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REVIEW

Metal−polyphenol network-based multifunctional materials for tumor therapy: Intrinsic properties, advances, and applications

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Clinical translation

Abstract Metal−polyphenol networks (MPNs), a novel class of nano-biomaterials, have recently emerged as promising candidates for tumor diagnosis and therapy due to their unique chemical tunability, excellent biocompatibility, and synergistic multifunctionality. Notably, MPNs can be synthesized *via* one-step or multi-step approaches, allowing precise control over their morphology, size, and drug-loading capacity. The versatility of MPNs is further demonstrated by their ability to integrate multiple therapeutic modalities, including chemotherapy, photothermal therapy, photodynamic therapy, and chemical dynamic therapy. Furthermore, through surface modification with targeted molecules, MPNs enable tumor-specific targeting while facilitating real-time therapeutic monitoring *via* multimodal imaging. Additionally, MPNs exhibit excellent biocompatibility and superior biodegradability, making them highly suitable for biomedical applications. This review systematically explores MPN synthesis strategies and physicochemical properties. It then comprehensively analyzes MPN-based biomaterials and their tumor therapeutic mechanisms. Furthermore, we evaluate the challenges in MPN clinical translation and propose future

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perspectives for precise tumor treatment using MPN-based platforms. Ultimately, this review highlights the transformative potential of MPNs in advancing tumor theranostics and lays the foundation for their future clinical applications.

1. Introduction

Polyphenols, a widely distributed class of bioactive phytochemicals in plants, possess distinct physicochemical properties and bioactivity determined by their molecular architecture and functional groups. These compounds are classified systematically based on the quantity of aromatic rings and the structural linkages between them. They primarily comprise flavonoids, phenolic acids, lignans, and stilbenes[1]. Polyphenols exhibit diverse pharmacological profiles—including antioxidant, anti-inflammatory, immunoregulatory, antimicrobial, and anticancer properties—making them promising therapeutic candidates[2]. However, their therapeutic potential is often limited by pharmacokinetic issues, such as poor solubility, rapid systemic clearance, and a lack of intrinsic targeting specificity. These issues significantly restrict their biomedical applications.

Nanotechnology advancements enable innovative approaches to targeted cancer therapy. Engineered nanomaterials offer prolonged circulation half-life, high surface-to-volume ratio, and distinct physicochemical characteristics that enhance their biomedical applications[3,4]. Among these, polyphenols, possessing abundant phenolic hydroxyl groups and aromatic rings, can chelate metal ions to form self-assembled metal–polyphenol networks (MPNs). As an emerging class of functional nanomaterials, MPNs attract significant interest due to their tunable surface chemistry and inherent bioactivity. Importantly, MPN serves as versatile nanocarriers for targeted delivery of chemotherapeutics and biomacromolecules to tumor microenvironments (TME), minimizing systemic toxicity. Their engineered architecture also facilitates biological barriers penetration, enhancing precision oncology potential[1]. Notably, MPNs exhibit intrinsic anticancer properties that directly contribute to therapeutic efficacy. They modulate multiple biological pathways by inducing oxidative stress, disrupting tumor cell metabolism, and inhibiting key cancer progression signaling pathways. Furthermore, MPN metal ions generate reactive oxygen species (ROS), promoting cancer cell apoptosis and chemosensitization. Additionally, polyphenols within MPNs exert anti-proliferative effects through immune modulation and suppression of angiogenesis. By integrating these multifaceted mechanisms, MPNs serve not only as efficient drug carriers but also function as active therapeutic agents, thereby reinforcing their potential for precision oncology.

This paper provides a systematic review of MPNs, detailing their structural characteristics, synthesis strategies, and bioactive properties. It highlights recent advancements in MPNs application for tumor intervention, showcasing their potential in targeted drug delivery, combination therapy, and immune modulation (Fig. 1). Overall, this review aims to offer new insights for designing next-generation MPN-based nanoplatforms with optimized tumor targeting and enhanced therapeutic efficacy.

2. Polyphenols

Polyphenols are bioactive compounds characterized by aromatic rings with multiple hydroxyl groups[5,6], widely distributed in plants such as fruits, vegetables, and tea. They are classified into four major subclasses based on their structural motifs: flavonoids (*e.g.*, quercetin (QUE), epigallocatechin gallate (EGCG)), phenolic acids (*e.g.*, gallic acid (GA), lignans (*e.g.*, phillygenin), and stilbenes (*e.g.*, resveratrol) (Table 1[7-33]). These compounds exhibit diverse pharmacological properties, including antioxidant, anti-inflammatory, and antitumor activities, which are pivotal for biomedical applications.

Flavonoids, the most abundant subclass, feature a C6–C3–C6 backbone and demonstrate strong metal-chelating capabilities thanks to their hydroxyl and ketone groups. For example, QUE modulates immune pathways (*e.g.*, IL-6/JAK/STAT3) and enhances chemotherapy sensitivity, while EGCG, a prominent catechin in green tea, regulates epigenetic modifications and redox balance[34-36]. Curcumin (CUR), a diarylheptanoid from turmeric, synergizes with metal ions to form stable nanocomplexes, amplifying its anticancer effects[20,37-40]. These intrinsic properties of polyphenols underpin their utility in constructing MPNs, enabling targeted drug delivery, ROS generation, and immune activation.

The structural diversity and functional versatility of polyphenols make them ideal ligands for coordinating transition metals (*e.g.*, Fe^{3+}, Cu^{2+}), forming MPNs with tunable physicochemical and therapeutic properties. Subsequent sections will explore how MPNs leverage these polyphenol–metal interactions to drive cutting-edge mechanisms, including immunomodulation, epigenetic reprogramming, and microbiota regulation, in tumor therapy.

3. MPNs: Synthesis and properties

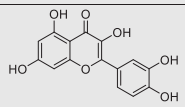
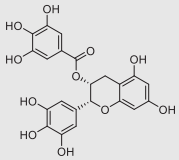
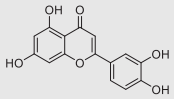
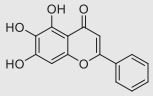
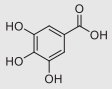
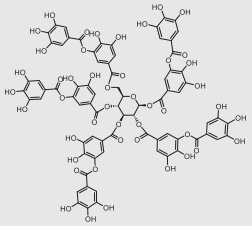
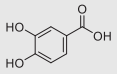
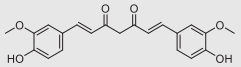
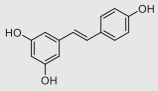
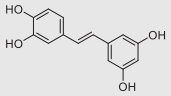
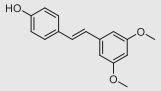
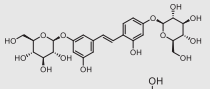
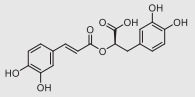
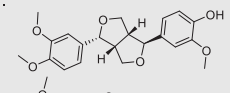
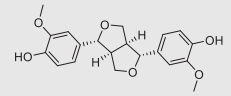
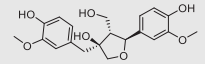
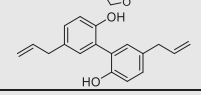
3.1. MPNs

The pioneering work by Caruso's team[41] at the University of Melbourne (Australia) in 2013 established the first multifunctional MPNs by introducing Fe^{3+}–TA coordination chemistry. Since then, MPNs have garnered increasing attention due to their unique structural versatility and biofunctional properties. In MPN architectures, transition metal cations such as Fe^{3+}, Cu^{2+}, and Ag^{+} predominantly serve as coordination centers and form stable complexes with bioactive polyphenols, including TA, QUE, EGCG, and GA. Notably, the diverse interactions between polyphenolic ligands and transition metal cations allow for precise modulation of MPN physicochemical properties (Fig. 2).

3.1.1. Key reaction parameters and bonding mechanisms of MPNs

The synthesis, stability, and functionalities of MPNs are governed by critical reaction parameters (pH, temperature, metal-to-polyphenol

Table 1 Chemical structures of representative polyphenols.

Class	Name	Structure	Ref.
Flavonoids	QUE		7 8 9
	EGCG		10
	Luteolin		11 12
	Baicalein		13
Phenolic acids	GA		14 9
	Tannic acid (TA)		15 16 17
	Protocatechuic acid		18 19
	CUR		20
Stilbenes	Resveratrol		21 22
	Piceatannol		23 24
	Pterostilbene		25
	Mulberroside A		26
Lignans	Rosmarinic acid		27 28
	Phillygenin		29
	Pinoresinol		30 31
	Olivil		32
	Magnolol		33

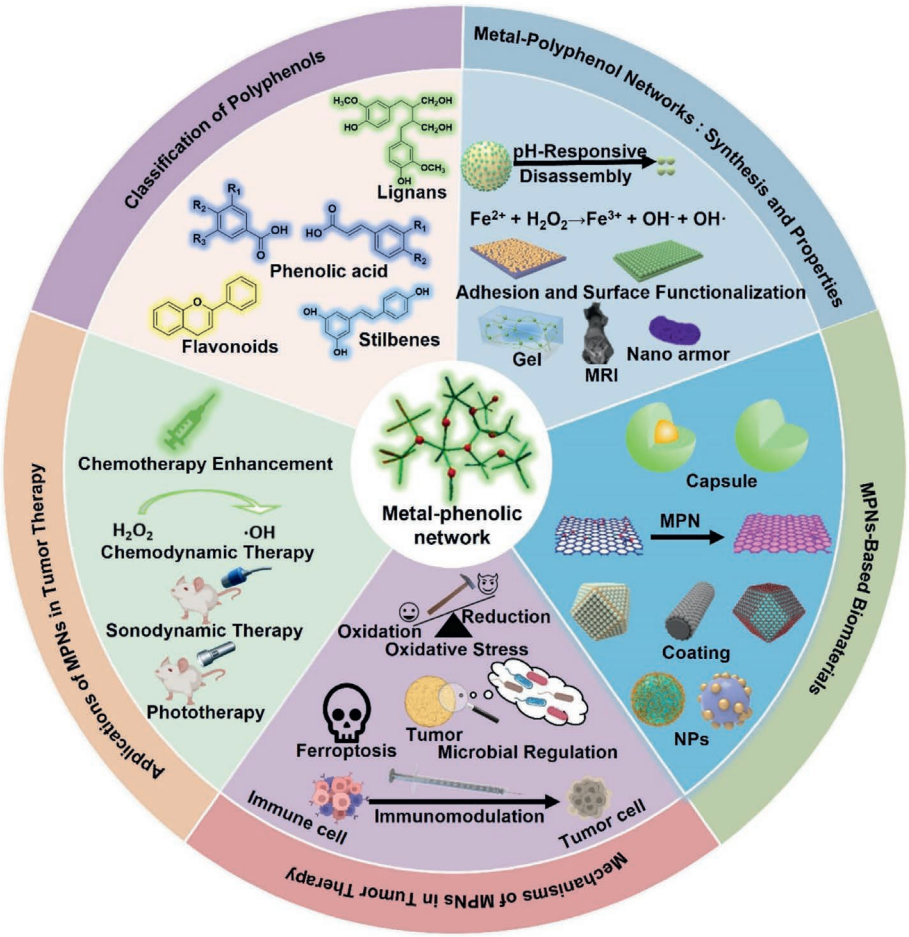


Figure 1 This review will emphasize the following five aspects of MPNs. (1) Classification of polyphenols. (2) Synthesis and properties of MPNs. (3) MPN-based biomaterials (capsules, coatings, nanoparticles). (4) Mechanisms of MPNs in tumor therapy. (5) Applications in tumor therapy.

ratio) and bonding mechanisms, which directly impact MPN performance in biomedical applications. Among reaction parameters, pH plays a crucial role in controlling coordination chemistry and structural stability. Acidic conditions (pH $<$ 5) favor the formation of monodentate complexes, enabling rapid drug release in the TME, while neutral/alkaline conditions (pH 7−9) stabilize bis-/tris-complexes, enhancing cargo retention[41,42]. Temperature also significantly affects the synthesis process. Ambient conditions help preserve bioactivity, whereas elevated temperatures accelerate coordination kinetics but may risk polyphenol oxidation[41]. The metal-to-polyphenol ratio influences MPN thickness and nanoparticle size; a higher metal excess generally increases MPN thickness and nanoparticle dimensions[43].

Bonding mechanisms further determine MPN properties. Coordination bonds, such as Fe^{3+}−catechol interactions, provide pH-responsive stability, making them ideal for targeted drug delivery systems but requiring specific triggers like redox or pH changes for degradation[44-48]. Hydrogen bonding enables stimuli-responsive drug release but exhibits limited stability under physiological conditions[49-51]. Hydrophobic and $\pi-\pi$ stacking interactions drive

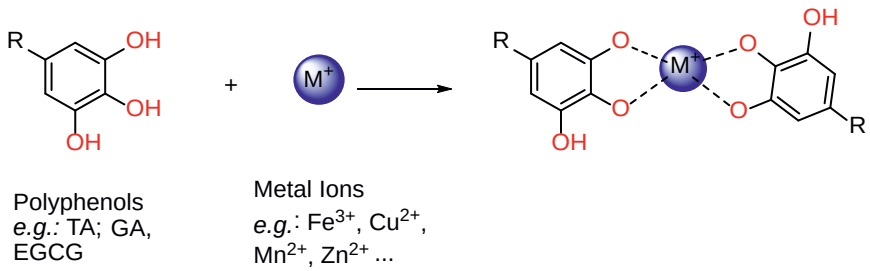


Figure 2 Coordination-driven self-assembly process for MPN formation. Polyphenolic ligands (*e.g.*, TA, EGCG) chelate transition metal ions (*e.g.*, Fe^{3+}, Cu^{2+}) to form stable nanostructures.

self-assembly but may lead to nonspecific aggregation, an issue that can be mitigated by surface PEGylation[52-54]. Polymer conjugation *via* covalent bonding offers superior stability but involves complex synthesis procedures[55-57]. Most MPNs combine multiple bonding mechanisms (*e.g.*, coordination + hydrogen bonding) to achieve a balance between stability, drug loading capacity, and stimuli responsiveness[46,51]. Similarly, the combination of covalent bonds and hydrophobic interactions can improve drug loading efficiency and release kinetics[47,48]. In addition, high encapsulation efficiency and antioxidant activity of polysaccharide−polyphenol complexes can be achieved by electrostatic interaction and $\pi-\pi$ stacking[58]. This multi-mechanism approach, balancing rapid assembly driven by hydrophobic interactions with structural stability provided by hydrogen and coordination bonds, allows NPs to achieve high drug loading and adaptability to various environments[48,52].

3.1.2. Comparative analysis of metal ions in MPNs

The selection of metal ions in MPNs is critical for optimizing their physicochemical properties, therapeutic efficacy, and biosafety. Next, the discussion will focus on the metal ions, including their coordination mechanisms, as well as advantages and disadvantages in terms of biosafety, cytotoxicity, biodegradability, and long-term compatibility (Table 2[41,61,63,69,70]). Iron (Fe^{3+}/Fe^{2+}) is favored for its biocompatibility and biodegradability, integrating with endogenous iron metabolism but requiring strict pH control during synthesis to prevent oxidative stress[41,59,60]. Cu^{2+} offers superior catalytic activity in acidic tumor environments, enhancing CDT and enabling antimicrobial applications, though its higher cytotoxicity and risk of systemic accumulation necessitate controlled release strategies[53,61,62]. Manganese (Mn^{2+}) uniquely activates the STING pathway for immunomodulation, promoting dendritic cell maturation with low acute toxicity and renal clearance, though chronic exposure may lead to manganism, emphasizing the need for dose optimization[53,63]. Zinc (Zn^{2+}) provides good biocompatibility and antibacterial properties against Gram-positive bacteria, but its limited Fenton activity restricts CDT applications, and excess levels may disrupt immune homeostasis[64].

