






Two-dimensional metal organic frameworks for biomedical applications

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Abstract

Two-dimensional (2D) metal organic frameworks (MOFs), are an emerging class of layered nanomaterials with well-defined structure and modular composition. The unique pore structure, high flexibility, tunability, and ability to introduce desired functionality within the structural framework, have led to potential use of MOFs in biomedical applications. This article critically reviews the application of 2D MOFs for therapeutic delivery, tissue engineering, bioimaging, and biosensing. Further, discussion on the challenges and strategies in next generation of 2D MOFs are also included.

This article is categorized under:

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KEYWORDS

bioimaging, biosensing, drug delivery, metal organic frameworks (MOFs), tissue engineering

1 | INTRODUCTION

Highly ordered and solid-state porous two-dimensional (2D) nanomaterials are a new class of materials (Karak et al., 2017; Karak, Kumar, Pachfule, & Banerjee, 2018; Zhang et al., 2019), that have shown wide-spread applications in catalysis (Chen, Zhang, Jiao, & Jiang, 2018), sensing (Das et al., 2015; Ding et al., 2016; Ma et al., 2018), biomedical (Fang, Kim, Kim, & Yu, 2013; Yang, Léonard, Lemaire, Tian, & Su, 2011), gas adsorption (Ma et al., 2018; Zhu et al., 2017), and energy storage (Kou et al., 2017). These 2D nanomaterials include graphitic carbon nitride (g-C₃N₄) (Wang, Zhang, Li, Li, & Wu, 2017; Zhang et al., 2013), transition metal dichalcogenides (TMDs; Carrow et al., 2020; Jaiswal, Singh, Lokhande, & Gaharwar, 2019; Lu, Yu, Ma, Chen, & Zhang, 2016; Zhang, Lai, Ma, & Zhang, 2018),

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covalent organic frameworks (COFs; Bhunia, Deo, & Gaharwar, 2020), hexagonal boron nitride (h-BN; Deshmukh, Jeong, Lee, Park, & Kim, 2019; He et al., 2019), layered double hydroxides (LDHs; Yu, Wang, O'Hare, & Sun, 2017; Zhao et al., 2017), layered silicates (nanoclay) (Gaharwar et al., 2019), polymer sheets (Clover et al., 2020), and noble metal nanosheets (Huang et al., 2011; Sancho-Albero et al., 2019). Diverse biomedical applications of these nanomaterials are owing to their versatile properties including high surface area, high conductivity, and superior optical properties (Brokesh & Gaharwar, 2020; Chimene, Alge, & Gaharwar, 2015; Gaharwar, Singh, & Khademhosseini, 2020; Lee & Gaharwar, 2020). Metal–organic frameworks (MOFs) are an emerging type of such solid-state porous materials that possess properties similar to that of other nanomaterials in addition to several unique properties including high structural tunability and biodegradability enabling them to be used for various biomedical applications (Beg et al., 2017; Yang & Yang, 2020). MOFs have high porosity with pore sizes between 0.4 and 6 nm making them ideal candidates for storage (Shao et al., 2018; Spanopoulos et al., 2016), capture (Wang, Bai, Lu, Pan, & You, 2016; Zhang et al., 2017), separation (Li, Sculley, & Zhou, 2012), sensing (Dolgoplova, Rice, Martin, & Shustova, 2018; Yu et al., 2020), catalysis (Dhakshinamoorthy, Li, & Garcia, 2018; Lee et al., 2009; Yang & Gates, 2019), and drug delivery (Cai, Huang, & Li, 2019; Keskin & Kızılel, 2011; McKinlay et al., 2010) applications. MOFs also belong to another class of porous materials with uniform pore size are called molecular sieves (Caro, 2016; Liu et al., 2018). Furthermore, fluorescent MOFs (Allendorf, Bauer, Bhakta, & Houk, 2009) have shown potential applications in sensing of ions (Zhao, Yang, Liu, & Ma, 2016), gases (Guo, Wang, & Cao, 2018; Lin, Liu, Ye, Li, & Zhang, 2016), and vapors (Du et al., 2018; Zhang et al., 2019).

The structure of MOFs is mainly composed of transition metal ions linked with organic moiety via functional linkages such as formate (Lu et al., 2017), cyanide (Dalapati et al., 2018), triazole (Qian et al., 2019), glutamate (Kathalikkattil et al., 2016), 1,2,4,5-tetracarboxylates (Smolders et al., 2018), and squarates (Li et al., 2019). These are interconnected with coordination bonds of moderate strength, hydrogen bonding, and electrostatic interactions or p–p stacking (Zhao et al., 2018). A miniaturized version of MOFs at the nanometer length scale is called 2D MOFs or nanoMOFs (NMOFs; Rojas, Guillou, & Horcajada, 2019; Figure 1a). In contrast to 3D MOFs, advantages of 2D MOFs include well refined surface area, high purity, and highly functional characteristics (3D MOFs; Zhao et al., 2018). The flexibility to fine tune their composition and structure makes 2D MOFs emerging nanomaterials (Figure 1b).

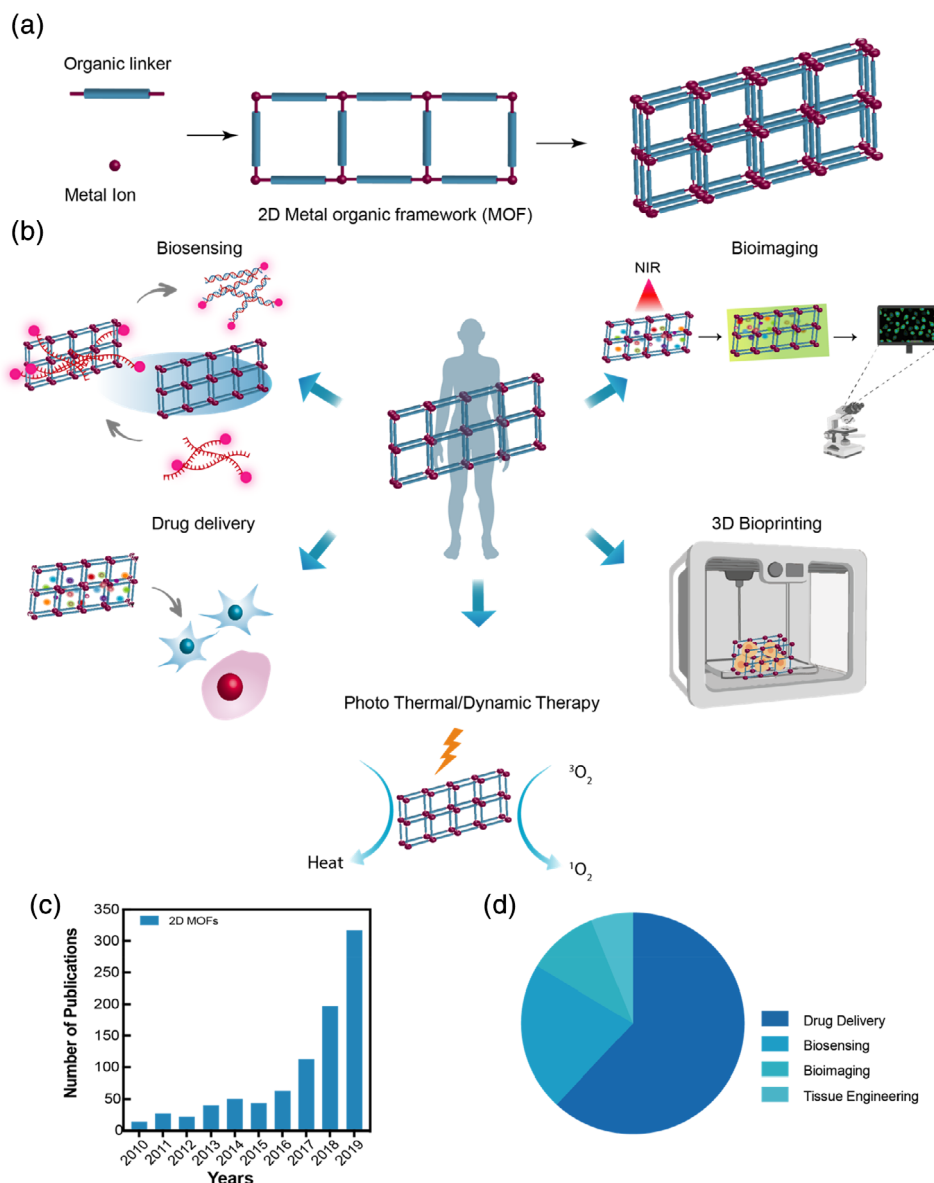
Variety of hybrid chemical materials can be obtained using the MOFs resulting these as attractive candidates for drug delivery fields. Some of the important characteristics of MOFs related to drug delivery include: (a) high porosity; (b) low toxicity; (c) biodegradability, (d) hydrophilic–hydrophobic microenvironment, (e) high chemical and thermal stabilities, and (g) crystallinity. Previous works include usage of MOFs as drug delivery hosts for several anti-cancer applications (Chen & Wu, 2018; Della Rocca, Liu, & Lin, 2011; Giménez-Marqués, Hidalgo, Serre, & Horcajada, 2016; Keskin & Kızılel, 2011; Wang et al., 2017). 2D MOFs are specifically suited for drug delivery applications because of their amphiphilic internal structure with ability to strongly adsorb biological agents including drugs, nucleic acids, and biologics (Chen & Wu, 2018; Della Rocca et al., 2011; Giménez-Marqués et al., 2016; Keskin & Kızılel, 2011; Wang, Li, et al., 2017). However, it is imperative to have 2D MOFs that are highly biocompatible and biodegradable (Majewski, Noh, Islamoglu, & Farha, 2018). Currently, there are only a few studies related to *in vivo* toxicity analysis of 2D MOFs (Baati et al., 2013; Chen & Wu, 2018; Giménez-Marqués et al., 2016; Grall et al., 2015).

