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Cellulose-MOFs hybrid materials: Chemistry and mechanism of applications in biomedical - A review

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A R T I C L E I N F O

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A B S T R A C T

Rising costs and performance limits of modern biomedical materials motivate the search for advanced, biocompatible alternatives. Cellulose-based metal-organic frameworks (cellulose-MOFs) emerge as distinctive hybrids combining renewable polymer chemistry with tunable porous architectures, enabling uncommon structure–function relationships. Their large surface area, controllable pore size, adaptable functional groups, and efficient host–guest interactions underpin diverse biomedical functions. Till now, no comprehensive, application-focused review has systematically summarized cellulose-MOFs synthesis for biomedical applications. This review critically analyzes cellulose-MOFs, emphasizing mechanistic links between chemistry, synthesis routes, interfacial interactions, and biomedical performance, rather than cataloging applications alone. Antibacterial action, targeted drug delivery, and sensing/biosensing are discussed through comparative insights. The article identifies unresolved challenges and proposes future research pathways to rationally design next-generation cellulose-MOFs systems, guiding researchers and clinicians alike.

1. Introduction

Though discovered in 1965, metal–organic frameworks (MOFs) have recently experienced renewed scientific attention as a class of highly coordinated materials and have emerged as one of the most diverse, dynamic, and rapidly expanding areas of chemical research (Bailey et al., 2017; Li et al., 2017; Rosi et al., 2003; Safarifard & Morsali, 2015; Zhou et al., 2021). MOFs are crystalline microporous materials constructed from metal ions or clusters interconnected by organic linkers through coordination bonds, forming two- or three-dimensional architectures. Owing to their tunable pore sizes, high surface areas, chemical stability, and abundant active sites, MOFs have demonstrated superior performance compared to conventional materials such as activated carbon and mesoporous silica (Abdelhameed et al., 2016; Block et al., 1962; Mohan et al., 2023a, 2024a, 2024b, 2024c; Tomic, 1965). These attributes have enabled their application across diverse fields (Fig. 1), including catalysis, sensing, energy, and increasingly, biomedicine (Mohan et al., 2023b; Rauf et al., 2020).

Driven by these multifunctional properties, extensive investigations have been conducted to exploit MOFs for biologically relevant applications (Duan et al., 2019; Ghahremani et al., 2021; Zhu et al., 2019). In particular, biomedical applications have gained momentum due to the growing recognition of MOFs' tunable cytotoxicity, biocompatibility, and *in vivo* bioactivity (Abdelhameed et al., 2017b). However, many conventional biomedical materials still suffer from inherent design limitations, including poor chemical stability, uncontrolled degradation in physiological environments, and insufficient drug-loading efficiency

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Nomenclature

AgNPs	silver nanoparticles
AI	artificial intelligence
AuNPs	gold nanoparticles
BDC	benzenedicarboxylate
CA	cellulose acetate
CMC	carboxymethyl cellulose
Cys	cysteine
DMF	dimethylformamide
DOX	doxorubicin
GO	graphene oxide
HSV	hue-saturation-value
LCA	life cycle assessment
MeOH	methanol
ML	machine learning
MOFs	metal-organic frameworks
SBMCP	nanoreactor colorimetric paper
PBS	poly (Butylene succinate)
PVA	poly(vinyl alcohol)
PVP	polyvinylpyrrolidone
ROS	reactive oxygen species
5FU	5-fluorouracil

(Lei et al., 2018). For example, traditional dry wound dressings fail to promote effective wound healing due to their limited moisture retention and lack of antibacterial functionality (Su et al., 2021). In contrast, MOFs provide a promising platform for moist wound environments owing to their intrinsic water-retention capacity and antimicrobial potential (Fouda et al., 2013; Gao & Cranston, 2008). Furthermore, MOFs have emerged as highly versatile drug-delivery carriers, offering controlled and stimuli-responsive release governed by pore chemistry, framework stability, and host–guest interactions (Cai et al., 2019; Rojas et al., 2018; Yang & Yang, 2020).

Despite these advantages, the direct biomedical deployment of MOFs is hindered by challenges such as metal ion toxicity, framework dissolution, non-specific biodistribution, and limited bioaccessibility (Quartapelle Procopio et al., 2011). To overcome these constraints, recent research has increasingly focused on biomolecule-based and biodegradable MOFs that integrate naturally derived components to enhance safety and functionality. In this context, the hybridization of MOFs with renewable biopolymers—particularly cellulose—has emerged as a strategically important approach. Cellulose–MOFs hybrid materials combine the structural tunability of MOFs with the biocompatibility, biodegradability, and mechanical robustness of cellulose, offering an environmentally responsible pathway for next-generation biomedical materials (H S et al., 2020; Quartapelle Procopio et al., 2011).

Cellulose, derived from lignocellulosic biomass, represents the most abundant and sustainable natural biopolymer on Earth (Ghahremani et al., 2023b; Liu et al., 2015; Wang et al., 2015). Accounting for nearly half of lignocellulosic dry mass, cellulose is a linear polysaccharide composed of β-1,4-glycosidic-linked d-glucose units, exhibiting high crystallinity and structural integrity. Its renewability, non-toxicity, biodegradability, and chemical modifiability have established cellulose as a cornerstone material for biomedical engineering (Ghahremani

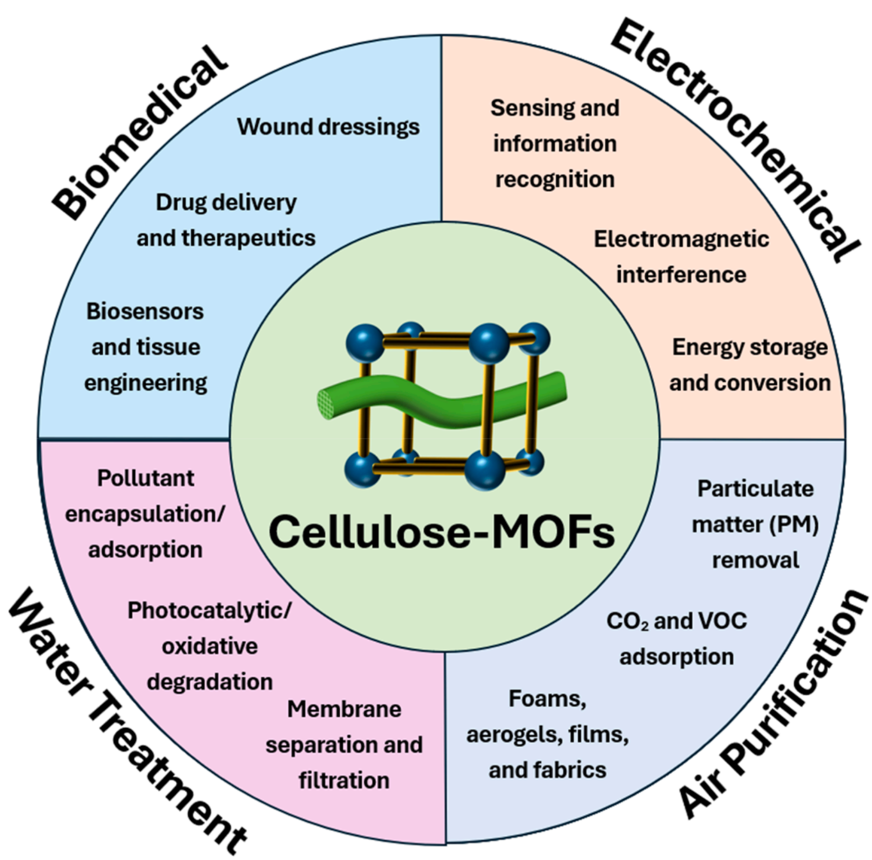

Fig. 1. Applications of cellulose-MOFs hybrid materials in a wide range of fields, including biomedical.

et al., 2023a; Pongchaiphol et al., 2021; Rakhshaei & Namazi, 2017). Among its derivatives, carboxymethyl cellulose (CMC) has attracted significant interest due to its pH responsiveness, excellent biocompatibility, and biodegradability, making it particularly suitable for drug delivery, wound healing, and tissue engineering applications (Javanbakht et al., 2019; Yadollahi et al., 2015; Rasoulzadeh & Namazi, 2017; Tsai et al., 2017).

The integration of cellulose and its derivatives with MOFs enables effective immobilization and dispersion of MOFs through coordination between metal centers and cellulose functional groups, particularly carboxyl moieties (Abdelhameed et al., 2016; Wang et al., 2020). This synergistic interaction not only enhances the structural stability and biocompatibility of MOFs but also expands their functional versatility for biomedical use. Consequently, cellulose–MOFs hybrid materials have emerged as promising candidates for antibacterial wound dressings, controlled drug delivery systems, and biosensing platforms.

Although research activity in this area has increased substantially, a critical gap remains in the literature. Existing review articles predominantly focus on pristine MOFs (Luo et al., 2021; Ma et al., 2021; Rao et al., 2022), specific metal-based MOFs (Chen et al., 2022; Li et al., 2022), or cellulose materials alone (Seddiqi et al., 2021), often addressing isolated applications such as drug delivery. To date, a comprehensive and application-oriented review that systematically consolidates cellulose-based materials employed in MOFs synthesis specifically for biomedical applications is lacking. This absence of a unified framework limits cross-disciplinary insight and slows the rational design of next-generation hybrid biomaterials.

Therefore, the novelty of this review lies in its integrated and focused compilation of cellulose–MOFs hybrid materials for biomedical applications, bridging material design, synthesis strategies, structure–function relationships, and biological performance. This review presents a concise yet comprehensive overview of recent advances in cellulose–MOFs hybrid systems, emphasizing antibacterial wound healing, drug delivery, and biosensing applications. Fundamental aspects of MOFs and cellulose-based hybrids are discussed alongside fabrication methodologies, functional mechanisms, advantages, limitations, and future biomedical prospects. By consolidating dispersed knowledge into a single coherent framework, this review aims to stimulate innovation and guide the development of sustainable, high-performance cellulose–MOFs hybrid biomaterials.

2. An overview of cellulose-MOFs hybrid materials

Metal ions and organic molecules combine to form MOFs (Abdelhameed et al., 2017b). The most often utilized metal ions are zinc, iron, zirconium, aluminum, and copper (Cai et al., 2019). Meanwhile, some common organic linkers are amino acids, peptides, and nucleotides (Anderson & Stylianou, 2017). Organic ions or molecules (functional groups) interact with the central metal ion to form complicated coordination MOFs (Mu et al., 2019; Pilgrim & Champness, 2020; Qi et al., 2019) and can be produced in zero-, one-, two-, and three-dimensions (Abdelhamid & Mathew, 2022). These materials exhibit changeable specific surface areas, porosity, and pore diameters despite their high degree of crystallinity and extraordinary surface areas and pore volumes (Maleki et al., 2015). They are mechanically, chemically, and thermally stable and have homogeneous micropores thanks to the existence of coordination bonds in the MOFs (Giliopoulos et al., 2020; Raptopoulou, 2021; Wuttke et al., 2015). However, MOFs have a low utilization efficiency due to low mass and diffusion transfer rate between the target analyte and MOFs since only their exterior surfaces may be accessible (Kou et al., 2020; Wang et al., 2020). In addition, MOFs available in powder form are difficult to extract and limit their implications (Bej et al., 2023; Raptopoulou, 2021). As a result, MOFs manufacturing on stiff, porous substrates is crucial, both for facilitating MOFs extraction and enabling access to MOFs' minuscule pores (Yeskendir et al., 2021). Considering this, it has become popular to grow MOFs on a fiber surface. The use of a cost-effective, renewable, and environmentally friendly substrate source is crucial. Subsequently, cellulose in micro- and nano-structures is a well-fitted substrate for MOFs (Mirkovic et al., 2019).

