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Innovations and challenges of polyphenol-based smart drug delivery systems

Yanan Wang[1,§], Jingwen Zhang[1,§], Yi Zhao[2], Minju Pu[1], Xinyu Song[1], Liangmin Yu[1] (✉), Xuefeng Yan[1], Jun Wu[2] (✉), and Zhiyu He[1] (✉)

[1] *Key Laboratory of Marine Chemistry Theory and Technology, Ministry of Education College of Chemistry and Chemical Engineering, Ocean University of China, Qingdao 266100, China*
[2] *School of Biomedical Engineering, Sun Yat-sen University, Shenzhen 518107, China*
[§] *Yanan Wang and Jingwen Zhang contributed equally to this work.*

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ABSTRACT

Polyphenols, as widely existing natural bioactive products, provide a vast array of advanced biomedical applications attributing to their potential health benefits that linked to antioxidant, anti-inflammatory, immunoregulatory, neuroprotective, cardioprotective function, etc. The polyphenol compounds could dynamically interact and bind with diverse species (such as polymers, metal ions, biomacromolecules, etc.) via multiple interactions, including hydrogen bond, hydrophobic, π–π, and cation–π interactions due to their unique chemical polyphenolic structures, providing far-ranging strategies for designing of polyphenol-based vehicles. Natural polyphenols emerged as multifaceted players, acting either as inherent therapeutics delivered to combat diverse diseases or as pivotal assemblies of drug delivery vehicles. In this review, we focused on the rational design and application of metal-phenolic network (MPN) based delivery systems, polyphenol-based coating films, polyphenol hollow capsules, polyphenol-incorporated hydrogels, and polymer-polyphenol-based nanoparticles (NPs) in various diseases therapeutic, including cancer, infection, cardiovascular disease, neurodegenerative disease, etc. Additionally. the versatility and mechanisms of polyphenols in the field of biomacromolecules (e.g., protein, peptide, nucleic acid, etc.) delivery and cell therapy have been comprehensively summarized. Going through the literature review, the remaining challenges of polyphenol-containing nanosystems need to be addressed are involved, including long-term stability, biosafety *in vivo*, feasibility of scale-up, etc., which may enlighten the further developments of this field. This review provides perspectives in utilizing natural polyphenol-based biomaterials to rationally design next generation versatile drug delivery system in the field of biomedicine, which eventually benefits public health.

KEYWORDS

polymer-phenolic nanoparticles, metal-phenolic network, metal-phenolic coatings, metal-phenolic hollow capsules, polyphenol–protein interactions

1 Introduction

Polyphenol is a general term for compounds with multiple hydroxyl groups in their molecular structure, including simple phenols with low molecular weight and highly polymerized polyphenols [1]. Polyphenols are secondary metabolites ubiquitously found in plants, particularly in plant barks, roots, woods, leaves, and fruits. They are extremely important and abundant compounds in nature with the second highest content, surpassed only by sugars, which have played pivotal roles in both plants and animals, including structural support and the oxidative stability to protect against ultraviolet (UV) radiation and pathogen invasion [2, 3]. According to the number and binding structure of phenol units, natural polyphenols can be classified into four major groups including flavonoids, stilbenes, lignans, and phenolic acids. Typical types include epigallocatechin gallate (EGCG), catechin, tannin acid (TA), ellagic acid (EA), gossypol, procyanidin, puerarin (PUE, 7,4′-Dihydroxy-8-C-glucosylisoflavone), etc. (Fig. 1) [4–7]. Polyphenols may provide health benefits, including antioxidant, anti-allergic, antimicrobial, immunoregulatory, anti-tumor, and myocardial protection activities, which therefore, are a good source of nutraceuticals for the application in the food and supplement industries. It is worth mention that ongoing researches on various phenolic molecules have indicated their potential in adjuvant therapeutic of various diseases, including cancer, diabetes, cardiovascular diseases, degenerative diseases, and among others [8–11]. As reported, excessive oxidative stress damage was identified major facilitator in the pathophysiology of inflammation, fibrosis, cancer, reperfusion injury, etc., which underlines the importance of antioxidant therapy [12–14]. Notably, the antioxidant properties of polyphenol provided by their redox characteristics have been described in detail in recent studies [15]. Concretely, the ortho phenolic hydroxyl in the phenolic hydroxyl structure of polyphenols (catechol or pyrogallol) is the main site of antioxidation and scavenging free radicals. The polyphenols could capture active oxygen and scavenge free radicals through the hydrogen atom transfer mechanism, endowing these components with robust antioxidant

Address correspondence to Zhiyu He, hezhiyu@ouc.edu.cn; Jun Wu, jw384@cornell.edu; Liangmin Yu, yuyan@ouc.edu.cn

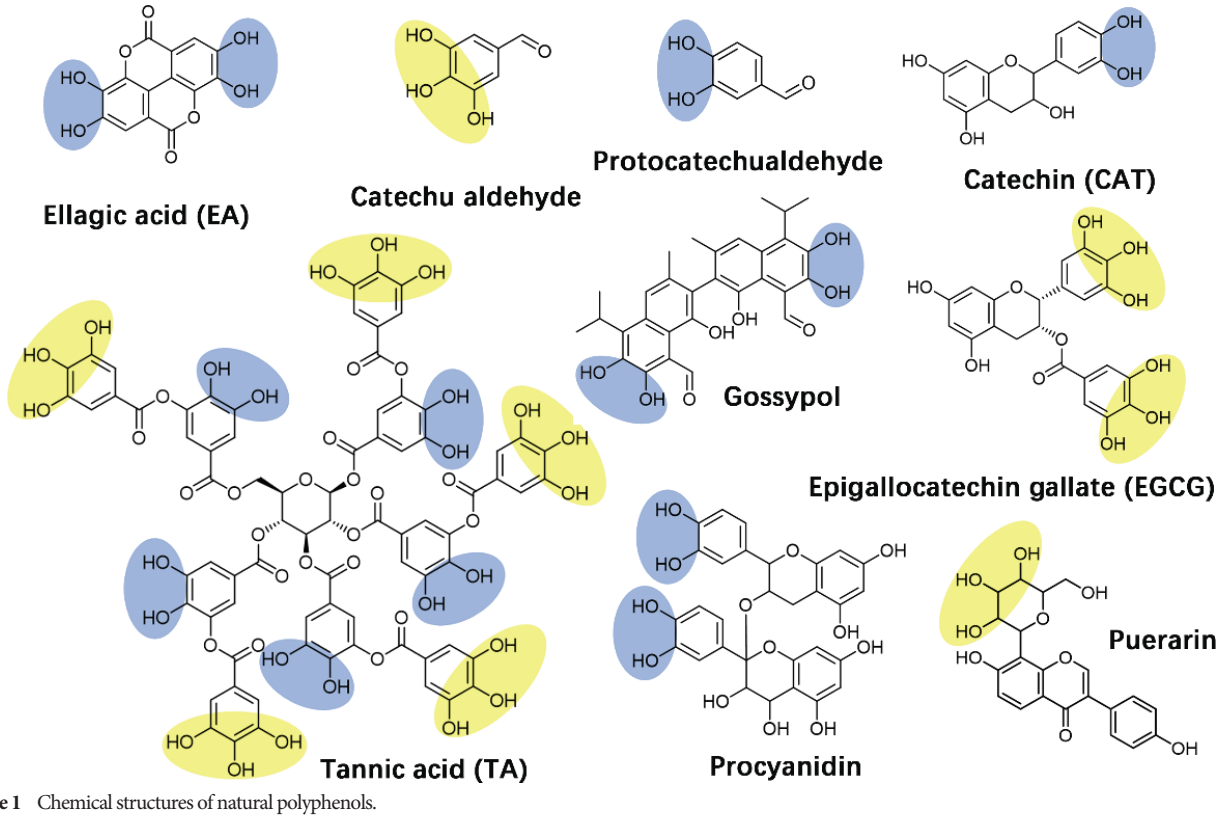

Figure 1 Chemical structures of natural polyphenols.

properties [16]. The incorporation of antioxidant polyphenol components into therapeutic strategies could help to maintain redox balance, ultimately restoring cell status. Additionally, several polyphenols have been reported to retard disease progression via modulating intracellular stress signaling pathways. For instance, catechins derived from green tea exhibit superb anti-tumor capability via interfering with multiple signaling pathways (e.g., mitogen-activated protein kinase (MAPK) signaling pathway, nuclear factor-kappaB (NF-κB) signaling pathway, etc.) and activating reactive oxygen species (ROS)-induced autophagy in tumor cells [17, 18]. Several polyphenols possess effective anti-tumor metastasis effect through multiple mechanisms, including restraining the transformation of epithelial cells into mesenchymal cells, down regulating the levels of matrix metalloproteinases (MMPs), anti-tumor angiogenesis, etc. Besides, some polyphenols play beneficial roles in preventing the progression of inflammation-related diseases by regulating immune cells populations as well as modulating cytokines and pro-inflammatory genes expression to regulate immunity and maintain tissue homeostasis [19, 20].

Apart from the diverse biofunctions, natural polyphenols have many unique physicochemical features due to their special structure of at least one benzene rings and one or more hydroxyl substituents. Notably, recent studies have indicated that these polyphenol compounds strongly interact and bind with diverse species (such as polymers, metal ions, biomacromolecules, small molecule compounds, etc.) via multiple interactions, including hydrogen bond, hydrophobic, π–π, cation–π interactions, etc., due to their unique chemical structures [21]. Concretely, polyphenol compounds can be used as suitable ligands to coordinate with a variety of metal cations (e.g., iron ions, zinc ions, copper ions, aluminum ions, manganese ions) for forming cyclic polyphenol-metal coordination complex [22, 23]. Additionally, because the oxygen atoms in hydroxyl groups are electronegative after the dissociation of hydrogen in aqueous solutions, polyphenols could bind with positively charged groups through electrostatic interactions [24]. Besides, the hydrophilicity from the phenolic hydroxyl groups, hydrophobicity from the benzene rings, and the electrostatic effects from phenolic oxygen atoms promote the strong interactions of polyphenol with biologically interesting molecules. Concretely, the abundant phenolic hydroxyl groups in polyphenols can be used as hydrogen bond donors/acceptors to form hydrogen bonds with carbonyl and hydroxy/amino moieties of proteins, respectively [25, 26]. For example, proline could specifically associate with polyphenols via the hydrogen bonds between these two components as well as the strong interaction between pyrrolidine ring of prolyl residues and aromatic ring of polyphenols. In addition, the planar aromatic nucleuses of polyphenols can form hydrophobic interactions with the hydrophobic sites of other biomacromolecules, such as proteins, chitosan, gelatin, etc. [27, 28]. In addition to the aforementioned non-covalent interactions, the catechol or pyrogallol moieties of polyphenol can conjugate with boronic acids via dynamic covalent linkage [29]. The specific acid cleavability and ROS-responsiveness of boronic ester bonds are benefit for the triggered release of drugs at the lesion when boronate-polyphenol complexation is used as building blocks for assembly [30, 31]. Based on the robust coordination between polyphenols and multiple molecules, polyphenol-inspired chemistry has opened new avenues for polyphenol-based surface functionalization, construction of self-assembled nanocomplexes, etc.

With the in-depth study on the inherent biological effects of polyphenols, the widely available interaction/combination of polyphenols with multiple species serves as building blocks for multiple functional nanomaterials, playing a pivotal role in the preparation of innovative drug delivery systems. Polyphenols are increasingly serving as components in small molecular drug delivery, protein/peptide delivery, gene delivery, hemostatic gel applications, etc., ascribing to their non-covalent/covalent interactions with small molecule compounds or biomacromolecules. Among them, polyphenols could interact with multiple metal ions via coordination reaction for the preparation of metal-phenolic network, surface coating, nanoparticles (NPs), and hydrogel [32]. Moreover, these natural polyphenolic components could also be utilized as coatings to

wrap or modify the surface of hydrophilic or hydrophobic vehicles via self-polymerization, thus improving drug loading content, release performance, endocytosis behaviors of carriers, etc. [33]. Besides, the polyphenols could also exert synergistic therapeutic effects with the payloads due to their inherent therapeutic properties [34]. In addition, polyphenol-based vehicles can provide other functions like targeting capability, stimulus-responsiveness, circulation stability, etc., through pre-functionalization of the assemblies and post-modification of the prepared vehicles.

Collectively, polyphenols have been increasingly used in the production of various biomedical materials. Benefiting from the excellent therapeutic effects and various physicochemical properties, polyphenols have achieved unprecedented development in the application of drug delivery. This review systematically introduces the application of these polyphenol-based carriers in the delivery of various small molecule drugs, proteins, peptide, gene drugs, etc., for multiple diseases treatment. By focusing on the design, synthesis of the polyphenol-containing materials, preparation processes of natural polyphenol-based carriers, and their pharmacokinetics, pharmacodynamics, drug biodistribution, biocompatibility, and therapeutic efficacy *in vivo* as well as biosafety, a comprehensive review on innovative polyphenol-based nanosystems in recent five years was provided. In addition, the advantages and disadvantages regarding the versatile polyphenol-based drug delivery systems were summarized in detail. The remaining challenges, including facile fabrication process in organic solvent-free aqueous medium, batch-to-batch reproducibility, long-term action safety, and feasibility of scale-up in pre-clinical applications were highlighted. This review provided an easily accessible guide for a diverse range of researchers active in the biomedical fields and promote the application of polyphenols.

2 Applications of natural polyphenols in small molecule drug delivery

2.1 Metal-phenolic network-based drug delivery systems

Metal-phenol network (MPN) is a supramolecular network mainly formed by the coordination of metal ions with polyphenols and the subsequent self-assembly process [35, 36]. The research of MPNs in the biomaterials science fields has achieved rapid progress, particularly in the application of MPNs in drug delivery systems including polyphenol coating on substrate surface, fabrication of MPNs-based nanoparticles and MPNs-based hollow capsules, etc. [37]. The pyrogallol group shared by most natural polyphenols could quickly chelate with metal ions (e.g., Fe^{3+}, Mn^{2+}, Al^{3+}, Gd^{3+}, and Cu^{2+}) to form MPNs, exhibiting a variety of catalysis, therapy, and imaging functions. In recent years, MPNs have become the focus of multi-functional drug delivery systems engineering due to its diverse potential advantages, including: (1) Excellent biocompatibility of polyphenol components makes the toxicity of the drug delivery systems negligible [38]; (2) good thermal stability, well controllable characteristics, high drug loading capacity, endosomal escape ability, as well as easy functionalization for stimulus-responsive drug release [39]; (3) inherent anti-inflammatory, anti-cancer, and antibacterial activities of polyphenol components promote the synergistic effects of the nanocarriers and therapeutic payloads [40]; (4) favorable adhesion capability is benefit for coating MPNs on a variety of nanomaterials to achieve multiple biofunctions [41]; (5) high photothermal conversion efficiency of MPNs provides a good basis for photothermal treatment of several diseases, including tumor, infection, etc. [42]; (6) easy fabrication processes provide the possibility of scale-up production [43]. The current progress of MPNs-based drug delivery systems in terms of materials, characterization, experimental models, and their mechanism of action was comprehensively summarized in Table 1.

2.1.1 Metal-phenolic coatings

By one-step mixing or multistep assembly, MPNs can wrap on the surface of various substrates (e.g., polymeric NPs, inorganic NPs, metal-organic frameworks, etc.) as multi-functional coatings, providing various biomedical functions and improving therapeutic outcome [44]. Single or multilayer MPNs can be anchored on the surface of various substrates through strong interfacial bonding or self-polymerization under enzymatic or alkaline pH conditions, respectively [45, 46]. Owing to those superior properties, e.g., flexible structures, pH responsive capability, mechanical stability, photothermal conversion ability, improved drug loading capacity, and tunable drug release kinetics, the MPN coating has aroused interests from researchers.