This review highlights the latest advances in 2D MOFs based biomaterials in various biomedical applications such as therapeutic delivery, tissue engineering, bioimaging, and biosensing (Figure 1c,d). Recent trends and novel strategies promoting 2D MOFs in biomedical applications are described. Furthermore, the challenges and facile strategies to motivate future design and formulation of 2D MOFs for advanced biomedical applications are discussed.

2 | SYNTHESIS AND FABRICATION

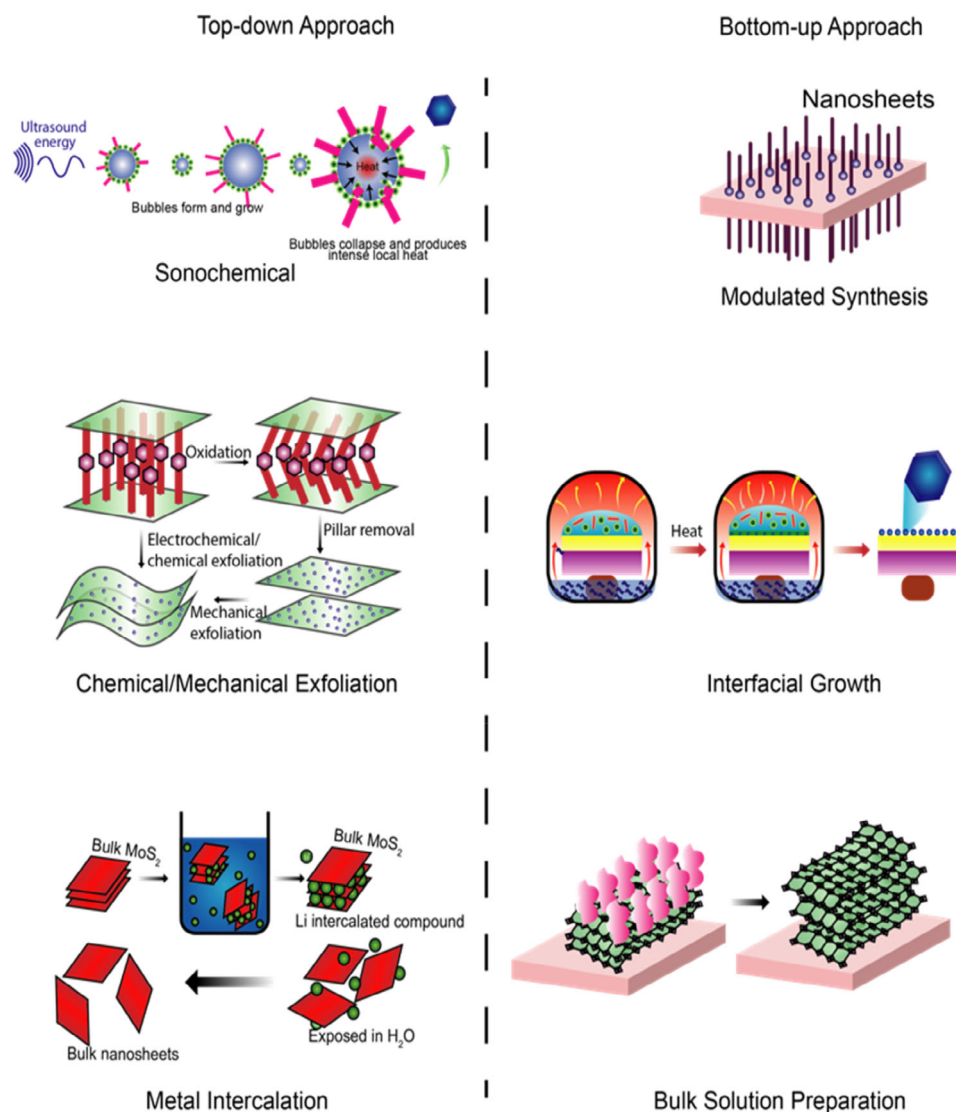
MOFs are commonly synthesized as crystals of 3D coordination networks; however, recent attention has been shifted to preparation and fabrication of the 2D MOFs (nanosheets). There are various approaches for synthesizing 2D MOFs including exfoliation (Amo-Ochoa et al., 2010; Au et al., 2019; Ding et al., 2017; Huang et al., 2018; López-Cabrelles et al., 2018; Peng et al., 2014), bulk solution preparation, interfacial growth (Dong, Zhang, & Feng, 2018; Haraguchi, Otsubo, Sakata, Fujiwara, & Kitagawa, 2016; Liu et al., 2019; Maeda, Sakamoto, & Nishihara, 2016; Makiura et al., 2014; Makiura, Tsuchiyama, & Sakata, 2011; Motoyama, Makiura, Sakata, & Kitagawa, 2011; Sakaida et al., 2016; Sakaida et al., 2017; Sakamoto et al., 2016; Xu, Otsubo, Yamada, Sakaida, & Kitagawa, 2013; Xu, Yamada, Otsubo, Sakaida, & Kitagawa, 2012), and metal intercalation (Falcato et al., 2016; Huang et al., 2017; Li, Liu, Wang, Qiu, &

FIGURE 1 2D MOFs. (a) Metal ions connected by organic linkers to form 2D MOF structures. (b) Number of publications since 2010, when keywords “2D MOFs” were used, indicating the recent increasing popularity of 2D MOFs (data obtained December 2019). (c) Overview of different biomedical applications of 2D MOFs. (d) Number of publications since 2010, when keywords “2D MOFs” and different biomedical application keywords were used like “drug delivery,” “biosensing,” “bioimaging,” and “tissue engineering” (data obtained December 2019)



Zhang, 2018; Wang, Li, et al., 2017) (Figure 2). Detailed summary on the synthesis of 2D materials using various synthetic procedures are included in the article by Zhao and co-workers (Zhao et al., 2018). Briefly, 2D MOFs synthesis approaches are generally categorized into two broad strategies, namely top-down and bottom-up approaches (Xu, Yang, & Gu, 2018; Zhao et al., 2018; Zhao, Lu, Ma, & Zhang, 2017). In the top-down approaches, MOF layers attached via weak interactions can be separated into individual nanosheets via mechanical exfoliation, chemical exfoliation, sonication exfoliation, and metal intercalation. Exfoliation method is the most commonly adopted top-down method and comprise of mechanical shaking, ball milling, and ultrasonic treatment (Liu et al., 2019). In a recent study, zinc- and copper-based 2D MOFs are synthesized using exfoliation (Xu et al., 2017). Specifically, bulk zinc- and copper-based MOF crystals were mechanically exfoliated to obtain 2D copper-MOF nanosheets. These 2D MOFs showed layered structures with large surface area and high aqueous stability, while acting as effective enzyme inhibitors (Zhao et al., 2016). These newly synthesized 2D zinc-based nanosheets open up a new direction toward exploring the MOF-bio interface in the area of catalytic and physiological systems. One of the limitations of top-down approach is limited control during the mechanical and chemical exfoliation processes often resulting in low yield. Exfoliation process can be optimized by intercalating other ligands between the MOF layers. Ding and group used a dipyrrolyl ligand as an intercalating agent between Zn-based MOF crystals (Ding et al., 2017). This ligand weakened the inter-layer interactions and enabled efficient exfoliation of ultrathin Zn-based MOF nanosheets.

Synthesis of 2D MOFs

FIGURE 2 Overview of top-down and bottom-up approaches for synthesis of 2D MOFs

In the bottom-up approach, building blocks and functional promoters are controlled at the initial synthesis stage. The composition and structure of MOF nanosheets are thus highly tunable in this bottom-up approach. This enables desired shape and size control of MOFs via selecting appropriate templates, and solution and growth control via suitable precursors. Recently, layered poly[$\text{Zn}_2(\text{benzimidazole})_4$] was produced from 3D zeolitic imidazolate framework ZIF-7 using hydrothermal method with combined exfoliation process through ballmilling and ultrasonication (Lin et al., 2018). Another bottom-up synthesis approach that is pursued to effectively control the thickness of 2D MOFs is known as bulk preparation approach. Small molecules or surfactants are often used in this method to direct the growth of 2D nanosheets. Zirconium-based nanosheets were synthesized by introducing modulator, or ligand, which in turn destabilized MOF crystals and resulted in the formation of 2D MOF nanosheets (Hu et al., 2016). Last, bottom-up approach—interfacial synthesis to synthesis 2D MOFs is recently investigated due to its ability to achieve single-layered and multi-layered 2D MOF (Kambe et al., 2013). This approach can help tune the structure and properties of the MOFs. Particularly, to prepare ultrathin 2D MOFs-based nanosheets, the preferred synthetic method is surfactant assisted strategy as this method results in preparation of pure and stable nanosheets (Zhao et al., 2018). Semi-conducting nickel bis(dithiolene) complexes were synthesized using the interfacial reaction between an organic liquid phase and an aqueous liquid phase (Kambe et al., 2013). This interfacial method also enabled modulation of oxidation states through chemical reduction further confirming the tunability of bottom-up approaches.

