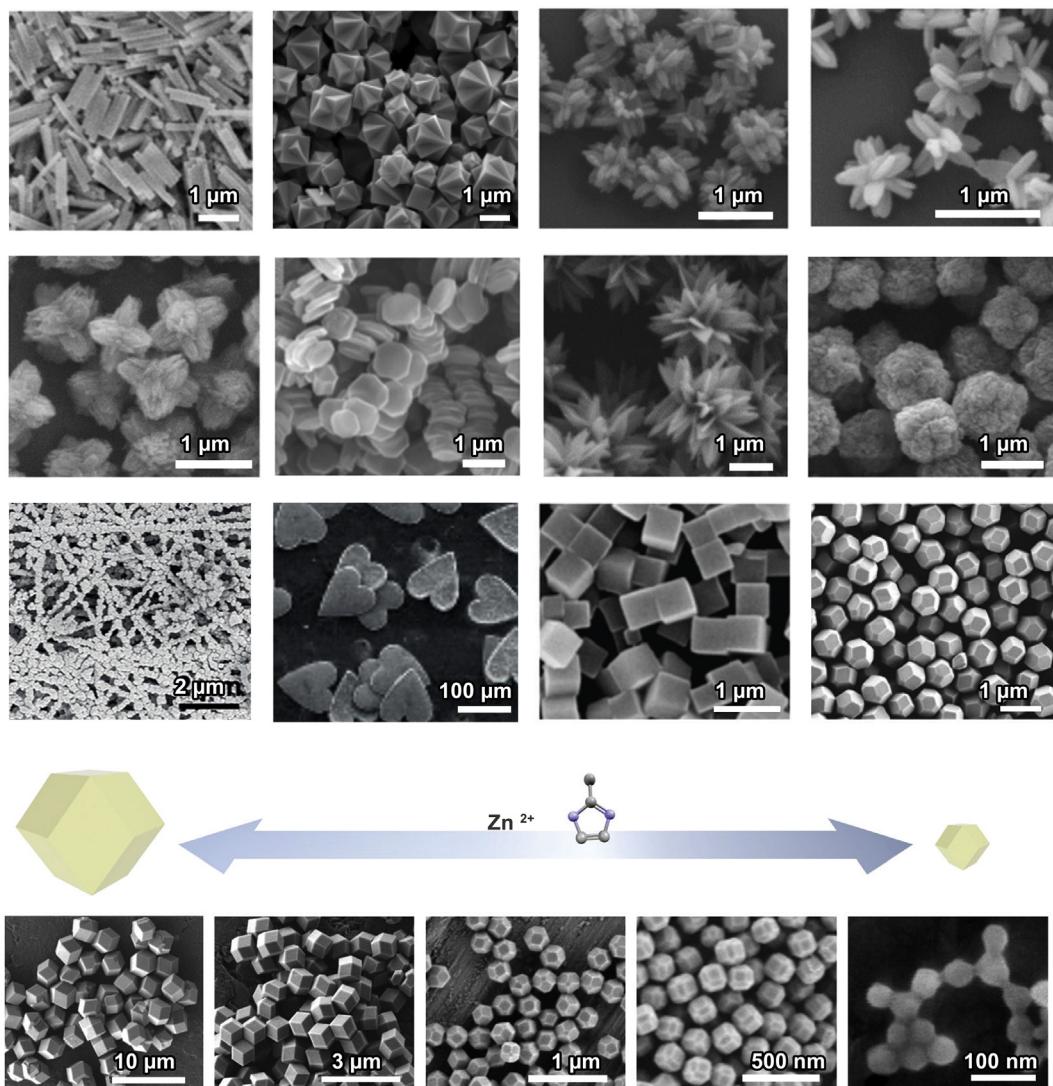
## 2. Nano-MOFs

MOFs, known as coordination polymers, are a class of crystalline microporous materials that include endless lattices constituted of metal ions or clusters [secondary building units (SBUs)] and organic ligands connected via strong coordinate bonds [47]. A wide range of variability in choosing SBUs and organic ligands leads to the fabrication of MOFs with different structures and properties [48]. However, MOFs commonly are in solid form and possess a well-defined crystalline structure with high surface area (500–4,500 m<sup>2</sup>/g) and low density (0.13–1 g/cm<sup>3</sup>) [47,49].

In general, the geometric structure of MOF is recognized as squares and octahedral. However, different crystal morphologies can be obtained by changing synthetic parameters. Annually, thousands of MOFs with different sizes, porosity, and structures are fabricated by varying SBUs and organic ligands or postmodification [48,50–56] (Fig. 1). The reaction with linkers provides the opportunity for the synthesis of MOFs with various functional groups and chirality. Generally, MOFs can be fabricated in one-dimensional (1D), two-dimensional (2D), three-dimensional (3D) frameworks, and their structure can be affected by the kind of metals and geometries of ligands such as lengths of ligand, bulkiness, bond angles, and chirality [53,57]. One of the most significant advantages of MOFs in biomedical applications is that their structure and functionality can be adjusted during fabrication. For instance, MOF possesses unique properties for drug delivery such as high porosity, high specific surface area, and their physicochemical properties such as pore size and morphology can be adjusted depending on the kinds of loaded drug and the purposes needed for drug delivery [58].

An extensive amount of research works has recently focused on using nano-MOFs in biomedical applications owing to their unique properties such as faster adsorption/desorption kinetics, accessibility to the internal active sites, suitable sizes, good biocompatibility, and tunability [20,52]. Furthermore, unlike bulk MOFs, nanoMOFs facilitate delivering small materials such as drugs and biomolecules into cells. In fact, the efficacy carriers loaded in tissue scaffolds are highly dependent on their size. Therefore, nanoMOFs in the range size of 200 nm are preferred in drug delivery more than bulk MOFs as they can efficiently distribute in the human body system, and they cannot be removed by the spleen as their size is less than enough to filter and retain in the pulp of the spleen [59].

The conventional method for nano-MOF fabrication is a solvothermal route in which the metals and organic ligands create crystals in the closed vessel in the presence of organic solvent at a temperature above the solvent's boiling point [52]. Some other nano-MOFs, such as zeolitic imidazolate framework-8 (ZIF-8) and zinc-induced facilitator-like family nanocrystals, can be formed at room temperature, and green solvents such as water and ethanol [60,61]. Other techniques of nano-MOF fabrications are emulsion system, interfacial synthesis, template, irradiation-assisted methods, and spray-drying mechanochemical synthesis [62]. These synthetic approaches mainly focused on confining the supramolecular assembly using emulsification, template or nucleation, and growth of crystals during precipitation or microwave [52,53]. Interestingly, a more comprehensive range of nano-MOFs can be obtained after modifying MOF through different approaches



**Fig. 1.** Schematic of control morphology and size of MOF crystals. Different crystal morphologies of MOFs such as square, octahedral, flake-shaped, or flower-like can be obtained by varying synthetic parameters. In addition to that, MOFs can be fabricated with the desired shape, such as fiber, heart, star, and so on, by changing synthetic methods. The size of MOF crystals can be adjusted by controlling the nucleation and growth rates [50–54].

such as modification of organic ligands after chemical reactions (such as click reactions, bromination, imine condensation, and amid coupling) after synthesis approaches via linker exchanges [62].

The metals implemented for the fabrication of MOF in scaffolds are zinc (Zn), copper (Cu), zirconium (Zr), iron (Fe), cobalt (Co), and magnesium (Mg), which some are also essential elements in the body. Table 1 shows the nano-MOFs that have been used for bone tissue engineering and wound healing. The prevalent nano-MOFs in tissue engineering scaffolds are classified by metal ions and discussed in the following.

### 2.1. Fe-nano-MOFs

Iron-based Fe-MOFs, with their low toxicity, have attracted considerable attention in biomedical applications. Fe-MOFs commonly used in biomedical and tissue engineering are in the family of MIL-53 (MIL  $\Rightarrow$  Matériaux de l'Institut Lavoisier). MIL was first established in 2002 by the Ferry group [63] and since then developed by other metal ions as flexible MOFs in drug delivery systems [64]. These MOFs include terephthalate-based linker (1,4-dicarboxylic

acid) connected to  $\text{Fe}^{3+}$  ions in which the Fe center is coordinated by six oxygen atoms and create 1D diamond-shaped pores [65] and possess advantages such as low toxicity, biodegradability, biocompatibility, large pore volume, and surface area with high drug loading capability [66]. The synthesis methods of Fe-MOF are straightforward and mainly based on hydrothermal and solvothermal processes [67,68]. In addition, another research group reported the green synthesis of MIL 53 at room temperature [69].

