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Review

Integrating Antioxidant Functionality into Polymer Materials: Fundamentals, Strategies, and Applications

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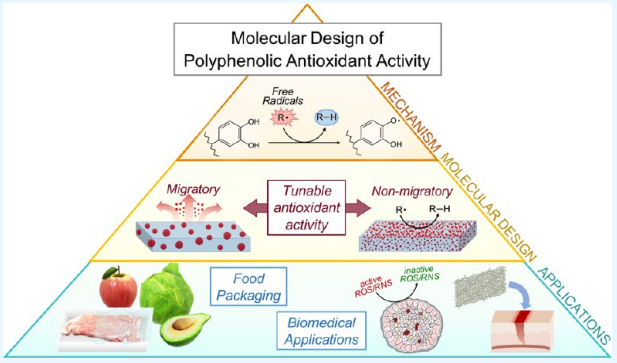
ABSTRACT: While antioxidants are widely known as natural components of healthy food and drinks or as additives to commercial polymer materials to prevent their degradation, recent years have seen increasing interest in enhancing the antioxidant functionality of newly developed polymer materials and coatings. This paper provides a critical overview and comparative analysis of multiple ways of integrating antioxidants within diverse polymer materials, including bulk films, electrospun fibers, and self-assembled coatings. Polyphenolic antioxidant moieties with varied molecular architecture are in the focus of this Review, because of their abundance, nontoxic nature, and potent antioxidant activity. Polymer materials with integrated polyphenolic functionality offer opportunities and challenges that span from the fundamentals to their applications. In addition to the traditional blending of antioxidants with polymer materials, developments in surface grafting and assembly via noncovalent interaction for controlling localization versus migration of antioxidant molecules are discussed. The versatile chemistry of polyphenolic antioxidants offers numerous possibilities for programmed inclusion of these molecules in polymer materials using not only van der Waals interactions or covalent tethering to polymers, but also via their hydrogen-bonding assembly with neutral molecules. An understanding and rational use of interactions of polyphenol moieties with surrounding molecules can enable precise control of concentration and retention versus delivery rate of antioxidants in polymer materials that are critical in food packaging, biomedical, and environmental applications.



KEYWORDS: *polyphenols, antioxidant, self-assembly, food packaging, polymer films, antimicrobial*

1. INTRODUCTION

Natural antioxidants, commonly found in fruits,[1] vegetables,[2] nuts,[3] cereals,[4] herbs and spices,[5] teas,[6] and wines,[7] are often associated with anti-inflammatory, anticancer, and antiaging benefits, because of their potential to minimize oxidative stress and unwanted damage to cells caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS).[8−10] The role of antioxidants, specifically polyphenols, in balancing ROS and RNS levels in biological systems is achieved through their inhibition of ROS-generating enzymes[11] and chelation with ROS-forming ferrous (Fe^{2+}) ions,[12] in addition to their powerful radical-scavenging abilities.[13] However, the need to scavenge free radicals is not only limited to biological systems; many industrial applications involving materials that are vulnerable to oxidative degradation require antioxidant protection, including most organic polymers.[14] For example, antioxidants are regularly used as stabilizing additives for commercial polymers, such as polypropylene (PP) and polyethylene (PE), to inhibit environmental degradation and extend the service life of the polymer, particularly in outdoor applications.[15] The incorporation of antioxidants within a polymeric matrix has significant advantages, such as protecting vulnerable polymers from active scavenging radicals and oxidation, along with the associated anti-inflammatory, antimicrobial, and immunomodulatory properties benefiting biological systems. This combination of properties is of specific importance to food packaging and biomedical applications,[16−18] yet an understanding of the principles of antioxidant inclusion in a polymer matrix is necessary to leverage their antioxidant activity.

This Review focuses on polyphenols as one of the most abundant classes of antioxidants (with over 8000 phenolic structures identified in plants[19]) that have no or low toxicity in

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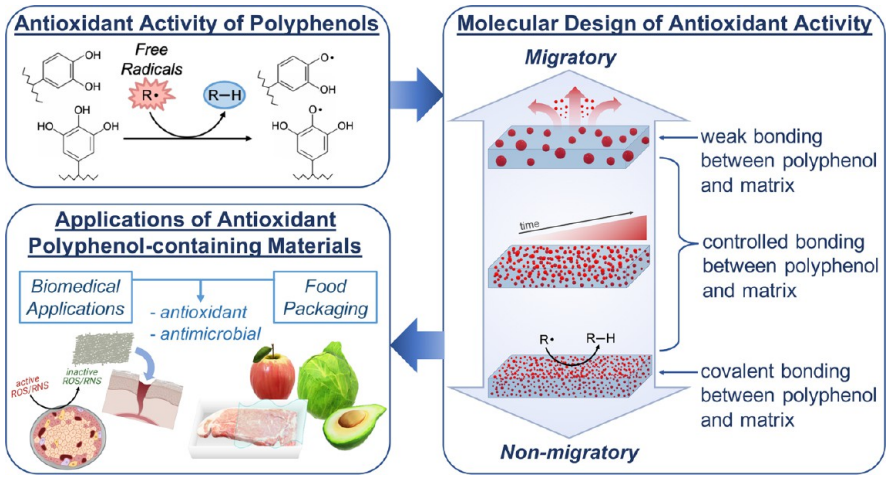

Figure 1. Outline for the structure of this Review. Graphics were created with BioRender.com.

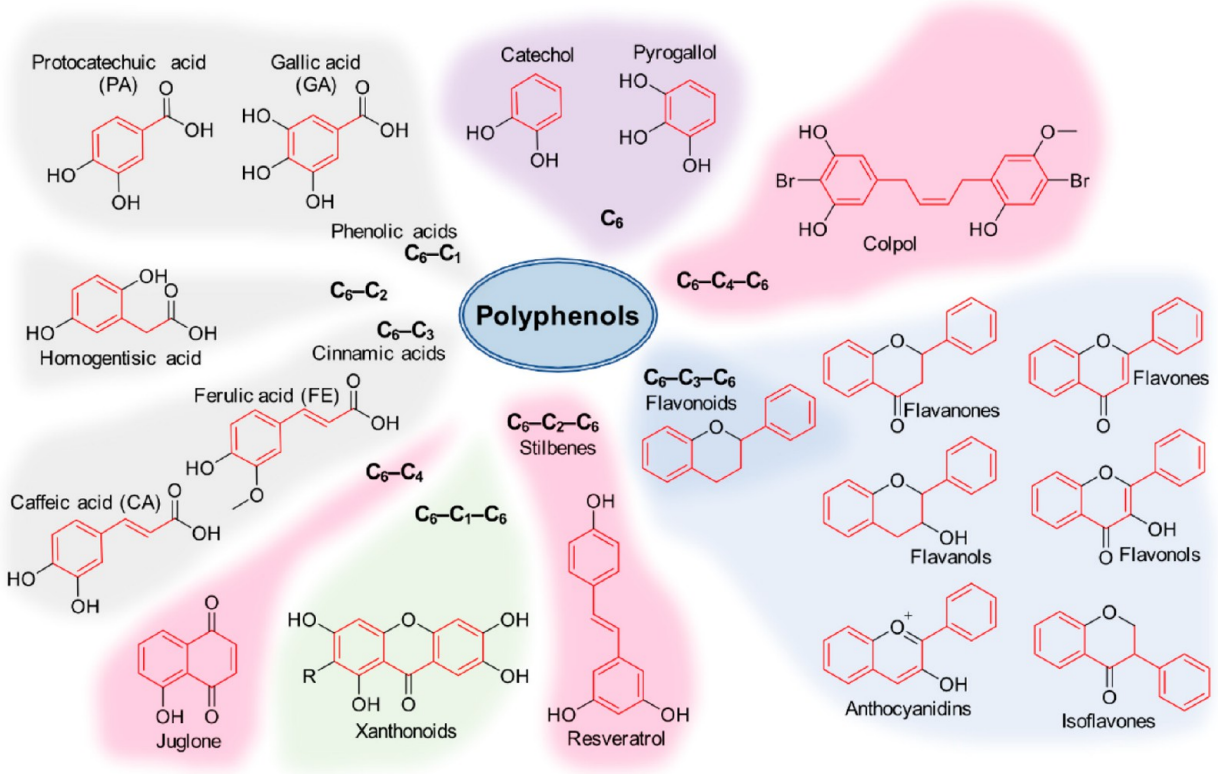

Figure 2. Classification of natural polyphenols based on the number of carbon atoms in the structure. The "C_6" label represents an aromatic ring.

reasonable doses[20,21] and highly potent antioxidant activity.[22] While recent reviews have discussed the general properties of polyphenol assemblies,[23−26] the health effects of polyphenol conjugates,[27] or specific applications of polyphenol−polymer materials,[28−33] this Review instead hopes to bring together the diverse areas of food science, biomedical engineering, analytical chemistry, and materials science by making fundamental connections between the antioxidant activity of polyphenols within polymer matrices to the strength, type of antioxidant−polymer interactions, and intended application. The diverse chemical structures of polyphenols enable strategic selection from a wide array of chemical properties, including the number of functional groups, molecular size, hydrophobicity, and intrinsic antioxidant activity. Moreover, the presence of polyphenol functional groups opens an opportunity for inclusion of these antioxidants in materials via hydrogen bonding, metal coordination, or covalent interactions. One promising example of using polyphenols as building blocks for synthesis of new materials, i.e., formation of metal-phenolic networks, has been widely summarized in recent years through many excellent reviews[34−38] and thus is not included in this discussion. The scope of this Review will not cover another important class of polyphenol adhesives—mussel-inspired dopamine-based materials—because of their prior extensive coverage,[39−44] and the mechanism of their activity (such as synergistic action of catechol groups with other amino acid groups and oxidation cross-linking)[45] being distinct from the polyphenols covered here.