In cellulose-MOFs, cellulose is used as a framework (Liang et al., 2016) where it acts as both a binder and a filler (da Silva Pinto et al., 2012). A computer-generated model of a generic cellulose-based MOF-199 is presented in Fig. 2. The presence of functional groups like carboxyl (COOH) and hydroxyl (OH) is crucial to interacting with positively charged metal ions to form cellulose-MOFs hybrid materials. The interaction depends on the strength of the anionic groups in cellulose, which is influenced by cellulose structure and any cellulose derivatives present. The extraction of cellulose nanocrystal (CNC) by acid hydrolysis leads to incorporating SO_3^- groups, which can help interact with metal ions, e.g., Ag^+ (Abdelhamid & Mathew, 2022). The existing OH^- group in cellulose offers functionalization to enhance the interaction with metal ions (Ghahremani et al., 2023a; Tao et al., 2023). Furthermore, a surface modification of cellulose by introducing a -COOH organic group using carboxymethylation further enhances the interaction with metal ions (Tao et al., 2023). It also promotes the *in-situ* synthesis of MOFs (Zhang et al., 2021b). Dopamine-treated cellulose contains amine and catechol functional groups, which allow the metal to make cellulose-MOFs hybrid materials (Mirkovic et al., 2019). Also, the esterification of modified cellulosic fibers can result in high metal-fiber interaction (Liang et al., 2016).

MOFs may be specifically tuned in terms of morphology, structure, and functionality by modularly tweaking the metal ions and organic ligands (Kang et al., 2017; Qiu et al., 2014; Wang et al., 2022). By combining cellulose with MOF materials, porous structures with improved flexibility and controllable topology have been created (Bunge et al., 2018; Zhang et al., 2021b). The synthesis procedure can help to obtain the desired quality of the cellulose-MOFs. The preparation technique, i.e., *in-situ* and *ex-situ* and post-treatment processing, i.e., freeze-drying, can help modify their properties for specific purposes (Abdelhamid & Mathew, 2022; Zhang et al., 2021b). Incorporation of cellulose significantly improves the physicochemical properties of cellulose–MOFs hybrid materials relative to pure MOFs, facilitating diverse functionalities and broadening their scope for advanced applications (Zhang et al., 2021b).

3. General overview of the synthesis of cellulose-MOFs hybrid materials

Numerous techniques for the synthesis of MOFs have become practical in light of the ongoing advancements in manufacturing technology, although further research is still required in this area (Rubio-Martinez et al., 2017). Scaling up MOFs synthesis conditions has been the subject of several studies on how to obtain high yields of solid products for industrial usage. Also included in several of these studies is how to achieve high yields for MOFs synthesis by optimizing the conditions (Bai et al., 2016; Stock & Biswas, 2012). As of this review, different methods have been employed for the *in-situ* or *ex-situ* growth of MOFs on porous substrates to synthesize composite materials (Molco et al., 2021). Similar to this, several methods, including *in-situ* and *ex-situ* synthesis, are used to fabricate cellulose-MOFs hybrid materials (Chen et al., 2023c).

After being synthesized in 1999, MOF-5 and HKUST-1 were two of the most widely studied MOFs in the years that followed (Bosch et al., 2017). Some of the common synthesis techniques include water/solvothermal synthesis (Zou & Liu, 2019), synthesis techniques involving microwave and ultrasonic assistance (Bakhshi et al., 2021), microemulsion-based synthesis (Sun et al., 2016), continuous flow synthesis (Bayliss et al., 2014), and electrochemical synthesis (Yang et al., 2015). The structural properties of different types of cellulose-MOFs hybrid materials have been presented in Table 1.

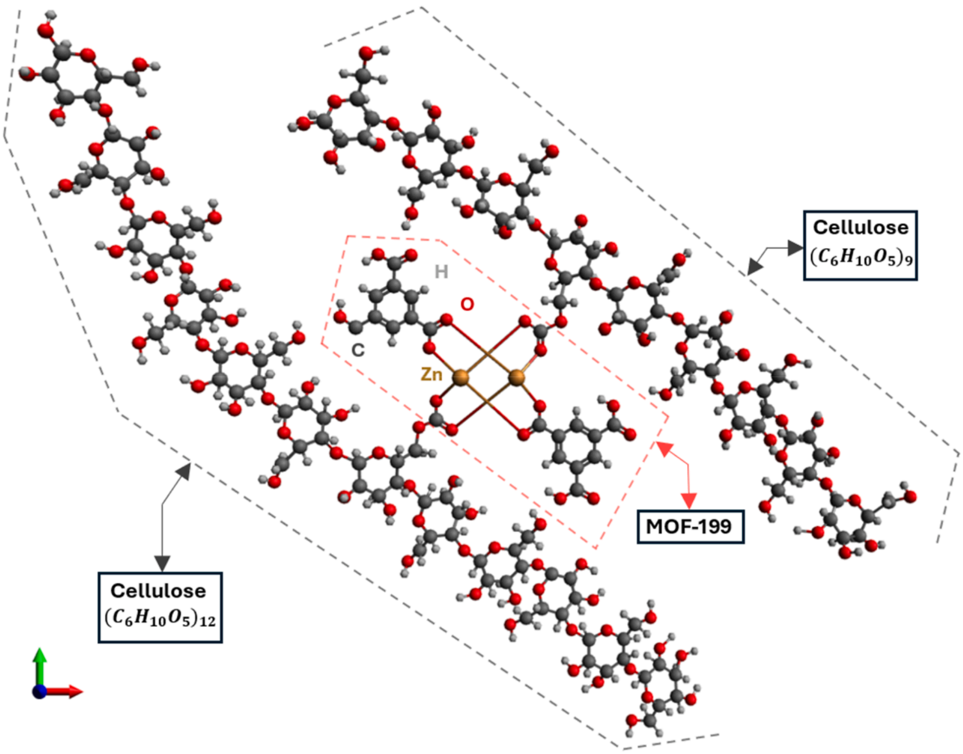

Fig. 2. Computer-generated model of a cellulose-based MOF-199 hybrid complex.

Table 1
An overview of cellulose-based metal-organic frameworks in biomedical applications.

Type of cellulose	Type of MOFs	Synthesis	Applications	Efficiency	Ref
Carboxymethylated cellulose	AgNPs@HKUST-1@ CFs	*In-situ* synthesis	Antibacterial	-	Duan et al. (2018)
	Cu-BTC based MOF	*In-situ* synthesis		100%	Rodríguez et al. (2014)
	CMC/TC@UiO-66	*Ex-situ*	Antibacterial wound dressing	High	Javanbakht et al. (2021)
	CMC/MOF-5/GO	*Ex-situ*	Anticancer drug delivery	Controlled release	Javanbakht et al. (2018)
	HA/DMOF	*Ex-situ*	Bone tissue engineering	-	Sarkar et al. (2019)
Cotton	MOF $Cu_3(NH_2BTC)_2$	Layer-by-layer	Antibacterial	Inhibit bacterial growth	Rubin et al. (2018)
Cotton fabric	BioMOF@cellulose	*In-situ* synthesis	Wound and cancer dressing	-	Noorian et al. (2019)
	MOF-199	*In-situ* synthesis	Antibacterial	-	López-R et al. (2022)
	ZIF-8@PDMS	*In-situ* synthesis		95-99%	Yang et al. (2020)
	Cotton@silicate@ZIF-67	*In-situ* synthesis	Antimicrobial	Good to excellent	Emam et al. (2020)
Woven cotton fabrics	PCN-224/WCF	*In situ* synthesis	Antibacterial photodynamic inactivation	High photobactericidal activity	Nie et al. (2020)
Bleached kraft pulp fiber	HKUST-1/CF	*In-situ* synthesis	Antibacterial	Effective	Wang et al. (2015)
Softwood Kraft pulp board	ZIF-8@CF and Ag-MOFs@CF	*In-situ* synthesis	Antibacterial	Remarkable	Ma et al. (2018)
Ethyl cellulose	ZIF-8@ethyl cellulose	*Ex-situ*	Skin tissue engineering	Possible for skin tissue-engineered constructs	Doustdar & Ghorbani (2022)
Pristine cotton fabric	ZnBDC-Ctn-8	Layer-by-layer (LbL)	Antimicrobial	Excellent	Lu et al. (2018)
Cellulose nanofiber (CNF)	Ag-MOFs@CNF@ZIF-8	*In-situ* synthesis	Antibacterial	Excellent	Ma et al. (2018)
Corncobs	HKUST-1/OCBs	*In-situ* synthesis	Microbial inactivation	Excellent	Duan et al. (2019)
Desized and bleached cotton plain-woven fabric	BioMOF	*In-situ* synthesis	Antibacterial and drug delivery	Controlled delivery	Noorian et al. (2019)
Naturalresized and bleached cotton	Cu_3(NH2BTC)$_2$	Layer-by-layer dip coating process	Kill bacteria	Excellent	Rubin et al. (2018) Rubin et al. (2018)
Cellulose acetate	CA/ZIF-8@enzyme	*In-situ* synthesis	Enzymatic biosensors	Excellent stable	Tan et al. (2024)
Cellulose paper	ZIF-8@enzyme	*In-situ* synthesis	Biosensor	Capable of detecting glucose and uric acid	Kou et al. (2020)

3.1. *In-situ synthesis of cellulose-MOFs hybrid materials*

In in-situ synthesis techniques, precursor components of MOFs, namely metal ions and organic linkers, are introduced into cellulose substrates prior to the formation of cellulose-based architectures such as aerogels and foams (Fig. 3a,b) (da Silva Pinto et al., 2012). During this process, the abundant hydroxyl (–OH) groups of cellulose play a crucial mechanistic role by coordinating with metal ions through lone-pair donation, thereby anchoring metal centers onto the cellulose backbone and creating localized nucleation sites (Lestari et al., 2022). Unlike

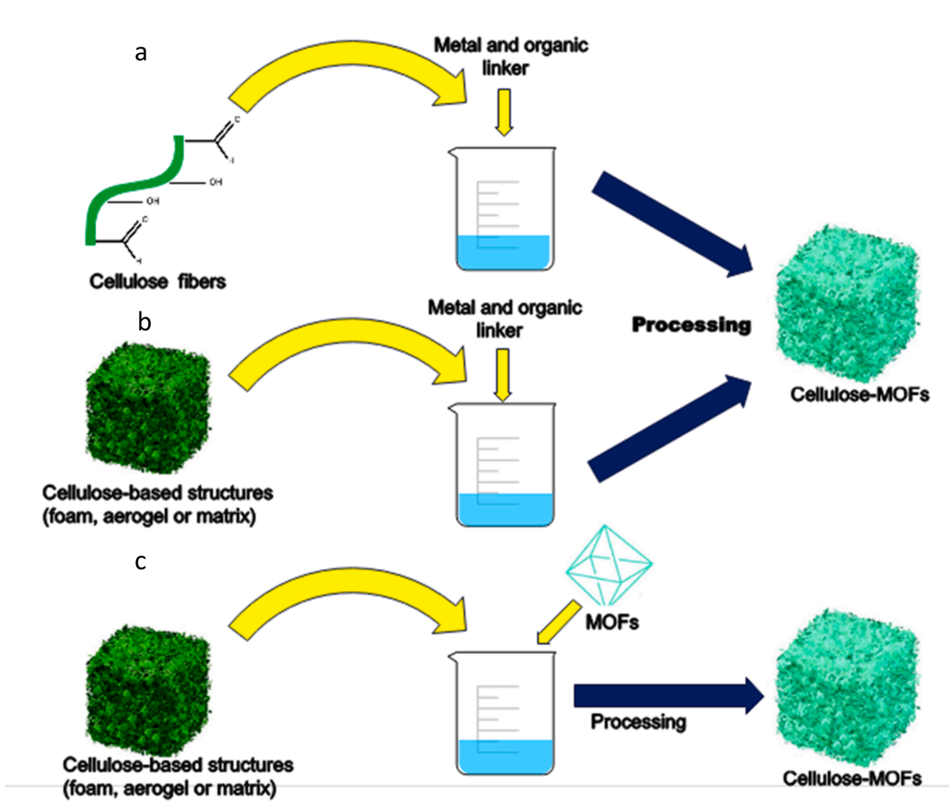

Fig. 3. The synthesis procedure of cellulose-MOFs hybrid materials. *In-situ* process (a,b), MOFs are grown on the cellulosic fibers, followed by forming desired structures, and in the *ex-situ* process (c), MOFs are grown on the desired cellulosic structures.

conventional solvothermal or hydrothermal methods that require elevated temperatures and organic solvents, *in-situ* synthesis enables MOFs crystallization within the cellulose matrix at room temperature, allowing crystal growth to occur directly along the cellulose fibers. The resulting cellulose–MOFs fibers can subsequently be shaped into desired forms using standard processing techniques (Liang et al., 2016).

