金属有机框架材料在中药抗菌成分递药系统中应用研究进展

黄俊峰, 谢子鸿, 张潇文, 胡文慧, 陈芳雯, 郑 琴, 杨 明, 岳鹏飞*

(江西中医药大学, 现代中药制剂教育部重点实验室, 江西 南昌 330004)

摘要: 抗生素滥用和细菌耐药性形势日益严重, 寻找新型抗菌剂迫在眉睫。中药许多成分具有显著的抗菌、抗炎、抗氧化等药理作用, 可通过多途径发挥作用, 是未来新型抗菌剂的重要来源之一。然而, 中药抗菌成分中存在稳定性差、溶解度低和智能释放水平低等问题, 限制了其抗菌制剂的广泛应用。金属有机框架材料因其具有高比表面积、高孔隙率、孔道可控、响应释放等优势, 成为中药抗菌成分良好的药物载体, 同时, 其不仅能显著改善中药抗菌成分的稳定性和溶解性, 还兼具抗菌、响应释放等能力。本文概述了细菌耐药机制及中药抗菌成分对抗耐药细菌的作用机制, 重点介绍了金属有机框架材料发展现状及其在中药抗菌成分递送系统方面的研究进展, 以期为中药抗菌成分制剂的研发创新提供参考。

关键词: 金属有机框架材料; 中药抗菌成分; 递药系统; 抗菌制剂

中图分类号: R943 **文献标识码**: A **文章编号**: 0513-4870(2025)05-1366-15

Research advances in metal-organic framework materials as the delivery system of antibacterial constituents of traditional Chinese medicine

HUANG Jun-feng, XIE Zi-hong, ZHANG Xiao-wen, HU Wen-hui, CHEN Fang-wen, ZHENG Qin, YANG Ming, YUE Peng-fei*

(*Key Laboratory of Modern Preparation of TCM, Ministry of Education, Jiangxi University of Chinese Medicine, Nanchang 330004, China*)

Abstract: With the increasing abuse of antibiotics and the growing resistance of bacteria, it is urgent to find new antibacterial agents. Numerous constituents of traditional Chinese medicine exhibit pronounced antibacterial, anti-inflammatory, and antioxidant pharmacological properties, often operating through multiple mechanisms, thereby positioning them as a vital source for the development of novel antibacterial agents in the future. Nevertheless, the antibacterial constituents of traditional Chinese medicine exhibit challenges such as inadequate stability, low solubility, and suboptimal intelligent release capabilities, which hinder their extensive application in antibacterial formulations. Metal-organic framework materials serve as highly effective drug carriers for antibacterial constituents of traditional Chinese medicine, attributed to their high specific surface area, elevated porosity, controllable pore dimensions, and responsive release properties. Furthermore, they not only enhance the stability and solubility of these antibacterial constituents while also exhibiting inherent antibacterial activity and responsive release capabilities. This paper presents a comprehensive overview of bacterial resistance mechanisms and the action pathways of antibacterial constituents of traditional Chinese medicine against resistant bacteria. Additionally, it highlights the current advancements in metal-organic framework materials and their application in

收稿日期: 2024-10-07; 修回日期: 2024-12-12.

基金项目: 江西省自然科学基金重点项目 (20242BAB26168); 国家自然科学基金面上项目 (82274108); 江西中医药大学中药制剂技术与制药装备创新团队 (CXTD-D-22006).

*通讯作者 E-mail: ypfpharm@126.com; pengfeiyue@jxutcm.edu.cn

DOI: 10.16438/j.0513-4870.2024-0960

the delivery systems for these antibacterial constituents, aiming to provide valuable insights for the research and innovation of formulations based on traditional Chinese medicine.

Key words: metal-organic framework material; antibacterial constituents of traditional Chinese medicine; drug delivery system; antibacterial preparation

抗生素滥用和细菌耐药性是当今全球面临的严重医疗挑战[1]。耐药细菌的出现使得治愈细菌感染变得愈加艰难, 因此, 寻找新型抗菌剂迫在眉睫。中药成分具有显著的抗菌作用, 可通过改变生物被膜和细胞膜的通透性、抑制细菌体内酶活性、影响细菌蛋白质核酸合成、逆转细菌耐药机制等多种途径发挥抗菌作用。但是, 中药抗菌成分仍存在着一定的局限性, 如溶解度低、稳定性差、智能释放能力低, 以及细菌感染微环境生物屏障, 一定程度上阻碍了其作为抗菌剂的广泛应用。

金属有机框架 (metal-organic framework, MOF) 材料是一类由金属簇或金属离子和有机配体构成的多孔物质, 具有高度可控结构、高比表面积、响应释放等特点[2]。基于其独特的优势, MOF 材料常被应用于多个领域, 包括医疗[3]、环境卫生[4]、食品保鲜[5]、气体吸附[6]、催化[7]、药物递送[8]等。MOF 材料在药物递送应用方面展现出巨大的潜力, 通过选择合适的金属簇或金属离子与有机配体及适宜的合成策略, 可制备出具有抗菌性能的 MOF 材料。此外, MOF 材料的多孔结构及高比表面积, 使其具有作为中药抗菌成分载体的潜力, 可改善中药抗菌成分溶解性、稳定性等问题。同时, MOF 材料具有响应释放特性, 可依赖外界或生理病理条件 (光、磁、温度、pH 等) 响应控制中药抗菌成分的释放。本文从上述方面概述细菌耐药机制及中药抗菌成分对耐药细菌的作用机制, 重点介绍金属有机框架材料的发展现状及其在中药抗菌成分递药系统方面的研究进展, 旨在为中药抗菌成分制剂的广泛应用提供参考与借鉴。

1 中药抗菌成分的研究现状与局限性

近年来, 细菌耐药性的产生已成为全球公共卫生领域面临的重要挑战。随着抗生素的广泛应用, 细菌通过多种机制逐渐发展出对常用药物的耐药性, 从而使传统治疗手段遭遇严峻考验。在此背景下, 中药抗菌成分因其多样化的作用机制, 对抗耐药细菌的研究受到越来越多学者的关注。然而, 中药抗菌成分在实际应用中仍存在一定局限性, 包括稳定性差、溶解度低及智能释放能力不足等。因此, 深入探讨中药抗菌成分及其作用机制, 并针对现有局限提出改进策略, 将为开发新型高效抗菌剂提供重要参考。

1.1 细菌耐药机制的产生

细菌耐药机制的形成不仅是当前抗菌治疗面临的重要挑战, 同时与中药抗菌成分的研究及其应用密切相关。深入理解细菌耐药的内在机制, 方能更准确地评估中药抗菌成分的价值和前景, 从而为开发更有效的抗菌策略提供坚实的理论基础和实践指导。细菌耐药机制可简单概括如下 (图 1): ① 生物被膜为细菌提供多种生理优势, 构筑了抵御宿主防御的物理屏障, 并通过减少抗菌剂扩散来保护细菌免受侵害, 提高其耐药性[9]; ② 细菌膜蛋白的改变降低了抗菌剂对细菌的敏感性, 从而使细菌产生耐药性[10]; ③ 细菌耐药基因出现后将表达生成抗生素降解酶—β-内酰胺酶, 水解破坏 β-内酰胺四元环, 导致含有该结构的抗生素失去作用[11]; ④ 群体感应 (quorum sensing, QS) 是细菌之间的通信系统, 细菌通过 QS 系统能够感知种群密度, 协调基因表达, 并调节其生理活动, 如抗生素耐药性的表达、毒力决定因子、运动、质粒转移、生物被膜的形成以及与真核宿主细胞的相互作用等, 从而有利于不断增长的群落, 并增加细菌性疾病的治疗难度[12]; ⑤ 细菌外排泵能够阻碍药物在细胞内的积累, 并致使细菌形成耐药性[13]。

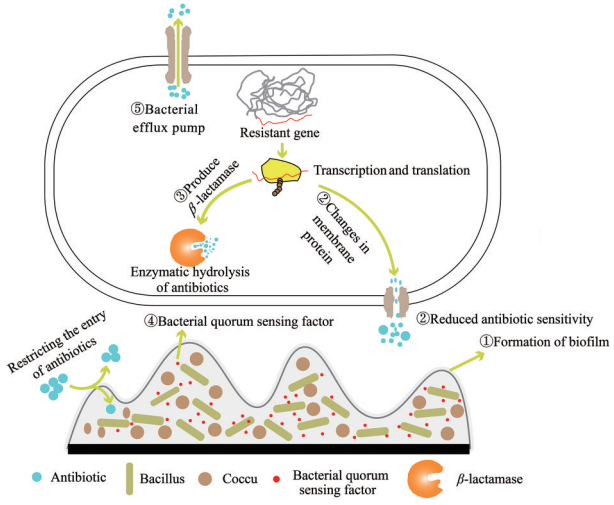

Figure 1 Mechanisms of bacterial drug resistance generation

1.2 中药抗菌成分及其作用机制

生物碱类、酚类、苷类、黄酮类、萜类、有机酸类以及有机硫化合物等中药抗菌成分通过多种机制对抗耐

药细菌。生物碱类和酚类成分主要通过破坏细菌细胞壁和细胞膜, 以及抑制细菌生物被膜形成等途径发挥抗菌作用; 同时, 它们还能够损伤细菌DNA, 干扰细菌群体感应, 并且抑制耐药基因表达。苷类和黄酮类成分都具备抑制细菌生物被膜形成和阻断细菌外排泵的能力。此外, 苷类还可破坏细菌的细胞膜, 降低耐药基因表达水平, 并干扰其代谢与免疫反应调节; 而黄酮则可阻止细菌群体感应现象发生, 并减少毒力因子及耐药相关酶的产量。至于萜类成分, 则通过增强细菌的质壁通透性, 干扰其能量代谢并提高对抗生素敏感性来对抗耐药细菌。最后, 有机酸和有机硫化合物主要是通过下调群体感应系统和毒力基因表达水平, 并影响细菌群体感应过程来对抗耐药细菌。各类中药抗菌成分的作用机制见表1[14-65]。

Table 1 Antibacterial constituents of traditional Chinese medicine and their antibacterial mechanisms