MPNs possess favorable treatment effect due to inherent biomedical activities of polyphenol materials (e.g., anti-inflammatory, antioxidant, immunoregulatory effect, etc.), which is conducive to achieving multimodal combination therapy and improving therapeutic efficacy. For example, TA, a naturally abundant polyphenol, is used for anti-tumor and anti-tumor metastasis therapy, which can reduce tumor vascularization and blood metastasis through down-regulating MMPs level [39]. Besides, TA is listed as a food supplement in the list of the Generally Recognized as Safe (GRAS) by the Food and Drug Administration (FDA) [47]. Several TA-metal networks have been reported to gradually disassemble under acidic pH, thus TA-metal coatings are commonly formed on the surface of NPs for controlled release of drugs in slightly acidic solid tumor microenvironment (5.6–6.5). Taking TA-gadolinium ions (Gd^{3+}) MPNs as an example, Fan et al. utilized TA/Gd^{3+} network (monolayer thickness ~ 10 nm) as a versatile coating to deposit on the surface of doxorubicin (DOX, an anti-tumor drug)-loaded mesoporous silica nanoparticle (MSN). Au nanorod (Au NR, a photothermal agent) was used as the inner core for photothermal therapy (Fig. 2(a)(i)) [48]. The prepared multifunctional nanosystem integrated photothermal therapy and chemotherapy to achieve the combined treatment of primary and metastatic tumors. Notably, the complex formation constant between Gd^{3+} and TA is pH-dependent, that is, the protonation of TA in the acidic microenvironment of tumor led to the decomposition of MPN membrane, causing responsive release of payload and high accumulation of DOX in HeLa cells (Figs. 2(a)(ii) and 2(a)(iii)). The addition of TA/Gd^{3+} MPNs normalized tumor microenvironment and inhibited tumor invasion by constraining MMPs activity. Compared with the phosphate buffered solution (PBS) control group, subcutaneous (s.c.) injection of the as-prepared formulation significantly reduced primary tumor volume by 81% in BALB/c mice bearing highly malignant primary H22 tumors and decreased the number of metastatic lung nodes by 58% in highly metastatic cell line B16-F10-induced C57BL/6 mice tumor model (Figs. 2(a)(iv) and 2(a)(v)). Of particular relevance to this characteristic, it has been reported that the coordination bonding between Fe^{3+} and TA is pH-dependent, allowing the films to rapidly form and decompose in response to different pH. Concretely, the main coordination forms of Fe^{3+}-TA can be mutually transformed among mono-complex (pH < 2, just 1 galloyl group interacts with Fe^{3+}), bis-complexation state (3 < pH < 6, two galloyl groups coordinate to each Fe^{3+}), or tris-complex

Table 1 Metal-phenolic network-based small molecule drug delivery systems

Types of metal-polyphenol materials	Loaded small molecular drugs	Characterization	Mechanism	Experimental models	Biomedical application	References
Gd^{3+}-TA	DOX	Particle size: 150 nm; zeta potential: −29 mV	Realize the synergistic treatment by photothermal therapy of Au nanorod and chemotherapy of DOX; Gd^{3+}-TA provides tumor diagnosis ability	BALB/c mice bearing highly malignancy H22 tumors, C57BL/6 mice injected with B16-F10 cells (subcutaneous injection)	Primary and metastatic tumors	[48]
Fe^{3+}/Al^{3+}-TA	DOX	Particle size: 100 nm; loading content: 15.7%; encapsulation efficiency: 68.2%	Enable dual photothermal therapy and pH-stimulus-responsive chemotherapy; outstanding drug loading capacity	A549 cells	Tumor therapy	[60]
Fe^{3+}-EGCG	Phenolic platinum (IV) prodrug	Average size: 122 nm; loading content: > 30%	EGCG makes the tumor cells more sensitive to chemotherapy; cisplatin-based chemotherapy uses self-supply H_2O_2 for Fenton reaction to achieve chemical/chemical kinetic cancer treatment; the block copolymer (PEG-b-PPOH) containing a polyphenol segment prolongs the circulation time	HepG2 cells; HepG2 tumor-bearing nude BALB/c mice (intravenous injection)	Tumor therapy	[72]
Fe^{3+}-EGCG	DOX	Hydrodynamic sizes (different proportions of iron ions): 77.4, 126, and 296 nm; zeta potential: −20 mV	EGCG could inhibit the expression of CBR1 protein, thereby inhibiting DOX from producing metabolite doxorubicin, reducing drug resistance and cardiotoxicity; high ratio of PEG acts as an external barrier to extend half-life	U87MG cells and 293T cells; U87MG tumor mice (intravenous injection)	Tumor therapy	[76]
Fe^{2+}-gossypol	PEG-Ce6 polyphenol	Hydrodynamic diameter: 32.7 nm; zeta potential: −8.8 mV	High drug accumulation in tumor sites; the combination of chemotherapy and photodynamic immunogenic therapy; inhibition of tumor proliferation and metastasis	Murine triple-negative 4T1 breast cancer cells; 4T1 tumor-bearing BALB/c mice (intravenous injection)	Tumor therapy	[79]
Al^{3+}-TA	DOX	Loading content: 1.31 pg per capsule	pH-dependent degradability of capsules, intracellular drug delivery	HeLa and MB231 cell lines	Tumor therapy	[87]
Cu^{2+}-EGCG	N/A	Average diameter: 2.5 μm; surface charge: −15.8 eV; copper ion content: 8.1%	EGCG could improve the microenvironment in ischemic muscles and the Cu^{2+} could promote angiogenesis through physical interaction or expression/release of VEGF	HUVEC, LPS-stimulated RAW264.7 cells, ICR mice model of hindlimb ischemia (intramuscular injection)	Peripheral artery disease	[93]
Zn^{2+}-EGCG	N/A	Average diameter: 2–3 μm; surface charge: −15.3 eV; the proportion of zinc ion: 2.2%–8.8%	Promote angiogenesis and cell proliferation in ischemic tissues; sustained release of Zn^{2+} to reduce cytotoxicity	NIH 3T3, RAW264.7, and HUVEC cell line, mice model of hindlimb ischemia (intramuscular injection)	Limb ischemia	[94]
Fe^{3+}-EGCG	DOX	Size: 347.8 nm; zeta potential: −35.1 mV; loading content: 197 μg/mg; encapsulation efficiency: 72.7%	Intracellular drug release greatly accelerated in the ROS-abundant tumor environment	B16 cells, SMC cells, B16-bearing C57BL6 mice melanoma model (intratumoral injection)	Tumor therapy	[95]

state (pH > 7, 3 galloyl groups from TA react with each Fe^{3+}) under different pH conditions [49]. Notably, the pH-disassembly kinetics could be tailored by the type of different metal ion. For instance, the coordination of TA-Al^{3+} will gradually disassembly as the pH dropped from 7.4 to 5.0. According to their pH-sensitive coordination profile, MPNs could adapt their properties as a function of different pH microenvironments *in vivo* (e.g., blood (pH 7.4), stomach (pH 0.9 to 2.0), duodenum (pH 5.0 to 8.0), etc.).

In general, the endo/lysosomal endocytosis or degradation effects have been considered as the key "bottleneck" for intracellular on-demand payload delivery via functional nanoparticles. Active small molecules and biomacromolecules (e.g., proteins, peptide, and nucleic acid) can be easily degraded or cleared in acidified late endosomes (pH ~ 5.5), thus reducing bioavailability of therapeutic drugs [50, 51]. The current research progress in promoting the escape of NPs from endosomes mainly involves the utilization of cationic polymer or cell penetrating peptide, both of which have limitations of potential toxicity and complex synthesis/coupling process. Recent studies have shown that the protonation of phenolic molecules of MPNs in the acidic endo/lysosomal environments could trigger a large inflow of protons into the endosomes or lysosomes. Thereby, the large inflowing protons cause osmotic swelling and endo/lysosomal membrane rupture (namely "proton–sponge effects"), which are conducive to aiding the endosomal escape of functional nanoparticles [52, 53]. Based on the aforementioned characteristics, a MPNs coating (~ 10 nm thick) was rapidly assembled (< 30 s) by TA and metal ions (Fe^{3+} or Al^{3+}) and then deposited on different types of NPs, including mesoporous silica NPs and organic nanoparticles (polystyrene or melamine formaldehyde NPs) to yield NPs@MPNs [54]. The MPN coating buffers the lysosomal acidification and triggers the "proton–sponge effects" for destabilizing lysosomal membrane, which further promoted the endosomal escape of NPs (Fig. 2(b)(i)). The MPNs-coated NPs exhibited significantly reduced colocalization with endosomes in cells according to *in vitro* experiment, compared with that of the pristine NPs (Fig. 2(b)(ii)).

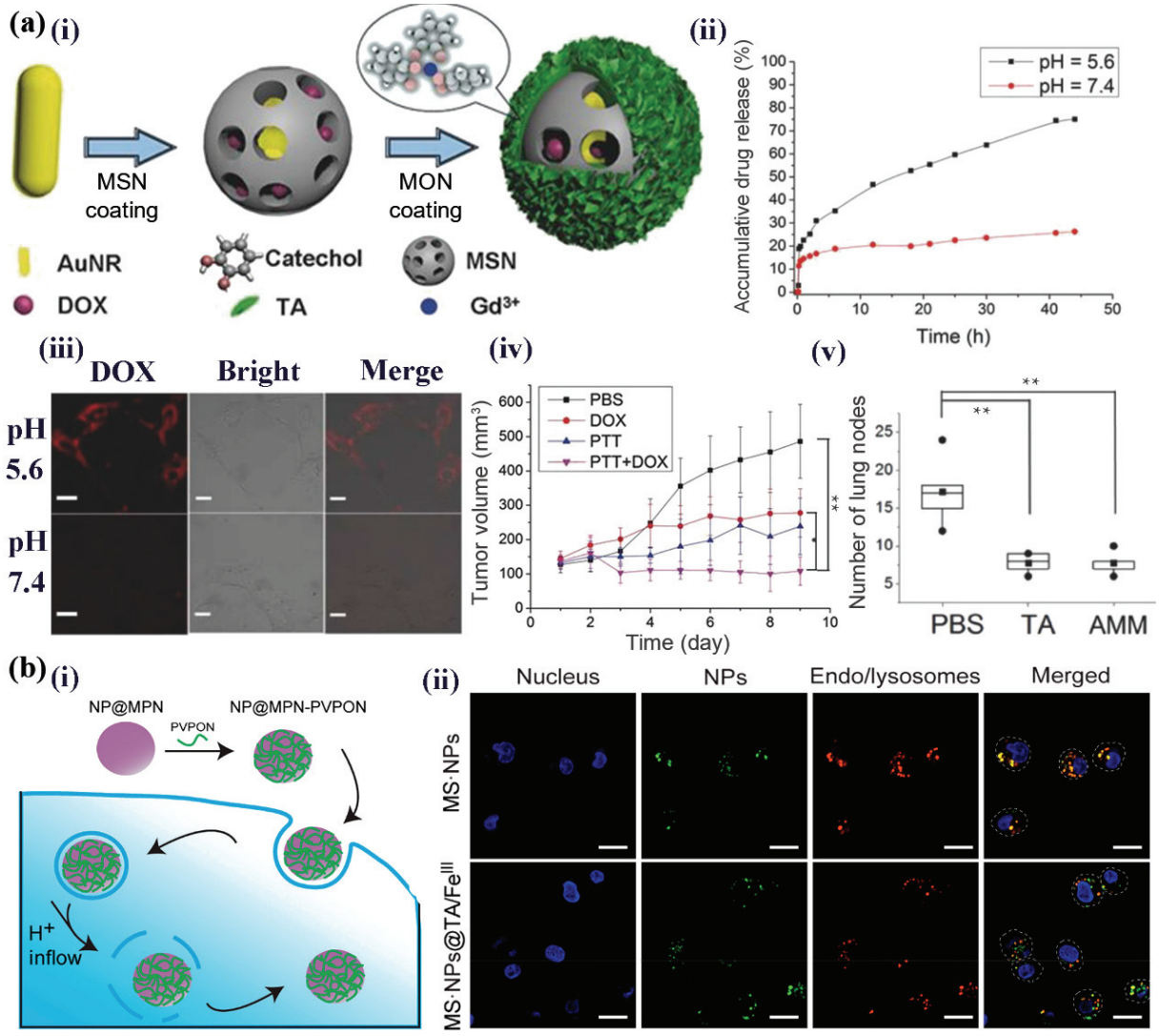

Figure 2 (a) (i) Schematic illustration of synthesis of TA/Gd^{3+} network-coated mesoporous silica nanoparticles that loaded with doxorubicin (DOX@AMM), (ii) drug release of the DOX@AMM in different pH, and (iii) confocal laser scanning microscopy (CLSM) images of DOX@AMM-incubated HeLa cells in different pH (scale bar: 10 μm). (iv) Relative tumor volume in a xenograft mice model of H22 cells after different treatments, (v) the number of tumor metastatic nodules in B16-F10-induced C57BL/6 mice tumor model after different treatments. Reproduced with permission from Ref. [48], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2017. (b) (i) Endosomal escape of PVPON-modified NPs@MPNs, (ii) representative merged CLSM images of MDA-MB-231 cells treated with MS·NPs or TA/Fe^{3+}-coated MS·NPs (scale bars: 20 μm). Reproduced with permission from Ref. [54], © American Chemical Society 2019.

Even the modification of a shielding layer of polymers (poly(N-vinylpyrrolidone), PVPON) can not impair their endosomal escape ability, suggesting the possibility of further functional modification of MPNs (Fig. 2(b)(i)). The inherent endo/lysosomal escape properties of MPNs are conducive to overcoming the endocytosis of therapeutic agents inside the endo/lysosome. Compared with gold standard material (poly(etherimide), PEI) to facilitate endosomal escape, the applied material TA that stands out the representative of polyphenols, does little influence toward cell viability. The facile preparation process, modifiability, and endosomal escape ability endow MPNs with great potential to more effective intracellular delivery of therapeutic drugs.

Notably, the TA components with hydroxyl-rich groups could strongly interact with the highly abundant proteins of the cardiac extracellular matrix (ECM) via hydrogen bonds and hydrophobic interactions [55]. Thus, the TA could be exploited as a targeting moiety for achieving on-demand cardiac drug delivery and enhancing the retention time of therapeutic drugs at the lesion. Torrieri et al. developed a spermine-acetalated dextran (AcDXSp) nanoparticles that coated by TA/Fe^{3+} film for myocardial infarction treatment [56]. Two hydrophobic drugs, p38 MAPK inhibitor and Wnt activator for stimulating the proliferation of cardiomyocytes, were encapsulated into the carriers. This nanosystem was highly retained in the cardiomyocytes attributing to strong affinity of TA for ECM. The presence of TA synergistically inhibited the expression of pro-fibrotic gene, showing potential benefits for cardiac tissue repair. Combining the anti-fibrotic capability of TA with anti-inflammatory property of two therapeutic agents that was able to induce cell proliferation, which eventually promote the cardiac function recovery after myocardial infarction.

Apart from the endosomal escape ability or tissue targeting capability of MPNs, recent studies have found that MPNs exhibited excellent photothermal conversion property that could convert near-infrared (NIR) light into heat [57, 58]. This may be attributed to the coordination effect between polyphenols and transition metals, causing d orbital splitting and subsequent d–d electron transitions, and thus generating the new absorption peak [59]. Yang et al. prepared pH and photothermal-responsive MPN-coated nanocomposites (MSN@MPN). The TA/metal ions (Fe^{3+} and Al^{3+}) MPN was deposited on the outer-shell layer of the negatively charged three-dimensional dendritic porous matrix that loaded with the positively charged model drug DOX via physical adsorption and electrostatic interactions [60]. MPN complex

serves as the photothermal conversion constitution as the temperature of MSN@MPN aqueous suspension under NIR laser irradiation increased with the coating time and number of the MPN coating layer. In particular, the temperature of MSN@MPN with four layers coating of MPN can increase up to 60.9 °C under NIR laser irradiation without affecting the release of drugs. This excellent photothermal property of MPN coating is conducive to killing tumor cells (high temperature of 42–47 °C exhibits killing effects on tumor cells). The as-prepared MSN@MPN achieved pH-responsive drug release in the acidic tumor macroenvironment (pH 5.0–6.0) with high cumulative DOX release (75.6% within 60 h) in contrast with the low drug release (less than 25%) in the neutral environment (pH 7.4), resulting in programmed apoptosis of tumor cells. This multifunctional pH-sensitive nanoplatform combined photothermal therapy and chemotherapy and produced a superb anti-tumor effect, showing potential for biomedical applications.

Recent studies have focused on the different biomedical applications of versatile forms of MPNs as surface coating nanomaterials. Utilizing the unique tunable physicochemical properties of MPNs, such as their optical property, pH-sensitive drug release property, inherent biomedical activities, photothermal conversion effect, etc., diverse MPNs coatings are expected to be widely applied in a range of disease treatments. However, there are remaining challenges for the biological applications of the metal-phenolic coatings. Firstly, MPNs coating is commonly exposed directly to physiological environments, which trends to form unexpected protein corona due to the non-specific interactions of polyphenols with biological molecules. To date, whether the long-term stability, therapeutic effects, or functional performance of MPNs coating could be influenced by the formed protein corona remains unexplored. Moreover, metal-phenolic coatings with different thicknesses can be produced via one-step or several steps assembly. Nevertheless, there are few studies on the potential influences of MPN films with different thicknesses on the functions of metal-phenolic coatings, bio-material interface interaction, and how to control biological processes. Finally, it would be of great significance to fully investigate the adhesion mechanism of different types of metal-phenolic coatings toward various surfaces as well as the MPN-mediated regulation of cell behaviors and biological processes, which are conducive to rational designing and synthesizing MPN coatings for specific functions.

2.1.2 *Metal-phenolic nanoparticles*

In addition to multi-functional coating, the MPNs can crosslink with various drugs based on electrostatic complexation, coordination complexation, etc. and further co-assemble into nanocomplexes for drug delivery [57, 61]. By virtue of their own inherent therapeutic effects and auxiliary effects on drug loading and responsive release, the MPNs-based nanocomplexes have been developed as a promising platform for various disease treatments.

Polyphenols could bind with several small-molecule anti-tumor therapeutics (e.g., DOX, paclitaxel) that contain hydrophobic or benzene structures via noncovalent interactions (π–π stacking and hydrophobic interactions), making polyphenols favorable carriers for anti-cancer treatment. Besides, the transition metal ion components, including Fe^{3+} or Cu^{2+}, can induce cyto-apoptosis by increasing toxic ROS through Fenton reactions. Combined with the anti-tumor effects of polyphenol and metal ions, the MPNs-based NPs could synergistically possess superb chemotherapeutic effects. Based on the excellent anti-cancer effect of natural polyphenols, several nanoparticle systems were prepared by coordinating polyphenols with metal ions (e.g., Fe^{2+}, Fe^{3+}, Gd^{3+}, Zn^{2+}, Mn^{2+}, etc.) for delivering anti-cancer drugs. Dai et al. designed a self-assembled ROS-enhanced platform, DOX@Pt/Fe^{3+} nanoparticles (DPPF NPs), to co-deliver anti-cancer drugs DOX and platinum prodrug for enhancing combinational chemotherapy. In this system, NPs were assembled by the coordination among platinum prodrug polyphenols, polyethylene glycol (PEG) polyphenols, Fe^{3+}, and hydrophobic DOX (Fig. 3(a)(i)) [62]. PEG polyphenols could prevent macrophage phagocytosis, improve surface shielding, and decrease the adsorption of NPs with serum components, thereby extending blood circulation time. The as-prepared formulation exhibited a preferable accumulation at the tumor site (Fig. 3(a)(ii)) and was internalized by cells through endocytosis. Then, the released DOX and platinum drugs induced the generation of toxic ROS, causing oxidative damage to tumor cells and thereby achieving superb anti-tumor effects (Fig. 3(a)(iii)) [63, 64]. Polyphenols not only act as chelating agents for the formation of DPPF NPs, but also further facilitate the conversion of $O_2^{\bullet-}$ to H_2O_2, significantly enhancing ROS production. Subsequently, the coordinated Fe^{3+} component could convert H_2O_2 into highly toxic HO• through Fenton reaction, thereby synergistically enhancing anti-tumor efficacy [65–67]. The group treated with this formulation demonstrated greater tumor growth inhibition, higher survival rates, prolonged survival time in comparison with that of free chemotherapy drug-treated group (Figs. 3(a)(iv) and 3(a)(v)). Similarly, in another study, the therapeutic platinum prodrug polyphenol derivatives and PEG-polyphenol derivatives were cross-linked with Fe^{3+} and further co-assembled into nanocomplexes through metal-polyphenol complexation in combination with emulsification, showing superb anti-tumor effects [68].

