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Review

Oxidative Coupling and Self-Assembly of Polyphenols for the Development of Novel Biomaterials

Jyoti Pal, Manu Sharma,* Abhishek Tiwari,* Varsha Tiwari, Manish Kumar, Ajay Sharma, Waleed Hassan Almalki, Sami I. Alzarea, Imran Kazmi, Gaurav Gupta, Vinoth Kumarasamy,* and Vetriselvan Subramaniyan*

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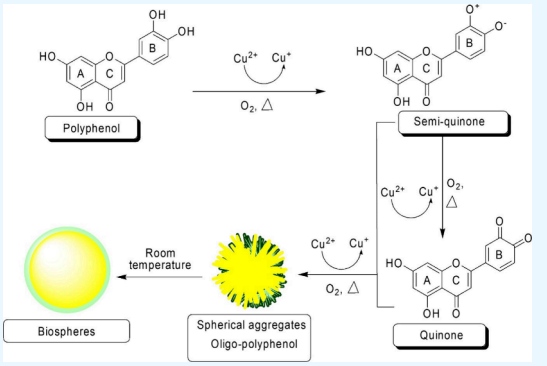
ABSTRACT: In recent years, the development of biomaterials from green organic sources with nontoxicity and hyposensitivity has been explored for a wide array of biotherapeutic applications. Polyphenolic compounds have unique structural features, and self-assembly by oxidative coupling allows molecular species to rearrange into complex biomaterial that can be used for multiple applications. Self-assembled polyphenolic structures, such as hollow spheres, can be designed to respond to various chemical and physical stimuli that can release therapeutic drugs smartly. The self-assembled metallic−phenol network (MPN) has been used for modulating interfacial properties and designing biomaterials, and there are several advantages and challenges associated with such biomaterials. This review comprehensively summarizes current challenges and prospects of self-assembled polyphenolic hollow spheres and MPN coatings and self-assembly for biomedical applications.



INTRODUCTION

Polyphenols are among the most prevalent secondary metabolites plants produce that can scavenge free radicals.[1] Based on their chemical makeup, polyphenols can be categorized into several distinct classes, ranging from simple compounds like phenolic acid to highly complex polymeric molecules like tannins.[2] Numerous disorders, including oxidative stress, type II diabetes, cardiovascular disease, and others, have been linked to the antioxidant capabilities of polyphenols. More than 8000 distinct polyphenols with different structural characteristics and bioactivities are present in plants.[3−5] Support, adhesion, pigmentation, radiation protection, and chemical defense are just a few of the many activities that catechol and gallol functionalities play in both plants and animals.[6,7] The unique structural and physiochemical properties of polyphenols and their biological activities have been documented in recent decades. Polyphenol compounds are susceptible to atmospheric oxidation due to their structural properties. The structural features of these polyphenolic molecules contribute to their antioxidant properties. In nature, the coloring of fruits and vegetables, leather tanning, and fermentation of green tea are examples of autoxidation and enzymatic and chemical oxidation. The autoxidation of polyphenols has been studied and documented to develop new procedures for chemical conversion and assembly of complex oligomers/polymers and biomaterials with several applications.[8−10]

In material sciences, developing carrier systems that accommodate guests has many applications in medical diagnosis and drug delivery. Carrier systems have been extensively studied in recent decades, including emulsions, nanoparticles, microspheres, hydrogels, micelles, and metal particles.[11−13] Simultaneously, porous or hollow structural spheres have been widely researched due to their free space or void to accommodate many guests. In medicine and materials science, loading and unloading biomolecules are challenges, and designing functional systems that respond to stimuli is one of the focus areas. Most of today's drug carrier systems are derived from nonrenewable petrochemical sources.[14] The development of green organic nano/microspheres from plant-based renewable natural polyphenols, which are nontoxic and hyposensitive, can be used for drug delivery and as a biomaterial. This interesting area has emerged in the past few years, and there has been much progress in this field. Meanwhile, the oxidative cross-linking mechanism of polyphenols has also been used to develop metal coatings and networks with various applications in biomedical and material

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sciences. This review summarizes the recent developments, applications, and future scope of oxidative coupling assembly and self-assembly of polyphenols as biomaterials.

POLYPHENOL OXIDATIVE COUPLING ASSEMBLY

Polyphenols can undergo an oxidative coupling assembly in the presence of copper(II) (Cu^{2+}) or $KMNO_4$, and the process is mediated by temperature and converts polyphenols to microspheres. Polyphenols transform to reactive semiquinones and quinones as an intermediate in the B ring at specific temperatures and ambient atmosphere. The nucleophilic addition involving a quinone is responsible for inter-flavan oligo/polyphenol successive coupling and formation. In this reaction, the formation of microparticles is mediated through quinone or semiquinone, and Cu^{2+} acts as a catalyst in this process.[15] The formation of oligomeric/polymeric polyphenols takes place with the reduction of temperature and the aggregation into spherical precipitates via noncovalent interaction. These polymeric polyphenols can be biodegraded by a thiolysis reaction and can be easily cleaved in the presence of glutathione (GSH). These microporous particles can be used to deliver various pharmaceuticals and diagnostic reagents.

POLYPHENOL BIOSPHERES BY OXIDATIVE COUPLING ASSEMBLY

Camellia sinensis leaves are known as green tea and have been widely studied for their health benefits, and there is evidence that various catechins are responsible for their pharmacological and biological actions.[16] Catechin is a polyphenolic compound that makes up 30% of the dry weight of plant leaves. The metal scavenging and antioxidant activity are related to the di- or trihydroxy vicinal functional groups of catechins, but at the same time, these structural features expose catechins to atmospheric oxidation.[17] Chen et al.[14] first described the water, temperature, and Cu^{2+}-directed oxidative coupling assembly of polyphenols of green tea to synthesize green fluorescent, monodisperse, smooth, porous, and hollow spheres. The important synergistic effect of temperature and Cu^{2+} was observed in enhancing the hydrophobic anchoring effect and expanding interfacial bonds, leading to the assembly of oligomeric/polymeric catechin spheres. The biosphere tea catechins were investigated by the MTT assay in MG63 human osteoblast-like cells, demonstrating cytocompatibility. Fluorescein isothiocyanate (FITC), rhodamine B isothiocyanate (RB), and doxorubicin hydrochloride (Dox) were loaded into these biospheres. The FITC- and RB-loaded biospheres were monodisperse green and red nanomaterials, indicating that biospheres can also be used for bioimaging purposes.[14]

Doxorubicin (Dox) was loaded into these biospheres, and the size of the Dox@biosphere (about 780 nm) was the same as that of the empty biosphere, confirming that Dox is mainly incorporated into the biosphere cavity. The positively charged Dox interacts strongly with the negatively charged biosphere, resulting in high Dox loading (15.4 wt %) into the biosphere. The presence or absence of different concentrations was used to evaluate glutathione (GSH)-mediated release of Dox from the Dox@biosphere under physiological conditions. A small amount of Dox (0.5 wt % Dox loaded into cells) was detected in the absence of GSH, while the release rate was increased to 30.2% in the presence of GSH (1.75 mM). About 96% of Dox was released from microspheres at 4.2 mM GSH. The thiolysis reaction led to the cleavage of the C4−C8(6) interfacial bond of proanthocyanidins and polyphenol monomers in the presence of GSH, suggesting the presence of procyanidin-like bonds in the biospheres (Figure 1). The cytosol of cells

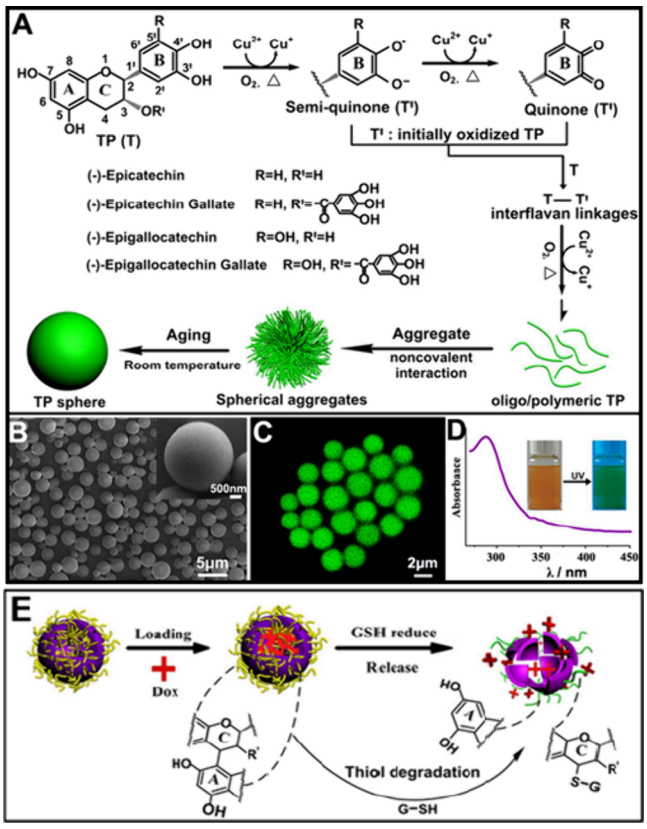

Figure 1. (A) Steps involved in the temperature controlled and Cu^{2+} directed oxidative assemblies of green tea polyphenols. (B) SEM of biospheres. (C) CLSM of tea polyphenol biospheres. (D) UV−vis spectra and suspended microspheres in water. (E) Various steps involved in the Dox loading and GSH-stimulus release.