Classification	Model drug	Target strain	Mechanism of action	Ref.
Alkaloids	Chelerythrine	*Staphylococcus aureus*, multidrug-resistant *Staphylococcus aureus*	Protein synthesis inhibitor; destroying bacterial cell walls and cell membranes	[14]
	Berberine	*Escherichia coli*, *Staphylococcus aureus*	Inhibiting DNA duplication, RNA transcription, protein biosynthesis and enzyme activities	[15]
	Matrine	*Escherichia coli*	Efflux pump inhibitor	[16]
	Piperine	*Pseudomonas aeruginosa*	Efflux pump inhibitor	[17]
	Sanguinarine	Carbapenem-resistant *Serratia marcescen*	Anti-biofilm agent	[18]
	Jatrorrhizine	Multidrug-resistant *Staphylococcus aureus SA1199B*	Inhibiting bacterial drug efflux and the expression of *NorA* in the mRNA level	[19]
	Caffeine	*Pseudomonas aeruginosa*	Inhibiting biofilm formation and quorum-sensing	[20]
Phenolic compounds	Vanillin	*Mycobacterium smegmati*	Inhibiting biofilm formation	[21]
	Magnolol	Multidrug-resistant *Staphylococcus aureus*	Modulating the bacterial cell membrane penetration	[22]
	Hypericin	*Methicillin-resistant Staphylococcus aureus*	Inhibiting biofilm formation, fibronectin binding and virulence-related gene expression; *sarA* inhibitor	[23]
	Honokiol	Multidrug-resistant *Staphylococcus aureus*	Disrupting the GTPase activity and cell division	[24]
	Paeonol	*Pseudomonas aeruginosa*	Inhibiting biofilm formation; quorum-sensing inhibitor	[25]
	Resveratrol	*Staphylococcus aureus*	Efflux pump inhibitor	[26]
	Gingerol	*Escherichia coli*	Inhibiting transfer of r-plasmid	[27]
	Guaiacol	*Pseudomonas aeruginosa*	Quorum sensing inhibitor; biofilm inhibitor	[28]
	Chlorinated emodin	Methicillin-resistant *Staphylococcus aureus Enterococcus faecium*	Destroying bacterial DNA and bacterial cell membrane	[29]
	Aloe-Emodin	*Staphylococcus epidermidi*	Bacterial biofilm inhibitor	[30]
Glycoside	Baicalin	*Staphylococcus aureus*	Inhibiting efflux pumps, biofilm formation	[31]
	Pectolinarin	*Enterococcus faecalis*, *Enterococcus faecium*	Inhibiting biofilm formation; reducing quorum sensing gene expression	[32]
	Forsythoside A	*Pseudomonas syringae pv. actinidiae*	Inhibiting biofilm formation; interfering energy metabolism	[33]
	Isoquercitrin	*Escherichia coli*	Damaging to bacterial cell membrane	[34]
	Vitexin	*Staphylococcus aureus*	Interfering biofilm formation	[35]
	Polydatin	*Klebsiella pneumoniae*	Interfering biofilm formation; inhibiting efflux pumps	[36]
	Naringin	*Pseudomonas aeruginosa*	Bacterial biofilm inhibitor	[37]
	Paeoniflorin	*Streptococcus suis*	Efflux pump inhibitor; inhibiting biofilm formation	[38]
	Nobiletin	*Pseudomonas fluorescens*, *Pseudomonas aeruginosa*	Inhibiting the protein synthesis; destroying the permeability of the cell membrane	[39]
	Rutin	*Pseudomonas aeruginosa*, multidrug-resistant *Staphylococcus aureus*	Bacterial biofilm inhibitor; downregulating gene expression; interference with enzyme and protein synthesis	[40]
Flavonoid	Curcumin	*Pseudomonas aeruginosa*	Efflux pump inhibitor	[41]
	Luteolin	Methicillin-resistant *Staphylococcus aureus*	Bacterial biofilm inhibitor	[42]
	Kaempferol	*Staphylococcus aureus*	Bacterial biofilm inhibitor	[43]
	Silybin	Methicillin-resistant *Staphylococcus aureus*	Efflux pump inhibitor	[44]
	Quercetin	Carbapenem-resistant *Escherichia coli*, *Klebsiella pneumoniae*	Efflux pump inhibitor	[45]
	Galangin	*Staphylococcus aureus* DMST 20651	Penicillinase andreus DMST 2 inhibitor	[46]
	Phloretin	*Listeria monocytogenes*	Bacterial biofilm inhibitor; bacterial quorum sensing factor inhibitor	[47]
Terpenoid	Terpinen-4-ol	*Staphylococcus aureus*	Bacterial biofilm inhibitor	[48]

Continued

Classification	Model drug	Target strain	Mechanism of action	Ref.
	(*R*)-(+)-pulegone	*Escherichia coli*	Bacterial biofilm inhibitor	[49]
	Thymol	Methicillin-resistant *Staphylococcus aureus*	Disrupting the structure of the biofilm and killing the bacteria	[50]
	Eugenol	Carbapenem-resistant *Klebsiella pneumoniae*	Disrupting the structure of the biofilm and killing the bacteria	[51]
	Carvacrol	Multidrug-resistant *Staphylococcus aureus*	Efflux pump inhibitor	[52]
	Cryptotanshinone	Methicillin-resistant *Staphylococcus aureus*	Bacterial energy metabolism disruptor	[53]
	Menthol	*Chromobacterium violaceum*, *Escherichia coli*, *Pseudomonas aeruginosa*	Bacterial biofilm inhibitor; bacterial quorum sensing inhibitor	[54]
	Linalool	*Chromobacterium violaceum*, *Pseudomonas aeruginosa*	Bacterial biofilm inhibitor; bacterial quorum sensing inhibitor	[55]
	Limonene	*Staphylococcus aureus* K2068	Efflux pump inhibitor	[56]
	Patchouli alcohol	*Helicobacter pylori*	Efflux pump inhibitor	[57]
	Cinnamaldehyde	Methicillin-resistant *Staphylococcus aureus*	*β*-Ethicillantibiotic adjuvant; bacterial biofilm inhibitor	[58]
	Perillaldehyde	*Pseudomonas aeruginosa*	Bacterial biofilm inhibitor	[59]
Organic acid	Gallic acid	Methicillin-resistant *Staphylococcus aureus*	Bacterial biofilm inhibitor	[60]
	Chlorogenic acid	Carbapenem-resistant *Klebsiella pneumoniae*	Downregulating the expression level of the quorum sensing system and virulence-related genes	[61]
	Ferulic acid	*Shigella flexneri*	Bacterial biofilm inhibitor	[62]
	Rosmarinic acid	*Staphylococcus aureus*	Bacterial biofilm inhibitor	[63]
Organic sulfur compounds	Allicin	*Pseudomonas aeruginosa*	Bacterial biofilm inhibitor	[64]
	Sulforaphane	*Pseudomonas aeruginosa*	Bacterial biofilm inhibitor; quorum sensing inhibitor	[65]

1.3 中药抗菌成分的局限性

中药抗菌成分面临多重限制, 其中稳定性差尤为显著。例如, 黄芩中的黄芩苷在不同pH值和温度下易发生降解, 从而导致其稳定性下降并削弱抑菌活性[66]。此外, 溶解度低也是一个亟需关注的问题。传统中药中的抗菌成分普遍存在溶解度不足的问题, 低溶解度导致药物浓度降低, 从而影响其对细菌感染的有效治疗效果。如姜黄根茎中的姜黄素, 其低溶解度及水溶性差使其应用受限。然而, 通过改善姜黄素的溶解度, 并结合亲水超支化聚甘油聚合物使用, 可以显著增强其对金黄葡萄球菌的抗菌效果[67]。更重要的是, 现有中药抗菌成分在智能释放能力方面也较为欠缺。由于无法根据感染部位的具体需求实现精准且适时的药物释放, 致使作用部位药物浓度难以有效维持, 从而影响了抗菌效果。

稳定性、溶解度和智能释放能力是影响中药成分抗菌作用的重要因素。这些因素的不理想表现在一定程度上削弱了其在外界环境及生理条件下的抗菌效能, 并限制了其在临床应用中的潜力。因此, 为充分发挥中药抗菌成分的最佳疗效, 应尽可能提高其溶解度、稳定性以及智能释放能力。MOF材料的发展为提升中药抗菌成分的疗效提供了一种有效策略。

2 MOF材料的发展概述

本节主要回顾了MOF材料的发展历程及一些常见类型的MOF材料, 重点分析这些常见MOF材料的基本性质, 这对提高中药抗菌成分的稳定性、溶解度及智能释放能力具有重要意义。表2[68-80]总结了一些常见MOF材料的基本性质。

2.1 MOF材料发展历程

MOF材料的概念最早在20世纪90年代由Yaghi等[81]在《自然》杂志上提出。随后, 各种最具代表性的MOF材料相继问世。Yaghi团队[82]通过从金属氧簇化学结构获得启示, 合成了经典三维结构的MOF-5材料, 该材料内含55%～61%空间可供客体分子进入, 并具有高达300 ℃的热稳定性。MOF-5的出现标志着MOF材料发展中一个重要里程碑。同年, 香港科技大学Chui等[76]报道了一种名为多孔骨架金属配位聚合物 (Hongkong University of Science and Technology-1, HKUST-1) 的新型复合材料, 其特点是包含一个由大方形孔 (9 Å) 组成的相交三维系统, 系统内部通道化学修饰能力强并具有高达240 ℃热稳定性。2004～2005年, Férey等[73,74]通过计算机辅助设计结合目标化学成功地合成了两种超大孔特征类分子筛型MOFs, 尺寸分别为25、29和34 Å, 并且比表面积高达3 100和5 900 $m^2 \cdot g^{-1}$。该团队不仅克服了传统单晶X射线衍射技术在分析大型单胞晶体结构时所面临局限性问题, 并创新地提出利用计算机模拟来辅助预期结构合成这一新途径, 在推动MOF材料发展方面起到巨大作用。至2006年, Yaghi团队[72]合成了12种沸石咪唑骨架材料——ZIF-1 (zeolitic imidazolate framework-1) 到 ZIF-

Table 2 Fundamental characteristics of various prevalent types of MOF materials. MOF: Metal-organic framework

MOF	Metal node	Organic linker	Structure type	Pore size	Researcher	Ref.
MOF-5	Zn^{2+}	1,4-Benzenedicarboxylate	3D porous network structure	18.5 Å	Eddaoudi M	[68]
IRMOF-10	Zn^{2+}	4,40-Biphenyldicarbonyl chloride	3D porous network structure	> 20 Å	Eddaoudi M, Yin DG	[68,69]
IRMOF-3	Zn^{2+}	2-Aminoterephthalic acid	3D porous network structure	18.6 Å	Eddaoudi M, Cheng HD	[68,70]
ZIF-8	Zn^{2+}	2-Methylimidazole	Zeolite imidazolium ester backbone structure	20 nm	Qi XY, Park KS	[71,72]
MIL-100	Cr^{3+}	Benzene-1,3,5-tricarboxylate	3D network of super tetrahedra	6.5−30 Å	Férey G	[73]
MIL-101	Cr^{3+}	Terephthalic acid	3D network of super tetrahedra	29−34 Å	Férey G, Khan NA	[74,75]
HKUST-1	Cu^{2+}	Benzene-1,3,5-tricarboxylic acid	3D network structure	1 nm	Chui S	[76]
PCN-222	Zr^{4+}	5,10,15,20-Tetra(4-carboxyphenyl) porphyrin	Rod-shaped structure	2.7 nm	Zhang FZ	[77]
UiO-66	Zr^{4+}	1,4-Benzenedicarboxylate	3D porous structure	< 10 Å	Kandiah M, Bambalaza SE	[78,79]
CD-MOF-1	K^{+}	γ-Cyclodextrin	Extended 3D networks structure	1.7 nm	Roy I	[80]