Gallium (Ga^{3+}), leveraging iron mimicry to disrupt pathogen and tumor iron uptake, is stable under physiological conditions but raises concerns about long-term metabolic clearance due to its non-biogenic nature[65,66]. Rare earth metals (Sm^{3+}, Ce^{3+}, Hf^{4+}) enable multimodal imaging and radiosensitization but require rigorous long-term toxicity assessment due to limited biodegradability[60]. Although tungsten (W^{6+}) can exert antitumor effects through immune regulation and oxidative stress, there is a lack of sufficient chronic safety data, and there is a potential risk of heavy metal toxicity[67,68].

The selection of metal ions demands a careful balance between therapeutic potency and biosafety. Iron and manganese excel in biodegradability and immunomodulation, while Cu^{2+} and Ga^{3+} provide robust catalytic and antimicrobial activity with controlled release requirements. Rare earth metals, despite imaging potential, need extensive safety validation. As shown in Table 2 [41,61,63,69,70], Fe^{3+} demonstrates high coordination efficiency with TA for pH-responsive drug release and Fenton activity. Cu^{2+} coordinates moderately with GA or stilbenes, suitable for GSH-triggered therapies. Mn^{2+}−TA networks exhibit redox sensitivity for immunomodulatory applications, while Ga^{3+}−TA complexes remain stable under physiological pH for microbiota modulation. This analysis offers key insights for tailoring MPNs to specific therapeutic needs like tumor-targeted drug delivery or immune activation.

3.1.3. Morphological characterization and synthesis uniformity

The structural diversity of MPNs is a critical determinant of their functional performance in biomedical applications. Advanced imaging techniques such as transmission electron microscopy and scanning electron microscopy (SEM) have revealed distinct morphological features across various MPN formulations. For instance, Fe^{3+}−TA capsules synthesized *via* one-step assembly exhibit spherical hollow structures with uniform wall thickness, enabling high drug-loading capacity[41]. Similarly, DOX@EGCG/Fe NCs display a well-defined spherical morphology with an average diameter of 399 nm, as confirmed by SEM imaging[71]. In contrast, Zn−GA nanocomposites (ZGNFs) adopt hierarchical flower-like architectures, which enhance bacterial adhesion in antimicrobial applications[64]. The uniformity of MPNs is highly dependent on synthesis strategies. While one-step assembly offers simplicity, rapid coordination kinetics often lead to heterogeneous structures, such as the films became thinner and rougher in TA−Fe^{3+} networks under acidic conditions (pH < 5)[41]. In contrast, multi-step assembly enables precise control over film thickness through sequential deposition of TA and Fe^{3+}, as

Table 2 Comparative summary of metal ions in MPNs.

Metal ion	Polyphenol type	Coordination efficiency	Stability	Key applications	Ref.
Fe^{3+}	TA	High	pH-sensitive; stable at pH 7.4	Drug delivery capsules, Fenton catalysis	41
Cu^{2+}	GA	Moderate	Stable in acidic TME	Nanoalgaecide	61
Mn^{2+}	TA	High	Redox-sensitive	STING pathway activation, immunotherapy	63
Cu^{2+}	Piceatannol	Moderate	GSH-responsive	Oxidative stress, polyamine depletion	69
Ga^{3+}	*Lactobacillus rhamnosus* GG (LGG)	High	Stable in physiological pH	Microbiota modulation, intratumoral targeting	70

Key observations: Fe^{3+} exhibits high coordination efficiency with TA, enabling pH-responsive drug release and Fenton activity; Cu^{2+}shows moderate efficiency with GA and stilbenes (*e.g.*, Picrasinol), suitable for GSH-triggered therapies. Mn^{2+}−TA networks demonstrate redox sensitivity, ideal for immunomodulatory applications. Stilbenes (*e.g.*, Picrasinol) coordinate effectively with Cu^{2+}, enabling oxidative stress amplification *via* polyamine depletion[69].

validated by QCM and UV−Vis spectroscopy[72]. Metal−polyphenol combinations further influence morphology; for example, Cu^{2+}−BWT coordination produces irregular nanoaggregates maybe due to competitive hydrogen bonding[61]. Such variability in particle size and shape across studies underscores the necessity of standardizing synthesis parameters (*e.g.*, pH, ionic strength, polyphenol/metal ratios) to enhance reproducibility[73].

3.1.4. Comparative analysis of assembly methods for MPNs

To facilitate the rational design of MPNs for tumor therapy, a systematic comparison of assembly methods is necessary[5]. One-step assembly, pioneered by Caruso's team[41] using TA and Fe^{3+}, involves mixing components simultaneously, resulting in rapid film deposition (evidenced by immediate color change). Its advantages include simplicity, cost-effectiveness, and scalability for mass production. However, it lacks morphological control and exhibits batch-to-batch variability. Multi-step assembly involves sequentially incubating TA and Fe^{3+} onto substrates, with washing between each step. This method produces uniform monolayers (∼2 nm per layer) with precise thickness control, monitored *via* QCM and UV−Vis spectroscopy[72]. While enabling superior stability and surface functionalization, it is labor-intensive and less scalable. When selecting an assembly method, structural precision, functional complexity, and economic feasibility should be considered[73]. Multi-step assembly excels in nanoscale control for applications like drug-targeting coatings, whereas one-step assembly is suitable for bulk fabrication. Multi-step assembly facilitates advanced modifications such as hyaluronic acid (HA) conjugation, while one-step assembly emphasizes intrinsic properties like ROS generation[42]. In terms of economic feasibility, one-step assembly minimizes costs for large-scale applications, whereas multi-step assembly is reserved for high-value precision therapies (Table 3[41,63,71-75]).

3.1.5. Green synthesis and alternative assembly strategies for metal-free polyphenol nanoparticles (MF-PPNs)

To circumvent the cytotoxicity, bioaccumulation, and environmental risks inherent to MPNs, researchers have pioneered diverse green synthesis strategies for MF-PPNs. These approaches harness the intrinsic physicochemical properties of polyphenols, such as aromaticity, hydroxyl groups, and amphiphilicity, to achieve structural stabilization through non-metallic mechanisms. Molecular self-assembly stands as a primary strategy, driven by $\pi-\pi$ stacking, hydrophobic interactions, hydrogen bonding, and van der Waals forces. For instance, TA leverages hydrophobic aromatic ring interactions to self-assemble into stable nanoparticles in aqueous solutions[76]. Similarly, EGCG forms nanovesicles at specific pH levels through intermolecular hydrogen bonds and $\pi-\pi$ stacking, while EGCG−PEG nanoparticles assemble *via* hydrophobic interactions, with their size regulated by the length of PEG chains[76]. Another approach involves oxidative polymerization to enhance stability, initiated by catalytic mechanisms such as enzymes (*e.g.*, laccase) or oxidants (*e.g.*, H_2O_2) to crosslink polyphenols. Laccase-catalyzed QUE oxidative polymerization, for example, yields nanogels with antioxidant and anti-inflammatory activities[77]. The formation of polyphenol−natural polymer composites, which utilize electrostatic attraction, hydrophobic interactions, and hydrogen bonds, has also been explored. Applications include EGCG−BSA nanocomposites that improve drug loading efficiency and tumor targeting[78], and pH-responsive chitosan−TA nanoparticles designed for controlled release in acidic TME[79]. Polymer covalent conjugation and physical encapsulation represent additional strategies, involving the covalent linking of polyphenols with synthetic or natural polymers (*e.g.*, PEG, chitosan, PLGA), as seen in CUR−PLGA conjugates formed *via* emulsification to enhance bioavailability, or the physical embedding of polyphenols within polymer matrices (*e.g.*, zein) to create metal-free nanoparticles[80]. Biotemplated synthesis, which employs biological molecules such as DNA and viral capsids as templates for guided assembly, has produced innovations like DNA-templated quercetin-nucleic acid nanoparticles for co-delivering genes and drugs[81], and EGCG-loaded tobacco mosaic virus capsids that inhibit melanoma metastasis[82]. Enzyme-mediated crosslinking and biomimetic mineralization further expand the toolkit, with examples including ROS-responsive hydrogels formed through catalysis by enzymes like horseradish peroxidase (HRP) and H_2O_2, and silicates/calcium carbonate used in biomimetic mineralization to boost drug loading efficiency, as observed in TA-silica hybrids[83,84]. Ionic liquid-assisted synthesis, which utilizes cholinium-based ionic liquids (*e.g.*, choline glutamate) to enhance polyphenol solubility and self-assembly, has also shown promise, with QUE nanoparticles exhibiting improved solubility and bioavailability[85]. Despite these advancements, challenges persist, particularly regarding stability in physiological environments and the bottleneck of scaled production. However, the advantages of MF-PPNs, including their low toxicity, environmental compatibility, and functional modifiability (*e.g.*, ligand conjugation), position them as promising candidates for future applications. Future research should focus on optimizing crosslinking strategies and developing cost-effective manufacturing processes to facilitate the clinical translation of these nanoparticles.

3.2. Physicochemical properties

3.2.1. pH-responsive disassembly

pH modulation plays a crucial role in regulating the formation, structural stability, and drug release kinetics of MPNs.

Table 3 Comparative analysis of one-step and multi-step assembly methods for MPN synthesis.

Comparison dimension	One-step assembly	Multi-step assembly
Advantages	Rapid synthesis[41]	Precise thickness control (∼2 nm/layer)[72]
	Cost-effective for bulk production[73]	Tailored surface functionality (*e.g.*, HA modification)[74]
	Suitable for pH-responsive capsules[71]	Enhanced stability in physiological conditions[73]
Limitations	Limited control over morphology[72]	Labor-intensive and time-consuming[72]
	Potential batch-to-batch variability[73]	Limited scalability for industrial applications
Application scenarios	Antibacterial coatings requiring rapid fabrication	Electrochemical sensors[75]
	Drug delivery systems with pH-triggered release	Multi-modal imaging agents
		(*e.g.*, Mn^{2+}−polyphenol nano complexes)[63]

Specifically, the pH-dependent deprotonation of catechol hydroxyl groups governs the formation and dissociation of catechol−Fe (III) complexes. Mono-complexes predominate at pH < 5.0, while bis- and tris-complexes are preferentially formed at pH > 7.0[86]. Caruso's group[41] demonstrated that Fe^{3+}−TA coordination exhibits pH-dependent behavior, influencing capsule stability and disassembly kinetics. The capsule suspension exhibited distinct color variations dependent on pH conditions, transitioning from colorless (pH < 2) to blue (pH 3−6) and finally to red (pH > 7) (Fig. 3A). Color transitions correspond to Fe(III)-catechol coordination states (Fig. 3B). Therefore, pH serves as a critical parameter in controlling the properties and behavior of MPN. Based on this pH-responsive property, Ming et al.[42] developed Cur@EGCG−Fe(III) NPs through the coordination of ferric chloride ($FeCl_3$) with EGCG and CUR. Their study demonstrated that at pH 5.0, CUR release was significantly accelerated, reaching a cumulative release of 91.4% within 24 h. In contrast, at physiological pH (7.4), only 34.7% of CUR was released over the same period (Fig. 3C). Overall, this pH-dependent release behavior can be attributed to the protonation of polyphenolic hydroxyl groups under acidic conditions, which induces competitive chelation between metal ions and protons, ultimately destabilizing the EGCG−Fe(III) complex.

3.2.2. Adhesion and surface functionalization

The inherent adhesive properties of polyphenols facilitate the self-assembly of MPNs on diverse template surfaces, facilitating the fabrication of MPNs with tunable structural architectures. MPNs have been successfully fabricated on various nanostructures, including nanorods[87], nano cloaks[63], capsules[88], nanosheets and nanospheres[89]. Furthermore, MPN-based adhesion technology has been extensively applied to diverse biological and material interfaces, encompassing cells, microorganisms, proteins, and organic/inorganic substrates[72]. Guo et al.[61] developed a biomass-derived nanoalgaecide (CuBes) through coordination between black wattle tannin (BWT) and copper ions (Cu^{2+}). The synergistic effects of hydrophobic interactions and hydrogen bonding facilitated efficient adhesion to algal cell surfaces, followed by controlled Cu^{2+} release for effective algal inhibition (Fig. 3D). Similarly, Jin's group[64] developed ZGNFs with unique flower-like morphologies. The specific affinity between ZGNFs and teichoic acid amino groups enabled selective adhesion to Gram-positive bacteria, while the subsequent release of Zn^{2+} conferred potent bactericidal activity against Gram-positive pathogens (Fig. 3E). Beyond antimicrobial applications, MPNs have been explored for their potential in encapsulating bacteria and cells, enabling various therapeutic applications. Pan et al.[90] engineered a TA−Fe (III) network coating for probiotics, creating a protective "nano armor" that enhances bacterial viability (Fig. 3F). This approach not only shielded probiotics from harsh gastrointestinal conditions but also enabled their co-administration with antibiotics, offering new therapeutic strategies for intestinal disorders.

3.2.3. Fenton reaction

The Fenton reaction involves the catalytic decomposition of hydrogen peroxide (H_2O_2) by ferrous ions (Fe^{2+}), generating hydroxyl radicals (•OH) and other ROS[91]. This principle has been widely exploited for tumor ablation, inspiring the development of diverse metal-based NPs, including those based on iron, Cu, and manganese. However, clinical translation of Fenton-based therapies remains constrained by the suboptimal catalytic efficiency of metal-based NPs. Notably, polyphenols, with their strong reducing capabilities, enable sustained Fenton reactions by continuously converting Fe^{3+} to Fe^{2+} within MPNs[92]. In this context, MPNs have emerged as promising Fenton reaction catalysts, garnering significant attention in biomedical research. Zhang et al.[59] developed an ATP-responsive Fenton nanosystem (GOx@ZIF@MPN) for targeted cancer therapy. In ATP-overexpressing tumor cells, the MPN shell decomposes into Fe^{3+} and TA, exposing the encapsulated glucose oxidase (GOx). The exposed GOx catalyzes endogenous glucose oxidation, generating a substantial amount of H_2O_2, while TA-mediated Fe^{3+} reduction to Fe^{2+} enhances Fenton reaction efficiency (Fig. 3G). To address the limitations of conventional chemotherapy in tumor treatment, Liu et al.[93] developed the EFPD nanoplatform through the coordinated assembly of EGCG, Pluronic F-127 (PF127), Fe^{3+} ions, and DOX (Fig. 3H). The nanocomposite enhanced DOX-mediated H_2O_2 production, synergistically promoting the Fenton reaction *via* EGCG-driven continuous Fe^{3+}/Fe^{2+} cycling. Additionally, the EGCG−Fe^{3+} network conferred photothermal conversion capabilities, further augmenting tumor cell elimination through synergistic chemo-photothermal therapy (PTT).

3.2.4. Other properties

Polyphenols contain abundant phenolic hydroxyl groups that form stable coordination complexes with metal ions, generating three-dimensional network gels with enhanced structural stability. These metal−polyphenol coordination gels exhibit remarkable resilience, flexibility, and scalability, along with facile assembly and cost-effectiveness, making them versatile materials for chemical, biological, and environmental applications[94]. Furthermore, the coordination between polyphenols and paramagnetic metal ions, such as Mn^{2+} and Fe^{3+}, enables the development of MPN-based contrast agents for magnetic resonance imaging (MRI). This unique property has expanded the application of MPNs to *in vivo* imaging, particularly in the detection and monitoring of inflammatory diseases[95] (Fig. 3I) and tumors[96] (Fig. 3J). These multifunctional properties highlight the versatility and biomedical potential of MPNs, providing evidence for their future integration into diagnostic and therapeutic strategies.