### 2.2. Zn nano-MOFs

Since the advance of nano zinc-based MOFs by Rojas et al. [70], nano Zn-MOFs have been widely explored in biomedical applications, drug delivery systems, and tissue engineering. These nano-MOFs consist of Zn (II) covalently linked with 1,4-bis(1*H*-pyrazol-4-yl)-2-X-benzene ( $\text{H}_2\text{BDP-X}$ ; X = H,  $\text{NO}_2$ ,  $\text{NH}_2$ , OH) and possess the porosity with the size of 11 Å [71]. The most significant advantage of nano Zn-MOFs in biomedicine applications is their tunability in which their structure can be tailored by changing synthetic parameters. For instance, various kinds of isoreticular metal-organic

**Table 1**

Example of typical nano-MOF used in tissue engineering.

NMOF Formula	Major components	Nanostructure	Tissue engineering application	Function	Drug loading	References
M-MOF74 M = Mg	Zn, 2,5-dihydroxybenzene-1,4-dicarboxylate (DBDC)	NPs	Bone healing	Antibacterial activity	Zn	[82]
M-ZIF-67 M = Co,-	Zn, 2-methylimidazol (2-MIM)	NPs	Wound healing	Antibacterial activity	(DMOG) Co	[83–85]
HKUST-1	Cu, 1,3,5-benzenetricarboxylic acid (H3BTC)	NPs	Wound healing, Tendon regeneration	Antibacterial activity, Vessel regeneration, nitric oxide (NO) delivery	Cu	[78,86,87]
Cu-TCPP	Cu, tetrakis (4-carboxyphenyl) porphyrin	Nanofilm and nanosheets	Bone healing	Killing bone tumors, enhancing osteogenic differentiation	GOx	[88,89]
ZIF-8	Zn, 2-methylimidazol (2-MIM)	NPs, nanofilm	Bone healing Wound healing	Enhancing osteogenic differentiation, releasing biomolecules at low pH	VAN, Levo, RB	[27,40,90]
MOF53 (Fe) MIL 53	FeCl <sub>3</sub> ·6H <sub>2</sub> O H2BDC 1,4-benzenedicarboxylic acid	NPs/nanocomposite	Bone healing	Enhancing mechanical stability, enhancing scaffold porosity	VAN	[21,38,91]
Ag (I) MOF	Ag, pyridine-3, 5-dicarboxylic acid (H2PYDC)	NPs, nano film	Wound healing	Antibacterial activity	Ag	[92,93]
MIL-88B	Fe <sup>3+</sup> , 1,4-benzenedicarboxylic acid (1,4-BDC)	Nanocomposite	Wound healing	Antibacterial activity	Ag	[94]
UiO66-NH <sub>2</sub>	Zr, 2-aminoterephthalic acid (H2ABDC)	Nanocomposite	Wound healing	Antibacterial activity	—	[95]
MOF1	Zn, 4, 4-biphenyl dicarboxylic	Nanofilm	Bone regeneration	Enhancing bioactivity and corrosion resistance	—	[96]
Ca Sr-MOF	Ca <sup>2+</sup> , Sr <sup>2+</sup> , 1,3,5 tricarboxylic acid (H3BTC)	Particles	Bone healing	Induce <i>in vitro</i> biominerilization, induce vascular endothelial production, induce VEGF production, upregulate osteogenic markers	Ca, Sr	[97]

Abbreviations: DMOG, dimethyloxalylglycine; VAN, vancomycin; GOx, glucose oxidase; Levo, Levofloxacin; RB, rose Bengal.

frameworks (IRMOFs), including IRMOF-1, IRMOF-8, IRMOF-10, IRMOF-14, and 1RMOF-16, with various pores sizes in the range of 3.8–28.8 Å can be fabricated only by changing organic ligands [72]. Furthermore, nano-ZnMOFs are sensitive to pH and can be used as a nanodrug carrier to release biomolecules and drugs by reducing pH (i.e. pH 5.5–6.8). One of the major subfamilies of nano Zn-MOFs is ZIFs in which Zn(II) ions are connected by imidazolate or imidazole derivatives as organic ligands. For example, ZIF-8 a subclass of ZIFs composed of ZnN<sub>4</sub> tetrahedral bonding with imidazolate anions possesses high stability in phosphate buffer at pH 7.4 and high degradability at low pH 5–4, which makes ZIF-8 a promising candidate for drug delivery systems [73].

### 2.3. Zr-nano-MOFs

Zr-MOFs can be considered promising MOFs in tissue engineering and biomedicine applications owing to their low toxicity, high mechanical, thermal, acidic, and aqueous stability [74,75]. The first Zr-nano-MOF, named UiO-66 (Universitetet i Oslo), was discovered by Cavka et al. [76] and composed of zirconium oxide complex bridged by 1,4-benzene dicarboxylic acid ligands. UiO66 can be synthesized by different functional groups such as –NH<sub>2</sub> and NO<sub>2</sub> which result in ZrMOFs with different size porosity and release behavior [77]. Generally, nano ZrMOFs have been considered low toxicity MOFs for biomedicine applications.

### 2.4. Cu-nano-MOFs

From the perspective of biocompatibility, Cu-nano-MOFs are an appropriate candidate for use in tissue engineering applications. The most Cu-nano-MOFs have been studied in tissue engineering is

HKUST-1 (Hong Kong University of Science and Technology-1) which possesses three dimensions formed by benzene-1,3,5-tricarboxylate linkers connected with copper ions and can be used as nanocarriers owing to their large pore size, stability, and biocompatibility [78,79]. Besides, copper-tetrakis (4-carboxyphenyl), porphyrin (Cu-TCPP) MOFs have been used in photothermal therapy owing to their strong near-infrared (NIR) light absorption properties. For instance, Cu-TCPP MOFs composed of Cu<sup>2+</sup>, Cu<sup>+</sup>, and TCPP possess a 2D MOF nanosheet structure. Therefore, when exposed to a NIR laser at wavelength 808, the d–d energy band transition of Cu<sup>2+</sup> leads to the effective heating need for cancer therapy [80,81].

### 3. Biocompatibility of nano-MOFs

Biological safety and biocompatibility are essential requirements for using biomaterials in tissue engineering and need to be determined by specific standard tests [98–100]. In terms of MOF-based nanostructures, the biocompatibility of both the metal and bridging ligand must be considered in designing nano-MOF scaffolds [101]. Although some metals such as chromium are poisons, a small number of heavy metal ions such as Zn<sup>2+</sup>, Cu, Fe, and Mn are necessary for the body. For example, iron is a hemoglobin component and is approximately 128.4 ± 18.1 g/l in blood plasma [102]. The tissues also contain various metals, such as Co (68 mM), manganese (Mn, 180 mM), nickel (Ni, two mM), and Zn (180 mM). The wildest metals used in biomedical engineering applications include Ca, Mg, Zn, iron (Fe), titanium(Ti), manganese (Mn), zirconium (Zr), and Co ions with lethal dose 50 (LD50) in the range of less than 25 g/kg [4,14]. Apart from the metal element, other factors such as metal contention, oxidation state, and toxicity can be

affected. Another factor affecting scaffold biocompatibility is organic linkers, which have to be restricted to non-toxic linkers and easily removed under physiological conditions. It has been reported that organic linkers such as polycarboxylic and imidazolate linkers, owing to their high polarity, are not very toxic and can be easily removed under physiological conditions [103].

#### 4. Nano-MOFs in bone tissue engineering

To implement tissue engineering and regenerative medicine-based therapeutic techniques to repair injured tissues or organs, it is crucial to first understand the physiology and histology of the natural healing process in our body along with the properties of biomaterials.