EGCG, a catechin monomer isolated from green tea, exhibits remarkable anti-inflammatory, antibacterial, and antiviral effects [69]. EGCG can affect the growth cycle of tumor cells and induce cell apoptosis with reduced organ toxicity. Besides, EGCG component in NPs has been reported to promote the internalization of loaded chemotherapy drugs (e.g., platinum drugs, anthracyclines, paclitaxel, etc.), being a favorable chemochaperone of anti-tumor agents, which exhibited great prospect in anti-cancer research [70, 71]. Ren et al. utilized Fe^{3+}, EGCG, phenolic platinum(IV) prodrug (Pt-OH), and pH-responsive polyphenol-modified PEG polymer to construct therapeutic nanodrugs (PTCG NPs) (Fig. 3(b)(i)) [72]. Due to the strong metal-polyphenol coordination, Fe^{3+}, EGCG, and Pt-OH were easily co-encapsulated by polyphenol-PEG polymer with high loading efficiency (> 90%). And the coordination also endowed PTCG NPs with a high mechanical stability in the blood circulation. Surface modification of PTCG NPs with PEG fragments forms a hydrophilic shell that evades the adsorption of proteins *in vivo*, thereby further prolonging blood circulation time. Cellular uptake rate of PTCG NPs was significantly higher than Pt-OH group under the optimal ratio of EGCG/Pt-OH (1:4) because the negatively charged Pt-OH was shielded by nanoparticles. Furthermore, the imine linker among the polyphenols and copolymer could be specifically cleaved under acidic and high glutathione (GSH) conditions. Thus, NPs achieved targeted-drug release with intratumoral level of platinum increased to 8.5%, which was 12.8 times higher than that of free cisplatin-treated mice post 24 h injection (Figs. 3(b)(ii) and 3(b)(iii)). Besides, the activation of Pt-OH into cisplatin further produced toxic ROS via Fenton reaction, resulting in strong anti-tumor effect and extending animal survival rate up to 40 days. In addition, metal Gd with imaging function can be doped into PTCG NPs for monitoring drug release behavior. With the satisfactory tumor accumulation, synergistic anti-tumor performance and excellent biocompatibility, MPNs-based NPs exhibited superb translational

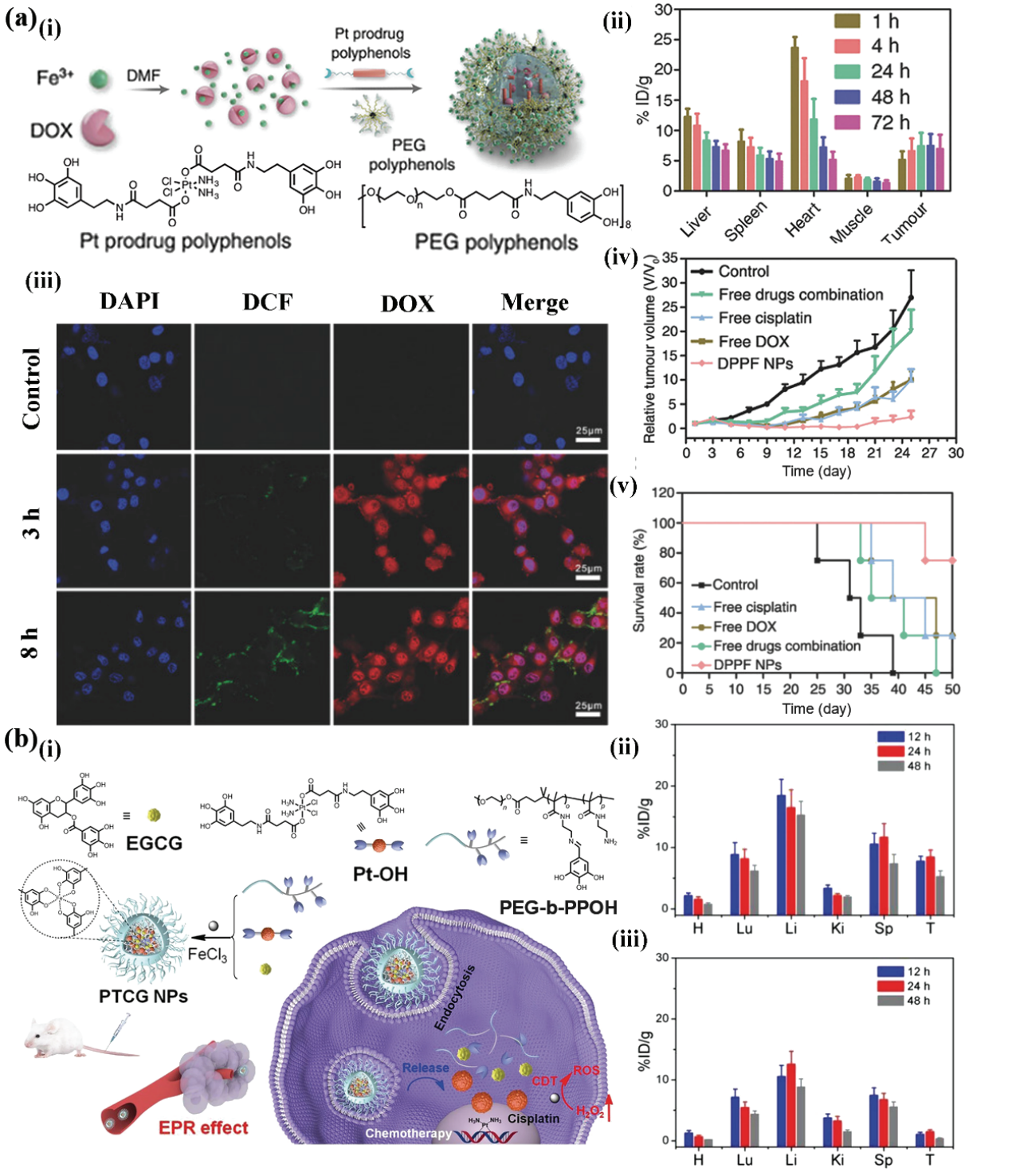

Figure 3 (a) (i) Preparation process of the self-assembled DPPF NPs, (ii) quantitative region of interest analysis of major organs post intravenous (i.v.) administration of DPPF NPs, (iii) ROS generation (green DCF probe fluorescence) and DOX release (red fluorescence) from DPPF NPs by confocal microscopy images, (iv) relative tumor volume, and (v) survival rate of tumor-bearing mice with various therapeutics. Reproduced with permission from Ref. [62], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2018. (b) (i) Chemical structures of EGCG, Pt-OH, PEG-b-PPOH and schematic illustration of PTCG NPs, (ii) tissue distributions of DPPF NPs, and (iii) tissue distributions of free drug cisplatin after i.v. injection, note: H, heart; Lu, lung; Li, liver; K, kidney; Sp, spleen; T, tumor. Reproduced with permission from Ref. [72], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2019.

potential compared with majority of traditional drug delivery systems. In summary, polyphenol and phenolic prodrugs could serve as chelators to assist the formation of NPs and substantially promote anti-tumor effects due to their inherent ROS generation enhancing properties and the abilities of inducing mitochondrial dysfunction, DNA damage, and tumor cell apoptosis.

Besides, the functional modification of polyphenol could be tailored to enhance the physiological stability of NPs in the blood circulation or achieve on-demand intracellular drug release [73, 74]. In sharp contrast to most traditional carriers, metal-ligand hybridization significantly promotes anti-cancer effects and enriches the therapeutic effects of resulting nanomedicines. For example, the bimetal-phenolic coordination polymer nanoparticles formed by Gd/Fe^{2+} and polyphenols can not only effectively inhibit tumor growth through photothermal therapy, but also enhance tumor signal to improve bioimaging capabilities [75]. In another study, exploiting the coordination chemistry between Fe^{3+} and polyphenols, Shan et al. integrated DOX, EGCG,

and PEG-polyphenol to form self-assembled nanoplatforms (FDEP NPs) (Fig. 4(a)(i)) [76]. DOX and EGCG were encapsulated in the core of the FDEP NPs, whereas the PEG polyphenol served as a physical barrier between the payload and external environments. EGCG components can inhibit the activity of overexpressed carbonyl reductase 1 (CBR1) in glioma cells to decrease the production of toxic metabolite doxorubicinol (DOXOL) of DOX, thereby reducing the drug resistance and cardiotoxicity. Based on the pH-dependent coordination between polyphenols and metals, the release of DOX and EGCG increased to 45.3% and 56.5% at acidic conditions (pH 5.5) comparing with slight release (13.0% of DOX and 16.6% of EGCG) at physiological environment (pH 7.4) after 48 h. FDEP NPs that prepared with different concentrations of Fe^{3+} all showed long-term stable circulation in the blood, reached a high tumor accumulation at 24 h in mice, while still remained high level at 72 h (Fig. 4(a)(ii)). Besides, the NPs prepared with lower volume of $FeCl_3$ showed the most prominent tumor growth inhibition rate reaching at 74.38% (Fig. 4(a)(iii)). Although the *in vivo* pharmacokinetic studies of this formulation have been discussed in detail, DOX loading capacity was not mentioned in this study, which makes it difficult to control the dosage of chemotherapeutic drugs during administration.

Gossypol, derived from natural cotton, can induce apoptosis in melanoma cell lines and colon cancer cell lines, and inhibit the tumor growth, showing great anti-cancer effects [7, 77]. Based on their phenolic hydroxyl structure, it is easy for gossypol to stably insert into the MPNs skeleton [78]. Zhang et al. utilized PEG-chlorin e6 (Ce6)-dopamine, Fe^{2+}, and gossypol to form MPNs (termed PFGs) with small particle size (~ 32.7 nm), negative surface charge (ζ potential: −8.8 mV), and high colloidal stability (within 7 days) by the coordination of metals and polyphenols (Fig. 4(b)(i)) [79]. Upon 660 nm laser irradiation, PFGs achieved combined therapeutic efficacy of chemotherapy and PDT that can

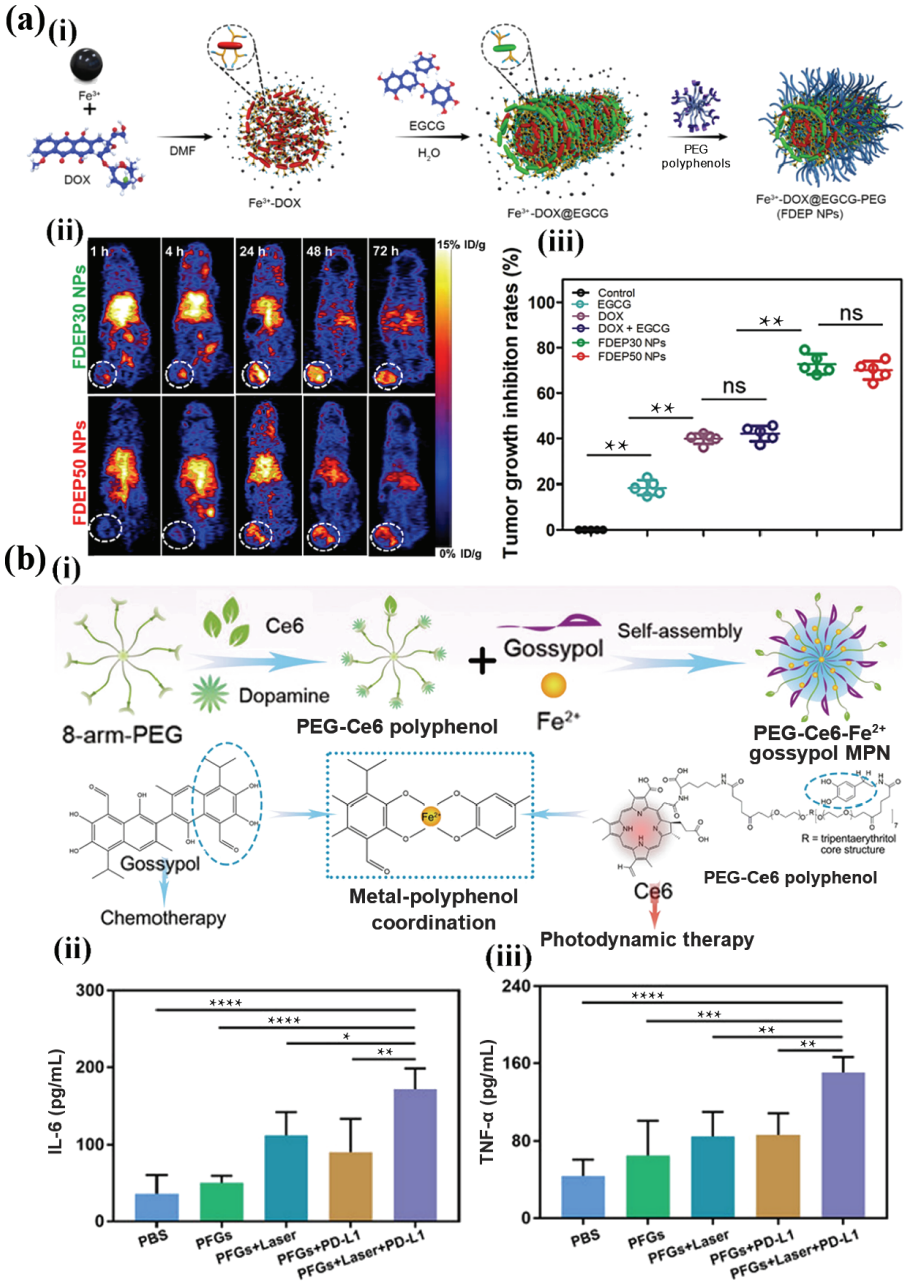

Figure 4 (a) (i) Procedures for the self-assembly of FDEP NPs, (ii) *in vivo* positron emission tomography (PET) images of different ^{89}Zr-labelled formulations (FDEP NPs that prepared with different Fe^{3+} concentrations) in U87MG xenograft mice, and (iii) tumor growth inhibition rates. Reproduced with permission from Ref. [76], © Elsevier Ltd. 2019. (b) (i) Synthesis of the PEG-chlorin e6 (Ce6)-Fe^{2+}-gossypol MPNs (PFGs), (ii) levels of cytokines IL-6, and (iii) TNF-α secreted by dendritic cells in the medium. Reproduced with permission from Ref. [79], © Wiley-VCH GmbH 2020.

effectively induce tumor cell death and realize synergistic enhancement of immune system by releasing damage-related molecular patterns. Furthermore, the infiltration of cytotoxic T lymphocytes in tumor tissues could be enhanced to increase the secretion of immune-related cytokines (e.g., pro-inflammatory IL-6 and TNF-α), thus fighting against tumor cells as well as inhibiting tumor proliferation and metastasis (Figs. 4(b)(ii) and 4(b)(iii)).

Collectively, these phenolic prodrug-metal based NPs with ultrahigh drug loading capacity, controllable drug release kinetics, and minor cytotoxicity, could facilitate the development of innovative nanomedicines for tumor therapy and exhibit great potential for clinical applications. Nevertheless, these aforementioned metal-phenolic NPs are mostly involved in cancer treatments. Taking advantage of the unique tunable physicochemical properties of metal-phenolic complexes, future researches may be inclined to apply these innovative formulations in the treatment of other diseases, such as ischemia-reperfusion injury-related diseases, inflammatory diseases, bacterial infections, etc.

2.1.3 *Metal-phenolic capsules*

Highly monodisperse hollow metal-phenolic capsules are commonly prepared by layer-by-layer adsorption of MPN films onto the template cores followed by the removal of the templates to host various cargo molecules [80, 81]. Generally, the template cores of the capsules are inorganic template particles composed of calcium carbonate ($CaCO_3$), manganese carbonate ($MnCO_3$), or cadmium carbonate ($CdCO_3$) that could be decomposed under relatively mild conditions, such as ethylene diamine tetraacetic acid (EDTA) or low pH, without affecting the loaded bioactive substances [82]. Besides, the wall of capsule could be functionalized by embedding specific moieties onto the multiple layers [83]. The strategy of assembling metal organic coordination materials into hollow capsules provides opportunities for the design of multifunctional systems in biomedical applications attributing to their ideal properties, such as excellent thermal and mechanical stability, selective permeability, and pH-responsive decomposition [84]. In addition, MPN capsules can undergo catechol-thiol reaction or boric acid-catechol complexation through the large number of reactive phenol hydroxyl groups on the surface, which is easy for various surface modification [85, 86]. These MPN capsules have attracted widespread interest as versatile vehicles, especially for small molecules delivery.

$CaCO_3$ particles are the most commonly used templates for the preparation of MPN capsules, owing to their facile synthesis processes and mild conditions for template removal. Ping et al. designed a pH-responsive MPN capsule (DOX-Al^{3+}-TA) based on the coordination between TA and Al^{3+} through a rapid and simple one-step assembly process for the intracellular delivery of DOX (Fig. 5(a)(i)) [87]. DOX was loaded in the $CaCO_3$ template doped with poly(styrene sulfonate) (PSS), forming PSS-DOX complex which was stabilized by hydrophobic interaction, electrostatic interaction, and hydrogen bonding interaction. The monodisperse DOX-loaded Al^{3+}-TA capsules were obtained by the formation of robust nanoscale films around the $CaCO_3$ templates, followed by the dissolution of the templates. As aforementioned, the coordination binding of Al^{3+}-TA undergoes pH-dependent disassembly within a physiologically relevant pH range (from 7.4 to 5). Thus, DOX-Al^{3+}-TA capsules can be degraded at acidic environment (pH 5.0 and pH 6.0) to release larger amount of DOX (62% and 53%, respectively) within 48 h compared with that (~ 30% release amount of DOX) at pH 7.4 (Fig. 5(a)(ii)). Due to the pH-dependent degradation properties of the as-formed MPN capsules, DOX was released in acidic endosomal compartments and readily spread to the cytoplasm through the endosome membrane without destroying the endosome.

It is worth pointing out that several studies have focused on incorporating a series of metals into the capsule shells to impart functionality into the carriers. Guo et al. provided an extensive library of functional MPN capsules that an organic ligand was coordinated with multiple metals [88]. Due to the diverse chelation capability of polyphenol materials, TA can coordinate with 18 different metal ions to form solid MPN films and then generate hollow capsules. Their physicochemical characteristics depending on the coordination metals, which enable the control of layer thickness, decomposition properties, and fluorescence manner. Among which, Al^{3+}-TA capsules exhibited high colloidal stability under physiological pH, while gradually disintegrated at 5.0–6.0 corresponding to the pH values of endo/lysosomal compartments. Notably, Zr^{4+}-TA capsules demonstrated a slower decomposition rate, which is benefit for sustained drug release, thereby holding potential of chronic diseases therapeutic that requires repeated administration. The different disassembly manners of metal ion-TA capsules are conducive to tailoring drug release behavior, which is of great importance for advanced drug delivery. It is also worth noting that the radioactive metal (like $^{64}Cu^{2+}$) which are commonly used in positron emission tomography and magnetic resonance imaging could be incorporated into the capsules to further extend the biomedical imaging function of MPN capsules. The use of plurality of metal for metal–organic coordination as multifunctional drug delivery capsules provides new opportunities for medical or pharmacological applications.