3.3. MPNs-based biomaterials

3.3.1. Capsules

MPNs represent a hybrid system composed of inorganic−organic components that can be engineered into hollow capsules with exceptional mechanical strength, thermal stability, stimuli-responsiveness, and selective permeability[97]. As previously mentioned, Caruso[41] pioneered the fabrication of metal−polyphenol capsules using TA and Fe^{3+} templating. These capsules exhibit pH-dependent degradation kinetics, with rapid dissociation under acidic conditions. Specifically, complete capsule disassembly occurred within 4 h at pH 3.0, whereas substantial degradation at pH 4.0 requires approximately 6 days. In contrast, 70%−90% of the capsules maintained structural integrity after 10 days at pH 5.0 and 7.4 (Fig. 4A). Recent advances have enabled the development of multifunctional MPN capsules for various biomedical applications. For instance, Wang et al.[71] developed EGCG−Fe(III) complex-coated NPs *via* co-precipitation, yielding 399 nm nanocapsules (DOX@EGCG/Fe NCs) following template removal (Fig. 4B). DOX@EGCG/Fe NCs rapidly internalized into cancer cells and released drugs in response to ROS, significantly increasing intracellular drug concentrations. This formulation achieved remarkable tumor growth inhibition (84.2%), demonstrating

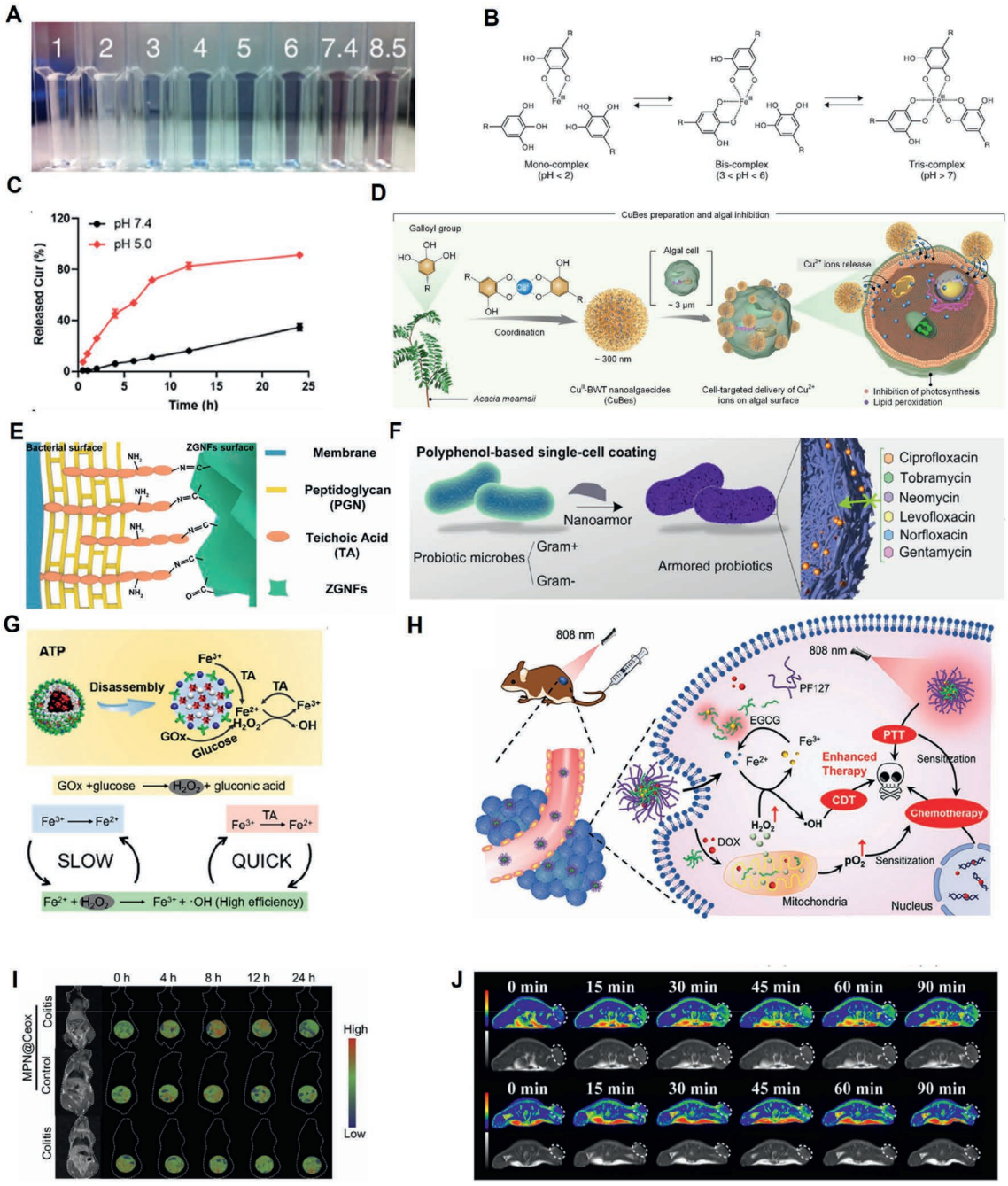


Figure 3 Physicochemical properties of metal polyphenol networks. (A) pH-dependent color changes in capsule suspensions. (B) Fe(III)-catechol coordination states at varying pH. Reprinted with the permission from Ref. 41. Copyright © 2013 American Association for the Advancement of Science. (C) Cur release from Cur@EGCG−Fe(III) NPs at pH 5.0 *vs.* 7.4. Reprinted with the permission from Ref. 42. Copyright © 2021 Elsevier B.V. (D) Schematic representation of the synthesis method and mechanism of action of CuBes in inhibiting algal cells. Reprinted with the permission from Ref. 61. Copyright © 2023 American Chemical Society. (E) Schematic representation of the mechanism of ZGNFs adhesion. Reprinted with the permission from Ref. 64. Copyright © 2023 Wiley-VCH GmbH. (F) Schematic diagram of nano-armoring to achieve single-cell encapsulation. Reprinted with the permission from Ref. 90. (G) Illustration of the mechanism of self-sufficient H_2O_2 and acceleration of Fe(III)/Fe(II) conversion in GOx@ZIF@MPN nanosystem. Reprinted with the permission from Ref. 59. Copyright © 2018 American Chemical Society. (H) Schematic diagram of the mechanism of PTT/chemodynamic therapy (CDT) chemotherapy mediated by EFPD. Reprinted with the permission from Ref. 93. Copyright © 2023 Wiley-VCH GmbH. (I) MPN-based MRI for inflammation monitoring. Reprinted with the permission from Ref. 95. Copyright © 2023 Elsevier B.V. (J) MPN imaging for Real-Time Tumor Surveillance. Reprinted with the permission from Ref. 96. Copyright © 2024 Acta Materialia Inc.

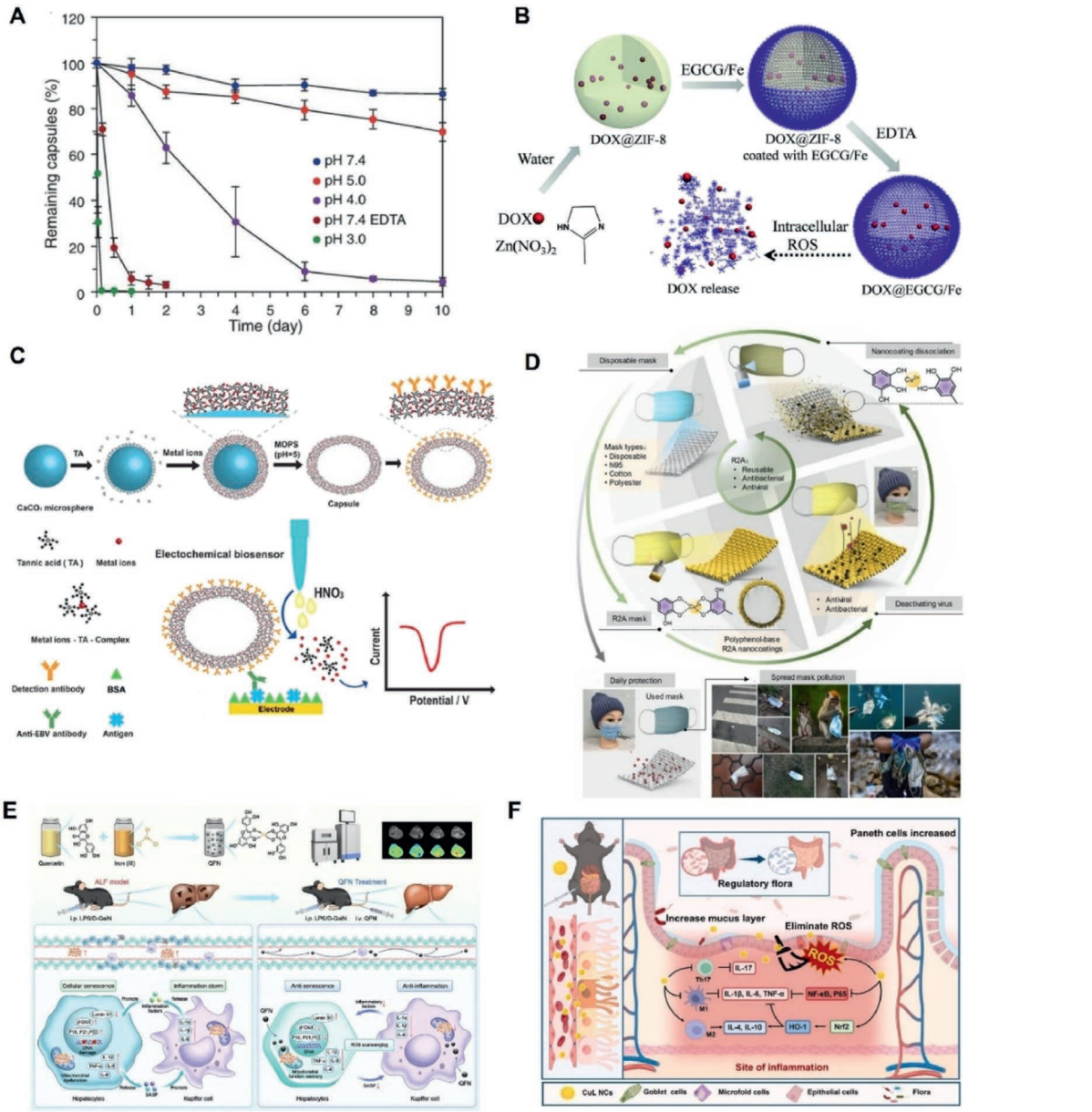


Figure 4 MPNs-based biomaterials. (A) pH-dependent degradation of Fe^{3+}−TA capsules. Reprinted with the permission from Ref. 41. Copyright © 2013 American Association for the Advancement of Science. (B) Synthesis of DOX@EGCG/Fe NCs for ROS-responsive drug delivery. Reprinted with the permission from Ref. 71. Copyright © 2018 The Royal Society of Chemistry. (C) Synthesis of sMPCs and schematic diagram of the electrochemical immunoassay principle. Reprinted with the permission from Ref. 75. Copyright © 2020 Elsevier B.V. (D) R2A Mask Preparation and Mechanism of Schematics. Reprinted with the permission from Ref. 102. Copyright © 2022 Elsevier B.V. (E) Synthesis of QFN and schematic diagram of the mechanism for the treatment of ALF. Reprinted with the permission from Ref. 105. (F) Schematic diagram of the mechanism of CuL NCs for the treatment of IBD. Reprinted with the permission from Ref. 106.

its exceptional therapeutic efficacy. Building on the MPN technology, Huang et al.[75] developed an innovative electrochemical detection platform for EBVCA-IgA using soft metal−phenolic capsules (sMPCs). In their approach, TA−metal ion complexes were deposited onto $CaCO_3$ microspheres, followed by pH-triggered dissolution to form hollow capsules, which were subsequently functionalized with anti-human IgA for electrochemical detection (Fig. 4C). This rapid, cost-effective strategy holds great promise for disease diagnostics, further expanding the potential applications of MPN-based materials.

3.3.2. *Coatings*

Polyphenols have the capability to form robust coatings *via* both covalent and non-covalent interactions with diverse substrates[98]. Due to their versatile nature, MPN-based coatings exhibit multifunctional properties, including antibacterial[99], anti-inflammatory[100], and anti-pollution characteristics[101]. Conventional masks present significant public health limitations due to insufficient antiviral, antibacterial, and reusable properties. To address these limitations, Wang et al.[102] developed R2A nanocoatings through TA−Cu^{2+} coordination and applied them to mask surfaces

(Fig. 4D). Experimental results demonstrated that the controlled release of polyphenols and metal ions from these nanocoatings exhibits potent antiviral activity. Furthermore, the coated masks maintained 93.62% particle filtration efficiency and 98% *Escherichia coli*. inhibition even after ten reuse cycles, highlighting their durability and effectiveness. In addition, MPNs-based coatings can interface with biological components, including cells, viruses, and proteins, expanding their potential for therapeutic use. For instance, TA−Mn^{2+} nanocoatings, when applied to tumor cell surfaces and further modified with bacterial lipopolysaccharide (LPS), enabled the development of an innovative whole-cell vaccine[63]. This vaccine effectively activates the stimulator of interferon genes (STING) signaling pathway in dendritic cells, promoting their maturation and the subsequent activation of tumor-specific T cells, ultimately inhibiting tumor growth. These findings underscore the potential of MPN coatings as a powerful platform for both protective and therapeutic biomedical applications.

3.3.3. *Nanoparticles (NPs)*

Nanomaterials are defined as materials with structural features ranging from 1 to 100 nm in at least one dimension[103]. NPs exhibit unique physicochemical properties, including enhanced stability and ease of functionalisation, as well as distinctive optical and electrical properties, a high surface-to-volume ratio and magnetic characteristics[104]. Leveraging these advantages, MPN NPs have been extensively explored in disease treatment, utilizing coordination-driven self-assembly between metal ions and polyphenols[105]. Among various polyphenolic compounds, QUE demonstrates remarkable anti-inflammatory and antioxidant properties, making it a promising therapeutic agent for various inflammatory disorders. Feng and colleagues developed ultrasmall quercetin-iron NPs (QFNs) through a controlled synthesis process (Fig. 4E)[105]. The QFNs demonstrated potent ROS scavenging capabilities, effectively suppressing macrophage-mediated inflammation, reducing apoptosis, and promoting hepatic regeneration, thereby exhibiting significant therapeutic efficacy in acute liver failure (ALF). In a related study, Fu et al.[106] developed multifunctional Cu^{2+}−luteolin nano complexes (CuL NCs) for inflammatory bowel disease (IBD) management (Fig. 4F). The CuL NCs exhibited superior anti-inflammatory and antioxidant properties, effectively modulating oxidative stress, restoring the intestinal barrier, and regulating gut microbiota. By integrating these three mechanisms, this nanoplatform provided a comprehensive strategy for IBD treatment. Collectively, these studies offer mechanistic insights into the therapeutic potential of MPN NPs and establish a foundation for the development of innovative multifunctional nanoplatforms for inflammatory disease management.