##### 4.1. Physiology of bone healing

The main goal of tissue engineering is to regenerate and repair damaged tissue by using progenitor cells, growth factors, and scaffolds [104,105]. Regarding the healing of bone fractures, the first physiological response at the fracture site is inflammation, which provides the conditions for stem cells to begin the healing process by releasing various inflammatory factors. In this stage, the hematoma is formed which means an area of blood collected outside of blood vessels. Hematoma occurs owing to bleeding and blood clotting at the fracture site and acts as a temporary scaffold and provides the necessities for migration, activation, and functionality of stem cells and angiogenesis. Subsequently, the hematoma turns into a soft callus (a type of soft bone) made of fibrous tissue, microscale vessels, cartilage, and spongy bone [106]. Soft callus starts to harden and strengthen when the ossification process occurs owing to osteogenic or chondrogenic differentiation of mesenchymal stem cells (MSCs) to form bones in the fracture site. Eventually, with the activity of osteoblasts and osteoclasts at the fracture site, bone remodeling is completed, callus is completely absorbed, and the lamellar bone is replaced within a few months [107].

The human body uses various growth factors during the bone healing process that regulate different cellular processes such as migration, proliferation, and differentiation. The transforming growth factor-beta (TGF- $\beta$ ), bone morphogenetic proteins (BMPs), platelet-derived growth factor, fibroblast growth factors (FGFs), and vascular endothelial growth factor (VEGF) are the main signaling molecules that play important roles in different stages of bone healing. Besides, the ions such as calcium ( $\text{Ca}^{2+}$ ), cobalt ( $\text{Co}^{2+}$ ), boron ( $\text{B}^{3+}$ ),  $\text{Cu}^{2+}$ , fluoride ( $\text{F}^-$ ), lithium ( $\text{Li}^+$ ), magnesium ( $\text{Mg}^{2+}$ ), niobium ( $\text{Nb}^{5+}$ ), silver ( $\text{Ag}^+$ ), strontium ( $\text{Sr}^{2+}$ ), vanadium ( $\text{V}^{5+}$ ), and  $\text{Zn}^{2+}$  play important roles in initiating different cellular pathways during bone regeneration [108].

##### 4.2. Applications of nano-MOFs in bone tissue engineering

Annually, a high rate of incidence for bone fractures, bone disorders, trauma, congenital bone malformations, and bone cancers increases the need for developing new strategies for the treatment of massive bone defects [109–111]. The traditional methods for treating bone defects are using autografts or allografts harvested from the patient or voluntarily donated human tissue from various sources, including an iliac crest, fibula, proximal tibia, and rib [112]. However, these grafts have some shortcomings, including a high risk of infection, limited bone supply, and immunogenic reactions such as graft rejection. Therefore, the advent of alternative therapeutic techniques such as bone tissue engineering can assist in overcoming the conventional method's limitations [113]. Tissue engineering aims to provide implantable

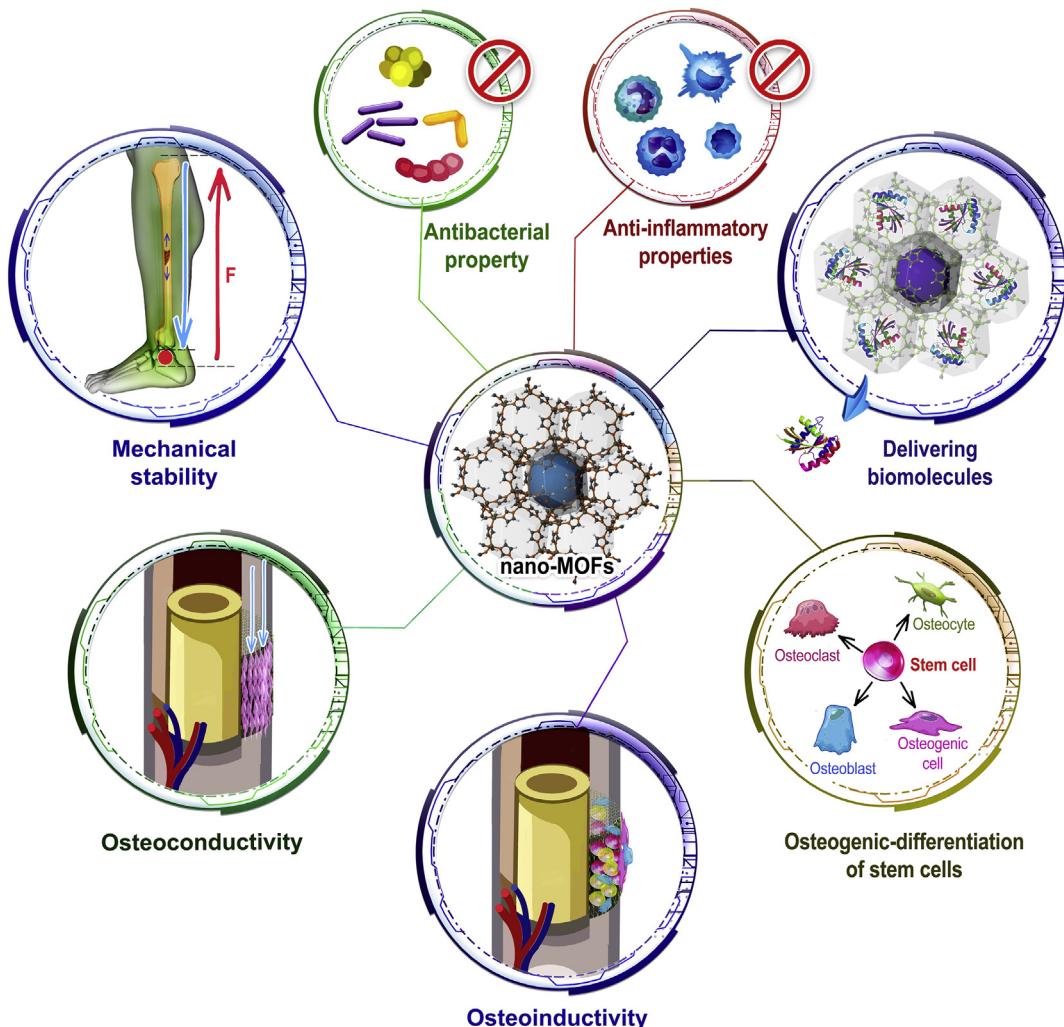
bone substitutes, including biomaterials, bone progenitor cells, and growth factors required for bone regeneration [114]. Therefore, the ideal scaffold for bone tissue engineering must be biocompatible, promote cell attachment and growth, and possess suitable mechanical stability and biodegradability. Various materials, including ceramics, metals, and natural and synthetic polymers, have been applied for bone tissue engineering [115–117]. Other requirements for the bone scaffold are good osteogenic and angiogenic properties and ability in biomolecule delivery [118]. However, the application of these materials in bone regeneration is limited owing to the lack of biodegradability, bioactivity, and osteoinductivity [119].

Recently nano-MOFs have gained a great deal of attention in the field of bone tissue engineering through implementing MOF nanoparticles (NPs) in polymer scaffolds, ceramics, or coating MOF thin films on the surface of implants or scaffolds. Nano-MOFs with high specific surface area, high mechanical stability, excellent biodegradability, and low cytotoxicity are great candidates for improving various features of bone scaffolds. In this section, different applications of nano-MOFs in bone tissue engineering, in terms of mechanical reinforcement, delivering biomolecules, antibacterial and anti-inflammatory properties, osteogenic differentiation capacity, osteoinduction, and osteoconduction, will be presented (Fig. 2).

##### 4.2.1. Implementing nano-MOFs for enhancing mechanical stability of bone scaffolds

Enhancement of scaffolds or implants' mechanical stability for regenerating fractured bones is a crucial factor in orthopedic surgeries [120,121]. The scaffolds designed for repairing different kinds of bones required additional mechanical strength depending on the functionality of each bone in the body, such as supporting body structure, moving functions, and protecting vital organs [122]. The significant drawbacks of common synthetic-based scaffolds for bone regeneration are their weak mechanical properties and low degradation rate [123,124]. Regarding this issue, MOFs and nano-MOFs can be implemented for efficient reinforcement of biomaterials because of their extraordinary mechanical properties and chemical interactions that can boost the strength of tissue engineering constructs. As a result, nano-MOFs have been widely implemented to enhance the mechanical properties of scaffolds made of different biomaterials.