Despite the advantages of these approaches, nearly a decade after their invention, the bulk-scale synthesis of 2D MOFs, with desirable and controllable properties, still remains in its infancy. Structure validation of 2D MOFs upon synthesis has not been achieved. This is due to the lack of suitable characterization techniques that can clearly differentiate 2D MOFs from 3D bulk MOFs. Thus, novel characterization techniques are required to visualize and determine the structure of 2D MOFs based materials. Complete understanding of the functions of 2D MOFs, compatible scaffolds to direct the formation of 2D MOFs, and determining optimal synthetic strategies to control the growth of 2D MOFs are also of utmost importance. Therefore, future studies should focus on formulating rational design and facile construction with enhanced “all-in-one” 2D MOFs for high-throughput applications.

3 | BIOCOMPATIBILITY

The potential development and approval of MOFs in various biomedical applications are dependent upon the safety, stability, ease of preparation, efficacy, and reproducibility of MOFs during bulk manufacturing. Currently, there are inadequate *in vitro* and molecular biology assessments of MOFs to ensure cytocompatibility of these materials. Relatively newer class of MOFs such as 2D MOFs has not been extensively characterized for safety. Smaller size of the 2D MOFs often leads to improved electrical, optical and magnetic properties that can be leveraged in many biomedical applications. However, surface modifications that are required for these properties can cause safety concerns (Lee et al., 2009; Li et al., 2019; Zhao et al., 2018). Many moieties are also used to improve the stability of MOFs including metal ions and ligands. Physiological conditions could disrupt the interactions between MOFs and the associated metal ions resulting in excess free ions and ligands in the body.

Metal-based compounds used in biomedical applications are often scrutinized for their potential long-term effects. High reactivity and small size of MOFs contribute to safety concerns for human health. There are limited toxicity studies that have been conducted to test cytocompatibility of MOFs and thus toxicity of these materials is not thoroughly characterized. 2D MOFs in particular could potentially accumulate in the cells owing to their smaller size. This metal accumulation over time may potentially be unsafe especially if MOFs are used as long-term therapeutic delivery systems. It is thus imperative to conduct extensive *in vitro* and *in vivo* toxicity studies to ensure biocompatibility. Correlation between *in vitro* and *in vivo* studies must be established to deduce optimal dosage within the safety limits.

4 | BIOMEDICAL APPLICATIONS OF 2D MOFS

Structural diversity, easy functionalization, and high porosity have made MOFs an attractive alternative over the conventional nanoporous materials (Agostoni et al., 2013). Within the last few years, there has been increasing focus on the use of MOFs in various applications including gas storage, gas adsorption/separation, conductors, and batteries. Recently, 2D MOFs have opened new avenues for advanced applications in many areas including medicine (Bai, Li, Ma, Cao, & Zheng, 2019; Ding et al., 2017; Keskin & Kızılel, 2011; Lin et al., 2018; Liu et al., 2019; Peng et al., 2014; Rodenas et al., 2014; Xu et al., 2017; Xue, Zheng, Xue, & Pang, 2019; Yi, Wang, Du, Fu, & Wang, 2018; Zhao et al., 2018). However, commercial biomedical applications often require stable structures to have specific morphology to ensure biocompatibility and precise functionality. New approaches have been carried out to incorporate 2D MOFs within polymer scaffolds. For example, *in situ* growth of MOFs was carried out using alginate hydrogel to facilitate production of controlled composite configurations (Zhu, Zhang, & Zhu, 2016). Zhu and group successfully formulated MOF-alginate compositions, with homogeneous distribution of MOFs, that enabled controlled physical structures. Another approach used to accurately modulate physical configuration of MOFs include sol-gel processing where colloidal solution formed a continuous gel via hydrolysis of precursors (Sumida et al., 2017). Different sol-gel processing strategies are applied to MOFs including direct modification of pores in MOF networks and using MOF network as a template for ceramic coating. This type of processing enhances physical properties of MOFs making them specifically useful for applications including photonics, and biosensing. In addition, MOFs are also investigated for tissue engineering and cancer therapy applications. In the following sections, we will highlight some of the recent applications of 2D MOFs.

4.1 | Biocatalysis

Since the discovery of graphene, there has been strong interest in 2D materials due to their extreme flexibility and malleability. Over the past few years, numerous approaches have been developed toward fabrication of 2D MOFs as the flexibility on functional tuning offers many opportunities and potential applications across biology and medicine (Wang et al., 2018; Xu et al., 2018; Zhao et al., 2018). Xu and group employed 2D MOFs nanosheets in their study to form 2D MOF nanosheet-bio interface to closely regulate enzyme modulation activity (Allendorf et al., 2009). For this study, α -Chymotrypsin (ChT, EC 3.4.21.1) was chosen as the model enzyme due to its well characterized structure, and for being an important serine protease in the alimentary canal. 2D Zn-MOF and Cu-MOF nanosheets were synthesized using a top down approach and were incubated with ChT. Enzymatic substrate, *N*-succinyl-L-phenylalanine-p-nitroanilide (SPNA), was then incubated with ChT/Cu-MOF to test activity of ChT. Cu-MOF nanosheets were observed to cause 96% inhibition of ChT. It was also noticed that MOFs acted as a binding competitor at ChT active sites through electrostatic interactions rather than altering the enzyme's native conformation. This study opens up new avenues for potential use of MOF-bio interfaces in catalytic assays.

2D MOFs can be further enhanced with superior characteristics toward biocatalysis applications by developing new formulations with custom surface properties. Previous work highlights the potential use of 2D MOF nanosheets in nanomedicine-related applications specifically via modulating surface charges and organic compositions of the 2D MOF nanosheets (Xu et al., 2017). These surface modifications or surface engineering of 2D MOFs can enable advanced functionalities for other targeted biocatalytic applications. Figure 3a displays the external surface functionalization scheme of the nanostructured 2D MOFs with chitosan (Giménez-Marqués et al., 2016). This functionalization of 2D MOFs for biocatalysis applications can be facilitated using other ligands similar to chitosan (Figure 3b). Other common functional groups that are used to modify chemical properties of 2D MOFs include OH, COOH, NH₂, Br, Cl, H, and SO₃H.

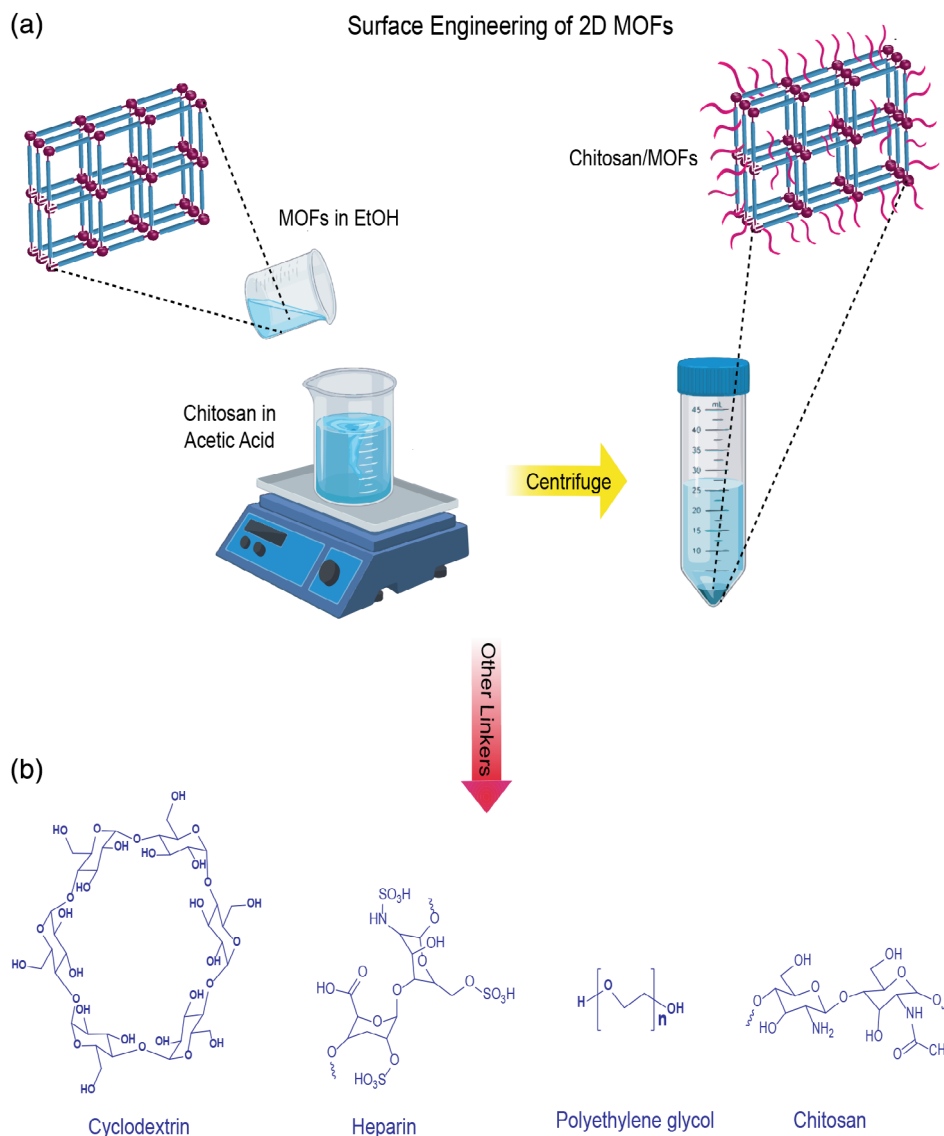
A recent study used metal clusters that had binuclear paddle-wheel and metalated tetrakis(4-carboxyphenyl)porphyrin (TCPP) ligands, which mimicked peroxidase for synthesizing different types of 2D MOFs (Figure 4a) (Cheng et al., 2017). This exhibited an enhanced peroxidase-mimicking activity compared to their 3D bulk analogues. Furthermore, 2D Zn-TCPP (Fe) nanosheets were utilized to design a bioassay with high selectivity and sensitivity as it helped in monitoring the elimination process of heparin (Hep) in live rats as shown (Figure 4b). Figure 4c shows that microdialyzed serum from rats that were treated with heparin showed activation of the 2D MOF nanozyme. AG73 peptides that are bound to the MOFs blocks the catalytic active sites on the MOF nanosheets. Highly specific interaction between AG73 and heparin results in the effective catalytic activity of the MOF nanosheets. In contrast, this catalytic activity is not observed in rats that were not treated with heparin thus supporting the specificity of the MOF nanozyme. Figure 4d shows dynamic changes occurred in the Hep concentrations in the live rat artery over 4 hours. Based on these experimental findings, it was concluded that 2D MOF nanosheets of TCPP (Fe)-based have the potential for in vivo detection of many biological targets. This study highlights the versatile potential of 2D MOF nanosheets to be used as effective biosensors.