12, 其中ZIF-8热稳定性可至550 ℃且在不同溶剂环境下显示优异化学稳定性而备受关注。此后两年内, ZIF家族被陆续报道了ZIF-20到ZIF-23、ZIF-68、ZIF-69、ZIF-70、ZIF-95和ZIF-100等多个新颖结构[83-85], 使得MOF材料得到进一步拓展。迄今为止, 已经开发出超过20 000多种MOF材料, 其中, 网状金属有机框架(isoreticular metal-organic frameworks, IRMOFs)、类沸石咪唑酯骨架 (zeolitic imidazolate frameworks, ZIFs)、拉瓦锡材料研究所骨架 (materials of institute Lavoisier frameworks, MILs) 和孔−通道式骨架(pocket-channel frameworks, PCNs)材料, 这4种MOFs的研究尤为广泛。

2.2 MOF材料作为药物载体的主要类型

2.2.1 IRMOFs 作为常见的MOF材料之一, IRMOFs以MOF-5为原型, 由八面体Zn-O-C簇与苯环连接构成。通过引入有机基团如-Br、-NH_2、-OC_3H_7、-OC_5H_{11}、-C_2H_4、-C_4H_4等进行功能化, 可以调整其三维多孔结构的孔径。联苯、三苯基、芘等长分子结构可进一步扩大孔径[68]。IRMOFs具备较大空腔和均匀孔隙结构, 能够容纳多种客体物质, 并表现出良好的稳定性、高负载能力以及生物安全性。Yin等[69]使用IRMOF-10 (isoreticular metal-organic framework-10) 作为药物载体成功实现了对姜黄素的63.96%负载率, 并且在400 ℃之前骨架相对稳定。在给定剂量 (5、10、15、20、25、30和35 μg·mL^{-1}) 下, IRMOF-10对HepG2细胞无毒性作用。Cheng等[70]利用IRMOF-3作为药物载体成功负载了抗癌药物10-羟基喜树碱, 载药量达到46%。即使在最高剂量 (100 μg·mL^{-1}) 下, HeLa细胞相对存活率仍超过90%, 表明IRMOF-3具有较低的细胞毒性。Cai等[86]采用IRMOF-16作为载体, 成功实现了姜黄素的负载, 载药量高达65.67%, 并且在300 ℃条件下保持骨架完整展示出优异热稳定性。体外生物相容性试验未发现该载体的明显毒性。

2.2.2 ZIFs 作为MOFs家族中的一员, ZIFs因其独特的优势备受生物医学研究关注, 包括可调孔径、高比表面积、高热稳定性、生物相容性和易于表面修饰等。ZIFs的可调孔径特性为其在各种生物医学应用中功能化和可行性奠定了基础。Qi等[71]开发了一种基于pH敏感沸石咪唑酸盐框架 (ZIF-8) 的超温和简单方法, 以增加孔隙度, 并提供最大20 nm的孔径, 比平均水平大8倍。他们还在ZIF-8中引入葡萄糖氧化酶用于生物蚀刻, 在产生稳定介孔装载乳糖酶时保留了良好的酶活性。此外, ZIFs具有高比表面积、高稳定性和孔隙率, 在药物封装和生物分子等方面具有潜力。De Moura Ferraz等[87]建立并表征了BNZ@ZIF-8体系来解决苯并硝唑 (benznidazole, BNZ) 药物毒性高且生物利用度低问题。溶出度研究证实pH敏感药物递送系统可以量化释放BNZ, 并可提高其生物利用度。MTT试验显示, BNZ@ZIF-8对细胞活力没有显著影响且统计学上无显著毒性作用。经过表面修饰的ZIFs能够有效改善其在非靶向治疗及体内生物相容性方面的局限性。Chen等[88]以叶酸 (folic acid, FA) 修饰的ZIF-8包封表没食子儿茶素-3-没食子酸 (epigallocatechin-3-gallatea, EGCG) 形成PEG (polyethylene glyco)-FA/EGCG@ZIF-8纳米颗粒, 纳米颗粒上叶酸与癌细胞过表达FA受体之间进行目标识别, 并能有效内化到细胞内部。经过叶酸修饰的ZIF-8纳米颗粒对HeLa细胞具有明显靶向抑制作用, 并增强了其生物相容性。此外, ZIFs与其他结构材料的结合可用于构建具有多功能治疗目的的智能系统。例如: 集抗菌、成骨、抗炎于一体的新型药物释放系统[89]; 集光动力、光热和化疗的联合治疗的ZIF-90生物相容性智能平台对抗肿瘤[90]等。

2.2.3 MILs MILs是一种特殊的MOF材料, 通过计算机辅助模拟形成的新型晶体MOFs。它由三价过渡

金属离子 (如Fe^{3+}、Cr^{3+}) 与羧酸基配体结合而成, 并具有极高的比表面积。其中最具代表性的是MIL-100 (materials of institute lavoisier-100) [73] 和 MIL-101[74]。介孔MIL-100因其极高的比表面积、孔隙率及可生物降解特性而备受关注, 已被Abucafy等[91]用于制备多孔胶囊封装抗肿瘤药物甲氨蝶呤和胶原酶。该胶囊对A-375癌细胞系表现出相对于正常细胞高达9倍的选择性毒性, 表明其在靶向癌细胞治疗中具有显著的应用潜力。除了极高的比表面积, MILs材料还具备和其他MOF材料相同的特性, 例如易于进行表面功能化及组合形成复合材料。Li等[92]合成了MIL-101 (Fe), 并将Ag^{+}取代Fe^{3+}均匀引入到MOF中, 得到了具有高效金属离子释放和强大抗菌效能的MIL-101 (Fe)@Ag。Silva等[93]为改善MIL-101 (Cr) 与布洛芬 (ibuprofen, IBU) 和尼美舒利 (nimesulide, NMS) 之间相互作用, 通过对MIL-101 (Cr) 进行氨基化修饰, 生成了NH_2-MIL-101 (Cr), 显著提升了其对IBU和NMS药物的负载能力。

2.2.4 PCNs PCNs材料具有复杂的孔型结构和三维正交通道, 与IRMOFs相比, PCNs结构更为复杂, 是一类高孔隙率、大孔径且具备良好生物相容性的多孔纳米异二聚体材料。通常由有机配体和金属离子通过配位键自组装而成, 形成三维网络结构。某些PCNs材料表现出卓越的热稳定性, 在高温环境下仍能保持优异性能。以HKUST-1为例, 这种材料具有三维通道系统和正交排列的1 nm孔径, 以固态形式呈现约40%的孔隙率。其通道内部可进行化学修饰, 并展现出高达240 ℃的热稳定性[76]。此外, PCN-222是由锆离子 (Zr^{4+}) 和5,10,15,20-四(4-羧基苯基)卟啉组成的六角形棱镜晶体MOF, 具备高孔隙率和良好的生物相容性。该材料可用于改善Ag纳米粒子缺陷并实现协同抑菌作用[77]。

2.2.5 其他MOF材料 除了上述材料外, 奥斯陆大学金属有机框架材料 (University of Oslo, UiO) 同样具有高度稳定性和可调控孔径的特点, 是一类由Zr^{4+}离子和二羧酸配体构成的三维多孔材料。例如, UiO-66是通过Zr与对苯二甲酸中的氧原子进行配位而形成的, 其热稳定性可达到540 ℃, 在对苯二甲酸连接下形成八面体结构[78]。UiO所具备的特殊八面体结构和高度稳定性使其在催化、气体吸附以及药物递送等领域表现出卓越性能。此外, 与其他MOF材料相比, 生物金属有机框架 (biological-metal organic framework, Bio-MOF) 主要区别在于引入了生物分子作为有机连接基团, 如糖、核苷酸、氨基酸、肽、蛋白质和卟啉等, 从而显著提高材料的生物相容性和多功能性。Lucena等[94]采用溶热法合成了一种带有4,4-联苯二甲酸和腺嘌呤组分的发光无毒多孔Zn (II) 配位聚合物 (biological-metal organic framework-Zn, Bio-MOF-Zn), 该Bio-MOF-Zn表现出优秀负载能力以及药物释放效果, 可应用于药物递送与成像领域。

3 MOF材料用于中药抗菌成分高效递送的研究进展

MOF材料种类繁多且具备高比表面积、可调孔径和高负载能力, 使其成为理想的药物递送载体。MOF材料不仅能够显著提高中药抗菌成分的稳定性和溶解度, 还展现出卓越的抗菌活性。许多金属离子 (例如Ag^{+}、Zn^{2+}、Cu^{2+}等) 本身就具有抗菌活性, 并且部分有机配体也具备良好的抑菌活性和生物相容性[95]。这使得MOF材料不仅可以在药物递送中发挥作用, 还可以直接用作抗菌剂。另外, 基于MOF材料易于表面修饰和功能化的优势, 可以构建多种智能响应型MOF药物递送系统, 这些系统能够对pH值、氧化还原物质、温度及光等单一刺激做出反应, 同时也能实现光–热和光–pH等多重响应。这为解决中药抗菌成分智能释放能力低下的问题提供了有效途径, 从而在中药抗菌成分的高效递送方面发挥重要作用。目前, 以智能响应型MOF药物递送系统应用于中药抗菌成分缺乏总结。因此, 本部分在概述MOF材料如何提高中药抗菌成分稳定性、溶解度的同时, 重点介绍用于中药抗菌成分高效递送的不同智能响应型MOF药物递送系统设计策略及其研究进展, 以期为新型中药抗菌成分制剂的研发和广泛应用提供参考。图2展示了不同智能响应型MOF药物递送系统应用于抗菌成分递送的设计策略。表3[96-108]列举了近年来应用于中药抗菌成分的智能响应型MOF递送系统。

