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Cyborg microbe biohybrids with metal–organic coating layers: Strategies, functionalisation and potential applications

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ABSTRACT

The integration of living microbes, specifically bacteria and fungi, with metal–organic nanocoatings has led to the recent development of cyborg microbe biohybrids, which show excellent adaptability and functionality for a wide range of potential applications in biotechnology and medicine. This review discusses the strategies, functionalisation, and applications of these biohybrids, which are categorised into two types of coatings: metal–organic frameworks (MOFs) and metal–phenolic networks (MPNs). Key advances in their synthetic approaches *via in-situ* and pre-synthesised coatings are crucially addressed, and yet the methodology details and specific advantages are highlighted. Despite the notable advancements, there are various limitations and challenges, such as determination of the long-term viability and stability of the biohybrids, insufficient work on their theranostic applications and essentially scaling-up difficulties for industrial and clinical translation. The latest advancements in the biohybrids and related technology have established a critical foundation for enhancing innovative studies through the strong interdisciplinary teamwork.

1. Introduction

Microbes play a fundamental role in shaping our world and influence various aspects of our lives, from health and agriculture to industry and the environment [1,2]. They significantly impact human health, as beneficial microbes in different body niches actively maintain microbiota balance, consequently contributing towards host–microbiota symbiosis and overall well-being [3]. Moreover, microbes significantly influence various environmental processes, such as carbon cycling, nitrogen fixation, and decomposition of organic matter. They help maintain ecosystem balance, support plant growth and contribute to maintaining air quality as well as the health of soils and water bodies [4]. As such, microbes are extensively used in biotechnological applications, such as food production, pharmaceuticals, bioremediation, and bioenergy.

While microbes offer numerous advantages in various biotechnological areas, there are limitations and research gaps that need to be addressed to fully realise their potential. One challenge lies in engineering microbes for specific biotechnological applications, because designing efficient pathways, optimizing metabolic fluxes, and achieving desired production levels often require advanced genetic and metabolic engineering techniques [5,6]. Similarly, maintaining microbial stability and viability under dynamic and harsh environmental conditions remains difficult [7]. Therefore, it is highly warranted to develop novel approaches to modifying or functionalizing different microbes to accommodate diverse biotechnological fields.

Biohybrids, a class of hybrid systems composed of biological components (*e.g.*, cells, tissues or organisms) and synthetic materials or devices exhibiting unique properties and capabilities, can be engineered to perform specific tasks, interact with their environment, or serve various applications across different fields [8]. As a type of biohybrid, "cyborg microbes" are developed to address the limitations of both the

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materials and microbes, enabling synergistic enhancements in their favourable effects [9–11]. In particular, through certain material-based surface coating, the cyborg microbes can perform roles such as sensing, secreting and moving without compromising their viability, while simultaneously enabling some new functions that are not naturally possible [12–15]. Collectively, cyborg microbes represent novel systems for interfacing biological systems with technology and material chemistry, opening new possibilities for creating advanced, integrated systems that can address complex challenges and expedite innovation in bioengineering.

To date, both inorganic and organic materials have been incorporated with microbes for various applications. Inorganic materials, such as gold nanoparticles [16–18], magnetic nanoparticles [19–22] and quantum dots [23–26], have been used to label or modify microbes for pathogen imaging, microbe separation/recycling, biological fixation of CO_2 and N_2, and therapeutic enhancement. Meanwhile, organic materials (*e.g.*, graphene/carbon quantum dots [27,28], carbon nanotubes [29,30], and polymers [31–34]) are also utilised to decorate microbes for live tracking, cytoprotective effects, *etc*. Specifically, metal–organic-based materials, namely metal–organic frameworks (MOFs) and metal–phenolic networks (MPNs), have shown versatility, controllability, and excellent biocompatibility in applications such as biocatalysis, biosensing, bioimaging, and cargo storage/delivery [35–37]. Some studies have integrated the imaging and cargo delivery properties of MOFs and MPNs to develop novel theranostic platforms for treating various diseases [38–43]. Moreover, by introducing stimuli-responsive groups, materials or guest molecules into their structures, metal–organic-based materials can deliver cargo molecules in a controlled-release manner as single- or multi-stimuli-responsive platforms [44,45]. Notably, these materials offer significant advantages over traditional inorganic and organic materials for incorporating microbes. They provide a versatile platform for creating biohybrids with tailored functionalities by combining the strengths of metal ions, organic ligands, and their resulting porous structures. Furthermore, their facile and cost-effective synthetic methods highlight their utility as coating materials for manufacturing cyborg microbes with exceptional biotechnological properties [46–48]. Current research on material-coated cyborg microbes indicates that metal–based material coating offers several benefits, including enhanced catalytic activity of the biohybrids [49–52] and increased stability by protecting cyborg microbes from environmental stresses and harsh conditions [53,54], suggesting a wide range of potential application in biotechnology, healthcare, environmental science, and energy production.

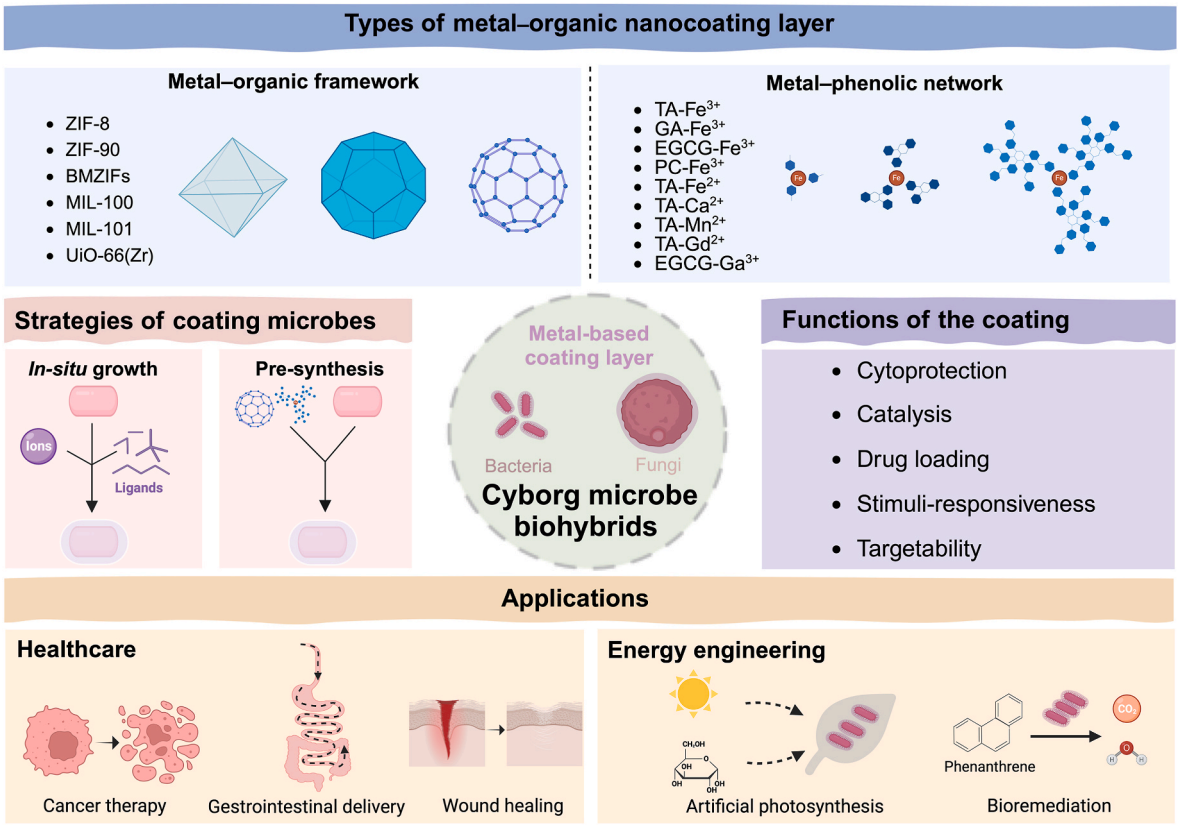
This review delves into the latest advancements in metal–organic-based nanocoatings (MOFs and MPNs) for microbes, specifically fungi and bacteria. Particularly, it outlines: i) the primary categories of MOF- or MPN-based coatings, ii) their main applications, iii) methods for functionalisation and iv) strategies for synthesis. Additionally, potential future opportunities for cyborg microbes with metal–organic coatings are highlighted to promote the utilisation of these biohybrid systems across various areas (Scheme 1).

2. Type of metal–organic nanocoating on microbes

Metal–organic nanocoating offers several benefits to microbe-derived platforms, such as enhanced environmental resistance, catalytic activity and drug delivery properties. Depending on the coating types, different metal ions with organic ligands are used, leading to varied synthetic approaches and biological functions. In this section, the major types of metal–organic based coating applied to microbes are introduced, and their main applications are described.