4.2 | Therapeutic delivery

2D MOFs have also been used as a candidate for drug delivery due to their high porosity, ease of synthesis, tailorable composition and structure, tunable size, controllable surface functionality, and biodegradability (Della Rocca et al., 2011; Furukawa, Cordova, O'Keeffe, & Yaghi, 2013; He, Liu, & Lin, 2015; Horcajada et al., 2009; Morris, Briley, Auyeung, Cabezas, & Mirkin, 2014). The unique properties and structure of 2D MOFs, including large surface area and hydrophilic characteristics, make them attractive candidates for delivery of therapeutic agents including small molecules, antigen, and nucleic acids.

2D MOFs have been extensively studied as drug carriers for cancer applications because of increased loading of chemotherapeutic drugs that in turn resulted from MOF's high specific surface area. Li and team synthesized iron porphyrin-based 2D MOFs with copper (Cu) and loaded the nanosheets with cisplatin (CDDP; Figure 5a; Li, Gao, et al., 2018). Release of cisplatin from the 2D MOF nanosheets was observed to be triggered by pH (Figure 5b). These CDDP-loaded nanosheets were delivered to lung cancer cells where Cu and CDDP were released upon degradation of nanosheets in the acidic tumor microenvironment (Figure 5c). Similarly, another widely used chemotherapy drug, called methotrexate (MTX), was loaded onto Cu-MOF nanosheets through electrostatic interactions between MOF and MTX (Nezhad-

FIGURE 3 Surface engineering of 2D MOFs. (a) Schematic illustration of functionalization of 2D MOFs with chitosan. (b) List of common ligands that are used to functionalize 2D MOFs. Created with BioRender.com



Mokhtari, Arsalani, Javanbakht, & Shaabani, 2019). To improve the uptake of these MOF drug carriers through proton-sponge effect, Cu-MOF/MTX nanosheets were further encapsulated in gelatin microspheres. This Cu-MOF/MTX@GM complex was shown to have higher killing efficacy in human breast adenocarcinoma cell line. These examples highlight the potential of MOFs to be used as an effective small molecule carrier.

In contrast, protein loading onto 2D MOFs has been challenging as larger molecules cannot be encapsulated within the pores of MOFs and proteins can possibly be denatured because of the solvents used during synthesis of MOFs. However, 2D MOFs with larger pores can be used to trap proteins and improve cellular uptake that can otherwise be inhibited by surface charge of proteins. Chen and team used ZIF-8 MOFs to improve loading efficiency and protection of insulin (Chen, Li, Modica, Drout, & Farha, 2018). Insulin is typically administered by direct injection, as oral administration can potentially expose insulin to stomach acid leading to denaturation. ZIF-8 MOFs were used to protect and encapsulate insulin effectively as MOFs can persist in acidic environment. ZIF-8 MOF-insulin facilitated high insulin loading (~40%), high insulin functionality (~84%) even after exposure to acidic conditions, and increased insulin release in physiological conditions. In addition to insulin delivery, ZIF-8 MOFs have also been studied to deliver subunit vaccines to illicit enhanced immune response. Nanoparticle-delivery platforms can potentially protect the vaccine from protease activity while also providing longer immunity through colocalized delivery of vaccine and immune adjuvants. Zhang and group encapsulated model antigen, ovalbumin (OVA), within ZIF-8 MOF which was further attached to a commonly used adjuvant, cytosine-phosphate-guanine oligodeoxynucleotides (CpG ODNs) (Zhang et al., 2016). Both in vitro and in vivo studies showed that OVA@ZIF-8-

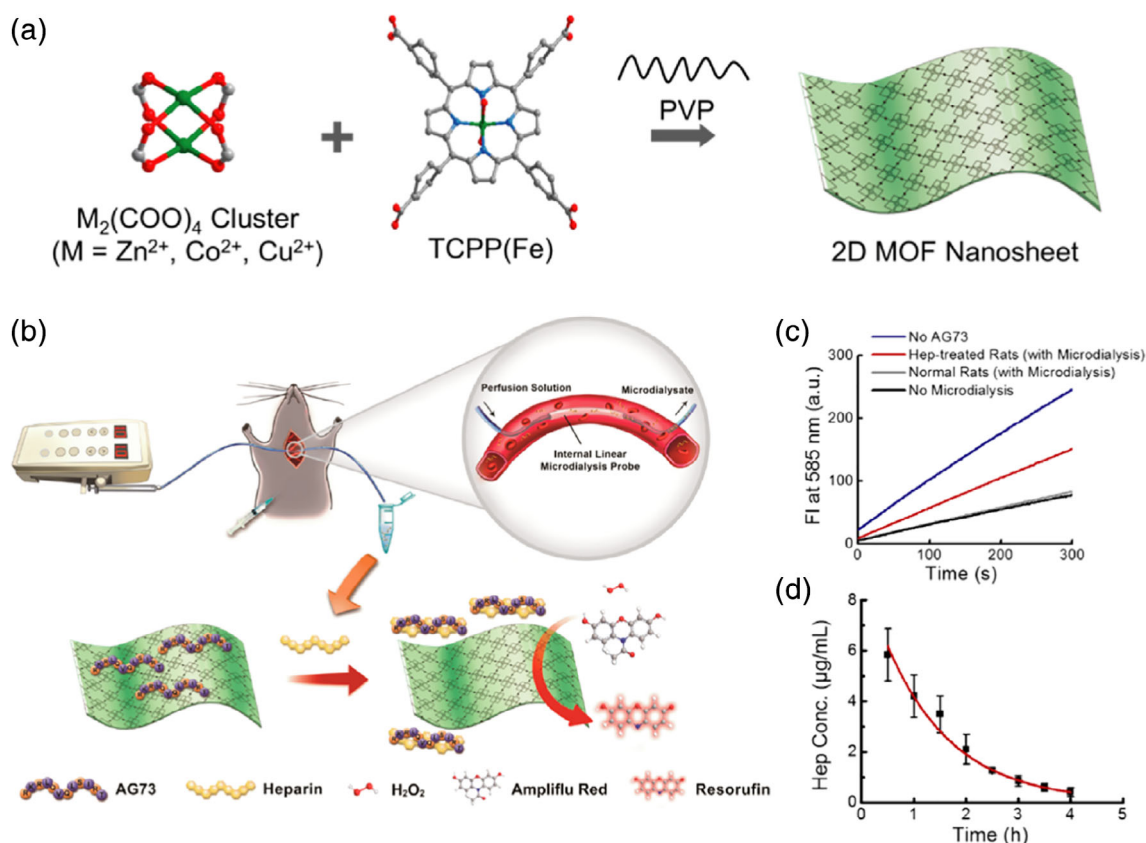


FIGURE 4 2D MOFs-based nanozyme. (a) Scheme representing the synthesis of 2D Zn-TCPP nanosheets. (b) Scheme representing the use of 2D MOF nanosheets with peroxidase activity to monitor the elimination of heparin in vivo. (c) Kinetic assay with time-dependent fluorescence intensity indicating increased activation of 2D nanosheets that is modified with anti-heparin peptide, AG73, in heparin-treated rats. (d) Heparin elimination was tracked by monitoring the heparin concentrations in the artery of live rats for 4 hr after heparin administration. (Reprinted with permission from Cheng et al. (2017). Copyright 2017, Analytical Chemistry)