3.1 金属有机框架材料改善中药抗菌成分稳定性与溶解度

3.1.1 金属有机框架材料改善中药抗菌成分稳定性 金属有机框架的多孔结构能够有效地将中药抗菌成分封装于其内部孔隙, 从而减小外部环境因素 (如光照、pH值及温度等) 对这些成分的影响, 进而提高其稳定性。众所周知, 姜黄素在中性和碱性条件下表现出显著的不稳定性, 易发生降解, 并生成姜阿魏酰甲烷、阿魏酸及香草醛。Moussa等[109]成功地将姜黄素封装于环糊精–金属有机框架 (byclodextrin-metal organic framework, CD-MOF) 中, 将装载有姜黄素的CD-MOF晶体溶解于水中, 会在姜黄素、γ-CD (γ-cyclodextrin) 及钾离子之间形成一种独特的复合物。在pH 11.5时, 与游离姜黄素及姜黄素-γ-CD相比, 该复合物中的姜黄素稳定性提高了至少3个数量级。Pan等[110]合成了3种具有不同三维结构的γ-环糊精金属有机框架 (γ-cyclodextrin-metal organic framework, γ-CD-MOF),

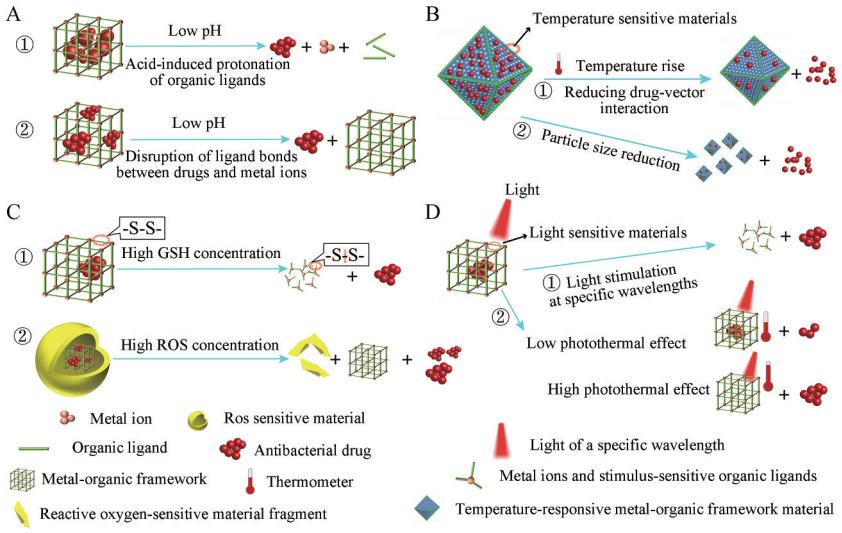

Figure 2 Schematic design strategy of different smart-responsive MOF drug delivery systems for antibacterial drug delivery. A: pH-responsive MOF drug delivery system. ①: Proton induced ligand bond breaking under acidic conditions; ②: Disrupting the formation of ligand bonds between drugs and metal ions; B: Temperature-sensitive MOF drug delivery system. ①: Reducing drug-vector interaction; ②: Particle size reduction; C: Redox-responsive MOF drug delivery system. ①: Breaking disulfide bonds under high glutathione conditions; ②: High reactive oxygen conditions destroy outer reactive oxygen sensitive materials such as poly-*L*-lysine; D: Light-responsive MOF drug delivery system. ①: MOF controls drug release by chemical bond cleavage under light stimulation at specific wavelengths; ②: MOF controls drug release through photothermal effect. ROS: Reactive oxygen species; GSH: Glutathione

并成功实现了百里香酚与γ-CD-MOF的结合, 从而显著提高了百里香酚的热稳定性。此外, 体外抑菌实验结果表明, 负载百里香酚的γ-CD-MOF在其包封量增加时, 其抑菌效果显著增强。Soomro等[111]采用直接纳米沉淀技术将大黄素 (physcion, PHY) 封装于ZIF-8, 成功制备了PHY@ZIF-8纳米颗粒, 该颗粒在25天后仍表现出显著的稳定性。热重分析结果显示, PHY自207 ℃起逐渐失重, 并在约300 ℃时分解约99%。而包封后的PHY则在260 ℃才开始分解, 这表明ZIF-8的包封有效抑制了PHY的降解, 从而提高了其稳定性。此外, 他们还通过琼脂孔扩散法研究了PHY@ZIF-8的抗菌活性, 结果表明, 与游离PHY相比, 包封形式的PHY对革兰阴性菌和革兰阳性菌具有显著的抑制效果。

3.1.2 金属有机框架材料改善中药抗菌成分溶解度

具有高比表面积、可调孔径和优异负载能力的MOF经过表面修饰, 通过引入亲水性物质, 可以显著提高整个体系的亲水性, 从而改善中药抗菌成分在水中的溶解度。Aykaç等[112]利用极性磷酸基团与纳米MOF表面不饱和金属路易斯酸位点之间的协同结合能力, 在MIL-100 (Fe) 表面形成了一个稳定的水溶性环状低聚糖β-CD (β-cyclodextrin) 聚合物壳层。经β-CD聚合物修饰后的MIL-100 (Fe) 能够显著提高药物的溶解度。另一方面, MOF作为药物载体, 通过其纳米级孔道限制药物的结晶, 并有效地将药物分子均匀分散于这些孔道内。在水介质中, 非晶态药物通过MOF的水解从药物@MOF复合物中迅速释放, 从而增强药物的溶解度。Suresh等[113]将药物包封于MOF-5中, 形成药物@MOF复合物。这一策略不仅有效抑制了药物的结晶, 还在MOF水解后促进了药物在溶解介质中的快速释放。具体而言, 将姜黄素 (curcumin, CUR) 包封于MOF-5中形成CUR@MOF-5, 通过MOF水解实现CUR分子的即时释放, 进而导致其快速溶解。在模拟胃液 (simulated gastric, SG) 介质中观察到最大质量浓度 (maximum mass concentration, C_{max}) 为8.5 mg·mL^{-1}, 而在磷酸盐缓冲液 (phosphate buffer saline, PBS) 介质中的C_{max}为13.9 mg·mL^{-1}; 相比之下, 纯CUR在SG中的C_{max}仅为2.12 mg·mL^{-1}, 在PBS中的C_{max}仅为0.95 mg·mL^{-1}。这表明, 与纯CUR相比, CUR@MOF-5在溶解时展现出更高的CUR质量浓度。Liu等[114]利用CD-MOF成功包封了不溶性化合物18β-甘草次酸 (18β-glycyrrhetinic acid, GA), 形成GA@CD-MOF纳米复合物, 其溶解度比纯GA高出7 780倍。He等[115]采用超临界二氧化碳辅助浸渍法, 将不溶性药物厚朴酚 (honokiol, HNK) 引入CD-MOF的孔隙中, 所获得的负载HNK的CD-MOF (HNK@CD-MOF) 表现出显著提高的表观溶解度和溶解速率。在pH为7.4的缓冲液中, HNK@CD-MOF对比原始HNK, 其表观溶解度提升了19.9倍。此外, HNK@CD-MOF在24 h内的累积释放率约为94%; 而

Table 3 Intelligent-responsive MOF delivery systems applied to antibacterial constituents of traditional Chinese medicine. ZIF: Zeolitic imidazolate framework; UiO: University of Oslo; PCN: Pocket-channel framework; Cupp: Cu (II) tetrakis (4-carboxyphenyl) porphyrin; PELA: Polyethylene glycol-polycaprolactone anhydride; TOCNF: 2,2,6,6-Tetramethylpiperidine-1-oxy radical oxidized cellulose nanofiber; Pec: Pectin; ICG: Indocyanine green; PLA: Polylactic acid; PCM: Phase-change material; PUL: Pullulan; PVA: Polyvinyl alcohol; Eu: Eugenol; APG: Apigenin; CCM: Curcumin; CT: Citral; BBH: Berberine hydrochloride; Cur: Curcumin; THY: Thymol; BBR: Berberine; Ac: Allicin; CAR: Carvacrol

Delivery system	Stimulus condition	Sensitive material	Drug	Advantage	Ref.
Honokiol@ZnO-ZIF-8	pH	ZIF-8	Honokiol	Honokiol@ZnO-ZIF-8 achieves pH-responsive release of honokiol, which improves the antimicrobial capacity of honokiol and prolongs the efficacy period.	[96]
Eu@B-UiO-66/Zn	pH	Eu@B-UiO-66/Zn	Eugenol	pH-responsive release of eugenol with potent, synergistic and long-lasting antimicrobial effects against *Escherichia coli.* and *Staphylococcus aureus.*	[97]
APG@ZIF-8	pH	ZIF-8	Apigenin	APG@ZIF-8 exhibits pH-responsive slow release and enhances the stability of apigenin and synergistically improves its antimicrobial activity.	[98]
CCM@ZIF-L	pH	ZIF-L	Curcumin	Enhanced curcumin stability and pH-responsive release of curcumin	[99]
CT@ZIF-8	pH	ZIF-8	Citral	CT@ZIF-8 exhibits pH-responsive release of citral andincreases stability of citral	[100]
BBH@ZIF-8@ZIF-67	pH	ZIF-8@ZIF-67	Berberine hydrochloride	pH-responsive release of berberine hydrochloride; enhancement of BBH antimicrobial effect	[101]
Zn-MOF@$Ti_3C_2T_x$	Near infrared	Zn-MOF	Curcumin	High photothermal efficiency and light-responsive stimulation for curcumin release; high ROS production at 808 nm near infrared radiation	[102]
Cur/CuPP-PELA	Near infrared	CuPP	Curcumin	Light-responsive release of curcumin; enhancement of curcumin antimicrobial activity	[103]
THY@PCN/PUL/PVA	Visible light	PCN-224	Thymol	Slow-release thymol; improving bactericidal properties under light stimulation	[104]
MOFs@Ag-B@BBR	Visible light	MOFs@Ag-B	Berberine	Photocatalytic activity and enhancement of antimicrobial activity of berberine	[105]
Ac@ZIF-8/Ag	pH	ZIF-8	Allicin	pH-responsive release of allicin; enhancement of allicin antimicrobial activity	[106]
CAR@ZIF-8/TOCNF/Pec	pH, enzyme	ZIF-8/TOCNF/Pec	Carvacrol	pH-responsive and enzyme-responsive to release of carvacrol	[107]
Cur-ICG@ZIF-8/PLA/PCM	Near infrared, pH	ICG@ZIF-8/PLA/PCM	Curcumin	Photothermal and pH-responsive release of curcumin; improving antimicrobial properties of curcumin	[108]