This Review aims to emphasize opportunities in rational development of polymeric materials with controllable incor-

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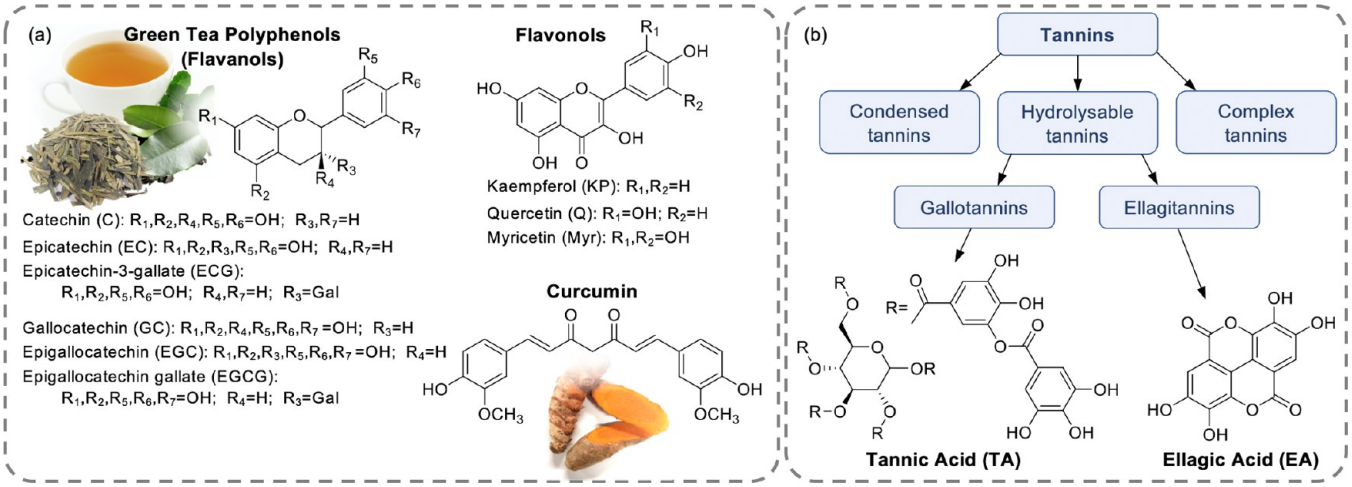

Figure 3. (a) Chemical structures of well-known low-molecular-weight polyphenols. (b) Classification of tannins, showing structures of extensively studied tannins: tannic acid (TA) and ellagic acid (EA).

poration and release of active antioxidant molecules and highlight their recent applications in food packaging and biomaterials. A schematic outline of this Review is presented in Figure 1. With specific focus on the chemically diverse family of polyphenols, the main goal is to provide an overview of the mechanisms of relevant interactions of varying strengths between polyphenols and polymers, including noncovalent and covalent bonding. Recent advances that employ these interactions in antioxidant polymer assemblies are critically analyzed and compared, with specific focus on the antioxidant retention and activity of the polyphenol-containing polymer materials. Finally, novel applications of these materials in food packaging and biomedical applications are highlighted, and outlooks on the future of polyphenol-polymer materials are provided.

2. POLYPHENOLS AS ORGANIC ANTIOXIDANTS

Antioxidants can be classified in various ways based on their origin, solubility, enzymatic activity, and chemical structure. Based on their origin, antioxidants are classified as natural (extracted from plants,[46] fungi,[47] etc.[48]), synthetic, or semisynthetic, which are made by chemical modification of natural antioxidants for enhanced stability or antioxidant activity.[49,50] Antioxidants can be classified as water-soluble or lipid-soluble,[51] as well as enzymatic (like superoxide dismutase, catalase, and glutathione peroxidase), which prevent oxidative damage to cells and biomolecules,[52] and nonenzymatic. Nonenzymatic antioxidants are represented by various classes of compounds such as polyphenols, carotenoids, vitamins C and E, and glutathione,[53] as well as some peptides, phospholipids, polysaccharides, and amines.[54]

2.1. Classifications of Polyphenols. The majority of natural antioxidants are represented by polyphenols, which are a vast class of phenol derivatives with more than one hydroxyl group attached to an aromatic ring.[53] Most natural polyphenols are small molecules that can be classified in several ways. As demonstrated in Figure 2, nonpolymeric natural polyphenols can be classified based on the number and arrangement of carbon atoms in the molecule.[55−57]

Catechol and pyrogallol represent the C_6 class of molecules containing a single aromatic ring. The C_6-C_1, C_6-C_2, and C_6-C_3 classifications are mainly represented by various phenolic acids and constitute about one-third of the polyphenols in plants.[55] $C_6-C_3-C_6$ compounds include chalcones, aurones, and flavonoids.[57] Flavonoids have a common structure consisting of three rings: one aromatic ring conjugated with a heterocycle that is substituted with another aromatic ring.[58] With modification of the common flavonoid structure, they can be classified as flavanones, flavanols, isoflavones, flavones, flavonols, and anthocyanidins.[59]

Structures of some of the most well-known low-molecular-weight, nonpolymeric polyphenols are presented in Figure 3a. A group of highly researched flavanols—green tea polyphenols—are typically extracted from green teas as a mixture of epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin gallate (EGCG), and are well-known for their potential health benefits.[60] Flavonols, including kaempferol, quercetin, and myricetin, are some of the most abundant flavonoids in foods.[61,62] Curcumin, one of the major components of turmeric, notably has a seven-carbon chain connecting partially methylated phenol rings. This hydrophobic compound is insoluble in water, yet soluble in nonpolar solvents and ethanol, making curcumin a great antioxidant agent for lipid-containing products.

Lignins, lignans, and tannins are distinguished among high-molecular-weight polyphenols. Lignin—a polymeric polyphenol that provides structural support in plants[57]—is built from phenylpropanoids polymerized through ester bonds, while lignans are dimers and oligomers built from the same building blocks. Tannins—named for their ability to tan animal skins into leather—are a wide variety of compounds with the ability to interact with proteins.[57] As shown in Figure 3b, tannins are classified in three groups: condensed tannins, hydrolyzable tannins, and complex tannins.[57] Condensed tannins, or proanthocyanidins, are formed by condensing flavanol units into oligomers that release anthocyanidins upon hydrolysis, hydrolyzable tannins release polyphenol molecules upon hydrolysis with the most important examples of tannic acid and ellagic acid. Lastly, complex tannins consist of a catechin unit with a glycosidic linkage to a gallotannin or ellagitannin.

The versatile chemical properties of natural polyphenols have inspired the development of new synthetic polymers that incorporate polyphenol functionalities. These novel polymers can be categorized by whether an existing polymer is modified with polyphenol groups, or if a new polymer is synthesized by polymerization of polyphenol-containing monomers. The

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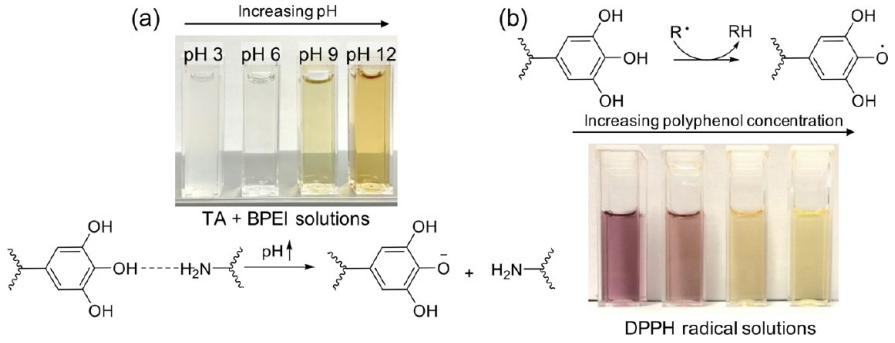

Figure 4. Schematic and graphic representation of (a) pH-dependent hydrogen-bonded complex formation between tannic acid (TA) hydroxyl groups and branched polyethylenimine (BPEI) amino groups, and (b) antioxidant activity of TA. Reduction of 2,2-diphenyl-1-picrylhydrazyl ($DPPH^{\bullet}$) is visualized by the loss of violet color.

former category achieves polyphenolic functionality; however, this process does not offer precise control over the polyphenol positioning or the regularity of polyphenol substitution. Alternatively, polymers in the latter category allow precise control over polyphenol content and have been shown to demonstrate high antioxidant activity in solution,[63,64] as well as in films.[65] These polymers were used for the production of films or coatings targeted toward applications as adhesives,[66−68] low-fouling materials,[69] or within batteries.[70−72]

2.2. Chemical Properties of Polyphenols. With the presence of hydroxyl-substituted aromatic rings, polyphenol molecules are able to participate in a variety of intermolecular and intramolecular interactions such as hydrogen bonding,[73] electrostatic interactions,[74] $\pi-\pi$ stacking,[75] covalent bonding,[76] and hydrophobic interactions.[77] Polar hydroxyl groups work as donors and acceptors of hydrogen bonds, resulting in a well-known propensity of polyphenols to intermolecular[78] and intramolecular[79−81] hydrogen bonding (Figure 4a). In addition, the combination of a relatively high acidity of hydroxyl groups with a flat-shaped active site provides polyphenols with chelating abilities for several transition-metal ions.[82,83] Finally, the conjugation between the aromatic ring and multiple hydroxyl groups leads to a higher acidity of polyphenols than alcohols, enhancing their antioxidant and radical scavenging capabilities (Figure 4b).

2.3. Proposed Mechanisms of Polyphenol Antioxidant Activity. Free radicals form under the impact of ionizing radiation (e.g., ultraviolet (UV) light), pollutants, inflammation, and other irritants and oxidizing agents.[84] An unpaired electron makes free radicals typically unstable and highly reactive toward organic molecules.[52,85] For example, the ROS/RNS cause oxidation of lipids in membranes,[86] starting a chain of oxidation reactions, which damage biomolecules. Antioxidants reduce highly reactive free radicals by turning into more stable radicals themselves, breaking the chain of radical reactions, or quenching initiators of chain reactions.[52,87]

The following reaction describes the general mechanism of polyphenol antioxidant activity:[88]

$$ArOH + R^{\bullet} \rightarrow ArO^{\bullet} + RH \quad (2.3.1)$$

Understanding the specific radical-scavenging mechanism of a polyphenol is necessary for an accurate evaluation of reaction kinetics and proper selection of an appropriate antioxidant. For example, flavonoids are not efficient against peroxides, preventing the radical lipid oxidation in the propagation stage, but they can efficiently scavenge in the initiation step.[89] Several mechanisms have been proposed[90] to describe polyphenol antioxidant activity, which differ in the first radical transfer process and intermediate structure formation. In most cases, the antioxidant donates or receives an electron from the free radical and provides a hydrogen ion to the free radical. However, the sequence of electron and proton transition may vary between antioxidants and conditions. The most common mechanisms described are *hydrogen-atom transfer* (HAT), *proton-coupled electron transfer* (PCET), *radical adduct formation* (RAF), *signal electron transfer* (SET), *electron transfer-proton transfer* (ET-PT), and *sequential proton-loss electron transfer* (SPLET).[90]

Two mechanisms—HAT and PCET—execute the proton and electron transfer in a single kinetic step, as shown in reaction 2.3.1. In HAT, the proton and electron transfer to the same orbital of the radical species simultaneously.[89] In PCET, several molecular orbitals of the radical and antioxidant engage in the transfer[89] through a hydrogen-bonded phenol-radical transition state, according to density functional theory (DFT) calculations.[91] The proton and electron also transfer simultaneously, but the proton and the electron are transferred between different pairs of atomic orbitals in the free radical and the antioxidant.[92] Typically, flavonoids follow PCET to transfer a hydrogen atom from the hydroxyl groups.[89]

SET involves the transfer of an electron and proton in several kinetic steps.[93,94] However, in contrast to prior mechanisms, the proton is transferred from another molecule:[94]

$$ArOH + R^{\bullet} \rightarrow ArOH^{+} + R^{-} \quad (2.3.2)$$

$$ArOH^{+} + H_2O \rightarrow ArO^{\bullet} + H_3O^{+} \quad (2.3.3)$$

$$R^{-} + H_3O^{+} \rightarrow RH + H_2O \quad (2.3.4)$$

The SET mechanism was observed, for example, for (+)-catechin and its analogues against peroxyl radicals,[95] and resveratrol against oxygen radicals.[96]