2.1. MOFs

MOFs, a class of crystalline hybrid materials with well-ordered architectures, have emerged as promising multifunctional platforms



Scheme 1. Illustrative scheme of cyborg microbe biohybrids armed with metal–organic coating layers and their synthesis strategies, functions and applications.

owing to their diverse features, including tuneable structures, adjustable porosity, and high surface area [55–58]. Studies have extensively investigated the use of MOF-based composites for encapsulating or immobilising materials, such as nanoparticles, polymers, quantum dots, and catalysts. The combination of these materials with MOFs has led to the enhancement or introduction of new properties in the final composites, outperforming the MOFs or the materials alone [57]. Recently, the design of MOF-based composites has been taken to a new level by incorporating MOFs with biologically active substances, such as amino acids [59], biomacromolecules (*e.g.*, proteins, enzymes and DNA) [60], viruses [61], and even microbial cell walls [62]. These studies prompt the integration of MOFs coatings with live cells to construct "cyborg cells" with diverse functions, enabling them to address complex challenges in the biomedical field. The synthesis and functionalisation of different MOF-coated microbes (microbes@MOFs) are summarised and discussed in this section, emphasising their design rationales and major applications (Table 1).

2.1.1. Synthesis of microbes@MOFs with cyto-protective and catalytic activities

Prior to construction on live microbes, MOF layers were synthesised on extracted microbial cell walls. In a study by Li et al., the cell walls of *Saccharomyces cerevisiae* were extracted as non-toxic, stable, and inexpensive support materials for assembling MOF microcapsules, *i.e.*, ZIF-8, CuBTC, and MIL-5, with size-selective permeability. The resulting MOF microcapsules exhibited excellent solvent resistance and long-term stability. Meanwhile, the successful deposition of MOF layers on cell walls of *Escherichia coli* highlighted the potential of using bacterial cells as templates for constructing MOF microcapsules by taking advantage of the enriched biomolecules on the cell walls as dense nucleation sites [62]. This *in-situ* crystallisation approach demonstrates the general applicability of both fungi and bacteria.

Since then, different types of MOF coating layers with cytoprotective effects and catalytic activities have been synthesised on live microbes. In fact, the cytoprotective effects of MOF layers, originating from their size-selective permeability and catalytic activity, are governed by their pore size and metal ion type. Their pores enable the passage of essential nutrients through MOF layers while excluding harmful molecules, thereby protecting the microorganisms underneath, and the specific metal ions in the system can catalytically degrade toxic chemicals. Previously, Liang and co-workers synthesised a ZIF-8 coating layer with a tunable thickness on live *S. cerevisiae* [63]. Since the biomolecule-enriched cell surface of the live fungi was capable of attracting zinc ions [62], a continuous ZIF-8 coating on individual cells could form by initiating an *in-situ* crystallisation. This ZIF-8 shell functioned as a cytoprotective exoskeleton, allowing the permeation of nutrients like glucose to support microbial growth while preventing the entrance of toxic agents like lyticase and filipin (Fig. 1A). Moreover, this

Table 1
Synthesis and functionalisation of different MOF-coated microbes and their functions.

Author-year	Microbe(s)	Coating(s)	Synthesis methods	Functionalisation	Functions or purposes
Liang, 2016 [63]	*Saccharomyces cerevisiae*; *Micrococcus lueteus*	ZIF-8	*In-situ*	–	Cytoprotection against lyticase and filipin
Liang, 2017 [64]	*S. cerevisiae*	β-gal + ZIF-8	*In-situ*	Pre-coating of microbes	Cytoprotection against oligotrophic environment
Ji, 2018 [49]	*Morella thermoacetica*	$Zr_6O_4(OH)_4(BTB)_2(OH)_6(H2O)_6$	Pre-synthesis	–	Cytoprotection against oxidative stress for continuous production of acetate
Yan, 2020 [65]	*Escherichia coli* MG1655	ZIF-8+Ce6+DOX	*In-situ*	Post-modification of MOF	Targeted drug delivery for tumour chemotherapy and photodynamic therapy
Chen, 2020 [66]	*S. cerevisiae*; *E. coli*	ZIF-8	*In-situ*	–	Comparison among three zinc precursors for *in-situ* synthesis of ZIF-8
Zhu, 2020 [67]	*Bacillus subtilis* P03 (expressing TreS)	GI + ZIF-8	*In-situ*	Bacterial transformation; pre-coating of microbes	Protection of both the cell and enzyme against lysozyme for efficient coproduction of trehalose and fructose
Li, 2021 [68]	*E. coli* (expressing mCherry)	ZIF-90	*In-situ*	Bacterial transformation	Cytoprotection against toxic bactericides
Wang, 2021 [69]	*Shewanella oneidensis*	MIL-101+DOX+HA	Pre-synthesis	Post-modification of MOF	Targeted drug delivery for tumour chemotherapy
Wei, 2021 [70]	*Lactobacillus acidophilus*; *Bifidobacterium infantis*	ZIF-8	*In-situ*	–	Comparison of interfacial interactions between bacteria and three protective shells (ZIF-8, alginate and SiO_2 nanoparticles)
Li, 2022 [71]	*E. coli MG1655*	ZIF-8+DOX+TA	Pre-synthesis	Post-modification of MOF	Cytoprotection against lysozyme; targeted drug delivery for cancer chemotherapy
Wang, 2022 [72]	*S. cerevisiae*	ZIF-8+LOX	Pre-synthesis	Post-modification of MOF	Consumption of glucose and lactate by yeast and lactate oxidase respectively for disruption of tumour metabolism
Li, 2023 [73]	*B. infantis*	MIL+DOX+CaO_2+PDA	Pre-synthesis	Post-modification of MOF	Targeted delivery of DOX and CaO_2 for chemotherapy and chemo-dynamic therapy
Permyakova, 2023 [74]	*Pseudomonas putida*	MIL-100	*In-situ*	–	Introduction and characterisation of the novel *in-situ* synthesised MIL-100 on bacteria
Zhao, 2023 [75]	*Clostridium tyrobutyricum*	UiO-66	Pre-synthesis	–	Improvement of butyrate production
Wang, 2024 [76]	*Lactobacillus rhamnosus* GG	ZIF-67+PAO	Pre-synthesis	Post-modification of MOF	Induction of tumour pyroptosis for enhanced immunotherapy
Fan, 2024 [77]	*E. coli*	ZIF-8	*In-situ*	–	Cytoprotection in Luria-Bertani (LB) medium; improvement of hydrogen production
Liu, 2024 [78]	*Bacillus subtilis* ZL09–26	ZIF-8+CA	*In-situ*	Post-modification of MOF	Cytoprotection against PHE; improvement of PHE biodegradation efficiency
Li, 2024 [79]	PP3244 (an engineered DH5α *E. coli*)	Iron-doped ZIF-8+TPZ	Pre-synthesis	Bacterial transformation; post-modification of MOF	Targeted delivery of drugs and launch of cascaded reactions for catalytical therapy, chemotherapy, and immunotherapy
Wu, 2025 [80]	*Salmonella typhimurium* (expressing bacterial luciferase)	UiO-66-NH_2+ICG+LUT	Pre-synthesis	Post-modification of MOF	Induction of excessive autophagy and mild hyperthermia for enhanced immunotherapy