相较之下, HNK@γ-CD 和单独使用 HNK 仅分别达到了 81% 和 69%。图 3 展示了 MOF 材料提高中药抗菌成分稳定性和溶解度的机制。

3.2 金属有机框架材料调控中药抗菌成分的体内递送

3.2.1 pH 响应型 MOF 药物递送系统 由于机体免疫反应和病原细菌的厌氧代谢, 感染组织周围环境的 pH 值通常较正常组织低。已有研究表明, 感染组织的 pH 范围为 5.0～6.5, 而正常组织的 pH 为 7.4[116]。因此, 基于 pH 值显著差异和 MOF 材料的独特优势, 研究者们开发设计了响应 pH 值信号的 MOF 药物递送系统。该递药系统能够在特定的 pH 值环境下释放药物, 并实现对感染组织精准靶向治疗, 从而提高治疗效果。

pH 响应型 MOF 药物递送系统的主要设计策略包括: ① 利用质子诱导的配位键断裂。在酸性条件下, 金属有机框架中含有可电离化学基团的有机配体易于质子化, 从而引起结构转变或破坏金属与有机配体之间的配位键, 进而导致 MOF 的崩溃。例如, 富含咪唑基的 ZIF 家族、富含羧基的 MIL 和 UiO 家族; ② 利用药物与金属离子形成对 pH 敏感的化学键。当 pH 值发生变化时, 药物与金属离子分离, 并释放到靶向部位, 以提高药物稳定性和利用率。

Yang 等[101] 合成了负载盐酸小檗碱 (berberine hydrochloride, BBH) 的复合材料 BBH@ZIF-8@ZIF-67, 在 pH 5.0、6.0 和 7.4 的 PBS 缓冲液中进行的体外释放实验结果显示, BBH@ZIF-8、BBH@ZIF-67 和

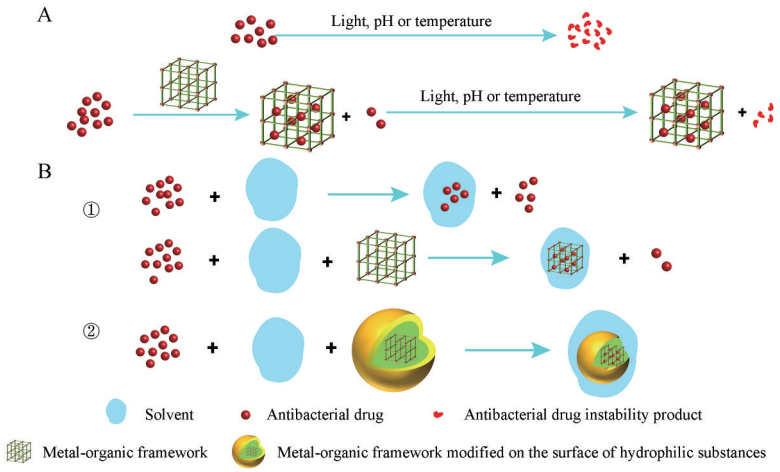

Figure 3 The mechanisms through which metal-organic framework materials improve the stability and solubility of antibacterial constituents in traditional Chinese medicine. A: Metal-organic frameworks significantly enhance the stability of antibacterial constituents in traditional Chinese medicine mechanism; B: Metal-organic frameworks significantly enhance the solubility of antibacterial constituents in traditional Chinese medicine mechanism. ①: Confinement effect in pore space; ②: Surface modification of hydrophilic substances

BBH@ZIF-8@ZIF-67均表现出pH响应释放行为。在酸性条件下, Co-N键与Zn-咪唑键导致金属离子释放, 并与BBH协同增强抗菌效果。Wang等[97]以层次化多孔B-UiO-66 (benzoic acid-university of oslo-66)作为载体, 负载天然抗菌物质丁香酚 (eugenol, Eu), 并进一步与二价锌离子络合形成协同抗菌体系Eu@B-UiO-66/Zn。该体系以丁香酚与Zn^{2+}离子之间配位键断裂作为“开关”, 实现了对丁香酚pH响应可控释放。在pH 5.8条件下, Eu@B-UiO-66/Zn的丁香酚释放量达到80%, 显著高于pH 8.0条件下的解离程度。此外, Eu@B-UiO-66/Zn在24 h后对大肠杆菌和金黄葡萄球菌分别展示出96.4%和99.7%的抑制效果, 显著优于游离态丁香酚和Eu@B-UiO-66。

3.2.2 氧化还原响应型MOF药物递送系统 氧化还原响应型MOF药物递送系统是一种通过控制药物在特定氧化还原环境下的释放来实现精准治疗的系统。其基本原理是根据细菌感染微环境与正常生理组织环境下还原物与氧化物的浓度差异进行调节。众所周知, 在细菌感染的组织微环境中, 超氧阴离子自由基 ($•O^{2-}$)、过氧化氢 (H_2O_2) 和单线态氧 ($_1O^2$) 等活性氧基团 (reactive oxygen species, ROS) 的水平和对应强还原性谷胱甘肽 (glutathione, GSH) 水平显著提升。

设计二硫键是氧化还原响应型MOF药物递送系统中常用的策略。通过利用二硫键连接药物和载体, 在高GSH浓度下, 共价键断裂, 从而实现药物的释放。Lei等[117]采用铁、铝或锆作为金属节点, 并以4,4′-二硫代双苯甲酸 (4,4′-dithiobisbenzoic acid, 4,4′-DTBA)作为有机配体, 在40 ℃条件下合成MOF-Zr, 通过将姜黄素引入到MOF-Zr中制备得到姜黄素@MOF-Zr纳米粒子。由于GSH在肿瘤细胞中通常过表达, 过量的GSH可以切割掉4,4′-DTBA中的二硫键。因此, 该纳米粒子在肿瘤环境下显示出更快速的药物释放行为, 并促进癌细胞死亡。

Xiang等[118]根据细菌感染微环境中ROS水平上升这一特点, 制备了聚-*L*-赖氨酸 (poly-*L*-lysine, PLL)修饰的ZIF-8纳米颗粒, 以实现ROS响应环丙沙星 (ciprofloxacin, CIP)释放和姜黄素触发光动力效应联合治疗耐药细菌感染。在细菌微环境下, 通过ROS响应性切割硫代酮连接物使PLL聚合链断裂, 并有效地释放CIP。此外, 负载的姜黄素可充当光敏剂产生单线态氧 ($_1O^2$) 和超氧阴离子自由基 ($•O^{2-}$)。因此, 该纳米颗粒能够有效杀灭MRSA并破坏细菌生物膜。在小鼠模型中进行测试时发现所制备纳米颗粒表现出优异的生物安全性和协同效果, 并成功治愈98.81% MRSA感染小鼠。

3.2.3 光响应型MOF药物递送系统 光响应型MOF药物递送系统是指利用金属有机框架作为药物载体, 在特定波长的光刺激下, 通过化学键裂解或光热转化来控制药物释放。Guo等[102]等通过在$Ti_3C_2T_x$纳米片上原位生长生物活性锌基金属有机框架 (zinc-based metal organic framework, Zn-MOF), 引入天然抗菌剂姜黄素作为配体, 构建了一种新型抗菌平台。Zn-MOF@$Ti_3C_2T_x$不仅具备优异的光热性能, 还可实现对Zn^{2+}和姜黄素的可控释放, 并展示出对金黄色葡萄球菌和大肠杆菌具有优异生物相容性和多模式抗菌能力。此外, He等[105]等设计了一种治疗感染伤口的光响应金属有机

框架水凝胶, 该水凝胶利用MOF装载天然药物小檗碱实现了抗炎药物缓释。同时, 在MOF表面引入银纳米颗粒不仅促进了其在可见光下产生ROS, 而且为硼酸基团附着在目标细菌上提供位点, 加速ROS传递。该水凝胶以低质量浓度 (37.5 μg·mL^{-1}) 对金黄色葡萄球菌和MRSA表现出强大的光动力抗菌活性。

3.2.4 温度响应型MOF药物递送系统 与光响应型MOF药物递送系统不同, 温度响应型MOF药物递送系统根据外界环境温度的变化来调控药物与载体之间的相互作用力, 并实现药物释放。Silva等[119]以金纳米粒子为核心, 通过修饰ZIF-8壳层上的镧系离子, 成功合成了具有热响应吸附、加热和监测温度三重功能的响应型MOF纳米材料, 并将其成功应用于咖啡因 (caffeine, CAF) 和5-氟尿嘧啶 (5-fluorouracil, 5-FU) 这两种药物的热控载体。通过在辐照、水浴和室温下进行热控释放行为测试发现, 随着温度升高, CAF与5-FU药物释放量明显增大。此外, 一些温度响应型MOF药物递送系统通过引起粒径减小或由液态转变为固态等方式, 在受到温度刺激时改变其性质或形态从而实现对药物的控制释放。Lin等[120]制备合成了具有对温度敏感的MIL载体材料, 随着温度升高, 其颗粒粒径逐渐减小。当将环境温度从25 ℃提高至37 ℃时, 该载体中所负载药物的释放率增加了1倍。Nie等[103]提出了一种用于治疗伤口感染的温度敏感型MOF水凝胶, 该水凝胶在表皮温度的刺激下由液体转化为固体提高其附着能力和抗菌活性。

3.2.5 其他智能响应型MOF药物递送系统 除了上述的单一刺激响应型MOF药物递送系统外, 多重刺激响应型MOF药物递送系统也是近年来研究的热点。Nong等[121]研发了一种基于MOF的纳米酶混合体 [Fe_3O_4@PVP@MIL-88B (Fe)-NH-lysozyme/carvacrol, FPMLC], 它集细菌捕获、磁性组装、溶菌酶水解、光触发热生成和香荆芥酚释放等功能于一体协同消灭细菌。FPMLC可通过静电吸引捕获细菌, 然后通过磁组装形成FPMLC-细菌复合体。溶菌酶层可以降解细菌细胞壁的肽聚糖, 释放出的香荆芥酚在近红外照射下可以破坏细菌细胞膜。抗菌实验结果表明, 在细菌数量为1×10^6 CFU·mL^{-1}时, 低剂量 (100 μg·mL^{-1}) 的FPMLC纳米酶混合物能够完全灭活大肠杆菌和金黄葡萄球菌。Cai等[122]开发了具有增强姜黄素抗菌活性的复合薄膜, 即聚己内酯/姜黄素@ZIF-8 (polycaprolactone/curcumin @zeolitic imidazolate framework-8, PCL/Cur@ZIF-8)。在细菌感染的酸性环境中, PCL/Cur@ZIF-8复合膜能够通过pH响应释放锌离子和姜黄素。此外, 在420～430 nm、2.2 mW·cm^{-2}的蓝光照射下, 姜黄素分子产生活性氧化物。在锌离子和活性氧的协同作用下, 该复合膜对细菌具有很强的抗黏附作用。经过光动力灭菌处理后, 细菌复苏试验表明该复合膜上黏附细菌数量减少了99.9%。pH与生物酶双重刺激响应型MOF药物递送系统鲜有报道。Min等[107]将ZIF-8纳米颗粒原位生长在TOCNF (2,2,6,6-tetramethylpiperidine-1-oxy radical oxidized cellulose nanofiber) 薄膜上, 并装载香荆芥酚 (carvacrol, CAR), 静电吸附果胶 (pectin, Pec) 作为“看门人”。制备得到的CAR@ZIF-8/TOCNF/Pec薄膜可以响应食品贮藏过程中真菌感染所引起的酸性条件和微生物产生的果胶酶, 并具备双重响应控释功能。在pH 5.0时, CAR的释放率约为86.83%, 而在存在果胶酶 (1.0 mg·mL^{-1}) 情况下, CAR的释放率达到88.65%。此外, CAR@ZIF-8/TOCNF/Pec对大肠杆菌、金黄葡萄球菌和黑曲霉均表现出良好的抑制效果。