Opposite to PCET, ET-PT involves the subsequent electron and proton transfer in a two-step process:[93]

$$ArOH + R^{\bullet} \rightarrow ArO^{+}H + R^{-} \quad (2.3.5)$$

$$ArO^{+}H + R^{-} \rightarrow ArO^{\bullet} + RH \quad (2.3.6)$$

The ET-PT mechanism described reactions between xanthones and radicals $^{\bullet}OH$ or $O_2^{\bullet -}$.[93]

At high pH, SPLET can be initiated first by a proton loss of the polyphenol, followed by protonation of the formed anion:[89]

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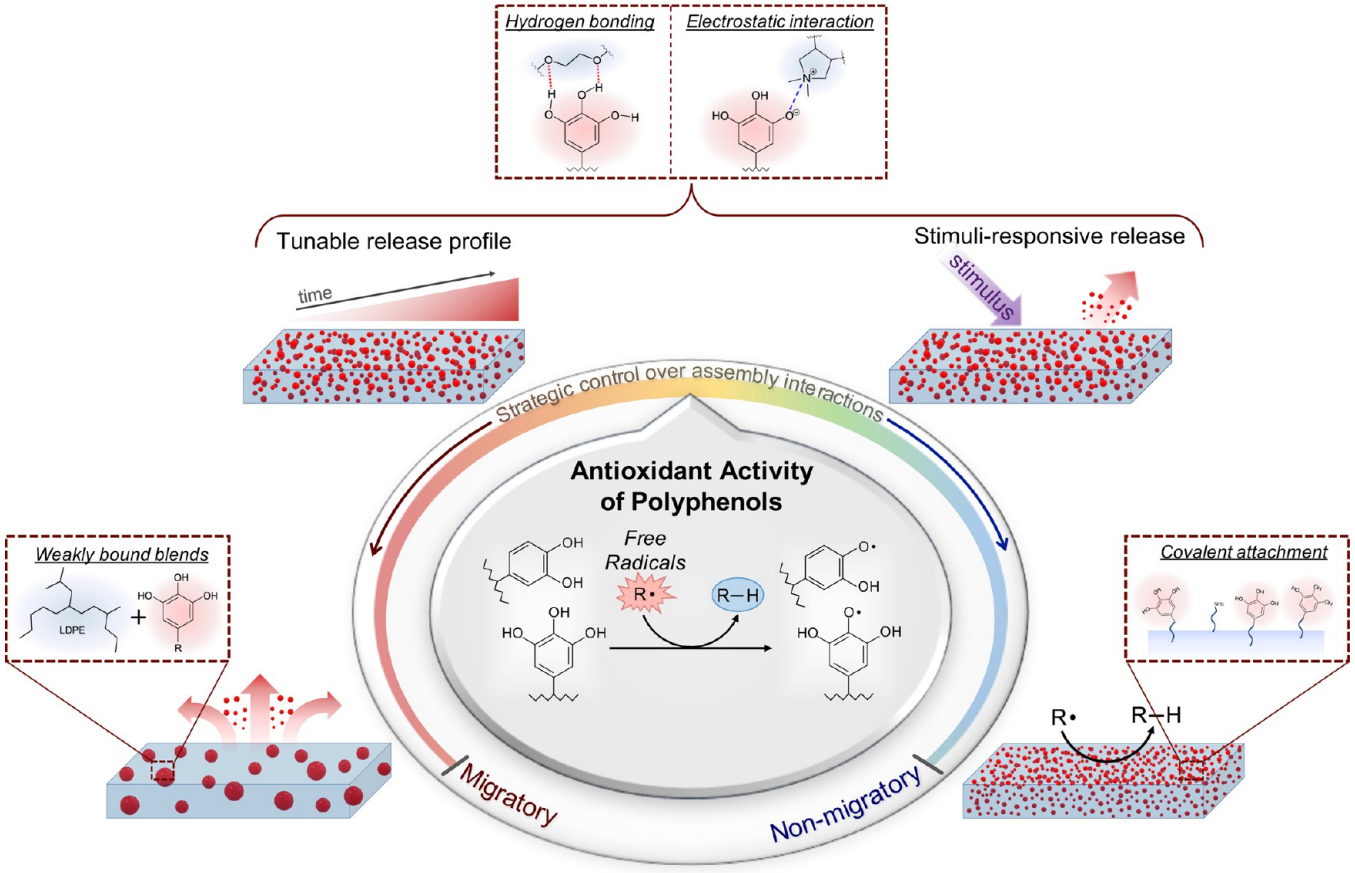

Figure 5. Schematic demonstrating the rational molecular design of interactions between polyphenol and surrounding polymers to enable controllable antioxidant activity.

$$ArOH + H_2O \rightarrow ArO^- + H_3O^+ \quad (2.3.7)$$

$$ArO^- + R^\bullet \rightarrow ArO^\bullet + R^- \quad (2.3.8)$$

$$R^- + H_3O^+ \rightarrow RH + H_2O \quad (2.3.9)$$

This three-step mechanism occurs when the environmental conditions favor antioxidant ionization and stabilization of the anion (ArO^-).[89] This mechanism describes scavenging of 2,2-diphenyl-1-picrylhydrazyl ($DPPH^\bullet$) with cinnamic acids[97] and phenol derivatives,[98,99] reactions of propyl gallate[100] and EA[101] with model lipid peroxides, and interaction of GA with hydroxyl and peroxyl radicals.[102]

HAT, PCET, ET-PT, and SPLET mechanisms have the same initial and final products; however, they differ in the kinetics of the limiting step, which is electron transfer in ET-PT and SPLET, and atom transfer in PCET.[89] However, in contrast, the RAF mechanism involves formation of antioxidant-radical adducts as shown below:[90]

$$ArOH + R^\bullet \rightarrow [ArOH - R]^\bullet \quad (2.3.10)$$

RAF occurs when a radical can electrophilically attach to a benzene ring, such as in hydroxybenzyl alcohols.[103] In addition, it occurs at the propagation step of a radical-scavenging reaction when the electron-deficient polyphenol recombines with another free radical, for example, in the case of interactions between $DPPH^\bullet$ and the glycoside of myricetin.[104]

3. INTEGRATION OF POLYPHENOLS WITH POLYMERIC MATERIALS

To increase the antioxidant functionality of polymer films in food packaging or polymer constructs for biomedical applications, antioxidant moieties are integrated with a polymer matrix. Different strengths of polyphenols–polymer interactions can affect the ability of polyphenols to release to aqueous or nonpolar media and can alter the antioxidant activity and physical properties of polyphenol-containing materials. Figure 5 illustrates that polyphenol-containing polymer materials can be grouped within three major categories,[105] which include (a) migratory materials,[106] (b) covalently bonded non-migratory materials,[107] and (c) materials assembled via hydrogen-bonding or electrostatic interactions that are capable of tunable antioxidant release in response to the environmental conditions.[108,109] In migratory polymer materials, polyphenols are held within polymer matrices via nonstoichiometric hydrogen bonding or other weak noncovalent interactions, and typically release when brought in contact with liquids.[106,110−112] Nonmigratory materials, on the other hand, contain covalently tethered polyphenols that do not release to the surroundings. These materials can either have polyphenols covalently grafted to the surface,[107,113,114] or can be fully made of individual polymers with covalently attached polyphenol groups.[115−117]

The molecular design of polyphenol-containing films is dictated by the desired antioxidant activity mode required by specific applications. Releasing films are widely used as active packaging material,[118,119] as they can prevent spoilage via penetration of antioxidants within packed food items. At the same time, nonreleasing films containing polyphenolic oxygen scavengers can be useful in the same application as they can inhibit penetration of oxidative species to the surface of goods,[120] prolonging their shelf life and reducing waste. Antioxidant films constructed by assembly, on the other hand, can be beneficial for

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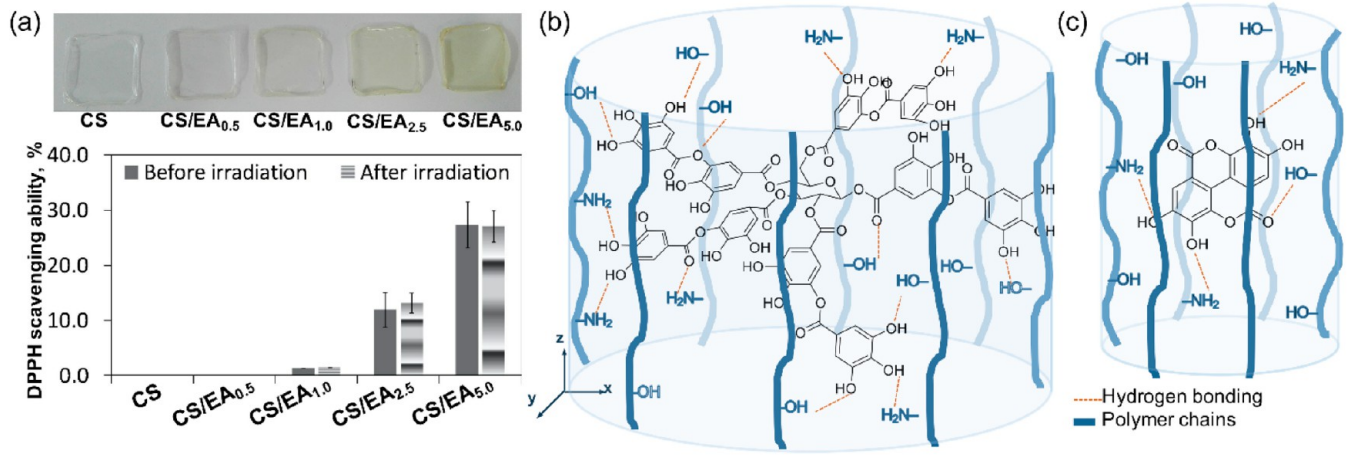

Figure 6. (a) Optical changes (top) and improvement of antioxidant activity (bottom) of a chitosan (CS) film loaded with various percentages of EA. [Adapted with permission from ref 150. Copyright 2017, Elsevier.] Also provided are 3D representations of possible hydrogen bonding between (b) large polyphenol TA or (c) small polyphenol EA with a CS matrix. Bold lines represent polymer chains, and dashed lines represent hydrogen bonds.

the mechanical properties and integrity of the films; however, they can potentially diminish their antioxidant efficiency as more functional moieties are occupied within the assemblies.[121] This section overviews different types of polyphenol-containing materials and discusses their benefits and shortcomings.

3.1. Migratory Films. Migratory films are constructed by noncovalently adding polyphenols to a bulk polymer via several paths, including direct blending of polyphenols or polyphenol extracts with a polymer matrix followed by extrusion[122] or solution casting,[105] blending of polyphenol-preloaded particles,[123] or coating of polyphenols on the top of the film as an active layer.[113,124,125]

The main mechanism of activity for migratory films is the release of active components that provide antioxidant, oxygen-scavenging, or antimicrobial protection. Migration of polyphenolic additives from the bulk polymer to vulnerable materials (e.g., foods[119]) occurs via diffusion and adsorption resulting from different partitioning of antioxidants, and is dependent on the packaging composition, temperature, time of contact, and hydrophilic or lipophilic nature of the media.[126] Importantly, this releasing mechanism implies a time-limited antioxidation protection as the antioxidants are depleted from the materials, which is appropriate for the protection of substances with a short shelf life, such as foods.