Using this approach, cellulose–MOFs hybrid materials can be fabricated via one-pot, step-wise, and layer-by-layer (LbL) growth methods (da Silva Pinto et al., 2012). In a one-pot method, metal ions, organic ligands, and cellulose fibers are simultaneously combined, where coordination between cellulose hydroxyl groups and metal ions initiates MOF nucleation, followed by crystal growth constrained within the cellulose network (Abdelhameed et al., 2017a). In the LbL process, MOFs are grown repetitively on the cellulosic fiber surface, with washing steps restoring active hydroxyl coordination sites before subsequent precursor addition (Li et al., 2020). This cyclic nucleation and growth mechanism enables controlled crystal thickness and uniform distribution along the cellulose substrate.

In-situ synthesis offers several advantages, including rapid MOFs formation and strong interfacial interactions with cellulose fibers. The coordination bonding between cellulose hydroxyl groups and metal nodes promotes firm anchoring, while hydrogen bonding further stabilizes the MOF–cellulose interface. The confinement effect of the cellulose matrix influences nucleation density, crystal size, and morphology during MOFs growth. As a result, *in-situ*-grown cellulose–MOFs typically exhibit enhanced mechanical integrity and interfacial stability. Although MOFs loading can be kinetically limited, sequential or LbL growth strategies improve incorporation efficiency and structural uniformity (Li et al., 2020).

3.2. *Ex-situ synthesis of cellulose-MOF hybrid materials*

In *ex-situ* synthesis, MOFs are synthesized independently before their incorporation into cellulosic materials (Fig. 3c). In this approach, the interaction between pre-formed MOFs particles and cellulose occurs after crystallization, and thus differs mechanistically from *in-situ* growth. Depending on the cellulose architecture, MOFs can be integrated either through direct mixing or via surface coating processes (Abdelhamid & Mathew, 2022; Bej et al., 2023). For instance, direct mixing is typically employed for fibrillated cellulose, whereas coating methods are preferred for structured cellulose scaffolds (Bej et al., 2023). In direct mixing, pre-synthesized MOFs are dispersed with cellulose in a manner analogous to the one-pot method; however, interfacial attachment relies primarily on hydrogen bonding and physical adsorption rather than coordination bonding.

During direct mixing, agitation and ultrasonication are used to enhance dispersion, minimize aggregation, and improve physical contact between MOFs and cellulose fibers (Abdelhamid & Mathew, 2022; Bej et al., 2023). The resulting mixture is then shaped using conventional processing techniques such as moulding, casting, or vacuum filtration (Abdelhamid & Mathew, 2022). In coating-based *ex-situ* methods, cellulosic substrates are immersed in MOFs dispersions or suspensions, allowing MOFs particles to adhere to the cellulose surface. The attachment mechanism is dominated by hydrogen bonding between cellulose hydroxyl groups and MOFs ligands, along with weak van der Waals interactions, rather than direct metal–oxygen coordination. The thickness and coverage of the MOFs layer depend on immersion cycles and MOFs concentration (Bej et al., 2023).

The *ex-situ* synthesis approach allows comparatively higher MOFs loading within the cellulose matrix, resulting in increased surface area and enhanced accessibility of active sites. Since MOFs are primarily located on the cellulose surface, reactants can readily access the porous structure. However, the weaker interfacial bonding—dominated by physical adsorption and hydrogen bonding—often leads to aggregation, non-uniform distribution, and reduced interfacial stability compared to *in-situ* synthesized hybrids (Abdelhamid & Mathew, 2022).

4. Applications of cellulose-MOFs hybrid materials in the biomedical field

In biomedical applications, it is crucial to assess a material's biocompatibility and confirm how it interacts with cells, especially when there is the possibility of cytotoxic effects when in contact with living tissue. Comparing cellulose to synthetic polymers, one can see that it has special advantages such as biodegradability, biocompatibility, inexpensive manufacturing costs, abundance, renewability, non-hazardous, and improved mechanical properties (Seddiqi et al., 2021). The potential application of engineered materials is significantly increased when MOFs and cellulose substrates are combined. Along with being flexible, foldable, and 3D-porous, cellulose-based MOFs have significant permeability, little MOFs powder leakage, and are relatively simple to reuse. Cellulose-MOFs hybrid materials are excellent for biological applications because of their biocompatibility and biodegradability. One of the most important uses of these composites is considered to be the strategic use of antibacterial materials. The main components for the antibacterial properties in composites are metal particles, namely zinc (Zn), silver (Ag), and copper (Cu) (Fan et al., 2021). The presence of metal ions in cellulose-MOFs may improve antibacterial characteristics (Duan et al., 2018; Zhang et al., 2020). This section compares and reviews the cellulose-based MOFs' production methods and performances for biomedical applications. Table 1 provides an overview of the synthesis and outcomes of cellulose-MOFs applied in the biomedical field.

4.1. Anti-microbial

Researchers have used different types of MOFs and cellulosic materials for fabricating cellulose-MOFs hybrid materials. Modified cellulose has also been used. In this section, the use of Cu, Zn, and Zirconium (Zr) in conjunction with cellulose MOFs is covered, as well as the efficacy of these materials and the mechanism of action.

4.1.1. Copper-based MOFs in cellulose-MOFs hybrid materials

One group of researchers used a stepwise process of the *in-situ* synthesis technique to grow MOFs on cellulosic fiber (da Silva Pinto et al., 2012). For this, woven cotton fabric was modified by the carboxymethylation technique to obtain CMC. Then, Cu was nucleated on the anionic CMC, followed by anchoring an organic linker of 1,3,5-benzenetricarboxylic acid (H_3BTC) to grow Cu-BTC metal-organic frameworks (MOF-199 or HKUST-1) onto CMC to form cellulose-MOF-199. Cellulose-MOF-199 was applied to investigate its antibacterial efficiency against *Escherichia coli* (Rodríguez et al., 2014). The authors have observed that it can prevent the growth of *E. coli*. This was also confirmed by the addition of Cu (II) acetate ($Cu(OAC)_2$), H_3BTC, and a mixture of DMF:ethanol:water individually in LB plates containing a confluent layer of *E. coli.* There was no inhibition zone in the growing media. Thus, it could be concluded that the incorporation of MOF-199 into CMC can work as an antibacterial material. In another study, Wang et al. (2015) synthesized cellulose-MOF-199 by a stepwise *in-situ* technique, but they used bleached kraft pulp without any modification. They found that the presence of Cu^{2+} in cellulose-MOF plays a crucial role in controlling bacterial growth – the material exhibited significant antibacterial efficiency against both Gram-positive *Staphylococcus aureus* and Gram-negative *E. coli* bacteria. However, it was observed that the cellulose-MOF-199 was more effective against *S. aureus* compared to *E. coli*. Silver nanoparticles (AgNPs), a well-known antibacterial agent, have also been added to the cellulose-MOFs (Duan et al., 2018). Researchers have applied a stepwise *in-situ* synthesis technique to produce AgNPs incorporated into AgNPs@HKUST-1@CFs (Fig. 4a). The hybrid material exhibited excellent antibacterial performance against *S. aureus* (Fig. 4b,c). The uniform distribution of AgNPs and the inherent antibacterial ability of HKUST-1 enhanced its antibacterial ability (Wang et al., 2015). Another group implemented a LbL technique using a mechanical dip coater (Rubin et al., 2018). For this, the authors used carboxymethylated cotton fabric as the cellulose component, the source of Cu was copper(II) nitrate, and the organic ligand was 2-aminobenzene-1,3,5-tricarboxylic acid (NH_2BTC). Around 15 cycles were applied to obtain cellulose-$Cu_3(NH2BTC)_2$. The product was soaked in a solution of valeric anhydride dissolved in $CHCl_3$ for the photosynthetic modification (PSM) of $Cu_3(NH2BTC)_2$. Antibacterial efficiency against *E. coli* was observed in both dry and wet conditions. The LbL technique allowed a uniform distribution of MOFs onto cellulose, and PSM helped to improve the physicochemical properties. Thus, it showed excellent antibacterial properties (Rubin et al., 2018).

The degree of deposition of Cu^{2+} on cellulose influences its antibacterial efficiency. The higher the deposition, the higher the antibacterial efficacy. The Cu^{2+} ions are water-soluble, so loading depends on chelation with carboxyl (COOH) groups. Therefore, the COOH groups of H_3BTC enhance deposition on cellulose. Thus, its deposition on cellulose alone is low (Wang et al., 2015). This also indicates that carboxymethylation can enhance the Cu^{2+} deposition on cellulose fibers (CFs) (da Silva Pinto et al., 2012). The deposition is higher when a high content of HKUST-1 is applied, and the deposition is not affected by the adsorption and reaction time. However, deposition is negatively correlated with temperature - as temperature increases, deposition decreases (Wang et al., 2015). The temperature dependency of Cu^{2+} ions deposition is a result of the exothermic characteristic of HKUST-1 during synthesis (Majano & Pérez-Ramírez, 2013). To grow more MOFs correlated to Cu^{2+} on CFs, an LbL technique was also followed using a mechanical dip coater (Rubin et al., 2018). The deposition of MOFs during LbL techniques depends on the number of cycles.

The adhesion of cells to the cellulosic surface can cause mechanical stress, leading to the inhibition of bacterial growth (Rodríguez et al., 2014). The presence of Cu^{2+} (Wang et al., 2015) and Ag^{+} (Duan et al., 2018) in cellulose-MOFs (cellulose- HKUST-1 and AgNPs@HKUST-1@CFs) plays a main role in controlling bacterial growth. The Cu^{2+} and Ag^{+} destroy the bacterial cell membrane, leading to inhibition of reproduction. The mechanism of bacterial killing by Cu and Ag-based cellulose-MOFs hybrid materials has been discussed in detail in Section 4.1.5.

4.1.2. Zinc-based MOFs in cellulose-MOF hybrid materials

Zn-based MOFs have also been grown on cellulose surfaces to produce cellulose-MOFs hybrid materials. Noorian et al. (2019) used a one-pot *in-situ* synthesis technique to grow zinc glutamate Bio Metal-Organic Framework (BioMOF) on woven cotton (Fig. 5a). The fabric was pretreated with alkaline and doped with Fe (II) 5-fluorouracil (5FU) to obtain 5Fu-BioMOF-Fa. The growth of both *Staphylococcus aureus* and *E. coli* was affected, albeit inhibition of *S. aureus* was more pronounced compared to the latter (Fig. 5b-e). The use of cellulosic material (Noorian et al., 2019) and Fe (II) (Yang et al., 2023) can facilitate a sufficient amount of drug loading. Thus, it has shown great antibacterial efficiency. Another group of researchers grew Zn-based zeolitic imidazolate framework-8 (ZIF-8) on the fresh cotton fabric to obtain cotton/ZIF-8 by a one-pot *in-situ* synthesis approach. It was then immersed and dipped into a tetrahydrofuran (THF) solution containing polydimethylsiloxane (PDMS) to achieve hydrophobicity, and the hybrid material was referred to as cotton/ZIF-8@PDMS. It showed antibacterial efficiency of 100% against *E. coli* and *S. aureus* (Yang et al., 2020). Similarly, one-pot *in-situ* synthesis was applied to obtain cotton@ZIF-8(Zn) (Emam et al., 2020). It showed excellent antibacterial efficiency against both Gram-positive bacteria, i.e., *S. aureus* and *Bacillus cereus,* and Gram-negative bacteria, i.e., *E. coli*. It also showed antifungal efficiency against fungi, i.e., *Candida albicans*. The LbL process was also applied to develop Zn-based cellulose-MOFs hybrid materials (Lu et al., 2018). Having undergone eight LbL cycles, the product was referred to as ZnBDC-Ctn-8, and it showed >99% antibacterial efficiency against *S. aureus* and *E. coli*.