contains different concentrations of GSH, and most normal cells have a GSH concentration of less than 2 μM, but cancer cells can have a GSH concentration of up to 10 μM.[18] This difference in GSH concentration can be used for targeted delivery of cancer drugs and helps in the design of biomaterials that can load high amounts of anticancer drugs and be cleaved inside cancer cells to release the drug molecules.

In the past decade, gene therapy has been thoroughly researched and investigated, and direction has been achieved for the clinical translation from the lab.[19,20] Recently, gene therapy has revolutionized traditional cancer therapy, and a gene therapy product was approved in 2020. Although there was tremendous advancement in this area, there are still various challenges, like poor stability of gene drugs.[21] Han et al.[22] developed a polyphenol−DNA nanocomplex with controllable assembly or disassembly behavior to release drugs in cancer cells in a responsive and sustained manner. The DNA having branches achieved the loading of multiple genes, and then tannic acid was used to form a nanocomplex. The disassembly of the nanocomplex led to efficient intracellular gene/drug release, and the acidic microenvironment of lysosomes induced nanocomplex disassembly to release tannic acid and branched DNA.[22] Cytoplasmic glutathione and

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DNase I initiated the controlled release of genes from the branched DNA.

Similarly, hollow nanoparticles developed using polyphenols have shown interesting characteristics as a biomaterial for drug delivery, catalysis, and energy storage.[23] An open (cup-shaped) nanoparticle architecture can perform better due to increased interior surface access. The synthesis of polyphenol-based hollow nanoparticles is mainly limited to tannic acid and lignin and involves various strategies such as cationic polymers, metal ions, and sacrificial templates.[24] To develop an improved assembly strategy for various polyphenol compounds, Chen et al.[25] prepared polyphenol nanoparticles with a spherical structure by self-assembling tea polyphenols by polymerization in a few minutes. The cup-shaped nanoparticles exhibited strong free radical scavenging, antitumor activity and high loading ability for guest molecules such as DOX and methylene blue.[25] Guest molecules were released pH-dependently, making them useful for the drug delivery of various drug molecules.

Amyloid disease in humans is characterized by the deposition of associated amyloid fibers.[26,27] In green tea, epigallocatechin-3-gallate (EGCG) has been considered one of the main health-promoting properties in various disorders, including amyloidogenic diseases.[28,29] The polyphenolic structure of EGCG works through an unknown mechanism to inhibit amyloidogenesis and cleave various amyloidogenic peptides that form amyloid fibrils *in vitro*. The pharmacological effects of EGCG may be related to its antioxidant potential.[30] However, the oxidized product of EGCG seems to be enough to remodel amyloid against certain polypeptides. Sequential and controlled oxidation of EGCG can produce microparticles and biomaterials for drug delivery. Fernandez et al.[31] developed oxidative coupling assembly mediated homogeneous EGCG microparticles and analyzed their activity in the protein aggregation associated with Parkinson's disease [alpha-synuclein (α-syn)]. Microspheres stimulated the remodeling of mature amyloid fibrils and prevented amyloidogenic α-syn aggregation. The microspheres revealed mild toxicity toward dopaminergic cells and microglial cells. At the same time, EGCG microspheres also decreased the toxic effect of α-syn oligomers.[31] In addition, EGCG microspheres loaded with other anti-amyloidogenic compounds demonstrated increased activity against amyloid aggregation.

Non-steroidal anti-inflammatory drugs (NSAIDs) like diclofenac sodium are among the most endorsed and utilized medications for pain relieving, antipyretic, and anti-inflammatory activities.[32] The utilization of NSAIDs is steadily rising with an increase in the cases of inflammatory disorders. Nevertheless, it has been reported that the continued utilization of NSAIDs leads to serious unfavorable consequences, including bleeding gastric ulcers, erosions of the mucosal layer, perforation, and strictures in the gastrointestinal (GI) tract.[33] Developing gastrointestinal system sparing NSAIDs or drug delivery systems is a critical and important area of research. Quercetin is a 3-hydroxyflavone of the anthoxanthin subgroup of flavonoids and is another abundant dietary flavonoid. Quercetin has a polyphenolic structure responsible for the different biological activities.[34] Quercetin and its microspheres have shown various potential biological and pharmacological applications in drug delivery, including antioxidant, antibacterial, anticancer, anti-inflammatory, and antiallergic impacts. Recently, we have synthesized quercetin microspheres using oxidative coupling assembly in the presence of Cu^{2+}. These microspheres were loaded with diclofenac sodium in the space of the microspheres.[15] The quercetin microspheres loaded with diclofenac showed *in vivo* gastrosparing anti-inflammatory activity better than diclofenac sodium in rodents.

Assembly of more than two constituents simultaneously with desired well-designed nanostructures can modulate various biochemical and physical properties.[35−38] However, the development of such nanoparticles involves tedious and time-consuming protocols. The development of single-step nano/microspheres has attracted attention in recent years.[39,40] One-pot large-scale preparation of autofluorescent tea polyphenol (TP)-based core@shell nanostructures by using irradiation of microwaves was reported by Fei et al.[41] The mechanism involved the microwave-assisted oxidative self-assembly and aggregation of homogeneously defined core@shell nanocomposites. This strategy was used to make Ag@TP and Au@TP nanocomposites. The same group synthesized near-infrared (NIR) absorption based hollow Au/Ag@TP bioconjugates using a simple galvanic replacement reaction.[41] A heterogeneous Ag@TP nanostructure exhibited strong antibacterial activity without typical cytotoxicity, making it an excellent low-toxicity biomaterial for antibacterial therapy.

Cardiovascular diseases (CVDs) remain one of the main causes of mortality in the entire globe.[42] The targeted drug therapy approach in heart disease is a challenging and new area of research. Qi et al.[43] designed a polyphenol-mediated self-assembly methodology for targeting cardiac diseases. Gallic acid, catechin, epigallocatechin gallate, and tannic acid (TA) were used, along with three carrier materials. Despite various carrier materials, TA-derived nanoparticles exhibited excellent free radical scavenging activity, particularly those produced from a cyclodextrin-derived bioactive material (TPCD). Cardiomyocytes took up the TPCD/TA nanoparticles (TPTN), protecting the cells from hypoxic−ischemic injury. In myocardial hypertrophic mice and rats with ventricular fibrillation cardiac arrest, the TPTN was deposited in the injured heart cells after intravenous injection, resulting in remarkable bioactivity in both heart disorders.[43] The TPTN also exhibited an excellent safety profile in preliminary experiments, and results further explained that TPTN can be a useful nanotherapy for targeted treatment of heart disorders.