Poly-L-lactic acid (PLLA), for instance, is one of the synthetic polymers which has been widely investigated in tissue engineering scaffolds owing to its high-grade biocompatibility [125]. However, its low mechanical stability and degradation rate limit this polymer to bone engineering's broader application [126,127]. In addition, the host bone cells and extracellular matrix (ECM) should gradually replace the scaffold (as a temporary supporter), so controlling the degrading rate of scaffolds during weeks is another critical factor that should be considered. In a recent study, Youwen et al. incorporated ZIF-8 NPs (average 500 nm) with different concentrations into PLLA scaffolds. Incorporating 2% ZIF-8 NPs as nano-MOFs with PLLA using selective laser sintering (SLS) methods leads to a strong interface bonding with PLLA, which favors uniform degradation of scaffolds and enhances tensile, compressive strength, as well as hardness compared with neat PLLA. Besides, when ZIF-8 NPs are hydrolyzed to  $\text{Zn}^{2+}$  ions and organic compounds, they created cavities on the surface of scaffolds, consequently assisting the invasion of water molecules and accelerating PLLA degradation (Fig. 3a) [128]. Furthermore, MOFs have also been used for enhancing the mechanical stability and corrosion resistance of implants. For instance, in a study, bio-MOF-1 (containing Zn as metal and 4-biphenyl dicarboxylic as a linker) was coated on Mg alloys. The



**Fig. 2.** Applications of nano-MOFs for bone tissue engineering. Nano-MOFs can enhance the mechanical properties of scaffolds in different bones with defects, fractures, or anomalies. Besides, incorporating these agents into scaffolds can prevent infection, the immune system's overreaction during inflammation, and increase regeneration. These NPs can be loaded with different biomolecules that increase the osteogenic differentiation of stem cells, leading to osteoinduction and osteoconduction in the transplanted site.

coating possesses high biocompatibility and could protect the Mg implant from corrosion even after 10 days in a corrosive medium [96].

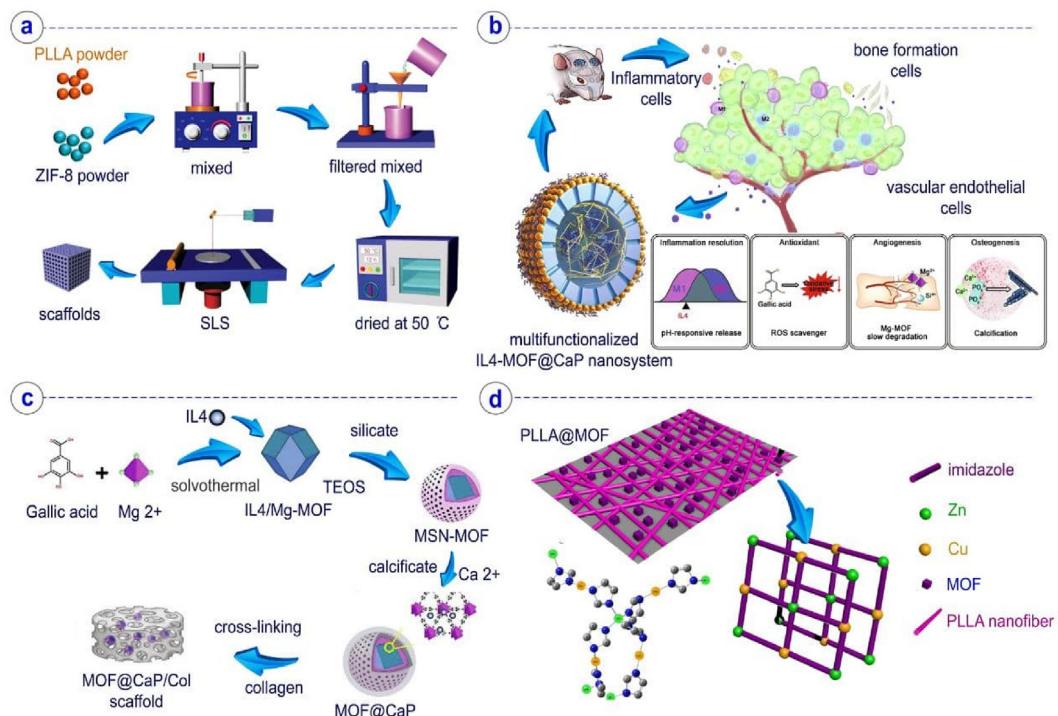
#### 4.2.2. MOF-based nanocomposites for delivering biomolecules

Incorporating various drugs, genes, small molecules, mRNAs, growth factors, and other biomolecules into scaffolds can significantly improve their efficacy for bone regeneration purposes [129]. Nano-MOFs can be considered great candidates for loading these signaling molecules and enhancing stem cells' osteogenic differentiation after transplantation because of their unique loading capacities. For instance, Chandrani et al. encapsulated dexamethasone (Dex) into ZIF-8 NPs (60–80 nm diameter) and then incorporated them into the 3D network of a nanocomposite made of cellulose and hydroxyapatite. As an osteogenic differentiation steroid, the MOFs enhanced the bioavailability and maintenance of Dex after encapsulation. This drug-loaded nanocomposite scaffold was a biocompatible and enhanced attachment, morphology, proliferation, and differentiation of cells. In addition, the drug was released slowly from this scaffold for four weeks and could enhance the expression of genes involved in alkaline phosphatase

(ALP) activity and the mineralization process. In terms of mechanical properties, the interactions of ZIF-8-based nanodrugs with base polymers improved the compressive modulus of neat scaffolds [19].

#### 4.2.3. Nano-MOFs with antibacterial and anti-inflammatory properties for bone healing

One helpful approach in designing scaffolds for bone tissue engineering is incorporating effective antibacterial delivery systems into scaffolds to inhibit osteomyelitis and manage bacterial infections [130,131]. The presence and expansion of infection in the damaged area significantly suppress the callus formation and bone regeneration process, and the fibrosis tissue, as a non-functional impractical tissue, fills the fracture site. Therefore, enriching bone scaffolds with antibacterial agents can significantly increase bone regenerative medicine success [132,133]. Nano-MOFs can be embedded with scaffolds and act as delivery vehicles for antibiotics and antibacterial ions owing to their excellent drug-loading capacities. Besides, their adjustment with stimuli-responsive systems, such as pH responsivity, enhances their functionality for releasing antibiotics in infection sites with acidic environments.



**Fig. 3.** Some strategies for the fabrication and incorporation of nano-MOFs in scaffolds for bone healing purposes. (a) The schematic illustration for fabricating PLLA/ZIF-8 scaffolds through the SLS method [128]. (b) Schematic of effecting mechanism and (c) fabrication method of the multifunctionalized IL4-MOF@Cap nanosystem. These antioxidant NPs have immunomodulatory properties and can induce neovascularization for bone healing. In addition, the fabrication process includes loading Mg-MOF NPs with an anti-inflammatory cytokine called interleukin 4 (IL4) and coated with a layer of calcium phosphate [136]. (d) Illustration of fabrication of Zn–Cu imidazole nano-MOFs coating on the surface of PLLA nanofibrous scaffolds. First, the PLLA nanofibers were synthesized by electrospinning, and then the scaffolds were immersed in the aqueous solution of Zn–Cu MOFs to form PLLA scaffolds modified with Zn–Cu MOFs [147].

Several studies have been conducted to incorporate various scaffolds with antibiotic-loaded nano-MOFs. For instance, Ayse et al. developed 3D fiber mesh chitosan scaffolds loaded with vancomycin (VAN) encapsulated with ZIF-8 nanocrystals. VAN is an antibiotic against Gram-positive pathogens, such as *Staphylococcus aureus* (*S. aureus*), which plays a prominent role in treating osteomyelitis. When VAN is loaded with ZIF-8 crystals as a nanocarrier and subsequently incorporated with fiber chitosan, the *S. aureus* activity decreases significantly. This subject is because the pH reduces from 7.4 to 5.5 through infection, collapsing the ZIF-8 structure and releasing higher VAN concentration. In addition, the chitosan scaffolds enriched by ZIF-8/VAN (5% w/w) enhanced the ALP activity of MC3T3-E1 preosteoblasts compared with neat chitosan [27]. Other kinds of MOFs, such as MOF-53 (Fe), also were able to carry antibiotics and exhibit high antibacterial properties. For instance, VAN can be easily loaded on them owing to electrostatic reaction between VAN-positive charge and the negatively charged MOF skeleton [91]. Delivery of anti-inflammatory cytokines using nano-MOF scaffolds is another effective method to improve angiogenesis and bone healing in fracture points [134,135]. Regarding this, Zhiwei et al. developed multifunctional scaffolds inspired by the scattershot pattern in the embryonal intra-membranous ossification process by fabricating Mg-MOF NPs loaded with an anti-inflammatory cytokine called interleukin 4 (IL-4) and coated with a layer of calcium phosphate. The calcium phosphate layer reduces the process of Mg-MOF NP degradation rate, controls releasing of IL-4, and promotes angiogenesis by releasing Mg<sup>2+</sup>. Furthermore, the release of cytokine antioxidative nano-MOFs increased immunomodulation and neovascularization, leading to bone healing in animal models (Fig. 3b and c) [136].