Like Cu^{2+}, the presence of Zn^{2+} ions works as an antibacterial agent (Lu et al., 2018). As expected, higher concentrations of Zn^{2+} ions lead to

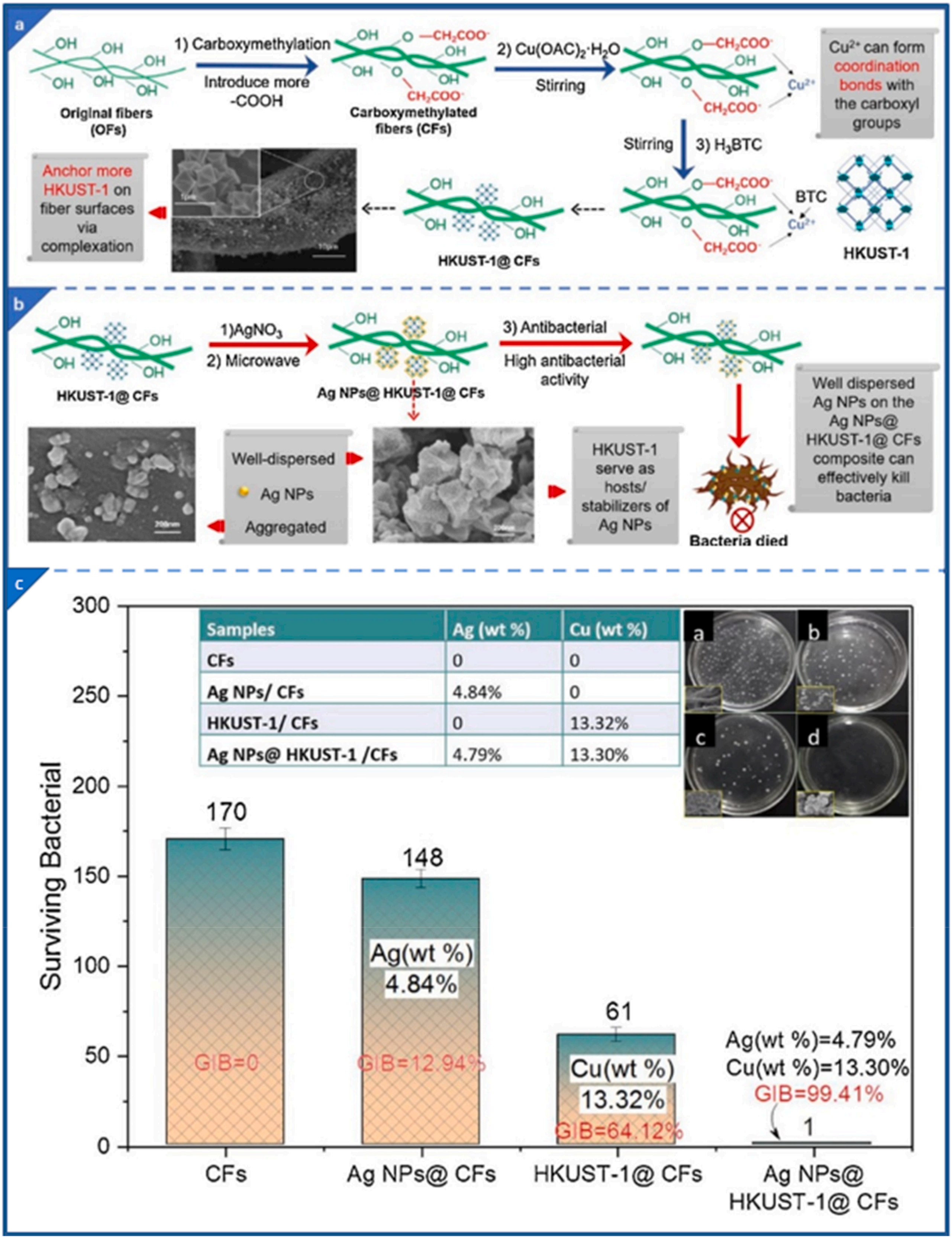

Fig. 4. (a) Schematic diagram of the synthesis of (a) HKUST-1@CFs and (b) AgNPs@HKUST-1@CFs composites; and (b) The bactericidal performance HKUST-1@CFs and AgNPs@HKUST-1@CFs against *S. aureus*, and bacterial colonies of blank CFs (inset a), AgNPs@CFs (inset b), HKUST-1@ CFs (inset c), and AgNPs@HKUST-1@CFs (inset d) (Duan et al., 2018).

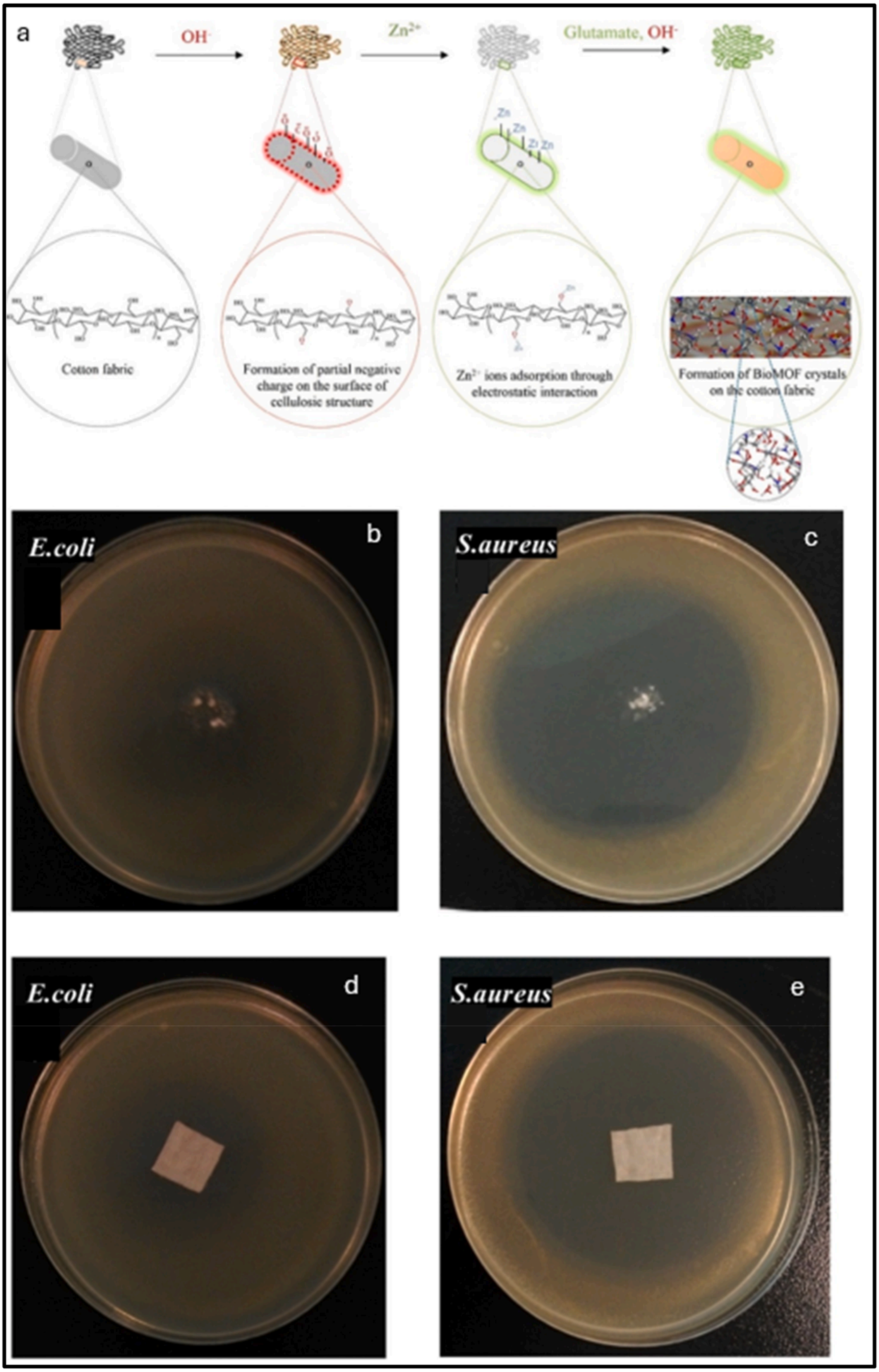

Fig. 5. (a) Schematic illustration of in situ synthesis of Zn-based cellulose-MOFs hybrid materials (5FU-BioMOF and 5FU-BioMOF-Fa), and antibacterial activity of 5FU-BioMOF (b, c), and 5FU-BioMOF-Fa (d, e) against E. coli and S. aureus bacteria (Noorian et al., 2019).

greater antibacterial efficiency. Therefore, different strategies have been taken to increase the loading of Zn^{2+} in the cellulosic matrix. In one study, researchers modified a cellulosic surface with silicate to load more Zn-based MOF in the cellulosic fiber matrix (Emam et al., 2020). The LbL process was also applied to load a high amount of MOFs, and an increased number of cycles enhanced the MOF content in the cellulosic matrix (Lu et al., 2018).

The presence of Zn^{2+} ions in Zn-based cellulose-MOFs hybrid materials plays a major role as an antibacterial agent (Lu et al., 2018). The release of Zn^{2+} ions damages the cellular structure by interacting with cell membranes and consequently leads to cell death caused by interaction with intercellular content (Lan et al., 2019; Ma et al., 2018). The principles of antibacterial activity of Zn^{2+} are described in detail in Section 4.1.5.

4.1.3. Zirconium-based MOFs in cellulose-MOFs hybrid materials

Other than Cu and Zn-based MOFs, researchers have also studied different types of metal ions in cellulose-MOFs hybrid materials. A CMC-based nanocomposite MOF hydrogel film was formed by *ex-situ* processing using tetracycline (TC) and UiO-66, referred to as CMC/TC@UiO-66 (Fig. 6) (Javanbakht et al., 2021). For this, the zirconium (Zr^{4+})-based MOF UiO-66 was formulated, followed by the encapsulation of TC to obtain the product of TC@UiO-66. Different concentrations of TC@UiO-66 (5, 10, and 15%) were used to produce the hydrogel film of CMC/TC@UiO-66. CMC/TC@UiO-66 showed a remarkable antibacterial efficiency against both *S. aureus* and *E. coli* bacteria. Porphyrinic metal-organic frameworks (PCN-224) were used as MOFs in another study, and Zr was used as the central metal (Nie et al., 2020). The authors used a one-pot *in situ* synthesis technique to obtain cellulose-PCN-224, and the woven cotton fabric was used as a cellulose substrate. It showed antibacterial efficiency of 99.9999% against Gram-negative, i.e., *E. coli,* and *P. aeruginosa*, as well as Gram-positive, i.e., *S. aureus* and *B. subtilis,* under visible light illumination.

Similarly to the other cellulose-MOFs, the extent of loading of TC@UiO-66 enhances the antibacterial efficiency - higher concentrations result in better antibacterial performance. The CMC/TC@UiO-66 with a high content of TC@UiO-66 has shown greater levels of bacteria-killing. The controlled release of TC leads to the enhancement of antibacterial efficiency (Javanbakht et al., 2021). A mechanistic study has revealed that singlet oxygen ($^1O_2$) is produced by CF/PCN-224 and causes severe damage to bacteria (Nie et al., 2020).

4.1.4. Effectiveness of different types of cellulose-MOFs hybrid materials against bacteria

The effect of metal ions on bacterial inhibition may vary. Therefore, researchers have also compared the antibacterial effectiveness of different types of cellulose-MOFs incorporating different metal ions. In the study, the researchers modified cotton fibers as CMC and applied an *in-situ* synthesis technique at room temperature to grow cellulose-MOFs hybrid materials (Ma et al., 2022). CMC was immersed in aqueous metal solutions with organic ligands to produce Zn-based MOFs referred to as CMC/MOF-74 and CMC/MOF-5, Al-based MOFs referred to as CMC/MIL-53, and Cu-based MOFs referred to as CMC/MOF-199. CMC/MOF-74 and CMC/MOF-5 showed antibacterial efficiency against *Klebsiella pneumoniae* and *E. coli* (Gram-negative) bacteria between 80% and 99%. CMC/MIL-53 showed antibacterial efficiency against *S. aureus, K. pneumoniae,* and *E. coli* bacteria of 50.2%, 53.6%, and 93.4%, respectively. CMC/MOF-199 showed >99% antibacterial efficiency against gram-negative bacteria. Ma et al. (2018) also conducted a comparative study to investigate the efficiency of ZIF-8@CF, MOF-199@CF, and Ag-MOF@CF (Fig. 7a-d). The authors used an *in-situ* method to grow MOFs on softwood kraft fiber as a cellulosic substrate. The order of antibacterial activity against *E. coli* was ZIF-8@CF < MOF-199@CF < Ag-MOF@CF (Fig. 7a-d). Ag-MOF@CF showed the highest protective zone against bacteria (Fig. 7d).