MPN-based biomaterials exhibit diverse functionalities depending on their structural design and application contexts. As summarized in Table 4[41,61-63,71,75,102,104,106], each platform possesses distinct advantages and limitations. For instance, MPN capsules demonstrate pH-responsive drug release and high mechanical strength but face challenges in stability at neutral pH. In contrast, MPN coatings excel in antibacterial properties and surface functionalization yet require multi-step assembly for precision. Nanoparticles (NPs) leverage high biocompatibility and scalable synthesis but may aggregate under physiological conditions. This comparative analysis provides critical insights for selecting optimal MPN platforms tailored to specific therapeutic requirements, such as tumor-targeted drug delivery or immunomodulation.

3.4. *Challenges and recommendations*

In the aspect of synthesis challenges, from the perspective of bonding mechanisms, coordination bonds like Fe^{3+}−catechol have pH dependent stability, limiting controlled drug release to the acidic TME. Hydrogen bonds have stimuli-responsive properties but poor stability under physiological conditions[41,46,48]. Hydrophobic/$\pi-\pi$ interactions can drive self-assembly but may cause nonspecific aggregation without surface modification[52,54]. Regarding batch-to-batch variability, the rapid oxidation of polyphenols such as EGCG and QUE during one-step assembly can lead to inconsistent morphology and nanoparticle size[41,73]. Although multi-step assembly improves uniformity, it is labor-intensive and difficult to scale[72]. Scalability barriers also exist, such as the inefficiency of multi-step layer-by-layer deposition for industrial production and the complications of template removal in capsule synthesis[41,71,97]. As for characterization and standardization challenges, conventional techniques are unable to monitor dynamic MPN behavior in living systems[95,107]. Moreover, there is a lack of standardized protocols for synthesis parameters and toxicity assessment criteria, resulting in poor reproducibility[60,73].

To address these challenges, the following recommendations are put forward. In terms of synthesis, microfluidics-enhanced synthesis can be utilized to precisely regulate factors like pH, flow rate, and reactant ratios, enabling high-throughput production of uniform MPNs[72,75]. Hybrid crosslinking strategies, which combine covalent bonds with coordination/hydrogen bonding, can enhance stability and drug-loading capacity[55,57]. Oxidation control can be achieved by conducting synthesis under inert atmospheres or adding antioxidants[41,73]. For characterization and standardization, multimodal real-time tracking can be integrated

Table 4 Advantages and limitations of different MPN platforms.

MPN Platform	Advantages	Limitations	Ref.
MPN capsules	pH-dependent degradation kinetics, with rapid dissociation under acidic conditions.	Stability challenges at neutral pH. Complex template removal processes.	41,71,75
MPN coatings	Multifunctional properties; durable and reusable; facile surface functionalization.	Limited adhesion on non-polar substrates. Multi-step assembly required for precision.	61,63,102
MPN NPs	High biocompatibility and scalable synthesis	Potential aggregation in physiological conditions. Challenges in controlling drug release kinetics.	62,104,106

to non-invasively monitor biodistribution and drug release kinetics[95,108]. Establishing a unified MPN database and protocols, standardizing synthesis/toxicity evaluation protocols[3,60], and adopting *in vitro/in vivo* correlation models can also be beneficial[95,109].

3.5. Comparative analysis of MPNs and traditional nanocarriers

MPNs present a promising alternative to conventional nanocarriers like liposomes and polymeric nanoparticles. Unlike these traditional systems, MPNs inherently integrate targeting, imaging, and therapeutic functionalities through metal−polyphenol coordination[3,93,110]. This unique integration allows MPNs to achieve pH-responsive drug release, Fenton activity, and photothermal conversion, offering advantages over non-degradable inorganic nanoparticles (*e.g.*, gold- or silicon-based systems) by degrading into naturally occurring polyphenols and metal ions, thereby minimizing long-term toxicity risks[41,107]. MPNs are also pH- and redox-sensitive, enabling precise drug release in the acidic TME and reducing off-target effects (Table 5 [41,42,59,62,63,73,107,108,110,111]).

3.5.1. Advantages of MPNs

MPNs demonstrate superior multifunctional capabilities, integrating synergistic therapeutic modalities (*e.g.*, chemotherapy and photothermal therapy) alongside imaging functionalities within a single platform[41,73]. Their biodegradability and pH-responsive disassembly enable stimuli-triggered drug release in acidic TME, enhancing spatiotemporal control[42]. Additionally, MPNs self-assemble into stable coatings *via* metal−polyphenol coordination chemistry, improving targeting precision and reducing off-tissue deposition[88]. A unique feature is their intrinsic bioactivity, where polyphenols exhibit direct anticancer effects independent of drug payloads[59].

3.5.2. Limitations of MPNs

Despite their advantages, MPNs face challenges. Metallic ion leakage from the network may induce cytotoxicity, particularly in cases of incomplete disassembly[73]. Furthermore, structural instability at neutral physiological pH may compromise cargo retention[41], limiting their application in systemic circulation. Lastly, complex synthesis protocols and scalability constraints hinder their translation to large-scale manufacturing[73].

3.5.3. Traditional nanocarriers

In contrast, traditional nanocarriers such as liposomes and polymer-based nanoparticles exhibit inherent limitations. Liposomes lack intrinsic multifunctionality, necessitating external modifications for multimodal applications[112]. Polymer-based nanoparticles, while biocompatible, often exhibit slower degradation rates, which may prolong systemic exposure and delay clearance[3].

4. Mechanisms of MPNs in tumor therapy

4.1. Oxidative stress

Oxidative stress arises from an imbalance between ROS production and clearance, leading to excessive accumulation of toxic molecules (*e.g.*, •OH) and compromised antioxidant defenses (*e.g.*,

Table 5 Comparative analysis of MPNs with other nanomaterial-based systems.

Nanomaterial	Advantages	Disadvantages	MPN advantages over this system
Liposomes	High biocompatibility; efficient drug encapsulation; tunable surface chemistry	Low stability; rapid clearance; limited stimuli-responsive drug release	MPNs exhibit pH-responsive degradation and superior stability under physiological conditions[41].
Polymeric NPs	Controlled drug release; customizable biodegradability	Complex synthesis; potential toxicity from synthetic polymers	MPNs are synthesized *via* simple coordination chemistry and use natural polyphenols, enhancing biosafety[41,73].
Gold/Silica NPs	Strong photothermal properties; imaging capabilities	Poor biodegradability; potential long-term toxicity	MPNs integrate photothermal effects with biodegradability and intrinsic anticancer activity[108,110].
Dendrimers	Precise size control; multivalent functionalization	High synthesis cost; potential immunogenicity	MPNs offer cost-effective one-step assembly and immunomodulatory properties[63,107].
Iron oxide NPs	MRI contrast agents; Fenton reaction catalysis	Aggregation *in vivo*; limited drug-loading capacity	MPNs enable simultaneous drug delivery, Fenton catalysis, and GSH depletion[62,111].
Carbon nanotubes	High surface area; photothermal efficacy	Poor solubility; unresolved long-term toxicity	MPNs combine photothermal therapy with pH-responsive drug release and minimal toxicity[59,110].

Key points:
1. Multifunctionality: MPNs integrate drug delivery, imaging, and intrinsic therapeutic effects (*e.g.*, ROS generation, ferroptosis induction) in a single platform, outperforming conventional single-function systems[93,112].
2. Biocompatibility: Unlike synthetic polymers or inorganic NPs, MPNs utilize natural polyphenols and transition metals, reducing toxicity risks[73,110].
3. Stimuli-responsiveness: MPNs degrade in acidic TME, enabling precise drug release, whereas liposomes and polymeric NPs require external triggers[42,71].
4. Cost-effectiveness: MPNs are synthesized *via* simple coordination chemistry, avoiding the complex fabrication processes of dendrimers or carbon nanotubes[41,73].

GSH, polyamines). This state causes cellular damage and exerts a bidirectional effect in cancer: it can drive tumorigenesis (*e.g.*, *via* DNA damage) or achieve therapeutic goals by inducing cancer cell apoptosis or oxidative collapse[113]. This duality reflects the broader biological role of ROS, which exert both beneficial and detrimental effects depending on context. On one hand, oxidative stress-mediated DNA damage represents a key driver of tumorigenesis[114]. On the other hand, sustained oxidative stress can induce apoptosis in cancer cells[115]. Therefore, oxidative stress-mediated tumor elimination has emerged as a promising therapeutic strategy. MPNs can release polyphenols and metal ions in response to TME stimuli. The released polyphenols and metal ions interact with endogenous glutathione (GSH), generating cytotoxic hydroxyl radicals (•OH), which effectively induce cancer cell apoptosis. However, tumor cells have evolved antioxidant defense mechanisms to mitigate ROS-induced cytotoxicity, significantly limiting the efficacy of ROS-based therapies. To overcome this limitation, Yu et al.[62] synthesized Cu^{2+}-coordinated GA NPs (Cu−GA NPs) through the coordination of copper chloride ($CuCl_2$) and GA (Fig. 5A). These Cu−GA NPs undergo GSH-triggered dissociation, releasing Cu^{+} and GA. The released Cu^{+} exhibits enhanced Fenton catalytic activity, converting H_2O_2 to cytotoxic hydroxyl radicals (•OH) and amplifying ROS generation. Simultaneously, the released GA exerts additional antitumor effects, leading to a synergistic tumor-killing effect.

Given the intricate self-regulatory mechanisms of tumors, a more comprehensive strategy beyond intracellular GSH depletion is required for effective cancer cell eradication. Polyamines, essential for tumor cell function and proliferation, also function as antioxidants in tumor cells, thereby significantly compromising the therapeutic efficacy[116]. In addition, piceatannol (PIC), a tetrahydroxylated stilbene abundant in fruits and vegetables, has been identified as a potent antitumor agent[117,118]. Dai et al.[69] developed multifunctional Cu−Pic/HA NPs (Cu−Pic/HA NPs) through a controlled synthesis approach. This nanocomposite induces comprehensive polyamine depletion, causing intracellular redox imbalance and multi-organelle dysfunction, ultimately leading to tumor cell elimination (Fig. 5B). Collectively, these advancements highlight the potential of MPN-based nanoplatforms as promising oxidative stress-mediated cancer therapeutics.

4.2. Ferroptosis

Ferroptosis is a form of regulatory cell death driven by iron-dependent redox imbalance, characterized by abnormal accumulation of lipid peroxidation (LPO) and loss of cell membrane integrity. It can be targeted and induced through mechanisms such as ROS storms mediated by nanomaterials, iron metabolism disorders, or collapse of the antioxidant defense system, and is used to enhance tumor treatment[119]. Since Stockwell et al.'s[120] seminal discovery of ferroptosis in 2012, extensive research has established strong connections between ferroptosis and nanomedicine, enabling the development of innovative nanomaterial-based tumor therapies. As a result, various metal-based nanomaterials have been designed to induce ferroptosis, primarily categorized as iron-based and non-iron-based systems. Following cellular internalization, these nanomaterials induce ferroptosis through ROS accumulation, disrupting tumor cell homeostasis. Among them, Iron-based NPs have emerged as the most extensively studied nanomaterials for ferroptosis-driven cancer therapy. Based on MPN formation, Wen et al.[121] developed Ce-aMOFs@Fe^{3+}−EGCG NPs (MEF) by integrating EGCG and Fe^{3+}-coated cerium-based amorphous metal-organic frameworks (Ce-aMOFs) for tumor theranostics (Fig. 6A). MEF enhances ferroptosis-mediated tumor therapy through GSH depletion and ROS elevation. Following tumor cell internalization, MEF rapidly releases Fe^{3+}, EGCG, and Ce-aMOF components. Within the TME, intracellular GSH is consumed during Fe^{3+} to Fe^{2+} reduction. Simultaneously, Ce-aMOF catalyzes endogenous superoxide conversion to H_2O_2, which reacts with Fe^{2+} to generate ROS, ultimately inducing ferroptotic cell death. Utilizing metal−polyphenol coordination chemistry, Chen et al.[122] engineered a self-assembled Fe−RA nanocomposite to circumvent tumor resistance to rosmarinic acid (RA). Within the TME, Fe−RA generates substantial hydroxyl radicals (•OH), disrupting cellular antioxidant defenses. Furthermore, the enhanced permeability and retention (EPR) effect facilitates Fe^{2+} delivery into tumor cells, disrupting iron homeostasis and promoting ferroptosis (Fig. 6B). To further enhance ferroptosis-based therapeutic efficacy, Sun et al.[123] developed novel GA−ASA−Fe(II) metal-chelated nanofibers (GAFs) through the coordination of GA, aspirin (ASA), Fe(II), and polyvinylpyrrolidone (PVP). GAFs exhibit potent photothermal properties and Fenton catalytic activity. Under near-infrared (NIR) irradiation, GAFs catalyze H_2O_2 conversion to •OH, leading to GSH depletion and LPO accumulation. This cascade ultimately induces ferroptosis, enhancing tumor therapy efficacy (Fig. 6C). Collectively, these ferroptosis-enhanced antitumor strategies offer novel perspectives for nanomaterial-based.

4.3. Microbial regulation

Microbial regulation is a therapeutic strategy targeting the abundance, function, or metabolic activity of specific microorganisms (*e.g.*, pathogens or tumor-associated microbiota). This approach aims to intervene in disease progression (such as tumorigenesis or treatment resistance) or enhance treatment efficacy. Microorganisms are ubiquitous in the human body and play crucial roles in maintaining health. Critically, studies demonstrate that specific microbial communities significantly influence tumor development, therapy response, prevention, and diagnosis[124-126]. Among them, *Fusobacterium nucleatum* (Fn), a pathogenic bacterium overexpressed in colorectal cancer (CRC) patients, has been shown to promote tumorigenesis and contribute to chemoresistance[127,128]. The effective eradication of Fn represents a critical strategy for CRC treatment. Taking advantage of the unique properties of MPNs, researchers have explored their potential for tumor-specific drug delivery and regulation of microbiota. Leveraging this property, Chen et al.[129] developed a therapeutic gel by encapsulating metronidazole (MTZ) and 5-fluorouracil (5-FU) in Fe^{3+}−EGCG-coated mesoporous silica NPs (MSNs) for CRC treatment. This biocompatible gel formulation responds to the acidic TME, enabling controlled drug release while effectively eliminating Fn, enhancing chemotherapy efficacy, and suppressing tumor growth (Fig. 7A).