POLYPHENOL COATING BASED ON OXIDATIVE COUPLING ASSEMBLY

Browning of fruits and vegetables, leather tanning, and fermentation of green tea are the oxidation of plant polyphenols to form high molecular weight species.[44] The formation of layers composed of epigallocatechin gallate (EGCG), epicatechin gallate (ECG), tannic acid (TA), and pyrogallol (PG) is influenced by factors such as the oxidation reaction.[45] The polyphenol-based layer forms readily in the presence of oxygen under slightly alkaline conditions (pH 7.8), facilitated by the phenolate ion intermediate. The reaction is very similar to that of the coating caused by polymerization and dopamine. Further research is needed to fully understand the coating synthesis mechanism. However, it has been observed that the oxidation process, particularly through oligomerization, diminishes the solubility of polyphenols and increases their affinity for surfaces, leading to surface deposition. Mass spectrometry detected high molecular weight species in the PG layer and polymerization solution.[46] The ability of plant polyphenols to produce coatings was first

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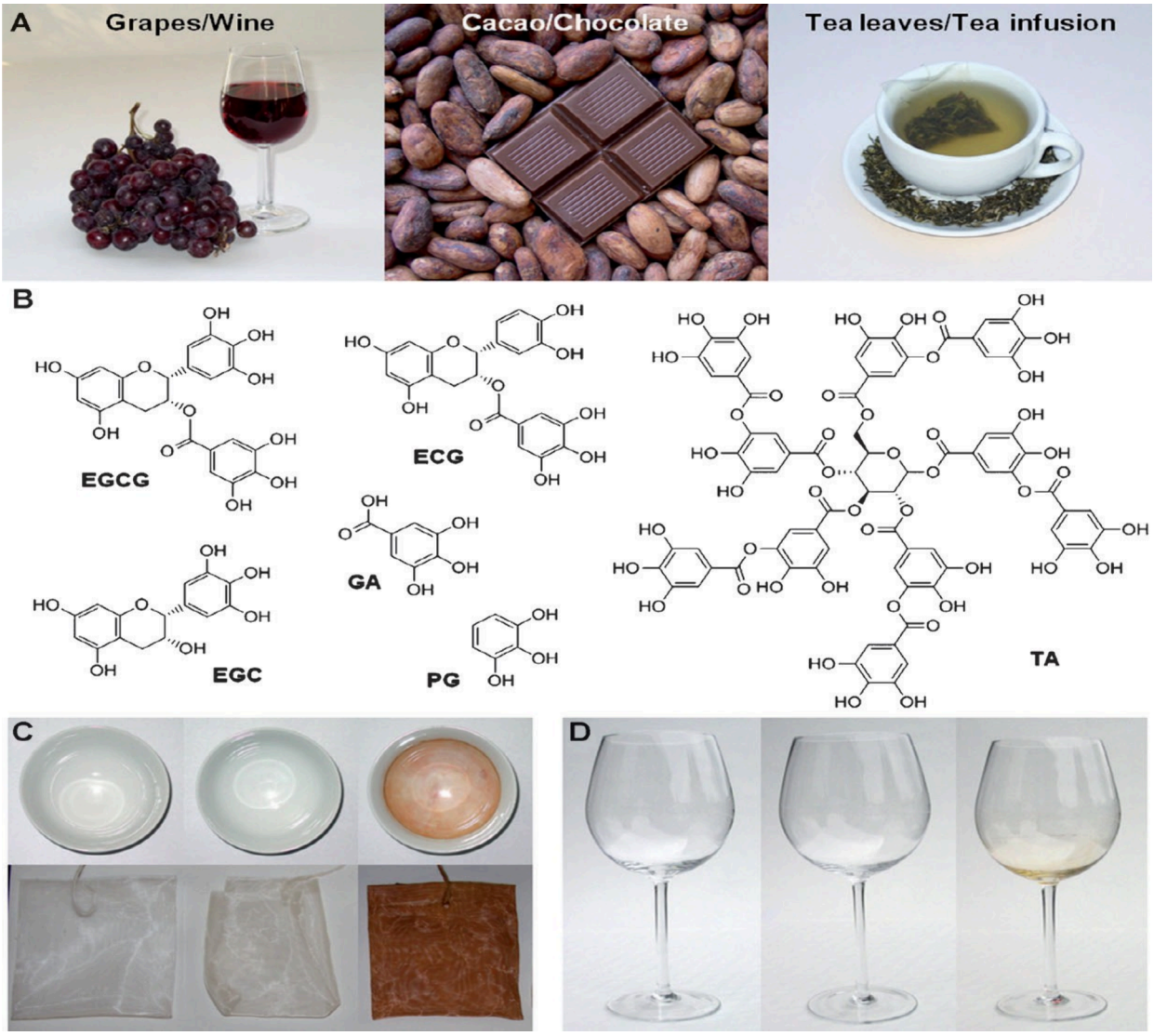

Figure 2. Polyphenol-rich foods and beverages showing surface coating. (A) Grapes/red wine, cacao beans, chocolate, green tea leaves, and tea decoction are rich in polyphenols and can be used as a source of coating. (B) Structures of plant polyphenols and polymers. (C) Coatings of polyphenols on the surface of cup with tea decoction and tea bag after silver nitrate treatment. (D) Coating on the surface of glass with wine polyphenols and after silver nitrate treatment.

demonstrated in a simple experiment, using pure wine and tea. Interestingly, this experiment showed that thin polyphenol coatings directly formed on surfaces exposed to these polyphenolic-rich drinks[47] (Figure 2). Green tea was brewed in a porcelain cup and left for several hours, and when the cup was washed with water, it did not show any color on the cup. However, by immersion of the tea cup in $AgNO_3$ solution, it was found to have a thin layer of polyphenols. The redox reaction between Ag^+ ions and the polyphenols resulted in a black metallic silver layer coating on the surface (Figure 2). The tea bags used for the decoction also did not change but turned dark after treatment with silver nitrate.

Many useful functions can be achieved through polyphenol coatings. Plant polyphenols are secondary metabolites used by biological defense systems in plants. Polyphenol coatings derived from TA and PG showed contact-dependent antibacterial properties against Gram-negative and Gram-positive strains.[48] After 3 h of exposure to TA-modified PC, *Pseudomonas aeruginosa* and *Staphylococcus aureus* were reduced 30-fold. At the same time, these coatings were nontoxic to mammals. This coating showed no cytotoxicity to NIH 3T3 fibroblast cells, and this coating also demonstrated the ability to neutralize free radicals and nonradical reactive oxygen species (ROS). Plain tissue culture polystyrene (TCPS) and polyphenol-coated silica nanoparticles (FS) have been demonstrated to exhibit antioxidant properties in chemical and cellular studies. It has also been observed that plant-inspired polyphenol coatings can modulate the optical properties of inorganic nanoparticles.[49] The modulation of gold nanorods (Au NRs) was achieved by PG-stabilized coating at 895 nm plasmon resonance. The suspension stabilized with cetyltrimethylammonium bromide (CTAB) containing Au NRs in 0.1 mg mL^{-1} of PG demonstrated the displacement of CTAB bonds and the formation of a thin closed PG layer on Au NRs (Au-PG NRs). The electron imaging displayed PG adlayers with an apparent density of less than 5 nm against the iron core. Energy-dispersive X-ray spectroscopy revealed a bimetallic nanorod structure (Au-PG-Ag) with a gold core and a silver shell after addition of silver nitrate to the suspension. The silver layer thickness increased

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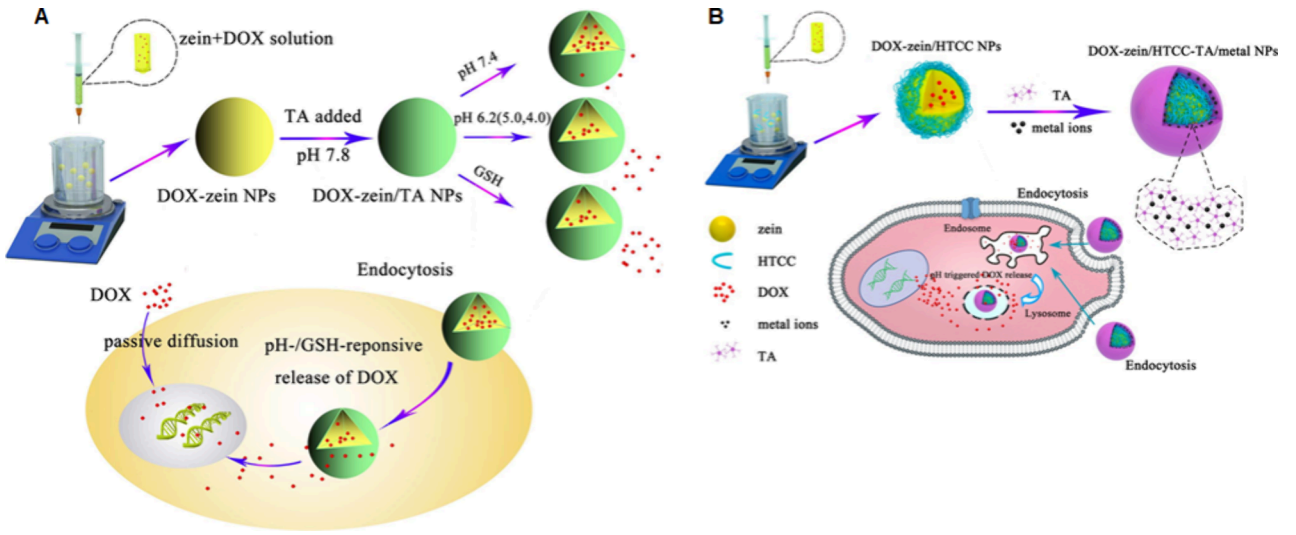