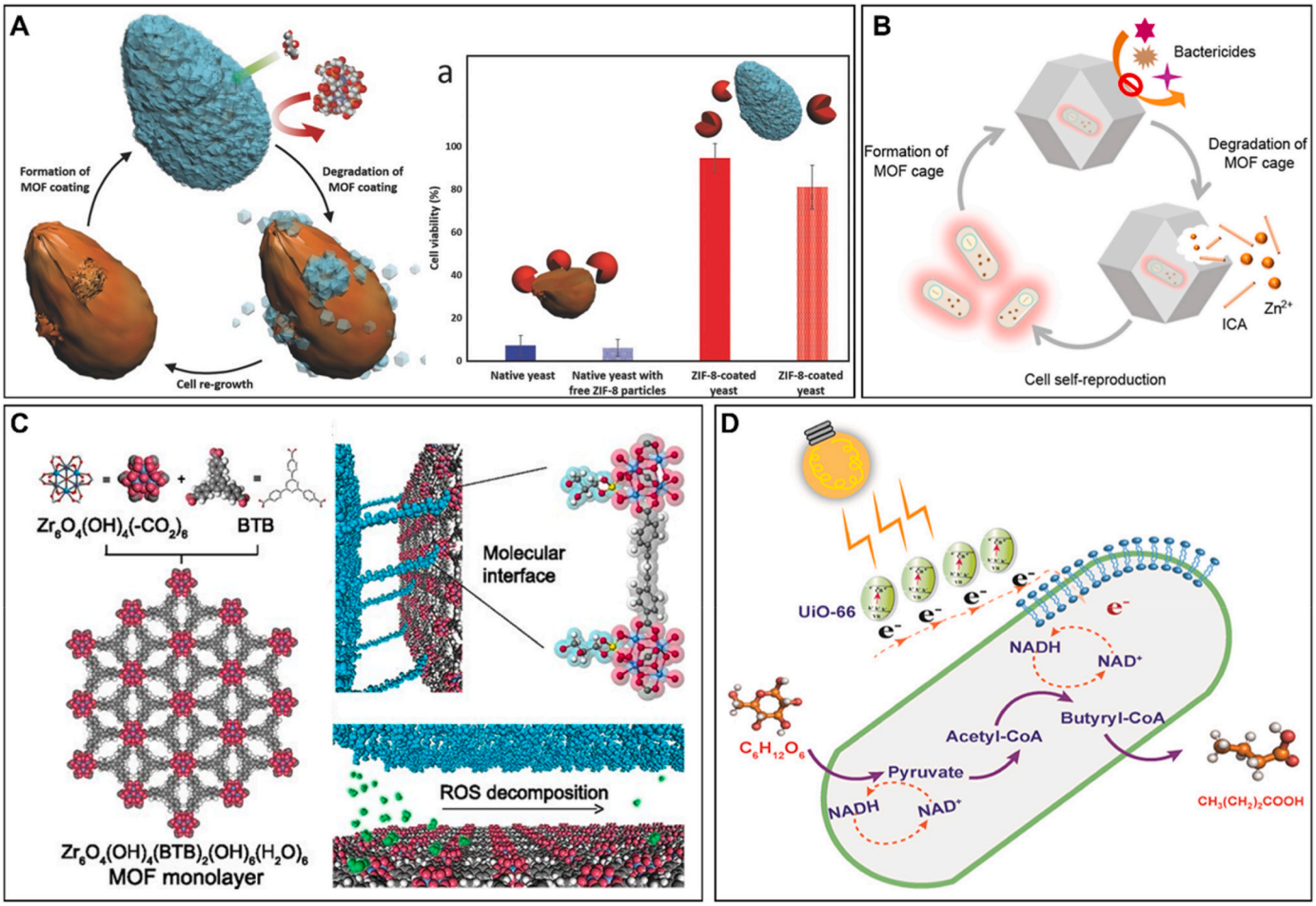


Fig. 1. Cyto-protective and catalytic activity of MOF-based coating on microbes. (A) Schematic illustration of constructing ZIF-8-coated yeast cells and the chart indicating retained cell viability of ZIF-8 coated yeast cells after being treated by cell lysis enzyme, namely lyticase. Reproduced with permission from ref. 63. Copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (B) Graphic abstract of fabricating *E. coli*@ZIF-90 with resistance to bactericides. Reprinted with permission from ref. 68. Copyright 2021 The Author(s). Published by Elsevier Ltd. (C) Schematic diagram showing the composition of $Zr_6O_4(OH)_4(BTB)_2(OH)_6(H_2O)_6$ (BTB = 1,3,5-benzenetribenzoate) MOF monolayer, and its binding to the *M. thermoacetica* cell wall to induce a catalytic decomposition of reactive oxygen species (ROS). Reproduced with permission from ref. 49. Copyright 2018 the Author(s). Published by Proceedings of the National Academy of Sciences of the United States of America. (D) Graphic abstract demonstrating *C. tyrobutyricum* with binding of UiO-66 utilised electrons generated from photocatalytic process to increase intracellular NADH concentration thereby promoting butyrate production. Reprinted with permission from ref. 75. Copyright 2023 American Chemical Society.

coating was also applicable to bacteria, such as *Micrococcus luteus* and *E. coli*, without compromising bacterial viability, suggesting a highly versatile and robust living microbial surface-coating method [63,65,66]. It was noted that the ZIF-8 shell might fail to effectively protect cells against toxins smaller than its pores. To address this problem, changing the type of MOFs can tailor the permeability of the protective coating according to the size of toxins. For example, ZIF-90 with smaller pore size compared to ZIF-8, could completely wrap *E. coli* in a cage-like structure, physically shielding the bacterial cells from small molecule bactericides, such as benzaldehyde, cinnamaldehyde, and kanamycin (Fig. 1B) [68]. Despite the protective effects provided by the MOF-based exoskeleton, this coating may inhibit the bacterial cell division to some extent. Notably, growth-inhibiting bacterial cells recover their growth on MOF coating-layer degradation, permitting microbial-growth control through MOF coating-layer degradation modulation. For instance, shells constructed from ZIF-8 and ZIF-90 can be removed by EDTA, along with the restoration of bacterial cells' growth and functionality [63,64,68].

Additionally, coatings with specific cytoprotective effects can be synthesised by using metal ions with intrinsic catalytic activities to construct the MOF layers, which can subsequently degrade toxic substances *via* catalytic reactions. Importantly, this approach can enhance the production efficiency of specific chemicals by the "cyborg microbes" through artificial photosynthesis or other biological related processes. For instance, the vulnerability of certain anaerobes to oxidative stress hinders their practical application in artificial photosynthesis. To address this, a 1,3,5-benzenetribenzoate and Zr-based MOF layer with catalytic properties for decomposing reactive oxygen species (ROS) was used to shield the anaerobic *Morella thermoacetica* from oxidative stress (Fig. 1C) [49]. The low-toxic and highly stable Zr-based MOF wrapping could sustain bacterial viability and reproductive capacity in anaerobic environment, extend the bacterial lifespan under oxidative stress and elevate the acetate yield from CO_2 fixation compared to uncoated bacteria. Comparably, the Zr-based MOF UiO-66 with excellent photo-catalytic performance could bind to the surface of *Clostridium tyrobutyricum* to form an artificial photosynthetic biohybrid system by donating electrons to *C. tyrobutyricum*, thereby increasing the $NADH/NAD^+$ ratio and subsequently boosting butyrate production (Fig. 1D) [75].

Collectively, these MOF-associated approaches, leveraging the enriched biomolecules on the cell walls, demonstrates their versatility as robust surface-coating methods for both yeasts and bacteria. Furthermore, MOF-based coatings can effectively manage bacterial growth,

underscoring the adaptability of MOF-based exoskeletons and their potential to inspire the development of novel stimuli-responsive "cyborg microbes" systems or platforms for targeted delivery and recovery of specific probiotic populations.

2.1.2. *Functionalisation of microbes@MOFs and their application in anti-cancer treatments*

To enrich the functionality of microbes@MOFs, different approaches, such as i) bacterial transformation, ii) pre-coating of microbes or iii) post-modification of MOF layers, have been employed. These strategies can enable the live tracking of the microbes@MOFs systems and enhance the protective abilities of the MOF layers, enabling microbes to survive in complex and extreme environments, thereby unlocking new therapeutic potentials of microbes@MOFs. Among these strategies, bacterial transformation, which fundamentally modifies the intrinsic properties of microbes@MOFs through gene editing, is particularly notable for functionalizing such systems. It introduces desirable features, such as *in-situ* fluorescence or the production of specific biomolecules, which are unattainable through simple coating or post-modification methods. A study involving the ZIF-90 encapsulation of *E. coli* introduced an mCherry-expression plasmid into the bacteria, enabling bacteria tracking *via* the expression of a red fluorescent protein, which facilitated the visualisation of the bacteria under fluorescent microscopy [68]. A more sophisticated approach to engineering *E. coli* was undertaken by Li and co-workers, where a tailor-made plasmid was introduced to the *E. coli* DH5*α* strain prior to coating the bacteria with functionalised ZIF-8 nanoparticles (Fig. 2A) [79]. Specifically, the plasmid which was inserted with three functional gene sequences responsible for initiating protein expression by sensing the hypoxia environment (the hypoxia-inducible promoter), expressing lactate oxidase (LOX, a lactate oxidase gene) and secreting the protein (a signal peptide gene), conferred the new capability of producing and secreting lactate oxidase to catalyse lactate, thereby generating hydrogen peroxide and intensifying hypoxia in the tumour microenvironment (TME). The engineered *E. coli* was further surface-armoured with the iron-doped ZIF-8 nanoparticles encapsulating tirapazamine (TPZ), allowing efficient inhibition of tumour growth and metastasis.

In addition to genetic engineering, pre-coating microbes with various enzymes or nutrients offers a cost-effective way to increase microbial viability or functionalise the microbes@MOFs with desirable performance. For instance, yeast cells coated with ZIF-8 could only sustain their activity in glucose-containing media [63], but required additional modification with an β-gal enzyme in oligotrophic conditions [64]. This strategic combination of enzyme pre-coating and ZIF-8 shielding effectively protected both yeast cells and enzymes, enabling cell survival in lactose media (Fig. 2B). In another study by Zhu et al., the trehalose synthase-overexpressed permeabilised *Bacillus subtilis* was decorated with glucose isomerase before ZIF-8 coating [67]. The glucose isomerase immobilised within the MOF and trehalose synthase generated by permeabilised *B. subtilis* cells shielded by the MOF layer, formed a two-enzyme system that facilitated trehalose production while minimising by-product (glucose) formation.