Beyond gut microbiota, intratumoral microorganisms significantly influence tumorigenesis and therapeutic outcomes. Intratumoral microorganisms exert carcinogenic effects through multiple mechanisms, including DNA damage, activation of oncogenic signaling pathways, and induction of inflammatory response[130]. Notably, intratumoral microorganisms have been identified in various cancers, including pancreatic, hepatic, and esophageal malignancies[131-133]. By promoting tumor progression and conferring resistance to conventional therapies, these

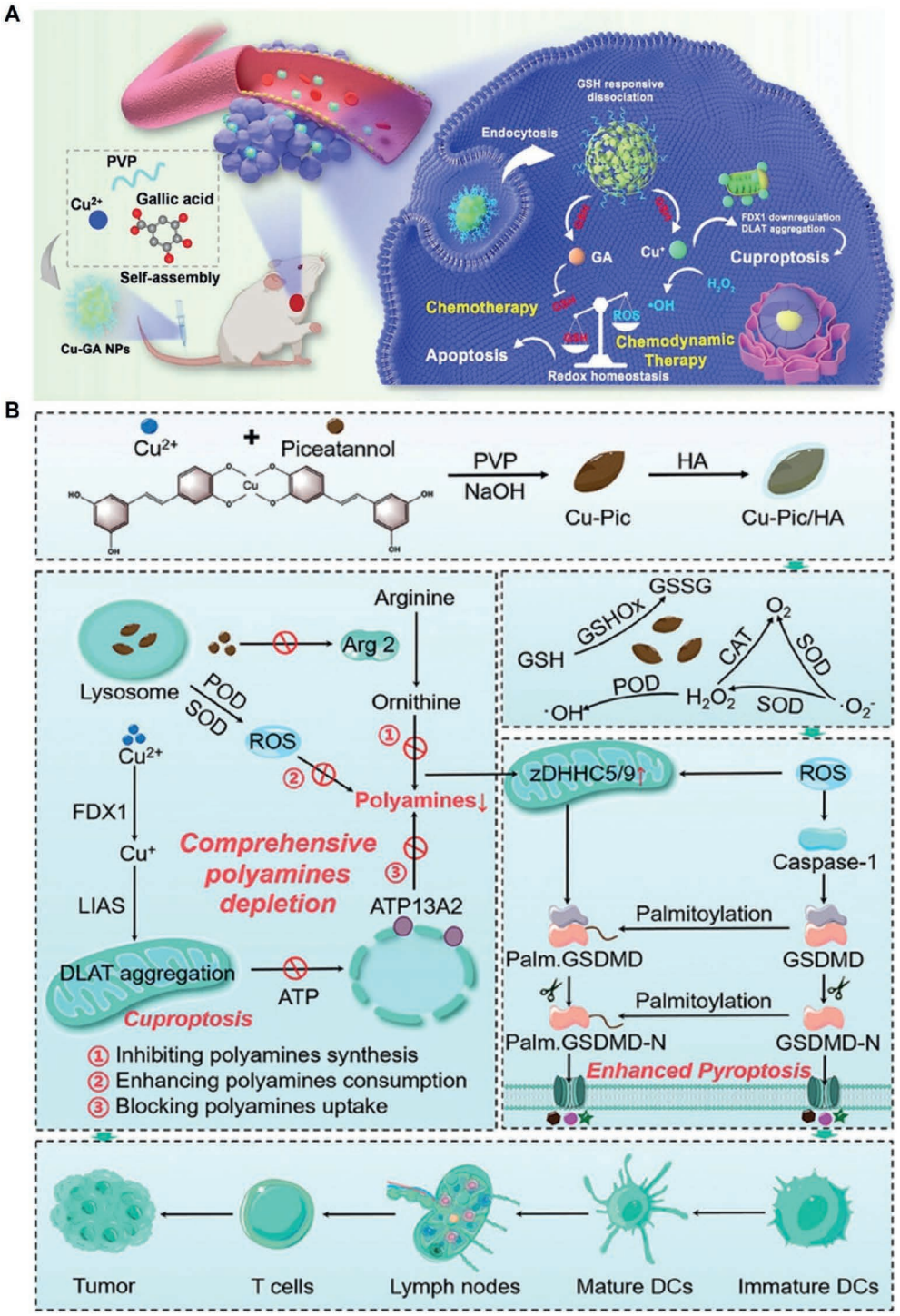


Figure 5 MPNs treat tumors by activating oxidative stress. (A) Oxidative stress amplification *via* Cu−GA NPs. Reprinted with the permission from Ref. 62. Copyright © 2023 Wiley-VCH GmbH. (B) Polyamine depletion *via* Cu−Pic/HA NPs. Reprinted with the permission from Ref. 69. Copyright © 2024 Wiley-VCH GmbH.

microbial communities pose a major challenge to cancer treatment. While antibiotics are commonly employed to target harmful intratumoral microorganisms, they may disrupt beneficial microbiota and promote microbial resistance[134,135]. To overcome these limitations, Han et al.[70] developed a GA−polyphenol network-functionalized Lactobacillus rhamnosus GG probiotic (LGG@Ga-poly) that modulates microbiota-immune interactions for pancreatic cancer therapy (Fig. 7B). LGG@Ga-poly specifically targets pancreatic ductal adenocarcinoma (PDA), eliminating Proteobacteria and microbial-derived LPS through Ga^{3+}-mediated iron metabolism inhibition. *In vivo* studies demonstrated its potent antitumor efficacy, highlighting its therapeutic potential. Similarly, Han et al.[66] synthesized GaTa−CP NPs through the coordination of Ga^{3+}, TA, and *Streptococcus*

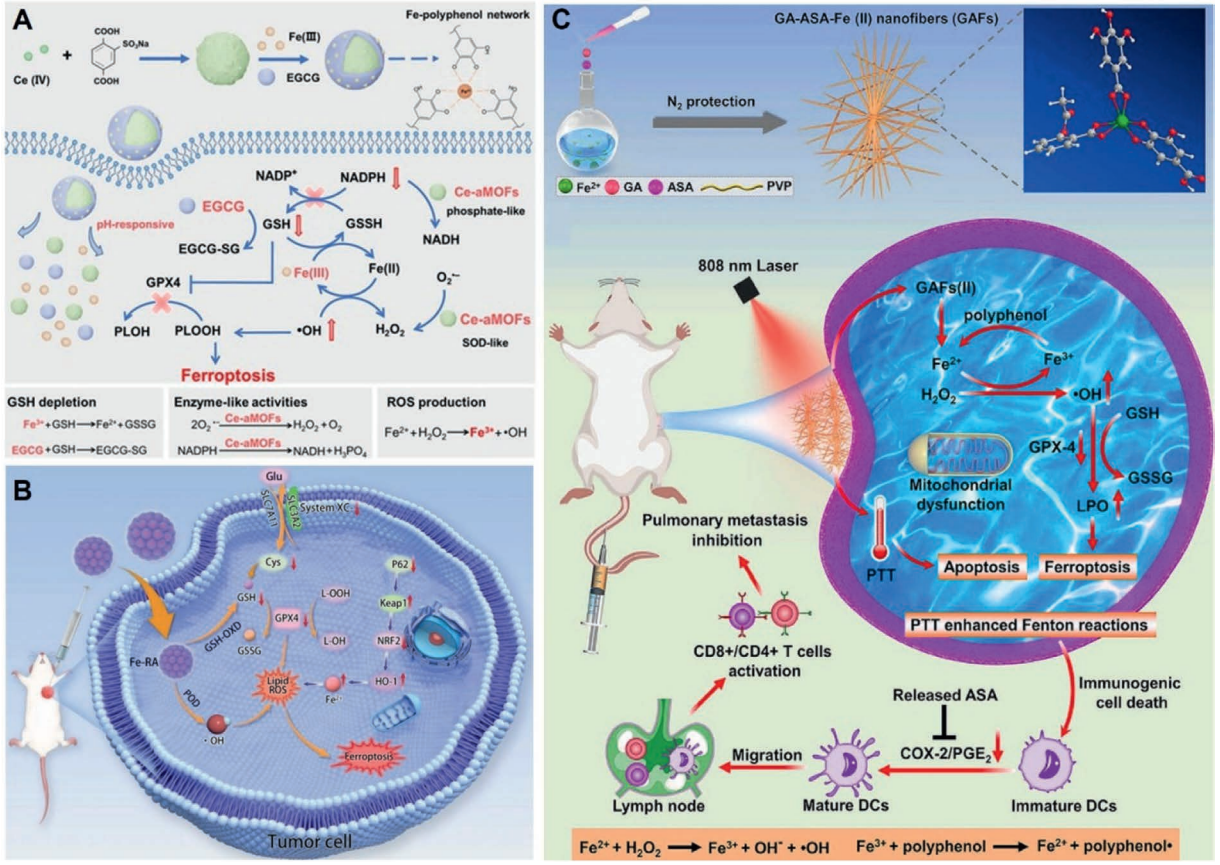


Figure 6 MPNs treat tumors by mediating ferroptosis. (A) Synthesis of MEF nanomaterials and schematic diagram of therapeutic mechanisms. Reprinted with the permission from Ref. 112. Copyright © 2023 The Royal Society of Chemistry. (B) Schematic diagram of the therapeutic mechanism of Fe−RA. Reprinted with the permission from Ref. 122. Copyright © 2024 Wiley-VCH GmbH. (C) Schematic diagram of the therapeutic mechanism of GAFs. Reprinted with the permission from Ref. 123. Copyright © 2023 Elsevier B.V.

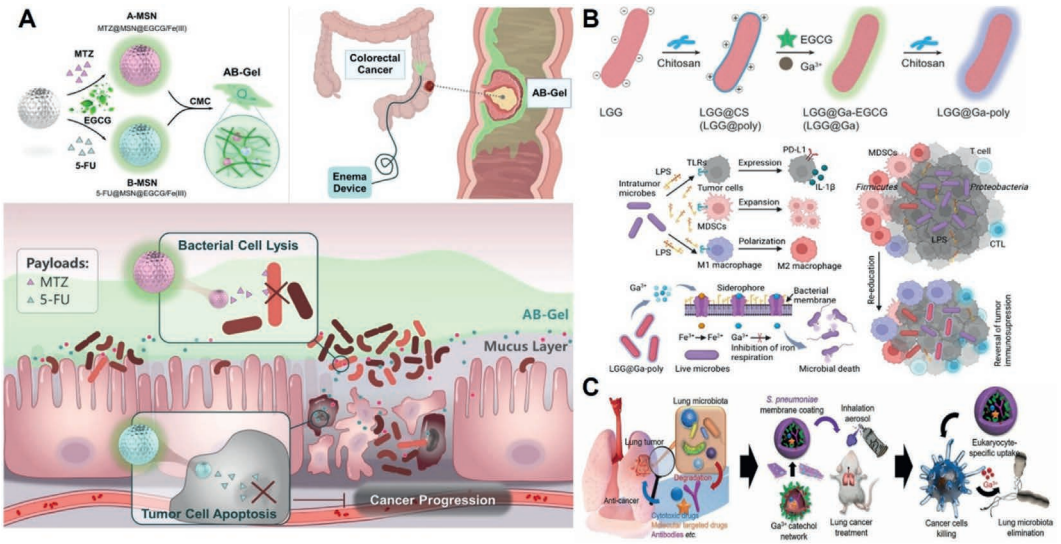


Figure 7 MPNs treat tumors by regulating microorganisms. (A) Synthesis and therapeutic mechanism of AB-Gel. Reprinted with the permission from Ref. 129. Copyright © 2021 Elsevier B.V. (B) Synthesis and therapeutic mechanism of LGG@Ga-poly. Reprinted with the permission from Ref. 70. (C) Synthesis and therapeutic mechanism of GaTa−CP NPs. Reprinted with the permission from Ref. 66. Copyright © 2023 Wiley-VCH GmbH.

pneumoniae-derived capsular polysaccharides (CPs). The released Ga^{3+} disrupts bacterial iron respiration. This effectively eliminates lung microbiota linked to tumor progression. *In vivo* studies further confirmed that GaTa−CP NPs significantly inhibited tumor growth and enhanced chemotherapy efficacy (Fig. 7C). Collectively, these microbiome-mediated strategies provide a novel framework for leveraging metal−polyphenol nanomaterials in cancer treatment.

4.4. Immunomodulation

Immunomodulation is a therapeutic strategy that enhances treatment efficacy by activating or reshaping anti-tumor immune responses. This is achieved through the targeted regulation of immune cell function, signaling pathways, or key inhibitory factors within the TME. In the context of cancer therapy, MPNs have emerged as promising immunomodulatory agents due to their ability to activate immune cells, remodel the tumor immune microenvironment, and modulate cytokine signaling pathways, thereby enhancing antitumor immunity[136,137]. Zhang et al.[107] developed a multifunctional MPN, QFN, through the coordination of QUE and Fe^{2+} (Fig. 8A). Upon release, QFN-released QUE inhibits JAK2/STAT3 phosphorylation, reducing PD-L1 expression on tumor cells and remodeling the extracellular matrix (ECM) by downregulating α-SMA^{+} fibroblast. Additionally, QFN induces cancer cell lysis and promotes tumor antigen release. These tumor-associated antigens are subsequently captured and transported to tumor-draining lymph nodes, thereby promoting dendritic cell maturation and T-cell activation. Beyond small-molecule immunomodulators, manganese (Mn), an essential trace element, has garnered significant interest as a natural immune activator. Research has established Mn's crucial role in immune regulation, particularly in the activation of the cyclic GMP−AMP synthase (cGAS)−STING pathway. This pathway plays a crucial role in innate immunity as cGAS, a cytoplasmic DNA sensor, detects viral or self-DNA and synthesizes the second messenger cGAMP. In turn, cGAMP activates STING, triggering the production of type I interferons and pro-inflammatory cytokines, which initiate antiviral immune responses and enhance immune surveillance against tumors. Given its fundamental role in host defense mechanisms, the cGAS−STING pathway has emerged as a critical target for cancer immunotherapy, anti-infective treatments, and autoimmune disease regulation. To harness these immunostimulatory properties, researchers have developed various Mn-based metal−polyphenol nanosystems for cancer immunotherapy (Fig. 8B and C)[63,138]. These Mn-containing MPNs not only potentiate STING activation but also contribute to a robust and sustained antitumor immune response, offering a promising strategy for next-generation cancer immunotherapy.

4.5. Other mechanisms

Epigenetic tumor therapies primarily target DNA methylation[139], histone modifications[140], and non-coding RNA regulation[141]. Research has demonstrated that polyphenols function as natural epigenetic modulators, counteracting aberrant epigenetic regulation through altering DNA methylation and histone modification[142]. Notably, gasdermin E (GSDME) is crucial for pyroptosis, and tumor cells often silence GSDME expression through abnormal DNA hypermethylation[143]. As a natural DNA methyltransferase inhibitor, EGCG effectively reverses tumor-associated hypermethylation, restoring GSDME expression. Besides, Wang et al.[144] developed a metal−polyphenol nanodrug (PWE) through the coordination of EGCG and tungsten ions (W^{6+}) (Fig. 9). This nanomedicine successfully reactivated GSDME expression, triggering epigenetically mediated pyroptosis. Furthermore, PWE significantly enhanced immune cell infiltration and upregulated pro-inflammatory cytokines, thereby amplifying antitumor immunity. These findings highlight the potential of MPNs as promising epigenetic modulators for cancer therapy.

5. Applications of MPNs in tumor therapy

5.1. Chemotherapy enhancement

Chemotherapy remains a cornerstone of cancer treatment, utilizing chemical drugs to selectively target and eliminate cancer cells. However, conventional chemotherapy often faces challenges such as poor drug bioavailability, systemic toxicity, and drug resistance. MPNs have emerged as promising nanocarriers, enhancing targeted drug delivery, improving therapeutic efficacy, and overcoming chemoresistance. Wang et al.[145] developed DOX-loaded mesoporous silica NPs coated with Fe−EGCG complexes (DMEFe NPs), which exhibited potent antitumor activity (Fig. 10A). This formulation demonstrated pH-responsive drug release, elevated intracellular ROS levels, and significant tumor cytotoxicity (Fig. 10B and C). Additionally, it effectively inhibited gene expression of the oxidative transcription factor *Nrf-2*, thereby enhancing chemotherapy efficacy (Fig. 10D). In a separate study, Mu et al.[146] synthesized Cabazitaxel (Cab)-loaded EGCG−Fe^{3+} MPNs modified with chitosan (CS) (Cab@MPN/CS NPs) through Fe^{3+}−EGCG coordination (Fig. 10E). This nanocomplex exhibited excellent biocompatibility and significantly suppressed melanoma growth (Fig. 10F). Mechanistically, it exerts its antitumor effects by restraining TUNEL, KI67, and CD31 expression (Fig. 10G). To further address chemotherapy limitations, Yi et al.[147] developed redox-responsive diPTX@Fe−TA nano complexes through Fe^{3+}−TA coordination with dimeric paclitaxel (diPTX) prodrugs. Under high-GSH conditions, the nanocomplex rapidly releases paclitaxel (PTX), facilitating its diffusion to microtubules, disrupting microtubule dynamics, and inducing tumor cell apoptosis (Fig. 10H). Moreover, Li et al.[148] developed a samarium−EGCG (Sm−EGCG) metal−polyphenol complex through the coordination of rare-earth samarium ions (Sm^{3+}) with EGCG (Fig. 10I). Sm−EGCG exhibited minimal cytotoxicity while effectively inhibiting melanoma cell proliferation and migration *in vitro* and *in vivo*. It induced mitochondria-dependent apoptosis and demonstrated superior antitumor exhibiting superior antitumor efficacy compared to clinical 5-FU (Fig. 10J and K). These findings highlight Sm−EGCG as a promising breakthrough therapy for melanoma treatment (Table 6) [145-148].