Notably, certain metals with inherent bioactivities can also be loaded in MPN capsules to synergistically increase the therapeutic effects. Many metal ions (e.g., Cu^{2+}, Zn^{2+}, Fe^{2+}/Fe^{3+}, etc.) have been found to promote the expression of vascular endothelial growth factor (VEGF), and thus can be used for angiogenesis and wound repair [89]. However, high concentration of metal ions may induce cytotoxicity [90–92]. To reduce the risk of Cu^{2+}-induced toxicity, Duan et al. synthesized MPN capsules (Cu-EGCG) to achieve sustained release of copper ions for the treatment of peripheral arterial diseases (Fig. 5(b)(i)) [93]. The as-formed Cu-EGCG capsules exhibited sustained release of Cu^{2+} within 72 h both in PBS and hydrogen peroxide solution, so as to maintain a stable blood concentration of Cu^{2+}, and thereby reducing potential side effects. Combining the antioxidant and anti-inflammatory capabilities of EGCG and the angiogenic ability of Cu^{2+}, Cu-EGCG capsules with favorable biocompatibility significantly inhibited the production of intracellular ROS and improved the ischemic conditions of model mice (Figs. 5(b)(ii)–5(b)(iv)). Similarly, Chen et al. designed Zn-EGCG capsules to provide sustained release of Zn^{2+} for modulating ischemic microenvironment of the limb [94]. Zn-EGCG capsules achieved desired angiogenesis effect with reduced cytotoxicity of Zn^{2+}. Besides, the EGCG effectively eliminated intracellular ROS and significantly inhibited the production of pro-inflammatory cytokines. It is worth mention that this study only focused on the angiogenesis outcomes within 14 days. It would be more valuable to explore the regeneration of blood vessels and their functions over a longer period of time. Besides, the cumulative Zn^{2+} release has already reached 80% in the first 48 h, and interval injection is required to guarantee the dynamic stability of the Zn^{2+} concentration. This dosing frequency indirectly increases the complexity of treatment, which is not conducive to patient therapeutic compliance in clinical practice.

$CaCO_3$ was not the only sacrificial template for the preparation of MPNs capsule. Metal-organic frameworks (MOFs) have also been frequently utilized attributing to large pore volumes that enables efficient drug loading and a variety of flexible physical

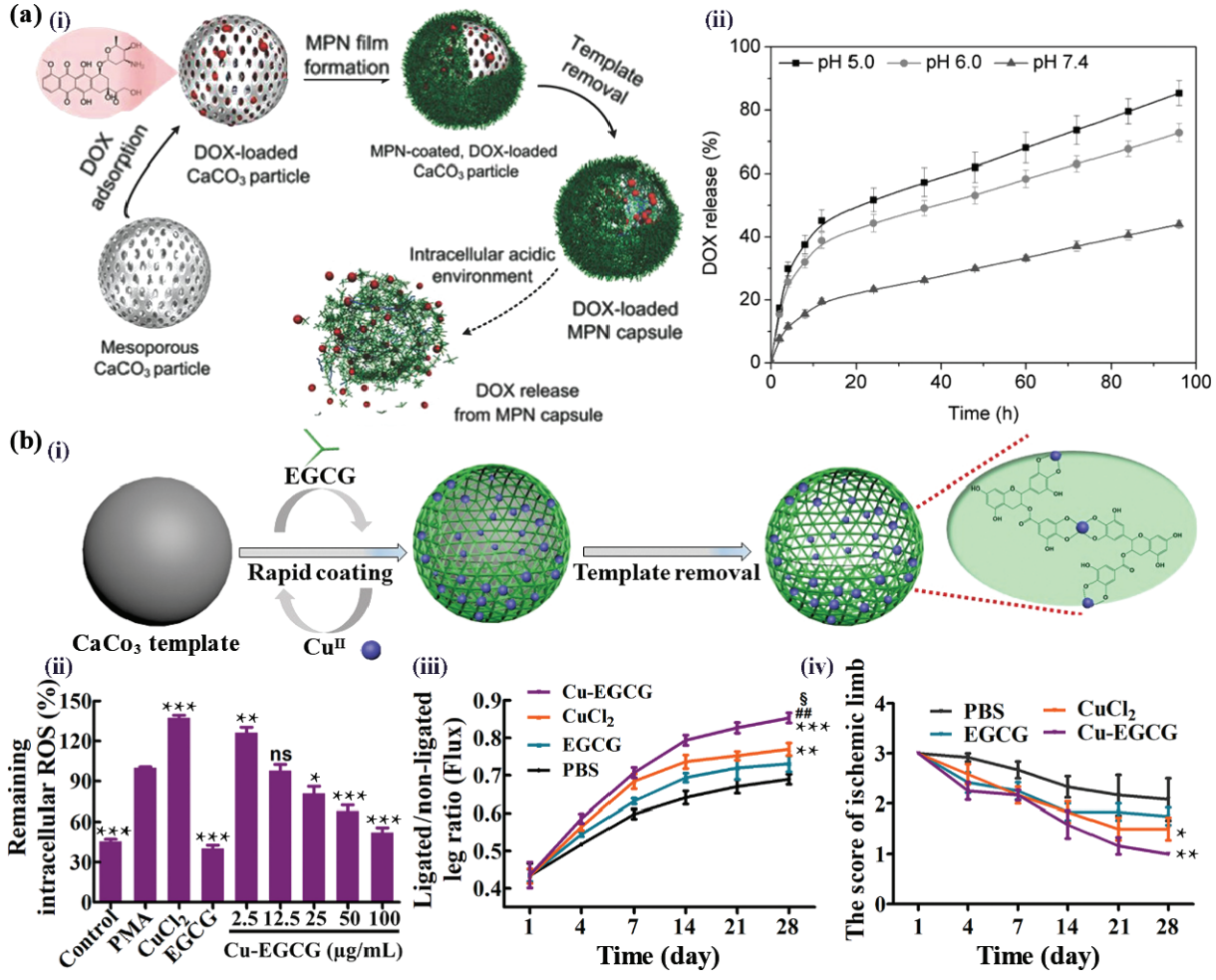

Figure 5 (a) (i) Preparation processes of DOX-loaded MPN capsules and DOX release mechanism, and (ii) release of DOX from DOX-Al^{3+}-TA capsules at different pH values. Reproduced with permission from Ref. [87], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2015. (b) (i) Schematic illustration of Cu-EGCG capsule, (ii) remaining intracellular ROS level after treating phorbol ester (PMA)-stimulated human umbilical vein endothelial cells with different formulations, (iii) quantification of blood flow recovery in the hindlimb ischaemia model, and (iv) score of limb ischaemia at different time points. Reproduced with permission from Ref. [93], © Elsevier Ltd. 2020.

structures. For example, Wang et al. used zeolitic imidazolate framework-8 (ZIF-8) particle as template, loaded with DOX through coprecipitation process and covered with EGCG/Fe layer under mild conditions to form ROS-responsive nanocapsules (DOX@EGCG/Fe NCs) [95]. This nanocapsules could be fast internalized by tumor cells through endocytosis and release drugs along with the degradation of DOX@EGCG/Fe NCs responding to excessive ROS under tumor microenvironments. Non-toxic Fe^{3+} and biodegradable EGCG render good biocompatibility of the formed nanocapsules, which is expected to be an effective nanocarrier for cancer treatment. Notably, size, shape, roughness, and composition of the capsules can be finely controlled by tuning the types of MOF particles. By coprecipitation process, multiple therapeutic agents could be encapsulated into the NPs, followed by the degradation of sacrificial template under mild conditions, which provide another candidate for the MPN capsules assembly.

Hollow MPN capsules have attracted much attention attributing to their controllable physicochemical and biological properties, such as a range of optional template materials, high mechanical/thermal stability, elective permeability, tunable structure/size, stimuli-responsive disassembly for controlled drug release, etc. Most importantly, unlike other copolymer-based capsule, considerable research progress in MPNs has substantially improved the treatment outcomes due to the inherent bioactivities of polyphenol and metal ions. In addition, the assembly of MPNs depends on the chelation ability of phenolic materials to form coordination complexes with metal ions, rather than the requirement of complicated preparation process and additional organic solvent. Hollow MPN capsules can be further engineered with functionality in response to the intracellular stimulus, e.g., pH, ROS, or enzymes, to initiate cargo release at the specific lesion.

2.2 Polymer-polyphenol based drug delivery nanosystems

Polymer micelles have been extensively studied as promising nanocarriers for drug delivery applications [93, 96–98]. They usually have a clear core–shell structure, which is fabricated by amphiphilic polymers. The inner hydrophobic core is generally used for encapsulating hydrophobic drugs, whereas hydrophilic shell is usually made of hydrophilic polymer, like linear PEG, to improve aqueous solubility and steric stability and extend the circulation time of NPs *in vivo* [95, 99, 100]. However, the clinical applications of the polymer-based micelles are impeded by the poor drug loading capacity and poor *in vivo* physiological stability. Polyphenols can be non-covalently or covalently cross-linked with polymers to form polymer micelles or nanoparticles [101]. Afterwards, the strong coordination interaction (e.g., hydrophobic interaction, hydrogen bonding, and π–π stacking interaction) of polyphenols with drugs provides driving force for the self-assembly of drug-loaded polyphenol-polymer micelles, resulting in superb structural stability and drug loading efficiency [102]. Most importantly, compared with other surfactant-based micelles,

polyphenol-polymer micelles possess lower critical micelle concentration (CMC) values, which are conducive to maintaining the micellar structures in severe diluted body fluid conditions. Thus, these micelles exhibited high physiological stability in the blood circulation and even in harsh gastrointestinal fluids [103]. In addition, the special physiochemical properties of polymer micelles contribute to achieving specific biomedical activities. For instance, the excellent nanosize (~ 100 nm) allows the polyphenol-polymer micelles passively aggregation at cancer lesion through enhanced permeability and retention (EPR) effects [104]. In combination with the inherent bioactivities of polymers (e.g., shielding effect, selective targeting effect, etc.) and polyphenol (e.g., antioxidant and anti-inflammation, immunoregulation, etc.), the polymer-polyphenol based micelles provide a new strategy for the delivery of small molecule drugs.

Liang et al. combined the A ring of EGCG and terminal aldehyde group of PEG to synthesize PEG-EGCG via aldehyde-mediated reaction, which further self-assembled into micellar nanocomposite (MNC), followed by loading hydrophobic anti-tumor drug DOX (DOX-MNC) (Fig. 6(a)(i)) [105]. Due to the similarity of the multiple-ringed structures of the DOX and EGCG, the strong intermolecular interaction between these two components was mainly π–π stacking, endowing the DOX-MNC with an unprecedented drug loading efficiency of 88% and superb thermodynamic stability. Besides, the low CMC values (0.15 μg/mL) of self-assembled micellar nanocomplexes are beneficial to preventing the premature drug release by NPs disassembly induced by body fluid dilution after systemic injection or infusion. Due to the selective tumor accumulation effects and the high biocompatibility of EGCG, the as-prepared formulation demonstrated minor toxicity on normal human hepatocytes (remained 80% cell viability after incubation with 0–100 μg/mL of DOX-MNC) (Fig. 6(a)(ii)). DOX-MNC exhibited extended serum retention time and showed 8- and 20-folds more DOX accumulation in tumor tissues in comparison with the free DOX at 4 and 24 h, respectively (Fig. 6(a)(iii)). Furthermore, DOX-MNC significantly inhibited tumor growth with minor effects on the body weight loss using the minimum effective dose (50 mg/kg) in HAK-1B-xenografted mice model. However, clinically approved PEGylated DOX-loaded liposomal formulation (10 mg/kg dose) severely reduced mouse body weight. It is worth noting that the addition of EGCG attenuated DOX-induced cardiotoxicity through inhibiting lactate dehydrogenase activity, apoptosis suppression, radical-scavenging, and antioxidant effects. Compared with the free DOX, DOX-MNC showed higher tumor-selective accumulation, providing an effective and safe strategy for cancer treatment. In another study, Chen et al. also assembled PEG-EGCG and photosensitizer Ce6 into nanocomposites (EGP-Ce6 NPs) with high drug loading (44%) and encapsulation capability (89%), achieving carrier-enhanced photodynamic cancer treatment based on the photodynamic effect of Ce6 and anti-tumor effect of PEG-EGCG [106]. Similarly, the chemical conjugation of PEG component endows its "stealth" characteristic during blood circulation. In addition to improve biosafety of the prepared formulations, the strong interaction between polymer-polyphenol and drugs is conducive to controlling the physicochemical properties of the self-assembled polymer micelles, including particle size, shape, surface charge, surface hydrophobicity, and rigidity [107].

Besides, the polyphenol could also conjugate to other polymer, like natural linear polysaccharide hyaluronic acid (HA), and then form stable MNCs to achieve targeted drug delivery. To give as an

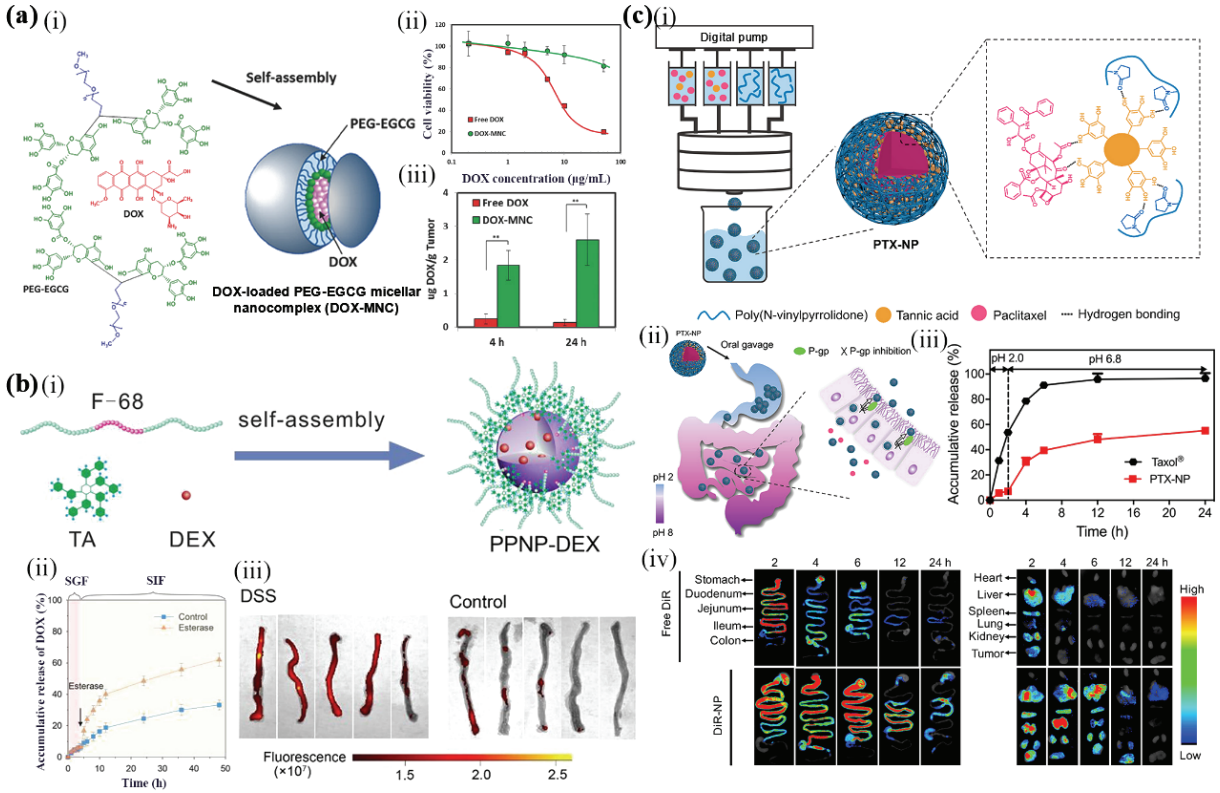

Figure 6 (a) (i) Self-assembly mechanism of DOX-MNCs, (ii) cytotoxicity of different formulation to normal human hepatocytes after 48 h incubation, and (iii) intratumoral DOX accumulation in the tumor after different treatment. Reproduced with permission from Ref. [105], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2018. (b) (i) Schematic diagram of PPNP-DEX drug loading process, (ii) accumulative DEX release with or without esterase, and (iii) fluorescence distribution of drugs in colitis mice. Reproduced with permission from Ref. [111], © American Chemical Society 2018. (c) (i) Schematic diagram of the production process and (ii) *in vivo* release mechanism of PTX-loaded TA/PVP NPs, (iii) drug release curve of PTX-NP at different pH values, (iv) *ex vivo* images of major organs and tumors post oral administration of free DiR and DiR-labelled nanoparticles. Reproduced with permission from Ref. [112], © American Chemical Society 2018.

example, Bae et al. proposed an amphiphilic copolymers that conjugated HA with EGCG [108]. HA-EGCG can self-assemble into MNCs and further load with cisplatin. The prepared MNCs exhibited negative surface charge (ζ potential: −26.5 mV) and small hydrodynamic size of ~ 57 nm. The tighter micelle structure may be attributed to the strong hydrophobic interactions or hydrogen bonding. Efficient treatment of tumors was achieved by the EPR-induced passive targeting and active targeting via the selective binding of HA towards the over-expressed CD44 ligand on tumors. Following the endocytosis, hyaluronidase in the endosomes destroyed the structures of MNCs by promoting the degradation of HA polymer chain, promoting the release of loaded drugs. The antioxidant activities of EGCG moieties minimized cisplatin-evoked oxidative stress to avoid non-target toxicity in normal tissues. Given lesion-targeting ability of HA-EGCG and the followed reduced cyto/tissue-toxicity of chemotherapy drugs, MNCs shall be broadly applicable for the therapeutic of multi-type cancer. Additionally, the polyphenol-based polymeric nanoparticles could be designed in response to microenvironment via adding stimuli-responsive functional moieties. Li et al. prepared a TA-poloxamer assembled nanodrug (DEX@PPNP) for dexamethasone (DEX) encapsulation [109]. Tetrahydroxydiboron served as a crosslinker for the formation of boronate-stabilized nanocarriers, which is sensitive to excessive H_2O_2 at the site of inflammation. The loaded DEX could be controlled release at the inflammatory microenvironment of joint as the DEX@PPNP can be broken by ROS. Combining with anti-inflammatory effects of DEX, the TA components can synergistically eliminate excess ROS, thereby controlling inflammation, alleviating cartilage damage, and inhibiting the progression of osteoarthritis in monosodium iodoacetate-induced osteoarthritis mice. In addition to the ROS-responsive parts, those polyphenol-based polymeric nanoparticles could also be modified with multiple-functionalized ligands for achieving controlled drug delivery responding to different stimulations including internal stimulus (e.g., acidic pH, GSH, etc.) or external stimulus (e.g., light, ultraviolet, magnetic, etc.) [110].