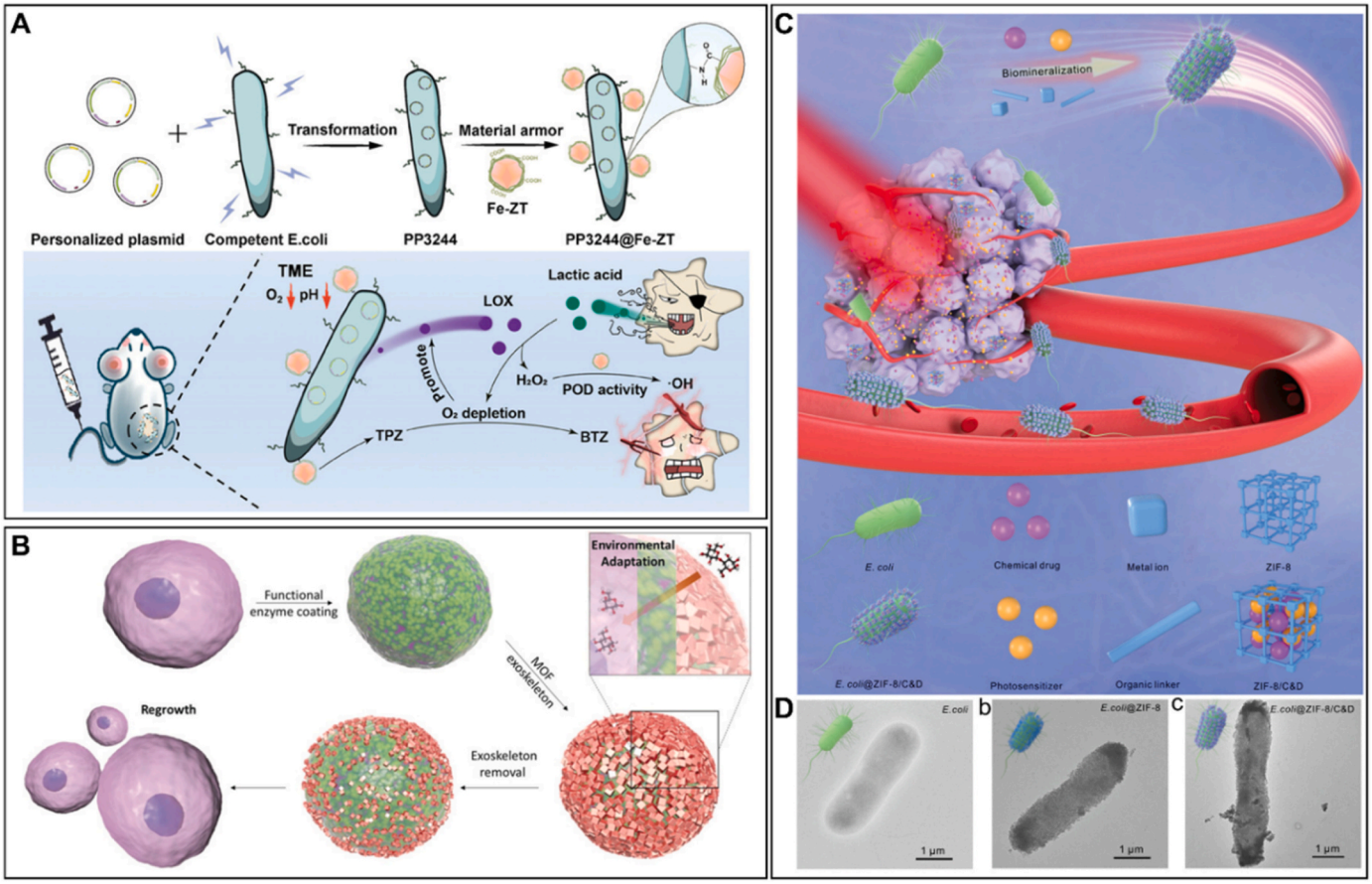


Fig. 2. Three strategies of functionalisation of microbes@MOFs bio-complexes. i) Bacteria transformation: (A) schematic diagram of design and functionalisation of engineered *E. coli* (PP3244) with material armour Fe-ZT. Reprinted with permission from ref. 79. Copyright 2024 Wiley-VCH GmbH. ii) Pre-coating of microbes: (B) schematic illustration showing that a yeast cell pre-coated with a layer of functional enzymes (β-gal) are further protected by an ZIF-8 exoskeleton layer to survive in harsh environment. Reused with permission from ref. 64. Copyright 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. iii) Post-modification of MOF layers: (C) schematic depiction of *E. coli*@ZIF-8 coloaded with a photosensitizer and chemical drug (*E. coli*@ZIF-8/C&D) for tumour-targeting delivery, (D) TEM images of *E. coli, E. coli*@ZIF-8, and *E. coli*@ZIF-8/C&D. Reproduced with permission from ref. 65. Copyright 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

Due to the exceptional porosity and large surface areas of MOF materials, the post-modification of microbes@MOFs usually involves the loading or encapsulation of various small molecules, enzymes, or nanoparticles into the MOF layers [81]. In addition, the pH-responsive degradation mode of MOFs renders MOF-coated bacteria a promising drug delivery system for cancer treatment in the acidic TME. Li and colleagues developed versatile bio-engines constructed from *E. coli* MG1655 wrapped with doxorubicin (DOX)-loaded ZIF-8 layer as a micro-swimmer system for targeted drug delivery. The release of DOX was accelerated at pH 5.0 compared to pH 7.4, suggesting a more effective drug release at low pH environment like tumour sites [71]. Moreover, Yan et al. loaded both chlorin e6 (Ce6) photosensitizer and DOX within ZIF-8 during its *in-situ* coating onto the surface of *E. coli* MG1655, creating a bacteria@MOFs hybrid for combined chemo-photodynamic anti-tumour therapy in TME (Fig. 2C and D). This hybrid leveraged the tumour-targeting properties of *E. coli* to selectively localise to tumour sites, where it generated ROS under laser irradiation, effectively killing cancer cells with released DOX, thereby delivering a synergistic, pH-responsive therapeutic effect *in vivo* [65]. Apart from small molecules, other nanoparticles can also be accommodated by MOFs with larger pore sizes, such as MIL-101 [82–84]. Recently, Li et al. reported a self-driven bio-motor constructed by coating *Bifidobacterium infantis* with polydopamine-coated MIL with encapsulation of DOX and CaO_2 nanoparticles. This bio-motor treated breast tumours in a synergistic manner by combining chemotherapy with chemo-dynamic therapy [73]. In a similar study, Wang et al. developed a bacteria@MOF biohybrid by integrating DOX-loaded MIL-101(Fe) with *Shewanella oneidensis* MR-1 (SO) for enhanced chemotherapy. This biohybrid responded to lactate at the tumour regions, triggering the degradation of MIL-101 and rapid release of DOX, while ferric ions participated in the catabolism of H_2O_2 with the generated radicals to amplify the chemotherapeutic effects [69]. These studies collectively highlight the versatility of microbes@MOFs in integrating multiple therapeutic functions, thereby showing significant potential as precision medicine in cancer treatment.

2.2. MPNs

MPNs are a class of coordination polymers formed by the self-assembly of metal ions or clusters with phenolic ligands. The metal ions or clusters serve as nodes in the network, while the phenolic ligands act as linkers. Thus, MPNs consist of extended and robust structures with high stability, showing great potential as drug delivery vehicles for the encapsulation and release of therapeutic agents [36].

Owing to their facile and cost-effective synthesis, MPNs have been developed for coating different substrates, such as bulk materials, nanoparticles and bio-interfaces, especially on microbes [85]. Specifically, similar to MOF-coating, MPN-coating on microbes also functions as protective layers. Nevertheless, since the organic ligands in MPNs are naturally sourced polyphenols (*e.g.*, flavonoids, lignans, phenolic acids and stilbenes), they possess attractive properties such as antioxidant, anti-inflammatory, anticancer and anti-radioactive effects, thereby MPN-coated microbes exhibit unique properties and are often applied in treating inflammation-related diseases or conditions. Due to the nature of the reaction, this section discusses the common metal ions and polyphenols used to construct MPN coating layers on microbes, along with their major biological applications, particularly in gastrointestinal (GI) delivery and cancer treatment (Table 2).

2.2.1. Common metal ions and polyphenols used for microbe coating

Among the polyphenols used for MPN synthesis in microbe coating, tannic acid (TA), as an approved food additive by US Food and Drug Administration, is the most commonly employed one for chelating metal ions, compared to gallic acid (GA), epigallocatechin gallate (EGCG),

Table 2
Synthesis of different MPN-coated microbes and their functions.