One of the systemic bacterial infections that can cause osteomyelitis is *Mycobacterium tuberculosis*. Nano-MOF-based scaffolds

can be used as an efficient delivery system for releasing antitubercular drugs. For instance, Peng et al. developed 3D-printed mesoporous bioactive glass scaffolds incorporated with isoniazid-loaded Fe-MOF particles to enhance bone regeneration and osteoarticular tuberculosis treatment. The combination of Fe-MOF particles with bioactive glass enhances the mechanical properties and bioactivity of scaffolds. Notably, the degradation of MOF did not produce acidic products and prevented reducing pH value and drug resistance of tubercle bacillus [137]. Other studies implemented other antibiotics into nano-MOFs for the treatment of bone infections. For instance, Bailong et al. reported Ti's surface modification by ZIF-8 NPs loaded with levofloxacin as an antibacterial agent using cathode electrophoresis deposition method (voltage of 40 V for 15 min). The NPs were coated with multilayers of gelatin and chitosan using a spin coating to reduce the hydrolysis rate of ZIF-8, prevent rapid degradation, and release of Zn<sup>2+</sup>. This modification enhances the surface's hydrophilicity and osteoblast attachment and antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* in a rat model [40].

In addition to implementing nano-MOFs as antibiotic nanocarriers, these nanostructures consist of metal ions that possess antibacterial properties. Thus, they can be directly applied as antibacterial agents for modifying scaffolds and implants to reduce bacterial infection after implantation [138–140]. These metals can be released in more significant concentrations from implants to kill pathogenic bacteria modified with nano-MOFs compared with methods modified with metal alone [141,142]. For instance, Ti implants modified with Mg/Zn-MOF74 nanostructures can enhance the antibacterial and anti-inflammatory properties of implants owing to releasing a considerable amount of Zn<sup>2+</sup> and Mg<sup>2+</sup>. In addition, releasing these ions can effectively enhance proliferation and osteogenic differentiation when loaded with bone scaffolds [82].

#### 4.2.4. Nano-MOFs for inducing osteoinductivity and osteoconductivity

The process of bone healing is highly dependent on osteoinduction and osteoconduction after transplanting scaffolds. Osteoinduction is the indispensable process of inducing osteogenesis through the stimulation of multipotent cells to differentiate into preosteoblasts and functional osteocytes and bone regeneration. Osteoconduction is the successful attachment of bone cells to the surface of a scaffold or implant, which plays an essential role in biomaterial-bone integration [143]. Today, several materials, including natural and synthetic materials, have been used to fabricate bone scaffolds, but many of them suffer from a lack of osteoconductive and osteoinductive capacity [144].

Many efforts have been made to enhance bone scaffolds' osteoinductivity by incorporating bioactive elements, growth factors, and other biomolecules [145]. A potential method for enhancing osteoinductivity of scaffolds is incorporating polymer scaffolds with MOFs. Releasing osteoinductive ions such as Zn, Sr, Mg, and Ca by nano-MOFs has proven to enhance osteoblast proliferation and increase osteogenic differentiation [82,97,146]. For instance, nano-MOFs containing  $Zn^{2+}$  elements such as ZIF-8 have been widely used in bone scaffolds to enhance osteoinductivity of scaffolds by releasing the  $Zn^{2+}$  during the degradation of scaffolds in the body. In a recent study, the surface of PLLA nanofibrous scaffolds was modified with Zn–Cu nano-MOFs, and then human adipose tissue-derived MSCs were cultured in the scaffold for three weeks. The presence of Zn and Cu as inorganic bioactive materials incorporated on the surface of PLLA nanofibers increased the osteogenic differentiation of stem cells leading to high calcium deposition and bone healing. Moreover, Zn–Cu nano-MOFs enhanced the hydrophilicity and bioactivity of scaffolds while not changing their morphology and mechanical properties (Fig. 3d) [147].

MOFs can also be incorporated into other polymers by using 3D printing techniques to fabricate osteoinductive microporous scaffolds with the desired dimensions, shapes, and architecture. In this technique, MOF powder can be mixed with various polymers, ceramics, or bioactive glass in different ratios to obtain injectable materials for 3D printing. Incorporating ion-releasing nano-MOFs with 3D printed scaffolds can result in higher bioactivity and osteoinductivity. For instance, in a recent study, ZIF-8 was used to manufacture a 3D printed scaffold by combining PCL and dicalcium phosphate dehydrate using extrusion-based 3D printing technology. The fabricated scaffolds were able to control  $Ca^{2+}$  and  $Zn^{2+}$  release for enhancing osteogenic differentiation of bone marrow-derived MSCs *in vitro* and promote bone regeneration of calvarial defect of rabbits [148]. In our previous studies, we have developed a facile method for modifying biphasic calcium phosphates, propylene, polystyrene, and other platforms to enhance osteoinductivity and osteoconductivity through coating a thin film layer made of ZIF-8, polydopamine, and polyethyleneimine. This modification could effectively increase wettability, surface energy and promote cell attachment and growth. In addition, compact ZIF-8 nanocrystals formed on the scaffolds' surface could significantly stimulate adipose stem cell growth and osteogenic differentiation [149–151].

The surgical barrier membranes are implemented during guided bone regeneration (GBR) surgeries for managing the dimension and direction of bone growth during periodontal bone healing [152]. The principle of GBR is using a membrane for initializing implants (such as titanium implants) for preventing intervening between osteogenic tissues and non-tissue osteogenic tissues and creating space for growing osteoblasts and regeneration of bone defects [153]. The shortcoming of the typical GBR membranes is their poor mechanical properties and low biocompatibilities. The nano-MOFs

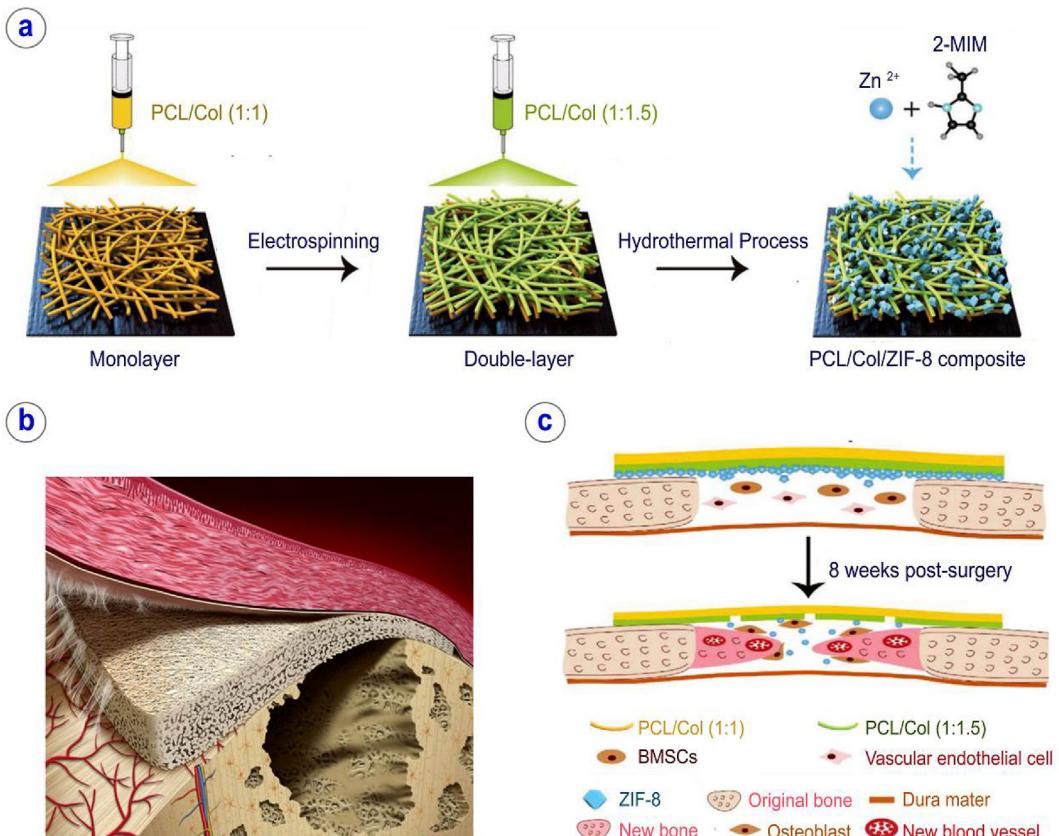
can also enhance the bioactivity of surgical barriers. For instance, Yiu et al. fabricated nano-MOFs enriched membranes using ZIF-8, polycaprolactone (PCL), and collagen, in which the core consisted of two layers of PCL, and collagen and shell was a layer of ZIF-8 coating. The ZIF-8 crystal coated on the membrane helps prevent fibroblast growth in unwanted directions, enhances cell growth and osteogenic differentiation of MSCs, and induces neovascularization by a gradual release of  $Zn^{2+}$  during the ZIF-8 degradation and changing morphology of membrane [39] (Fig. 4).