Figure 3. (A) Development of DOX-loaded zein nanoparticles with tannic acid coating layers and the hypothesized mechanism for GSH and pH-mediated drug release in the cancer cells. (B) Development of DOX-loaded zein/HTCC nanoparticles coated by metallic-tannic acid layer and the hypothesized mechanism for the pH-sensitive release of DOX in HepG2 cancer cells.

with $AgNO_3$ concentration with the plasmon resonance wavelength ending with a blue shift. Metal nanoparticles are often used for diagnostic and therapeutic purposes, and their ability to modulate their optical properties can be utilized in various applications.[48]

The micro- or macro-organism deposition on wetted surfaces, also called biofouling, has been a major issue, leading to a burden to the maritime industry of approximately 30 to 50 billion dollars per year.[50] Decreasing the deposition of microorganisms and preventing microbial biofilm synthesis by altering the surface properties are emerging areas of research. Bio-organic functional polymer coatings with designed antifouling and antimicrobial properties deliver a green substitute.[51−53] In the oxidative coupling assembly based polyphenolic coating, tannic acid (TA) was used as an anchor in polymer brushes. Brominated tannic acid (TABr) precursor was prepared by substituting tannic acid with the alkyl bromide functionality. TABr with trihydroxyphenyl groups can easily anchor to metals, metal oxides, polymers, glass, and silicon. The terminal alkyl bromide is the starting point for atomic radical polymerization (ATRP). The stainless steel surface was coated with TABr and it was graft polymerized with cationic [2-(methacryloxy)ethyl]trimethylammonium chloride (META) and zwitterionic 2-methacryloyloxyethyl phosphorylcholine (MPC) and *N*-(3-sulfopropyl)-*N*-(methacryloxyethyl)-*N*,*N*-dimethylammonium betaine (SBMA). Brushes with cationic polymers were found to be bactericidal, while resistance to bacterial adhesion was observed with zwitterionic coatings. At the same time, microalgal adhesion and barnacle cyprid settlement on functionalized polymer-coated layers was decreased when compared with pure stainless steel surfaces.[54] Therefore, bidirectional TABr initiator initiation provided an effective means of preventing microfouling and macrofouling of polymer brushes.

Instability due to the oxidation of food items, medicine, and other consumer goods can be enhanced by trace elements, like iron and copper, and scavenging free radicals afterward.[55] After polymerization, plant-derived phenolic compounds containing catechols have free radical scavenging, metal coating, and surface adhesive properties. Roman et al.[56] synthesized biomimetic polyphenol coatings to develop antioxidant-active coatings. Two synthetic routes were studied for applying polyphenol coatings on polypropylene surfaces by *in situ* polymerization of catechol and catechin and by oxidative polymerization by lacquer and alkali salts. Both layers of polyphenols showed strong metallocatalytic and radical scavenging abilities, indicating antioxidant ability. The dual function of polyphenolic coatings as efficacious free radical scavengers and anchors makes them prominent candidates for an active coating that can prevent metal oxidative damage.[56]

Developing antimicrobial fabrics and textiles capable of protection from a broad range of microbes is essential and has wide applications.[57] However, fabricating antimicrobial textiles is difficult due to desirable colorless and breathable properties, harmful or harsh chemicals, tedious synthetic routes, and complex and time-consuming development processes.[58−63] Richardson et al.[64] developed a quick approach for depositing antimicrobial coatings using polyphenols and silver ions. Interestingly, the coating was colorless, thin (<10 nm), quickly collected, and could be easily coated by dipping or spraying. It was observed that metal−phenolic coatings on textiles retained lipid-encapsulated viruses thousands of times better than other metal-ion coatings while maintaining their effectiveness after five washes.[64] In addition, coating layers also inhibited Gram-positive and Gram-negative bacteria and fungi and prevented odors on clothes even after ten washes. Since the coating can be synthesized easily, uses simple and reliable precursors, and can be applied at home or in the workplace, it presents a wide array of applications.

New versatile coated zein nanoparticles based on a polyphenol oxidative conjugation mechanism were synthesized by Liang et al.[65] This layer was formed by the oxidative polymerization of polyphenols in basic conditions, which can be biodegraded by acidic pH and can affect the pH-sensitive properties of the system.[65] A high concentration of cellular glutathione (GSH) can lead to degradation of the polyphenolic layer, exhibiting the rapid release of antitumor drugs encapsulated in the cells (Figure 3A). Drug-coated polyphenol-loaded zein NPs were observed to have marked internalization and cytotoxic effects in HeLa cells. Delayed

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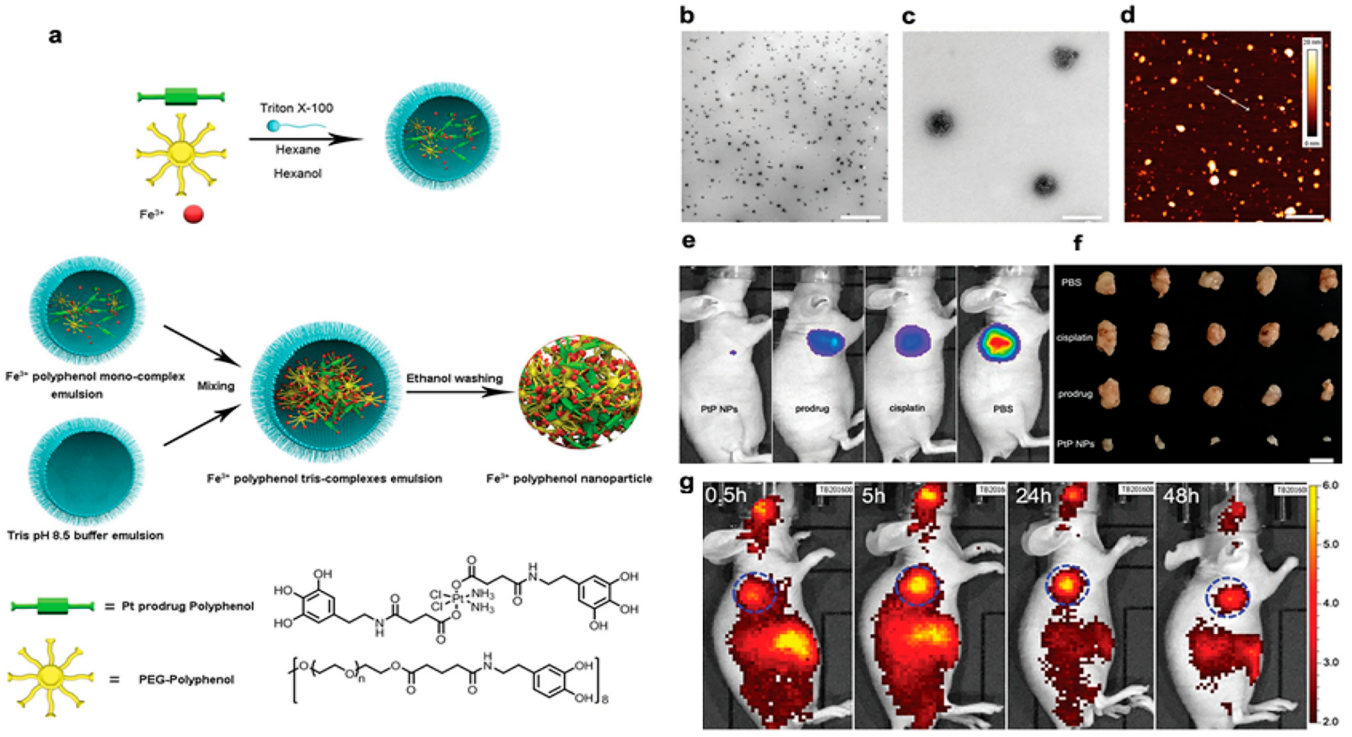

Figure 4. (a) Self-assembly of PtP NP. (b, c) Transmission electron microscopy of PtP NPs. (d) Atomic force microscopy image of PtP NPs after air-drying. (e) Bioluminescence images of mice bearing luciferase PC3 cell xenograft tumors after 10 days of treatment. (f) Luciferase-expressing PC3 tumors from experimental groups at the 21st day. (g) Time-dependent fluorescence imaging of Ce6-labeled PtP NPs intravenously injected into mice with luciferase-expressing PC3 xenograft tumors; the blue circle shows the site of the tumor.

drug release from coated zein nanoparticles compared to free or DOX-loaded zein nanoparticles was revealed by pH-responsive release of DOX in the extracellular medium. At the same time, acute toxicity and morphological monitoring exhibited delayed drug release from the coated nanoparticles.