5.2. CDT

CDT is an emerging tumor treatment strategy that selectively kills cancer cells by leveraging the TME to generate ROS through Fenton or Fenton-like reactions. In these reactions, transition metal ions (*e.g.*, Fe^{2+}, Cu^{+}) catalyze the decomposition of H_2O_2 to produce cytotoxic hydroxyl radicals (•OH)[149]. The TME exhibits weak acidity[149], a high H_2O_2 concentration[150], and hypoxia[151], creating optimal conditions for Fenton reactions. As previously discussed, numerous MPNs-based nanomedicines have

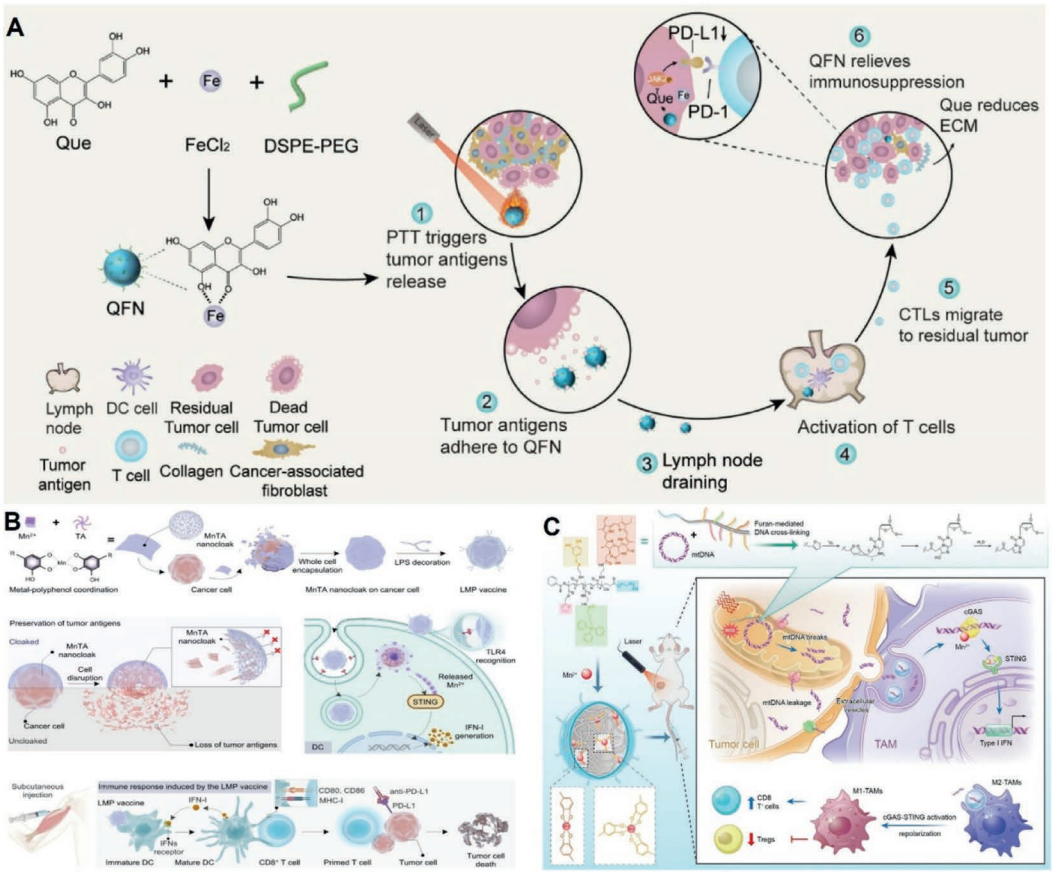


Figure 8 MPNs exert antitumor effects by activating the immune system. (A) Schematic illustration of the synthesis and therapeutic mechanism of QFN. Reprinted with the permission from Ref. 107. Copyright © 2022 Acta Materialia Inc. (B) Synthesis and therapeutic mechanism of an MPN-based whole-cell cancer vaccine. Reprinted with the permission from Ref. 63. Copyright © 2024 Wiley-VCH GmbH. (C) Fabrication and immunotherapeutic mechanism of manganese ion (Mn^{2+})-polyphenol nanocomplexes. Reprinted with the permission from Ref. 138.

been successfully developed, harnessing Fenton reactions for effective tumor elimination. For instance, Zhu et al.[152] developed a nanocomplex (AHD@TA/Cu) for cancer therapy (Fig. 11A). The researchers loaded disulfiram (DSF) onto hollow mesoporous silica NPs (HMSNs) and coated them with the TA−Cu^{2+} network. Within the acidic TME, the TA−Cu^{2+} network undergoes hydrolysis, leading to the release of DSF and Cu^{2+}. Subsequently, Cu^{2+} reacts with DSF to form cytotoxic $Cu(DTC)_2$, effectively inhibiting tumor growth. Additionally, Cu^{2+} catalyze Fenton reactions in the TME, generating abundant •OH for tumor therapy. In another study, Cheng et al.[111] developed a bimetallic polyphenolic nanocomplex (MnO_2@GA−Fe@CAI) for tumor CDT (Fig. 11B). The nanocomplex was fabricated by coating MnO_2 with GA−Fe complexes, followed by conjugation of carbonic anhydrase inhibitor (CAI) to GA. CAI significantly acidifies the TME, enhancing Fenton reaction efficiency. Simultaneously, MnO_2 is reduced by GSH to Mn^{2+}, while GA simultaneously reduces Fe^{3+} to Fe^{2+}. These reduced metal ions (Mn^{2+} and Fe^{2+}) then react with endogenous H_2O_2, generating a substantial amount of cytotoxic •OH, which induces tumor cell death. Notably, the nanocomplex demonstrated excellent biosafety and achieved a tumor inhibition rate of 58.09% ± 5.77% (Fig. 11C and D). These findings highlight the potential of CDT-based strategies, particularly those utilizing MPNs, in enhancing tumor treatment efficacy through precise ROS generation within the TME (Table 7[111,152]).

5.3. *Phototherapy (PTT & PDT)*

5.3.1. *PTT via MPNs*

Traditional cancer treatments, including radiation, chemotherapy, and surgery, have long been the standard approaches for tumor management. However, despite their effectiveness, these treatments often cause severe side effects, significantly affecting patients' quality of life. To address these challenges, phototherapy, which includes PTT and PDT, has emerged as an innovative approach to cancer treatment[153]. PTT converts light energy (*e.g.*, NIR radiation) into thermal energy *via* nanocomposite-mediated photothermal conversion. This process generates localized hyperthermia, selectively ablating cancer cells. Given that the efficacy of PTT largely depends on the performance of photothermal materials, the development of high-efficiency photothermal nanomaterials is crucial for optimizing therapeutic outcomes. Notably, MPNs exhibit intrinsic photothermal properties and can be functionalized with photosensitizers for targeted tumor therapy. For instance, Wang et al.[110] developed baicalein-ferrous NPs (HFBNPs) through the coordination of baicalein, Fe^{2+}, and HA (Fig. 12A). The HFBNPs demonstrated excellent high photothermal conversion efficiency under 808 nm NIR irradiation (Fig. 12B and C). *In vivo* studies confirmed that HFBNPs significantly inhibited tumor growth upon NIR irradiation, demonstrating their strong therapeutic potential (Fig. 12D and E).

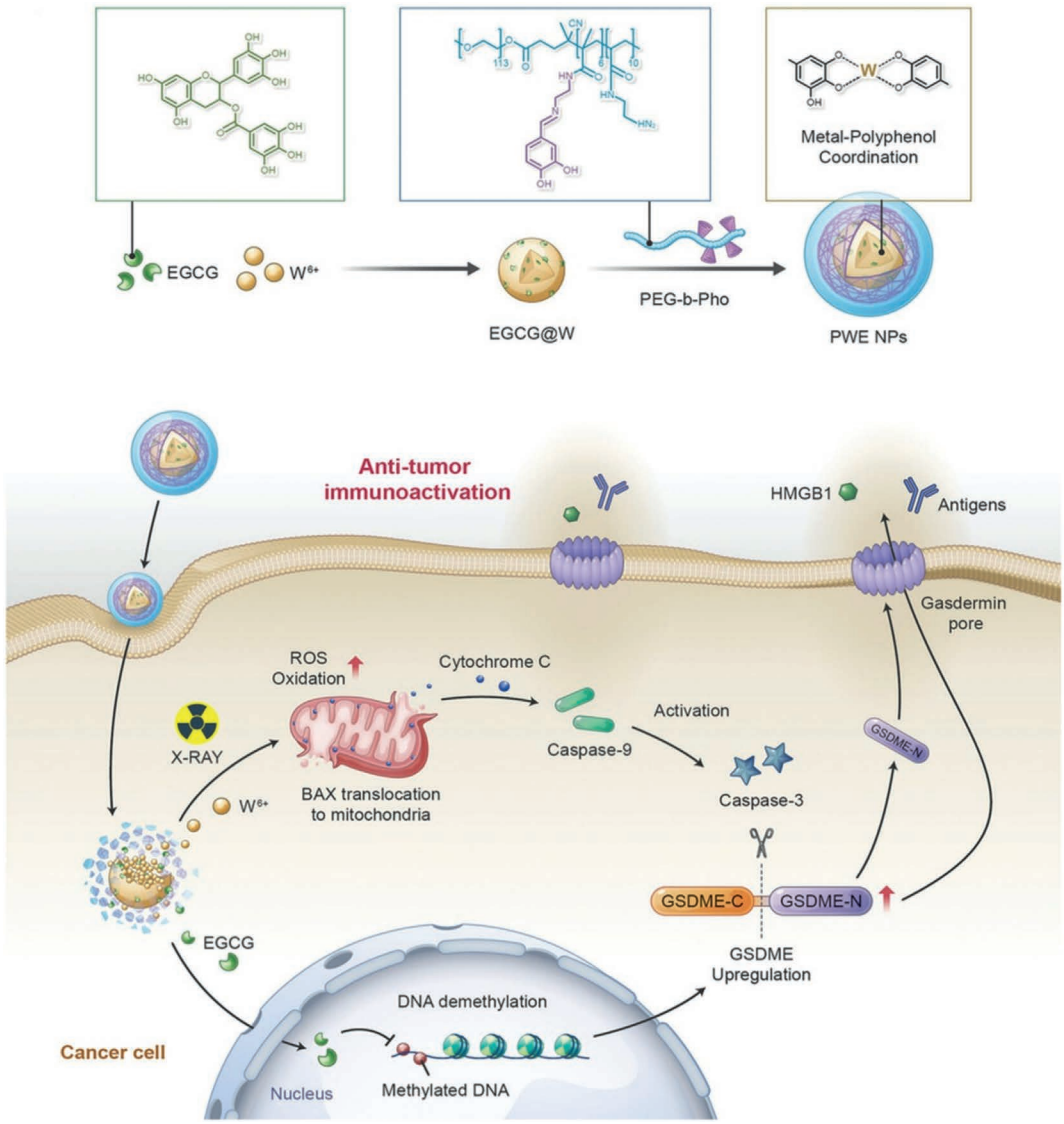


Figure 9 MPNs exerts anti-tumor effects by mediating epigenetics. Schematic diagram of the synthesis and therapeutic mechanism of PWE Nps. Reprinted with the permission from Ref. 144. Copyright © 2023 Wiley-VCH GmbH.

Similarly, Dai et al.[108] synthesized CPPDA-Hf@Poloxamer by chelating hafnium ions (Hf^{4+}) with a polyphenol-functionalized semiconducting polymer (CPPDA), followed by capping with an amphiphilic polymer (Pluronic F127) (Fig. 12F). These nanocomplexes exhibited NIR-II fluorescence for precise tumor imaging and demonstrated efficient photothermal conversion (Fig. 12G and H). Additionally, Hf^{4+} ions served as effective radiosensitizers for tumor therapy. CPPDA-Hf@Poloxamer achieved a 92% tumor growth inhibition, demonstrating remarkable therapeutic efficacy (Fig. 12I). This study provides novel insights into combined tumor therapy strategies (Table 8[108,110,154]). Similarly, gold nanorods have been used for targeted PTT of head and neck squamous cell carcinoma through surface modification (*e.g.*, EGFR antibodies)[155]. However, the unique advantage of MPNs lies in their metal−polyphenol network, which not only provides photothermal conversion capabilities but also enables pH-responsive drug release, thereby achieving multimodal synergistic therapy.

5.3.2. PDT and ROS amplification

On the other hand, PDT represents another light-mediated anti-tumor strategy. When exposed to specific light wavelengths, photosensitizers are activated, triggering localized photochemical reactions that eliminate tumor cells[156,157]. The therapeutic efficacy of PDT primarily depends on ROS generation, which induces oxidative stress and subsequent tumor cell apoptosis[158]. Di et al.[154] developed chlorin e6 (Ce6)-loaded metal−polyphenol nanocomposites (Ce6@HSF NPs) through the coordination of GA-modified HA−SS−GA and Fe^{3+} (Fig. 12J). Upon irradiation with 660 nm NIR light, the nanocomplex generated a substantial amount of ROS, effectively inducing tumor cell death. Additionally, the decomposition of the MPN network triggered Fenton reactions, generating •OH and synergistically enhancing the Ce6-mediated PDT effect. Likewise, Liu et al.[159] reported another MPN-based PDT system for tumor therapy (Fig. 12K). They developed SRF@FeIII−TA NPs (SFT) by encapsulating sorafenib (SRF) within Fe^{3+}−TA networks. The nanomaterial efficiently loaded the

