

# Metal-Phenolic Networks: A Promising Frontier in Cancer Theranostics

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**Abstract:** The burgeoning field of cancer theranostics has been significantly advanced by the development of Metal-Phenolic Networks (MPNs), a new class of supramolecular architectures that integrate the advantages of metals and polyphenols. This review focuses on MPNs and their promising applications in cancer theranostics. Through a systematic literature search spanning from 2010 to 2023 in databases including PubMed, Scopus, and Web of Science. The period of search was justified by the rapid evolution of nanomaterials in cancer therapy, with MPNs emerging as a significant player in biomedical applications within the specified timeframe. This review discusses the classification and structure of polyphenolic compounds, as well as their mechanisms of action in cancer treatment. The applications of MPNs in chemotherapy drug delivery, photothermal therapy, chemodynamic therapy, biomedical imaging, and synergistic therapy are especially detailed. The authors emphasize the significance of MPNs in cancer nanomedicine and look forward to their future development directions.

**Keywords:** MPN, cancer, theranostics, polyphenolic compounds

## Introduction

Carcinogenesis is a multifaceted condition that encompasses a diverse array of cellular entities, extracellular matrix components, immunological elements, signaling pathways, and physiological processes.<sup>1</sup> The fundamental characteristics of malignancy encompass sustained proliferative signals, indefinite replication potential, neovascularization, invasive behavior, metastatic dissemination, defiance of apoptotic cues, escape from growth inhibitors, immunity subversion, and metabolic rewiring.<sup>2</sup> Contemporary therapeutic strategies for cancer encompass surgical resection, pharmacological interventions, radiation therapy, and targeted modalities including hormonal, immunological, and genetic approaches; however, these are beset by drawbacks such as elevated likelihood of neoplastic resurgence, irreversible tissue alterations, operative hazards, and unwanted sequelae.<sup>3</sup> Moreover, chemotherapeutics, predominantly small molecule agents, frequently grapple with issues like diminished bioavailability, polypharmacological resistance, inadequate specificity, and deleterious collateral effects. Radiation therapy, in addition, may inflict unwarranted injury upon healthy tissues, culminating in grave adverse reactions.<sup>4</sup> The differences between the tumor microenvironment (TME) and normal physiological conditions in organs become crucial for the precise targeting of drug delivery platforms. Cancer is viewed as an evolutionary and ecological process,<sup>5</sup> involving constant, dynamic, and static interactions between cancer cells and the TME. Due to the genomic instability of cancer cells, they readily develop drug resistance. In contrast, non-tumor cells within the TME have relatively stable genetic characteristics while being susceptible to external factors.<sup>6</sup> The TME has a lower pH, reduced permeability, and considerable barrier effects through various mechanisms.<sup>7</sup> Components of the TME, such as abnormal tumor vasculature, disordered extracellular matrix composition, and interstitial hypertension (elevated interstitial fluid pressure), which significantly determine the distribution of drug within the tumor tissue, are important parameters to be considered upon designing drugs for cancer treatment.<sup>8</sup> Nanoplatfoms, due to their small size, can preferentially accumulate at target sites, enhancing treatment efficacy while significantly reducing toxicity and side

effects.<sup>9</sup> With advancements in biomedicine and materials science, nanoplateforms that deliver drugs with good targeting, high drug loading capacity, excellent biocompatibility, and bioavailability have become a research hotspot for better cancer management.<sup>9–12</sup>

Polyphenolic compounds, endowed with potent antioxidant, antiplatelet aggregation, and anti-inflammatory activities, are recognized for their capacity to mitigate or avert the clinical manifestations of a spectrum of metabolic disorders. A wealth of scientific literature supports the notion that a diet replete with polyphenols or fortified with these phenolic substances can exert positive effects on the treatment and management of systemic disorders, neurodegenerative conditions, and amyloidopathies. Furthermore, polyphenols have established themselves as significant players in cancer prevention, with a plethora of evidence from animal studies demonstrating their efficacy in averting the onset of a diverse range of malignancies, including gastric cancer,<sup>13</sup> ovarian cancer, breast cancer,<sup>14,15</sup> colorectal cancer,<sup>16</sup> prostate cancer,<sup>17</sup> lymphoma,<sup>18</sup> and lung cancer.<sup>19</sup> Phenolic drugs act as cytotoxic anticancer agents, demonstrating significant promise in promoting apoptosis, reducing proliferation, and targeting various aspects in cancer progression (angiogenesis, growth, differentiation, and metastasis). However, stability and targeted delivery are critical factors for polyphenols to exert their biological activity while the bioavailability of polyphenolic compounds is a significant hurdle in their use as cancer therapeutic agents. Reports shown that polyphenols usually reach the desired targets at very low concentrations only while nano-formulated polyphenols represent a promising solution to this issue.<sup>20,21</sup>

Emerging research on nanodrugs composed of common metallic elements for tumor treatment and diagnostics has become a hotspot, with some metal-based nanodrugs successfully transitioning from laboratory to clinic and market due to their excellent biocompatibility and diverse application potentials, making them one of the most successful nanoplateforms.<sup>22</sup> The catechol and gallol parts of polyphenols interact with other substances through hydrogen bonding,  $\pi$ -interactions, hydrophobic interactions, metal chelation, covalent bonds, and electrostatic interactions,<sup>23</sup> with metal ion chelation being a significant characteristic of polyphenolic compounds.<sup>24–26</sup> As common organic ligands, polyphenolic compounds can coordinate with metal ions to form self-assembled metal phenolic networks (MPNs)<sup>27</sup> constitute a class of supramolecular amorphous structures, arising from the coordination bonding between polyvalent metal ions and polyphenolic constituents, attracting widespread attention for their remarkable physicochemical properties in various biomedical applications such as bioimaging, drug delivery, and surface coatings.<sup>28</sup>