SELF-ASSEMBLY OF METAL–PHENOLIC NETWORK

Research and interest in fabricating assembly based coordination networks of polyphenols and metal ions, known as metal–phenolic networks (MPNs), has increased in recent years for biodesign, drug delivery, and many biological applications.[66,67] Self-assembly of organic compounds and metallic functionalization significantly contribute to therapeutic applications. The galloyl and catechol phenol groups behave as versatile pH-sensitive chiral sites for coordinating metals such as Fe^{3+}. The polyphenol hydroxyl structure can chemically react with organic or inorganic materials, among which MPNs formed by coordination with metal ions and polyphenol derivatives formed by interactions with organic matter exhibit specific properties and functions. Hence, MPNs have been researched extensively in nanomaterials, bimolecular interfaces, molecular engineering, targeted delivery systems, and anticancer therapy.[68] These MPN complexes have pH sensitivity, desirable size, strength, and tunable permeability based on polyphenol–metal ion pair selectivity. The development of self-assembled metal–phenolic meshes has been studied for various applications over the past decade.[69−73]

Polyphenol–Metal Networks and Anticancer Activity. Liang et al. developed a pH-responsive stimuli-based system using the coordination of metal–tannic acid networks integrated in zein/tetragonal chitosan (HTCC) nanoparticles.[74] The coordination bond between NH_2–metal and metal–TA was sensitive to pH changes that helped release the coated drug under constant pH conditions. Zein/HTCC nanoparticles coated with a metal–TA film have a spherical outlay with a particle size of 110–120 nm. Doxorubicin (DOX), an antitumor agent, was studied for cell secretion and viability. The *in vitro* drug release profile of DOX-loaded metal–TA layers showed significant pH sensitivity when coated with zein/HTCC nanoparticles (DOX–zein/HTCC–TA/metal NPs), and the sensitivity was changed with the amount or type of metal ions. In an *in vitro* cell study, bare zein/HTCC–TA/metal nanoparticles demonstrated decreased toxicity toward cells, but DOX-loaded nanoparticles showed higher cytotoxic activity against HepG2 cancer cells. The proposed mechanism of release of DOX inside HepG2 cancer cells is represented in Figure 3B.

Similarly, a self-assembled PEGylated MPN emulsion at the interface of oleic acid was developed by Besford et al.[75] Coated emulsions, called E-MPNs, were about 100–250 nm in diameter, were stabilized in the presence of serum proteins, and exhibited *in vivo* cellular binding and secretory activity with a half-life of about 50 min. The E-MPNs are mostly deposited in the liver and were biodegraded after 1 day. Furthermore, it has been shown that Dox can accumulate inside E-MPNs with a high encapsulation capacity of about 5.3 fg of Dox per particle. Drug release was pH-mediated and was demonstrated using MPNs as an encapsulation layer. Dox drug-encapsulating E-MPNs demonstrated strong cytotoxicity toward human breast cells, indicating clear cellular internalization and active drug release. The results showed a simple self-assembly methodology to produce a low-degradability nanomaterial emulsion with pH-sensitive dissociation charac-

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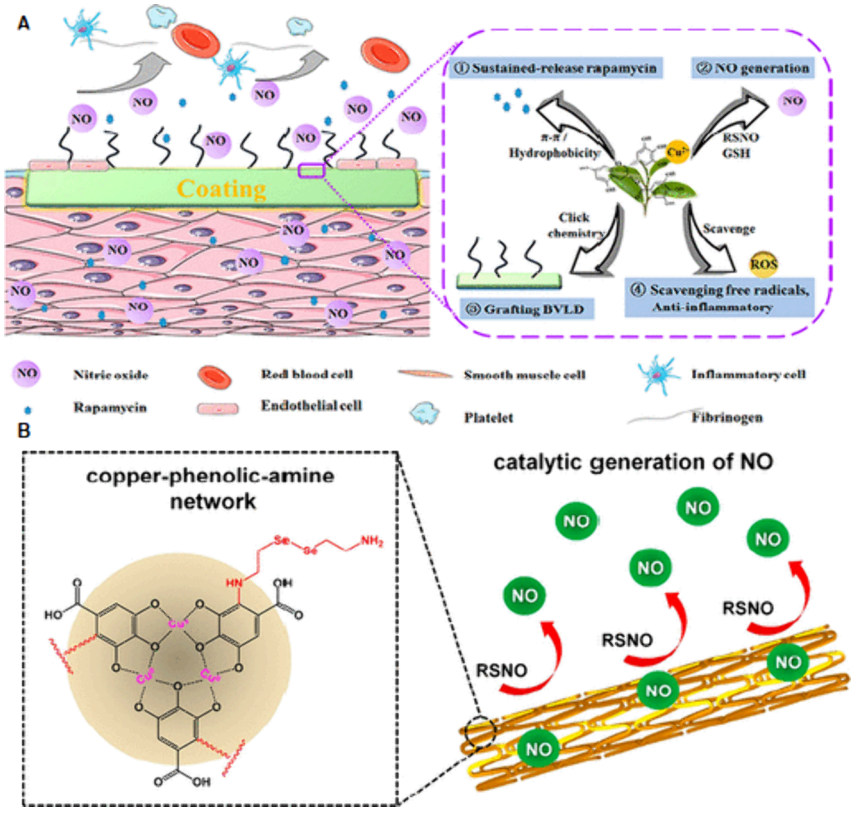

Figure 5. (A) Metal−EGCG network was incorporated with rapamycin, and immobilized bivalirudin (BVLD) provided sustained rapamycin and NO release. (B) GA/Cu^{2+}/SeCA coating and catalytic release of NO.

teristics that can be optimized for various therapeutic applications.[75]

Therapeutic nanoparticles have markedly improved cancer treatment as they avoid the limitations of traditional therapeutics.[75−78] Dai et al.[79] developed a simple and fast methodology to assemble poly(ethylene glycol)-modified Pt nanocomplexes synthesized using metal−polyphenol complexation (Figure 4a−d). The nanoemulsion (PtP NPs) was about 100 nm in diameter, exhibiting excellent encapsulation and mild pollutant properties. PtP NPs have been evaluated for their productive use as an antitumor agent. Mass cytometry was used *in vitro* to determine the number of nanoparticles and the drug concentration per cell. The emulsion (PtP NPs) has a high circulation time, with a half-life of about 18 h in mice. A human prostate tumor xenograft mouse model was used to screen the anticancer activity of PtP NPs.[79] The results showed four times better tumor growth inhibition when compared with the free product or cisplatin (Figure 4e−g).

NO-Releasing Polyphenol−Metal Network. In the study by Zhang et al.,[80] a micro/nanoscale copper ion assembly was made by $\pi-\pi$ interactions, coordination of metal, and oxidative polymerization of epigallocatechin gallate (EGCG). The metallo-EGCG system is conjugated to rapamycin and immobilized bivalirudin (BVLD) by thiolene "click chemistry" and yielded sustained release of rapamycin and NO (Figure 5A). In contrast to rapamycin-eluting stents, those coated with the EGCG−Cu−rapamycin−BVLD complex competitively promoted endothelial cell (EC) growth of smooth muscle cells, showed long-lasting antithrombotic effects, and demonstrated the negative effect of rapamycin on ECs. In the animal model, stent implantation showed that the coating exhibited endothelial regeneration and avoided restenosis.[80]

In another study, Yang et al.[81] demonstrated that the gallic acid−copper (GA-Cu^{2+}) layer has a catalytic activity similar to glutathione peroxidase (GPx). It showed continuous NO gas production from endogenous nitrosothiol (RSNO). The NO-producing layer of GA, selenocysteine (SeCA), and Cu^{2+} demonstrated stable, long-lasting, and controllable NO production (Figure 5B). The optimal coating stopped platelet activation and favored the adhesion and proliferation of human umbilical vein endothelial cells (HUVEC). Furthermore, this coating markedly improved the antithrombotic and antirestenosis abilities of the stent in animal models, which could be an interesting strategy for treating cardiovascular disease. Since metal ions have excellent catalytic abilities, especially transition metals, this strategy may be used to study catalytic reactions processed by MPN interfaces for other pharmacological applications.[81]

Antimicrobial and Antifouling Applications. *Bacillus subtilis* is currently an important probiotic microbe that can be formulated as spores for delivery, but its ability to colonize inside the gut remains controversial.[82,83] To improve its use, the cells must be transported in a vegetative state, which is prevented because of the sensitivity of *B. subtilis*. The *B. subtilis* was protected from lyophilization using a self-assembled metal−phenolic network (MPN) on the cell membrane. These MPNs are classified as a novel class of self-assembled biomaterials composed of polyphenols and metallic ions, and the protection efficiency of MPNs has been ascertained to depend on the MPN constituents used to assemble them. The size of polyphenols and the stability of metal−phenol complexes are critical criteria that affect cell protection.