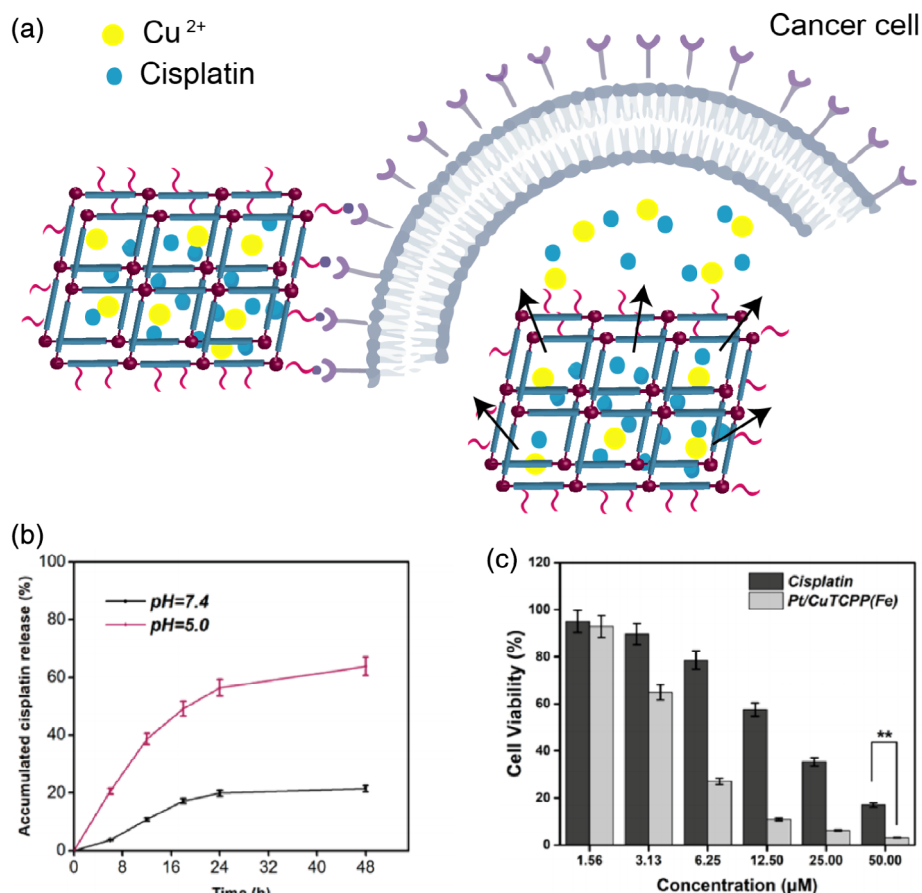
CpG samples had heightened immunostimulatory activity compared to that of mixture of OVA, ZIF-8, and CpG. This strong immune activation is likely due to ZIF-8 MOFs-facilitated co-delivery of OVA and CpG to the same antigen-presenting cells. These successful MOF-based platforms further validate the versatility and effectiveness of 2D MOFs in facilitating the release of functional antigens.

2D MOFs have also recently been engineered for efficient delivery of nucleic acids, specifically small interfering RNAs (siRNA). ZIF-8 MOF has previously been used for delivery of small molecules and antigens because of its high surface area and pH-responsiveness (Sun et al., 2012; Zhuang et al., 2020). Feng and team used combination of ZIF-8 and polydopamine nanoparticles (PDAs) to form a pH-sensitive scaffold called PZ for controlled delivery of siRNA (Feng et al., 2020). Therapeutic efficacy of siRNA loaded PZ (PSZ) were studied using in vitro (HeLa cells) and in vivo (Balb/c mice) models. In in vitro studies, PSZ samples showed increased cellular uptake of siRNA and increased gene silencing with about ~70% efficiency. Similarly, in vivo studies also showed tumor-specific uptake of PSZ and increased anticancer efficacy in mice treated with PSZ and photothermal therapy. Similar 2D MOF-based platform was developed by He and team for the delivery of combination anticancer therapy. A hexagonal 2D MOF with ~100 nm diameter and ~30 nm width was reported for co-delivery of cisplatin and siRNAs to drug resistant ovarian cancer cells (He et al., 2015). 2D MOFs used in this study are based on $Zr_6(\mu_3-O)_4(\mu_3-OH)_4$ as secondary building units (SBUs) and dicarboxylate as bridging ligands. High connectivity of the SBUs and the strong interaction between zirconium and oxygen imparts their stability in aqueous medium. Their high porosity allows efficient encapsulation of cisplatin while coordination to Zr sites facilitate siRNAs attachment to the 2D MOF surface. These 2D MOFs enhanced cellular uptake of negatively charged siRNAs compared to uncharged siRNA. Thus, 2D MOFs co-loaded with cisplatin and siRNAs showed enhanced cell killing efficiency against multi-drug resistant genes in drug resistant ovarian cancer cells via

FIGURE 5 2D MOFs used for drug delivery applications.

(a) Schematic representation of 2D MOFs used for delivery of cisplatin and Cu into the cancer cells.

(b) Accumulated release of cisplatin from Cu-TCPP(Fe) nanosheets at pH 5.0 and 7.4. (c) Significant reduction in viability of A549 cells were observed upon treatment with Cu-TCPP(Fe) compared to that of cells treated with free cisplatin (Li et al., 2018). Copyright 2018, American Chemical Society



sensitization (He, Lu, Liu, & Lin, 2014). These MOF-based delivery systems pave a way for expanding the use of MOFs in diverse combination therapeutic strategies.

4.3 | Photodynamic therapy

Besides chemotherapy, 2D hybrid MOFs have also gained attention as promising photosensitizers for photodynamic therapy (PDT). Hypoxic environment that is often observed in many solid tumors reduces the efficacy of PDT. In the presence of light, photosensitizers like porphyrins can be used to convert molecular oxygen into singlet oxygen thereby improving the therapeutic efficacy of PDT. Loading of porphyrin in 2D MOFs can enable the hybrid structure to enable effective conversion of surrounding tissue oxygen into cytotoxic singlet oxygen (reactive oxygen species) causing temperature increase in the cells. This effective photothermal conversion in turn causes enhanced apoptosis and necrosis of cells making porphyrin-based 2D MOFs an effective oxygen sensor in cells.

Recently, a porphyrin derivative, 5,15-di(*p*-benzoato)porphyrin (H_2DBP) was used to form DBP-UiO MOFs to be used as a potential photosensitizer towards PDT for resistant head and neck cancer (Figure 6a; Schellenberg et al., 2014). DBP-UiO nanoplate with ~ 100 nm diameter and ~ 10 nm thickness can efficiently generate singlet oxygen due to site isolation of porphyrin ligands (Figure 6b). These nanoplates can also increase intersystem crossing (ISC) by heavy metal Hf centers, and facilitate the diffusion of nascent singlet oxygen through porous DBP-UiO nanoplates. In this study, DBP-UiO has been demonstrated as a promising candidate for PDT both in vitro and in vivo studies. This resulted in complete eradication of head and neck cancer in 50% of mice receiving a single dose, while no such therapeutic effect was observed in the mouse group treated with only H_2DBP ligand (Figure 6c,d; Lu, He, & Lin, 2014). It was also reported that the development of chlorine-based plate like 2D MOFs (diameter 100–200 nm, width 3.3–7.5 nm) called DBC-UiO, using partially reduced form of DBP as ligand, demonstrated improved photophysical properties of DBC-UiO compared to DBP-UiO. DBC-UiO also resulted in greater PDT cytotoxicity in colon cancer cells, and in the mouse model of two different colorectal adenocarcinoma cell lines.