Author-year	Microbe(s)	Coating(s)	Synthesis methods	Functions or purposes
Park, 2014 [86]	*S. cerevisiae*	TA-Fe^{3+}	*In-situ*	Cytoprotection against UV-C irradiation, lytic enzymes, and Ag nanoparticles
Li, 2015 [87]	*S. cerevisiae*; *E. coli*	TA-Fe^{3+}; TA-Mn^{2+}; TA-Gd^{3+}	*In-situ*	Cytoprotection from UV light radiation and ROS; a platform for cell modification with nanoparticles, bioactive molecules, and imaging contrast agents
Kim, 2017 [88]	*S. cerevisiae*	TA-Fe^{3+}	*In-situ*	Cytoprotection and growth control
Kim, 2020 [89]	*S. cerevisiae*	CM-Fe^{3+} + ESMH	*In-situ*	–
Lee, 2020 [90]	*S. cerevisiae*	TA-Fe^{3+}	*In-situ*	Reductive disassembly of the MPN coating with ascorbic acid
Liu, 2021 [91]	*E. coli* Nissle 1917 (EcN)	TA-Fe^{3+} + Eudragit L100	*In-situ*	Cytoprotection against harsh conditions in GI tract; targeted delivery of the probiotic to the intestine
Wasuwanich, 2022 [92]	*B. subtilis*	TA-Fe^{3+}; GA-Fe^{3+}	*In-situ*	Cytoprotection from lyophilisation
Fan, 2022 [93]	*E. coli*; *Bacteroides thetaiotaomicron*	TA-Fe^{3+}; GA-Fe^{3+}; EGCG-Fe^{3+}	*In-situ*	Cytoprotection from oxygen exposure and lyophilisation
Pan, 2022 [94]	*E. coli* Nissle 1917 (EcN); *Lactobacillus casei* ATCC393T; CVS Health Probiotic Capsules (CVS HPC)	TA-Fe^{3+}	*In-situ*	Cytoprotection against six clinically relevant antibiotics for enhanced amelioration of antibiotic-associated diarrhoea
Yang, 2022 [95]	*E. coli* Nissle 1917 (EcN)	TA-Ca^{2+} + Mucin	*In-situ*	Cytoprotection against assaults in GI tract; enhanced adhesion to mucus; regulation of the pathological microenvironment
Han, 2022 [96]	*S. cerevisiae*	$[ESMH/CM]_{10}$-Fe^{3+}	*In-situ*	Cytoprotection from heavy metals, UV-B irradiation; enhanced stability under a wide range of pH values
Han, 2023 [97]	*L. acidophilus; Lactobacillus brevis*	ESMH/CM-Fe^{3+}	*In-situ*	Cytoprotection in simulated gastric fluid
Zhou, 2023 [98]	*Lactobacillus reuteri*	TA-Fe^{3+} + hydrogel	*In-situ*	Cytoprotection against antibiotics; acceleration of wound healing
Luo, 2023 [99]	*E. coli* Nissle 1917 (EcN)	TA-Fe^{3+}	*In-situ*	Cytoprotection against UV irradiation, antibiotics and GI fluids; carrying small molecular drugs and macromolecular biologicals
Ma, 2023 [100]	*Methanosarcina acetivorans* C2A	TA-Fe^{2+}	*In-situ*	Cytoprotection against oxygen stress; promotion of methane production
Fang, 2024 [101]	*E. coli Nissle* 1917 (EcN)	TA-Ca^{2+} + hydrogel	*In-situ*	Cytoprotection against harsh condition in GI tract; therapeutic efficacy on colitis
Zhu, 2024 [102]	*E. coli Nissle* 1917 (EcN)	PC-Fe^{3+} + HMW-HA	Pre-synthesis	Cytoprotection against harsh condition in GI tract; targeted delivery to inflamed sites
Han, 2024 [103]	*L. rhamnosus* GG	EGCG-Ga^{3+} + chitosan	*In-situ*	Targeted delivery to pancreatic tumour; selective elimination of tumour-promoting proteobacteria and microbiota-derived lipopolysaccharides
Kim, 2024 [104]	*Lactobacillus plantarum*; *L. brevis*	TA-Fe^{3+} + hydrogel	*In-situ*	Cytoprotection against freeze-thaw cycles; healing effects on transdermal wounds

coffee melanoidin (CM), and procyanidin (PC). Owing to the presence of numerous catechol and pyrogallol structures, TA not only chelates with metal cations, but also facilitates the formation of a three-dimensionally stabilised TA-based MPN network. Among the metal ions used in microbe coatings, Fe^{3+} has emerged as a promising candidate owing to its involvement in microbial growth and anti-tumour activities. Hence, the coordination of TA and ferric ions has been widely used to build versatile coatings on various substrates. Previously, Ejima et al. developed a facile and scalable one-step method to synthesise TA-Fe^{3+} films by aqueous deposition, with the resulting MPNs could disassemble by changing the local environment to acidic conditions [105]. This study suggested the feasibility of *in-situ* constructing MPNs with a pH-responsive degradation manner, paving the way for coating layers on microbial surfaces. Following this pioneering work, Park and colleagues designed a cyto-compatible TA-Fe^{3+} nanoshell coating on *S. cerevisiae* to protect the yeast against different environmental stresses, including UV-C irradiation, lyticase and even silver nanoparticles. Interestingly, while this nanoshell coating could potentially suppress yeast growth, it can be degraded upon exposure to an acidic environment, which consequently helps restore the yeast cells to a vital state. This suggests a flexible approach to controlling "sporulation and germination" through the on-demand degradation of the MPN coating [86]. Extended work was carried out by Li's group to further improve the MPN coating, not only by applying it to multiple living cell types, *e.g.*, yeasts, bacteria and mammalian cells, but also by demonstrating the successful functionalisation of MPN coating layers with magnetic nanoparticles. This straightforward approach exhibited great applicability for constructing MPN coating layers on microbes using TA and other metal ions (*i.e.*, Mn^{2+} and Gd^{3+}), offering a universal method for MPN-based microbial surface engineering (Fig. 3A) [87].

In addition to ferric ions (Fe^{3+}), ferrous ions (Fe^{2+}) have been utilised to construct MPN coatings for protecting anaerobic bacteria. For instance, TA and ferrous chloride were treated with a methanogenetic anaerobe *Methanosarcina acetivorans* C2A to form a TA-Fe^{2+} nanocoating, which was then converted to TA-Fe^{3+} nanocoating upon exposure to 21 % O_2. This antioxidant MPN coating enhanced the oxygen tolerance of *M. acetivorans* by reducing permeable oxygen, thereby preserving the viability and activity of the bacteria in ambient oxygen. On the other hand, the permeability of the MPN coating to methanol remained unaffected, ensuring the methanogenesis of MPN-coated *M. acetivorans*. Importantly, the MPN coating increased microbial viability and methane yield compared to uncoated bacteria under oxidative stress, demonstrating its potential to protect anaerobes and facilitate energy production catalysed by methanogens [100].

As mentioned, the polyphenols used for constructing MPNs varied according to their structures and the number of phenol groups. Thus, the choice of different polyphenols is crucial for determining the properties of the resulting MPNs. Fan et al. selected TA, GA and EGCG as representative polyphenols with different molecular size and phenol groups to form MPN-based coating on the microbial surface with Fe^{3+} (Fig. 3B). Similar to MOF coatings, MPN coatings suppress cell division in both solid and liquid cultures without affecting cell viability and metabolism. Thus, MPN coating layers can function as rigid barriers that prevent nutrient acquisition by microbes. Notably, the three MPNs, *i.e.*, TA-Fe^{3+}, GA-Fe^{3+} and EGCG-Fe^{3+}, show distinct inhibitory effects, indicating that the phenol structure influences the physical properties of MPNs and their modulatory effects on controlling microbial growth [93].

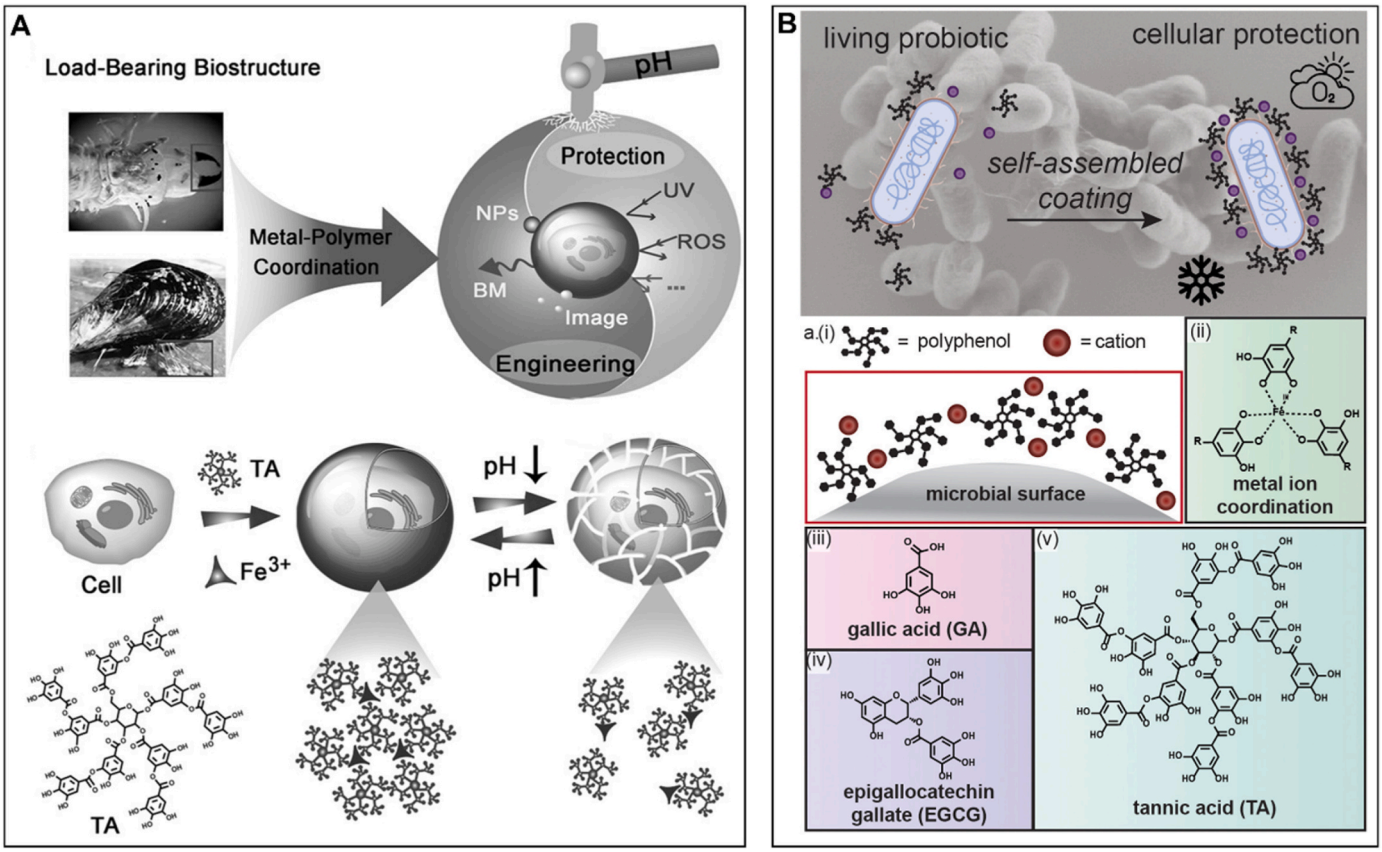


Fig. 3. Common metal–phenolic networks used for microbe coating. (A) Schematic of protective effects of low-pH degradable TA-Fe^{3+} coating inspired by load-bearing biostructures on UV irradiation and oxidative stress. Reprinted with permission from ref. 87. Copyright 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (B) Illustration of self-assembled metal–phenolic networks coated on microbial surface, including GA-Fe^{3+}, EGCG-Fe^{3+}, TA-Fe^{3+}. Reproduced with permission from ref. 93. Copyright 2021 The Authors. Published by American Chemical Society.