4 展望与挑战

MOFs作为一类新兴的多孔材料, 在递送中药抗菌成分方面展现出了巨大的潜力。具有高比表面积、可控孔道、响应释放及抗菌等优势的MOF材料, 不但能够显著改善中药抗菌成分的稳定性与溶解度, 而且可以增强中药抗菌成分智能释放能力。尽管已取得一些可喜的研究成果, 但MOF材料在递送中药抗菌成分方面仍然面临诸多挑战。首先, 有必要进一步探究并优化MOF材料的抗菌性能, 以提高其抗菌效果和负载率; 其次, 在构建智能响应型MOF递药系统时, 需考虑所采用的材料及各种修饰基团与生物体之间的安全性问题等; 再者, 部分MOF材料的合成工艺较为复杂，难以实现工业化大规模生产；同时，其长期使用过程中的潜在毒性风险仍有待系统评估。伴随研究的持续深入, MOF材料在中药抗菌成分递送方面应用将会越来越广泛与深入, 有望研发出具有更强抗菌活性和更低耐药性的新型中药药物制剂, 并为解决细菌耐药性等问题提供全新的思路与方法。

作者贡献: 黄俊峰负责文章的文献调研和撰写; 谢子鸿、张潇文负责图表设计及排版; 胡文慧、陈芳雯负责参考文献的整理; 郑琴、杨明负责对文章进行指导完善; 岳鹏飞负责文章整体思路的提出、设计和修改。

利益冲突: 本文所有作者声明不存在利益冲突关系。

References

[1] Bravo A, Moreno-Blanco A, Espinosa M. One earth: the equilibrium between the human and the bacterial worlds [J]. Int J Mol Sci, 2023, 24: 15047.

[2] Cao ZW, Momen R, Tao SS, et al. Metal-organic framework materials for electrochemical supercapacitors [J]. Nanomicro

Lett, 2022, 14: 181.

[3] Chai WW, Chen XC, Liu J, et al. Recent progress in functional metal-organic frameworks for bio-medical application [J]. Regen Biomater, 2023, 11: rbad115.

[4] Su LF, Liu XY, Xia W, et al. Simultaneous photothermal and photocatalytic MOF-derived C/TiO_2composites for high-efficiency solar driven purification of sewage [J]. J Colloid Interface Sci, 2023, 650: 613-621.

[5] Geng C, Jiang YF, Bian HD, et al. Selective gas-permeation films with nanoMOFs as gas "switches" for mango preservation [J]. Chem Eng J, 2024, 481: 148757.

[6] Gang SQ, Yan JW, Liu ZY, et al. An anionic In(III)-MOF for efficient adsorption of CO_2 from CO_2/N_2 mixture and dye removal [J]. Chem Eng Sci, 2024, 283: 119409.

[7] Yang M, Bao YS, Zhou ML, et al. An efficient bifunctional core-shell MIL-101(Cr)@MOF-867 composite to catalyze deacetalization-knoevenagel tandem reaction [J]. Catal Lett, 2023, 153: 1-8.

[8] Su XY, Li B, Chen SY, et al. Research and application of porous materials adsorption technology to improve the stability of volatile oil of traditional chinese medicine [J]. Acta Pharm Sin (药学学报), 2022, 57: 3301-3309.

[9] Dade-Robertson M, Keren-Paz A, Zhang M, et al. Architects of nature: growing buildings with bacterial biofilms [J]. Microb Biotechnol, 2017, 10: 1157-1163.

[10] Rosas NC, Lithgow T. Targeting bacterial outer-membrane remodelling to impact antimicrobial drug resistance [J]. Trends Microbiol, 2022, 30: 544-552.

[11] Sawa T, Kooguchi K, Moriyama K. Molecular diversity of extended-spectrum β-lactamases and carbapenemases, and antimicrobial resistance [J]. J Intensive Care, 2020, 8: 13.

[12] Stacy DM, Welsh MA, Rather PN, et al. Attenuation of quorum sensing in the pathogen *Acinetobacter baumannii* using non-native *N*-acyl homoserine lactones [J]. ACS Chem Biol, 2012, 7: 1719-1728.

[13] Verma P, Tiwari M, Tiwari V. Strategies to combat bacterial antimicrobial resistance: a focus on mechanism of the efflux pumps inhibitors [J]. SN Compr Clin Med, 2021, 3: 510-527.

[14] He N, Wang PQ, Wang PY, et al. Antibacterial mechanism of chelerythrine isolated from root of *Toddalia asiatica* (Linn) lam [J]. BMC Complement Altern Med, 2018, 18: 261.

[15] Ling JJ, Qiang HG, Zhen M, et al. Antibacterial mechanisms of berberine and reasons for little resistance of bacteria [J]. Chin Tradit Herb Drugs (中草药), 2011, 3: 27-35.

[16] Jaktaji RP, Mohammadi P. Effect of total alkaloid extract of local *Sophora alopecuroides* on minimum inhibitory concentration and intracellular accumulation of ciprofloxacin, and acrA expression in highly resistant *Escherichia coli* clones [J]. J Glob Antimicrob Resist, 2018, 12: 55-60.

[17] Liu Y, Zhu R, Liu XW, et al. Effect of piperine on the inhibitory potential of MexAB-OprM efflux pump and imipenem resistance in carbapenem-resistant *Pseudomonas aeruginosa* [J]. Microb Pathog, 2023, 185: 106397.

[18] Fu YT, Liu WT, Liu M, et al. *In vitro* anti-biofilm efficacy of sanguinarine against carbapenem-resistant *Serratia marcescens* [J]. Biofouling, 2021, 37: 341-351.

[19] Yu HM, Wang YF, Wang XQ, et al. Jatrorrhizine suppresses the antimicrobial resistance of methicillin-resistant *Staphylococcus aureus* [J]. Exp Ther Med, 2019, 18: 3715-3722.

[20] Chakraborty P, Dastidar DG, Paul P, et al. Inhibition of biofilm formation of *Pseudomonas aeruginosa* by caffeine: a potential approach for sustainable management of biofilm [J]. Arch Microbiol, 2020, 202: 623-635.

[21] Sharma S, Pal R, Hameed S, et al. Antimycobacterial mechanism of vanillin involves disruption of cell-surface integrity, virulence attributes, and iron homeostasis [J]. Int J Mycobacteriol, 2016, 5: 460-468.

[22] Zuo GY, Zhang XJ, Han J, et al. *In vitro* synergism of magnolol and honokiol in combination with antibacterial agents against clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) [J]. BMC Complement Altern Med, 2015, 15: 425.

[23] Wang GZ, Li L, Wang XK, et al. Hypericin enhances β-lactam antibiotics activity by inhibiting *sarA* expression in methicillin-resistant *Staphylococcus aureus* [J]. Acta Pharm Sin B , 2019, 9: 1174-1182.

[24] Sun N, Zhi ZL, Xiao T, et al. The study of honokiol as a natural product-based antimicrobial agent and its potential interaction with FtsZ protein [J]. Front Microbiol , 2024, 15: 1361508.

[25] Yang D, Hao SQ, Zhao L, et al. Paeonol attenuates quorum-sensing regulated virulence and biofilm formation in *Pseudomonas aeruginosa* [J]. Front Microbiol, 2021, 12: 692474.

[26] Santos M, Santos R, Soeiro P, et al. Resveratrol as an inhibitor of the NorA efflux pump and resistance modulator in *Staphylococcus aureus* [J]. Antibiotics (Basel), 2023, 12: 1168.

[27] Oyedemi BO, Kotsia EM, Stapleton PD, et al. Capsaicin and gingerol analogues inhibit the growth of efflux-multidrug resistant bacteria and r-plasmids conjugal transfer [J]. J Ethnopharmacol, 2019, 245: 111871.

[28] Mangal S, Chhibber S, Singh V, et al. Guaiacol augments quorum quenching potential of ciprofloxacin against *Pseudomonas aeruginosa* [J]. J Appl Microbiol, 2022, 133: 2235-2254.

[29] Duan FX, Xin G, Niu H, et al. Chlorinated emodin as a natural antibacterial agent against drug-resistant bacteria through dual influence on bacterial cell membranes and DNA [J]. Sci Rep, 2017, 7: 12721.

[30] Li T, Lu Y, Zhang H, et al. Antibacterial activity and membrane-targeting mechanism of aloe-emodin against *Staphylococcus epidermidis* [J]. Front Microbiol, 2021, 12: 621866.

[31] Wang JL, Jiao HH, Meng JW, et al. Baicalin inhibits biofilm formation and the quorum-sensing system by regulating the

MsrA drug efflux pump in *Staphylococcus saprophyticus* [J]. Front Microbiol, 2019, 10: 2800.

[32] Kim D, Kim KY. Pectolinarin inhibits the bacterial biofilm formation and thereby reduces bacterial pathogenicity [J]. Antibiotics (Basel), 2022, 11: 598.

[33] Pei HR, Lu MX, Long L, et al. Antibacterial mechanism of forsythoside a against *Pseudomonas syringae pv. actinidiae* [J]. Microb Pathog, 2022, 173: 105858.

[34] Yun J, Woo ER, Lee DG. Effect of isoquercitrin on membrane dynamics and apoptosis-like death in *Escherichia coli* [J]. Biochim Biophys Acta Biomembr, 2018, 1860: 357-363.