3.1.1. Noncovalent Polyphenol–Polymer Blends. In blended migratory films, weak, noncovalent bonding should exist between the polyphenols and polymer matrix so that polyphenols diffuse from the matrix and provide antioxidant activity to the surrounding. Assuming a simplified system where polyphenols are not bound with a matrix, the antioxidant migration should only be dependent on simple molecular diffusion, exhibiting a burst release as all polyphenols near the surface diffuse out rapidly, followed by slower diffusion of internal polyphenols out of the bulk. However, in addition to complex polymer dynamics, the previously described chemical properties of polyphenols invoke diverse interactions with a wide variety of polymers, further complicating the delivery of active antioxidants.[127]

An understanding of the physicochemical properties of both the polymer and polyphenol are necessary for the strategic design of migratory films. Depending on the intended environment for the film, the selection of the polymer should consider swelling/deswelling, which could accelerate/inhibit antioxidant release, and chemistry of functional groups, which could influence the formation of intermolecular bonds.[128,129] Among the most popular polymers used for the production of migratory films are chitosan (CS),[130−133] gelatin,[134] ethylene vinyl alcohol (EVOH),[110,112,135] and poly(vinyl alcohol) (PVA),[111,136] which are all considered to be safe for consumers.[137−139] Other relevant properties of these polymers include the potential to form crosslinks via hydrogen bonding and electrostatic interactions (CS, gelatin, and PVA)[121,136] and low oxygen permeability (EVOH).[140] Polyphenols that are typically used for blending within polymer films include phenolic acids,[111,141−143] cinnamic acids,[110,135] flavonols,[111,144] stilbenes,[145] green tea polyphenols,[146−149] EA,[150] TA,[136,143] and various polyphenol extracts.[151−153] However, it is not always possible to predict the effects of incorporated polyphenol-rich natural extracts, because they may contain a wide spectrum of interacting and noninteracting chemical compounds. Nonetheless, in many cases, polyphenol–polymer blends provide simultaneous benefits of enhancing the antioxidant and antibacterial properties of materials.[150,154,155]

As shown in Figure 6a, the antioxidant activity of blended CS/EA films was strongly improved with increased concentrations of polyphenol up to 5% EA.[150] The gradual development of a yellow color in the films is expected as polyphenolic rings typically absorb light in the wavelength range of 200−400 nm.

Because of the diffusion-dependent release mechanism of blended films, the effect of the polyphenol miscibility in both the polymer and the media on the antioxidant activity is more pronounced in these systems. For example, diffusion of hydrophilic extracts from a polar film into a lipophilic environment was low, preventing antioxidant delivery to fatty foods, but still providing an improved barrier against light, water, and oxygen.[156] In contrast, active films containing curcumin[154,155,157] and its derivatives[158] have been developed for antioxidant protection of lipophilic materials as these polyphenols have good solubility in nonpolar solvents, relevant for antioxidant delivery to fatty foods, tissues, and other oil-based products. Similarly, essential oils were shown to actively release into a lipophilic environment, providing antioxidant protection to the medium;[156] however, the high volatility of essential oils limits their retention time in dry films, so nonvolatile polyphenols are more favorable for applications in films.[159]

The effects of miscibility make the selection of processing method important to the properties of the resulting film. The most common method to create blended films is film casting, where polyphenols are added to a polymer solution, casted to the mold, and dried.[150,160,161] The dissolution required for casting enhances intermixing of the components; however, residual solvent may be left in the film. To avoid the possibility of solvent contamination, one may use melt-blending technology[159] and coextrusion, which is popular for mixing polyphenols with nonpolar bulk polymers, such as high- and low-density polyethylene (HDPE and LDPE, respectively).[114,162] However, these methods may have limited polyphenol–polymer intermixing, leading to a nonuniform distribution and release of active components.

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Table 1. Mechanical Properties of Migratory Films Containing Polyphenols

polyphenol additive[a]	thickness [μm]	tensile strength [MPa]	elongation at break [%]	ref
Film Matrix: Chitosan				
–	61 ± 1	40.84 ± 1.31	62.80 ± 6.82	141
PA, 0.5%	65 ± 2	49.59 ± 1.50	35.10 ± 2.77	
PA, 1%	74 ± 2	46.86 ± 2.19	33.49 ± 6.76	
PA, 1.5%	79 ± 1	34.66 ± 2.01	20.70 ± 1.59	
PA, 2%	83 ± 2	26.71 ± 3.15	7.86 ± 1.10	
–	107 ± 6	13.876 ± 0.604	32.36 ± 1.18	142
GA, 0.5%	108 ± 9	23.773 ± 0.453	33.15 ± 2.53	
GA, 1%	111 ± 1	18.394 ± 1.405	25.56 ± 0.58	
GA, 1.5%	141 ± 1	9.207 ± 0.616	10.97 ± 0.95	
–	30.5 ± 3.0	55.3 ± 5.1	22.0 ± 1.4	150
EA, 0.5%	33.1 ± 3.1	49.5 ± 5.4	23.6 ± 2.6	
EA, 1%	34.1 ± 2.9	52.3 ± 4.6	26.8 ± 2.9	
EA, 2.5%	36.3 ± 1.8	48.0 ± 3.4	25.5 ± 3.8	
EA, 5%	38.3 ± 1.6	48.5 ± 5.7	25.6 ± 3.7	
–	62.08 ± 6.31	23.66 ± 2.63	54.62 ± 3.12	149
GTE, 2%		25.00 ± 2.68	54.76 ± 3.14	
GTE, 5%		25.13 ± 1.91	58.14 ± 4.24	
GTE, 10%		28.35 ± 3.51	60.39 ± 3.60	
GTE, 20%		27.55 ± 3.46	60.73 ± 3.37	
Film Matrix: Ethylene-Vinyl Alcohol Copolymer				
–	83 ± 3	62 ± 1	33 ± 3	135
FE, 0.25 wt %	78 ± 5	61 ± 3	38 ± 6	
FE, 0.5 wt %	81 ± 4	63 ± 2	41 ± 2	
FE, 0.75 wt %	84 ± 7	60 ± 1	43 ± 7	
FE, 1 wt %	77 ± 3	64 ± 2	54 ± 4	
–		45 ± 4	265 ± 28	110
CA, 5%		41 ± 3	310 ± 26	
CA, 15%		58 ± 4	263 ± 11	
Film Matrix: Poly(vinyl alcohol)				
–	45 ± 5	67 ± 12	195 ± 45	111
GA, 5%	40 ± 5	75 ± 10	280 ± 70	
GA, 10%	50 ± 8	55 ± 10	190 ± 80	
Q, 5%	40 ± 7	74 ± 10	255 ± 35	
Q, 10%	50 ± 7	60 ± 10	170 ± 10	
–		63 ± 6	81 ± 9	136
TA, 1 wt %		70 ± 7	105 ± 12	
TA, 3 wt %		91 ± 4	108 ± 4	
TA, 5 wt %		98 ± 4	81 ± 10	
TA, 7 wt %		95 ± 4	38 ± 4	
TA, 10 wt %		89 ± 4	12 ± 2	
Film Matrix: Gluten + Glycerol				
–		1.08 ± 0.04	204.90 ± 9.78	143
GA, 1%		1.04 ± 0.11	196.44 ± 26.10	
GA, 2%		0.94 ± 0.10	187.70 ± 19.62	
GA, 5%		0.85 ± 0.10	238.23 ± 11.19	
GA, 10%		0.53 ± 0.07	296.8 ± 13.98	
TA, 5%		1.36 ± 0.33	87.88 ± 15.51	
TA, 10%		2.14 ± 0.37	84.05 ± 8.57	
TA, 20%		2.66 ± 0.41	9.45 ± 1.80	
TA, 30%		3.22 ± 0.57	3.59 ± 0.43	

[a]Abbreviations: PA, protocatechuic acid; GA, gallic acid; EA, ellagic acid; GTE, green tea extract; FE, ferulic acid; CA, caffeic acid; Q, quercetin; and TA, tannic acid. See Figure 2 for PA, GA, EA, and FE structures. See Figure 3 for GTE, Q, and TA structures.

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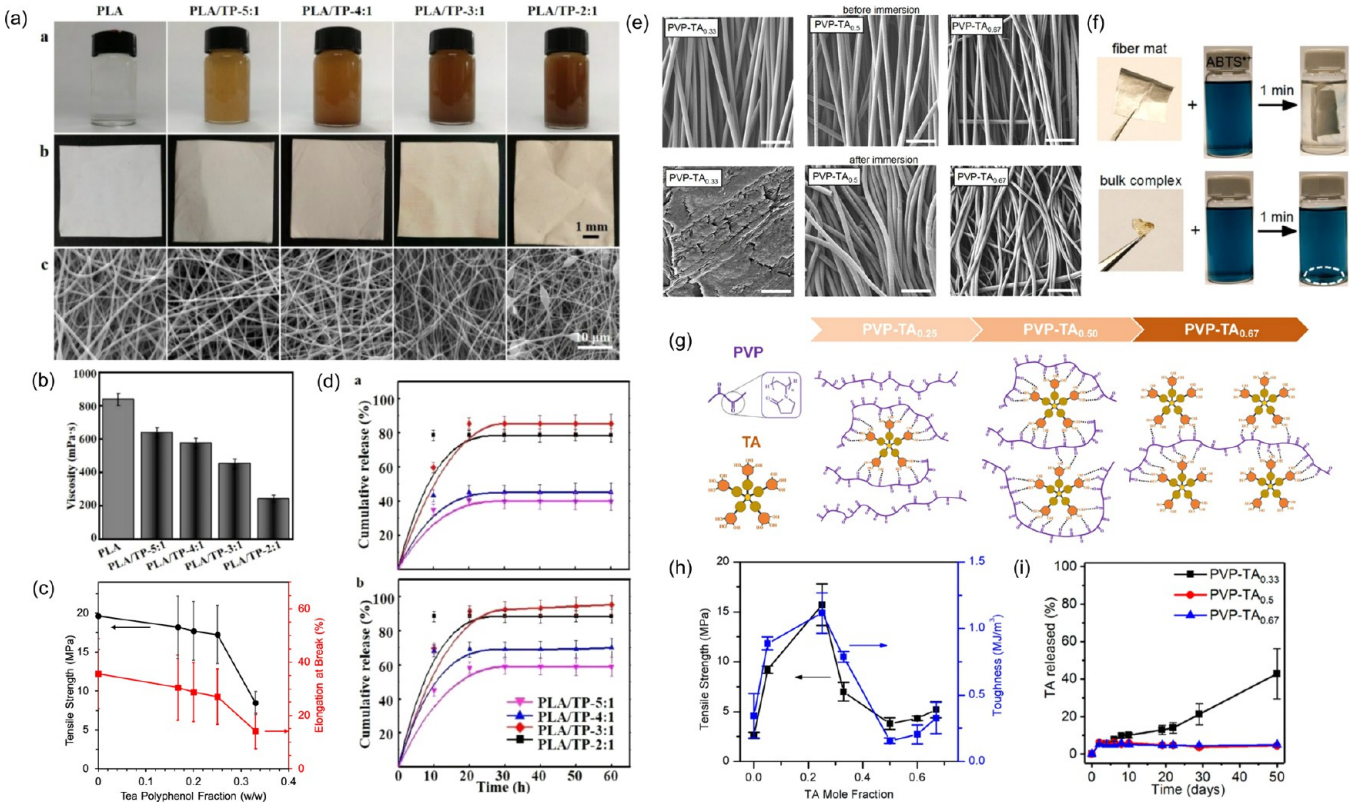

Figure 7. Comparison of antioxidant release and mechanical properties for polylactic acid (PLA)/tea polyphenol (TP) or poly(vinylpyrrolidone) (PVP)/TA nanofibers (NFs). (a–d) Demonstration of the ratio dependence of PLA/TP on optical and morphological changes (panel (a)), viscosity (panel (b)), NF tensile strength and elongation at break (panel (c)), and temporal TP release in 95% (top) and 50% (bottom) ethanol (panel (d)). [Adapted with permission from ref 182 (CC BY 4.0). Copyright 2018, MDPI.] Also shown is a demonstration of (e, g, h, i) the ratio and (f) surface area dependence of PVP/TA NFs on stability in an aqueous solution (panel (e)), $ABTS^{\bullet+}$ scavenging (panel (f)), proposed evolution of PVP/TA hydrogen bonding (panel (g)), NF tensile strength and toughness (panel (h)), and temporal TA release in an aqueous solution (panel (i)). [Adapted with permission from ref 185. Copyright 2020, American Chemical Society, Washington, DC.]