2.2.2. MPN-coated bacteria for GI delivery

Owing to its microbe-friendly feature that maintains cell viability, as well as the on-demand release mode of coated microbes, MPN coating has been developed to shield probiotics for gastrointestinal (GI) delivery. However, MPN layers could be degraded at low pH, limiting their feasibility for GI probiotic delivery. To address this, synthetic approaches have been optimised by adding an extra layer to MPN-coated probiotics for preventing the MPN shell from collapsing in the gastric environment. For instance, in a recent study, *E. coli* Nissle1917 (EcN) was sequentially encapsulated in a double-layer system composed of TA-Fe^{3+} and Eudragit L100 (Fig. 4A). The outer layer Eudragit L100, an enteric polymer that dissolves in the intestinal environment (pH > 6.0), could stabilise the inner TA-Fe^{3+} layer, consequently protecting and releasing the EcN cells at the desired location in the GI tract. Moreover, the coated EcN showed enhanced adhesive capability to the intestinal mucosa due to the affinity between TA and mucin, thus leading to prolonged retention in the intestine [91]. Pan and co-workers employed a similar strategy by lyophilising TA-Fe^{3+}-coated probiotics to preserve their viability and growth before encapsulating them in enteric capsule for effective and protective delivery against acidic gastric fluid and antibiotics [94]. These highlight the functionalisation of MPN-coated probiotics with an additional acid-resistant layer for GI delivery.

In addition to Eudragit L100, other biomolecules, such as mucin and high-molecular-weight hyaluronan (HMW-HA), can enhance the environmental resistance and colonisation of the probiotics. Recently, a strategy developed by Yang et al. showed that the decoration of acid-resistant glycoprotein mucin on TA-Ca^{2+}-coated probiotic EcN could protect the probiotic from harsh conditions and increase the interaction of the "cyborg bacteria" with the intestinal mucus layer [95]. Meanwhile, HMW-HA-functionalised procyanidine (PC)-Fe^{3+}-armoured EcN (PC-Fe^{3+}@EcN) offered multiple advantages for treating inflammatory bowel disease (Fig. 4B). Of note, this PC-Fe^{3+}@EcN system could release the coated EcN in response to high concentrations of the iron-binding protein transferrin (Tf) in the inflamed colonic mucosa and restore the probiotic growth through Tf-mediated MPN degradation, thus enabling the precise delivery of probiotics to disease sites and effectively maintaining gut barrier homeostasis while modulating intestinal microbiota dysbiosis [102].

Apart from their stimuli-responsive characteristics, MPN-coated microbes can deliver different agents for multimodal therapy, thanks to the porous structure of MPNs for encapsulating cargo molecules. As introduced by Luo et al., the TA-Fe^{3+}@EcN encapsulated with small molecules (*i.e.*, doxorubicin or berberine) and biomacromolecules (*i.e.*, ovalbumin and anti-programmed cell death protein 1 antibody) could increase the intestinal colonisation while promoting the adhesion of EcN on a wide variety of murine and porcine bio-interfaces, thereby further enhancing treatment efficacy (Fig. 4C) [99]. These studies emphasise the great potential of applying MPN-coated probiotics with cargo

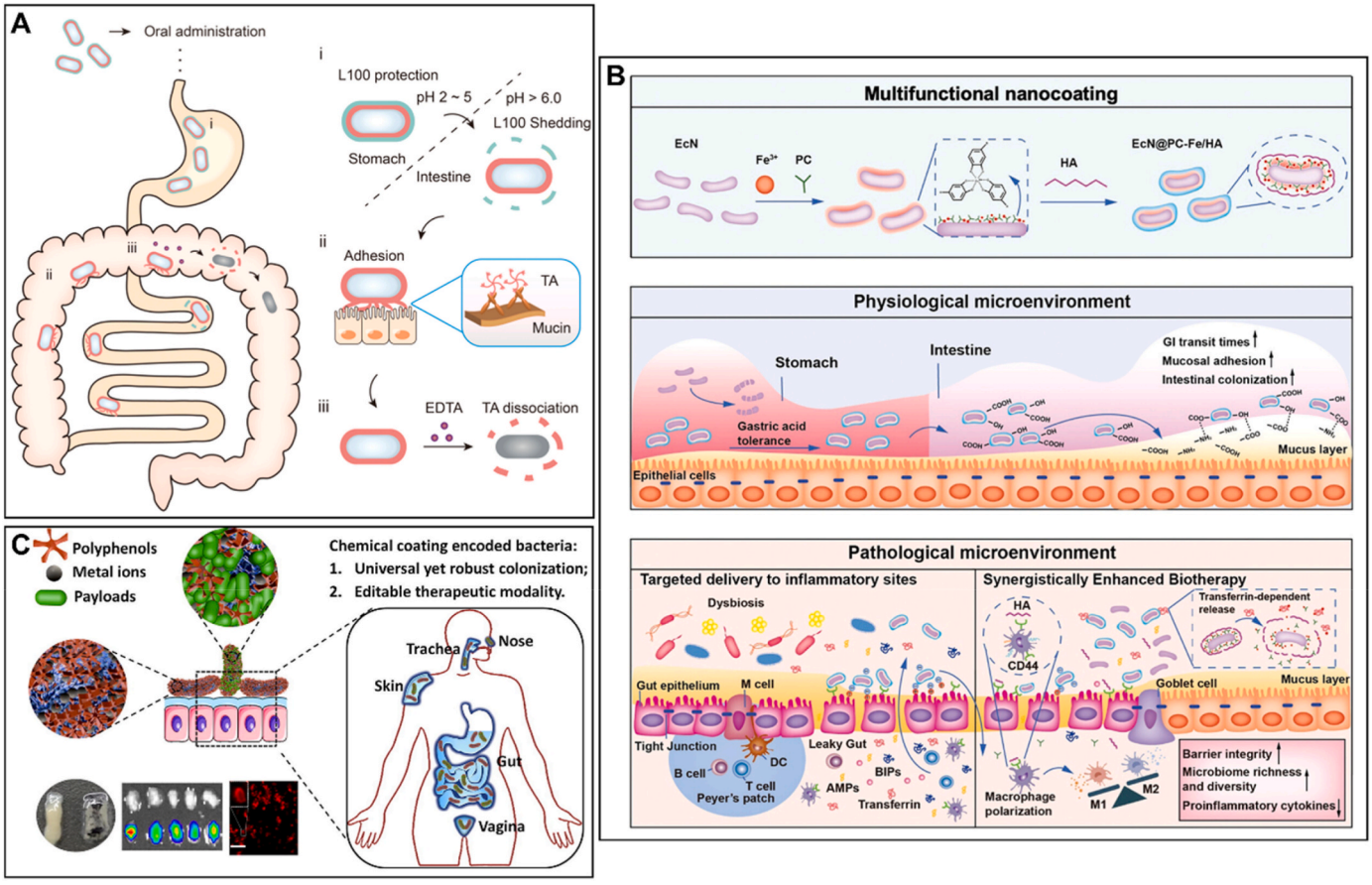


Fig. 4. MPN-coated probiotics for gastrointestinal delivery. (A) Schematics of the protective L100-TA double-layer coating on EcN bacteria and the configurable retention of the system on mucosal epithelium owing to the TA–Fe^{3+} layer; the L100 layer protects the TA coating from pH-triggered degradation as the molecule moves from the stomach to the intestine. Reprinted with permission from ref. 91. Copyright 2021 Elsevier Ltd. (B) Schematics of the synthetic strategy and gastrointestinal delivery under physiological and inflammatory conditions of a superior probiotic EcN coated by layer-by-layer multifunctional nano-armour, PC-Fe^{3+}/HMW-HA, for synergistically enhanced targeted biotherapy for colitis through HA-CD44 binding for inflamed-site targetability and transferrin-induced degradation for "awakening" probiotics. Reused with permission from ref. 102. Copyright 2024 Wiley-VCH GmbH. (C) Illustration of versatile microbial therapy mediated by bacteria encoded with a drug-loadable MPN nanocoating, showing universal yet robust colonisation on diverse bio-interfaces and editable therapeutic modality by loading different drugs. Reproduced with permission from ref. 99. Copyright 2023 Elsevier Ltd.

delivery capacity for advanced microbial therapy.