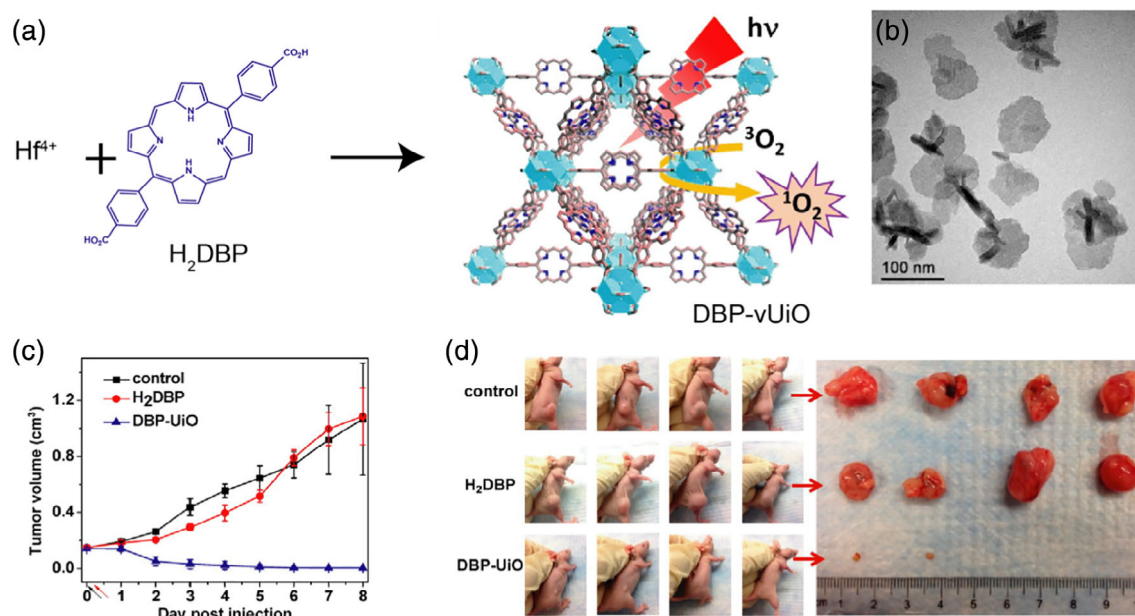


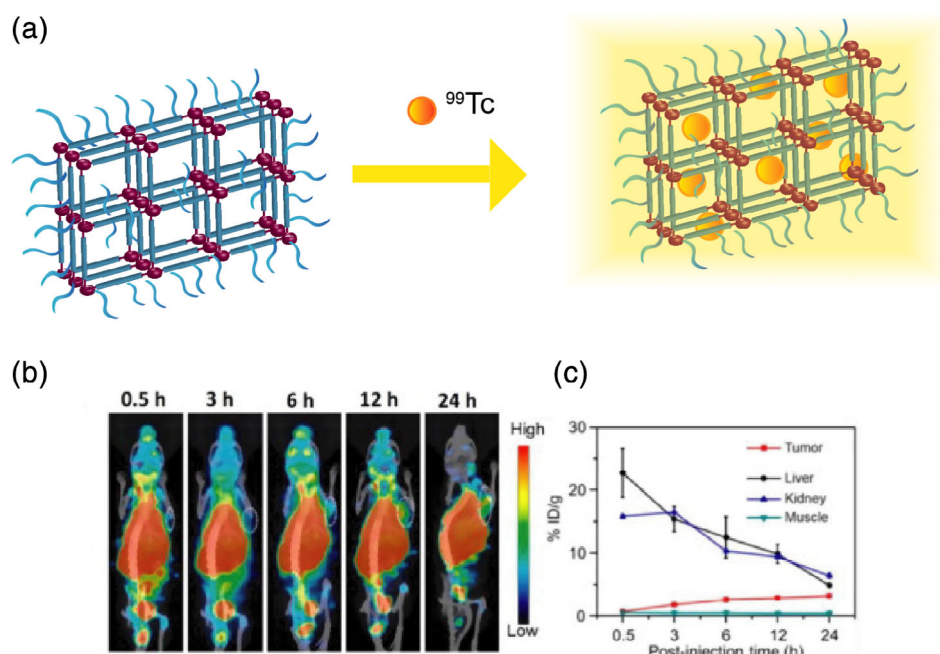
FIGURE 6 2D MOFs for photodynamic therapy (PDT). (a) Scheme for the synthesis of hafnium-and porphyrin-based MOF. (b) TEM image of DBP- Uio MOF with nanoplate morphology. (c) PDT caused improved tumor growth inhibition in mice treated with DBP- Uio MOFs. (d) DBP- Uio MOFs resulted in tumor size shrinkage after 8 days of PDT treatment. (Reproduced with permission from Schellenberg et al. (2014). Copyright 2014, Journal of the American Chemical Society)

Copper-based 2D MOFs have also been used as photosensitizers for PDT upon near-infrared (NIR) activation. Li and team fabricated NIR-sensitive copper- tetrakis(4-carboxyphenyl) porphyrin (Cu-TCPP) using solvothermal method (Li, Liu, et al., 2018). Cu-TCPP MOFs were observed to have low toxicity in vitro and in vivo and also successfully generated singlet oxygen in vitro when exposed to NIR laser. These MOFs were then delivered to human osteosarcoma (Saos-2) cells in combination with PDT and photothermal therapy (PTT). Cell mortality increased up to ~90% in the group exposed to combination therapy of Cu-TCPP, PTT, and PDT. In vivo studies using nude mice with Saos-2 tumors showed that the combination approach resulted in almost complete tumor regression. These results show promise for the use of 2D MOFs in combinational approach for treating cancer.

4.4 | Bioimaging

2D MOFs can be used for ion detection through chemical modification of their functional groups with fluorescent probes. This functionality enables the use of 2D MOFs in image-guided therapy for theranostic applications. Recently, Zinc and TCPP based 2D MOF nanosheets were fabricated and functionalized with PEG at its surface (Zn-TCPP@PEG) and were used as a chemo-photodynamic therapy (Figure 7a; Zhu et al., 2018). It was demonstrated that the 2D Zn-TCPP@PEG nanosheets exhibited greater efficiency in terms of light triggered ROS generation as well as doxorubicin (DOX) loading compared to bulk Zn-TCPP@PEG nanoparticles. This further resulted in greater anti-cancer effect of DOX-loaded 2D Zn-TCPP@PEG nanosheets in vivo. Additionally, in vivo tracking of these nanosheets were enabled by chelating $^{99\text{m}}\text{Tc}$, a gamma emissive diagnostic radioisotope, to the TCPP component of 2D Zn-TCPP@PEG nanosheets. Single photon emission computer topography (SPECT) was used to track the nanosheets after injecting into the Balb/c mice. Uptake of the nanosheets in various regions of the mice were quantified using SPECT images which in turn showed time-dependent homing of nanosheets at the tumor site. These results highlight the potential use of 2D Zn-TCPP MOFs as a nano-theranostic platform. Similarly, Chao and co-workers also fabricated a PEGylated porphyrin-based MOF, $^{99\text{m}}\text{Tc-Hf-TCPP-PEG}$, that was labeled with $^{99\text{m}}\text{Tc}$ (Figure 7a). This labeling was quantitatively assessed in vivo by injecting these MOFs into the tumor site. Labeled MOFs showed greater accumulation in the tumor compared to that of the free radioisotope (Figure 7b). Diffusion of the labeled MOFs in other organs was also assessed in the homogenized organs by quantifying Hf^{4+} using mass spectrometry (Figure 7c). These studies show that variety of 2D MOFs can be used for tracking the tumor location for effective anti-cancer therapy.

FIGURE 7 2D MOFs for bioimaging applications. (a) Schematic representation of radioactive isotope-tagged 2D MOFs for bioimaging. (b) *in vivo* SPECT images of tumor-bearing Balb/c mice post i.v. injection of ^{99m}Tc -Hf-TCPP MOFs. (c) Quantitative distribution of the MOFs in tumor, liver, kidney, and muscle. (Reprinted with permission from Zhu et al. (2018). Copyright 2019, Coordination Chemistry Reviews)



Another study showed the use of aluminum (III)-based MOFs as a bioimaging agent. Al-MOF was combined with iron and Rhodamine B (RhB) to form $\text{Fe}_3\text{O}_4/\text{RhB}@\text{Al-MOFs}$ (Gao, Gao, Qi, & Han, 2019). The emission spectra of these MOFs had two maxima, one at 440 nm (from Al-MOF) and another at 610 nm (from RhB). *In vitro* studies showed that the fluorescent signal at 440 nm was selectively enhanced with increasing concentration of magnesium ions (Mg^{2+}). Sensitivity tests of these MOFs to intracellular Mg^{2+} using HeLa cells showed that the 440 nm fluorescence signal was higher in cells treated with 1 mM Mg^{2+} compared to that of the control group. Collectively, these imaging studies further demonstrates the potential use of 2D MOFs as fluorescent probes in bioimaging applications in live cells.

4.5 | Biosensing

In addition to therapeutic and imaging potential of 2D MOFs, recently there have been advances in the use of 2D MOFs for biosensing. In recent years, certain metal cations including Zn, Fe, Co, Cu, and Zr have been observed to possess exceptional ability to form MOFs with peroxidase-like characteristics using organic linkers like TCPP ([tetrakis 4-carboxyphenyl] porphyrin) (Chen et al., 2018; Qin, Wang, Liu, & Wei, 2018) and HBTC-1 (Tan et al., 2017). In particular, 2D MOFs enable determination of biological entities based on dimensionality and chemical composition, increased specificity for glucose sensing, DNA discrimination, and cancer biomarker detection through selective conjugation of aptamer.

In metabolic cellular cycles, the phosphates play disparate and essential roles in several key biological functions including cell signaling and energy transfers among cellular organelles. To perform all the complex cycles, phosphates transform into a variety of biochemical entities such as ATP, ADP, AMP, PPI, and Pi. Cellular levels of these entities are a direct indication of healthy metabolic processes. Their hydrolytic interconversion from one to another during several cellular events is a continuous mechanism and any dysregulation could potentially cause metabolism-related disorders. For instance, irregular hydrolysis of ATP to ADP conversion can indicate hypoglycemia, ischemia or/and circulatory shock. To ascertain the phosphate levels in such complex biochemical hydrolytic processes, increased surface area of 2D MOFs render high enzyme-mimicking activity that can be appropriately designed as an array of sensors (Qin et al., 2018). Qin and co-workers developed metal ions (M) conjugated TCPP-Fe (III) MOFs ($\text{M} = \text{Zn}, \text{Co}, \text{or Cu}$) based on an array of nanozyme sensors, which were able to discriminate the phosphate levels during hydrolysis in biological settings because of their peroxidase-mimicking activity (Figure 8a). The principle of the detection was based on the strong ionic interaction of metal ions (from MOFs) with the phosphates and not their organic ligands (Figure 8b). This led to the collapse of the MOFs structure which is a direct