Therefore, the antibacterial efficiency depends on the types of MOFs. The inherent antibacterial characteristics of metal inhibit bacterial growth. The ligand type can also influence the antibacterial performance (Awwad et al., 2025). Ag is well known for its antibacterial efficiency. The antibacterial efficiency is also dependent on the deposition of MOFs on the cellulosic surface. In one study, the order of MOFs deposition has been observed as ZIF-8@CF < Ag-MOF@CF < MOF-199@CF (Ma et al., 2018). They have observed that the deposition of MOFs and antibacterial efficiency are different. Electronegativity via electrostatic interaction and hydrogen interaction plays a main role in the adsorption of Zn^{2+} onto the CF (Su et al., 2018). Again, the interaction between Zn^{2+} and the OH groups of CF and the hydrogen bonding between Zn and OH groups enhance the adsorption of Zn^{2+} on CF (Chauhan et al., 2015). Furthermore, the interaction between 2-methylimidazole molecules and Zn^{2+} results in the deposition of ZIF-8 onto the surface of CF (Bux et al., 2009). H_3BTC, on the other hand, works as an organic ligand, resulting in interaction with the OH groups of CF (Yang et al., 2017). Cu^{2+} then interacts with modified CF, resulting in the growth of MOF-199 on CF by the *in-situ* process (Kayaert et al., 2011). These strategies are similar to CF-Ag-MOF. The volatile electrostatic adsorption and nanostructure lower the deposition of ZIF-8 (Ma et al.,

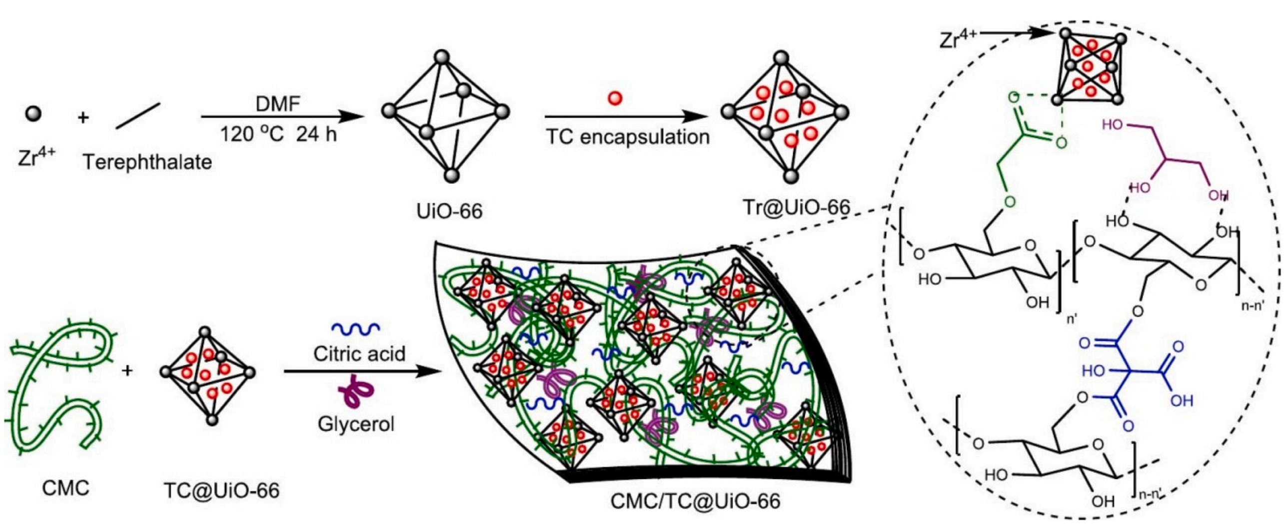

Fig. 6. Schematic diagram of the synthesis of CMC/TC@UiO-66 using citric acid as a crosslinker (Javanbakht et al., 2021).

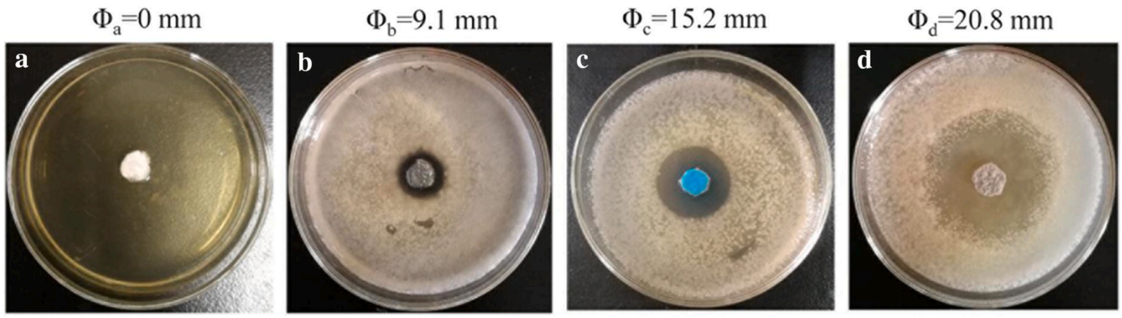

Fig. 7. Antibacterial activity of different types of cellulose-MOFs: (a) Blank sample without the addition of *E. coli* and (b) ZIF-8@CF, (c) MOF-199@CF, and (d) Ag-MOFs@CF composite sample against *E. coli* (Ma et al., 2018).

2018). Thus, the antibacterial efficiency of cellulose-MOFs hybrid materials depends on the degree of deposition and type of cellulosic surface and metal ions.

4.1.5. Mechanism of antibacterial activity of cellulose-MOFs hybrid materials

The release of metal oxides from the cellulose-MOFs hybrid materials results in damaging bacterial cells and plasma membrane compounds, leading to the death of bacteria (Abdul Khalil et al., 2014; Wyszogrodzka et al., 2016). The negative charge of bacterial cells' phospholipids and the positive charge of metal ions cause the electrostatic interaction, leading to the breakdown of the plasma membrane of bacterial cells (Seil & Webster, 2012). Zn^{2+} ions cause cell breakage and death of microorganisms by adsorbing on the outer cell membrane of microorganisms with electrostatic interaction, followed by penetrating the cell membrane using interaction with OH groups of the peptidoglycan membrane (Wahab et al., 2010). Cu^{2+} ions cause cell membrane breakage and lysis by oxidizing proteins and fatty acids of the cell membrane or transforming the transmembrane (Hong et al., 2012). Ag^{+} ions, on the other hand, can penetrate bacteria and inhibit enzymatic activity by interacting with the thiol groups of proteins, resulting in the disruption of the cell membrane (Feng et al., 2000; Matsumura et al., 2003). Furthermore, ligands and functional groups interact with chelating agents of cells and can modify and fragment the DNA (Lu et al., 2014; Pulido & Parrish, 2003). Ag is more stable and has a high affinity to nitrogen in extracellular and intracellular spaces (Zhang et al., 2022). Thus, Ag-incorporated cellulose-MOFs can have a significant impact on bacterial growth. Ma et al. (2018) reported that the antibacterial efficiency of the examined metal ions decreased in the order $Ag^{+} > Cu^{2+} > Zn^{2+}$, with silver ions demonstrating the highest antibacterial activity. This trend is attributed to differences in ion–cell interactions, membrane disruption capability, and affinity for intracellular biomolecules. Furthermore, the OH group is a reactive radical that can cause the death of bacteria (Ghattavi & Nezamzadeh-Ejhieh, 2020, 2021; Mirsalari & Nezamzadeh-Ejhieh, 2020; Rezaei & Nezamzadeh-Ejhieha, 2020). Cellulose contains ample OH groups in its structure. Thus, the cellulosic structure in the substrate can also enhance the inhibition of bacterial growth. The mechanism of antibacterial activity of different MOFs is presented in Fig. 8.

The potential antimicrobial efficiency of cellulose-MOFs hybrid materials has been documented in the reported literature. These have demonstrated antibacterial and antifungal properties. The effectiveness of cellulose-MOFs is paving the way for the fabrication of antibacterial clinical fabrics (Rodríguez et al., 2014), bandages (Rubin et al., 2018), and materials for health care (López-R et al., 2022; Ma et al., 2018). These can be used in the packaging of medications, in health and medical services (Duan et al., 2018), and perhaps even in antibacterial wound dressings (Javanbakht et al., 2021).

4.2. Drug delivery

The controlled and targeted release of drugs is important for their effectiveness and for reducing their release into the environment (Arabpour & Nezamzadeh-Ejhieh, 2016). A photodegradation technique using nanosized particles has been explored as a way to help against pollution (Arabpour & Nezamzadeh-Ejhieh, 2016; Cumsille et al., 2018;

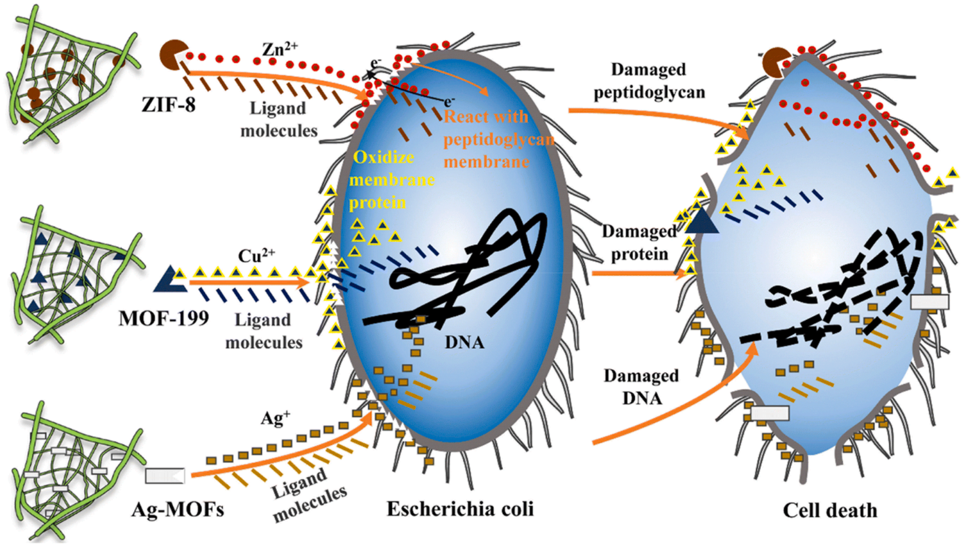

Fig. 8. Schematic diagram of the bactericidal mechanism for different types of cellulose-MOFs hybrid materials against *E. coli* (Ma et al., 2018).

Mohammadyari & Nezamzadeh-Ejhieh, 2015; Soleimani & Nezamzadeh-Ejhieh, 2020; Yousefi & Nezamzadeh-Ejhieh, 2021). The MOFs allow for a wide range of particles because of their porous structure with high surface area, and have the opportunity to avoid pollution with the optimal use of drugs due to their self-degradation. Therefore, the specific characteristics of MOFs appeal to applying them in drug delivery (Rao et al., 2022). Cellulose-MOFs hybrid materials have also been employed in drug delivery in different treatments.

4.2.1. Cancer therapy

The preservation of nature-derived properties of biomolecules and the enhancement of catalytic properties by MOFs present exceptional opportunities for application in cancer therapy (Li et al., 2023; Zeng et al., 2022). The carrier capacity due to high porosity in MOFs urges researchers to apply them in cancer treatment (Chen et al., 2023a; Liao et al., 2023; Luo et al., 2023). Researchers have investigated the ability of the 5Fu hybrid materials to treat tumor cells. They have synthesized 5Fu-BioMOF-Fa to understand the 5Fu release behavior. It has shown controlled delivery and can degrade in acidic conditions, similar to those found in tumor tissue, to release the drug (Kumari & Kondapi, 2017; Noorian et al., 2019). Thus, it can target tumor cells for drug release. The combined effect of diffusion and interaction has helped control the 5-FU release. Furthermore, the bonding with zinc or hydrogen can enhance the targeted drug delivery (Noorian et al., 2019; Zeng et al., 2023). Investigation of the delivery of doxorubicin (DOX) as an anticancer agent has also been studied (Javanbakht et al., 2019). For this, the researchers synthesized CMC, MOF-5, and graphene oxide (GO) based MOF (MOF-5/GO) by an *ex-situ* approach. The product was then immersed in a DOX solution for loading. DOX release rates were significantly higher under tumor cell microenvironment conditions at pH 5 than under physiological conditions at pH 7.4. The release of DOX was slower for CMC/MOF-5/GO compared to GO at pH 7.4 and pH 5. The total amount of release and loading of DOX, on the other hand, was higher for CMC/MOF-5/GO than for GO. The presence of electrostatic, π-π stacking, and H-bonding in CMC/MOF-5/GO results in a higher content of DOX. The controlled release of DOX by the use of cellulose-MOFs hybrid materials was also observed by another group of researchers (Zhang et al., 2021a). It can be concluded that extended-release and higher concentrations enhance the effectiveness of these materials against cancer tissues (Javanbakht et al., 2019).