The addition of polyphenols to a polymer matrix can also affect the optical, thermal, and mechanical properties, depending on the miscibility of the components and their ability to stabilize the mixture. Often, the small polyphenolic additives disrupt existing intramolecular/intermolecular bonding within the polymer matrix; however, the formation of stronger intermolecular bonds between the polyphenol and polymer can stabilize the film, and, in some cases, decrease water vapor permeation.[121,163] Development of opacity and loss of transparency is often a sign of phase separation within the film, which can lead to decreased mechanical strength of materials.[145] Stabilization of a mixture by hydrogen bonding is likely the reason for improvement of thermal stability of these blended materials, as in the case of walnut green husk polyphenols impregnated into biodegradable polyesters,[164] and increased oxidation and denaturation temperature, as demonstrated with EGCG/gelatin films.[121] In many cases of polyphenol-blended films, the mechanical properties declined with increasing blended polyphenol concentration.[165] This effect is also shown in Table 1, which contains the tensile strength and elongation at break data from select recent publications.

Notably, large molecules, like TA and green tea polyphenols, achieved significant improvement of mechanical properties. These molecules have many polar hydroxyl groups and can form multiple hydrogen bonds with polar polymers (Figure 6b), which is likely the reason for this improvement. On the other hand, small molecules, like EA, rarely improve the mechanical properties of the films;[150] however, they may still form few hydrogen bonds with the polymer (Figure 6c) causing a minimal effect on the mechanical properties. This balance of hydrogen bonding will be discussed further in following sections as they fall in the spectrum of tunable antioxidant activity.

3.1.2. Noncovalent Surface Modification with Polyphenols. For rapid, nondiffusion-limited migration and/or surface activity, antioxidants can be deposited on a polymer surface through noncovalent interactions, including van der Waals or hydrogen bonding interactions.[166,167] This has been done by direct spraying of polyphenols onto a surface,[166,168] or by depositing a layer of polyphenol-based particles or thin film.[169,170] Polymers with surface-specific functionality maintain the properties of the underlying material while benefiting from the reduced use of the active component, elimination of additional processing steps needed for blended bulk materials, and convenience for inert plastics, such as LDPE[113,171] or polyethylene terephthalate (PET).[166,168,169] For instance, PET sprayed with citrus extract delayed lipid oxidation of cooked meat.[168] When sprayed on a plasma-treated PET surface, the coatings had enhanced stability, likely due to the dipole–dipole interactions or hydrogen bonding.[167] In another case, beneficial for high-humidity applications, an LDPE-sodium carbonate mixture was further coated with a pyrogallol–polyurethane formulation, displaying enhanced oxygen scavenging as the hydrolyzed sodium carbonate increased the pH.[113,171]

3.2. Tunable Antioxidant Activity by Controlled Assembly Interactions. Unlike the weakly bound polyphenols that are characteristic of migratory films, the strategic consideration of polyphenol–polymer assembly interactions can be used to control polyphenol retention and stimuli-responsive release. The relatively high pK_a of polyphenols enables both strong hydrogen bonding and electrostatic interactions, depending on the conditions of the assembly.[23] These intermolecular interactions are advantageous to creating constructs with functional architectures, including hydrogen-bonded nanofibers and layer-by-layer assemblies.

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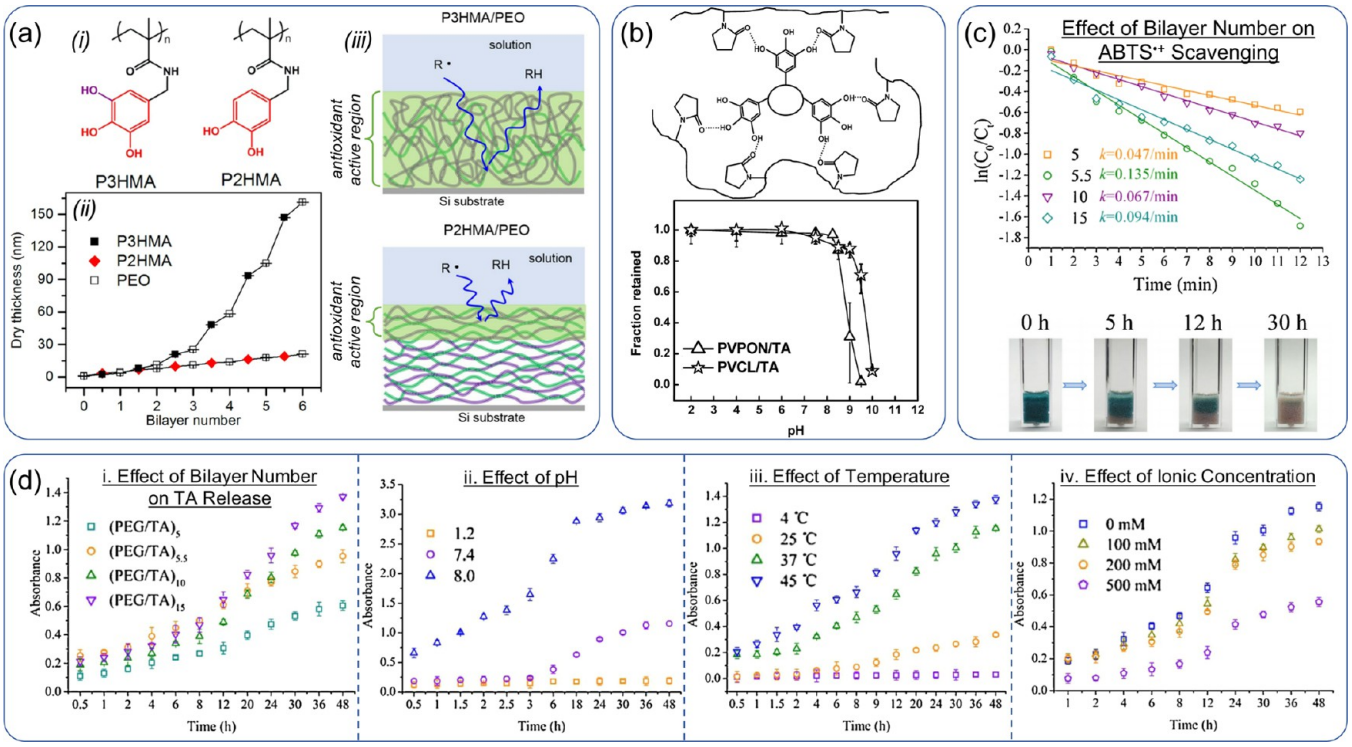

Figure 8. (a) Structures of P3HMA and P2HMA (i), resulting growth curves (ii), and schematic representation of antioxidant active regions (iii) for LbL coatings formed via hydrogen bonding with poly(ethylene oxide) (PEO). [Adapted with permission from ref 65. Copyright 2020, American Chemical Society.] (b) Proposed interaction mechanism (top) and pH stability (bottom) for hydrogen-bonded LbL coatings of poly(*N*-vinylpyrrolidone) (PVPON, or PVP)/TA and poly(*N*-vinylcaprolactam) (PVCL)/TA. [Adapted with permission from ref 109. Copyright 2008 American Chemical Society.] (c) $ABTS^{\bullet+}$ scavenging ability for hydrogen-bonded poly(ethylene glycol) (PEG)/TA LbL films of 5, 5.5, 10, and 15 bilayers. Images show the change in solution color with time. (d) From left to right: temporal release of TA from $(PEG/TA)_x$ films (x = 5, 5.5, 10, or 15), and release of TA from $(PEG/TA)_{15}$ in response to pH (1.2, 7.4, or 8.0), temperature (4 °C, 25 °C, 37 °C, or 45 °C), and ionic concentration (0, 100, 200, or 500 mM NaCl). [Adapted with permission from ref 108. Copyright 2016, Elsevier.]

3.2.1. Hydrogen-Bonded Nanofibers. Nanofibers have significantly higher surface-area-to-volume ratios than coatings, which can enhance the surface availability and diffusive release of incorporated active components,[172] finding diverse applications in medical and food fields.[173] Polymeric nanofibers loaded with polyphenols showed controlled release properties based on various formulation and process conditions reviewed recently,[174] including polyphenol concentration, polymer hydrophilic−hydrophobic balance, and applied spinning voltage.[175−178] However, in many cases, the claim of controlled release is only supported by altered solution viscosity causing changes in nanofiber diameter, with rapid burst release from small-diameter nanofibers and longer instances of sustained release from large-diameter nanofibers as the central polyphenols diffuse through the polymer matrix.[179−181] The reduced viscosity with increasing small-molecule incorporation is expected as the existing polymer−polymer interactions are interrupted, eventually causing beading along the fiber or nanoparticle formation.