[35] Das MC, Samaddar S, Jawed JJ, et al. Vitexin alters *Staphylococcus aureus* surface hydrophobicity to obstruct biofilm formation [J]. Microbiol Res, 2022, 263: 127126.

[36] Guan XD, Jin L, Zhou HF, et al. Polydatin prevent lung epithelial cell from carbapenem-resistant *Klebsiella pneumoniae* injury by inhibiting biofilm formation and oxidative stress [J]. Sci Rep, 2023, 13: 17736.

[37] Dey P, Parai D, Banerjee M, et al. Naringin sensitizes the antibiofilm effect of ciprofloxacin and tetracycline against *Pseudomonas aeruginosa* biofilm [J]. Int J Med Microbiol, 2020, 310: 151410.

[38] Li JP, Fan QY, Zuo J, et al. Paeoniflorin combined with norfloxacin ameliorates drug-resistant *Streptococcus suis* infection [J]. J Antimicrob Chemother, 2022, 77: 3275-3282.

[39] Yao XL, Zhu XR, Pan SY, et al. Antimicrobial activity of nobiletin and tangeretin against *Pseudomonas* [J]. Food Chem, 2012, 132: 1883-1890.

[40] Ivanov M, Novović K, Malešević M, et al. Polyphenols as inhibitors of antibiotic resistant bacteria-mechanisms underlying rutin interference with bacterial virulence [J]. Pharmaceuticals (Basel), 2022, 15: 385.

[41] Rahbar Takrami S, Ranji N, Sadeghizadeh M. Antibacterial effects of curcumin encapsulated in nanoparticles on clinical isolates of *Pseudomonas aeruginosa* through downregulation of efflux pumps [J]. Mol Biol Rep, 2019, 46: 2395-2404.

[42] Sun YX, Sun FJ, Feng W, et al. Luteolin inhibits the biofilm formation and cytotoxicity of methicillin-resistant *Staphylococcus aureus via* decreasing bacterial toxin synthesis [J]. Evid Based Complement Alternat Med, 2022, 2022: 4476339.

[43] Ming D, Wang DC, Cao FJ, et al. Kaempferol inhibits the primary attachment phase of biofilm formation in *Staphylococcus aureus* [J]. Front Microbiol, 2017, 8: 2263.

[44] Wang D, Xie KP, Zou D, et al. Inhibitory effects of silybin on the efflux pump of methicillin-resistant *Staphylococcus aureus* [J]. Mol Med Rep, 2018, 18: 827-833.

[45] Pal A, Tripathi A. Quercetin inhibits carbapenemase and efflux pump activities among carbapenem-resistant gram-negative bacteria [J].APMIS, 2020, 128: 251-259.

[46] Eumkeb G, Sakdarat S, Siriwong S. Reversing β-lactam antibiotic resistance of *Staphylococcus aureus* with galangin from *Alpinia officinarum* Hance and synergism with ceftazidime [J]. Phytomedicine, 2010, 18: 40-45.

[47] Wei LN, Shi CZ, Luo CX, et al. Phloretin inhibits biofilm formation by affecting quorum sensing under different temperature [J]. LWT-Food Sci Technol, 2020, 131: 109668.

[48] Cordeiro L, Figueiredo P, Souza H, et al. Terpinen-4-ol as an antibacterial and antibiofilm agent against *Staphylococcus aureus* [J]. Int J Mol Sci, 2020, 21: 4531.

[49] Gong HY, He LJ, Zhao ZL, et al. The specific effect of (*R*)-(+)-pulegone on growth and biofilm formation in multi-drug resistant *Escherichia coli* and molecular mechanisms underlying the expression of *pgaABCD* genes. [J]. Biomed Pharmacother, 2021, 134: 111149.

[50] Yuan ZW, Dai YY, Ouyang P, et al. Thymol inhibits biofilm formation, eliminates pre-existing biofilms, and enhances clearance of methicillin-resistant *Staphylococcus aureus* (MRSA) in a mouse peritoneal implant infection model [J]. Microorganisms, 2020, 8: 99.

[51] Liu W, Chen G, Dou KK, et al. Eugenol eliminates carbapenem-resistant *Klebsiella pneumoniae via* reactive oxygen species mechanism [J]. Front Microbiol, 2023, 14: 1090787.

[52] Dos Santos Barbosa CR, Scherf JR, De Freitas TS, et al. Effect of carvacrol and thymol on NorA efflux pump inhibition in multidrug-resistant (MDR) *Staphylococcus aureus* strains [J]. J Bioenerg Biomembr, 2021, 53: 489-498.

[53] Zhong JW, Wang HD, Zhuang Y, et al. Identification of the antibacterial mechanism of cryptotanshinone on methicillin-resistant *Staphylococcus aureus* using bioinformatics analysis [J]. Sci Rep, 2021, 11: 21726.

[54] Husain FM, Ahmad I, Khan MS, et al. Sub-MICs of *Mentha piperita* essential oil and menthol inhibits AHL mediated quorum sensing and biofilm of gram-negative bacteria [J]. Front Microbiol, 2015, 6: 420.

[55] Alyousef AA, Mabood Husain F, Arshad M, et al. *Myrtus communis* and its bioactive phytoconstituent, linalool, interferes with quorum sensing regulated virulence functions and biofilm of uropathogenic bacteria: *in vitro* and *in silico* insights [J]. J King Saud Univ Sci, 2021, 33: 101588.

[56] Freitas PR, De Araújo ACJ, Dos Santos Barbosa CR, et al. Inhibition of the MepA efflux pump by limonene demonstrated by *in vitro* and *in silico* methods [J]. Folia Microbiol (Praha), 2022, 67: 15-20.

[57] Zhong YZ, Tang LY, Deng QH, et al. Unraveling the novel effect of patchouli alcohol against the antibiotic resistance of *Helicobacter pylori* [J]. Front Microbiol, 2021, 12: 674560.

[58] Li JG, Lu TY, Chu YF, et al. Cinnamaldehyde targets SarA to enhance β-lactam antibiotic activity against methicillin-resistant *Staphylococcus aureus* [J]. mLife , 2024, 3: 291-306.

[59] Benny AT, Rathinam P, Dev S, et al. Perillaldehyde mitigates virulence factors and biofilm formation of *Pseudomonas aerugi-*

nosa clinical isolates, by acting on the quorum sensing mechanism *in vitro* [J]. J Appl Microbiol, 2022, 133: 385-399.

[60] Sang H, Jin H, Song P, et al. Gallic acid exerts antibiofilm activity by inhibiting methicillin-resistant *Staphylococcus aureus* adhesion [J]. Sci Rep, 2024, 14: 17220.

[61] Wang LB, Zhang Y, Liu Y, et al. Effects of chlorogenic acid on antimicrobial, antivirulence, and anti-quorum sensing of carbapenem-resistant *Klebsiella pneumoniae* [J]. Front Microbiol, 2022, 13: 997310.

[62] Kang JM, Liu L, Liu YF, et al. Ferulic acid inactivates shigella flexneri through cell membrane destruction, biofilm retardation, and altered gene expression [J]. J Agric Food Chem, 2020, 68: 7121-7131.

[63] Ivanov M, Kostić M, Stojković D, et al. Rosmarinic acid-modes of antimicrobial and antibiofilm activities of a common plant polyphenol [J]. S Afr J Bot, 2022, 146: 521-527.

[64] Hua LL, Hui WJ, Lin YJ, et al. Effects of allicin on the formation of *Pseudomonas aeruginosa* biofilm and the production of quorum-sensing controlled virulence factors [J]. Pol J Microbiol, 2013, 62: 243-251.

[65] Bendary MM, Ali MAM, Abdel Halim AS, et al. Investigating sulforaphane′s anti-virulence and anti-quorum sensing properties against *Pseudomonas aeruginosa* [J]. Front Pharmacol, 2024, 15: 1406653.

[66] Feng ZQ, Zhou J, Shang XY, et al. Comparative research on stability of baicalin and baicalein administrated in monomer and total flavonoid fraction form of radix scutellariae in biological fluids *in vitro* [J]. Pharm Biol, 2017, 55: 1177-1184.

[67] Omidi S, Rafiee Z, Kakanejadifard A. Design and synthesis of curcumin nanostructures: evaluation of solubility, stability, antibacterial and antioxidant activities [J]. Bioorg Chem, 2021, 116: 105308.

[68] Eddaoudi M, Kim J, Rosi N, et al. Systematic design of pore size and functionality in isoreticular MOFs and their application in methane storage [J]. Science, 2002, 295: 469-472.

[69] Yin DG, Hu XL, Cai MR, et al. Preparation, characterization, and *in vitro* release of curcumin-loaded IRMOF-10 nanoparticles and investigation of their pro-apoptotic effects on human hepatoma HepG2 cells [J]. Molecules , 2022, 27: 3940.

[70] Cheng HD. One-pot preparation of HCPT@IRMOF-3 nanoparticles for pH-responsive anticancer drug delivery [J]. Molecules, 2023, 28: 7703.

[71] Qi XY, Chen QZ, Chang ZY, et al. Breaking pore size limit of metal-organic frameworks: bio-etched ZIF-8 for lactase immobilization and delivery *in vivo* [J]. Nano Res, 2022, 15: 5646-5652.

[72] Park KS, Ni Z, Côté AP, et al. Exceptional chemical and thermal stability of zeolitic imidazolate frameworks [J]. Proc Natl Acad Sci U S A, 2006, 103: 10186-10191.

[73] Férey G, Serre C, Mellot-Draznieks C, et al. A hybrid solid with giant pores prepared by a combination of targeted chemistry, simulation, and powder diffraction [J]. Angew Chem Int Ed Engl, 2004, 43: 6296-6301.

[74] Férey G, Mellot-Draznieks C, Serre C, et al. A chromium terephthalate-based solid with unusually large pore volumes and surface area [J]. Science, 2005, 309: 2040-2042.

[75] Khan NA, Kang IJ, Seok HY, et al. Facile synthesis of nano-sized metal-organic frameworks, chromium-benzenedicarboxylate, MIL-101 [J]. Chem Eng J, 2011, 166: 1152-1157.

[76] Chui S, Lo S, Charmant JP, et al. A chemically functionalizable nanoporous material $[Cu_3(TMA)_2(H_2O)_3]_n$ [J]. Science, 1999, 283: 1148-1150.

[77] Zhang FZ, Zeng Y, Zheng MY, et al. Photocatalytic activity and synergistic antibacterial effects of PCN-222@AgNPs under visible light irradiation [J]. J Coord Chem, 2024, 77: 188-202.