2.2.3. MPN-coated bacteria for other applications

Intratumoural microbiota have been associated with the initiation and progression of cancers, as well as the efficacy of anti-cancer therapy. Therefore, the modulation of the imbalanced intratumoural microbiota may benefit anti-tumour treatment by contributing towards the activation of immunotherapy and reduction of the treatment resistance [106]. Concurrently, the metal ions used in MPN-coated probiotic systems can synergize with the probiotics to uplift the modulatory effects on intratumoural microbiota and the immunotherapy efficacy. For example, an MPN layer of gallium ion (Ga^{3+}) and EGCG, constructed on *Lactobacillus rhamnosus* GG (LGG) and followed by chitosan nanocoating (LGG@Ga-poly), could selectively target pancreatic ductal adenocarcinoma through oral administration. Particularly, the chitosan coating could prevent Ga^{3+} leakage in gastric fluid to ensure the therapeutic efficacy of the biohybrid in the delivery process, while the released Ga^{3+} could eradicate tumour-promoting *Proteobacteria* by disrupting the bacterial iron metabolism and reduce microbiome-derived lipopolysaccharide at tumour sites. As a result, the activation of Toll-like receptor was inhibited, in turn reversing the immunosuppressive TME and increasing T cell recruitment to help the overall efficacy of immune checkpoint blockade in pancreatic ductal adenocarcinoma treatments [103].

The incorporation of other biomaterials with MPN-coated probiotics can also improve the efficacy, stability, and targeted delivery of the probiotic-based biohybrids, offering potential benefits and synergistic effects on treatment outcomes. As reported by Kim and colleagues, TA-Fe^{3+}-coated probiotics were loaded in a mannitol and polyvinyl alcohol-based hydrogel dressing for obtaining better wound healing efficacy. *Lactobacillus brevis* and *Lactobacillus plantarum* with positive effects on skin health were selected for coating on MPN layers, which could retain high viability in the hydrogel dressings. The final nanocoated-probiotic-loaded hydrogel dressing was capable of accelerating wound healing, producing a thicker recovered stratum corneum with a smoother surface [104].

3. Synthetic strategies of metal–organic nanocoating on microbes

In light of the basic synthesis principles of MOFs and MPNs, they share some similarities but differ in their preparation methods, leading to diverse strategies for coating microbes. In general, both MOFs and MPNs can form coordination networks using metal ions/clusters and organic ligands. Yet, MOFs often use rigid organic linkers and are prepared *via* solvothermal or hydrothermal methods, whereas MPNs are typically assembled through coordination chemistry with polyphenolic ligands and metal ions at room temperature [85,107,108].

In addition to differences in synthetic methods, the organic ligands used in the synthesis of MOFs and MPNs vary in their structural properties and functionalities, thereby resulting in a wide variation in coating configurations and microbial surface coating strategies. For MOFs, organic ligands show several structural characteristics, including multiple coordination sites, rigid structures, aromaticity and containing various functional groups (such as carboxylates, amines, or imidazole). In particular, aromatic ligands, such as benzene-based or pyridine-based ligands, are commonly used in MOF synthesis due to their stability and ability to form π-π interactions, simultaneously contributing to the stability and structural integrity of MOFs [109,110]. Interestingly, except 2-methylimidazole (2-ME) in ZIF-8 synthesis, the aromatic ligands with poor water solubility are rarely employed in constructing *in-situ* MOF coatings on microbes, as aqueous conditions severely limit their binding efficiency with metal ions. Hence, MOFs made from hydrophobic ligands are usually constructed and/or functionalised separately before being adhered to or conjugated with microbes. Regarding MPNs, their ligands are predominantly polyphenolic compounds with phenols serving as the metal-coordinating sites to extend networks [111]. Depending on the number of phenol groups, these polyphenols can influence the water solubility of the compounds, suggesting a similar microbial surface coating method to MOF-coatings in aqueous solutions. Based on the spatiotemporal relationship between the coating materials and microbial substrates, coating formation strategies are divided into *in-situ* growth and pre-synthesis methods with their synthetic principles discussed in this section (Scheme 2).

3.1. In-situ growth of the coating on the microbial cells

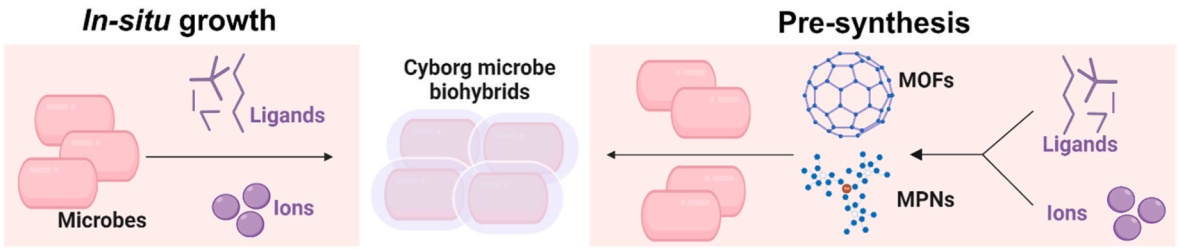
In-situ growth is widely used for direct synthesis of metal–organic layers on different substrates [112–115]. Generally, it offers several advantages: i) facile synthesis, ii) precise control over shell thickness, and iii) improved encapsulation efficiency of cargo molecules. As a result, this robust and facile method is commonly used as the primary approach in most studies of MOF- or MPN-based coatings on live microbes (Tables 1 and 2). Coating microbes with ZIF-8, and MIL-100 MOFs is straightforward and avoids the complex reaction conditions typical of conventional MOF synthesis. Under mild conditions, the *in-situ* growth of ZIF-8 only involves two main steps: suspension of microbial cells in a 2-ME water solution and addition of zinc ions. The ZIF-8 shell can form within 10 min, significantly shortening the synthetic procedure and demonstrating potential for commercial-scale applications. Regarding MPNs, EGCG, GA and TA are usually selected, with TA being the most frequently used polyphenol for *in-situ* synthesis due to its excellent water solubility from numerous structural phenol groups. In terms of synthetic methods, they are almost identical to MOFs. Briefly, polyphenolic solution (mostly TA) and metallic salt solution (mainly ferric chloride) were separately added to microbial suspension to directly synthesise MPN shells on individual cells.

As mentioned, one advantage of *in-situ* grown metal–organic coatings on microbe is precise control over shell thickness. Indeed, the thickness could be tuned by altering the number of coating cycles or the concentration of metal ions and organic linkers. Taking ZIF-8 coating as an example, its thickness increased from 100 to approximately 250 nm on repeating the coating procedure four times [63]. Similarly, the coating thickness of MPNs can be increased by repeating the coating process multiple times [86]. Moreover, Fan and co-workers modified the thickness of TA-Fe^{3+} coatings on *B. thetaiotaomicron* by changing the concentrations of tannic acid and ferric chloride, which consequently affected bacterial exponential growth delay [93]. Referring to the enhanced encapsulation efficiency brought by the *in-situ* coating, cargo molecules are usually added to the reaction solution and encapsulated into the metal–organic coating layer during *in-situ* growth, maximising their loading efficiency for better application outcomes [65].

3.2. Pre-synthesis of the metal–organic materials before coating

Although the *in-situ* growth of metal–organic coatings on microbial cell surfaces is a rapid and facile approach with attractive advantages, there are still limitations regarding the types of applicable coating material and reactants, including metal ions and organic linkers. For certain types of MOFs with specific metal ions and larger pore sizes, they can only be synthesised from organic solvents through hydrothermal reactions, making the *in-situ* growth unfeasible. Moreover, *in situ* growth cannot be used for the fabrication of MPN coatings comprising certain polyphenol compounds with extremely poor water solubility under microbial-friendly conditions. As such, the pre-synthesis of metal–organic materials, with or without further functionalisation, is an alternative approach to coating the microbial surface.

To date, pre-synthesised MOFs are more commonly employed than MPNs, particularly those with catalytic functions and benzene-based hydrophobic ligands, like zirconia-based MOF (*e.g.*, $Zr_6O_4(OH)_4(BTB)_2(OH)_6(H_2O)_6$ and UiO-66) and iron-based MOFs (*e.g.*, MIL-101) [49,69,73,75]. These MOFs, while exhibiting catalytic activity or high



Scheme 2. Schematic diagram of two kinds of synthetic strategies of MOFs and MPNs coated on microbes.

loading ability, are typically prepared through hydrothermal reactions in organic solvents, thus requiring the addition of living microbial cells after their preparation. In contrast, there is only one MPN study of coating the EcN surface with pre-synthesised PC-Fe^{3+}, possibly due to the slightly alkaline reaction condition of PC-Fe^{3+} (pH = 8.2) which may compromise bacterial viability under long-term exposure [102].

Given that pre-synthesised metal–organic materials lack the inherent moieties to coordinate with the microbial surface, additional modification or functionalisation is required to facilitate coating on the microbes. Currently, three methods have been developed and utilised: i) electrostatic interaction, ii) adhesive polymer coating, and iii) covalent conjugation. For electrostatic interaction, various polymers are used to functionalise the pre-synthesised metal–organic materials/nanoparticles, while the microbe surface is coated with oppositely charged polymers to enhance the electrostatic adsorption of the functionalised materials/nanoparticles [69]. Meanwhile, pre-synthesised materials can also be decorated with adhesive polymers (such as polydopamine, PDA) to improve their adhesion to the microbial surface [73]. Concerning covalent conjugation, the carboxyl-amine coupling is the most popular option in biomedical fields, as the enriched biomacromolecules on the microbial surface provide abundant amino groups for the coupling process [116]. Particularly, the introduction of carboxyl group-containing agents to the metal–organic materials could enable covalent bindings using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and N-hydroxysuccinimide (NHS) [72,79].