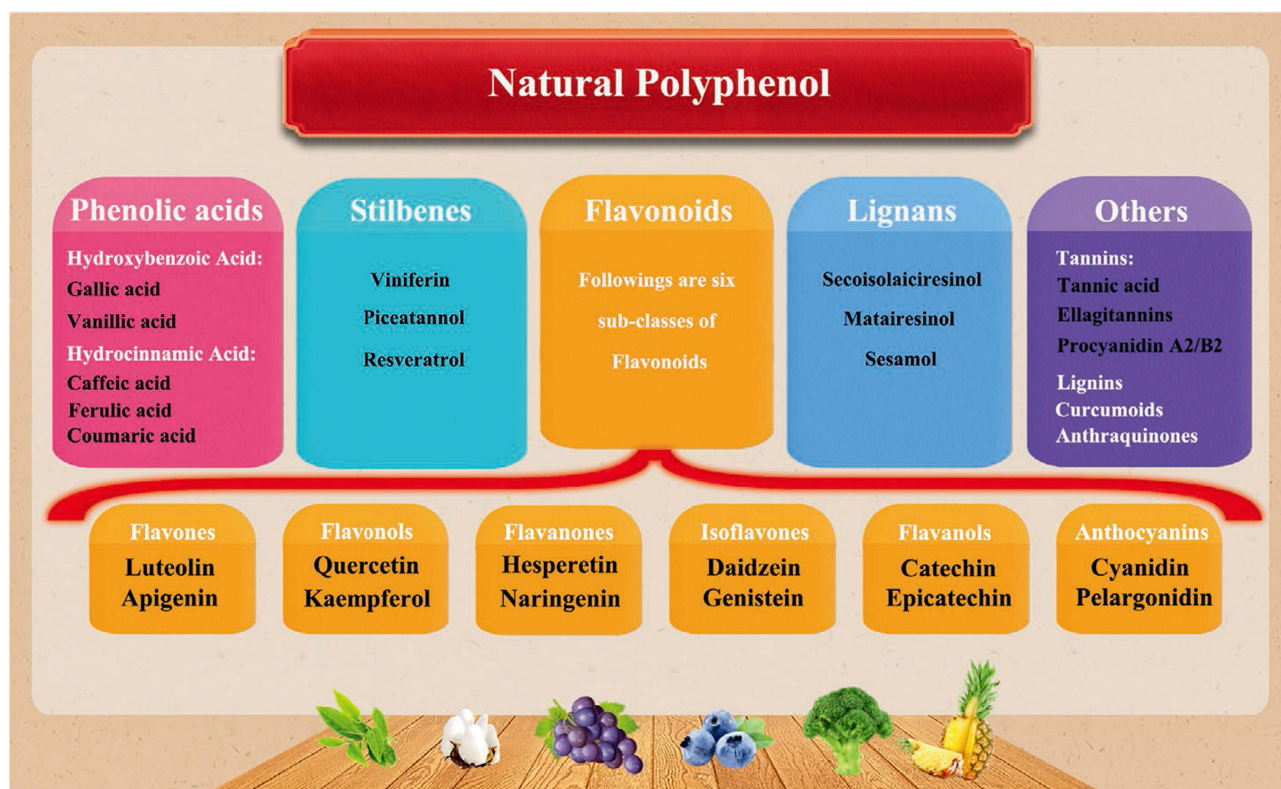
The purpose of this review is to introduce the classification and structure of phenolic compounds, the potential actin mechanism of these compounds and summarize the main features of MPNs and their various applications in cancer treatments. Although many previous studies have summarized the recent advances of MPNs,<sup>29–31</sup> we focus on the cutting-edge applications of MPNs in the integrated treatment of cancer. This not only serves as a beneficial supplement to the frontier research of MPNs but also points the way for their subsequent development.

## Classification and Examples of Polyphenolic Compounds

Plant-derived polyphenols are inherently present in a diverse range of plant-based foods, including vegetables, fruits, cereals, tea, coffee, and other botanical sources. Given their ubiquity and relative abundance as chemical constituents within the plant kingdom, these polyphenols have garnered escalating interest among the scientific research community (Figure 1).<sup>32</sup> Phenolic compounds play important roles in the clearance of hydrogen peroxide and the production of secondary metabolites in plant cells. Up to approximately 10,000 polyphenol structures have been identified and described in plants so far.<sup>33</sup> Polyphenols are a large class of compounds generally characterized by benzene rings with two or more phenolic hydroxy groups. Their distinctive chemical and biological properties arise from the presence of multiple phenol structural units. The biological activity of polyphenols is related to many oxidative stress-related diseases and the activation of cell death through various mechanisms.<sup>34</sup> Based on structural features, they are generally categorized into phenolic acids, flavonoids, lignans, stilbenes, tannins, and coumarins.<sup>35</sup> These compounds feature phenolic rings as basic monomers with complex structures (Table 1).

## Phenolic Acids

Phenolic acids represent a subset of phenolic compounds intrinsic to the plant kingdom, ubiquitously present in a vast array of plant-based consumables and forming a substantial component of the typical human diet. Their biosynthesis originates from the shikimate pathway, branching off from either L-phenylalanine or L-tyrosine.<sup>36</sup> The classification of phenolic acids is further bifurcated into benzoic acid derivatives, characterized by a 6-carbon framework, and cinnamic acid derivatives, which



**Figure 1** Classification of natural polyphenols. Reprinted from Zhang Z, Xie L, Ju Y, Dai Y. Recent advances in metal-phenolic networks for cancer theranostics. *Small*. 2021;17(43):2100314. © 2021 Wiley-VCH GmbH.<sup>32</sup>

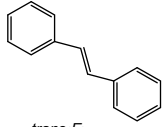
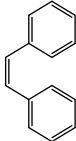
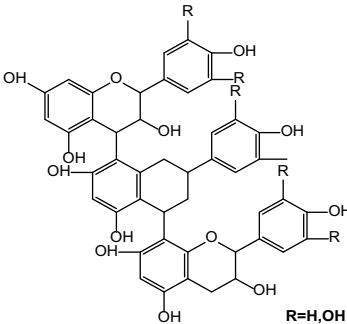
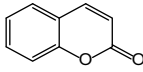
possess a 9-carbon backbone. These molecules are distinguished by the presence of a carboxylic acid moiety linked to an aromatic ring, often accompanied by one or more hydroxyl or methoxy substituents.<sup>37</sup> Notable representatives within this class encompass gallic acid, eugenol, cinnamic acid, ferulic acid, caffeic acid, and sinapic acid.

**Table 1** Representative Polyphenols and Corresponding Chemical Structure

Polyphenols	Chemical Structure
Phenolic Acids	<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>vanillic acid</p> </div> <div style="text-align: center;"> <p>sinapic acid</p> </div> </div>
Flavonoids	<p>flavonoid backbone</p>
Lignans	<p>aryltetralin</p>

(Continued)

Table I (Continued).

Polyphenols	Chemical Structure	
Stilbenes	 <p><i>trans(E)-stilbene</i></p>	 <p><i>cis(Z)-stilbene</i></p>
Tannins	 <p>condensed tannin R=H,OH</p>	
Coumarins	 <p>osthol</p>	

## Flavonoids

In general, flavonoid compounds are characterized by a 15-carbon skeleton (C6-C3-C6), consisting of two aromatic rings (C6) connected by a three-carbon chain (C3), with both C6 units (rings A and B) exhibiting phenolic properties. The variation in hydroxylation patterns and the chromene ring (ring C) allows flavonoids to be further classified into distinct subclasses: flavonols, flavanones, flavan-3-ols, flavones, anthocyanidins, and isoflavones;<sup>38</sup> (1) Flavonol Compounds: quercetin, kaempferol, myricetin, luteolin, etc.; (2) Flavanone Compounds: naringenin, hesperetin, eriodictyol, isosakuranetin; (3) Flavan-3-ol Compounds: Catechin, epicatechin, epigallocatechin, etc.; (4) Flavone Compounds: Luteolin, apigenin, chrysin, etc.; (5) Anthocyanidins: Cyanidin, pelargonidin; (6) Isoflavone Compounds: Genistein, daidzein, formononetin, biochanin A, prunetin, etc.<sup>35</sup>

## Lignans

Lignans are a significant group of phenolic compounds that occur naturally and are extensively found throughout various species within the plant kingdom, originating from the shikimate biosynthetic pathway. These compounds display a dimeric structure characterized by a  $\beta,\beta'$ -bond between two phenylpropane units, with varying degrees of oxidation in the side chains and differing substitution patterns in the aromatic segments. According to the structural motifs of lignans (carbon skeleton, the mode of oxygen incorporation into the skeleton, and cyclization patterns), they are classified into eight categories: arylneolignans, aryltetrahydronaphthalenes, dibenzocyclooctadienes, dibenzylbutanes, dibenzylbutyrolactones, dibenzylbutyrolactols, and furans.<sup>39</sup> Notable lignan compounds include magnolol, matairesinol, sesamin, silymarin, taxifolin A, bicycolol, forsythoside B, and epicatechin, among others.