Notably, polyphenol-based amphiphilic polymeric micelles have also been increasingly investigated as promising carriers for oral drug delivery. Those carriers can enable more frequent agent exposure to target tissues within therapeutic window thereby enhancing oral bioavailability of therapeutic agents. Wang et al. utilized different types of polyphenols and polymers to prepare a series of polyphenol-polymer self-assembled nanoparticles with anti-inflammatory corticosteroid DEX loaded (PPNP-DEX) for oral drug delivery [111]. By changing polyphenols with different formyl densities (TA, EGCG, and catechins) and polymers (PEG, poloxamer 407 (Pluronic F-127), and poloxamer 188 (Pluronic F-68)), the properties of particles were regulated. Among which, the poloxamer is a copolymer composed of hydrophilic PEG and hydrophobic polypropylene oxide (PPO) blocks, which is considered to be safe for biomedical application by the FDA. Results showed that formulation prepared from TA and F-68 exhibited small and uniform size (~ 60 nm, PDI: 0.05), adjustable and repeatable sphere structures (Fig. 6(b)(i)). Hydrophobic drugs can be encapsulated by PPNP with encapsulation efficiency of 22.7%. In the acidic environment of simulated gastric fluid, the release amount of drug was reduced. The main reason was the formation of PPNP-DEX aggregation as more catechol and galloyl groups were protonated under acidic pH, thereby enhancing the hydrogen bonding interaction. Comparatively, in the environment of esterase-stimulated colitis, the release amount of DEX was increased significantly (Fig. 6(b)(ii)). Due to the favorable mucosal adhesion of TA as well as the electrostatic interaction between PPNP and inflamed colonic epithelium, the as-prepared formulation exhibited colitis targeting ability with enhanced drug accumulation in the inflamed colons at 24 and 48 h after administration (Fig. 6(b)(iii)). In addition, the polyphenol components could be hydrolyzed by the up-regulated esterase in the inflammatory intestine, resulting in the release of DEX from NPs. The PPNP-DEX can remarkably scavenge active oxygen free radicals and reduce inflammatory factors, showing great potential as a highly effective inflammatory bowel disease therapeutic agent. Remarkably, the colitis therapeutic effects of PPNP also benefit from anti-inflammatory and vascular-protective functionality of TA component.

Besides, as for oral chemotherapy in the cancer treatment, Le et al. synthesized and optimized paclitaxel-loaded TA/poly(N-vinylpyrrolidone) NPs (PTX-NP) via flash nanoprecipitation (FNP) method [112]. TA condensed the structures of PTX-NPs through the hydrogen bonding between poly(N-vinylpyrrolidone) and paclitaxel (Fig. 6(c)(i)). The optimized PTX-NP demonstrated a small particle size (~ 54 nm), negative surface charge (ζ potential: −16.7 mV), and high drug encapsulation efficiency (80%). Similar to the aforementioned mechanism, the enhanced hydrogen bonding between PTX-NP induced the formation of microaggregates under acidic gastric conditions. Under bowel simulation condition (~ pH 6.8), the increased ionization degree of TA molecules led to the weakening of hydrogen bonding, inducing the dissociation of microaggregates to release PTX (Figs. 6(c)(ii) and 6(c)(iii)). TA could inhibit P-gp-mediated efflux pump through the intestinal epithelial transport mechanism to improve the absorption of hydrophobic drugs in the gastrointestinal tract [47]. Thus, DiR-labelled PTX-NP (DiR-NP)-treated group exhibited enhanced retention time and NPs accumulation in the small intestine of the MCF-7 tumor-bearing mice model post 24 h oral administration (Fig. 6(c)(iv)). Assisting with continuous, facile, high production throughput, and high reproducibility technology (i.e., FNP process), the as-prepared nanoparticles showed enhanced clinical translation potential. Besides, another amphiphilic natural polymer-polyphenol (carboxymethyl chitosan-quercetin conjugate)-based micelles were also used for oral chemotherapy [113]. With the help of mucosal adhesion properties and tight junction (TJ) opening ability of chitosan, chitosan-based nanocomplex can enhance the absorption of loaded drugs in the gastrointestinal tract. Combined with P-gp inhibitory mechanism of TA and enhancement of oral drug absorption by chitosan, this amphiphilic natural polymer-polyphenol provided a potential strategy for oral paclitaxel delivery. However, the potential *in vivo* toxicity of the formulation was only examined by the body weight change of model mice. *In vivo* hepatotoxicity and nephrotoxicity as well as tissue damages of major organs, including heart, spleen, and lung, should also be examined to further confirm the clinical translation potential of this oral drug formulation for chemotherapy. In addition, several natural polymers containing hydrogen bond receptors with excellent solubility and biocompatibility can also be utilized to form hydrogen bonded nanoparticles [114]. As a natural polyamino acid, bovine serum albumin (BSA) has the advantages of fairly good water solubility and low cost, which can bond with TA by hydrogen bonding. Lomova et al. manufactured carriers composed of BSA and TA to encapsulate hydrophilic fluorescent dyes-labeled BSA (TRITC-BSA) or hydrophobic 3,4,9,10-tetra-(hectoxy-carbonyl)-perylene [114]. The designed carriers not only exhibited versatile ability of encapsulating both hydrophobic or hydrophilic drugs, but also demonstrated evident protease-specific degradation properties, being a promising polymer-polyphenol-based drug delivery nanosystems. Polymer-polyphenol assisted oral drug delivery strategy may play essential roles in the ideal treatments toward diverse diseases.

Polyphenol-polymer-based micelles could enhance drug loading efficiencies by forming various noncovalent interactions with the agents. Besides, polyphenols conjugate with multifunctional polymers, endowing the carriers with different properties, including prolonged circulation, reduced clearance by the reticuloendothelial system, targeted drug delivery to the lesion. Especially, those polyphenol-polymer micelles also provide a possibility to enhance the bioavailability of specific hydrophobic small molecular drugs *in vivo*. However, the polyphenol-polymer conjugations are commonly involved in complex synthesis processes. Besides, the incorporated organic chemical reagents are difficult to remove completely, inevitably increasing the potential risk of cytotoxicity and tissue-toxicity. In the current research, the choice of polymers should be more inclined to natural polymers with facile extraction process and specific functions, good biosafety, thereby accelerating their clinical transformation.

3 Applications of natural polyphenols in biomacromolecules delivery

Compared with small therapeutic molecules, biomacromolecule-based therapies (e.g., polypeptide, growth factors, enzymes, antibodies, cytokines, etc.) exhibit various advantages such as limited immunogenicity, minimal toxicity, high therapeutic efficacy, versatility, as well as inherent bioactivity, which have been regarded as attractive treatment options for different diseases in recent years, including cancer, diabetes, inflammatory diseases, neurodegenerative-related diseases, etc. [115, 116]. However, those macromolecules generally face problems of unfavorable degradation and denaturation, which significantly reduce their effective cellular internalization for therapeutic purpose, limiting their further clinical translation [117]. Several strategies have been developed, such as PEGylation, modification with cell-penetrating peptides or other aptamers, formation complexes with polymers, etc., to enhance the thermo-stability, pH-stability, and mechanical stability of the biomacromolecules *in vivo* [118–120]. However, PEGylation approach is not applicable to all macromolecules as it may reduce the bioactivities of macromolecules because of the steric interference of the active sites by PEG [121]. Besides, the PEG-conjugated substances and PEGylated nanocarriers could cause unexpected immunogenic response, i.e., accelerated blood clearance (ABC) phenomenon, resulting in fast clearance of cargoes. Such immunogenicity may cause serious concerns that the established antibody responses could compromise the biosafety and efficacy of the associated payloads (e.g., proteins, nucleic acids, peptides, etc.) [122]. Also, the limited binding sites and relatively large molecules of protein increase the difficulty of forming stable complexes with the polymers [123]. The nanoparticle-based biomacromolecules delivery systems, like liposomes, polymer-based NPs and inorganic NPs, are the most prevalent choice so far [124–126]. Among which, polyphenols could form complexes with biological macromolecules through noncovalent interactions (e.g., hydrogen bonding, van der Waals interactions, etc.), stabilizing the secondary structure of proteins/polypeptides and minimizing the risk of biomacromolecule denaturation. Thus, polyphenol-based nanosystems have aroused interests in the field of biomacromolecules delivery (Tables 2 and 3).

3.1 Natural polyphenol-based protein delivery systems

For on-demond delivering therapeutic proteins to specific disease sites, the delivery vehicles are better to involve organ-specific (or tissue-specific) targeting properties. TA possesses strong affinity with biomacromolecules (e.g., targeting protein) through diverse hydrogen bonds and hydrophobic interactions based on phenolic hydroxyl-rich moieties of TA (five gallol groups and five catechol groups). This property of TA is conducive to forming complexes with therapeutic proteins [127]. Besides, given interaction between polyphenol and protein, polyphenol could also be designed as targeting moieties for binding with specific receptors in the lesion. As aforementioned, TA shows a strong interaction with proteins exposed in ECM of cardiac tissues. Shin et al. combined TA with model green fluorescent protein (GFP) and coronary artery blood vessel vasodilation peptide to obtain TA-modified (TANNylated) protein-formulation (hydrodynamic diameter of ~ 52.7 nm), which can specifically target live cardiac tissue for improving the treatment efficacy of heart disease [55]. Similar to the concept of PEGylation, the as-prepared formulation demonstrated increased circulation time in the blood and extended half-life of the model protein. However, different from the conventional PEGylation, TA component can attach to the extracellular matrix (elastin and collagen), thus targeting cardiac tissue. TANNylation confers the formulation to specifically bind to the heart and myocardium, which could be efficiently taken up by myocardial cells, providing an effective alternative for the treatment of heart disease. Assisting with the properties of polyphenol that directly interact with protein receptors on the target organ, polyphenol-based carriers could deliver therapeutic peptide/protein specifically to the heart without the requirement of invasive surgical procedures, which are conducive to facilitating multiple administration process. This targeting effect allows for long-term residence of administered therapeutics in the cardiac tissue. In another study, the heart targeting benefits of polyphenol-assisted self-assembling nanoparticles were also demonstrated in mouse model with pathological myocardial hypertrophy or ventricular fibrillation [128]. Different polyphenols (EA, catechin, EGCG, and TA) with varied numbers of phenolic hydroxyl groups were used as multifunctional building blocks. Correspondingly, the NPs (namely TPTN) were self-assembled by polyphenol, PLGA, and β-cyclodextrin via nanoprecipitation approach. The β-cyclodextrin was modified with 4-(hydroxymethyl) phenylboronic acid pinacol ester and redox cycling nitroxide (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl, Tempol) for ROS-responsive and scavenging properties. Taking advantage of the high affinity of polyphenols to the heart tissue, polyphenol-assisted NPs exhibited considerable accumulation in the damaged cardiac tissue post i.v. administration. TPTN effectively prevented and attenuated myocardial injury by reducing oxidative stress, inflammatory response, and myocardial fibrosis. Based on the aforementioned non-covalent interaction of polyphenol with proteins, this carrier is a promising candidate to deliver protein for upholding heart disease treatment without the requirement of complex cardiac surgery or traumatic *in situ* cardiac drugs administration. Polyphenols that possess organ/tissue (e.g., esophageal mucus, colon, tumors, myocardium, etc.)-specific targeting capability could also be used for other disease treatments.

However, due to the strong adhesive property towards proteins, intravenously injected TA-based vehicles could also non-specifically interact with various biological proteins (e.g., albumin, ovalbumin, and β-Lactoglobulin) in the blood, limiting the use of protein-TA complexes for systematic protein delivery [129, 130]. To address this problem, Honda et al. reported a TA-based carriers constituted by GFP protein/TA/polymer ternary nanocomplex with a core of protein and TA that surrounded by phenylboronic acid (PBA)-PEG corona, which this nanocomplex was formed by self-assembly of the three components in aqueous medium (Fig. 7(a)(i)) [131]. It is worth mention that the gallol group of TA could be gradually oxidized to quinone group in aqueous solution, destroying the structure of the ternary complex [32, 85]. Notably, the formation of boric acid esters between TA

Table 2 Polyphenol based protein/peptide delivery systems

Types of polyphenol materials	Loaded biomacromolecule drugs	Characterization	Mechanism	Experimental models	Biomedical application	References
TA	Protein (green fluorescent protein and basic fibroblast growth factor)	Hydrodynamic diameter: 52.7 nm	The modification of TA endows the ability of the therapeutic formulation to specifically target the heart tissue	HeLa cells; H9C2 cells, rat model of myocardial ischemia-reperfusion injury (intravenous injection)	Heart-targetingtherapies in heart diseases	[55]
TA	Protein (green fluorescent protein)	Hydrodynamic diameter: 17 nm ([FPBA]/[GFP] ratio of 500)	TA can easily form complexes with proteins and help to adhere to extracellular matrices; the addition of PEG inhibits the unfavorable adhesion of complex with serum tissue and prolong blood circulation time	CT26 cells; mice bearing subcutaneous murine colon CT26 tumors (intravenous injection)	Tumor therapy	[131]
EGCG/catechin hydrate / procyanidin / ellagic acid	Protein (bovine serum albumin, R-phycoerythrin, and ribonuclease A)	Particle size: ~ 100 nm	Polyphenols promote the binding affinity between proteins and boronic acid-containing polymers; catechol- boronic ester endows the formulation with pH-sensitive property; maintained biological activity of the protein and improved cytosolic delivery efficiency	HeLa cells and breast cancer MDA-MB-231 cells	Protein-based therapeutics	[132]
TA	Protein (cytochrome C, immunoglobulin G, and β-galactosidase)	Hydrodynamic size: ~ 250 nm; zata potential: 20 mV under pH 4.5, −30 mV under pH 7.4	The surface charge reversal of the complex in an acidic endosomal environment induces the endosomal escape of protein/TA NPs; glutathione could induce supramolecular breakdown of NPs by forming competitive non-covalent interactions with proteins and TA	Jurkat cells, MDA-MB-231 cells	Intracellular protein delivery	[133]
TA	Protein (milk proteins)	Thickness: 15.6 nm ((BSA-TA)4)	Protect the protein from being degraded in stomach conditions while maintaining its adhesion ability	Caco-2 cells	Microencapsulation of bioactive substances	[127]
TA	Enzyme (glucose oxidase)	Average size: 180 nm; zeta potential: −17.9 mV	Up-regulated ATP in the tumor triggers the decomposition of the complex for burst release of enzyme; TA reduced Fe^{3+} to Fe^{2+} to induce Fenton reaction; glucose oxidase catalyzed glucose to produce plenty of H_2O_2 and then induce the generation of toxic •OH.	4T1 cells; 4T1 tumor-bearing mice (intravenousinjection)	Tumor therapy	[140]
TA	Enzyme (glucose oxidase)	Average size: ~ 24.8 nm; PDI: 0.294; zeta potential: −12.1 mV	TA/Fe^{3+} form complex with human serum albumin/glucose oxidase to enhance chemokinetic therapy	4T1 cells; 4T1 tumor-bearing mice (intravenous injection)	Tumor therapy	[141]
EGCG	Enzyme (granzyme B)	Particle size: 159.8 nm; PDI: 0.101	Self-assembly of hyaluronic acid-epigallocatechin gallate conjugates (HA–EGCG), linear PEI, and enzyme. EGCG was used to bind with proteins; HA effectively target CD44 receptors that overexpressed in tumor	HCT-116 colon cancer cells; HepG2 human liver carcinoma cells	Tumor therapy	[143]
TA	Peptide (exendin-4)	Average size: ~ 115 nm; zeta potential: −23 mV	Controlled smaller size, high degrees of uniformity, high drug loading efficiency, and sustained release of peptides	Caco-2 cells; type 2 diabetes mice model. (intraperitoneal injection)	Type-II diabetes	[159]
TA	Peptide (liraglutide)	Average size: 50~100 nm; zeta potential: −22 mV	Sustained release of peptides and improved bioavailability; robust and extended glycemic control	Caco-2 cells; type 2 diabetes mice model (intraperitoneal injection)	Type-II diabetes	[160]
EGCG	Peptide (Melittin)	Mean particle size: 127.67 nm; PDI: 0.24; zeta potential: +25.40 mV	CD44 receptor-mediated cellular endocytosis, melittin -aided lysosomal escape and ROS-responsive boronate ester coordination bond triggered structural collapse; both melittin	B16F10 cells and NIH3T3 cells; the xenograft B16F10 tumor-bearing mice	Tumor therapy	[161]

and boric acid could inhibit this unfavorable oxidation. In addition, PEG shell further inhibited the unfavorable adhesion of serum components to the ternary complex, achieving prolonged plasma retention after 2 and 6 h intravenous injection into subcutaneous colon CT26 tumor mice model (Fig. 7(a)(ii)). Likewise, Liu et al. proposed a facile and efficient approach to cytosolic delivery of proteins with diverse molecular sizes and isoelectric points through interaction among the proteins, natural polyphenols (e.g., EGCG, catechin hydrate, procyanidin, or EA), and boronate-containing polymers [132]. The modification of natural polyphenols through non-covalent interaction or reversible dynamic bonding increased the binding affinity of proteins (e.g., negatively charged BSA and phycoerythrin, and positively charged protein RNase A) with boronic acid-modified polymers, forming stable complexes. The bound proteins can be specifically released in the acidic tumor microenvironments or inflammatory sites due to the pH-sensitive properties of boronic ester bond, greatly improving the cytosolic delivery efficacy. This innovative approach that used boronic acid-containing polymers based on polyphenol-boronate complexation exhibited high intracellular delivery efficacy of various therapeutic proteins without affecting their bioactivities, contributing to developing polyphenol-involved polymer platforms for effectively delivering proteins.