4. Conclusions and perspectives

At present, there is an increasing trend in applying various microbes for healthcare purposes, environmental bioremediation and renewable energy. Surface coating of the living microbes offers an efficient and versatile approach to endowing them with exogenous capabilities, resulting in the recent development of the so-called “cyborg” cells that integrate the functions of both targeting microbes and coating materials. Notably, MOFs and MPNs serve as protective exoskeleton for living cells and multipurpose platforms for functionalising biohybrids, owing to their biocompatibility, stability, durability, adsorption and catalytic properties. This review summarises the latest advancements in constructing MOF- or MPN-based coating on microbes, specifically focusing on the functionalisation approaches and synthetic strategies as well as potential applications and future perspectives.

To date, the developed metal–organic-coated microbes are still associated with certain challenges, and these limitations and possible solutions are stated as below.

1) Unexplored theranostic potential: until now, MOFs and MPNs have been applied as promising candidates for theranostic application [117–119], while biohybrids constructed from MOF- or MPN-coated microbes have been developed primarily for treating cancer, inflammatory bowel disease or skin wounds with limited focus on sensing and imaging capabilities.
2) Unknown long-term viability and stability of the biohybrids: although microbial cells have been proven viable after coating, few studies have assessed the long-term viability and stability of these biohybrids. In particular, the selected metal ions and ligands used to construct the metal–organic coating layers, despite being relatively biocompatible, may impact microbial metabolism due to direct contact with microbial cells, potentially affecting their long-term viability. Additionally, as previously mentioned, these metal–organic coating layers could restrict the passage of large molecules and suppress microbial cell division. As a result, delayed or incomplete degradation of the coating layers can impair microbial viability and dampen the advantages of the cyborg microbe systems. Furthermore, the mechanisms of how the encapsulation would alter the substance exchanges and cellular communications remain to be studied.

   Given the possible application fields, the developed biohybrids are constantly facing the challenges raising from the surrounding environment. Therefore, the changes of the chemicals and mechanical forces can show some certain influences on the stability of the coating layers. To address these possible issues or challenges, a separating layer containing essential nutrients to support microbial growth can be performed on the microbes before metal–organic coating. Proper modifications on the microbes can optimise the microbial surface characteristics and further enhance their integration with the metal–organic coating layers with improved overall stability of the biohybrid systems.

   It remains unclear about the interaction of the cyborg microbes with other microbial species, while the complex microbial communities can also bring certain effects on the long-term viability and stability of the biohybrids. Advanced techniques and systems, including high-throughput sequencing, single-cell analysis, super-resolution microscopy, multi-omics approaches, and microfluidic systems, can be employed to comprehensively investigate the interactions of cyborg microbes with microbial communities. These tools enable researchers to analyse the composition of microbial communities, characterise individual microbial cells, visualise the spatial distribution of specific microbes, and assess microbial molecular responses in a thorough manner.

3) Potential environmental impacts: it is important to note that the degradation of these coatings may release metal ions and organic ligands, posing potential environmental impacts. Depending on the metal types, these ions can be toxic to certain life forms, potentially leading to bioaccumulation and biomagnification in the food chain. Furthermore, some MOFs and MPNs may be resistant to natural degradation processes, resulting in the accumulation in soil and water bodies. Also, the introduction of metal–organic coated microbes into the environment can affect local microbial communities and disrupt ecological balances by potentially inhibiting the growth of certain microorganisms while promoting the growth of others. Therefore, while metal–organic coatings offer benefits like cytoprotection to the microbes, monitoring their environmental risks is still crucial to prevent contamination and maintain ecosystem balance.

Hence, based on current advancements, limitations, and challenges of the metal–organic-coated microbial biohybrids, we propose the following future directions for this promising technology.

1) Biosensing and theranostic platforms: due to MOF- or MPN-coated microbe systems that act as biohybrid sensors for detecting environmental changes in pH or other stimuli, and certain microbes selectively accumulating at pathological sites, the emerging approaches such as genetic engineering and therapeutic payload delivery can be used to functionalise the biohybrid system for theranostic purposes. By genetically modifying the microorganisms to incorporate diagnostic and therapeutic elements, genes-encoded therapeutic proteins, imaging-detecting agents or other diagnostic tools can be introduced into the genome, while encapsulating therapeutic payloads in the MOF or MPN layers further enhances treatment outcomes significantly. Additionally, utilizing metal ions with imaging properties, *e.g.,* gadolinium or iron, can add diagnostic capabilities to the biohybrid systems.
2) Advanced microbial therapy for the recovery of microbiota balance: microbiota balance is essential for maintaining health and well-being across various body niches like the gut, skin, oral cavity and reproductive tract. Disruption of microbial communities can lead to dysbiosis, subsequent infections, uncontrolled inflammation and various resultant diseases. Therefore, targeted microbial intervention like probiotic supplementation can help replenish and restore microbial balance, consequently promoting overall health. In this context, applying metal–organic coating to selected probiotics, along with encapsulating prebiotics or other beneficial agents, can effectively modulate host–microbiota interactions and accelerate the microbiota recovery.
3) Safety and toxicity assessment of metal–organic-coated microbial biohybrids: metal–organic-coated microbial biohybrids may have broad application prospects in both the biomedical field and the food industry. Therefore, ensuring their short- and long-term safety and toxicity is critical for practical use. Apart from assessing the biocompatibility of the metal–organic coating layers with the microbes, it is also essential to fully study and evaluate whether the constructed biohybrids are compatible with living tissues. In addition to traditional *in vitro* and *in vivo* models, the state-of-the-art biomimetic platforms, such as organ-on-a-chip and organoids, can serve as innovative systems to investigate the safety and toxicity for managing and controlling the exposure risks associated with the use of biohybrids.
4) Enriching the diversity of metal–organic-coated microbes: while existing research predominantly focuses on fungi and bacteria, limited studies have explored the application of metal–organic coatings on microalgae [53,120], a distinct group of photosynthetic microorganisms. Given their broad distribution in ecosystem and utility in fields such as food, cosmetics, pharmaceuticals, nutraceuticals, and biomedicine, the metal–organic coatings are anticipated to significantly enhance the functionality of microalgae in these domains. Furthermore, current research indicates a considerable disparity in the number of studies and applications involving metal–organic-coated fungi and bacteria. Although initial experiments were performed on yeasts due to their low-cost accessibility and easy cultivation, subsequent investigations have extended the technology to various bacterial strains. The resulting biohybrids exhibit diverse applications in biomedicine, environmental bioremediation, and renewable energy sectors. Therefore, expanding the application of metal–organic-coated microorganisms on the microbial types and species stands to yield substantial benefits across a wide range of applications.

Taken together, rational construction of cyborg microbes with metal–organic coating involves integration of various synthetic components with microbial systems to create hybrid organisms with specifically enhanced functionalities. These novel cyborg microbes hold great promises for therapeutic applications by harnessing the unique properties of engineered microbial systems, while the application in renewable energy allows tailor-made microbial systems with tunable metabolic pathways for higher chemical production and energy conversion rates. Overall, the exciting advancement represents a cutting-edge approach to developing and creating hybrid organisms with diverse functionalities for promising applications. This review is expected to function as a repository of information on recent advances in microbes with surface coatings and expedite the development of advanced systems with unique properties for a wide variety of emergent applications.

CRediT authorship contribution statement

Zichen Wu: Writing – review & editing, Writing – original draft, Conceptualization. **Ke Xu:** Writing – review & editing, Visualization. **Regina Huang:** Writing – review & editing, Writing – original draft. **Xinna Wang:** Writing – review & editing, Writing – original draft. **Jade Lee-Lee Teng:** Writing – review & editing. **Xiaolin Yu:** Writing – review & editing. **Lijian Jin:** Writing – review & editing. **Quanli Li:** Writing – review & editing. **Ken Cham-Fai Leung:** Writing – review & editing. **Hai Ming Wong:** Writing – review & editing, Supervision, Conceptualization. **Xuan Li:** Writing – original draft, Funding acquisition, Conceptualization.

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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Abbreviations

β-gal	β-galactosidase
2-ME	2-Methylimidazole
BTB	1,3,5-Benzenetribenzoate
CA	Citric acid
Ce6	Chlorin e6
CuBTC	Cu-benzene tricarboxylate
DOX	Doxorubicin
EcN	*E. coli* Nissle 1917
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA	Ethylenediaminetetraacetic acid
EGCG	Epigallocatechin gallate
GA	Gallic acid
GI	Gastrointestinal
CM	Coffee melanoidin
ESMH	Egg shell membrane hydrolysates
HA	Hyaluronic acid
HPC	Health Probiotic Capsules
HMW-HA	High-molecular-weight hyaluronan
ICG	Indocyanine green
LGG	*Lactobacillus rhamnosus* GG
LOX	Lactate oxidase
LUT	Luteolin
MIL	Materials of Institute Lavoisier
MOF	Metal–organic framework
MPN	Metal–phenolic network
NAD	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide hydrogen
NHS	*N*-hydroxysuccinimide

PAO	Polyamine oxidase
PC	Procyanidin
PDA	Polydopamine
ROS	Reactive oxygen species
SO	*Shewanella oneidensis* MR-1
TA	Tannic acid
Tf	Transferrin
TME	Tumour microenvironment
TPZ	Tirapazamine
TreS	Trehalose synthase
UiO	Universitetet i Oslo
UV	Ultraviolet
ZIF	Zeolite imidazolate framework

Data availability

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

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