Besides ions, other osteoinductive biomolecules such as growth factors can be carried using nano-MOFs. For instance, BMPs are one of the most effective osteoinductive growth factors categorized in the TGF superfamily, and among them, BMP-2, BMP-4, BMP-5, BMP-6, and BMP-7 are the most potent osteoinductive agent in this family [154]. Ozge et al. successfully developed a PCL fibrous scaffold immobilized with nano-MOFs as an efficient growth factor delivery system for bone regeneration where BMP-6 was encapsulated in ZIF-8 during the crystallization of nano-MOFs. The BMP-6 release study indicated a gradual release of BMP-6 over 30 days, whereas bioactivity of BMP-6 was preserved during the encapsulation inside of the ZIF-8 crystals. Furthermore, osteogenic differentiation of MC3T-E1 cells has been shown enhanced by releasing BMP-6. Results obtained from *in vitro* experiments indicate increasing the ALP activity and expression of osteogenic-related genes such as type I collagen, runt-related transcription factor 2, and osteopontin. *In vivo* studies showed a sustained release of BMP-6 loaded with ZIF8 incorporated with PCL can increase bone formation significantly than neat PCL in a rat cranial defect model [41].

#### 4.2.5. Anticancer properties of MOFs in bone healing

The removal of bone tumors by the surgical processes typically causes a significant loss in bone structure that should be replaced by scaffolds, grafts, or implants. In addition, another major issue of this orthopedic procedure is cancer reoccurrence after removing the tumors that incorporating antitumor agents inside the substitute implant or scaffold significantly helps surgeons and oncologists address this challenge [155,156]. One of the advantages of modifying bone scaffolds with nano-MOFs is that they can be competent in killing cancerous bone cells, which may not be removed during surgical operation.

The MOFs and nano-MOFs can act as photothermal conversion materials in which irritation of NIR light stimulates them to release heat energy for hypothermia and in the tumor site [157]. The released energy can kill the cancer cells and decrease the chance of their proliferation and metastasis. In a recent study, a type of Cu-MOFs, Cu-TCPP, has been investigated for bone tumor therapy applications. These nano-MOFs have 2D structures and can effectively adsorb NIR owing to the d-d transition of  $Cu^{2+}$  and turn it into heat. In addition, they can release  $Cu^{2+}$  that is a vital element in regulating bone metabolism and enhancing osteogenic differentiation [158]. In another study, Dang et al. decorated the surface of  $\beta$ -tricalcium phosphate 3D printed scaffold via *in situ* growth of copper-coordinated Cu-TCCP nanosheets through a solvothermal system. Their nanocomposite exhibited an excellent ability to kill cultured osteosarcoma cells by NIR light irritation (power density: 1.0 W/cm<sup>2</sup>, duration time: 10 min) in *in vitro* and *in vivo* studies. This type of tumor model's temperature increased to 55 °C and prevented tumor growth after 18 days of observation. More importantly, incorporating Cu-TCCP enhanced the osteogenic differentiation of human bone marrow stromal cells that support the bone regeneration process. Besides this, this 3D structure improved angiogenesis after the seeding of umbilical vein endothelial cells, and transplantation of these scaffolds into bone defects in rabbits promoted bone formation [42].



**Fig. 4.** Schematic of the principle of guided bone regeneration (GBR) and its modification with nano-MOFs. The modification of GBR membranes with nano-MOFs could effectively enhance cell growth, osteogenic differentiation of MSCs, and enhance neovascularization, consequently enhancing bone regeneration and blood vessel formation [39,151].

#### 4.2.6. Nano-MOFs for osteointegration of implants

Osteointegration, defined as the connection between living bone and the implant's surface, is one of the vital requirements for a successful implant procedure. One of the examples of implants used widely in orthopedic procedures is titanium (Ti) and its alloys, which have attracted considerable attention owing to their biocompatibility, high mechanical, and chemical stability, but they are entirely bioinert; and they suffer from a lack of integrability, osteoconductivity, and osteoinductivity properties for bone healing [159]. The osteointegration of implants such as Ti can be enhanced through modifying physicochemical properties of surfaces with bioactive material such as MOFs, leading to attachment, proliferation, and osteogenic differentiation of stem cells. For instance, the nanoscale coating of ZIF-8 on Ti implants surface can enhance the osteogenic activity by releasing the Zn<sup>2+</sup> ions and increasing the surface roughness, osteogenic differentiation, and mineralization [160].

#### 4.2.7. Tendon regeneration

Tendons are fibrosis connective tissues that are in direct interaction with bone and muscles for transferring mechanical forces. The complicated bone injuries are sometimes accompanied by tendon damages that cannot be easily addressed. The nano-MOF-based tissue engineering field can also assist the regeneration of this tissue by delivering vial gases such as nitric oxide (NO). This aim is because one of the capacities of nano-MOFs is storing and releasing biologically active gases, such as NO. The therapeutic potential of NO gas is highly concentration-dependent; therefore, high porosity, surface area, and stimulative-responsive properties of nano-MOFs make them great vehicles for capturing and releasing

NO to the damaged tendon. For instance, Jun et al. loaded NO to the Cu-based HKUST-1 and immobilized the HKUST-1/NO into polycaprolactone/gelatine scaffold for tendon regeneration. The nano-MOF used in this study contains Cu, which can promote agenesis and the porosity of MOF to capture NO and release it gradually during the 15 days and consequently repair the injured tendon [86].

### 5. Nano-MOFs in wound healing

#### 5.1. Physiology of wound healing

Physiological repair of wounds in the human body is performed by synchronized collaboration between various cells, signaling molecules, cytokines, and the vascular system [161]. The first physiological response in wound healing is the hemostasis phase that stops bleeding through vasoconstriction of blood vessels, platelet aggregation, and plug formation. Next, the inflammatory cells and their secretions prevent the risk of infection and induce cellular migration, differentiation, and angiogenesis. In the proliferative and stage, a red and bumpy tissue named granulation tissue is formed on the wound site by fibroblasts through producing an ECM. This ECM acts as a scaffold supporting different cells for angiogenesis and neovascularization. In this step, the proliferation of keratinocytes leads to the re-epithelialization of the wound [162]. Finally, in the remodeling phase, granulation tissue becomes disappear, the vascular network decrease and collagen type III replace with type I in the ECM to form the integral layers of skin with the normal shape [162,163].

A variety of cytokines and growth factors, such as epidermal growth factor (EGF), TGF, VEGF, and FGF, play regulating role in the

complicated process of wound healing [164]. Furthermore, in the process of wound healing, the NO gas plays a vital role in the angiogenesis, inflammation, proliferation, and remodeling phase [165]. In the following chapters, the biocompatibility and specific applications of nano-MOFs for improving different physiological steps in bone and wound healing are described and discussed.

## 5.2. Applications of nano-MOFs in wound healing

Wounds are among the most prevalent forms of injuries in the clinic, caused in skin tissue by various factors such as diabetes, trauma, burning, or surgery [166]. The healing time and regeneration quality of these wounds can be developed using stem cell therapy, gene therapy, and tissue engineering [167–169]. In the last few years, several scaffolds have been fabricated using nanofabrication-based techniques for wound healing applications using various NPs, ECM proteins, drugs, and growth factors to provide a suitable platform supporting stem cells to mimic the tissue architecture and repair damaged layers [170,171]. However, despite current advances in wound healing, there are still unsolved challenges, such as bacterial infection, ischemia, tissue hypoxia, pain, and scar formation [172,173]. These challenges can be addressed by designing multifunctional scaffolds and improving wound healing efficiency [174]. In this section, applications of different nano-MOFs in wound healing in delivering biomolecules, antibacterial and anti-inflammatory properties, and angiogenic capacity will be presented and discussed.