## Stilbenes

Stilbenes are synthesized by plants as a defense mechanism against a variety of stressors, including pathogen attack, elevated temperatures, and oxidative challenges.<sup>40</sup> Predominantly functioning as antimicrobial phytoalexins, these substances are specifically induced following plant injury or upon encountering pathogens. The core structure of stilbenes is a 14-carbon framework (C6-C2-C6), featuring two phenyl groups linked by an ethylene bridge. One phenyl group typically has two hydroxyl groups, while the other may have hydroxyl or methoxy groups at various positions. The unique architecture of stilbenes, which differs from that of flavonoids, arises from the polyketide segment's susceptibility to cyclization and decarboxylation reactions, allowing them to exist in monomeric or oligomeric forms.<sup>41</sup> Monomeric stilbenes can adopt two geometric isomers: the trans (E) configuration, which is sterically hindered, and the cis (Z) configuration, which is less hindered but less stable. Resveratrol, pterostilbene, and piceatannol are notable examples of this class of polyphenols.

## Tannins

Plant-derived tannins, often simply termed “tannins” or “tannic acids”, are ubiquitous components found in the natural flora. They are classified, according to their molecular structure and chemical behavior, into two primary groups: hydrolysable and condensed tannins. The former comprises polyphenolic cores with molecular weights varying from 500 to 3000 Da, encompassing gallotannins and ellagitannins that yield gallic acid and ellagic acid upon hydrolysis, respectively. Condensed tannins, alternatively named proanthocyanidins or leucoanthocyanidins, originate from flavan-3-ols and are oligomeric forms of flavan-3,4-diols. These are predominantly linked by carbon-carbon bonds, though carbon-oxygen-carbon linkages may also occur, contributing to their significant structural heterogeneity. Under acidic alcoholic conditions, condensed tannins break down, yielding a pigment known as phloroglucinol.<sup>42,43</sup>

## Coumarins

Coumarins consist of a 1,2-benzopyranone skeleton ( $\alpha$ -chromone), often existing in isoprenylated forms. Coumarin derivatives, as secondary metabolites, are naturally present in over 150 plant species across more than 30 plant families. Depending on their chemical composition and structural characteristics, natural coumarins can be classified into various categories, including but not limited to furanocoumarins, simple coumarins, biscoumarins, isocoumarins, pyranocoumarins, and phenylcoumarins.<sup>44</sup> The coumarin core is often used as a template for synthesizing various pharmacologically important novel compounds, such as scopolamine, serpentine, phloroglucinol, etc.

## Research on the Antitumor Activity of Polyphenolic Compounds

Essential architectural elements that contribute to the anticancer efficacy of phenolic compounds encompass the presence of aromatic ring systems, unsaturated side chains, and the quantity and spatial arrangement of unsubstituted hydroxyl moieties. In studies of structure-activity relationships, key functional groups that confer potent antitumor effects on phenolic compounds include aromatic rings and hydroxyl groups. Compounds with more hydroxyl groups exhibit superior antitumor activity compared to those without hydroxyl groups or those containing  $-\text{OCH}_3$  moieties.<sup>45</sup>

The anticancer mechanisms of polyphenols are multifaceted, encompassing the initiation of cell cycle halt, manifestation of antioxidant properties, enhancement of pro-oxidant actions, and suppression of specific kinases and enzymes that lead to the modulation of intracellular signaling pathways. Additionally, they impede angiogenesis, exert anti-estrogenic effects, curb cell proliferation, and possess immunomodulatory and anti-inflammatory capabilities.<sup>46</sup> The strength of polyphenols as anti-neoplastic agents is predominantly due to their antioxidant potential. They also act as potent scavengers of free radicals, chelators of metal ions, and modulators of the body's innate defenses, including enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), as well as regulators of the glutathione (GSH) redox cycle and various proteins and transcription factors like nuclear factor erythroid 2-related factor 2 (NRF2). Furthermore, their antitumor efficacy is characterized by the inhibition of cell proliferation markers (such as extracellular signal-regulated kinase, cyclin D, cyclin-dependent kinases, angiogenic factors, vascular

endothelial growth factor, oncogenic signaling cascade proteins, and protein kinase B), the induction of programmed cell death (apoptosis), and the prevention of cell migration and metastatic processes.<sup>47</sup>

## Antioxidant Activity

Within the context of cancer cells, reactive oxygen species (ROS) are integral to the modulation and initiation of apoptosis, exerting a pivotal influence on the regulation of cancer cell expansion, viability, and chemoresistance. Tumor hypoxia, a condition arising when the tumor vasculature fails to sufficiently nourish the proliferating mass, also leads to an escalation in ROS concentration. ROS, acting as intracellular signaling molecules, can inflict harm upon cellular macromolecules such as DNA, RNA, and proteins when in surplus. The consumption of polyphenolic compounds has demonstrated a significant protective role against ROS-induced damage and other reactive species within the human body, primarily due to their robust antioxidant capacity. Polyphenols mitigate ROS through a variety of pathways, which include 1) Engaging in direct radical scavenging, neutralizing both free radicals and diverse ROS species, including superoxide and peroxynitrite; 2) Exerting metal-chelating actions, thereby diminishing the catalytic potential of metal ions in ROS generation; 3) Augmenting the activity of intrinsic antioxidant defenses, such as the synthesis of superoxide dismutase (SOD) and glutathione (GSH); 4) Suppressing the activity of enzymes that generate ROS within the cell, including xanthine oxidase, myeloperoxidase, and NADPH oxidase. This multi-pronged approach by polyphenolic compounds contributes to their efficacy in countering oxidative stress and supports their potential utility in cancer therapy and prevention. Flavonoids exert fundamental antioxidant mechanisms by reacting with free radicals, which forms more stable, less reactive radicals. The antioxidant capacity of polyphenolic compounds stems from several structural features, such as the hydroxyl groups on the B-ring and the conjugated 2,3-double bond with the 4-oxo functional group in flavonoids, which can reduce ROS. Umbelliferone exhibits anticancer activity against human oral cancer (KB) cell lines, which was found to be associated with the ROS mediated mitochondrial depolarization.<sup>48</sup> Meanwhile, studies demonstrate the ability of flavonoids to prevent cardiomyocyte apoptosis, supporting their anti-apoptotic function under oxidative damage. Fruits and vegetables rich in anthocyanins and other flavonoids (such as quercetin, rutin, apigenin, etc.) significantly improve myocardial antioxidant status in models of drug-induced (doxorubicin), ischemia-induced heart dysfunction and alleviate the oxidative related damages in other organs.<sup>49–51</sup> A plethora of research indicates that a diverse array of polyphenolic compounds and botanical extracts abundant in these constituents exert beneficial impacts on cardiovascular health. They achieve this by modulating oxidative stress at the cellular level, mitigating inflammatory responses, and influencing a spectrum of intracellular signaling cascades. Specifically, flavonoids have been observed to counteract oxidative stress in myocardial tissues. They accomplish this by suppressing the generation of reactive oxygen species (ROS) intrinsic to the cell, reducing the expression of inflammatory cytokines, and ameliorating the function of the mitochondrial respiratory chain. These actions collectively contribute to the cardioprotective effects of flavonoid-rich substances.