In addition to the polymer-polyphenol-based protein delivery systems, supramolecular interaction-based protein delivery strategies show great prospects in the intracellular natural protein delivery. Han et al. prepared protein-polyphenol nanoparticles composed of the complex of TA and therapeutic proteins cytochrome C (CYC), followed by the dissolution of mesoporous silica template (CYC-TA NPs) (Fig. 7(b)(i)) [133]. CYC-TA NPs achieved controlled size by adjusting the size of mesoporous silica template. In the physiological environment (~ pH 7.4), the surface charge of CYC-TA NPs was negative due to the presence of phenolic groups, endowing the NPs with high colloidal stability and less non-specific binding and clustering. When the pH value is switched from 7.4 to 5, the negative surface charge reversed into positive charge owing to the protonation of the hydroxyl group in the galloyl groups of TA, making NPs more inclined to escape endosomal compartments (Fig. 7(b)(ii)). After reaching the cytoplasm, therapeutic protein was released because intracellular GSH triggered the breakdown of supramolecular NPs by forming competitive noncovalent interactions with proteins and TA. This simple and practical type of polyphenol-based protein delivery strategy has proven the templated assembly of multiple proteins with polyphenols via diverse supramolecular interactions, which did not affect the function of proteins. This strategy may become a promising platform for potential applications in the field of protein therapy.

Notably, for oral protein delivery, delivery vehicle should meet the requirements of breaking through essential biological barriers, such as gastric acid, gastrointestinal enzyme system, intestinal mucus layer, and intestinal epithelial cells [134, 135]. In one study, the layer-by-layer assembly of protein-TA films were developed with the incorporation of adhesive proteins (i.e., β-lactoglobulin and immunoglobulin G (IgG)) that promoted adhesive effects of the formulations toward human intestinal surface [127]. The introduction of IgG into the middle layer of the BSA-TA multilayer film protected protein from gastric degradation and simultaneously maintained the adhesive function. This formulation exhibited potentials in the oral delivery of various active food ingredients, especially bioactive proteins, which require both protection from harsh gastric environments and specific targeted release in intestines.

Enzymes are biological catalysts which speed up reactions within cells. Due to their high specificity, defined mechanism of action, outstanding catalytic efficiency, and superb biocompatibility, enzyme therapeutics have received increasing attentions. The delivery of therapeutic enzymes generally relies on the electrostatic or covalent binding with carriers, facing issues of enzyme inactivation and low loading capability [136, 137]. Polyphenol compounds can form a physical barrier between the enzyme and external environment to protect enzyme from inactivation and degradation. Besides, polyphenol-enzymes complex is directly formed by the combination of polyphenols and enzymes via non-covalent interactions, which commonly possess high loading efficiency. Dai et al. coordinated Fe^{3+} with two functional polyphenol derivatives (i.e., platinum prodrug polyphenol and PEG-polyphenol) to load myeloperoxidase (MPO) for the killing of tumor cells [138]. Negatively charged platinum prodrug polyphenols and PEG polyphenols were adsorbed on the surface of MPO through electrostatic interaction and crosslinked with Fe^{3+} to form nanoparticles (MPP NPs) (Fig. 7(c)(i)). The polyphenol derivatives created a physical barrier that protects MPO from being damaged by the external environment, resulting in a high residual enzyme bioactivity of 40% (Fig. 7(c)(ii)). PEG-polyphenols reduced non-specific protein adsorption and enabled prolonged circulation in the blood. Platinum prodrug polyphenols promoted the generation of H_2O_2, which was catalyzed by MPO into more toxic HOCl (a powerful ROS). Besides, Fe^{3+} further converted H_2O_2 to HO•. Both HOCl and HO• can significantly damage lipids on the membrane of tumor cells. MPP NPs showed effective anti-cancer effect in terms of inhibiting tumor growth and prolonging survival time (Figs. 7(c)(iii) and 7(c)(iv)).

Glucose oxidase (GOx) can act as a catalyst to facilitate H_2O_2 production and simultaneously consume oxygen and glucose in the tumor microenvironment, resulting in promoting hypoxia, acidity, and ROS level, thereby causing tumor cell damage [139]. TA/Fe^{3+} is used to coat GOx-embeded zeolitic imidazolate framework to form nanoparticles (GOx@ZIF@MPN) (Fig. 7(d)(i)) [140]. The prepared nanoparticles exhibited decreased clearance by the reticuloendothelial systems and enhanced accumulation at tumor lesion via EPR effect. The upregulated ATP in tumor cells triggered the decomposition of the TA/Fe^{3+} coating, realizing "burst release" of the payload (GOx) at the targeted tumor site and consuming glucose to produce H_2O_2. Due to its reductive ability, TA could reduce Fe^{3+} into Fe^{2+}. The self-produced H_2O_2 was vigorously catalyzed by Fe^{2+} for generating toxic hydroxyl radical (•OH) via Fenton reaction (Fig. 7(d)(ii)). Both the increased Fenton reaction and aggravated starvation effects of cells by glucose consuming could lead to superb anti-tumor ability in 4T1 tumor-bearing mice indicated by the significantly reduced tumor volumes (Fig. 7(d)(iii)). Besides, water-soluble human serum albumin (HSA) with superb biocompatibility, physiological stability, and tumor-targeting capability has been commonly used as a carrier to load GOx for better treatment outcomes of chemodynamic therapy. To fabricate a stable HSA/GOx co-loaded vehicle, Guo et al. loaded HSA-GOx and tirapazamine (TPZ) into the TA/Fe^{3+} polyphenol network, obtaining a nanoreactor with excellent tumor inhibition efficacy (97.8%) [141]. Previous reports have shown that macromolecular derivatives of EGCG can self-assemble with anti-cancer enzymes to form stable micellar nanocomposites [142]. Liang et al. prepared a novel nanogel composed of hyaluronic acid-EGCG conjugate (HA-EGCG) and linear PEI to deliver Granzyme B (GzmB) for the killing of malignant cells [143]. The strong binding between the EGCG moieties and hydrophobic amino acid residues of model protein GzmB is conducive to assembling stable and homogeneous nanoparticles. HA-EGCG coating endowed the

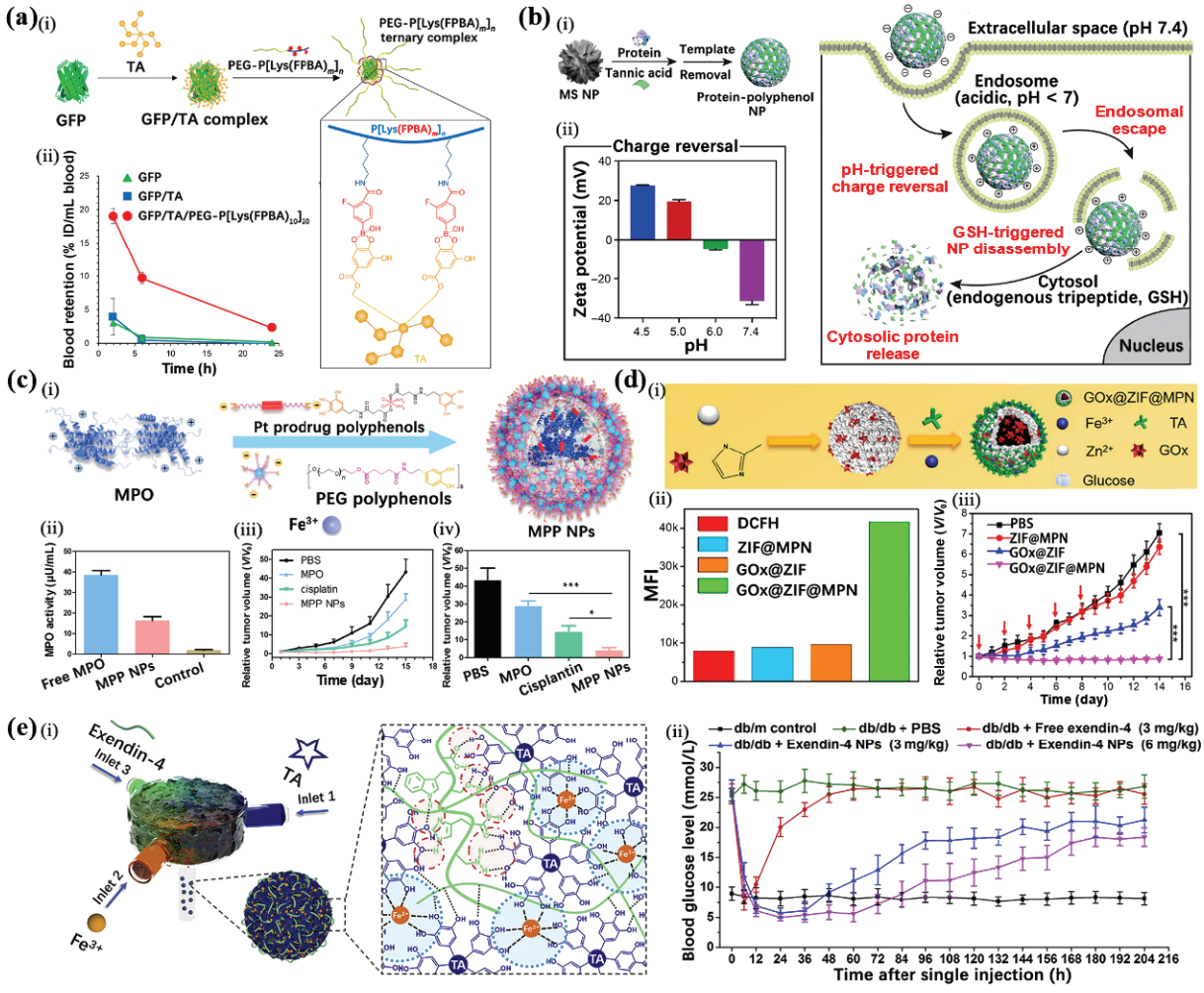

Figure 7 (a) (i) Schematic of the ternary complex and (ii) blood retention after intravenous injection of the ternary complex. Reproduced with permission from Ref. [131], © American Chemical Society, 2020. (b) (i) Mechanism of protein-TA NPs supramolecular assembly and intracellular protein delivery mechanism and (ii) charge reversal of protein-TA NPs. Reproduced with permission from Ref. [133], © American Chemical Society 2020. (c) (i) Self-assembly of myeloperoxidase (MPO)-loaded nanoparticles (MPP NPs), (ii) bioactivity of MPO, (iii) tumor growth curve after various treatments, and (iv) relative tumor volume on the 15th day with various treatments. Reproduced with permission from Ref. [138], © American Chemical Society 2018. (d) (i) Schematic of the preparation of GOx@ZIF@MPN nanoparticles, (ii) MFI values corresponding to •OH generated, and (iii) relative tumor volume of mice. Reproduced with permission from Ref. [140], © American Chemical Society 2018. (e) (i) Schematic illustration of the preparation and cross-linked structure of TA/exendin-4/Fe^{3+} nanoparticles and (ii) blood glucose levels of db/db mice with type 2 diabetes with different treatments. Reproduced with permission from Ref. [159], © Elsevier B.V. 2019.

nanogel with active targeting ability via the high affinity of HA to CD44 overexpressed on cancer cells. After CD44-mediated endocytosis, PEI ruptured lysosomal membranes by the "proton sponge effects", facilitating the GzmB release into the cytosol and then causing tumor cell apoptosis.

It is worth noting that the polyphenols might interfere with the spatial structure of several proteins when forming protein-polyphenol complexes. In some cases, the secondary conformation of the protein would be altered through the transition of α-helical, β-sheet, β-turn, and random coil. Ge et al. investigated the interaction of tea polyphenol (TP) with soymilk protein and reported that tea polyphenols enhanced the amounts of α-helix structure while decreasing the random coil with looser structure, which contributed to a more stable conformation of the protein [144]. In another study, Skrt et al. studied the binding of several polyphenols to BSA and determined the potential modes of action of these polyphenols [145]. This study revealed that (−)-epicatechin-3-gallate induced small conformational changes of BSA via increasing the contents of α-helix while other different types of flavonoids did not significantly change the molar ellipticity of BSA according to the circular dichroism spectra assay. Notably, the alternation of protein structure when binding with polyphenols is pH-dependent in several cases [146]. Relevant studies have reported that polyphenol extracts prevented β–α non-native transition in β-lactoglobulin at pH 1.2, while increased α-helix and random coil and decreased β-sheet contents at neutral pH 7.2. The effects of polyphenols on protein structures vary on a case-by-case basis, which is mainly related to the polyphenol species, pH value, the concentration of the reaction solution, etc. However, not all proteins are affected by polyphenols, and the perturbation of secondary structures depend on the applied phenolic compounds. For instance, flavonoids can interact with β-casein but have no impact on the secondary structure of the protein [147].

In addition, polyphenol would induce the change of the polar microenvironments in protein which is associated with the alternation of tertiary structures of proteins. As reported, the binding of resveratrol with soy protein isolates promoted the movement of protein from hydrophilic to hydrophobic environments in a dose-dependent manner, which was indicated by the increased fluorescence intensity and blue shift of λmax [148]. Xu et al. revealed that theaflavin, chlorogenic acid, and delphinidin-3-O-glucoside components could interact with β-lactoglobulin and changed the hydrophobicity of the microenvironments of the aromatic amino acid residues, thereby affecting the tertiary structure of the protein [149]. Besides,

another related study has also revealed that three kinds of polyphenols (i.e., chlorogenic acid, ferulic acid (FA), and EGCG) have an impact on the conformational changes in the β-lactoglobulin as their interactions decreased the polarity and slightly changed the originally hydrophobic structure of the protein [150].

The influence of polyphenol on the protein conformation might be further related to changes in the activities of several enzymes. For instance, upon the resveratrol-trypsin binding, resveratrol would induce the conformational changes of trypsin, thereby loosening the spatial structure of trypsin, decreasing hydrophobicity, increasing the polarity of enzyme molecules, and finally reducing the catalytic activity of trypsin. Fluorescence spectroscopy has demonstrated that resveratrol could quench the intrinsic fluorescence of trypsin (reflected by intrinsic fluorophores, Trp and Tyr residues) via a static quenching mechanism [151]. However, the destruction of secondary structures of the enzyme by polyphenol could not directly influence the catalytic activity of enzymes. Yu et al. demonstrated that ferulic acid could induce the conformational changes of tyrosinase, but it had little influence on the enzyme activity [152].

Overall, the studies of the effect of polyphenols on protein structure play pivotal roles in optimizing the fabrication processes as well as preferably preparing specific protein-polyphenol systems without interfering with the spatial structures of proteins. Future research on polyphenol-based biomacromolecules delivery systems should comprehensively explore the changes in the conformational and functional properties of the loaded proteins.

3.2 Natural polyphenol-based peptide delivery systems

Therapeutic peptides have come a long way with more than 60 types of peptide-based drugs now commercialized, such as oxytocin used for uterine contraction therapy, GLP-1 receptor agonist that owns prominent treatment effects in diabetes, opioid peptides that used for central nervous system disorders therapy, etc. [153–155]. Similar to protein drugs, the application of peptide also limited by the short circulation time, low therapeutic window, low bioavailability of oral administration, etc., which accelerate the requirement of designing effective systems for peptide delivery and accurate onset [156].

Furthermore, the sustained peptide release systems have attracted increasing attention for their promising application in chronic diseases treatment that requires repeated administration [157]. TA could complex with peptides via hydrogen bonding under low pH values (pH < 6.0). While the formed complex could dissociate and trigger peptide release due to the partial ionization in physiological environments (pH 7.4) that weakens the hydrogen bonding [158]. He et al. explored the feasibility of developing a biocompatible ternary platform that composed of multiple components (TA, exendin-4, and trivalent metal ions) for the controlled peptide release in type 2 diabetes (T2D) therapy. Fe^{3+} was introduced to quench excessive phenol groups through coordination complexation, avoiding the formation of heterogeneous TA/exendin-4 complex precipitation or overgrowth into larger aggregates (Fig. 7(e)(i)) [159]. Flash nanocomplexation (FNC) platform was utilized to facilitate rapid and effective mixing of the three constitutes in the complexation processes and kinetically control the assembly process, achieving nanoscale and injectable exendin-4/TA/Fe^{3+} nanocomplexes with controlled small size (~ 110 nm), high uniformity (PDI: 0.15), high drug encapsulation efficiency (nearly 100%), and tunable drug release kinetics. Higher TA concentration increased crosslinking density of the ternary nanoparticles, which helps to decrease the dissociation rate of peptide, reduce burst release, and extend overall release profile to 12 days. The as-prepared formulation rapidly reduced the alert blood glucose level (25 mmol/L) to the base line that found in healthy mice (< 10 mmol/L) at 6 h and still maintain a hypoglycemic effect over 8 days after intraperitoneal (i.p.) administration in type 2 diabetes mice (Fig. 7(e)(ii)). However, this NPs may be not ideal for injectable administration in the clinical practice as phenol-Fe^{3+} coordination developed a dark purple color, which may cause skin color changes. Thus, this research group tried to replace Fe^{3+} ions with Al^{3+} ions as crosslinker, and developed a Liraglutide (Lira)/TA/Al^{3+} ternary NPs. This formulation was also used for overcoming the key issues (like low bioavailability) of Lira (glucagon-like peptide-1 receptor agonist) as well as achieve sustained drug release [160]. Similarly, the hydrogen bonds between Lira and TA are the major driving force for the formation of NPs, while the additional crosslinker Al^{3+} was used for stabilizing the ternary complexes and controlling particle size. More importantly, the extended release of Lira in ternary particles provided a robust and extended glycemic control with cardiac protect effects after multiple injections in type 2 diabetes mice. These systems exhibited huge potential for the treatment of type II diabetes due to its superb control capability on blood glucose and body weight, improved efficacy on cardiovascular complications, as well as high biosafety, assisting with the continuous, large-scale, and aqueous preparation process with good batch-to-batch reproducibility. These polyphenol-based ternary long-acting peptide release systems that assisted with the facile, scalable, and highly reproducible FNC method exhibit great clinical significance for chronic disease treatments.

Melittin (Mel), a kind of water-soluble host defense peptide extracted from honeybees, possesses anticancer effects. Qiao et al. prepared a ROS-responsive platform composed of Mel, condensed EGCG (pEGCG), and PBA-derivatized HA (pHA) [161]. EGCG was concentrated on condensed tannins (pEGCG) for preferably binding with Mel to directly form Mel-pEGCG nanocomplex (NC). Subsequently, the nanocomplexes were further coated with pHA via boronate ester coordination, eventually yielding pHA-NC. After actively accumulating at the tumor region via the high affinity of HA with CD44, the hyaluronidase and high ROS level at the tumor sites would promote the degradation of the outer HA layer and disruption of the boronate ester bonds, respectively, to facilitate the exposure of the inner NC. After that, the released EGCG components and Mel peptide could synergistically amplify the anti-tumor efficacy. The formulation promoted tumor cell apoptosis and significantly enhanced the survival rates of B16F10 tumor-bearing mice, while simultaneously exhibiting negligible systemic toxicity. The complexation of polyphenol derived from natural products and natural anti-tumor peptides are more desirable, which would offer feasible options for the combinational cancer therapy.