### 5.2.1. Antibacterial MOFs for wound healing

The residence and cloning of bacteria in the wound site, especially in chronic ones, is one of the biggest challenges in the wound healing area that can be addressed by implementing antibacterial wound dressers and scaffolds. The scaffolds can be enriched by antibacterial properties against different species of bacteria using different methods. For instance, wound dressings and scaffolds can be incorporated with inorganic nanomaterials with high antibacterial capacities such as silver (Ag), copper (Cu), cobalt (Co), zinc oxide (ZnO), and titanium oxide (TiO<sub>2</sub>) NPs [175–180]. However, rigid attachments and interactions should be established between these NPs and scaffolds to increase the antibacterial period. In addition, storage or controlled-localized delivery of metal ions is highly beneficial in tissue engineering and clinical treatment [181,182]. These NPs damage the bacterial membrane and decrease the infection at the wound site. A variety of studies implemented these NPs inside the scaffolds to defeat the infection [183,184].

The nano-MOFs can store and release metal ions based on their physical and external stimuli. Therefore, incorporating these nano-MOFs into scaffolds using different fabrication methods can provide us with antibacterial scaffolds. For instance, Zhang et al. incorporated silver (I) MOF Ag<sub>2</sub>[1,3,5-benzenetricarboxylate][imidazole] NPs into polylactic acid (PLA) nanofibers through the electro-spinning method and showed that this antibacterial nano-composite scaffold hastens the healing in rat infectious wounds in two weeks [176,185]. In another study, Co-based MOFs exhibit high antibacterial properties in the wound healing process by releasing Co ions and inhibiting the growth of Gram-negative and Gram-positive bacteria [186]. Qian et al. also fabricated antibacterial and photodynamic nano-MOFs by encapsulating rose Bengal into ZIF-8. These antibacterial agents were then incorporated into PCL nanofibers via the electrospinning method. The scaffold released defined amounts of rose Bengal after transplantation through irritation with visible light and speed-up the wound healing process (Fig. 5a) [44]. In other work, Cu and Zn ions were encapsulated with alginate using a microfluidic electrospray device and applied to the wound site using an airbrush. These MOF-laden microspheres can release

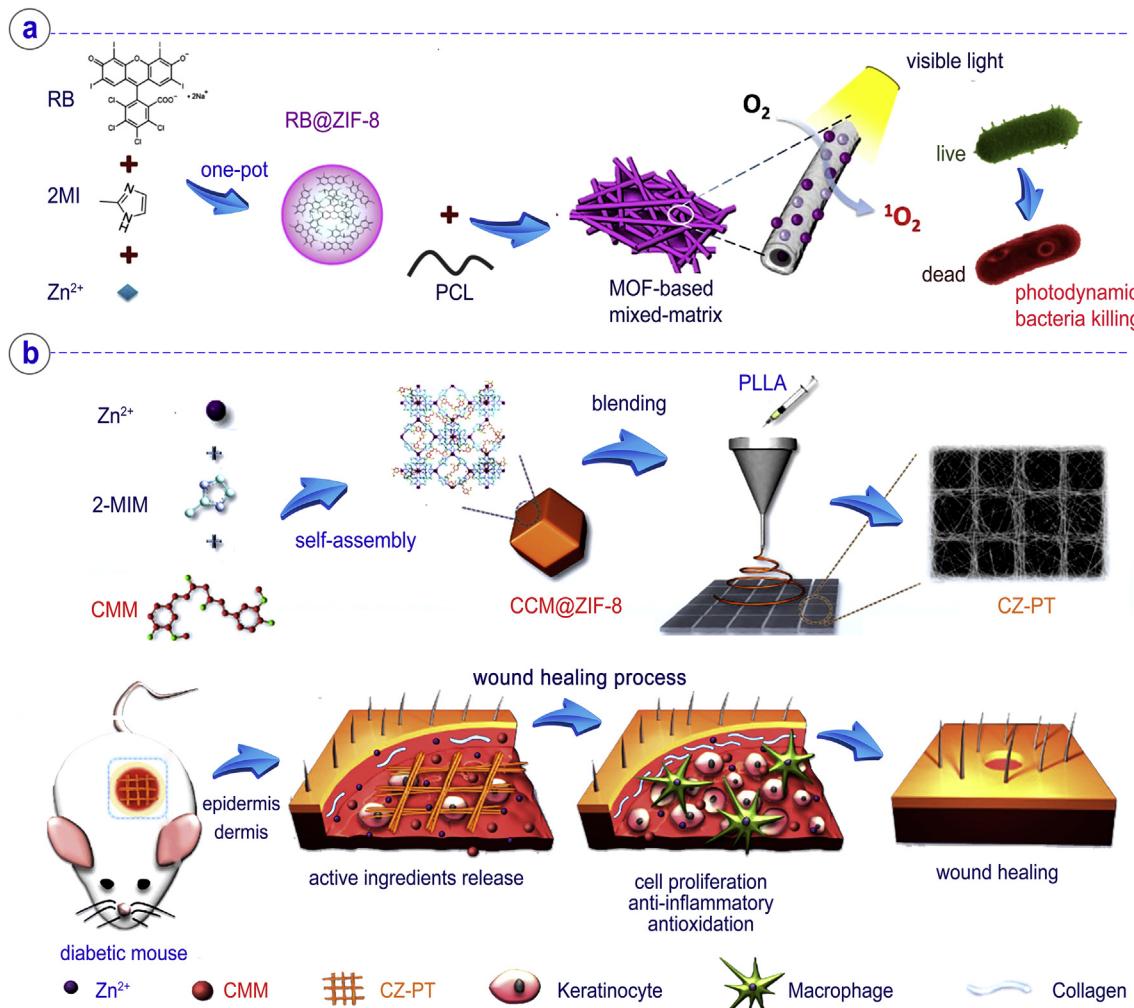
Ca<sup>2+</sup>, Cu<sup>2+</sup>, and Zn<sup>2+</sup> ions in different degrees of infections and eliminate bacteria via corrupting their membrane [187]. Some studies used the catalytic property of nano-MOFs for producing antibacterial components. For instance, Liu et al. [89] developed a novel 2D MOF-based nanocatalyst, Cu-TCP(Fe), for physically absorbing glucose oxidase, producing hydrogen peroxide, reducing pH, and killing bacteria in the acidic microenvironment of the wound.

Some research groups implemented microfluidic systems for encapsulating MOFs inside Food and Drug Administration-approved hydrogels such as alginate. For instance, Yu et al. [188] encapsulated a kind of vitamin, Zn, and Cu-based MOFs simultaneously inside alginate microfibers using microfluidic with coaxial capillary geometry for regenerating wound models infected by *Escherichia coli*. In another study, Zheng et al. [84] fabricated antibacterial microfiber by incorporating ZIF-67 particles into alginate. Huang et al. [85] also fabricated universal antibacterial and wound healing substrates by binding ZIF-67 nano-MOFs tightly to the carboxymethylated filter paper. The nano-MOFs can also be incorporated into hydrogels with innate natural antimicrobial properties such as chitosan. For instance, Wang et al. incorporated a new type of nano-MOFs, UiO-66-NH<sub>2</sub>, into chitosan. They found that these NPs have peroxidase and oxidase mimetic activities and showed antibacterial activity in the presence of H<sub>2</sub>O<sub>2</sub> [95]. Zhang et al. also incorporated Ag-based MOFs into chitosan NPs and were implemented to coat the wound dressing surface made of polyvinyl alcohol, alginate, and chitosan. As a result, their dresser shows a high level of antibacterial properties and is able to accelerate blood coagulation, cell proliferation, and re-epithelialization for wound healing [92].