4.2.2. Anti-inflammatory drug delivery

Ibuprofen (IBU) is used to get relief from inflammation, fever, and pain. The traditional IBU carrier has side effects on the gastrointestinal tract. Therefore, researchers have studied the possible use of cellulose-MOFs hybrid materials to release IBU (Javanbakht et al., 2018). The

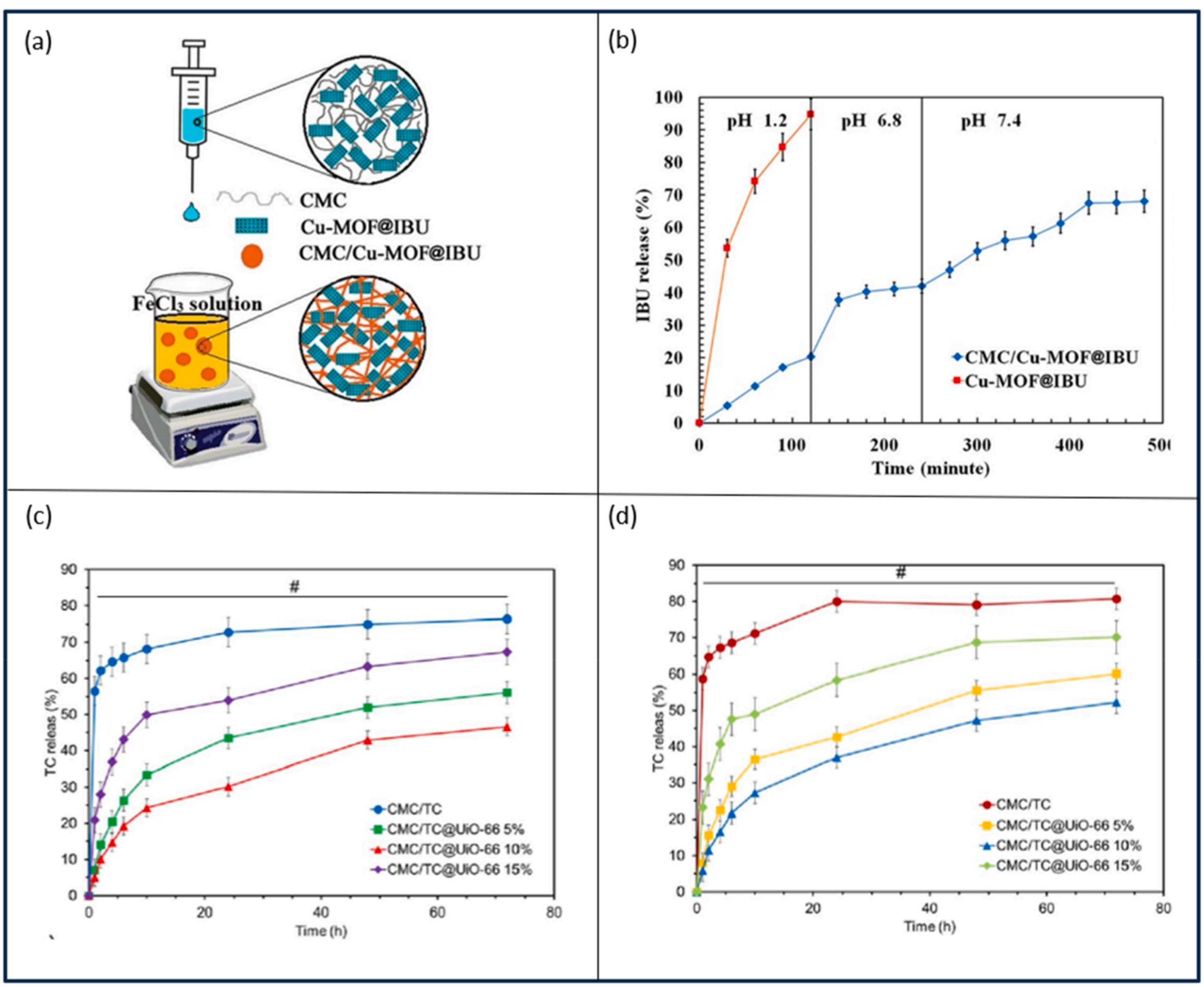

Fig. 9. (a) Schematic diagram of the synthesis of CMC/Cu-MOF@IBU (Javanbakht et al., 2018); (b) IBU release from Cu-MOF@IBU and CMC/Cu-MOF@IBU in conditions that simulate the gastrointestinal tract passage (pH and time) (Javanbakht et al., 2018); (c) TC release at artificial sweat (Javanbakht et al., 2021); and (d) TC release at PBS (pH 7.4) in 37°C (n = 3, #$P < 0.05$) (Javanbakht et al., 2021).

authors used Cu-based MOFs and prepared CMC/Cu-MOF@IBU hydrogel bead by an *ex-situ* process. For this, the authors prepared Cu-MOF, followed by encapsulating IBU to obtain Cu-MOF@IBU before the synthesis of a CMC/Cu-MOF@IBU hydrogel bead (Fig. 9a). They observed a controlled release of IBU in intestinal tract conditions. CMC swelling depends on pH, and this controls IBU release (Fig. 9b). The COOH group of CMC deprotonates with increasing pH, resulting in electrostatic repulsion between carboxylate anions. Thus, the material swells at a higher pH, and the optimum pH level is 6 to 8. The swelling ratio is higher at pH 6.8 because of MOF decomposition by penetrating acidic fluids into the CMC network beads (Javanbakht et al., 2018).

4.2.3. Anti-microbial drug delivery

The exceptional drug loading capacity and controlled release of drug capability of MOFs encourage their use to treat wounds (Huang et al., 2024). For example, the controlled release of TC from CMC/TC@UiO-66 was observed in artificial sweat (pH 6.5) (Fig. 9c) and simulated wound exudate (PBS, pH 7.4) (Fig. 9d) at 37 °C over 72 h (Javanbakht et al., 2021). The initial burst release, on the other hand, was observed for CMC/TC in both media. TC and CMC possess a negative charge (Colaizzi & Klink, 1969), resulting in a strong repulsive force that leads to the release of CMC/TC from the matrix. The inhibition of initial high burst release can help to deliver a certain amount of TC to the targeted tissue (Colaizzi & Klink, 1969). Electrostatic interaction and hydrogen bonding, due to CMC as a host and the interaction of TC and UiO-66 nanoparticles in CMC/TC@UiO-66, lead to the controlled release of TC (Javanbakht et al., 2021). Therefore, an internal bonding in the matrix is important to control the drug release, and cellulose can inhibit the burst release, leading to the target drug delivery.

4.2.4. Mechanism and factors affecting drug delivery

Drugs can be incorporated into MOFs through various mechanisms that exploit the structural and chemical versatility of these materials. In one common approach, drug molecules are confined within the pores of MOFs through noncovalent interactions such as hydrogen bonding, π–π stacking, and van der Waals forces. These interactions enable stable yet reversible drug encapsulation, allowing for controlled release under appropriate conditions. In another strategy, drugs act as ligands by coordinating directly with metal ions during the synthesis of the MOFs, resulting in their uniform distribution throughout the framework. Post-synthetic modification offers an additional route, whereby drugs are attached to the MOF surface or incorporated into its pores via adsorption or covalent bonding (Khulood et al., 2025).

The efficiency of drug loading and subsequent release is strongly influenced by both the morphology and chemical composition of the MOFs (Benny et al., 2024; He et al., 2021). Morphological characteristics—including pore size, shape, and surface area—govern the extent of drug encapsulation and diffusion behavior. Meanwhile, the chemical composition, defined by the nature of the metal ions and organic linkers, determines the framework's stability, hydrophilicity, and interaction with drug molecules. Surface functionalization further allows the tuning of these chemical properties, facilitating specific drug–MOFs interactions and enhancing targeted delivery capabilities (Khulood et al., 2025).

Drug release from MOFs is often designed to be stimuli-responsive, enabling spatially and temporally controlled delivery. Such stimuli may include variations in pH, temperature, light irradiation, magnetic fields, enzymatic activity, or redox conditions (Khulood et al., 2025). Stimuli-responsive MOFs can therefore achieve targeted drug release in response to the unique microenvironment of diseased tissues (Maranescu & Visa, 2022). Upon exposure to specific stimuli, MOFs can undergo swelling, structural deformation, or partial decomposition, triggering the release of the encapsulated drug (Javanbakht et al., 2018). For example, dual-responsive systems that react to both pH and temperature changes can form complex dynamic structures, allowing for precise and sustained drug release (Wei & Lu, 2024).

4.3. Biosensors for clinical diagnosis

The characteristics of MOFs are well-suited to develop biosensors for early-stage disease diagnosis (Guo et al., 2023), and the opportunity to tune their properties allows for the detection of specific signal compounds (Tan et al., 2024). In contrast, the hydrophilic nature and inherent porosity of cellulose enable its effective use as an electrolyte reservoir and facilitate the transport of diffusing ions. Moreover, the intrinsic flexibility and mechanical robustness of cellulose make it well-suited for the development of flexible electronic devices (Li et al., 2021). Consequently, cellulose-MOFs have been investigated in developing point-of-care (POC) devices for diagnosis (Kou et al., 2020). Researchers have referred to them as smartphone-assisted biomimetic MOFs nanoreactor colorimetric paper (SBMCP). Biomimetic enzymes@MOFs (BEMs) have been synthesized. Enzyme, e.g., urease, was added in 2-methylimidazole, followed by adding polyvinylpyrrolidone (PVP), cysteine (Cys), and zinc acetate solution. The BEMs were also prepared with single and multiple enzymes. This mixture was dispersed in a poly(vinyl alcohol) (PVA) solution and dropped on a round paper to yield an enzymes@MOFs-based paper biosensor (Fig. 10a). The raw paper was perforated to make small round paper, followed by washing before introducing enzymes@MOFs. The PVA enhanced the uniform distribution of BEMs and improved the homogeneity of color measurements (Zhao et al., 2008). The SEM image showed a uniform distribution of the three enzyme-based MOFs on the paper surface (Fig. 10b). A powder X-ray diffraction (PXRD) study confirmed the presence of ZIF-8 in the paper biosensor (Fig. 10c). The addition of glucose showed a change of color from white to shiny blue – this indicated the high efficiency of catalytic cascades. There was a strong correlation between glucose concentration and smartphone applications with Hue-Saturation-Value (HSV) values. The paper matrix holds the microporous ZIF-8 exoskeleton, and it is analogous to the intercellular enzyme cascade signal transduction. ZIF-8 traps enzymes, ensuring their stability in the paper matrix. After receiving the target analyte, the enzymes use the cascade reaction to recognize the event and send a visual color signal. The smartphone can read the signal to provide the test report. In the SBMCP experiment, glucose displayed a substantially high color signal. The SBMCP biosensor's cross-reactivity with various interferences was also assessed, and the computed values, which varied from 1.0% to 8.9%, were suitable for biological analysis. A similar idea of enzyme-encapsulated ZIF-8 was used for developing biosensors (Li et al., 2021). However, cellulose acetate (CA) nanofiber membrane was used instead of paper, and it was produced by electrospinning of CA. It was immersed in zinc nitrate solution containing the enzyme, followed by washing, immersion in 2-methylimidazole solution, and washing to produce CA/ZIF-8@enzyme. It was then soaked in CNTs dispersion, followed by drying and adsorbing gold nanoparticles (AuNPs) to obtain CA/ZIF-8@enzyme/MWCNTs/Au. It showed an excellent correlation between E^{OCP} and glucose concentration. This product can be used for chronic disease and clinical diagnosis.