The delivery of therapeutic protein/peptide molecules is challenging. Concretely, effective encapsulation of biomacromolecules is limited by their large and complex structures. Delivery of proteins and peptides is limited by the difficulty in transporting across cell membranes, degradation in acidic lysosomal conditions, and low drug release from later period endosomes. Polyphenol-based nanosystems could overcome various challenges in the protein/peptide delivery, regarding of improving drug loading capability and physiological stability, as well as controlling the release of proteins/peptides. Future designs of polyphenol-based nanomaterials can focus on the targeted delivery to specific organs, tissues, cells, and even organelles. In addition, combining polyphenol raw materials that possess different bioactivities and specific therapeutic proteins/peptides, and then further modified with functional polymers, is promising for the treatment of different diseases.

3.3 Polyphenols-based gene delivery systems

In recent years, gene drugs have been rapidly developed and several of them have been approved by the FDA and applied in clinical applications [162]. Gene therapy has several advantages over other strategies, such as unrestricted choice of targets, the specificity from complementary base pairing, and prolonged duration of action, but the cytoplasmic delivery efficacy is a challenge for the effective therapy [163]. Especially in the delivery of siRNA, the loose and short structure of siRNA is extremely unstable and the siRNA multimers can be easily digested by serum nucleases, hindering the efficacy of siRNA therapy *in vivo* [164]. Over the past decades, multiple gene delivery systems have been developed. However various limitations impede the treatment efficacy of gene delivery, such as large particle size, poor endosomal escape, low colloidal stability, cellular and tissue toxicity induced by the high positive charge density of polymers, etc. Thus, it is necessary to develop impactful, universal, biocompatible, and more efficient approaches for intracellular gene delivery with high cellular uptake, endosomal escape capability, cytosolic localization, etc.

Natural polyphenols with strong antioxidant, antibacterial, and anti-tumor bioactivities have been widely utilized as functional subunits for constructing innovative functional gene carriers [165]. The strong binding affinity of those polyphenols to various biological nucleic acids through non-covalent interactions, promotes the formation of nanocomplex, potently delivering gene therapeutics into the cytosol of living cells without affecting their bioactivities. Natural polyphenols are rich in benzene rings and hydroxyl structures, which can effectively form hydrogen bonds with macromolecular nucleic acids to increase their stability *in vivo* [166]. For example, EGCG and nucleic acid can form a complex via cooperative hydrogen-bond, π–π stacking, and hydrophobic interactions [167]. Besides, considering the pH buffering capability of polyphenol, the polyphenol/gene drugs are easily escaping from the endosome, which are conducive to reducing the degradation of nucleic acid by nucleases in the endosome.

Shen et al. designed core–shell-structured NPs with the pre-complexed siRNA/EGCG as the negatively charged core (ζ potential: −8.4 mV) and cationic polymers as shell (Fig. 8(a)(i)) [168]. EGCG facilitates siRNA condensation via low-molecular-weight polymers, thus promoting the formation of uniform nanoparticles, which solves the key issue that the two components are difficult to form polyplex. Six polymers (including linear, hyperbranched, and branched polymers) were investigated to balance the correlation of siRNA delivery efficiency with toxicity. Compared with the more toxic high-molecular-weight polymers, all the screened-out polymer-based core–shell nanoparticles exhibited minor cytotoxicity at optimal transfection concentrations of siRNA. Notably, the as-prepared nanoparticles exhibited high gene silencing efficiencies of model siRNA firefly luciferase (~ 80%) compared with other NPs without adding EGCG (< 5%) (Fig. 8(a)(ii)). Furthermore, the PHD2 siRNA-loaded nanoparticles significantly decreased PHD2 gene expression in the colons, inhibited prolyl hydroxylases function, and remarkably suppressed inflammatory cells populations (e.g., white blood cells and neutrophils) and inflammatory cytokine levels (e.g., TNF-α), achieving a superb treatment outcome in intestinal injury mice model (Fig. 8(a)(iii)). The beneficial biomedical activities of EGCG assisted with polymer/polyphenol materials-mediated gene delivery strategies permit a promising platform for diverse disease treatments. Especially the poly-L-lysine (PLL), as a type of food additive, is mostly preferred polymer material for the preparation of the aforementioned core–shell nanoparticles due to its high siRNA delivery efficiency and biocompatibility [169]. In addition to serve as a constitute to facilitate the "condensing effects" of siRNA by cationic polymers, multiple catechol moieties can also be grafted into cationic polymers to form cationic polycatechols, thus promoting their siRNA binding ability. The flexibility of the polycatechol backbone was reported to affect entire siRNA delivery processes. For instance, Fan et al. used a list of cationic polycatechols to construct siRNA complexes, in which polycatechols was synthesized by conjugating multiple catechol moieties into cationic polymers (i.e., PLL) to enhance their siRNA binding capability, physiological stability, and cellular internalization capability for improving gene silencing efficiency (Fig. 8(b)) [170]. The screened-out cationic polycatechol with 50% catechol molar ratio possessed high gene delivery efficiency toward different cell lines, significantly down-regulating different target genes even under the conditions of abundant serum proteins.

Notably, the polyphenol structure could also be functionally modified to endow the vehicle with the ability of active targeting and receptor-mediated cellular uptake, resulting in increasing gene transfection efficiency. Liang et al. developed a ternary complex composed of pDNA, dendritic PEI, and a HA-EGCG conjugate for gene delivery (Fig. 8(c)(i)) [171]. Concretely, pDNA/PEI complexes could be stabilized by the HA-EGCG conjugate through the strong binding affinity between pDNA and EGCG. Besides, EGCG could inhibit the activity of various serum proteases *in vivo* by irreversibly blocking their active sites to protect pDNA from degradation and increase their resistance to nuclease attack. Notably, HA further promoted the transportation of the ternary nanocomplex into CD44-overexpressed cells via receptor-mediated endocytosis, achieving targeted gene delivery. The as-prepared formulation with pDNA/PEI ratios of 30 exhibited 73.8% of transfection efficiency, meanwhile maintaining high cell viability (~ 80%) in human embryonic kidney HEK293 cell lines (Fig. 8(c)(ii)). Besides, highest uptake efficiency (~ 43.7%) of the ternary complex was obtained at the C/P ratio (the number of carboxylic groups in HA/phosphate groups in pDNA) of 0.5 in CD44-overexpressed HCT-116 cells, which was 2.3 order of magnitude than that of pDNA/PEI complexes (19.0%) (a common benchmark for gene delivery) (Figs. 8(c)(iii) and 8(c)(iv)). In the future, this nanoscale ternary complexes could be explored in the delivery of diverse therapeutic genes to expand their application in different disease treatments.

For the co-delivery of anti-tumor agents and gene drugs in the cancer therapy, the ideal carriers entail high drug loading capacity, targeting ability that enabled drug accumulation at the tumor regions while causing minor damage toward normal tissues. Catechin, natural anti-tumor compounds extracted from green tea, could be methylated or glycosylated by enzymes after ingested by the human body, exhibiting outstanding performance in anti-allergic and decrease drug resistance of tumor cells [172]. Mg^{2+}, the essential element in human body, acts as an agonist and catalyst in bio-progress, which has been confirmed to play protective roles in cancer therapy [173]. Chen et al. constructed nanocomposites (Mg(II)-Cat NPs) using natural catechin, Mg^{2+}, and siRNA (siEIF5A2 gene that targets oncogene) via a facile one-step strategy under room temperature [174]. The as-prepared complexes promoted cellular uptake of siRNA in dose dependent manner, exhibiting similar transfection efficiency to commercial lipofectamine at a loaded dose of 150 nM. This formulation successfully knocked down EIF5A2 gene in tumors and significantly reduced tumor volume and weight (Figs. 8(d)(i) and 8(d)(ii)). The utilization of synergistic therapeutic methods, combining the anti-tumor effects of natural catechin/Mg^{2+} complex with the silencing effect of siRNA, is a promising strategy for cancer therapy. Besides, Ding et al. developed a self-assembled

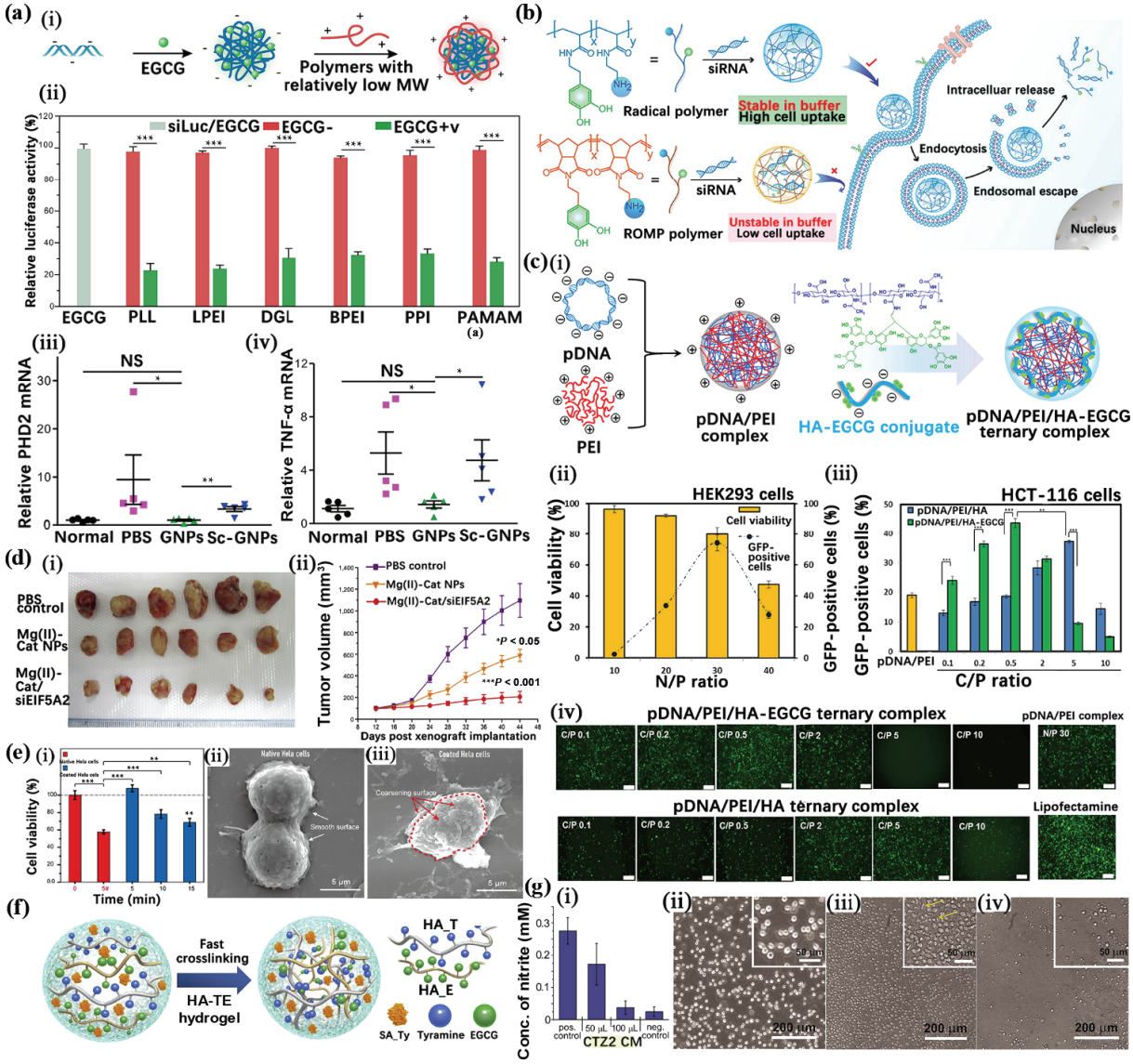

Figure 8 (a) (i) Schematic illustration of nanocomplex formulation, (ii) gene silencing efficiencies of polymer-based core–shell nanoparticles that consisting of different type of polymers (green bars) in HeLa–Luc cells, in comparison with that of polyplexes without additional EGCG (red bars), (iii) PHD2 mRNA, and (iv) TNF-α mRNA levels in the colon tissues after various treatments. Reproduced with permission from Ref. [168], © American Chemical Society 2018. (b) Structures of the designed polymers and intracellular siRNA delivery mechanism. Reproduced with permission from Ref. [170], © Wiley-VCH GmbH 2021. (c) (i) Preparation of pDNA/PEI/HA-EGCG ternary complex, (ii) cell viability and GFP expression levels of HEK293 cells transfected with pDNA/PEI/HA-EGCG complexes formed at various N/P ratios, (iii) GFP expression levels of HCT-116 cells transfected with varous polyelectrolyte complexes, and (iv) fluorescence microscopy images of HCT-116 cells transfected with various polyelectrolyte complexes. Reproduced with permission from Ref. [171], © Elsevier B.V. 2016. (d) (i) Actual sizes of representative tumors and (ii) mean tumor volume after the treatment of Mg(II)-Cat/siEIF5A2 complex. Reproduced with permission from Ref. [174], © Elsevier Ltd. 2015. (e) (i) Cell viability and (ii) and (iii) SEM images of uncoated or coated HeLa under different UV irradiation time. Reproduced with permission from Ref. [184], © American Chemical Society 2021. (f) Schematic representation of preparation HA-TE hydrogel. Reproduced with permission from Ref. [192], © Elsevier Ltd. 2020. (g) Quantized anti-inflammatory activity and phase contrast microscopy images of (i) U937 cells exposed with PBS, (iii) CTZ2 hydrogel and lipopolysaccharide and (ii) lipopolysaccharide alone, as determined by a Griess assay. Reproduced with permission from Ref. [199], © American Chemical Society 2016.

"stealth" drug carrier with a core composed of siRNA, EGCG, and protamine sulfate and a shell made by HA and tumor-homing cell-penetrating peptide for the treatment of breast cancer [175]. Firstly, siRNA was condensed by protamine sulfate via electrostatic interaction for forming dense nanocomplexes, followed by loading EGCG via the interaction with siRNA, which is conducive to protecting siRNA from the enzymatic degradation. Secondly, surface-coated HA could specifically target CD44 receptor at tumor cellular surface. Thirdly, cell-penetrating peptide was grafted on the outer layer for the specific binging with the overexpressed proline aminopeptidase on the breast tumor cells. This formulation could effectively accumulate in the tumor and penetrated into cells attributing to the dual targeting effects of HA and cell-penetrating peptide. Subsequently, after the degradation of HA by the endogenous hyaluronidase, the nanocomplexes were dissociated and released siRNA and EGCG to silence target gene and inhibit TNF-α production. The assembled nanocomplex demonstrated 15-fold higher cytotoxicity towards drug-resistant MDA-MB-231 tumor cell in comparison with the single chemotherapy with EGCG. Furthermore, the as-prepared nanocomplex exhibited superb tumor selectivity and tumor growth inhibition rates over free drug in tumor-bearing mice.

Although several good outcomes have been achieved in the researches of polyphenol-based gene delivery systems, there are still multiple barriers for effective gene transfection, such as circulatory instability, poor targeting, lysosome degradation, etc., that cannot be overcame by single complexation of polyphenol and gene therapeutic drugs. One of the important strategies is to

Table 3 Polyphenol based nucleic acid delivery systems

Types of polyphenol materials	Loaded biomacromolecule drugs	Characterization	Mechanism	Experimental models	Biomedical application	References
EGCG	Nucleic acid (siRNA PHD2)	Particle size: within 200 nm; zeta potential: −8.4 mV	EGCG significantly improves the siRNA complexation capability of low-molecular-weight polymers; achieving high transfection efficiency with minimal toxicity	HeLa cells, RAW 264.7 cells, and U87 cells; dextran sulfate sodium induced intestinal injury mice model (intrarectal administration)	Intestinal inflammation	[168]
Catechol	Nucleic acid (siRNA TNF-α)	Particle size: ~ 250 nm; PDI: 0.27	The introduction of multiple catechol groups into the cationic polymer can enhance its siRNA binding ability; improved biological stability, cell internalization and gene silencing efficiency	HeLa cells, HeLa-Luc cells, RAW 264.7 cells, NIH 3T3 cells, and LX-2 cells; dextran sulfate sodium induced intestinal injury mice model) (intrarectal administration)	Ulcerative colitis	[170]
EGCG	Nucleic acid (pDNA)	Average size: 167 nm; zeta potential: −7.5 mV	Self-assembled ternary complexes of pDNA, PEI, and HA-EGCG conjugates for CD44-targeted gene delivery	HCT-116 cells and HEK293 cells; HCT-116 tumor bearing mice (intertumoral injection)	colon cancer	[171]
Catechin	Nucleic acid (siRNA EIF5A2)	Particle size: 10–20 nm; zeta potential: +23.6 mV	Catechin, Mg^{2+}, siRNA was used to form nanocomposite particles in an easy one-step approach; excellent biocompatibility and high cell uptake rate; high siRNA loading efficiency and high gene transfection efficiency *in vitro* and tumor sites *in vivo*	T24 cells; subcutaneous bladder cancer mice model (intravenousinjection)	Bladder cancer	[174]
EGCG	Nucleic acid (siRNA CTGF)	Average size: 80 nm; zeta potential: −20 mV	Protamine is used as an assembled skeleton to fully load drugs and reduce side effects; double targeting effect of hyaluronic acid and tumor homing cell penetrating peptide	MDA-MB-231 cells and MCF-7 cells; MDA-MB-231 tumor-bearing Balb/c mice (intravenousinjection)	Resistant breast cancer therapy	[175]

introduce targeting moieties into the complex, which aims to provide improved targeting capability for on-demand gene delivery and reduced non-specific accumulation. Besides, owing to the desirable properties of polyphenols and their design flexibility, polyphenols can also be used as functional residues to modify polymers for increasing gene transfection efficiency.

4 Polyphenol-based biocompatible coating for cell therapy

Cell encapsulation is an innovative method that imparts exogenous physicochemical characteristics to living cells and provides cyto-protection of the encapsulated cells against lethal factors in the body, exhibiting broad prospects in various biomedical fields including cell transplantation, therapeutic agents delivery, tissue regeneration, etc. [176–178]. Recent researches have suggested that biocompatible polyphenol-based complex coating on cells via one-pot precipitation method could protect cells from multiple harsh environments like lytic enzymes, changes of temperature, immune cell attack, protein adsorption, etc. [179].