[78] Kandiah M, Nilsen MH, Usseglio S, et al. Synthesis and stability of tagged UiO-66 Zr-MOFs [J]. Chem Mater, 2010, 22: 6632-6640.

[79] Bambalaza SE, Langmi HW, Mokaya R, et al. Co-pelletization of a zirconium-based metal-organic framework (UiO-66) with polymer nanofibers for improved useable capacity in hydrogen storage [J]. Int J Hydrogen Energy, 2021, 46: 8607-8620.

[80] Roy I, Stoddart JF. Cyclodextrin metal-organic frameworks and their applications [J]. Acc Chem Res, 2021, 54: 1440-1453.

[81] Yaghi OM, Li GM, Li HL. Selective binding and removal of guests in a microporous metal-organic framework [J]. Nature, 1995, 378: 703-706.

[82] Li HL, Eddaoudi M, O'Keeffe M, et al. Design and synthesis of an exceptionally stable and highly porous metal-organic framework [J]. Nature, 1999, 402: 276-279.

[83] Hayashi H, Côté AP, Furukawa H, et al. Zeolite a imidazolate frameworks [J]. Nat Mater, 2007, 6: 501-506.

[84] Banerjee R, Phan A, Wang B, et al. High-throughput synthesis of zeolitic imidazolate frameworks and application to CO_2 capture [J]. Science, 2008, 319: 939-943.

[85] Wang B, Côté AP, Furukawa H, et al. Colossal cages in zeolitic imidazolate frameworks as selective carbon dioxide reservoirs [J]. Nature, 2008, 453: 207-211.

[86] Cai MR, Ni BR, Hu XL, et al. An investigation of IRMOF-16 as a pH-responsive drug delivery carrier of curcumin [J]. J Sci Adv Mater Device, 2022, 7: 100507.

[87] De Moura Ferraz LR, Tabosa AÉGA, Da Silva Nascimento DDS, et al. ZIF-8 as a promising drug delivery system for benznidazole: development, characterization, *in vitro* dialysis release and cytotoxicity [J]. Sci Rep, 2020, 10: 16815.

[88] Chen XR, Shi ZQ, Tong RL, et al. Derivative of epigallocatechin-3-gallatea encapsulated in ZIF-8 with polyethylene glycol-folic acid modification for target and pH-responsive drug release in anticancer research [J]. ACS Biomater Sci Eng, 2018, 4: 4183-4192.

[89] Ge YM, Wang K, Liu JY, et al. A ZIF-8-based multifunctional

intelligent drug release system for chronic osteomyelitis [J]. Colloids Surf B Biointerfaces, 2022, 212: 112354.

[90] Dou JL, Bian WW, Zheng X, et al. A ZIF-based drug delivery system as three-in-one platform for joint cancer therapy [J]. Mater Chem Phys, 2023, 297: 127345.

[91] Abuçafy MP, Frem RCG, Polinario G, et al. MIL-100(Fe) sub-micrometric capsules as a dual drug delivery system [J]. Int J Mol Sci, 2022, 23: 7670.

[92] Li X, Zheng HY, Chen JH, et al. MIL-101 (Fe)@Ag rapid synergistic antimicrobial and biosafety evaluation of nanomaterials [J]. Molecules, 2022, 27: 3497.

[93] Silva IMP, Carvalho MA, Oliveira CS, et al. Enhanced performance of a metal-organic framework analogue to MIL-101(Cr) containing amine groups for ibuprofen and nimesulide controlled release [J]. Inorg Chem Commun, 2016, 70: 47-50.

[94] Lucena GN, Alves RC, Abuçafy MP, et al. Zn-based porous coordination solid as diclofenac sodium carrier [J]. J Solid State Chem, 2018, 260: 67-72.

[95] Han DL, Liu XM, Wu SL. Metal organic framework-based antibacterial agents and their underlying mechanisms [J]. Chem Soc Rev, 2022, 51: 7138-7169.

[96] Huang XL, Xing Y, Jiang H, et al. Nonphytotoxic and pH-responsive ZnO-ZIF-8 loaded with honokiol as a "nanoweapon" effectively controls the soil-borne bacterial pathogen *Ralstonia solanacearum* [J]. J Hazard Mater, 2024, 472: 134502.

[97] Wang J, Li L, Hu XY, et al. pH-responsive on-demand release of eugenol from metal-organic frameworks for synergistic bacterial killing [J]. Dalton Trans, 2024, 53: 2826-2832.

[98] Wang LH, Cheng SS, Qin KW, et al. Apigenin@ZIF-8 with pH-responsive sustained release function added to propolis-gelatin films achieved an outstanding antibacterial effect [J]. Food Packag Shelf Life, 2023, 40: 101191.

[99] Liu ZX, Wu Q, He J, et al. Crystal-seeded growth of pH-responsive metal-organic frameworks for enhancing encapsulation, stability, and bioactivity of hydrophobicity compounds [J]. ACS Biomater Sci Eng, 2019, 5: 6581-6589.

[100] Ding Y, Yuan J, Mo FX, et al. A pH-responsive essential oil delivery system based on metal-organic framework (ZIF-8) for preventing fungal disease [J]. J Agric Food Chem, 2023, 71: 18312-18322.

[101] Yang JJ, Chen YW, Cao YT, et al. pH-responsive bimetallic MOFs ZIF-8@ZIF-67 for enhanced antibacterial activity [J]. ChemistrySelect, 2024, 9: 2365-6549.

[102] Guo CP, Cheng F, Liang GL, et al. Multimodal antibacterial platform constructed by the schottky junction of curcumin-based bio metal-organic frameworks and $Ti_3C_2T_x$ MXene nanosheets for efficient wound healing [J]. Adv NanoBiomed Res, 2022, 2: 2699-9307.

[103] Nie W, Huang YX, Wang YL, et al. Temperature sensitive poly-MOF hydrogel formed by *in situ* open-ring polymerization for infected chronic wound treatment [J]. Chem Eng J, 2022, 446: 136948.

[104] Min TT, Sun XL, Zhou LP, et al. Electrospun pullulan/PVA nanofibers integrated with thymol-loaded porphyrin metal-organic framework for antibacterial food packaging [J]. Carbohydr Polym, 2021, 270: 118391.

[105] He QT, Qian PP, Yang XY, et al. Rational design of bacteria-targeted and photo-responsive MOF gel with antibacterial and anti-inflammatory function for infected wound healing [J]. Chem Eng J, 2024, 493: 152760.

[106] Pang YP, Zhao MF, Xie YH, et al. Multifunctional Ac@ZIF-8/AgNPs nanoplatform with pH-responsive and ROS scavenging antibacterial properties promotes infected wound healing [J]. Chem Eng J, 2024, 489: 151485.

[107] Min TT, Yue J, Cheng CX, et al. ZIF-8/TOCNF carrier coated with pectin "gatekeeper" for pH/enzyme dual-responsive releasing of carvacrol and its preservation effect on fruits [J]. Chem Eng J, 2024, 496: 153686.

[108] Zhang SQ, Ye JW, Liu X, et al. Dual stimuli-responsive smart fibrous membranes for efficient photothermal/photodynamic/chemo-therapy of drug-resistant bacterial infection [J]. Chem Eng J, 2022, 432: 134351.

[109] Moussa Z, Hmadeh M, Abiad MG, et al. Encapsulation of curcumin in cyclodextrin-metal organic frameworks: dissociation of loaded CD-MOFs enhances stability of curcumin [J]. Food Chem, 2016, 212: 485-494.

[110] Pan XD, Junejo SA, Tan CP, et al. Effect of potassium salts on the structure of γ-cyclodextrin MOF and the encapsulation properties with thymol [J]. J Sci Food Agric, 2022, 102: 6387-6396.

[111] Soomro NA, Wu Q, Amur SA, et al. Natural drug physcion encapsulated zeolitic imidazolate framework, and their application as antimicrobial agent [J]. Colloids Surf B Biointerfaces, 2019, 182: 110364.

[112] Aykaç A, Noiray M, Malanga M, et al. A non-covalent "click chemistry" strategy to efficiently coat highly porous MOF nanoparticles with a stable polymeric shell [J]. Biochim Biophys Acta Gen Subj, 2017, 1861: 1606-1616.

[113] Suresh K, Matzger AJ. Enhanced drug delivery by dissolution of amorphous drug encapsulated in a water unstable metal-organic framework (MOF) [J]. Angew Chem Int Ed Engl , 2019, 58: 16790-16794.

[114] Liu YJ, Zhou PP, Cao ZY, et al. Simultaneous solubilization and extended release of insoluble drug as payload in highly soluble particles of γ-cyclodextrin metal-organic frameworks [J]. Int J Pharm, 2022, 619: 121685.

[115] He YZ, Hou XF, Guo JW, et al. Activation of a gamma-cyclodextrin-based metal-organic framework using supercritical carbon dioxide for high-efficient delivery of honokiol [J]. Carbohydr Polym, 2020, 235: 115935.

[116] Wu SM, Xu C, Zhu YW, et al. Biofilm-sensitive photodynamic nanoparticles for enhanced penetration and antibacterial efficiency [J]. Adv Funct Mater, 2021, 31: 2103591.

[117] Lei BQ, Wang MF, Jiang ZL, et al. Constructing redox-responsive metal-organic framework nanocarriers for anticancer drug delivery [J]. ACS Appl Mater Interfaces, 2018, 10: 16698-16706.

[118] Xiang YL, Tang DY, Yan LL, et al. Poly-*L*-lysine modified MOF nanoparticles with pH/ROS sensitive CIP release and CUR triggered photodynamic therapy against drug-resistant bacterial infection [J]. Int J Biol Macromol, 2024, 266: 131330.

[119] Silva JYR, Proenza YG, Luz LLD, et al. A thermo-responsive adsorbent-heater-thermometer nanomaterial for controlled drug release: (ZIF-8, Eu_xTb_y)@AuNP core-shell [J]. Mater Sci Eng C Mater Biol Appl, 2019, 102: 578-588.

[120] Lin YS, Lin KS. Characterization of the size and porous temperature sensitivity of Pluronic F127-coated MIL-88B(Fe) for drug release [J]. Microporous Mesoporous Mater, 2021, 328: 111456.

[121] Nong WQ, Chen YL, Lv DY, et al. Metal-organic framework based nanozyme hybrid for synergistic bacterial eradication by lysozyme and light-triggered carvacrol release [J]. Chem Eng J, 2022, 431: 134003.

[122] Cai Y, Guan JW, Wang W, et al. pH and light-responsive polycaprolactone/curcumin@ZIF-8 composite films with enhanced antibacterial activity [J]. J Food Sci, 2021, 86: 3550-3562.