## Cell Signal Regulation and Apoptosis

Cancer arises from imbalances and aberrant mechanisms in the apoptotic pathways. Apoptosis, a programmed cell death, responds to various signals of intracellular damage and is crucial for tissue homeostasis. The condition is distinguished by the presence of bleb-like protrusions on the cell membrane, a reduction in cellular volume, disintegration of the nucleus, and fragmentation of chromosomal DNA.<sup>34</sup> The B lymphocyte leukemia/lymphoma-2 (Bcl-2) family regulates cell behavior through programmed cell death, primarily located on the outer mitochondrial membrane, chiefly regulating the release of cytochrome C. Apoptosis eliminates misplaced cells, effectively inhibiting the occurrence of metastatic dissemination. Thus, apoptosis plays an irreplaceably important role in preventing cell metastasis. Whether malignant cells evade the apoptotic process determines the success of metastasis. Resistance to apoptosis is essential for all steps of metastatic progression. Polyphenolic compounds modulate key components of the extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK), and protein kinase B (AKT) signaling pathways, demonstrating significant anticancer properties. Their efficacy is notable in aggressive breast malignancies, including the challenging triple-negative breast cancer subtypes.<sup>52</sup> In human breast cancer cells MCF-7, quercetin induces apoptosis by increasing the expression of the pro-apoptotic gene Bax.<sup>53</sup> Kaempferol induces DNA fragmentation and enhances the expression of

the tumor suppressor gene p53, blocking the transmission of cell proliferation signals, thereby inducing cells to undergo self-apoptosis.<sup>54</sup> Simultaneously, kaempferol effectively activates the MAPK cascade, a critical signaling pathway for normal cell proliferation, survival, and differentiation, and simultaneously activates the MEK1 and ELK1 pathways to reduce cell adhesion, migration, and invasion.<sup>55</sup> Curcumin is capable of inhibiting the proliferation of cervical cancer cells, which is associated with the suppression of transcription factors such as nuclear factor kappa B (NF- $\kappa$ B).<sup>56</sup>

## Transporter Regulation

Resistance to pharmaceuticals poses a significant impediment to the enduring efficacy of clinical cancer treatments. The phenomenon of multidrug resistance (MDR) arises when both microbial and cancerous cells develop an acquired imperviousness to a diverse array of chemotherapeutic agents that vary in chemical composition and functional mechanisms. The ATP-binding cassette (ABC) transporters represent a vast superfamily of proteins, comprising 49 distinct members, categorized according to genetic sequence and structural homology.<sup>57</sup> Notably, a subset of at least 11 ABC transporters, such as P-glycoprotein (P-gp/ABCB1), multidrug resistance-associated proteins (MRPs/ABCCs including MRP1, MRP2, and others), and breast cancer resistance protein (BCRP/ABCG2), are implicated in the emergence of MDR. Specifically, ABC transporters like P-gp and MRP can exhibit heightened expression levels in cancerous cells, resulting in suboptimal intracellular drug concentrations that fall short of therapeutic requirements.<sup>58</sup> P-gp stands out as the most extensively studied efflux pump associated with MDR in cancer. Its subcellular localization and expression levels are believed to significantly influence MDR across various cancer types. Resistance to chemotherapeutic agents, including taxanes like paclitaxel, vinca alkaloids such as vincristine, and anthracyclines like daunorubicin, is a leading cause of mortality in the majority of patients afflicted with advanced cancer stages, accounting for over 90% of deaths in this population.<sup>59</sup> To overcome cancer resistance, alternative treatment strategies are necessary with combinations of drugs with natural molecules represent an excellent strategy. This strategy not only effectively overcomes cancer resistance but also contribute significantly to increased antitumor action and reduced systemic toxicity.<sup>60</sup> The structural features of flavonoids give them strong affinity for P-gp, positively impacting the inhibition of P-gp, MRP1, MRP2, and BCRP.<sup>61</sup> The anticancer and chemosensitizing activities of quercetin has been demonstrated in vitro and in vivo tests.<sup>62</sup> Quercetin isolated from ginkgo leaves was shown to significantly inhibit ATPase activity, thus strongly inhibiting the transport of Hoechst-33342 (a fluorescent probe and P-gp substrate).<sup>63</sup> Rutin, structurally similar to quercetin, significantly decreases the accumulation of P-gp substrates in the human colon adenocarcinoma cell line LS180 and reduces the bioavailability of cyclosporine by decreasing P-gp activation.<sup>64</sup> Catecholamines, tannic acid, curcumin combined with doxorubicin (DOX) can enhance the sensitivity of MDR cells to DOX.

## Influence on Microbiota

Studies indicate that the microbial metabolism of polyphenols is associated with cancer prevention, with differences in gut microbiota levels observed between patients with colorectal cancer and healthy individuals.<sup>65</sup> In vitro and specific microbiota studies in rats suggest that lignans can transform the gut microbiome consortium. Furthermore, symbiosis with the lignan microbiota community protects germ-free rats from 7,12-dimethylbenz[a]anthracene-induced cancer, significantly reducing tumor numbers, sizes, and cellular proliferation while increasing tumor cell apoptosis.<sup>66</sup> Certain polyphenols may also affect bacterial metabolic enzymes, influencing overall cancer risk. Resveratrol, a stilbene compound, is a treatment for colon cancer and exerts anti-inflammatory effects. In rat models, supplementation with resveratrol significantly reduced the activity of fecal and host colonic mucosal enzymes and decreased bacterial enzyme activity, resulting in a significant reduction in the incidence of colonic tumors.<sup>67</sup>

## Multifunctional MPNs in Cancer Therapy

The variability of polyphenols and metals endows composite materials with unique characteristics and capabilities. A hallmark of most polyphenolic compounds is the presence of catechol groups within their molecular architecture, which offer specific binding sites for metal ions. The phenolic hydroxyl functionalities and aromatic ring structures of polyphenols facilitate their interaction with a range of metal ions, as well as other molecules and substrates, through both covalent (eg, Michael addition, Schiff base formation, and coordination chemistry) and non-covalent (eg, hydrogen

bonding,  $\pi$ - $\pi$  stacking, and electrostatic forces) interactions.<sup>25,68–72</sup> The formation of metal-polyphenol coordination polymers arises from the synergistic combination of metal ions with phenolic ligands. The metal ions bring a spectrum of attributes to these polymers, including electronic, optical, radioactive, magnetic, and catalytic properties, which render MPNs as unique nanoplatforms suitable for applications in imaging and therapeutics.<sup>29</sup>

MPNs exhibit many superior properties in biomedicine due to their unique and novel structures, including adhesiveness, multifunctional drug-loading capabilities, stimulus-responsive dissociation, high photothermal conversion efficiency, and Fenton reaction activity.<sup>73</sup> The variety of metal ions and polyphenols allows for the creation of nanomaterials with different shapes and functions, enabling flexible integration of various therapeutic modalities.