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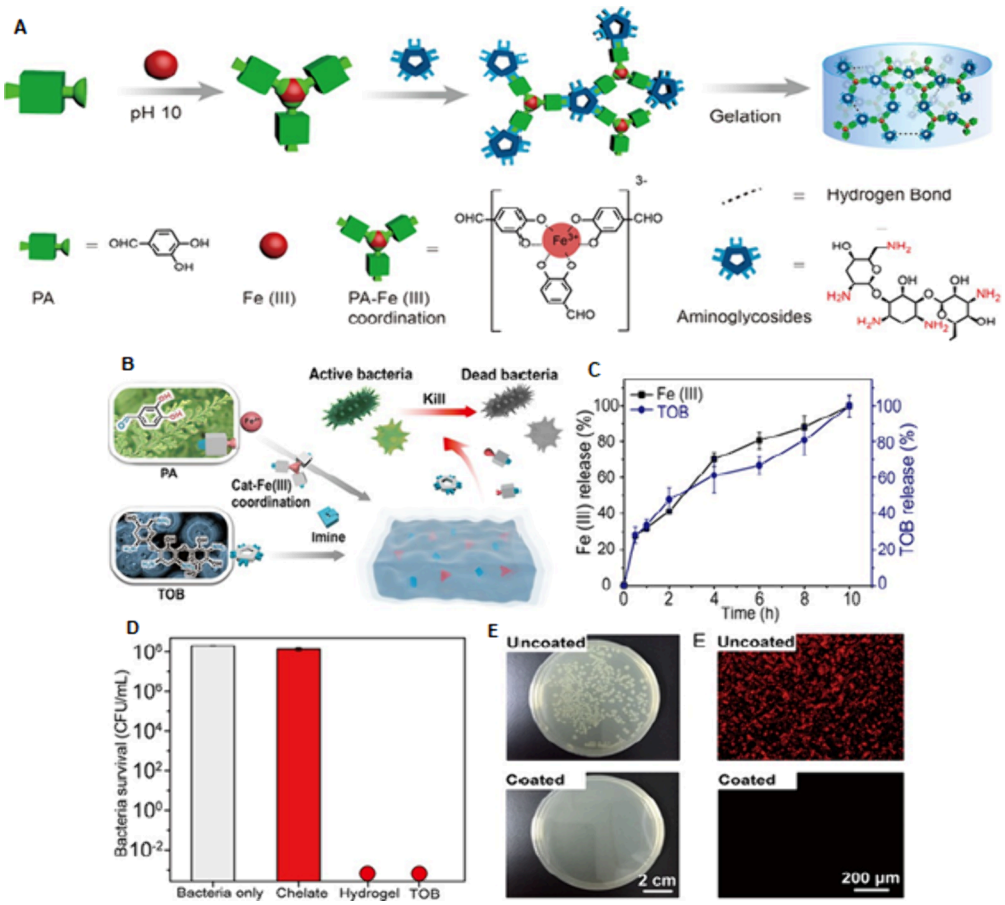

Figure 6. (A) Dynamic covalent bonds used to develop smart hydrogel by using PA/Fe^{3+}/aminoglycoside. (B) Antibacterial activity of the PA/Fe^{3+}/tobramycin hydrogel. (C) Release studies of tobramycin and Fe^{3+} from hydrogel *in vitro*. (D) *In vitro* bactericidal activity of PA/Fe^{3+}/tobramycin hydrogel against *E. coli*. (E) Optical images of agar media cultured with bacteria and fluorescence images of RFP-expressing *E. coli* incubated on uncoated and coated substrates.

Bacterial colonization involves exposure to gut acidic conditions and intestinal fluids. MPN coatings were quickly degraded by a fairly acidic environment but were found to protect *B. subtilis* from the adverse effects of acid. The MPNs were optimized to protect vegetative *B. subtilis* cells from the stress of lyophilization and for a better understanding of the role of each constituent in MPNs.[83]

Smart hydrogels are functional materials with three-dimensional networking that can dramatically change their shape or mechanical nature in stimulus to different physical and chemical responses.[84−90] Interest in recent years has developed in hydrogels due to their promising application in stored medicine, sensors, tissue science, and actuators. Li et al.[91] studied the synthesis of a smart hydrogel by using low molecular weight organic and inorganic blocks including aminoglycoside, protocatechualdehyde (PA), and Fe^{3+}. These smart hydrogels are unique and have several advantages compared to other fabrication methodologies. These gels are superior gelators with intermittent gelation properties and marked antibacterial activity.[91] The presence of multiple dynamic and reversible cross-links and hydrogen bonds in the gel network can lead to dynamic properties, i.e., thixotropic and self-healing properties, and can be affected by various stimuli (e.g., temperature, light, redox, pH). Aminoglycoside smart gels have shown potent antibacterial activity (Figure 6) and can be further optimized for commercial development.

Several biological substances, proteins, and cells on a medical device's surface can cause plaque deposition, infection, and functional damage to the implants.[91−96] Metal−phenol networks (MPNs) have presented promising interest among chemicals and biomaterials due to their biocompatibility, versatility, and multifunctionality. Zheng et al.[97] developed a facile method to prepare an antifouling, antimicrobial, and substrate-free coating that can be modulated from the metallic coordination bond and catecholic groups. Various polymers like dopamine methacrylamide (DMA) and poly(ethylene glycol) methyl methacrylate (PEGMA) were used to synthesize the catecholic hydrophilic copolymers. A comparative study was done between ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions along with p(PEGMA-*co*-DMA) to evaluate the formation of MPN films. Various spectroscopic and microscopic techniques evaluated the bonding sequence between p-(PEGMA-*co*-DMA) and the iron ions. At the same time, ellipsometric assessments were performed to yield film thickness and bonding density, and the pH-sensitive behavior of the MPN film was evaluated at various pH, demonstrating rapid disassembly of the network at low pH. The antifouling coating characteristics were investigated by exposure to *Escherichia coli* and *Staphylococcus epidermidis* bacteria and NIH-3T3 fibroblasts under a fluorescence microscope and cell imaging analysis. The results showed that the MPN from complexation p(PEGMA-*co*-DMA) and metallic ions provided remarkable antifouling, pH-sensitive, and compatible charac-

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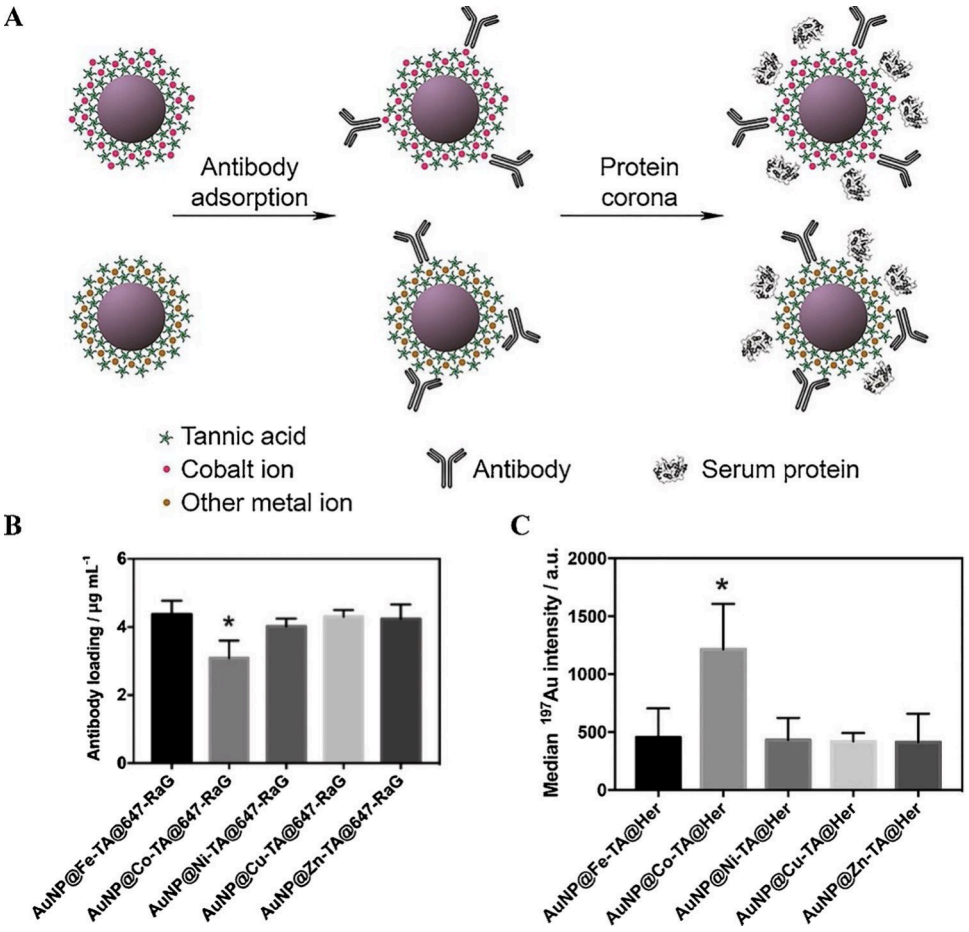