### 5.2.2. Nano-MOFs carrying biomolecules and ions for increasing wound healing

Angiogenesis plays a vital role in the process of wound healing for initial clot formation, delivering nutrients, small molecules, growth factors, oxygenating, and immune cell migration for removing bacterial agents and dead cells [163]. Therefore, developing angiogenic biomaterials and nanomaterials, including nano-MOFs, can significantly enhance the wound healing efficacy in various diseases such as diabetes [168,189]. The nano-MOFs can help improve the healing of chronic wounds in patients with diabetes by carrying drugs that stimulate angiogenesis in the wound site. For instance, Li et al. loaded dimethyloxalylglycine, known as a proangiogenic drug, into zeolitic imidazole ester skeleton-67 NPs (400 nm in diameter), then incorporated them into hybrid nanofibrous scaffolds made of poly (L-lactic acid) and gelatine. Their study showed that the scaffolds could increase angiogenesis and collagen deposition in diabetic wounds via the slow releasing of Co ions and dimethyloxalylglycine [83]. Some research focused on incorporating HKUST-1 with scaffolds for the controlled release of Cu ions. The slow release of Cu ions reduces the toxicity of Cu ions and thus enhances cell migration, angiogenesis, and consequently wound healing [78,190]. Cu-based MOF scaffolds can also play an important role in the controlled release of NO and inducing angiogenesis. Zhang et al. incorporated a copper-based MOF, HKUST-1, into the core-shell PCL/gelatine scaffolds via electrospinning for controlled release of NO. The implantation of these scaffolds in diabetic mice wound models increased angiogenesis and decreased inflammation because of the slow-releasing property of scaffolds for NO and copper ions.

Despite the important role of inflammation in the beginning stages of wound healing, in some cases, acute or chronic inflammation can delay the healing process and cause fibrosis in injured tissue [43,191]. Therefore, implementing anti-inflammatory agents into scaffolds can significantly increase wound repair [192,193]. A



**Fig. 5.** Fabrication of nano-MOF scaffolds in wound tissue engineering. (a) Schematic for fabrication of antibacterial hybrid consisting of ZIF-8 and PCL. The ZIF-8 NPs were loaded with rose Bengal to obtain photodynamic and antimicrobial properties in the final product of RB@ZIF-8 NPs [44]. (b) Illustration of preparation of patterned poly-L-lactic acid (PLLA) composite electrospun scaffolds incorporated with CCM@ZIF-8 MOFs. Incorporating CCM@ZIF nano-MOFs into wounds increases cell proliferation, antioxidation, and anti-inflammatory properties for wound healing [45].

variety of nanocarriers, including nano-MOFs, can act as anti-inflammatory carriers. For instance, Wang et al. incorporated curcumin and ZIF-8 nano-MOFs ( $125.74 \pm 6.94$  nm in diameter) into PLA nanofibrous scaffold. They observed that these nano-MOFs boost the bioavailability of curcumin and significantly help curcumin decrease the severity of acute inflammation via continuous releasing of  $Zn^{2+}$  ions in diabetic mice wound models (Fig. 5b) [45]. In another study, Gwon et al. [46] combined Cu, Co, and Zn-based MOFs inside the structure of diacrylated polyethylene glycol (PEG) and 4-arm-thiolated PEG via ultraviolet (UV) light-mediated photo polymerization method. In addition, some studies incorporated the antioxidant or vitamin-loaded nano-MOFs for improving wound healing. For instance, Xiao et al. [194] incorporated HKUST-1 NPs into poly-(PEG citrate-co-N-isopropyl acrylamide) as an antioxidant thermos-responsive hydrogel and implemented them as a dressing for healing chronic wounds in the diabetic mouse.

Besides the above-mentioned properties, the nano-MOFs are also known for their high internal surface area, porosity, and incorporation of synthetic polymer biomaterials, leading to higher surface area for cell attachment [195]. For instance, poly-acrylonitrile (PAN) fibrous possesses high mechanical elasticity, chemical stability, but they do not have an adequate surface area in bulk fabrication methods for tissue engineering purposes. To

address this issue, Omar et al. [21] showed that incorporating Fe-MOF into PAN through electrospinning technique increases scaffold's specific surface area and enhances human umbilical vein endothelial cells (HUEVCs) attachment during *in vitro* studies and develops vessel regeneration in wound site.

## 6. Challenges and future outlooks

The nano-MOFs are a new generation of porous nanomaterials that showed a variety of benefits for bone tissue engineering and wound healing. This category of nanomaterials showed acceptable levels of biocompatibilities in the *in vitro* and *in vivo* studies and enhanced mechanical properties, biomolecule delivery capacity, antibacterial properties, and osteogenic differentiation potency of scaffolds toward osteocyte cell in bone regenerations. Besides these, nano-MOFs can induce osteoinduction, osteoconduction, and osteointegrity in scaffolds. The unique properties of nano-MOFs also make them suitable NPs for enriching scaffolds for wound healing applications. These NPs can have antibacterial effects and load and release various biomolecules, ions, vitamins, and antioxidants from supporting scaffolds. Therefore, these scaffolds can enhance wound healing through enhancing angiogenesis, anti-inflammation activities, and antibacterial properties. However,

the reported nano-MOF-based studies are mostly limited to small animal studies that can be expanded to large animals and clinical trials. Besides, the possible effect of nano-MOFs on renal and liver functions has been rarely investigated [196].

The most critical point in designing nano-MOF-enriched scaffolds and implants for orthopedic applications is to consider the location of the injury, the type of fracture, which requires high-level coordination between the orthopedic surgeon, nanotechnologist, biomechanical engineer, and biomedical scientists. In addition, the requirements and strategies for repairing fractures in different parts of the bone, including the epiphysis, diaphysis, and metaphysis, are different. Therefore, the mechanical, physiological, immunohematological, and surgical conditions for designing and implementing nano-MOFs into scaffolds should be explicitly considered. This means for each pathophysiological condition suitable nano-MOFs should be specifically designed for specific demands. To be more precise, choosing appropriate metal ions, organic ligand, supporter biomaterial, drugs or, and biological agents are a complicated interdisciplinary issue that should encompass fabrication method, mechanical concept, desired physiology consequences, and orthopedic operations. For instance, the most important requirement in diaphysis healing is establishing mechanical strength, whereas in metaphysis, flexibility is the most critical factor. Besides, the proportional forming of these materials into 3D shapes for filling damage is fundamental, drawing attention to selecting a proportional manufacturing technique. In addition, the tunable porosity of MOFs allows the loading and release of various biomolecules required for each clinical purpose.

The physical stability and mechanical properties of nano-MOFs have been attracted considerable attention in the fabrication of scaffolds for the bone and skin. However, still more studies are required for optimizing the degradability and mechanical properties of scaffolds using nano-MOFs. For example, the effect of different MOFs on the flexibility of scaffolds or implants in animal models needs further investigation. This issue can prevent deformity through weight and trauma in scaffold-assisted engineered bones [116,197]. Extensive studies can also be performed on the effect of porosity of these substances on tissue nutrition, essential phenomena in tissue healing and viability, such as osmosis and tissue perfusion [198,199]. Another critical challenge in orthopedic surgery is the development of angiogenesis and remodeling immunological phenomena in patients. Owing to the high potential of MOFs in these areas, more extensive studies in large animals with more similar immune systems to humans can be performed.

MOFs can be implemented to repair various wounds such as burns, tissue loss, dirty wounds, and ulcers. For example, the design and fabrication of nano-MOF-based dressings to heal dirty wounds should have antibacterial and fibrinolytic properties and stimulate granulation formation [200]. In burns, on the other hand, large volumes of scaffolding and wound dressing are needed to cover a high percentage of the body surface (e.g., up to 50 percent) in a limited time so that the patient does not lose water owing to severe dehydration and survives [201]. In addition, as mentioned previously, the nano-MOFs used to heal diabetic wounds need to be designed to stimulate angiogenesis and collagen production [202].

The possible toxicity of organic linkers, metal ions, solvents, and chemical residues is a big challenge in this area that should be addressed in more detail [203]. Interestingly, there is no clinical trial report in this area that is highly recommended for future studies. Besides, the applications of nano-MOFs have been investigated for some specific steps of bone and wound healing. Therefore, our knowledge about the effect of these NPs, their ions, and cargo on intracellular organelles and signaling

pathways is vague that can be studied more in the future. Furthermore, the fabrication techniques for incorporating these extensive polymeric crystalline materials are mostly limited to specific methods such as electrospinning, 3D printing, and SLS that can be extended to advanced techniques such as 3D bio-printing methods [204,205].

## Declaration of competing interest

The authors declare no conflict of interest.

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