4.4. Tissue engineering

At present, tissue engineering is a promising development for regenerating tissue in medical science (Esmailzadeh et al., 2024). The mimicking of any tissue depends on biological agents, cells, and scaffolds, where scaffolds play a great role by providing an environment for the adhesion and proliferation of cells (Dobriţa et al., 2023; Sharma et al., 2023). The mechanical properties of scaffolds, along with the surface morphology of cells, chemical interactions, and localizations, are all important factors for tissue regeneration (Cakmak et al., 2020; Hama et al., 2023). The biodegradability and biocompatibility of cellulosic materials can meet the required criteria for application in tissue engineering (Janmohammadi et al., 2023; Pandele et al., 2018; Tarrahi et al., 2022). The presence of OH groups helps adhere to the cells (Deng et al., 2022). MOFs are biodegradable, biocompatible, and

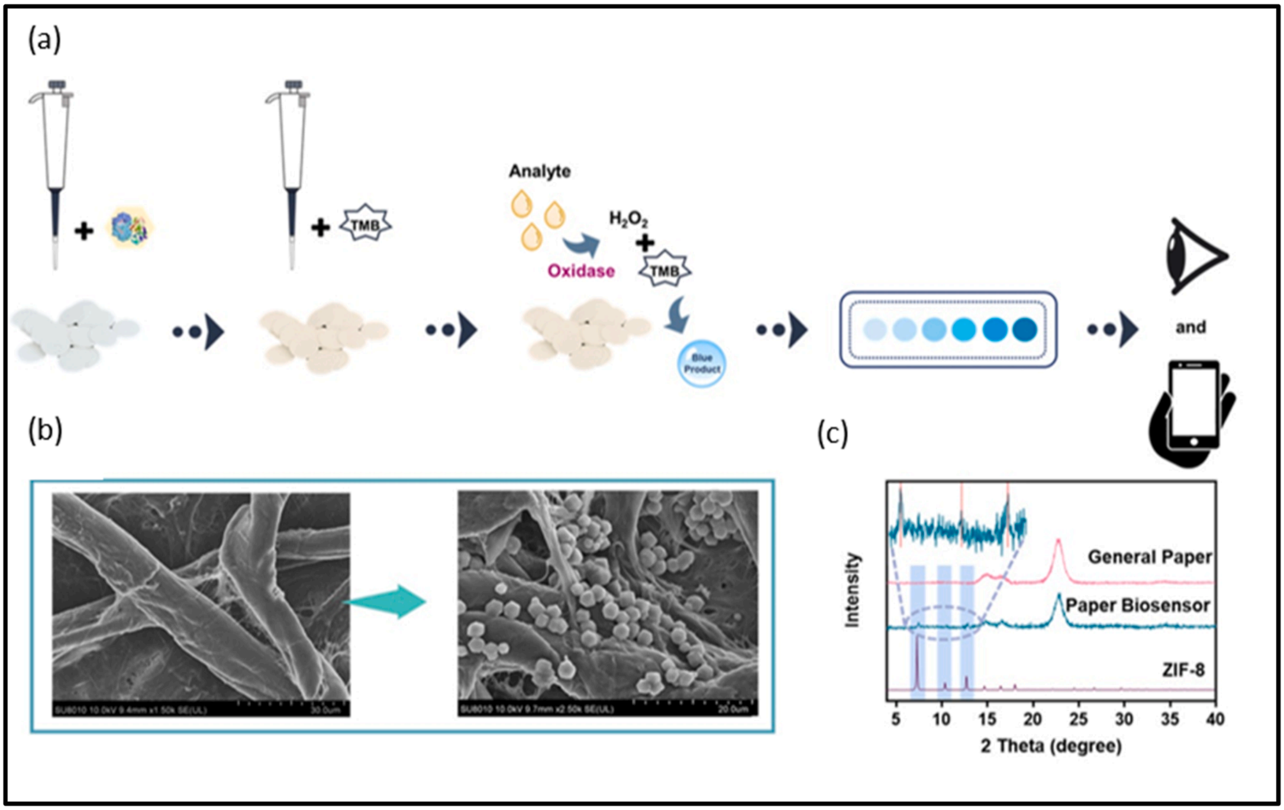

Fig. 10. (a) Schematic diagram of the synthesis and working principle of cellulose-MOFs biosensor; (b) The morphology of the paper before (left) and after (right) MOFs incorporation; and (c) The PXRD patterns of the general paper, paper biosensor, and pure ZIF-8 (Kou et al., 2020).

relatively non-toxic (Asadniaye Fardjahromi et al., 2022). These can be applied with cellulosic substrates for tissue engineering (Rabiee et al., 2022). The cellulose-MOFs hybrid materials possess good mechanical strength properties, i.e., Young's modulus. The structural integrity can be maintained after multiple cycles of use and regeneration (Fijoł et al., 2023). The properties, i.e., mechanical and biological, of cellulose-MOFs hybrid materials are promising for applying them in tissue engineering (Esmailzadeh et al., 2024).

Researchers have investigated the potential of cellulose-MOFs hybrid materials for bone tissue engineering. A group of researchers prepared ZFI-8 and ethyl cellulose-based cellulose-MOFs (ZIF-8@ethyl cellulose) by an *ex-situ* process (Doustdar & Ghorbani, 2022) (11a). The material was used as a scaffold for cell growth, and the cell viability cultured NIH3T3 fibroblast cell performance was high for the composite material (11b). The degree of Zn^{2+} release enhanced the growth of cells and cell viability. The potential use for this product is in skin tissue engineering. Another group of researchers prepared Dex-loaded ZIF-8 (DMOF) and modified CMC with calcium and ammonia solution, referred to as cellulose-hydroxyapatite (HA) based composite HA/DMOF, by an *ex-situ* process (Sarkar et al., 2019). The in-vitro cell differentiation study by the authors has shown that the activity of alkaline phosphatase (ALP) of MC3T3 cells is higher for HA/DMOF (Fig. 11c). This was verified through alizarin red (AR) and von Kossa (VK) staining methods (Fig. 11d). The presence of Dex and HA enhances the ALP activity. The release of Dex helps cell proliferation for HA/DMOF (Son et al., 2011). The capability of controlled release of metal ions and drugs can attract researchers to more future studies in tissue engineering.

5. Toxicity and biodegradability of cellulose-MOFs hybrid materials

A thorough understanding of the toxicity and biodegradability of cellulose–MOFs hybrid materials is crucial for assessing their environmental and biomedical safety. The toxicological profile of these hybrids is largely dictated by the MOFs component and depends on factors such as metal ion composition, ligand chemistry, framework stability, and degradation behavior under physiological or environmentally relevant conditions. A primary mechanism of MOFs related toxicity is metal ion leaching, which occurs when metal–ligand coordination is destabilized under acidic, oxidative, or enzymatic environments. In physiological media (pH 5.7–7.8) and acidic intracellular compartments such as lysosomes (pH 4.5–5.0), ligand protonation can weaken coordination bonds, resulting in partial framework degradation and release of free metal ions (Liu et al., 2024). Toxic metals, including cadmium and lead, can disrupt cellular homeostasis by interacting with proteins and nucleic acids, thereby inducing oxidative stress, mitochondrial dysfunction, and inflammatory responses (Cheng et al., 2025; Jomova et al., 2025). In contrast, MOFs based on biologically essential metals such as iron, zinc, or magnesium generally exhibit lower toxicity, as released ions can be regulated or metabolized by endogenous pathways (Sousa et al., 2019).

Framework stability plays a decisive role in governing both toxicity and degradation kinetics. MOFs with strong metal–ligand coordination, such as Zr–O or Fe–O clusters, typically display enhanced stability under physiological conditions, leading to slower metal release and reduced acute toxicity. Conversely, MOFs constructed from weaker coordination bonds or hydrolytically labile ligands are more susceptible to structural collapse, accelerating metal ion leaching (Mosca et al., 2023). In addition, ligand degradation products may contribute to toxicity, particularly when hydrolysis generates reactive or acidic by-products (Kumar et al., 2019).

Incorporation of cellulose substantially modulates the toxicological behavior of MOFs. The cellulose matrix can encapsulate MOFs particles, limiting direct cell contact and reducing metal ion release. Surface hydroxyl groups of cellulose may further chelate leached metal ions, lowering their bioavailability. Moreover, cellulose alters cellular uptake

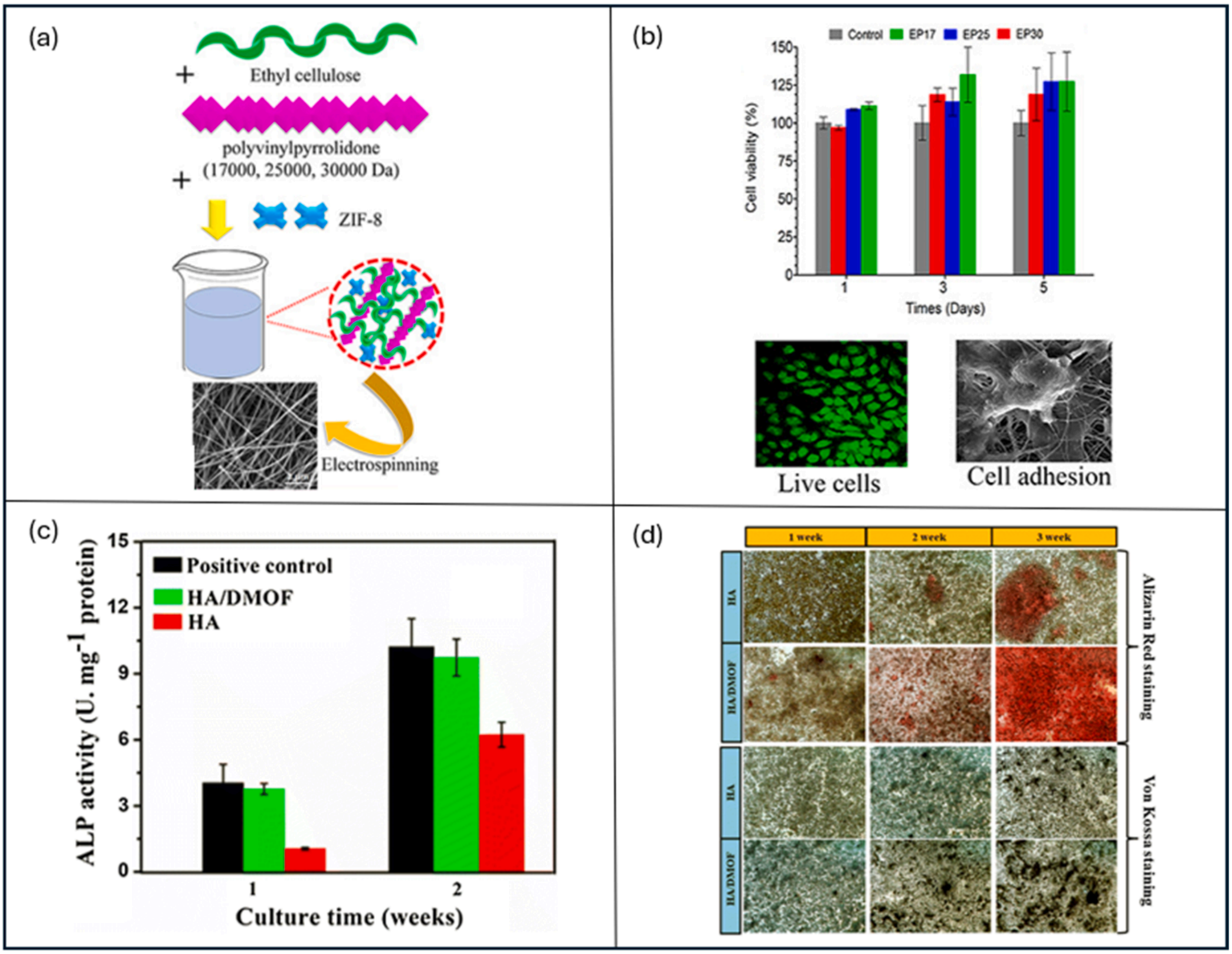

Fig. 11. (a) A set of zeolitic imidazolate framework-8 (ZIF-8) incorporated ethyl cellulose/polyvinylpyrrolidone scaffolds cell viability was pre (Doustdar & Ghorbani, 2022) and (c) ALP assay and (d) in-vitro extracellular mineralization of MC3T3 cells in the presence of HA and HA/DMOF nanocomposites (Magnification= × 4) (Sarkar et al., 2019).

pathways: whereas nanoscale MOFs are readily internalized via endocytosis, cellulose–MOFs hybrids often exhibit reduced uptake due to increased particle size and enhanced surface hydrophilicity. This reduced internalization suppresses intracellular reactive oxygen species (ROS) generation, a major driver of MOF-induced cytotoxicity. Accordingly, cellulose-MOFs have been shown to attenuate oxidative stress and pro-inflammatory responses relative to pristine MOFs (Javanbakht et al., 2019; Yadollahi et al., 2015).