## Delivery of Chemotherapy Drugs

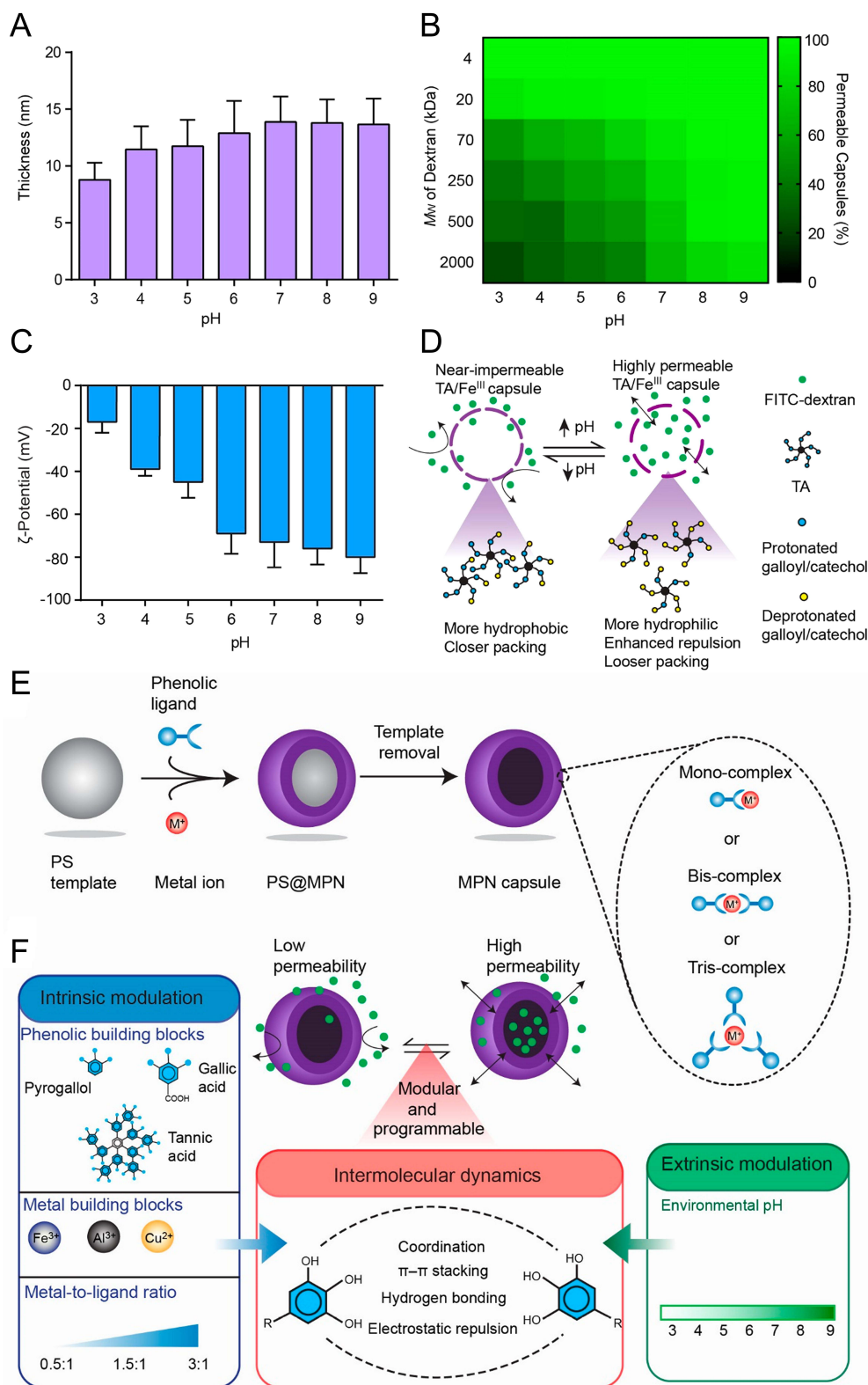
Compared to free drugs, nanodrug offer numerous advantages.<sup>74</sup> They protect drugs from degradation during in vivo transport, control drug release in specific areas or cells in response to specific signals, increase specificity for tumor targeting, reduce cytotoxic side effects on normal cells, decrease systemic side effects, increase drug solubility, and augment maximum tolerated doses.<sup>75</sup> Nanodrugs with covalent bonds are stable in the circulatory system, but excessive stability may hinder drug release within the body. Additionally, covalently-based nanodrugs involves numerous chemical reactions and toxic reagents, with low reproducibility due to complex preparation procedures, potentially affecting drug activity.<sup>76</sup> An alternative strategy uses non-covalent interactions to construct nanomaterials through supramolecular self-assembly, mainly involving non-covalent interactions such as hydrophobic, electrostatic, and hydrogen bonding.<sup>77</sup> However, non-covalent bonds can be somewhat unstable, leading to the disruption and leakage of nanodrugs after entering the complex circulatory system, potentially harming normal tissues and failing to achieve desired therapeutic outcomes.<sup>78</sup> Recently, strategies utilizing metal-ion coordination to guide the self-assembly of different organic molecules have attracted considerable attention. Since coordination bonds exhibit stability intermediate between strong covalent bonds and weak non-covalent interactions, they maintain stability in complex in vivo environments while possessing dynamic behavior. The porous structure of MPNs offers favorable conditions for loading chemotherapy drugs.<sup>28,79–81</sup>

Caruso et al<sup>82</sup> developed MPN-based capsules featuring a responsive gating system, modulated by adjusting intermolecular forces. These capsules are sensitive to pH fluctuations between 4 and 9, enabling reversible “closed” to “open” state changes, which in turn allow for the precise management of drug encapsulation and release kinetics, as depicted in Figure 2. In another study, Gang et al<sup>83</sup> fabricated a delivery system for cabazitaxel (Cab), integrating MPNs with chitosan (CS) to enhance Cab delivery efficacy in melanoma therapy. The application of a CS layer resulted in an elevated drug payload, rising from 7.56% to 9.28%. The Cab@MPN/CS system was shown to release Cab in a sustained manner within the acidic TME, effectively inhibiting melanoma growth in both cellular and animal models.