As described, reduced diameter (Figure 7a), viscosity (Figure 7b), and mechanical properties (Figure 7c) were observed for increasing concentrations of tea polyphenols (TP) in poly(lactic acid) (PLA).[182] The smaller-diameter 2:1 and 3:1 PLA/TP nanofibers exhibited the aforementioned rapid burst release compared to thicker 5:1 nanofibers, especially after partial swelling in a 50% ethanol solution (Figure 7d).[182] Burst release due to rapid polymer swelling and erosion was also reported for electrospun nanofibers with *Garcinia mangostana* extracts (GME) in CS-ethylenediaminetetraacetic acid (CS-EDTA)/PVA, although incorporation of the hydrophobic GME compounds was thought to decrease the degree of swelling.[183] In this case, increasing GME concentration in the CS-EDTA/PVA mixtures also reduced the solution viscosity. Polycaprolactone (PCL) fibers loaded with *Clerodendrum phlomidis* leaves extract (CP) displayed similar burst release, with up to 36% cumulative release; however, the remaining CP exhibited sustained release, possibly through a combination of slow hydrolytic PCL degradation and solid-state diffusion through the hydrophobic, nonswelling PCL fibers.[184]

Conversely, polyphenols that form strong, stoichiometric hydrogen-bonded complexes with the polymer matrix display controlled retention within the fiber, rather than diffusion-based release. In addition, hydrogen-bonded nanofibers can release polyphenols in response to pH changes if the ions infiltrate and destabilize the assemblies.[185] For example, both polyvinylpyrrolidone (PVP, sometimes abbreviated as PVPON) and TA are soluble in water; however, PVP/TA fibers mixed at 1:0.5 and 1:0.67 stochiometric ratios maintained their structure after immersion in aqueous conditions (Figure 7e).[185] The high-surface-area fiber mat demonstrated excellent antioxidant activity compared to a bulk complex (Figure 7f), attributed to both the TA held by hydrogen bonds with the fiber, proposed in Figure 7g, and the TA released into the surroundings (Figure 7i). The PVP/TA fibers also displayed enhanced mechanical properties at a ratio of 1:0.25 (Figure 7h), implying stronger interactions within the PVP/TA mixture than pure PVP and consistent with previous reports of hydrogen-bond self-assembly.[186] Similar enhanced properties were reported for hydrogen-bonded nanofibers of poly(*N*-vinylcaprolactam) (PVCL)/TA and PVP/GME.[187,188]

3.2.2. Layer-by-Layer Assemblies. Layer-by-layer (LbL) deposition is a powerful technique that can be used to modulate antioxidant activity through the design of electrostatically pairing or hydrogen-bonding systems. Rational selection of the polyphenol, polymer, and assembly conditions (e.g., pH, ionic strength, solvent) enables tunable thickness, morphology, and functionality of the LbL coating.[189] Although the discussion in this section will focus on planar LbL coatings and their antioxidant activity, the diverse architectures enabled via LbL assembly, such as microtubules, microcubes, and

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microcapsules,[74,190] allow for wide-ranging applications in biomedical fields.[191] LbL capsules for drug delivery, nanofiber coatings for enhanced tissue engineering, and cellular modifications for immunomodulation will be discussed in later sections.

Importantly, a significant amount of LbL antioxidant research has used TA as a polyphenolic binding partner. In addition to its high availability and suspected anticancer, antibacterial, and immunomodulatory benefits,[192] TA is considered as Generally Recognized As Safe (GRAS) for use as a food additive by the U.S. Food & Drug Administration. With a pK_a of 8.5, TA can act as an efficient hydrogen-bond donor or anionic partner at near-physiological conditions.[109] The beneficial, biorelevant properties of TA, combined with the versatility of polymer binding partners and mild assembly conditions for LbL systems, stimulate applications for sensitive biological environments. More recently, various polyphenolic polymers have been used in antioxidant LbL assemblies, including a commercial cationic tannin derivative (TN)[193] and linear synthetic polymers poly(3,4-dihydroxybenzyl methacrylamide) (P2HMA) and poly(3,4,5-trihydroxybenzyl methacrylamide) (P3HMA).[65]

In the earlier work of TA assembly into LbL films, TA was assembled with strong polyelectrolyte poly(diallyldimethylammonium chloride) (PDADMAC) and weak polyelectrolyte poly(allylamine hydrochloride) (PAH). Important fundamental discoveries from these original works include (1) the pH-dependent permeability and film dissolution of both strong, electrostatic system PDADMAC/TA and weakly electrostatic or hydrogen-bonding system PAH/TA;[74] (2) the dependence of radical scavenging on thickness and capping layer, signifying a retention of TA antioxidant activity even when held by interactions within the film, and an accelerated antioxidant activity when TA is at the surface;[194] and (3) the evolution of the effective radical-scavenging volume, starting at the film surface and gradually propagating through the PAH/TA film.[195]

The elucidation of the radical-scavenging permeation volume in the LbL film was key to designing films capable of protecting oxidation of encapsulated species. This idea of an antioxidant-active region was further developed recently using linear synthetic polymers—P2HMA and P3HMA—with phenolic structures that differ by one hydroxyl group.[65] As seen in Figure 8a, the slight difference in the chemical structure led to different growth regimes when P2HMA and P3HMA were assembled via hydrogen bonding with poly(ethylene oxide) (PEO). In particular, P2HMA/PEO films demonstrated linear growth, indicating stronger interactions and stratified layers, while P3HMA/PEO films showed exponential growth, indicating weak interactions and a high intermixing of the layers. The difference in growth regimes was attributed to stronger intramolecular binding (i.e., self-association) of the P3HMA gallol moieties relative to the P2HMA catechol moieties. The more compact assembly of P2HMA/PEO remained almost unswollen, limiting radical diffusion and antioxidant activity to the top 30−35 nm of the film. This limited radical diffusion is relevant to applications that require ultimate protection of encapsulated materials. In contrast, the looser P3HMA/PEO film swelled up to 30% in solution and displayed radical-scavenging functionality through the entire film, as demonstrated in Figure 8a. Altogether, these results inform the strategic design of antioxidant LbL films, such as the necessary thickness of films for full protection of encapsulated materials, or the arrangement of layers in which an active component should be incorporated.

In addition, LbL films have been shown to disassemble in response to changes in the surrounding media, imparting a valuable stimuli-responsive release behavior.[108,109,196,197] Hydrogen-bonded PVP/TA and PVCL/TA LbL films were stable in both acidic and neutral conditions, but disassembled under basic conditions, because of the interruption of existing hydrogen bonds (Figure 8b) by electrostatic repulsion as phenolic hydroxyl groups dissociated.[109] The achievement of hydrogen-bonded LbL films that are stable under neutral conditions was advantageous, compared to hydrogen-bonded assemblies based on poly(carboxylic acid)s that become ionized and disintegrate at neutral pH values.[196,197] Furthermore, this significant achievement paved way for the biomedical application of these films, in which stability is needed during exposure to phosphate-buffered saline (PBS) at physiological pH values. Another study of hydrogen-bonded PVP/TA LbL films further explored the effect of solution conditions on TA release.[198] As expected for hydrogen-bonded systems, the films gradually disassembled in all solutions; however, their dissolution rates could be controlled by changing the pH, temperature, and ionic strength of the solution. TA release was very slow in acidic and neutral conditions and rapid in alkaline conditions, consistent with the prior study.[109] Furthermore, higher temperatures induced faster TA release, because of increased dissociation of the hydrogen bonds. Ionic strength had a slight inverse effect on TA release, possibly due to reduced electrostatic repulsion of ionized species.[196]

Although poly(ethylene glycol) (PEG)/TA hydrogen bonding is weaker than PVP/TA, hydrogen-bonded PEG/TA films on planar and spherical surfaces exhibited a similar zero-order erosion mechanism as PVP/TA.[199,200] In addition, the molecular weight of PEG was shown to inversely impact the rate of TA release.[199] When deposited on cellulose nanofiber mats, PEG/TA films confirmed the earlier discovery of the dependence of antioxidant activity on film thickness and capping layer (Figure 8c), and displayed interesting bimodal TA release that followed similar pH-, temperature-, and salt-responsive release trends as PVP/TA (Figure 8d).[108] The bimodal release was attributed to the increasing surface-area-to-volume ratio as the PEG/TA layers dissolved, which was supported by a near-linear TA release of thin PEG/TA films, and subsequent depletion of TA from the film.

Another important feature of LbL films is the ability to load natural anti-inflammatory/anticancer lipophilic polyphenols into LbL films after assembly. In one example, multilayers of strong polyelectrolytes poly(sodium 4-styrenesulfonate) (PSS) and PDADMAC were assembled and exposed to curcumin dispersed in water/ethanol solutions.[201,202] A direct relationship between curcumin uptake and film thickness, independent of the top layer, was observed, with up to 8 $\mu g/cm^2$ loaded into a 20-layer film.[202] At the same time, the dependence of multilayer swelling on ionic strength enabled ion-responsive release of loaded curcumin.[201] Polyphenolic chalcones were also loaded into and released from PSS/PDADMAC multilayers to demonstrate controlled drug delivery.[203] Hydrophobic interactions and $\pi-\pi$ stacking between the aromatic rings of curcumin, chalcones, and PSS were thought to encourage polyphenol uptake into the multilayers.[201−203]

3.3. Nonmigratory Films. Nonmigratory films are defined by inhibiting the release of loaded molecules to the environment. In cases where the release of active molecules is not favorable, the antioxidant activity should be retained at the surface or within the bulk of the material, such as in the case of juice packaging.[107] Furthermore, the release of small molecules, characteristic of migratory films, can open pathways for water penetration and weaken the integrity of the film. Finally, diffusion-controlled release leads to a gradual decrease in film activity, because of the loss of active component, which limits the time of service of such materials. Thus, nonmigratory polymers that provide continuous antioxidant activity at the surface of the films and do not release polyphenols into the surrounding have been created.[120,204] Materials with polyphenols covalently attached to the surface or to individual polymer chains in the bulk will be discussed separately in the following sections.

3.3.1. Surface-Grafted Polyphenols. One approach to creating nonmigratory films is by grafting antioxidant functionality to the surface of the polymer film, which allows modification of even relatively inert polymers, such as PP.[107,205] In a typical modification process, an inert surface is irradiated with UV light to initiate active centers which can be grafted with antioxidant moieties. In the case of PP grafted with hydroxyethyl methacrylate (HEMA) and further modified with CA, the ability to reduce $DPPH^{\bullet}$ by surface-grafted CA was comparable with the activity of CA grafted on a water-soluble polymer in solution, which suggests good availability of the polyphenol at the surface.[107] In addition, polyphenols can be oxidatively polymerized on the surface of inert film-forming materials, as demonstrated with catechol and catechin grafted to a UV/ozone-treated PP surface that was modified with CS.[206] Importantly, surface-