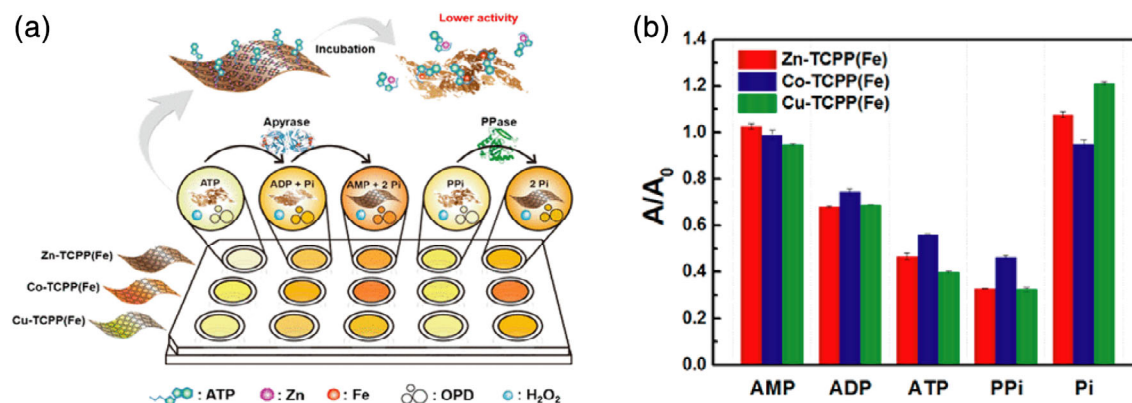


FIGURE 8 2D MOF-based sensor arrays. (a) Scheme of 2D MOF nanozyme sensor arrays to discriminate phosphates. (b) Catalytic activity with the nanozymes were differentially modulated based on the presence of different phosphates. (Reprinted with permission from Qin et al. (2018). Copyright 2018, Analytical Chemistry)

indication of the phosphate level in the solution. The corresponding colorimetric changes were observed and quantified by using molybdenum blue with UV-visible spectrophotometer after digesting them in an organophosphate solution.

The enzyme-mimicking activity of 2D MOFs can further be enhanced by growing low reactive transition metals like platinum (Pt) on their surface to form hybrid nanosheets (Chen, Qiu, et al., 2018). Surface tailoring of MOFs with Pt can potentially extend biological applications of MOFs. One such application involves the use of Pt nanoparticles (NPs)-coated Cu-TCPP(Fe)MOFs for glucose sensing via detecting hydrogen peroxide (H₂O₂) formation at the cellular level upon oxidation of glucose by glucose oxidase (Chen, Qiu, et al., 2018). As a proof-of-concept, this study used colorimetric based changes using TMB (3,3',5,5'-tetramethylbenzidine) solution mixed with H₂O₂ both in the presence and absence of Pt NPs decorated MOFs (Pt-Cu-TCPP(Fe)) and Cu-TCPP(Fe). The obtained results indicated more than a two-fold increase in the absorbance signals with Pt NPs on MOFs surface, thus rendering their utility for high precision detection of glucose levels. Furthermore, the specificity of MOFs' glucose sensing was established by using other forms of glucose; namely fructose, lactose and maltose.

Decoration of NPs onto the MOFs surface has thus been recognized as a significant multiplier to improve the accuracy level of glucose sensing. Bimetallic NPs were also decorated on the MOFs surface in order to increase the detection level of H₂O₂ up to the nanomolar level (Tan et al., 2017). In this study, researchers synthesized Cu (HBTC)-1/Fe₃O₄-Au nanosheets where the MOFs surfaces were tailored with magnetite and gold NPs. They observed that the use of NPs led to an increase in detection limit for H₂O₂. Precisely, the detection range was found to be 2.86–71.43 nM which would in turn render the glucose detection range between 12.86 and 257.14 μ M. Such a bimetallic configuration further enabled them to regulate the catalytic activity of the system by conjugating the MOF surfaces with single strand DNA (ssDNA) via π - π stacking. These regulatory systems can thus be used for cancer cell detection specifically by determining the presence of reactive oxygen species (ROS) and quantifying them at nanomolar level. This group used ssDNA conjugated with NP-coated MOFs on human breast cancer cell lines (MCF-7). Due to synergistic effect of NPs and MOFs in the system, ssDNA expressed a high level of quenching leading to accurate determination of ROS in the cancer cells.

Despite the accuracy of bimetallic 2D MOFs in cancer cell detection, this system has limitations including high detection range. Thus, this system cannot be used for early stage diagnosis where the expressed markers are in the range of picograms. Alternate strategies have been used to circumvent this limitation including the use of aptamers that can target and measure tumor markers. For example, zirconium-based MOFs (521-MOFs) have strong affinity for oligonucleotides sequences that can aid in immobilization of specially designed protein sensitive aptamers (He et al., 2018). This group of aptamer-functionalized MOFs was used to detect early marker protein mucin 1 (MUC1). Configured electrochemical MOF-aptasensor was coupled with surface plasmon resonance activity to give rise to high detection sensitivity for MUC1 to the limit as low as 0.12 pg ml⁻¹ by using electrical impedance method. This approach further highlights the use of functionalized MOFs for effective biosensing applications.

4.6 | Regenerative medicine and 3D printing

High tunability and low toxicity of 2D MOFs makes them ideal candidates for implantable medical devices. However, MOFs are typically in powder form and improving physical integrity without compromising chemical properties of MOFs has been challenging. To circumvent this limitation, 3D printing approaches have been combined with MOFs to yield MOF-infused mechanically strong composites (Evans et al., 2018). 3D printing is an additive manufacturing technique to obtain solid object via layer-by-layer deposition of ink. This approach is useful for generating tissue engineered grafts or in vitro models for bioengineering (Ashammakhi et al., 2019; Chimene et al., 2020; Deo, Singh, Peak, Alge, & Gaharwar, 2020; Peak, Singh, Ma, Chen, & Gaharwar, 2019). For example, Evans and co-workers formed MOF-thermoplastic polymer composites using ZIF-8 and PLA via extrusion-based additive manufacturing technique. These hybrid composites successfully maintained mechanical rigidity, high porosity, and increased surface area. Another study combined a variety of MOF powders with hydroxyethyl cellulose as a binder and poly(vinyl alcohol) as a plasticizer to achieve optimal shear-thinning properties that is otherwise difficult to achieve in inks containing powders (Dhainaut, Bonneau, Ueoka, Kanamori, & Furukawa, 2020). These inks were then 3D printed via extrusion to form solids with similar structural and porous properties as that of the powders. Mechanical testing of these solids showed that higher compressive strength was achieved with the use of 2D MOFs and cellulose binders.

In addition to zirconium-based MOFs, cobalt MOF (Co-MOF)-based conductive matrix was also fabricated using extrusion printer. Co-MOF was 3D printed using a binder, Pluronic F127, resulting in a mechanically strong porous matrix (Lyu et al., 2019). This matrix was also found to be conductive specifically for increasing specific energy of Li-O₂ batteries. These strategies could be adopted in the future to enable 3D bioprinted scaffolds for tissue engineering applications including bone tissue regeneration (Shadjou & Hasanzadeh, 2015). However, MOF composites fabricated using 3D printing often result in rigid matrices consequently compromising MOF porosity and causing particle aggregation. To circumvent this challenge, Liu and co-workers fabricated hydrogels with MOF ligands using direct ink writing 3D printing approach (Liu, Erol, & Gracias, 2020). Highly stretchable composites were first grown with uniform distribution of MOF within the hydrogel. 3D printed composites were then subjected to UV curing, in situ MOF growth, and ionic crosslinking to yield mechanically tunable scaffolds (Figure 9) (Liu et al., 2020). Optimal uniform pore distribution was achieved with this formulation as indicated by the SEM images of the cross-section of cured hydrogels. Mechanical properties of this composite were further tuned by varying monomer concentrations and this tunability was confirmed using tensile strength tests. Similar 3D printing approaches can be used in the future to fabricate flexible MOF composites with tunable properties making them promising candidates for tissue scaffolds.

Recently, 3D printed MOF scaffolds were used for anti-tumor and tissue regeneration applications. Dang and co-workers designed and 3D printed a β -tricalcium phosphate (TCP)-based scaffold using pluronic-F127 as a binder (Dang et al., 2020). This scaffold was then incorporated within Cu-TCCP nanosheets using an in-situ method (Figure 10a). Cu-TCCP-TCP scaffolds were used to kill bone tumor cells and repair bone defects that were caused as a result of tumor excision (Figure 10b). Tumor cells were killed by using Cu-TCCP's intrinsic photothermal properties to irradiate the scaffold with NIR light. Osteosarcoma cells were first cultured on the surface of Cu-TCCP-TCP scaffolds and were exposed to NIR light for 10 minutes after 24 hours of culturing. Viability of the cells was significantly reduced due to