## Photothermal Therapy

Photothermal therapy (PTT) is an emerging, widely applied treatment modality in oncology, offering advantages such as high selectivity, low invasiveness, and minimal side effects. PTT mechanisms primarily involve the selective enrichment of photothermal agents (PTAs) in tumor tissues, converting absorbed near-infrared light into localized heat to kill cancer cells.<sup>84,85</sup> However, traditional PTAs have limitations due to poor biocompatibility, low photothermal conversion efficiency, and complex synthesis processes.<sup>86</sup> In contrast, MPNs with exceptional photothermal conversion efficiency, good photothermal stability, and biocompatibility hold greater promise and warrant further investigation. Combining PTT with other treatments, such as chemotherapy, can produce synergistic effects, significantly enhancing the efficacy of chemotherapeutics. Moreover, PTT can facilitate the release of chemotherapeutics upon near-infrared light stimulation, amplifying their antitumor effects.<sup>87,88</sup> MPNs are excellent photothermal materials due to their versatile and superior physical-chemical properties. The mechanism may be attributed to the coordination interaction between metal ions and polyphenols in MPNs, leading to the splitting of metal ions' d-orbitals and d-d electron transitions, resulting in new absorption peaks. Given that the d-d electron transitions of metal ions are largely determined by the nature of their ligands, the near-infrared (NIR) absorption capability can be controlled through judicious design of coordinating ligands.<sup>89</sup> Feng et al<sup>90</sup> systematically explored the photothermal capabilities of MPNs induced by various metal ions, including  $Gd^{3+}$ ,  $Ru^{3+}$ ,  $Fe^{3+}$ ,  $Cu^{2+}$ ,  $Ni^{2+}$ ,  $Mn^{2+}$ , and  $V^{3+}$ . Under near-infrared 808 nm laser irradiation, the temperature of





**Figure 2** (A) Graphical representation of the wall thickness for MPN MPN capsules fabricated across a pH range of 3 to 9. (B) A heatmap depicting the permeability of capsules to FITC-dextran across a molecular weight spectrum of 4 to 2000 kDa at varying pH levels; the assessment was based on 100 capsules per pH condition. (C) The  $\zeta$ -Potential measurements of MPN capsules dispersed under a range of pH environments. (D) A conceptual model illustrating the influence of pH on the permeability characteristics of the capsules. (E) A stepwise schematic outlining the fabrication of an MPN film on a polystyrene template particle, resulting in the formation of a PS@MPN construct, and the subsequent generation of an MPN capsule post-template elimination. (F) A diagrammatic representation of the process to programmatically regulate the permeability of MPN capsules by manipulating intermolecular interactions through a combination of intrinsic properties and extrinsic factors. Reprinted with permission from Chen J, Pan S, Zhou J, et al. Programmable permeability of metal-phenolic network microcapsules. *Chem Mater.* 2020;32(16):6975–6982. Copyright 2020, ACS Publications.<sup>82</sup>

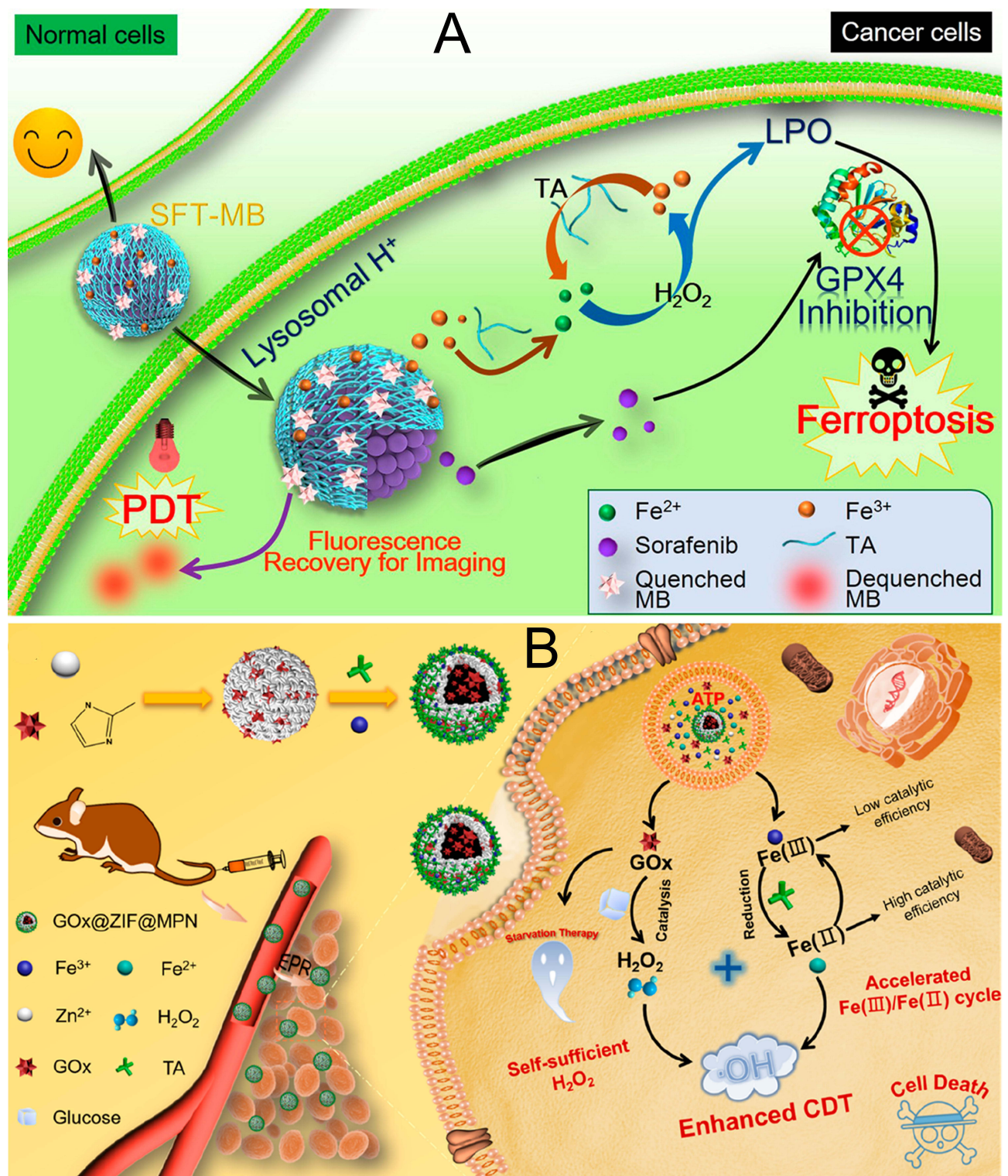
200 µg/mL Fe-TA nanoparticles increased by approximately 44.5 °C above water's 3.8 °C. Further measurements showed that V-TA and Ru-TA nanoparticles exhibited broad absorption in the near-infrared window and near-infrared-activated photothermal conversion. Gd<sup>3+</sup>, Cu<sup>2+</sup>, Ni<sup>2+</sup>, and Mn<sup>2+</sup>-based MPNs also showed broad absorption. Chen's team<sup>91</sup> developed a nano-complex FeAP-NPs using natural cyanidin (CAN), Fe<sup>3+</sup>, and PLG-g-mPEG. Photothermal conversion assays demonstrated that FeAP-NPs exhibited photothermal heating efficacy that was contingent upon their concentration upon irradiation with an 808 nm laser. Following five sequential photothermal cycles, the temperature elevation profiles were found to be nearly indistinguishable from one another, thereby validating the superior photothermal stability of FeAP-NPs. These nanoparticles also displayed exceptional dual-modal photoacoustic (PA) and magnetic resonance (MR) imaging properties coupled with high photothermal conversion efficiency. In vivo studies conducted on mice bearing MCF-7 tumors resulted in the complete eradication of the tumors upon PTT treatment.