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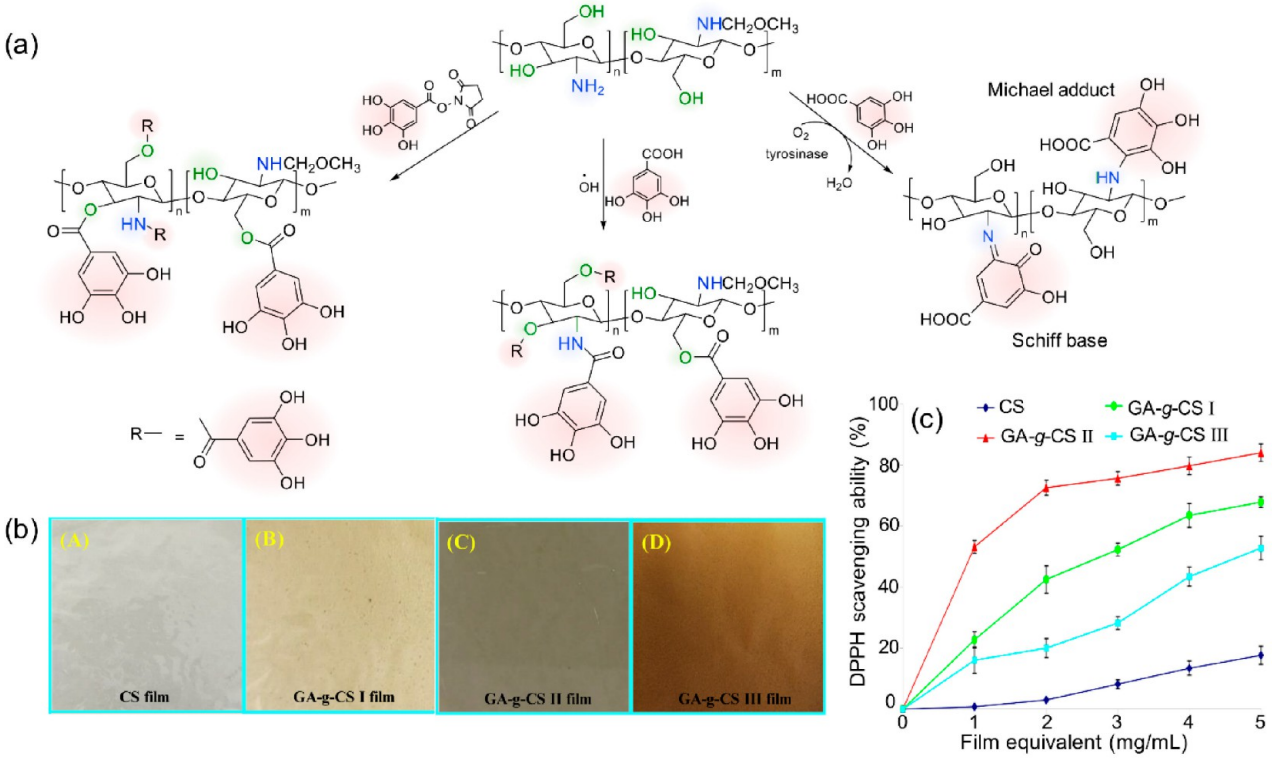

Figure 9. (a) Chemical modification of chitosan (CS) with gallic acid (GA), from left to right: carbodiimide-mediated grafting (II), free radical-mediated grafting (I), and enzymatic oxidation followed by grafting (III). Highlighted are reactive amino (blue), reactive hydroxyl (green), and polyphenol (red) groups. (b, c) Comparison of the appearance (panel (b)) and DPPH$^{\bullet}$ scavenging ability (panel (c)) of GA-*g*-CS polymer films synthesized from routes I–III. [Adapted with permission from ref 76. Copyright 2018, Elsevier.]

grafted polyphenols retain their antioxidant and metal-chelating capabilities.[205−207]

3.3.2. Covalent Attachment of Polyphenol Pendant Groups for Bulk Modification. In contrast with grafting limited to surfaces, covalent attachment of polyphenol pendant groups can occur along a polymer chain when dissolved in solution. Polyphenol-modified polymers can be further processed into bulk materials with nonmigratory antioxidant activity that are especially efficient in the form of hydrogels, as they swell in the presence of water and provide rapid access to polyphenols throughout the bulk.[208] The attached polyphenol moieties can impact the mechanical and thermal properties of the original polymer by either stabilizing the polymer matrix with hydrogen bonds or by disrupting existing intermolecular interactions. The latter was thought to occur in films made of GA-functionalized CS, in which irregular substitution of GA moieties along the CS chain disturbed the close packing of CS, weakening the intermolecular interactions.[120] Grafting of phenolic acids, such as GA, PA, and CA, is often done to polymers that have reactive hydroxyl and amino groups, popularly including CS,[115−117] gelatin,[209,210] and other proteins,[211] which can be modified through various chemical reactions.[76,117] The most common synthetic routes include Schiff base reactions,[116] nonenzymatic oxidation by peroxides,[212−214] ascorbic acid−peroxide systems,[215−217] and enzymatic modification with laccase,[115,218−220] as well as 1-ethyl-3-(3-(dimethylamino)-propyl) carbodiimide (EDC) and *N*-hydroxysuccinimide (NHS) coupling.[120] EDC/NHS coupling facilitates grafting to the polymer through the formation of amide or ester bonds, so polyphenols do not lose their activity since polyphenols rings are not involved in the chemical reaction.[107,120] As expected, oxidative nonenzymatic grafting uses oxidative species, such as peroxides and cerium(IV) nitrate,[208,221] to facilitate the formation of reactive groups. Ascorbic acid with hydrogen peroxide generates free hydroxyl radicals, which, in turn, initiate radicals on CS, activating amino and hydroxyl groups and mediating possible amidation and esterification.[115,211] Enzymatic modification is beneficial for sensitive species, as it typically occurs at room temperature without the use of organic solvents, and provides high substrate conversion. Laccase, a multicopper oxidase,[222] selectively mediates one-electron oxidation in phenols. Once the radical is formed,[223] it reacts with an amino group of glucosamine in CS, forming a covalent C−N bond in a nonoccupied position of the aromatic ring. Sometimes, Schiff base formation can occur as a side reaction, leading to the loss of aromaticity. Another enzyme, tyrosinase, acts by oxidizing catechol groups to quinone, which further form Schiff bases or Michael-type adducts with amino and hydroxyl groups and trigger loss of aromaticity. Importantly, the potential loss of aromaticity caused by enzyme-mediated grafting may prevent antioxidant capabilities. However, polymers modified by tyrosinase-mediated grafting find applications as adhesives.[117]

Schematics in Figure 9a show grafting of CS with GA using three different initiation reactions: carbodiimide coupling, free radical initiation with peroxide-ascorbic acid system, and tyrosinase catalysis. Depending on the modification method, the GA-modified CS films possess differing optical, antioxidant, mechanical, and permeation properties.[76] In all three methods, free hydroxyl and amino groups can participate in grafting reactions, and they cause different degrees of polyphenol oxidation. The degree of polyphenol oxidation can be correlated with the development of yellow color in the GA-modified CS films (Figure 9b).[76] The enzymatically modified CS film developed the deepest yellow color and revealed carboxyl peaks at 1730 cm^{-1} in FTIR, suggesting polyphenol oxidation. The film made by carbodiimide-assisted grafting had the least noticeable color change and the highest grafting ratio—twice as high as the free radical-mediated grafting and almost three times higher than enzymatic grafting. In addition, the film made by carbodiimide-assisted grafting demonstrated the highest antioxidant activity (Figure 9c) and mechanical strength, yet the lowest water vapor permeation. This comparison suggests that polyphenol grafting methods that preserve the aromaticity of aromatic rings can retain the highest polyphenolic functionality, sustaining the radical-scavenging and hydrogen-bonding capabilities.

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4. APPLICATIONS IN FOOD PACKAGING AND BIOMEDICAL ENGINEERING

Antioxidant activity is important to protecting oxidation-prone materials in industrial applications, including as additives to commercial plastics and corrosion-resistant coatings;[224−227] however, the vulnerability of complex biological environments in food and the body encourages the design of materials with more precise control of antioxidant activity. A diverse set of properties associated with polyphenols, including low toxicity, antioxidant, antibacterial, and antiviral activity,[228] led to their wide applications in materials for food packaging and biomedical engineering, which have been reviewed extensively.[31,228−231] After summarizing the mechanisms of polyphenolic antimicrobial activity necessary for further discussions, the following chapter will focus mainly on novel applications of polyphenols as antioxidant species within polymer materials, while briefly mentioning complementary properties that are relevant to the specified application.

4.1. Polyphenols as Antimicrobial Agents. Based on interactions between polyphenols and biomolecules, polyphenols provide antimicrobial properties that are not directly associated with the redox activity. As simplistically summarized in Figure 10, these nonredox antimicrobial properties result

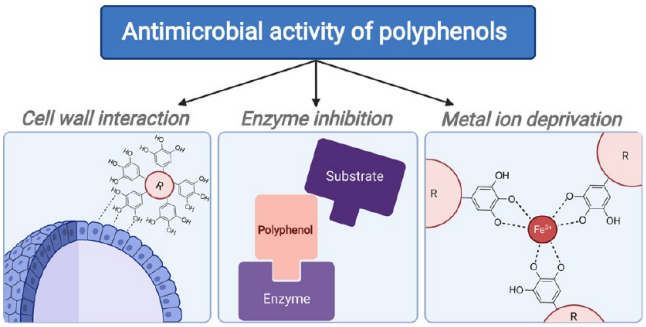

Figure 10. Possible mechanisms of antimicrobial activity for polyphenols. Graphics were created with BioRender.com.

from the polyphenol's inhibition of enzymes, interactions with cell wall and membranes, or deprivation of metal ions through metal chelation, among other mechanisms.[232,233] The activity of certain enzymes, such as amylases,[234] cellulases,[235] lipases,[236] pectinases,[237] and proteases[238] have decreased or even halted after binding with polyphenols. Interestingly, TA showed more efficient inhibition of enzymes in comparison to other low-molecular-weight polyphenols.[234−236] This effect is likely related to the strong binding between the enzyme and the numerous phenolic hydroxy groups in TA. Furthermore, strong binding of polyphenols with the lipid membranes of bacterial cells can interfere with wall integrity, increase wall permeability, and inhibit further adhesions.[239−241] Moreover, the propensity of polyphenols to form complexes with metal ions essential for bacteria growth, such as iron, copper, and zinc, leads to a deprivation that can strongly affect a microorganisms' vitality.[242−244] However, bacteria can develop a resistance to polyphenols through different mechanisms, such as cleavage and excretion of hydrolyzable polyphenols, metal ion sequestration, altering enzymes, and modification or repair of bacterial membrane.[232,245] Because of this ability, as well as the overall lower magnitude of antimicrobial effects of polyphenols, compared to their antioxidant activity, polyphenols are primarily sought for their prominent radical scavenging activity, while their antimicrobial properties are typically considered as a complementary beneficial feature.

Antimicrobial properties of polyphenol-based materials have been demonstrated for a variety of architectures, including LbL assemblies,[246−248] solvent-cast films,[249] and electrospun nanofibers.[177,250] Interestingly, the antibacterial properties of collagen (COL)/TA LbL films were strongly dependent on the buffer selection.[246] COL/TA films assembled in citrate buffer displayed higher rates and concentrations of TA release that were especially effective at release-killing *S. aureus*, in contrast to the films formed in acetate buffer, demonstrating an interesting effect of the nature of type of ions in the immediate environment on functionality of antioxidant materials. In several cases, both for LbL assembly of TA-graphene oxide (TA-GO)/lysozyme (Lys) planar films[247] and CS/TA coatings on cellulose nanofibers,[251] the efficient synergy of assembled systems was demonstrated. Specifically, while each component had only slight antibacterial activity, the assemblies showed excellent antibacterial properties against Gram-positive and Gram-negative bacteria. In nanofiber geometry, mixtures of PLA and TP showed good antibacterial activity against Gram-positive and Gram-negative bacteria,[182] perhaps due to the high surface area of the electrospun material. Finally, integration of polyphenols with polymers can not only achieve good antimicrobial properties, but also enhance materials' mechanical properties, as this was shown for solvent-cast films from mixtures of various polyphenol and PVA.[249]

4.2. Food Packaging. Food packaging that intentionally releases or absorbs active substances, known as active packaging, is an innovative approach to prolonging food freshness and shelf life and has been the subject of many recent reviews and books.[105,119,252−260] Furthermore, a recent focus on edible packaging has provoked the use of antioxidants within biodegradable polymers, such as polysaccharides.[261,262] With these recent advances in food packaging technology, this Review uniquely aims to bridge the gap between materials and food sciences by providing strategies to modify antioxidant release and retention while maintaining other necessary material properties.