Figure 7. (A) Representation of adsorption of antibody on various metallic ion-based AuNP@MPNs. (B) Antibody encapsulation capacity of AuNP@MPN particles. (C) Antibody-conjugated AuNP@MPN particles to target cells.

teristics in various substrates. In addition, releasing iron ions can significantly reduce bacteria growth.[97]

Silica and metallic nanoparticles have also been studied for their antibacterial properties; however, it is still challenging to develop a degradable carrier to achieve a sustained release profile, high bacterial efficacy, and biocompatibility.[98−103] Zhang et al.[104] produced nanosilver-decorated mesoporous organosilica nanoparticles (MONs) using an organic polyphenolic compound, tannic acid (TA), as a reducing agent to produce nanosilver. This green reaction is a simple one-pot method that did not require presynthesis of silver NPs, template deprotection, or the utilization of any toxic reducing agents. The resulting Ag-MONs formed by dispersed nanosilver exhibited matrix-based silver ion degradation in response to glutathione (GSH), resulting in impermeable Ag-mesoporous silica nanoparticles (MSNs), Ag NPs, with strong antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*. Moreover, Ag-MONs exhibited superior biocompliance compared to Ag NPs and $AgNO_3$ at a similar dose of silver.[104]

Miscellaneous Applications. Cardiovascular diseases (CVDs) are considered to be the foremost reason for death worldwide, mainly caused by a sedentary lifestyle, consumption of alcohol, smoking, and obesity.[105] For improving and prolonging the life of cardiovascular disease patients, nondegradable stents are now extensively used in hospitals. However, nondegradable implants have many issues, like late thrombus and stent restenosis, and can be life-threatening.[106] Therefore, it is important to design biodegradable implants to treat CVD. Metallic material magnesium (Mg) and its alloys have been extensively researched as a biomaterial for implants. However, the challenge remains because of the high corrosion rate and inadequate acceptability after implantation.[107] Zhang et al.[108] developed a layer-by-layer (LBL) methodology on a magnesium alloy (AZ31) substrate to coat it with Mg-doped epigallocatechin gallate (EGCG). The surface morphology results showed that the EGCG/Mg layer formed polyphenol−Mg complexes and showed a crack-free, dense homogeneous layer, compared to the EGCG layer alone. Electrochemistry and other processes examined the resistance to corrosion and the degradation rate, which showed that the corrosion rate was significantly reduced after EGCG/Mg protection compared to AZ31 alone. Thrombogenicity tests *in vitro* and *ex vivo* showed that the EGCG/Mg coating was effective in improving reducing adhesion as well as activation of platelets and erythrocytes, partial thromboplastin time (APTT) and antithrombogenicity in comparison to AZ31 alone. At the same time, *in vivo* subcutaneous testing showed that the EGCG/Mg coating had a better soft tissue response due to increased resistance to the corrosion of the surrounding microenvironment.

Furthermore, for the abdominal aorta assay, the AZ31 wire coated with EGCG/Mg showed improved resistance to corrosion and increased re-endothelialization compared to the AZ31 wire alone. The findings revealed that the EGCG-coated Mg^{2+} multilayer coating increased the protection from corrosion and biocompatibility of biodegradable cardiovascular

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stents.[108] In another study by Lee et al.,[109] EGCG and magnesium ions (Mg^{2+}) in a metal−polyphenol network (MPN) were formed on a titanium alloy (Ti-6Al-4V, Ti). The EGCG-Mg^{2+}-coated Ti drastically increased the ALP activity and mRNA expression when cultured on human adipose-derived stem cells (hADSCs) *in vitro*. At the same time, the EGCG-Mg^{2+}-coated Ti markedly increased the calcium content and increased mineralization of hADSCs when compared to cells grown on Ti. The EGCG-Mg^{2+} coating markedly decreased the osteoclastic maturation of Raw264.7 cells by reducing tartrate-resistant acid phosphatase activity compared to cells grown on Ti.[109] Along similar lines, Han et al.[110] designed and developed mussel-inspired self-assembly of a tannic acid layer on the surface of titanium implants by using poly(ethylene glycol) (PEG) and 8DSS (8 repeating units of aspartate−serine−serine). The coating layer was developed to decrease bacterial deposition through the superhydrophilic effect of PEG and potentiate osseointegration via biomineralization of 8DSS. The obtained Ti/8DSS/PEG implant exhibited better anti-biofouling ability against *S. aureus* and *E. coli*, as well as better biocompatibility. At the same time, this implant improved osteoblast differentiation and demonstrated better osteogenic capability than titanium implants *in vivo*.[110]

Similarly, Zhang et al.[111] developed a sandwich-like layer-by-layer (LBL) metallic−polyphenol network by using polyelectrolyte chitosan and heparin and the embedment of the EGCG-Cu complex. The network was made stable by EGCG with different intermolecular interactions in the LBL coating and helped sustain heparin release over 90 days. The catalytic decomposition of endogenous *S*-nitrosothiols by copper ions led to the sustained release of heparin and continuous *in situ* nitric oxide production. The result revealed the enhanced durability of anticoagulation and suppression of the inflammatory response.[111] At the same time, the vascular endothelial growth factor was upregulated, and the coating helped the growth of endothelial cells with a significant reduction in the proliferation and migration of smooth muscle cells (SMCs).

Using natural building blocks for tissue engineering is an interesting approach via decellularization. Unfortunately, natural scaffolds that are not cross-linked have weak biomechanics and fast degradation and cannot be used in cardiovascular surgeries. Li et al.[112] developed a cross-linked and functionalized building block by self-assembly of copper@tea polyphenol nanoparticles (Cu@TP-dBPs). The Cu@TP-dBPs were compatible and could reduce bacterial reproduction and potentiate the development of capillary-like networks. Cardiac patch graft models confirmed that Cu@TP-dBP patches demonstrated improved in-growth of functional blood vessels and extracellular matrix remodeling within 60 days. These functional patches possessed antibacterial and proangiogenic activities.[112]

Antibody immobilization on the surface of nanoparticles to prevent recognition by antigen is an important area of research in nano-biotherapeutics.[113] Electrostatic and hydrophobic interactions are responsible for antibody binding on nanoparticles; these binding forces are usually difficult to control. In addition, antibodies can be fixed, denatured, or misdirected after the next washing step, leading to reduced antigen recognition. In 2020, Zhang et al.[114] developed MPN (Figure 7A) gold nanoparticles (AuNPs) by using different metals (Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, or Zn^{2+}) and studied their physical adsorption of antibodies to reveal their targeting abilities for antigens. Iron ions added to gold nanoparticles coated with MPNs (AuNP@MPNs) are modified particles coated with antibodies. However, Co^{2+} containing AuNP@MPNs showed the highest enhancement of antigen recognition even at lower antibody loading compared to other metallic systems (Figure 7B). Covalent MPNs can improve targeting ability because the transition metal ion binds to the histidine-rich part of the Fc segment using an inorganic coordination bond. Co^{2+} has been shown to have a higher solvent-reactive ion concentration than that of other metals, facilitating binding to histidine-rich regions of the antibody.