## Chemodynamic Therapy

Chemodynamic therapy (CDT) refers to an emerging in situ treatment strategy utilizing Fenton or Fenton-like reactions to generate hydroxyl radicals ( $\cdot\text{OH}$ ) at the tumor site. Compared to chemotherapy, CDT offers significant advantages, which includes high locality and selectivity, and initiation by endogenous stimuli.<sup>92–97</sup> Ferroptosis is a non-apoptotic form of cell death induced by iron-mediated lipid peroxidation accumulation, causing lipid peroxidation and membrane damage.<sup>98</sup> Ferrous ion (Fe<sup>2+</sup>) can directly catalyze H<sub>2</sub>O<sub>2</sub> decomposition into  $\cdot\text{OH}$  through the Fenton reaction, promoting intracellular ROS accumulation and lipid peroxidation.<sup>99</sup> Excessive free Fe<sup>2+</sup> can directly or indirectly promote lipid peroxidation, making iron overload and triggers ferroptosis. Ferric ions (Fe<sup>3+</sup>) are stable and can react with many chemical drugs to form complexes with small particle sizes, exhibiting good stability in the body. However, the catalytic activity of Fe<sup>3+</sup> is much lower than that of Fe<sup>2+</sup>. To address this bottleneck, in many studies, Fe<sup>3+</sup> serve as precursors to chelate with chemical drugs upon in vitro assembly while transferring into Fe<sup>2+</sup> in vivo for ferroptosis therapy. Liu et al<sup>100</sup> combined ferroptosis inducers, iron ions, and an excess of acid-activated reductant for concurrent drug delivery to tumors with continuously supplying exogenous Fe<sup>2+</sup>. Specifically, Fe<sup>3+</sup> was self-deposited onto sorafenib (SRF) along with tannic acid (TA), forming a core-shell structured nanocrystal SRF@FeIII. TA, acting as an activated reductant, reduced Fe<sup>3+</sup> to Fe<sup>2+</sup> within the lysosomes of tumor cells, initiating the Fenton reaction, while SRF inhibited glutathione peroxidase GPX4 (Figure 3). However, due to limited H<sub>2</sub>O<sub>2</sub> availability and low catalytic efficiency, the Fenton reaction often falls short of expectations. Numerous MPNs designed to catalyze Fenton reactions have emerged. Zhang et al<sup>101</sup> synthesized an ATP-responsive self-catalytic Fenton nanosystem (GOx@ZIF@MPN) for tumor ablation. Overexpression of ATP in tumor cells led to the degradation of the MPN-coated GOx@ZIF@MPN complex, releasing Fe<sup>3+</sup> and TA, exposing the internal GOx complex. Subsequently, GOx reacted with endogenous glucose to produce abundant H<sub>2</sub>O<sub>2</sub>, followed by TA reducing Fe<sup>3+</sup> to Fe<sup>2+</sup>, generating toxic  $\cdot\text{OH}$  via H<sub>2</sub>O<sub>2</sub> catalyzation through Fe<sup>2+</sup>. The Fe<sup>3+</sup> was rapidly reduced to reactive Fe<sup>2+</sup> under TA mediation, forming an accelerated Fe<sup>3+</sup>/Fe<sup>2+</sup> conversion, ensuring effective CDT mediated by the Fenton reaction. Zheng et al<sup>102</sup> formed MPNs on the surface of PEI/p53 complexes through chemical bonding between TA and Fe<sup>3+</sup>, successfully preparing MON-p53 complexes. The prepared complexes could effectively enhance the ferroptosis-inducing effect of p53 through MON coating, holding great potential for application.

## Biomedical Imaging

In the recent past, the utilization of nanomaterials for imaging purposes has garnered significant interest in the medical field for diagnosing and treating a spectrum of conditions. Standard imaging techniques encompass photoacoustic imaging (PAI), positron emission tomography (PET), computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US).<sup>103–105</sup> The realm of MRI contrast agents extends from paramagnetic molecular complexes to nanoscale materials embedded with such complexes, as well as inorganic magnetic nanomaterials. The synergistic integration of the distinctive attributes of metal ions with the adaptable network structures of nanomaterials facilitates the convergence of diagnostic and therapeutic applications. Frequently employed magnetic metals ions such as Mn<sup>2+</sup>, Gd<sup>3+</sup>, and Fe<sup>3+</sup> can engage in coordination with polyphenols, yielding MPNs suitable for biomedical imaging. These imaging modalities are favored for their minimally invasive nature, heightened sensitivity, precise spatial resolution, and the ability to penetrate deeply into tissues, attracting considerable attention from researchers in the field. They overcome drawbacks of conventional small molecule contrast agents, such as high cytotoxicity, poor photostability, and inadequate



**Figure 3** (A) Schematic Illustration of SFT-Mediated Combination of Ferroptosis and Image-Guided PDT. Reprinted with permission from Liu T, Liu W, Zhang M, et al. Ferrous-supply-regeneration nanoengineering for cancer-cell-specific ferroptosis in combination with imaging-guided photodynamic therapy. *ACS Nano*. 2018;12(12):12181–12192. Copyright 2018, ACS Publications.<sup>100</sup> (B) Schematic Illustration of GOx@ZIF@MPN as an ATP-Responsive Autocatalytic Fenton Nanoparticle for Tumor Ablation. Reprinted with permission from Zhang L, Wan -S-S, Li C-X, Xu L, Cheng H, Zhang X-Z. An adenosine triphosphate-responsive autocatalytic Fenton nanoparticle for tumor ablation with self-supplied  $H_2O_2$  and acceleration of  $Fe(III)/Fe(II)$  conversion. *Nano Lett*. 2018;18(12):7609–7618. Copyright 2018, ACS Publications.<sup>101</sup>