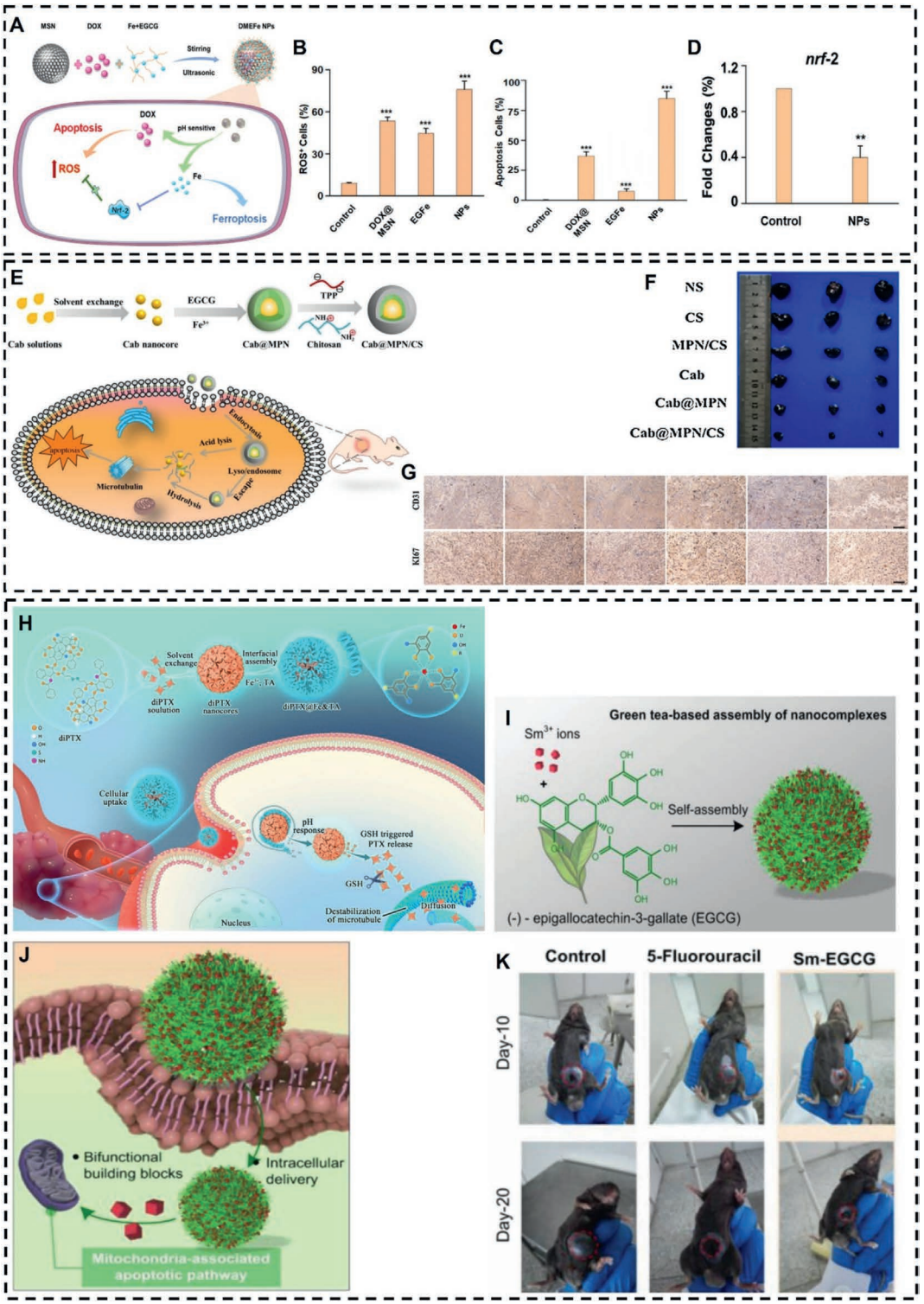


Figure 10 Application of MPNs in chemotherapy. (A) Synthesis and therapeutic mechanism of DMEFe NPs. (B) Quantitative analysis of ROS positive cells under different treatments. (C) The proportion of apoptosis after different treatment groups. (D) Statistical map of DMEFe NPs inhibiting the expression of the *Nrf-2* gene. Reprinted with the permission from Ref. 145. Copyright © 2024 American Chemical Society. (E) Cab@MPN/CS NPs schematic diagram of synthesis and therapeutic mechanism. (F) Images of mouse tumors after different treatments. (G) CD31 and KI67 staining images of tumor tissue after different treatments. Reprinted with the permission from Ref. 146. Copyright © 2021 Elsevier B.V. (H) Synthesis of diPTX@Fe&TA nanocomplexes and schematic diagram of therapeutic mechanism. Reprinted with the permission from Ref. 147. Copyright © 2021 Tsinghua University Press and Springer-Verlag GmbH Germany. (I) Synthesis diagram of Sm−EGCG. (J) Sm−EGCG induces mitochondrial-dependent apoptosis. (K) Image of Sm−EGCG treated melanoma *in vivo*. Reprinted with the permission from Ref. 148.

Table 6 Applications of MPNs in chemotherapy enhancement.

MPN material	Composition	Application	Key characteristics	Ref.
DMEFe NPs	Fe−EGCG-coated mesoporous silica NPs	Targeted drug delivery for oral cancer	pH-responsive release, ROS elevation, Nrf-2 inhibition	145
Cab@MPN/CS NPs	EGCG−Fe^{3+}/chitosan NPs	Melanoma therapy	Biocompatibility, suppression of TUNEL/KI67/CD31	146
diPTX@Fe&TA	Fe^{3+}−TA + dimeric paclitaxel	Redox-responsive drug release	GSH-triggered PTX release, microtubule disruption	147
Sm-EGCG	Samarium−EGCG complex	Melanoma apoptosis	Mitochondria-dependent apoptosis, outperforms 5-FU	148

methylene blue (MB) photosensitizer, leveraging TA's exceptional adhesive properties. MB-loaded SRF@FeIII−TA exhibited pH-responsive tumor imaging and PDT for complete tumor eradication. In conclusion, these studies highlight the great potential of MPN-based nanoplatforms in phototherapy. By integrating photothermal and photodynamic mechanisms, these nanomaterials offer innovative solutions for enhancing cancer treatment efficacy while minimizing adverse effects (Table 8 [108,110,154]).

5.4. *Sonodynamic therapy (SDT) and synergistic effects*

SDT is a non-invasive cancer treatment that utilizes ultrasound to activate tumor-localized acoustic sensitizers, thereby generating ROS for selective cancer cell elimination. One of the key advantages of SDT is the deep tissue penetration of ultrasound, which enables precise lesion targeting while overcoming the depth limitations of PDT[160]. Functionalized MPN NPs have been designed to enhance acoustic sensitizer delivery, tumor targeting, acid-responsive drug release, and catalytic ROS generation, significantly improving therapeutic efficacy while reducing systemic toxicity for solid tumor treatment. Dai et al.[161] developed PP18−Pt NPs by integrating a metal−polyphenol nanoplatform with platinum (Pt) radiosensitizers and PEG-purpurin 18 (PEG-P18) acoustic sensitizers (Fig. 13A). They implemented a two-step therapeutic strategy for tumor treatment. In the first step, low-intensity pulsed ultrasound (LIPUS) is applied to ameliorate tumor hypoxia. Subsequently, the second step combines X-ray and ultrasound (US) to activate PP18−Pt NPs, generating high-intensity ROS for breast cancer therapy. The LIPUS + X-ray combination significantly alleviated tumor hypoxia. *In vivo* studies demonstrated that this two-step approach effectively inhibited 4T1 breast tumor growth and activated antitumor immunity, further enhancing therapeutic outcomes (Table 9[161,162]). In addition, naphthacil, featuring dual quinone and phenolic hydroxyl functionalities, holds significant potential in natural product chemistry, drug discovery, and materials science. Ma et al.[162] developed MPN-based FNCP nanofibers incorporating Ce6, naphthalene, and Fe^{3+} (Fig. 13B). In this system, ultrasound-activated Ce6 generated substantial ROS, while naphthysine depleted GSH, enhancing Fe^{2+}-mediated CDT. This process downregulated GPX4 expression, increased LPO accumulation, and induced tumor cell ferroptosis. As a result, FNCP NFs effectively inhibited tumor growth through the synergistic effects of sonodynamic and CDT. These studies highlight the promising potential of SDT in cancer treatment, especially when combined with other therapeutic modalities. The strategic design of multifunctional metal−polyphenol nanoplatforms provides an innovative approach to overcoming the current limitations of traditional SDT, ultimately improving clinical outcomes in solid tumor therapy.

5.5. *Combined therapeutic modalities*

The multifunctional nature of MPNs makes them suitable for synergistic therapeutic strategies that integrate multiple treatment modalities. This combination enhances efficacy and overcomes limitations of monotherapies. Here are key examples of combination therapies facilitated by MPNs.

5.5.1. *Chemotherapy + PTT*

Wang et al.[110] developed baicalein-ferrous NPs (HFBNPs) that combined chemotherapy with photothermal effects. Under NIR irradiation, HFBNPs generated localized hyperthermia to ablate tumors while releasing chemotherapeutic agents, achieving dual therapeutic effects. Similarly, Dai et al.[108] engineered CPPDA-Hf@Poloxamer, which integrated NIR-II imaging-guided PTT with radiotherapy, achieving a 92% tumor inhibition rate.

5.5.2. *CDT + chemotherapy*

Zhu et al.[152] designed AHD@TA/Cu nanocomplexes, where the TA−Cu^{2+} network enabled pH-triggered release of disulfiram (DSF) and Cu^{2+}. The latter catalyzed Fenton reactions for CDT, while DSF formed cytotoxic $Cu(DTC)_2$, synergizing chemotherapy and CDT. Cheng et al.[111] further combined MnO_2@GA−Fe@CAI with acidification of the TME to amplify ROS generation, enhancing both CDT and chemotherapy.

5.5.3. *Immunotherapy + PTT*

Zhang et al.[107] demonstrated that QFN not only induced tumor cell lysis but also promoted dendritic cell maturation and T-cell activation, linking photothermal effects with immune activation. Additionally, Mn^{2+}−polyphenol nanocomplexes activated the cGAS−STING pathway, enhancing antitumor immunity while leveraging photothermal conversion for ablation[138].

5.5.4. *SDT + CDT*

Dai et al.[138] developed PP18−Pt NPs for a two-step strategy: low-intensity ultrasound alleviated tumor hypoxia, followed by X-ray and ultrasound activation to generate ROS *via* SDT and CDT. This approach significantly inhibited breast tumor growth and activated systemic immunity. Ma et al.[162] engineered FNCP nanofibers combining SDT-triggered ROS with GSH depletion and Fe^{2+}-mediated CDT, inducing ferroptosis.

5.5.5. *Triple-modal therapy (PTT/CDT/chemotherapy)*

Liu et al.[93] designed EFPD nanoplatforms that integrated EGCG−Fe^{3+}-mediated PTT, DOX-based chemotherapy, and Fenton-driven CDT. The platform exhibited synergistic tumor suppression through thermal ablation, drug release, and ROS amplification.

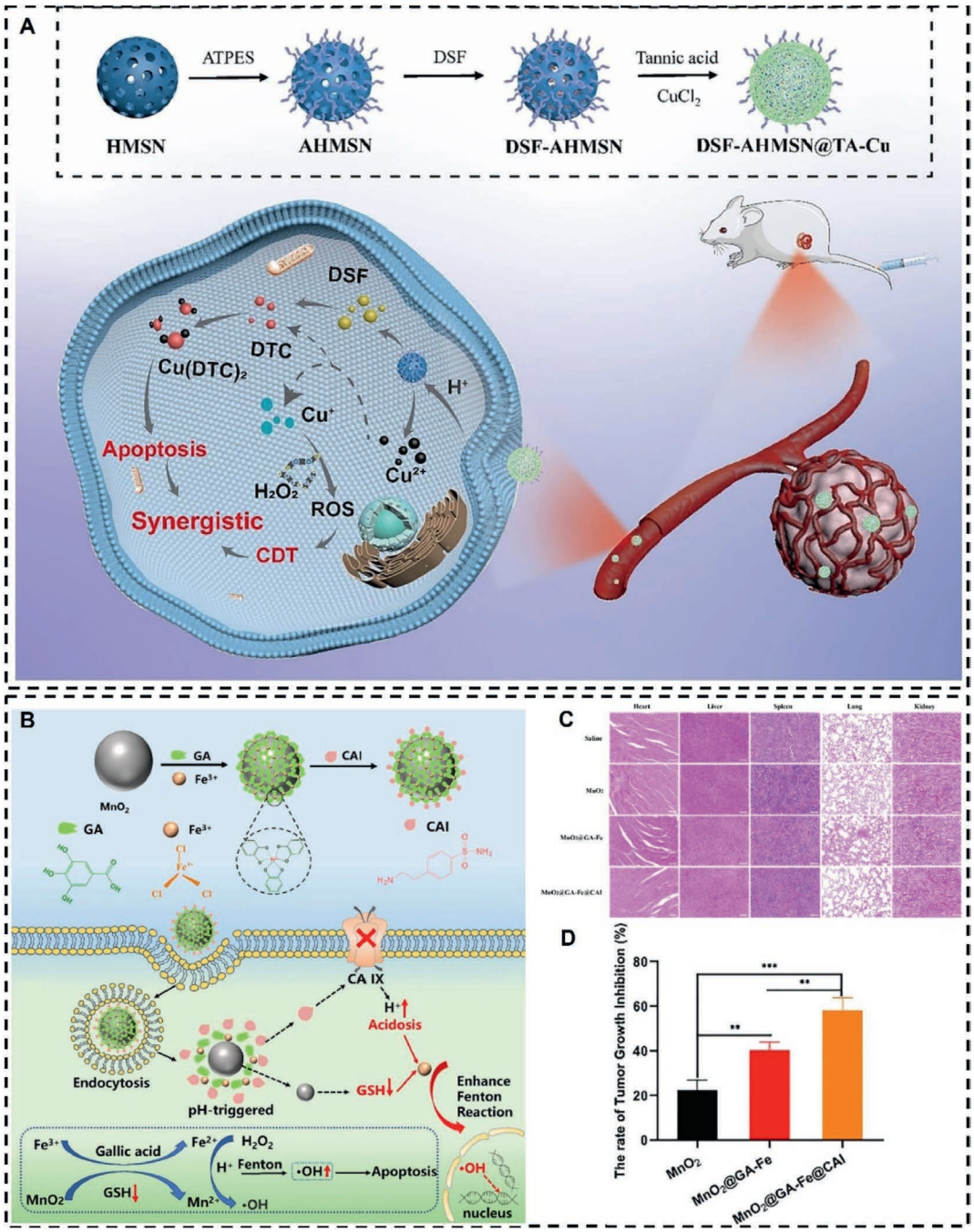


Figure 11 Application of MPNs in CDT. (A) Schematic diagram of the preparation process and therapeutic mechanism of AHD@TA/Cu. Reprinted with the permission from Ref. 152. Copyright © 2024 Elsevier B.V. (B) Synthesis and therapeutic mechanism of MnO_2@GA−Fe@CAI. (C) HE staining of different treated mouse organs (scale: 100 μm). (D) Tumor growth inhibition rate after different treatments. Reprinted with the permission from Ref. 111.

Table 7 Applications of MPNs in CDT.