Furthermore, the protein corona can stabilize AuNP@MPNs after antibody adsorption without significantly reducing their ability to target them (Figure 7C). To improve particle targeting using MPNs, this strategy may be useful for diagnosis and targeted drug delivery.[114] In another recent study, metal−phenolic self-assembly shielded probiotics in a hydrogel, stimulating wound healing with antibiotic treatment. Probiotic microbes release various secondary metabolites that help to speed up the process of wound healing, but unfortunately, the excessive use of antibiotics hampers the survival of probiotic flora. Zhou et al.[115] designed a metal−phenolic self-assembly that can protect probiotics (*Lactobacillus reuteri*, *L. reuteri*@FeTA) to avoid the effect of antibiotics. The surface of *L. reuteri* was covered with a metal−phenolic layer to adsorb and inactivate antibiotics. An injectable hydrogel (Gel/L@FeTA) formed by carboxylated chitosan and oxidized hyaluronan was loaded with shielded probiotics. Gel/L@FeTA helped the survival of probiotics and led to the continuous secretion of lactic acid to perform biological functions in gentamicin. At the same time, the Gel/L@FeTA hydrogels showed a better result than Gel/L in inflammatory regulation, angiogenesis, and tissue regeneration *in vitro* and *in vivo* in the presence of antibiotics.[115]

A flexible metal−polyphenol material that can respond to various external solutes like glucose and dextran was developed by Wanjun Xu et al.[116] Experiments have inferred the biomolecular mechanisms underlying the host behavior of MPNs computationally. The study showed the multimodal coordination sites and binding affinity between ligands and metal ions.[116] After the exposure to guest stimuli, glucose is somewhat replaced by quercetin and installed in MPNs due to its comparable single-particle interactions, thus leading to the remodeling of the metal−polyphenol network and the change in the physiochemical properties. Insulin was added to the MPNs, and external stimuli regulated their release. Glucose molecules can be dynamically incorporated into MPNs after mixing, leading to the configuration of metal−phenolic networks and changing their physicochemical properties for practical purposes. The study expands understanding of the basic interactions between metal−phenolic biomaterials and single guests, which is important for developing effective biomaterials for different applications.

REGULATORY CHALLENGES AND TOXICITY ISSUES

Biomaterials developed by using oxidative coupling assembly of polyphenols have many advantages, such as nontoxicity, biocompatibility, and biodegradability, and their use has been steadily increased due to the high demand for medical applications. These materials have been successfully used as hydrogels, scaffolds, matrices, and implants in tissue engineering, wound management, drug delivery, and nanotechnology. The use of natural biomaterials may lead to cost savings in

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healthcare because they can be safely absorbed by the body without additional surgeries. However, biodegradability is also a disadvantage of natural materials because they may not be as durable as traditional synthetic materials and can easily suffer from wear and tear due to intensive interaction with the body. Despite these limitations, the biocompatibility and nontoxicity of natural biomaterials can outweigh their biodegradability disadvantages in many medical applications.[117] But at the same time, more data on their toxicity profile is required, and evaluation of toxicity of these biomaterials is a challenge.

The safety of a biomaterial should be viewed from a risk management perspective, and its complete life span should be considered in order to analyze its associated risks. Generally, not only the biomaterial but also its potential degradation products and sterilization residuals should not cause any harmful local or systemic effects in the host tissues. A wide range of *in vitro* and *in vivo* tests may be used to evaluate cytotoxicity, genotoxicity, pyrogenicity, local effects following implantation, hemocompatibility, sensitization potential, and systemic toxic effects of biomaterials.[118] If further information on the carcinogenicity or reproductive/developmental toxicity is published, then they will also be considered. In very rare cases, additional tests are also carried out if required by regulators. Evaluation of biomaterials has not kept pace with the development of new biomaterials. According to the "Innovation or Stagnation" report issued by the FDA in 2004: "Not enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated. Approval requirements for a specific biomaterial are not the same in different regulatory systems and dissimilar regulations for a specific product makes development of biomaterials a costly and time-consuming process."[119]

CONCLUSION AND FUTURE SCOPE

This review is dedicated to the recent advancements in the development of oxidative self-assembly based biospheres and biological interfaces modulated by the assembly of MPNs. With the fast development of materials science with numerous biomedical applications, several self-assembled nano/microspheres and coating materials have been prepared to modulate surface characteristics. The oxidative self-assembled biomaterials and coatings with potential for biological and therapeutic applications have been extensively researched in the past few years. These polyphenolic self-assembled biomaterials can modulate the bioapplications of the designed materials, which can have a critical impact on the therapeutic outputs. Traditionally, nano/microspheres and coatings are synthesized using petrochemicals; many are hypersensitive. Developing biospheres and coatings using naturally occurring organic molecules is an interesting and newer area in biomaterials. The pH- and GSH-responsive biomaterials can be effective for the delivery of anticancer and antimicrobial substances selectively inside cells and can also contribute to the decrease of side effects and resistance problems. Moreover, these biomaterials are developed from organic and naturally occurring polyphenols, which may be nontoxic and hyposensitive.

Bioactive interfaces can be developed using metallic−phenol network (MPN) coatings. MPNs have demonstrated various advantageous properties, such as adhesion-controlled composition, desired pore size, stimuli responsiveness, selective permeability, and heat stability. The dietary polyphenols are abundant, and various metal ions can be used to design and develop a wide array of MPNs as biomaterials. At the same time, MPNs can intrinsically interact with several biomolecules, modify various molecular mechanisms, and control biochemical properties. The polyphenol-based oxidative assembly based biospheres and coatings have emerged as potential candidates for drug delivery, antibody immobilization, NO-releasing material, and antimicrobial gels.

Although the assembly process and control of MPN formation are among the biggest challenges, several techniques have been tried to control the dynamics, structure, and properties of MPNs and biospheres. The polyphenols can interact nonspecifically with the biomolecules. At the same time, polyphenols are converted into quinones on oxidation; these quinones can covalently bind to amine-containing biomolecules. The probable toxicity risk of quinones and heavy metal ions used in synthesizing these coatings and biospheres is a matter of concern for biosafety. The *in vivo* biodegradation of MPN coatings and biospheres developed by oxidative coupling assembly is another critical issue for their commercial applications. This area of research has only just started to explore the real potential of biospheres and MPN coatings, and there is still important scope for further research. More insight and additional studies are required to develop safe, effective, and green biomaterials for various biomedical and therapeutic uses.

AUTHOR INFORMATION

Corresponding Authors

Manu Sharma − *Department of Chemistry and Toxicology, National Forensic Sciences University, Delhi 110085, India*; Email: lantadene@hotmail.com

Abhishek Tiwari − *Pharmacy Academy, IFTM University, Moradabad, U.P. 244102, India*; Email: abhishekt1983@gmail.com

Vinoth Kumarasamy − *Department of Parasitology and Medical Entomology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur 56000, Malaysia*; Email: vinoth@ukm.edu.my

Vetriselvan Subramaniyan − *Pharmacology Unit, Jeffrey Cheah School of Medicine and Health Sciences, Monash University, Bandar Sunway 47500 Selangor Darul Ehsan, Malaysia*; orcid.org/0009-0009-1027-5714; Email: subramaniyan.vetriselvan@monash.edu

Authors

Jyoti Pal − *Department of Chemistry and Toxicology, National Forensic Sciences University, Delhi 110085, India*

Varsha Tiwari − *Pharmacy Academy, IFTM University, Moradabad, U.P. 244102, India*

Manish Kumar − *Department of Pharmaceutics, ISF College of Pharmacy, Moga, Punjab 142001, India*

Ajay Sharma − *School of Pharmaceutical Sciences, Delhi Pharmaceutical Sciences and Research University, New Delhi 110017, India*

Waleed Hassan Almalki − *Department of Pharmacology, College of Pharmacy, Umm Al-Qura University, Makkah 21421, Saudi Arabia*; orcid.org/0000-0003-2584-8510

Sami I. Alzarea − *Department of Pharmacology, College of Pharmacy, Jouf University, Sakaka 72388, Saudi Arabia*

Imran Kazmi − *Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia*

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Gaurav Gupta − *Centre for Global Health Research, Saveetha Medical College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu 602105, India; School of Pharmacy, Graphic Era Hill University, Dehradun 248007, India; School of Pharmacy, Suresh Gyan Vihar University, 302017 Jaipur, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c08528

Author Contributions

Jyoti Pal, Vinoth Kumarasamy, and Vetriselvan Subramaniyan contributed to writing the manuscript and literature search. Varsha Tiwari, Manish Kumar, and Ajay Sharma contributed to formal analysis, methodology, and supervision. Waleed Hassan Almalki, Sami I. Alzarea, and Imran Kazmi prepared figures. Manu Sharma, Abhishek Tiwari, and Gaurav Kumar contributed supervision and writing the manuscript. All authors agree to take responsibility for all aspects of their work to ensure integrity and accuracy.

Notes

The authors declare no competing financial interest.

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