biological stability. PET is a molecular imaging technique based on radioactive nuclides. Traditional PET contrast agents require additional chelators, whereas the polyphenols in MPNs have strong chelating abilities, allowing for rapid and easy binding with radioactive nuclides. Wang's research team<sup>106</sup> reported the formation of supramolecular nanoparticles (PPNPs) through self-assembly of TA and Poloxamer. PPNPs were synthesized through the interaction of TA with F-127. The phenolic hydroxyl groups present in TA engaged in hydrogen bonding with the ether oxygen atoms in the Polyoxyethylene segments of F-127. The hydrophobic nature of the Polyoxypropylene chains in F-127 facilitated the encapsulation of the near-infrared fluorescent dye IR780 within the PPNPs, allowing for near-infrared fluorescence (NIRF) imaging. Furthermore, the presence of numerous free -OH groups in the PPNPs enabled the chelation of the positron-emitting radioisotope  $^{89}\text{ZrIV}$ , forming stable O-Zr linkages. NIRF and PET imaging effectively detected tumors in mice bearing human breast cancer cell line tumors (SKBR3) overexpressing human epidermal growth factor receptor 2 (Her2). Additionally, nanoporous metal-phenolic granules (npFe<sup>III</sup>-TA RPs) and nanoporous CaCO<sub>3</sub> granules were prepared through self-assembly coordination of Fe<sup>3+</sup> and TA. Fe<sup>3+</sup> chelated in the npFe<sup>III</sup>-TA RP network catalyzed the conversion of H<sub>2</sub>O<sub>2</sub> to O<sub>2</sub>, serving as a reagent for US imaging.<sup>107</sup> Xie et al<sup>79</sup> developed a novel phototherapeutic MPN using phenolic semiconductor polymers and PEG-modified semiconductor polymers. Within this nanoscale construct, the Fe<sup>3+</sup>, an efficacious inducer of ferroptosis, was coordinated with the phenolic moieties present on the phenolic polymer backbone. To enhance the nanoparticles' surface properties, hydrophilic PEG polymers were integrated, endowing the nanoparticles with amphiphilic characteristics and resulting in the formation of PEGylated, polymer-encapsulated Fe<sup>3+</sup> Metal-Polyphenolate Nanoparticles (PF MPN). The hydrophobic exosome inhibitor GW4869 was embedded within the core of the PF MPN, serving the dual purpose of phototherapy and diagnostic imaging. Upon accumulation at the tumor site, the PF MPNs demonstrated enhanced NIRF and PA imaging capabilities under the influence of near-infrared laser irradiation.

## Synergistic Therapy

From the aforementioned summary, MPNs can be flexibly designed into multifunctional, multi-pathway nanosystems for cancer diagnosis and therapy. For instance, Yao's team<sup>108</sup> developed a combinatorial therapy using DOX as a chemotherapeutic agent, ferric chloride (FeCl<sub>3</sub>) as a ferroptosis inducer, and TA as an activator for the SOD-like reaction in intracellular cascades, for breast cancer treatment. DFTA nanoparticles, with dimensions of  $106.4 \pm 0.7$  nm and an irregular nanomesh morphology, were observed to generate a pronounced photothermal response upon aggregation. The release of the encapsulated drug from DFTA was demonstrated to be efficiently activated by photothermal stimulation. ELISA-based assays revealed that the combination of DFTA with laser irradiation significantly depleted intracellular GSH levels, an effect attributed to the intensified oxidative stress induced by ROS and the ROS-mediated PTT. Yu and colleagues<sup>109</sup> reported the self-assembly synthesis of Fe-GA@BSA nanoparticles, incorporating the chemotherapeutic agent SRF to create the Fe-GA@BSA-SRF nanomedicine. Experimental data suggested that this nanomedicine could trigger ferroptosis in cancer cells by enhancing the Fenton reaction. The inherent photothermal properties of Fe-GA@BSA-SRF were harnessed for mild thermotherapy to augment the ferrous therapy. The nanoformulation exhibited potent anticancer efficacy by inducing ROS production and suppressing the expression of glutathione peroxidase 4 (GPX4) in both in vitro and in vivo settings. Xu et al<sup>110</sup> described the development of a synergistic theranostic nanoplatform, which involved the in situ coordination of TA with Fe<sup>3+</sup> to form DOX-loaded TAF nanocomplexes. These were further functionalized with a fibronectin (FN) coating on the DOX-TAF surface through hydrogen bonding interactions, yielding DOX-TAF@FN nanocomplexes. This nanosystem integrated chemotherapy and CDT to activate immune responses, with the aim of enhancing tumor treatment efficacy. The therapeutic approach was further complemented by the use of an anti-PD-L1 strategy to target immune checkpoint blockade (ICB), thereby eliciting a robust immune response against the tumor.

## Conclusion and Perspective

The preceding sections reviewed the structure and classification of polyphenolic compounds, elucidated their mechanisms against tumors, introduced the application of MPNs formed by the chelation of polyphenols and metal ions in cancer therapy, and cited various studies on multifunctional MPNs. Generally, the construction of MPNs encompasses multiple antitumor pathways. These multifunctional MPNs exhibit potent antitumor capabilities, and depending on the type of

polyphenolic compound, metal ion, and surface coating, various tumor treatment strategies can be flexibly developed. As a critical component of the field of anticancer nanomedicines, the reticular porous structure of MPNs not only facilitates the construction of drug delivery systems suitable for conventional chemotherapeutics but also promotes the release of chemotherapy drugs at specific target sites, mitigating the various side effects associated with chemotherapy. With the advancement of nanomedicine, the role of MPNs in antitumor treatment has become increasingly prominent, encompassing light-mediated PTT, multimodal bioimaging, among others. Compared to traditional nanomaterial fabrication strategies, the coordination between metal-polyphenol compounds is relatively facile, requiring inexpensive and readily available raw materials, employing relatively simple equipment during the reaction process, and permitting adjustments. MPNs possess green, nontoxic, and pH-sensitive characteristics, displaying excellent photothermal performance, good tunability, and good biocompatibility.

Despite the demonstrated superior and broad biological properties of MPNs, they are still in the nascent stage, with many issues yet to be addressed. Further emphasis should be placed on integrating the carrier function of MPNs with the characteristics of the loaded drugs to achieve synergistic therapeutic effects, which goes beyond merely stacking several effects together. On another front, the stability of MPNs as carriers deserves significant attention. A sufficiently stable carrier can prevent damage to normal tissues and reduction in drug efficacy during drug delivery, but overly stable carriers may lead to difficulties in drug release. Therefore, the underlying mechanisms responsible for the stability adjustment of MPNs should be explored in future works. Moreover, regarding preparation strategies, in the design process of MPNs, more importance should be given to exploring the possibility of multifunctional platforms, including the integration of tumor targetability and TME responsiveness. Additionally, the biosafety of MPNs is also worthy of exploration for their further application into clinic.

## Declaration of Generative AI in Scientific Writing

In the composition of this manuscript, the authors have employed artificial intelligence tools, specifically Kimi and Tongyi QianWen, to refine the manuscript's prose. Following the application of these AI-based technologies, the authors have conducted a thorough review and revision of the manuscript content. The authors assume complete accountability for all aspects of the published work, ensuring that the final submission aligns with the highest standards of academic integrity and scholarly communication.

## Data Sharing Statement

Data will be made available on request from Hongbin Xu (drxu@njmu.edu.cn).

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## Disclosure

The authors report no conflicts of interest in this work.

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