MPN Material	Composition	Application	Key characteristics	Ref.
AHD@TA/Cu	TA−Cu^{2+} + disulfiram	ROS generation *via* Fenton reaction	Acid-triggered $Cu(DTC)_2$ formation, dual chemo/CDT activity	152
MnO_2@GA−Fe@CAI	MnO_2 + GA−Fe + CAI	TME acidification	GSH depletion, Mn^{2+}/Fe^{2+} -mediated •OH generation, 58% tumor inhibition	111

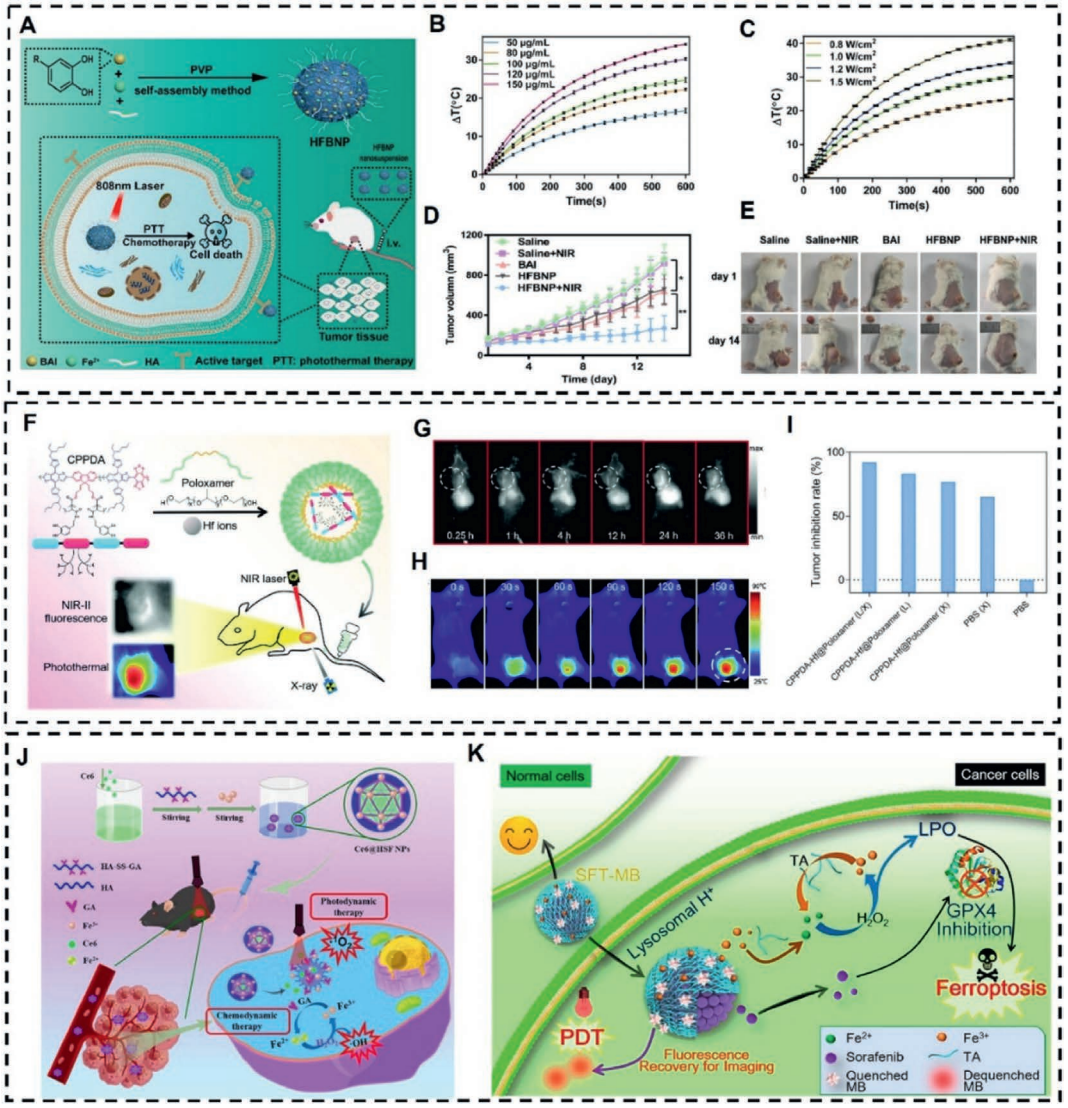


Figure 12 Application of MPNs in phototherapy. (A) Schematic diagram of synthesis and therapeutic mechanism of HFBNP. (B) Photothermal curves of HFBNP at different concentrations under 808 nm laser. (C) Photothermal curves of HFBNP irradiated with different power densities. (D) Tumor volume change curves within 14 days of different treatments. (E) Images of tumor changes in mice before and after treatment. Reprinted with the permission from Ref. 110. Copyright © 2022 Elsevier B.V. (F) Schematic diagram of synthesis and treatment of CPPDA−Hf@Poloxamer. (G) CPPDA−Hf@Poloxamer fluorescence imaging of NIR-II in treated tumor mice. (H) Photothermal imaging images of tumorous mice 24 h after injection of CPPDA−Hf@Poloxamer. Reprinted with the permission from Ref. 108. Copyright © 2021 The Royal Society of Chemistry. (I) Statistics of tumor inhibition rate after different treatments. (J) Synthesis and therapeutic mechanism of Ce6@HSF. Reprinted with the permission from Ref. 158. Copyright © 2023 Elsevier B.V. (K) Schematic diagram of the therapeutic mechanism of SRF@FeIIITA. Reprinted with the permission from Ref. 159. Copyright © 2018 American Chemical Society.

Table 8 Applications of MPNs in PTT & PDT.

MPN material	Composition	Application	Key characteristics	Ref.
HFBNP	Baicalein-Fe^{2+} + HA	NIR-triggered PTT	High photothermal conversion efficiency (808 nm)	110
CPPDA−Hf@Poloxamer	Hf^{4+} + polyphenol-semiconductor	NIR-II imaging + PTT/radiotherapy	92% tumor inhibition, radiosensitization	108
Ce6@HSF	GA−Fe^{3+} + chlorin e6	PDT with Fenton synergy	ROS amplification, pH/ROS dual-responsive release	158

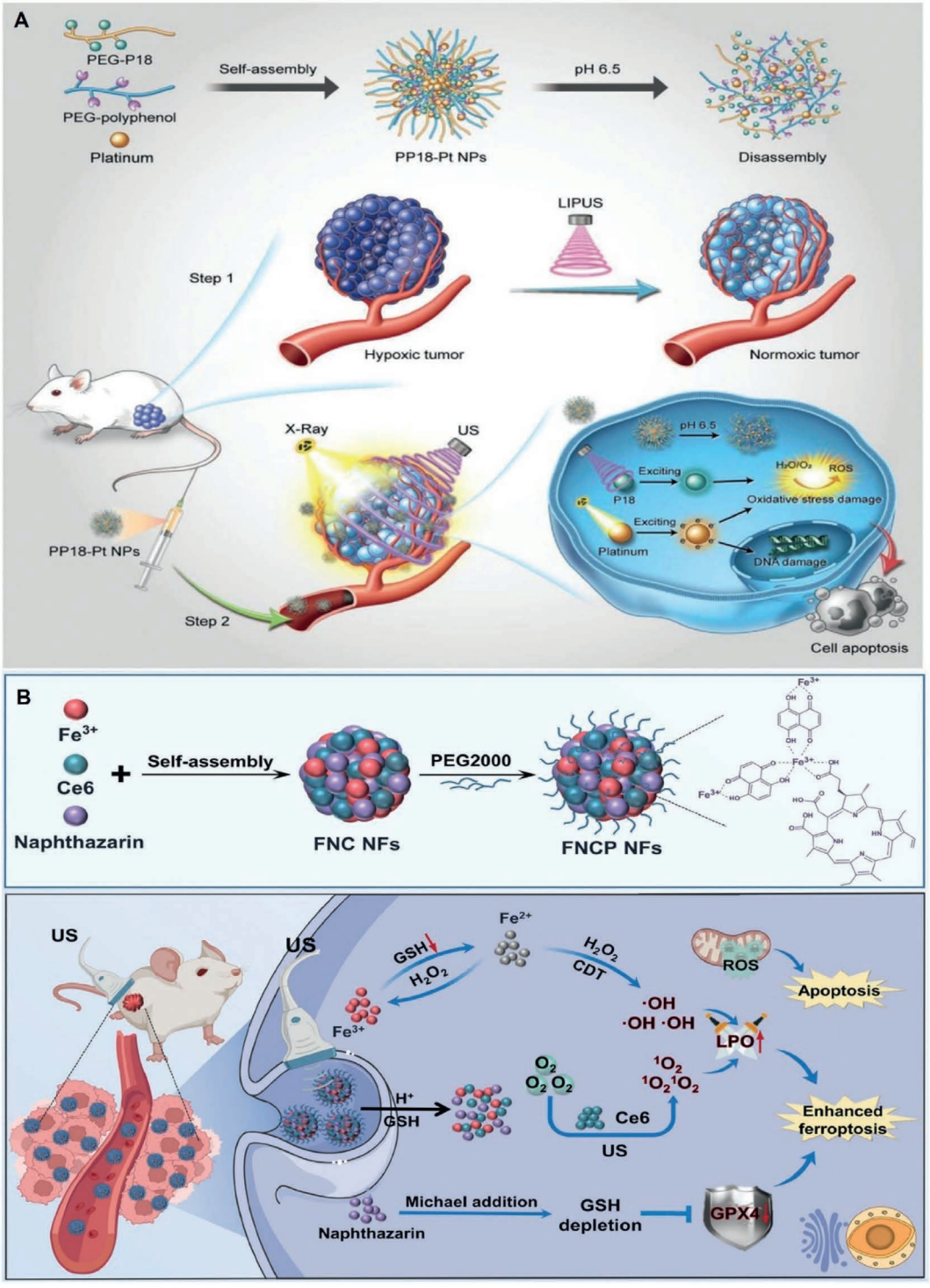


Figure 13 Application of MPNs in SDT. (A) Assembly of PP18−Pt NPs and schematic diagram of its two-step treatment mechanism. Reprinted with the permission from Ref. 161. Copyright © 2022 Wiley-VCH GmbH. (B) Synthesis of FNCP NFs and its mechanism of tumor elimination. Reprinted with the permission from Ref. 162. Copyright © 2024 Wiley-VCH GmbH.

These examples highlight the versatility of MPNs in bridging diverse therapeutic mechanisms. By leveraging pH-responsiveness, ROS generation, and targeted delivery, MPNs enable precise spatiotemporal control over combination therapies, minimizing off-target effects and maximizing therapeutic outcomes. Future research should focus on optimizing multi-mechanism coordination and clinical translation of these platforms.

Table 9 Applications of MPNs in SDT.

MPN material	Composition	Application	Key characteristics	Ref.
PP18−Pt NPs	Pt + PEG-purpurin 18	Ultrasound/X-ray combo therapy	Alleviates hypoxia, activates antitumor immunity	161
FNCP NFs	Ce6 + naphthacil + Fe^{3+}	Ferroptosis-enhanced SDT	Ultrasound-triggered ROS, GSH depletion, GPX4 downregulation	162

6. Personalized medicine and clinical translation

Personalized medicine (PM) has ushered in a new era for oncology, hinging on the analysis of patient-specific molecular profiles to enhance therapeutic efficacy[163,164]. MPN-based platforms are pivotal in this paradigm, affording precise customization of nanoparticle composition, targeting ligands, and theranostic functions. Imaging-guided therapy is a prime example, where MPNs incorporating diagnostic agents like Mn^{2+} or Fe^{3+} enable real-time MRI monitoring of tumor localization and drug delivery, while NIR-II fluorescent MPNs facilitate deep-tissue imaging[95,96,108]. Additionally, pH-responsive MPNs can be engineered to release drugs selectively within the acidic TME, with dual-responsive MPNs (pH/ROS) offering further spatiotemporal control for tumors with heterogeneous pH profiles[42]. MPNs can also be tailored to modulate the immune microenvironment, such as activating the cGAS−STING pathway or depleting immunosuppressive cells, based on patients' specific immune signatures[63,107,138]. A combinatorial workflow begins with biopsy-driven biomarker identification, followed by the design of MPNs with corresponding targeting ligands, therapeutic payloads, and imaging agents. Subsequent steps involve administration, multimodal imaging monitoring, and therapy adjustment based on imaging feedback and biomarker evolution.

Recent preclinical studies have demonstrated the translational potential of MPNs, such as Sm−EGCG nanoparticles exhibiting negligible systemic toxicity in murine models[148]. However, several challenges must be addressed to ensure their smooth clinical translation. The long-term biocompatibility of porous networks remains underexplored, with potential risks from metal ion accumulation and polyphenol-derived metabolites. To mitigate these concerns, comprehensive biodistribution studies using imaging techniques[107,109], the use of biodegradable metal ions and polyphenols with established safety profiles[95,165], and long-term toxicity assessments in preclinical models are necessary[105]. Batch-to-batch variation in MPN synthesis can affect reproducibility and therapeutic consistency, which can be resolved by standardizing synthesis protocols *via* microfluidic systems[71,166], implementing quality control measures[60,97], and optimizing lyophilization techniques[42,59,146]. Clarifying the metabolic fate of MPNs, including hepatic/renal clearance and enzymatic degradation, is crucial and can be achieved through pharmacokinetic studies with radiolabeled MPNs[107,109] and investigating renal clearance in conjunction with hepatic processing[105,167]. The integration of therapies carries the risk of off-target effects and toxicity overlap, which can be managed by computational modeling[137,168], developing stimulus-responsive MPNs[59,93,147], and adopting a PM approach[65,169]. Interdisciplinary collaboration is vital to address these challenges. Advances in bioinformatics, scalable nanofabrication, and precision oncology will accelerate MPN translation[63]. Hybrid MPN platforms integrating immunotherapies or gene editing tools hold the potential to revolutionize multimodal cancer treatment[170]. Notably, MPNs have applications beyond oncology, such as in orthopedics for antimicrobial coatings and bone regeneration[171], highlighting their broad clinical value. Furthermore, the regulatory framework must evolve to accommodate the unique nature of MPNs to ensure rigorous and effective clinical evaluation.

7. Conclusions

MPNs have emerged as promising nanoplatforms in tumor therapy, offering significant advantages such as multifunctionality, excellent biocompatibility, and stimuli-responsiveness. MPNs integrate drug delivery, imaging, and therapeutic functionalities, enabling precise targeting and real-time monitoring of tumor lesions. Their biodegradability and pH-responsive drug release mechanisms allow for controlled therapeutic agent deployment in the acidic TME, thereby minimizing off-target effects and reducing systemic toxicity. Additionally, MPNs exhibit excellent photothermal properties and can be functionalized with photosensitizers for targeted tumor therapy, providing a versatile toolkit for cancer treatment.

Despite their potential, MPNs face several challenges that must be addressed to facilitate their clinical translation. Long-term biosafety concerns, particularly regarding metal-ion accumulation and metabolic fate, remain unresolved. Batch-to-batch variability in MPN synthesis can compromise reproducibility and therapeutic consistency. The targeting efficiency of MPNs is influenced by the TME, such as matrix barriers and heterogeneous receptor expression, which may reduce their effectiveness. Furthermore, optimizing the synergy of multiple therapeutic mechanisms is challenging, as the spatiotemporal coordination among different modalities is not yet fully understood, potentially leading to efficacy cancellation or toxicity overlap.

Future research directions should focus on the precise design of MPNs and the development of intelligent response systems. "Smart" MPNs that respond to multiple stimuli should be developed to achieve on-demand drug release and spatiotemporal control. AI-assisted design can optimize metal−polyphenol ratios and surface functionalization strategies to enhance targeting specificity. In-depth analysis of the *in vivo* behavior and toxicity mechanisms of MPNs is crucial, leveraging techniques like *in vivo* imaging and single-cell sequencing to track their distribution and interactions with the immune system. Establishing a standardized toxicity evaluation system is necessary to focus on liver and kidney function, immune responses, and genetic toxicity. Additionally, personalized and combination therapy innovations should be explored, developing individualized MPN formulations based on patient tumor genomics and microenvironments. The integration of MPNs with emerging therapies like CAR-T and oncolytic viruses could overcome drug resistance. Green synthesis and sustainable development are also important, aiming to reduce

toxic reagent use and enhance material reproducibility and scalability. Finally, promoting clinical translation and multidisciplinary collaboration is essential to accelerate the transition of MPNs from laboratory research to clinical application, offering more efficient and safer solutions for cancer therapy.

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Author contribution

Conceptualization, Qin Wang; Writing − original draft, Qin Wang, Chen Ma, Jian Gu, Shuai Wang, and Fen-Er Chen; Writing − review and editing, Qin Wang, Chen Ma, Qian Xu, Lingwen Ding, Phuong-Thao Tran, Shuai Wang, Fen-Er Chen; Supervision, Qin Wang, Chen Ma, Xinya Liu, Junkai Cheng, Yiman Wang, Lu Liu, and Jiaqi Xian; Funding acquisition, Qin Wang, Jian Gu, Shuai Wang, and Fen-Er Chen. All authors approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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