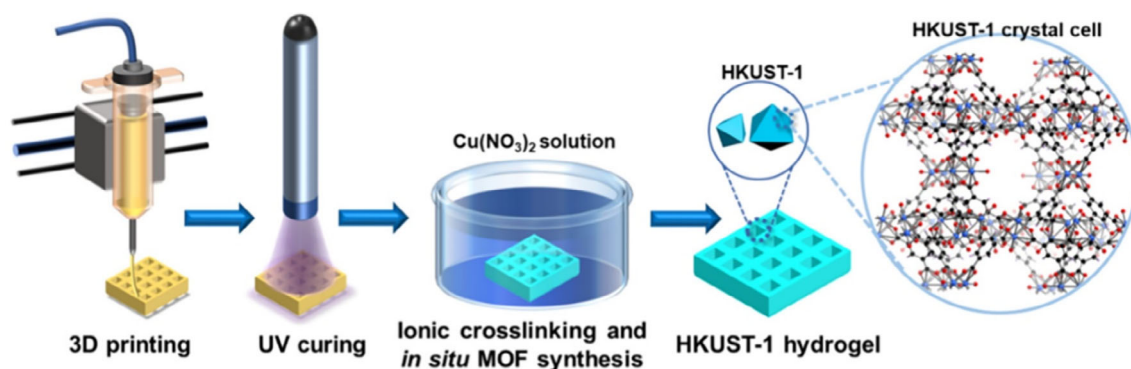


FIGURE 9 Fabrication of tunable hydrogel-MOF composites by 3D printing hydrogel MOF precursor mixture followed by UV curing of the printed structure. The cured structure was then ionically crosslinked in $\text{Cu}(\text{NO}_3)_2$ solution to facilitate in situ synthesis of HKUST to yield hydrogel-MOF composites. (Reprinted with permission from Liu et al. (2020). Copyright 2020, American Chemical Society)

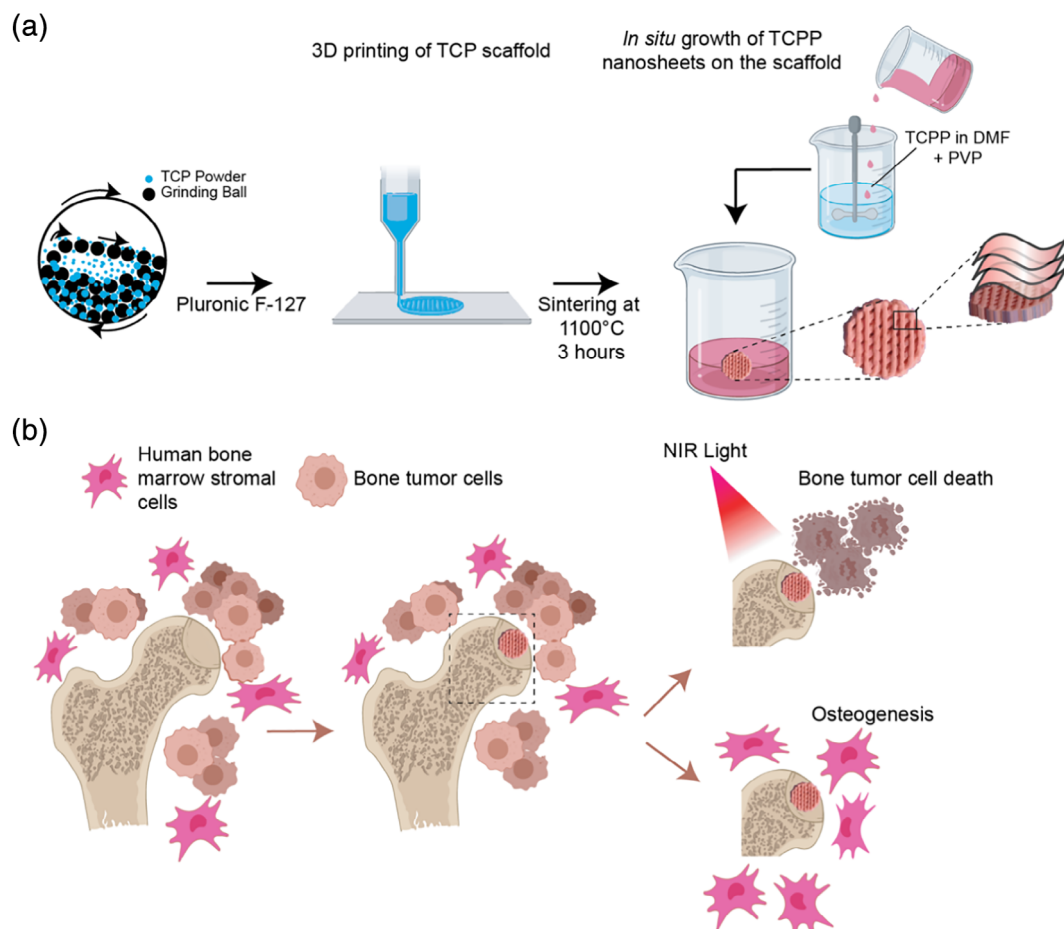


FIGURE 10 MOFs loaded scaffolds used to ablate bone tumors and promote osteogenesis at the defect site. (a) Scheme of fabrication of 3D printed TCP scaffolds and in situ growth of Cu-TCCP nanosheets on the surface of the scaffold. (b) Cu-TCCP-TCP scaffolds enabled killing of bone tumor cells using the thermal energy generated upon NIR light activation and also promoted osteogenesis at the bone defect site because of release of bioactive ions Cu^{2+} , PO_4^{3-} , and Ca^{2+} . Created with BioRender.com

the hyperthermia induced after NIR irradiation of Cu-TCCP-TCP scaffolds. Subsequently, in vivo studies were also carried out in nude mice with subcutaneous tumor model by implanting Cu-TCCP-TCP scaffolds into the center of the tumors. Assessment of the tumor size 18 days after tumor implantation indicated that tumor growth was inhibited in the group with Cu-TCCP-TCP scaffolds that were irradiated with NIR light. Histological analysis also showed evidence of cell necrosis in the mice group that were implanted with Cu-TCCP-TCP scaffolds. In addition to the photothermal-assisted anti-tumor activity, Cu-TCCP-TCP scaffolds were also shown to upregulate osteogenesis-related genes, OCN and RUNX2, and consequently promote osteogenic differentiation in vitro. Osteogenesis capability of Cu-TCCP-TCP scaffolds was also assessed in vivo. Regeneration of new bone tissue was observed 8 weeks after implantation of Cu-TCCP-TCP scaffolds on rabbit femoral defect models. This mechanically strong 3D printed MOF-scaffold enabled integration of photothermal-induced ablation of bone tumor and bone regeneration at the site of bone defects. Multifunctional scaffolds similar to that of Cu-TCCP-TCP scaffolds will pave way for new generation biomaterials focused on tissue engineering applications.

5 | CONCLUSION

2D MOFs have unique properties including high surface area, tunable functionality, and high porosity enabling them to be used for biomedical applications. In this review, the benefits of MOFs have been highlighted for various biomedical applications including therapeutic delivery, bioimaging, biosensing, photodynamic therapy, and tissue engineering. High surface area of 2D MOFs allows for high loading of therapeutic agents and smaller size of 2D MOFs enable

increased tumor cell uptake of these drug-MOF complexes through enhanced permeability and retention effect. External surface of MOFs can also be modified for conjugation of fluorophores to enable live cellular tracking of MOFs. This tunability combined with the high porosity of 2D MOFs enable them to be used for sensing of biomolecules. 2D MOFs have also been recently identified as promising photosensitizers and can thus be leveraged for photodynamic therapies against cancer. Additionally, 2D MOFs can also be 3D printed using biocompatible binders to fabricate scaffolds that can further be used for tissue engineering applications.

Notwithstanding the ample opportunities provided by 2D MOFs as advanced materials with subtle functional characteristics, there are few unaddressed questions on how to expedite development of 2D MOFs for biomedical applications. Specific characterization techniques are needed to demonstrate the difference between bulk MOFs and 2D MOFs. This will effectively characterize the structure of 2D MOFs and aid in understanding their defect sites to better optimize synthesis protocols. The structural versatility of the 2D MOFs could be strengthened if we expand our understanding of crystallography of 2D MOFs using computational and advanced characterizations. In addition, scaling up the production of mechanically stable 2D MOFs using cost effective synthesis while controlling the size, shape, and porosity of MOFs is critical and warrants more focus in future studies. In-situ and *in-operando* experiments combined with durability aspects of 2D MOFs are recommended in order to promote device-based applications. This would expedite the design and fabrication of 2D MOFs for controlled particle size especially useful for optical and photothermal applications. The challenges with preparing ultrathin 2D MOFs also needs to be addressed to ensure successful application of MOFs in biosensing and biomimetic applications. The problem of aggregation of 2D MOFs and the subsequent instability are currently also limiting their use in biomedical applications. Therefore, processing strategies to improve stabilization of MOFs are needed. Upon optimizing 2D MOF synthesis strategies, there is also need for extensive toxicology and biocompatibility studies to aid in translation efforts of 2D MOFs. Judicious selection of input materials including biocompatible metals, and effective non-toxic linker materials can overcome current challenges. Further, addressing these challenges could help in optimized design and fabrication of MOFs that can further expedite clinical translation of 2D MOFs.

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS

Shreedevi Arun Kumar: Conceptualization; investigation; methodology; visualization; writing-original draft; writing-review and editing. **Bhuvaneshwari Balasubramaniam:** Conceptualization; data curation; investigation; methodology; visualization; writing-original draft; writing-review and editing. **Sukanya Bhunia:** Data curation; investigation; writing-original draft. **Manish Jaiswal:** Data curation; investigation; writing-original draft. **Kartikey Verma:** Formal analysis; methodology; writing-original draft. **Prateek Prateek:** Formal analysis; visualization. **Ali Khademhosseini:** Conceptualization; methodology; writing-review and editing. **Raju Gupta:** Conceptualization; formal analysis; funding acquisition; project administration; visualization; writing-original draft; writing-review and editing. **Akhilesh Gaharwar:** Conceptualization; funding acquisition; project administration; visualization; writing-original draft; writing-review and editing.

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