The biodegradability of cellulose–MOFs hybrids is governed by the combined degradation pathways of both components. Cellulose, a renewable biopolymer, is readily degraded by cellulolytic microorganisms in soil and aquatic environments into low-molecular-weight products (Datta, 2024). In contrast, MOFs biodegradation depends on the hydrolytic and enzymatic susceptibility of its ligands and the environmental stability of its metal nodes. MOFs containing hydrolysis-prone ligands are more likely to undergo gradual decomposition, although inorganic residues may persist as metal oxides or hydroxides (Mosca et al., 2023; Liu et al., 2024). Notably, the presence of cellulose can enhance biodegradation by promoting microbial colonization and enzymatic activity at the composite surface, thereby accelerating structural disintegration and reducing long-term persistence.

In summary, cellulose–MOFs hybrid materials generally exhibit reduced toxicity and improved biodegradability compared with pristine MOFs, owing to diminished metal ion leaching, moderated cellular uptake, and attenuated oxidative and inflammatory responses. Nevertheless, their environmental and biological safety remains highly dependent on MOFs design parameters, including metal identity, coordination strength, and ligand stability. The rational selection of environmentally benign metals, controlled ligand chemistry, and systematic evaluation of degradation and release behavior under relevant conditions are therefore essential for the safe and sustainable development of cellulose–MOFs hybrid systems.

6. Limitations of cellulose incorporation in mitigating cellulose–MOFs toxicity

Although cellulose incorporation can reduce the toxicity of MOFs, this effect is not universal. For example, MOFs containing toxic or redox-active metals (e.g., Cu, Co, or Ni) can continue to induce cytotoxicity due to sustained metal ion release, especially under acidic or oxidative conditions where cellulose cannot fully inhibit framework degradation. In such systems, cellulose primarily serves as a physical barrier rather than eliminating ion leaching, leading to chronic low-dose exposure that may trigger oxidative stress, inflammation, or genotoxic effects. An excessive incorporation of MOFs, on the other hand, can lead to particle agglomeration within the cellulose matrix, resulting in a reduced elastic response. This structural inhomogeneity may further facilitate the leaching of MOFs from the composite, leading to toxicity.

Toxicity can also persist due to unfavorable particle size and dispersion. Poorly embedded or loosely attached MOF nanoparticles may detach from cellulose matrices during use or degradation and behave similarly to pristine MOFs, including cellular internalization and intracellular ROS generation. Additionally, when cellulose degrades faster than the MOF component—such as in enzyme-rich or microbially active environments—the protective effect may be transient, re-exposing the MOFs phase and restoring its toxic potential.

The spatial distribution of MOFs within the cellulose matrix further influences biological responses. Surface-bound MOFs, while beneficial for catalysis or antimicrobial activity, remain highly accessible to biological media and can promote membrane damage, protein interactions, and localized metal ion release, resulting in moderate cytotoxic or inflammatory effects. In contrast, embedded MOFs generally exhibit reduced biological reactivity due to limited cell contact, slower ion diffusion, and improved particle retention. Nevertheless, even embedded systems may pose long-term risks if gradual degradation leads to metal ion accumulation or if ligand degradation products are toxic.

Overall, cellulose incorporation should not be assumed to universally neutralize MOFs toxicity. Effective mitigation depends on MOFs composition, framework stability, degradation behavior, and spatial organization within the cellulose matrix. Comprehensive evaluation of both acute and long-term toxicity, including post-degradation effects, is therefore critical for the safe design of cellulose–MOF hybrid materials.

7. Challenges and future outlook

Cellulose-MOFs hybrid materials have some interesting characteristics that allow them to be considered for versatile applications. However, the problems associated with cellulose-MOFs also need to be considered. While the use of cellulosic materials enhances the number of MOFs, drug loading, and efficient delivery, the increasing content of nanosized particles degrades the rheological properties of nanocomposites due to their aggregation in the polymeric matrix (Javanbakht et al., 2021). Consequently, the stability of the composite and drug loading may be affected. Efforts must be shifted to also consider improvement in rheological properties (Esmailzadeh et al., 2024). The surface modification of nanosized particles using surfactants can enhance drug loading and drug delivery (Nezamzadeh-Ejhieh & Tavakoli-Ghinani, 2014).

Studies are limited to the application of cellulose-MOFs against particular cancer cell types. There are different types of therapies, e.g., chemotherapy, sonodynamic therapy, gene therapy, etc. (Li et al., 2023). The effectiveness of MOFs against cancer using sonodynamic therapy has been confirmed by researchers (Liao et al., 2023). However, the use of cellulose-MOFs in different therapies is limited. As a result, *in vivo* tests of various cancer cells are necessary to confirm the efficacy with high assurance (Noorian et al., 2019) and expand to other therapeutic applications.

It is crucial to consider research on biodegradability and biocompatibility, as these considerations will make biomedical applications easier. Studies conducted on cellulose-MOFs hybrid materials on cytotoxicity and drug release kinetics are also limited. The possible release of drugs after application in the environment needs to be considered. The inclusion of these considerations will allow for the determination of prospective applications. The toxicity problems related to MOFs should be addressed before or during clinical trials. MOFs are harmful because of their composition, shape, size, or stability, and the complex environment in which organisms exist. For example, zirconium can cause allergic skin reactions from long-term contact. Therefore, a thorough evaluation of MOFs toxicity is required. Functional groups on the cellulose or MOFs surfaces can reduce toxicity by improving biocompatibility or stability. Coatings or modifications may also reduce the leaching of toxic components. Thus, the detailed studies are essential to ensure their safe use in applications and their minimal environmental impact. The consideration of the synthesis process, i.e., *in-situ* and *ex-situ*, on the biodegradability and biocompatibility should also be undertaken.

Studies on short-term *in vivo* and acute toxicity have often been more prevalent, but a long-term toxicity study is needed. The absence of robust long-term safety data remains a fundamental and under-addressed bottleneck. Systematic investigations into chronic toxicity, long-term biodistribution, metabolic fate, and clearance pathways of cellulose–MOFs hybrids are exceedingly scarce. In particular, the persistence of metal nodes (e.g., Zr, Cu, Fe, or Zn) and organic linkers following prolonged exposure raises unresolved concerns regarding bioaccumulation, delayed inflammatory responses, and organ-specific toxicity. Moreover, the interfacial chemistry that confers enhanced stability and functionality to cellulose–MOFs hybrids may also alter degradation kinetics *in vivo*, complicating predictions of long-term behavior based solely on short-term assays. Current evidence is largely limited to in vitro models or short-duration animal studies, which are insufficient to support clinical translation. Therefore, comprehensive chronic toxicity, pharmacokinetic, and biodistribution studies—using standardized protocols and clinically relevant exposure windows—must be recognized as a priority research direction. Addressing this gap is essential not only for regulatory approval but also for establishing structure–safety relationships that can guide the rational design of next-generation cellulose–MOFs biomaterials with predictable and safe long-term performance (Horcajada et al., 2012; Rojas & Horcajada, 2020). Furthermore, cytotoxicity is strongly influenced by both the type of metal ion and its concentration (Zhou et al., 2022). In this context, the selection of metal ions and careful control of their loading levels are critical factors when designing cellulose–MOFs hybrid materials, as variations in metal identity and concentration can significantly affect their cytotoxic responses. Therefore, a systematic evaluation of metal ion type and concentration is necessary to ensure the biocompatibility and safe application of cellulose–MOFs hybrids, particularly for biomedical and environmental uses.

Again, these products take a longer time and are more costly to prepare (Chen et al., 2023b). The lengthy formulation process should be shortened, and cost-effectiveness should be a key consideration. Additionally, CMC and cotton are the primary research materials. Consideration must be given to other sources of cellulose and cellulose derivatives, such as nanocellulose. It might look into how cellulose is used across a variety of applications. A cellulose-MOFs substitute is still an experimental product, and cellulose-MOFs are still in the early stages of development. The development of a cellulose-MOFs substitute that is uniform, stable, green, and biocompatible in the human body requires significant effort and research.

Besides the developments of cellulose-MOFs composites, the rational design of stimuli-responsive and biodegradable linkers presents a compelling strategy to enhance functional adaptability and environmental compatibility. By integrating dynamic molecular motifs that undergo reversible conformational changes or cleavage in response to specific physical (e.g., pH, light) or biological stimuli (e.g., enzymes, redox gradients), MOFs can achieve on-demand modulation of porosity, guest release, and framework integrity tailored to application contexts such as targeted delivery and smart sensing. Such stimuli-responsive behaviors arise from the engineered flexibility of organic linkers within the coordination network, which can translate external cues into controlled structural transformations or bond scission events. Simultaneously, incorporating biodegradable linkers—constructed from bio-derived or labile chemical bonds—into the MOFs architecture ensures that, after functional deployment, the composite materials can break down into benign products, thus addressing concerns of persistence and toxicity in biological and environmental settings (Liu et al., 2024). The convergence of these design principles in cellulose-MOFs, leveraging the inherent biocompatibility and renewable nature of cellulose with tailored responsive and degradable coordination chemistry, offers a promising pathway toward next-generation sustainable smart materials (e.g., controlled release systems and adaptive scaffolds) with minimized ecological impact.

Furthermore, life cycle assessment (LCA) is essential for comprehensively evaluating the environmental footprint and sustainability of cellulose–MOF composites. The integration of cellulose with MOFs has the potential to significantly reduce overall environmental burdens compared with conventional materials, owing to cellulose's renewability, biodegradability, and low toxicity, while still maintaining the high functional performance required for diverse applications, i.e., water purification (Shen et al., 2025). Consequently, incorporating LCA into the design and evaluation of cellulose–MOFs is particularly important for biomedical applications, where environmental sustainability, safety, and regulatory considerations are critical. In parallel, artificial intelligence (AI) and machine learning (ML) approaches offer powerful tools for the rational design and optimization of advanced materials. These data-driven methods can be leveraged to accelerate the development of cellulose–MOFs with enhanced structural, functional, and biological performance, thereby advancing their potential in biomedical applications.

8. Conclusion

This study explores the potential of integrating active molecules, polymers, metals, and metal oxides into cellulose-MOFs hybrid materials for a wide range of biomedical applications. The exceptional properties of cellulose-MOFs—including their adaptability, high surface area, porosity, crystallinity, superior loading capacity, as well as their thermal and chemical stability—make them highly suitable as biomedical support materials. Additionally, their tunable affinity further enhances their versatility for targeted applications in drug delivery, biosensing, and tissue engineering. Despite these promising attributes, several challenges must be addressed before cellulose-MOFs can be fully developed for biomedical use. A particularly critical concern is the need for comprehensive research into their potential toxicity in human systems. Furthermore, to secure regulatory approval and facilitate their translation into clinical settings, it is essential to establish standardized, controlled, and reproducible production techniques. Addressing these factors will be pivotal in advancing cellulose-MOFs hybrids from laboratory research to practical biomedical applications. With continued investigation and refinement, cellulose-MOFs have the potential to emerge as commercially viable materials for biomedical applications. The findings presented in this study aim to provide researchers with a deeper understanding of the encapsulation capabilities of cellulose-MOFs, while also inspiring further innovations in this exciting and rapidly evolving field. This paper serves as a valuable resource for scientists, medical professionals, and industry experts interested in exploring the diverse biomedical applications of these hybrid materials.

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Declaration of competing interest

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

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Data availability

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

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