In diabetes treatment, transplantation of pancreatic islets (insulin-producing cell clusters) offers a promising curative treatment to restore endogenous insulin secretion. Microencapsulation coating and surface modification of islet cell were generally used to stabilize islet morphology and functionality or modulate immunogenic reactions [180]. However, these methods suffer from various problems. The islet cell entrapped into thick polymer coatings (even 5–50 μm) via microencapsulation methods is likely trend to hypoxic necrosis. The cellular immune reactions of the encapsulated cells are difficult to modulate by regulating permeability of coatings. Besides, only few specific functional molecules that are in line with cell physiology permit the covalent immobilization of islet cells [181]. Those biocompatible coating constructed with natural polyphenols could be directly coated on the cells to assist cell transplantation. A hydrogen-bonded layer-by-layer assembly coating films of TA have attracted great attention attributing to their high stability and the inherent antioxidant and antibacterial properties of TA. Kozlovskaya et al. used the strong hydrogen bond between PVPON and TA to form a layer-by-layer biocompatible coating on the surface of islet cells [182]. TA can strongly bind to the proteins on islet cell surfaces attributing to the multiple hydrogen bonds between phenolic hydroxyl group of TA and carbonyl functional group of the proteins. The antioxidant TA can scavenge ROS produced by the pathological islet cell while the hydrophilic PVPON can prevent surface adsorption of proteins. The non-toxic and non-immunogenic PVPON/TA coating was stable up to 7 days *in vitro* and demonstrated minor effects on islet viability and functions. Notably, the PVPON/TA coating was efficient in suppressing immune rejection in transplantation through attenuating the production of pro-inflammatory cytokines. In another study, the abilities of PVPON/TA to maintain islet functions and therapeutic efficacy were further explored in diabetic mice [183]. The (PVPON/TA)-coated islets remarkably reduced the chemokine generation and diabetogenic T cell migration and further restored blood glucose level after transplantation into diabetic mice, demonstrating great potential for enhancing islet allograft acceptance in patients. This formulation involved non-cationic polyphenols with high biocompatibility, and the components could be easily modified with functional molecules (e.g., fluorescence moieties) and directly deposited on the islet surface.

Except from its potential application in organ transplantation, polyphenol-based coating could also be used for living cell encapsulation to protect them from multiple external aggressors.

For instance, a polymer shell formed by tea polyphenol and polyvinyl pyrrolidone was reported [184]. The as-prepared polymer shells protected most of the model *Saccharomyces cerevisiae* (yeast) cell, achieving high survival rate (~ 95%) of yeast cell in the high temperature environment (60 °C). It is well known that UV radiation could generate ROS, causing DNA damage. TP, as an antioxidant, possesses effective ROS-scavenging property, exhibiting significant protective functions against photocarcinogenesis and phototoxicity. Polyphenol coatings offered physical barriers for the encapsulated agents, maintaining cell viability (i.e., HeLa cells) up to ~ 64.7% even under UV irradiation of 15 min, in contrast with only 54.4% cell viability of the native one after 5 min irradiation (Figs. 8(e)(i)–8(e)(iii)). Besides, metal-organic film composed of coordination complexes of natural TA and Fe^{3+} could also be used as a highly biocompatible coating for yeast cell protection [185]. The TA/Fe^{3+} complex-based artificial shell could controllably degrade on-demand and act as a protective layer of individual yeast against external lethal stressors, including UV irradiation, enzymatic degradation, etc.

Collectively, the polyphenol/polymer-based films could not only be used to modulate surface but also serve as a reservoir for the active therapeutic cargo (like living cells and organ) with cryo-protection effects. However, these polyphenol-based coating for cell therapy still face several challenges. For instance, various polyphenol-derived coatings require additional synthetic polymers, multivalent metal ions, or involve multistep deposition progress. It is also necessary to further optimize the preparation process, thus reducing cell damage caused by the addition of organic solvents and mechanical stress during the complicated preparation process. Also, the uniformity and stability of the self-deposited biocompatible coating on the cell surface need further improvement to ensure physiological stability of the cells *in vivo*.

5 Polyphenol-based functional hydrogel systems

Hydrogels are three-dimensional structure networks composed of crosslinked hydrophilic polymer chains and are able to absorb large amounts of water or biological fluids [186]. Hydrogels have been widely applied in biomedical fields, including cell/drug delivery as well as tissue engineering. Hydrogels with specific characteristics can be advantageous in the application of translational medicine: (1) tissue adhesive properties that can adapt to diverse environments [187]; (2) injectable and rapid gelation properties that could serve as auxiliary strategy for minimally invasive surgery [188]; (3) high drug loading efficiency for the delivery of hydrophilic drugs [189]; (4) biocompatible and biodegradable, etc. In general, the structure of polyphenols with abundant phenolic hydroxyl groups and benzene ring can provide sufficient intermolecular interactions with diverse materials, which is beneficial for the formation of hydrogels [190]. Most of the current researches focus on the utilization of EGCG and TA to form hydrogel with specific properties.

Polyphenols could be used as the dopant and crosslinker to interact with neutral polymers via multiple reaction mechanism, preparing biocompatible, multifunctional hydrogels with appropriate mechanical properties and required bioactivities [191]. For instance, since the B and D rings of EGCG contain 1,2,3-trihydroxyphenyl moiety that can be easily oxidized to form highly reactive quinone, EGCG could conjugate with biopolymer (with amine, thiol, imidazole, or other phenolic moieties) to form adhesive hydrogel without affecting its original biomedical activities. Recent study has proven that EGCG possesses high affinity to a kind of tyrosinase (isolated from *Streptomyces avermitillis*), allowing EGCG to be rapidly oxidized [192]. After the tyrosinase-mediated oxidized reaction, the oxidized EGCG-HA conjugation was crosslinked to tyramine-HA conjugation to form an adhesive hydrogel (Fig. 8(f)). The intrinsic characteristics of trihydroxyl phenols in EGCG endow the as-prepared hydrogel with strong adhesive and anti-inflammatory properties. The mixed hydrogel displayed higher tissue adhesiveness and successfully repaired skin incision in skin incision wound closure mice model. Another EGCG-chitosan hydrogel was also formed through enzyme-mediated crosslinking between polyphenol and biopolymer, which could facilitate skin regeneration in a full-skin defect wound model [193]. Through the enzymatic reaction, EGCG could form hydrogel with polymers in one-pot crosslinking process without additional organic synthesis steps. In addition to the EGCG, pyrogallol (PG) moiety-containing polyphenols (e.g., PG in tea catechins) have also been reported to mediate gelation with other polymers or molecules via oxidative process, contributing to the formation of functional hydrogel. For instance, a kind of medical adhesive hydrogel was developed by intermolecular hydrogen bonding among PEG, DNA, and PG moiety-containing TA. This simple and controllable preparation strategy of polyphenol-based NPs in the presence of diverse catalyzed enzyme may facilitate the fabrication of functional biomaterials without using toxic and expensive subunits, as well as the involvement of multistep synthetic processes and redundant purification works. Relevant studies have also reported the application of enzymatic polymerization approach in the direct fabrication of polyphenol-based formulations with controlled size, superb biocompatibility, and excellent ROS scavenging abilities [194, 195]. This kind of green and convenient fabrication process achieved one-step reaction and mild reaction condition, which contributing to the development of low-cost, biosafe, and therapeutic effective biomass-based nanomaterials.

Notably, an alternative approach to form hydrogel is developed through incorporating the chemically modified low-molecular-weight gelling agents and synthetic copolymers into three-dimensional structured hydrogel networks, which is driven by hydrophobic interactions and hydrogen bonding. In one study, a reversible and thermal-resistant hydrogel with antibacterial activities was self-assembled by the TA and amyloid fibrils (produced from globular peptidoglycans, lysozyme, and lysostaphin M23 endopeptidase) driven by hydrogen bonding, π–π stacking, and hydrophobic interactions [196]. The as-prepared polyphenol-based hydrogel has effectively removed bacteria without influencing the viability of colonic epithelial cells, showing great potential for further application in the treatment of small intestine infected diseases.

Stimuli-responsive hydrogels can specifically respond to external triggers (e.g., pH, enzyme, light, and temperature) to control the release of the payloads, which is of great significance in hydrogel-based drug delivery [197, 198]. Ninan et al. developed a pH-responsive hydrogel (CTZ2) composed of TA, Zn^{2+}, and carboxylated agarose (CA) derivative for the controlled release of TA through the physical crosslink provided by CA and the ionic crosslink between Zn^{2+}, CA chains, as well as TA [199]. Under the physiological condition (~ pH 7.4), TA was slightly released from the hydrogel (< 5%) and further gradually released due to the disruption of ionic interactions, protonation of TA, and hydrogel swelling under the lower pH. The prepared hydrogel maintained favorable antibacterial activity and displayed anti-inflammatory activities indicated by the significant suppressed production of pro-inflammatory NO in the human macrophage cell line U-937 (Figs. 8(g)(i)–8(g)(iv)). TA possesses antioxidant, antimicrobial, and anti-inflammatory effects, agarose-based hydrogels exhibit high hydrophilicity and antiadhesive properties, and Zn^{2+} is a vital component for enzymes activity including maintenance of

structural integrity of proteins and regulation of gene expression. Combining the advantageous properties of the three components, the hydrogel provides superb antibacterial, anti-inflammatory effects, inducing the healing of heavily exudate wounds that require frequent changes of dressings. In another study, a glucose-responsive hydrogel platform was prepared for enhancing diabetic wound repair [200]. Concretely, gallic acid-grafted chitosan (GA-CS) was incorporated into the PEG diacrylate matrix to yield antioxidant hybrid hydrogels. Meanwhile, PBA-modified PEI (PBA-PEI) nanoparticles with insulin encapsulated were immobilized in the as-prepared hybrid hydrogel via the dynamic borate bonds between PBA and the phenolic groups on GA, thereby forming PEG/PEI-PBA/insulin/CS-GA hydrogel platform. GA is a polyphenol with high antioxidant activities, while PBA moieties endow the hydrogel with glucose-responsive insulin release characteristics for regulating hyperglycemia. Through the synergy of hyperglycemia reduction and antioxidant activity, this fabricated hydrogel platform significantly regulated the blood glucose levels and effectively reshaped the inflammatory wound microenvironments in diabetic mice models via alleviating inflammation, promoting angiogenesis and ECM deposition. Collectively, this innovative hydrogel possesses great potential in further optimizing diabetic wound treatment.

It is worth mention that the polyphenol could also interact with biomacromolecules (such as protein, nucleic acid) to form hydrogels through non-covalent interactions for drug delivery [201]. Puerarin, a polyphenol (isoflavonoid) found in Pueraria lobata root, has been used as functional food additive or nutraceutical product for benefiting human health [202]. However, PUE is a hydrophobic substance which makes it insoluble in gastrointestinal fluids and relatively not easily incorporate into various food matrices, resulting in a relatively low bioavailability. Zhong et al. used PUE to form whey protein isolate (WPI) hydrogels based on the hydrogen bonding interactions between WPI and PUE [203]. The PUE components act as both the gelling agents and the loaded nutraceuticals in the formulation of semi-solid functional hydrogels. In particular, the interactions between WPI and PUE and impacts on hydrogel formation and properties were further characterized. It has been found that the increase of PUE concentration (increase from 0.3% to 0.9%) could enhance the elasticity and hardness of hydrogels. As for nucleic acid-based hydrogel, TA can act as a "molecular glue" that could reversibly connect with DNA through a simple mixing process of the two components. In one study, TA with five catechols and five gallols at termini interacted with the phosphate backbone of DNA via hydrogen bonds, forming mechanically stable (> 10 kPa) DNA-based hydrogels without chemically modification [204]. The hydrogel exhibited strong adhesive properties toward tissues during pulling, attributing to the rich polyphenol groups in the TA (ten phenols per TA). The hydrogel was degraded to release DNA, attributing to the degradation of ester bonds between pyrogallol groups of the TA. The as-prepared DNA-based hydrogel displayed superior *in vivo* hemostatic ability in a mouse liver bleeding model. The degradable, extensible, adhesive, and hemostatic hydrogels could be used for further applied in wound dressing.

6 Conclusion and future perspectives

The excellent antioxidant, anti-inflammatory, antibacterial, and anti-cancer effects of polyphenols favor their versatile roles in the prevention and treatment of various diseases. Natural polyphenols with unique physicochemical properties and excellent biocompatibility can be combined with a variety of components (e.g., metal ions, polymers, proteins, nucleic acids, etc.) through multiple interactions, including coordination bonds, covalent bonds, hydrogen bonds, hydrophobic interactions, and electrostatic interactions, designing diverse therapeutic drug delivery systems. This review systematically elaborated the articles published in the recent five years related to polyphenol-based drug delivery systems from multiple perspectives, including host materials, fabrication process, assembly mechanism, *in vitro* performance, *in vivo* therapeutic efficacy, clinical translational potential, etc., and discussed their possible limitations and risks in clinical practice.

Compared with the previously published reviews with the same topic, we emphasized the factors affecting assembly/disassembly process, the requirements for the physicochemical properties of loaded agents, as well as the relationship and regulation mechanism between structural components and properties (e.g., particle size, particle morphology, surface properties, structural compactness, encapsulation efficiency, *in vitro* drug release behavior, colloidal stability, cytotoxicity, etc.). We detailly elucidated the *in vivo* drug biodistribution (pharmacokinetics results) and treatment effects (pharmacodynamics results) by comparing with marketed drugs, as well as provided the mechanism by which these formulations intervene the pathophysiological processes of various diseases at the molecular level. Besides, we highlighted the *in vivo* treatment effects reproducibility and biosafety especially for the formulations that require multi-doses administration, to provide references for the rational design of smart polyphenol-related nanocarriers with high clinical application value. In addition to focusing on the application of polyphenol-based delivery vehicles in cancer theranostics like most other published reviews, we are more interested in their applications in a broad range of diseases including chronic disease treatment (such as diabetes, inflammatory bowel disease), ischemia-reperfusion injury-related diseases, bacterial infection, cell therapy, wound healing, etc. The purpose of this review is to provide an easily accessible guide for a diverse range of researchers active in the biomedical fields and promote the application of polyphenols.

Besides, we also introduced the latest and promising nanosystems for the targeted delivery and controlled release of protein, i.e., sustained drug delivery ternary system based on a variety of non-covalent interactions among protein, polyphenol, and polyvalent metal ions (such as electrostatic complexation, hydrophobicity, hydrogen bond, metal coordination complexation, etc.). This system exhibited huge potential for the treatment of type II diabetes due to its superb control capability on blood glucose and body weight, improved efficacy on cardiovascular complications, as well as high biosafety, assisting with the continuous, large-scale, and aqueous preparation process with good batch-to-batch reproducibility. The review also highlighted that natural polyphenolic materials can also be designed as targeting moieties as it could strongly interact with the highly abundant proteins of tissues or organs, thereby achieving precise/on-demand drug delivery. Taking advantage of this property, future designs of polyphenol-based nanomaterials can focus on the targeted delivery to specific organs, tissues, cells, and even organelles.

Additionally, batch-to-batch reproducibility is extremely important for cost-effective scale up and clinical translation. Thus, some novel and promising preparation methods and technologies, such as one-pot precipitation method, green enzymatic polymerization approach, FNC method, etc., are involved and summarized in this review. It serves as a reference to guide those translational researches to achieve facile, continuous, rapid, large-scale, and batch-to-batch reproducibility preparation process under mild reaction conditions (e.g., organic solvent-free aqueous

medium, and low shear force). We also summarized the key factors involved in the preparation process of formulations, including the selection of organic solvents and crosslinkers, salt concentration, initial pH values, mass ratio of reactants, Reynolds number in the mixing reactor, lyophilization parameters, etc., providing new theoretical support for the rapid development and translation of natural polyphenol-based functional formulations.

Although numerous fascinating outcomes have been obtained in the research of polyphenol-based carriers, there are still many obstacles in the exploration of these systems for improved drug delivery efficacy and eventually in future clinical application. Firstly, the poor stability of polyphenols resulted from easy oxidation in environments leads to poor long-term mechanical stability. Secondly, the drug loading efficiency and active targeting ability of polyphenols could not meet specific treatment requirement for clinical use. Although the strong binding of natural polyphenols to proteins and nucleic acids is conducive to delivering several macromolecules, there is potential danger of polyphenols interacting with multiple bioactive molecules on the surface of organs and tissues *in vivo*, leading to reduce physiological stability and even adverse effects. The current researches have expanded the application of polyphenols in the biomedicine from cancer therapy to the treatment of other diseases, such as bacterial infections, cardiovascular diseases, diabetes, etc. Without any doubt, there is still lack of a complete understanding of the mechanisms of the ingestion, absorption, metabolism, and excretion possesses of polyphenol-based delivery systems *in vivo*, which may threaten the effective and safe use of the polyphenol-based therapeutic systems in clinical settings. In addition, on the way towards clinical translation of polyphenol-based drug delivery systems, more efforts are required, including but not limited to choosing materials with facile extraction process, exploration of continuous, reproducible, scalable preparation techniques, establishment of matched administration method and dosage, and prevention of potential side effects. We proposed that the future improvements of polyphenol-based vehicles in biomedical applications should focus on the following points: (i) the introduction of multiple interaction during the assembly process to obtain higher drug loading and more stable particle structures; (ii) a more clear elucidation of the relationships between particle properties (particle size, surface charge, structural components, encapsulation efficiency, etc.) and *in vitro*/*in vivo* functions (drug release behavior, colloidal stability, cellular uptake and transport, drug biodistribution, treatment effect, biosafety, etc.) as well as their potential regulation mechanism; (iii) exploration of the optimized storage conditions of particle suspension and lyophilization parameters to render them long-term storage stability; (iv) the development of facile, continuous preparation methods with batch-to-batch reproducibility and scalable production manners; (v) making use of well-established safety screening procedures and standard-dose strategies. These aforementioned guidelines further promote the practical applications of natural polyphenol-based carriers and provide new theoretical support for the rapid development and clinical transformation of natural bio-based functional formulations.

The polyphenol-based drug delivery systems with flexible structure, simple preparation process, and reliable biosafety exhibit broad prospects in the field of biomedicine. Although there is a long way to go from conceptual design to actual commercial products, polyphenols have provided a unique avenue for the design of functional nanomaterials for biomedical practice, providing profound impact on overcoming long-standing scientific and technological issues in the clinical settings and eventually benefiting human health.

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