Active food packaging utilizes various types of films, including migratory, nonmigratory, films with tunable antioxidant activity, and surface-modified films, depending on the type of food and expected environment. Most active packaging films work by releasing antioxidants into the stored food,[263,264] protecting it from oxidation. Moreover, some active packaging utilizes multilayer films in which each layer brings a desirable property to the packaging material.[119] Active substances in food packaging should prevent microbial growth and have antioxidant activity to prevent lipid oxidation, a primary cause of nonmicrobial quality deterioration in meat and meat products.[265,266] In addition to mechanical strength, antioxidant and antimicrobial activity, and appearance, water vapor permeability,[263,264,267,268] oxygen permeation,[161] and adsorption[125] are important parameters that are considered for food applications. Films with low water vapor permeability prevent the produce from losing or absorbing excess moisture, while low oxygen permeation decreases the oxidation rates of produce. In many cases, the addition of antioxidants decreases water permeability; however, adding excessive amounts of a polyphenol can also slightly increase film permeability, because of disruption of the polymer matrix.[113]

The main functionality of polyphenols as oxygen scavengers in food packaging applications is to decrease oxygen

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permeation through the film and prolong freshness of the produce. This functionality was demonstrated for GA, which was either mixed with a polymer matrix[267] or deposited as an active layer.[125] Furthermore, complementary to radical scavengers, some metal ions in low oxidation states can be considered as oxygen scavengers, such as the iron-based scavenger sachets found in enclosed food packaging.[269] One of the most important considerations in food applications is the safety and nontoxicity of antioxidants, because they can diffuse into the produce. For this reason, natural antioxidants are typically preferred for these applications. Table 2 provides recent examples of active packaging containing polyphenols.

Table 2. Examples of Polyphenol-Containing Films for Active Packaging

polyphenol	polymer matrix	application
Malaysian herbs extract	semirefined carrageenan	active packaging film for beef patties[270]
C and Q	EVOH	improved antioxidant stability of packaged food[263]
GA and Q	solvent-cast PVA film	color-changing active food packaging[271]
GA	LDPE film	active packaging of high-moisture foods[267]
apple peel extract	CS	active packaging with improved antimicrobial and antioxidant activity[268]
CA	Ca^{2+} cross-linked CS and methylcellulose	potential alternative approach to reduced lipid oxidation in fish oil[264]
immobilized CA	hydroxyethyl methacrylate-grafted PP film	protective against ascorbic acid oxidation in orange juice[107]

4.3. Biomedical Applications. Many applications of polyphenols in biomedical engineering harness the antioxidant activity to regulate ROS/RNS species with the body and modulate immunogenicity, accelerate wound healing and tissue generation, and provide synergistic antioxidant activity and targeted drug delivery.[28,33,272] TA has played a significant role in the development of antioxidant materials for medical applications, as reviewed recently;[273] however, we envision an expansion of antioxidant biomaterials to include other polyphenols, such as green tea extracts, curcumin, and synthesized polyphenolic polymers.

4.3.1. Coatings for Immunomodulation. The transplant of foreign materials into the body, including blood transfusions, organ implants, and other biomedical implants, often invokes an immune response from the host, potentially leading to rejection of the material. Camouflaging with a coating may protect the foreign material from T-cell recognition and rejection.[274] For example, in experimental treatment of Type 1 diabetes, modifications of pancreatic islets with hydrogen-bonded TA-based LbL coatings have demonstrated immunomodulatory effects.[275−277] In one study, hydrogen-bonded PVP/TA and PVCL/TA LbL films had dual antioxidant and immunomodulatory properties that suppressed the synthesis of proinflammatory cytokines, while dissipating proinflammatory ROS/RNS species (Figure 11a).[276] The incorporation of TA into both PVP/TA and PVCL/TA suppressed ROS production, in stark contrast to control coatings without TA (Figure 11b), suggesting that the antioxidant activity is due to the TA in the shells.[276] In addition to ROS-scavenging properties, these shells reduced nitrite concentrations (Figure 11c), which can be reduced within the body to nitric oxide—the primary mediator of cytokine-induced islet damage.[276] The conformal PVP/TA LbL coating on pancreatic islets were stable for at least 7 days (Figure 11d) and did not change the functions of rat, nonhuman primate (NHP), or human pancreatic islets (Figure 11e).[277] Also, PVP/TA coatings showed promising results in in vivo transplantation of encapsulated islets, because of the localized immunosuppression and nontoxicity of the coatings.[278]

PVP/TA LbL coatings have also been used to encapsulate live cancer cells for the development of effective anticancer vaccines.[279] Although the viability of cell decreased as the number of bilayers increased, especially for coatings with a TA starting layer, the PVP/TA LbL coating effectively retained cellular proteins after cell lysis.[279] In addition, this procedure permitted the pretreatment of cells with a heat shock prior to encapsulation to potentially modulate the immunogenicity of the capsule. In another case, tocopherol polyethylene glycol 1000 succinate (TPGS) formed stable hydrogen-bonded nanocomplexes with polyphenols containing at least 8 hydroxyl groups, i.e., EGCG, procyanidin, and TA, which showed therapeutic efficacy in the treatment of acute lung inflammation.[280] In vivo studies suggested that the EGCG/TPGS nanocomplex decreased inflammation processes of lung tissue, leading to significant remission.[280]

4.3.2. Nanofibers, Films, and Hydrogels for Tissue Engineering. Materials for accelerated wound healing and tissue engineering benefit from the combined antioxidant, antimicrobial, biocompatible, and bioadhesive properties of polyphenols.[28,281,282] For these applications, biodegradable biomaterials are usually desired.

One approach of integrating polyphenols with hydrolyzable polymers is through surface modification of a precontracted polymer material. For example, biodegradable poly(caprolactone)/collagen nanofibers (PCL/Coll NFs) modified with LbL coatings of peptide-based block copolymer micelles (BCM) and TA provided a multifunctional approach for accelerated wound healing and vascularization (Figure 12a).[283] Incorporation of clindamycin into BCM micelles inhibited bacterial growth (Figure 12b) while transforming growth factor (TGF-1) stimulated wound healing. Extended deposition time enhanced the distribution of micelles on the nanofibers (Figure 12c), adding nanosized roughness to the fibers that regulated the adhesion, spreading, proliferation, and enhanced migration of fibroblasts.[283] Another way of incorporating antioxidant functionality to a biomaterial for wound healing applications is to integrate a polyphenol within a polymer bulk during electrospinning or cryogel preparation. In one study, electrospun fibers of PLA and date palm polyphenols displayed promising cell proliferation and migration in vitro.[284] Furthermore, cryogel scaffold made of CS, silk fibroin (SF), and TA/Fe^{3+} complexes (CSTFe (3)) showed robust mechanical, antibacterial, and hemostatic properties, as well as promising cell proliferation, which accelerated wound repair in vivo (Figure 12d).[285]

Polyphenols were also integrated with nanofibers for bone regeneration applications. For example, biodegradable poly(L-lactic acid) (PLLA) nanofibers dip-coated with EGCG (E-PL) displayed improved stem cell adhesion and protection from external oxidative stress resulting in enhanced osteogenesis and suppressed adipogenesis of stem cells in vivo, providing efficient bone fracture healing (Figure 12e).[286] In addition, a multifunctional lysozyme/TA LbL coating was used to impart

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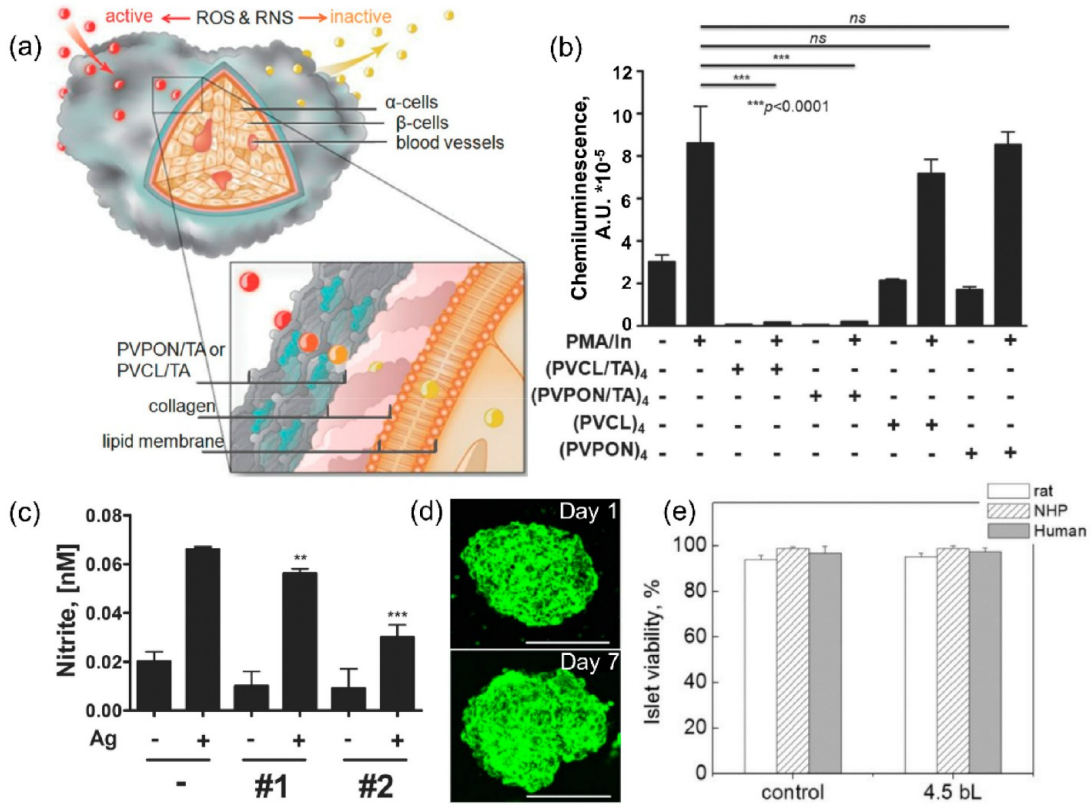

Figure 11. Hydrogen-bonded (PVCL/TA) or (PVP/TA) LbL coatings encapsulate islets to modulate immunogenicity. (a) Schematic of ROS/RNS deactivation by coated islets. (b) Luminol oxidation assay after stimulation of splenocytes in the presence (+) or absence (−) of TA-containing or TA-free LbL shells. (c) Nitrite levels in tissue culture supernatants after stimulation of splenocytes in the presence (+) or absence (−) of $(PVP/TA)_5$ (#1) and $(PVCL/TA)_5$ (#2) capsules. [Adapted with permission from ref 276. Copyright 2014, Wiley−VCH.] (d) Images of evenly distributed fluorescent PVP* on as-deposited and cultured $(PVP/TA)_{4.5}$-coated islets. (e) Viability of noncoated (control) and $(PVP/TA)_{4.5}$-coated rat, nonhuman primate (NHP), and human islets. [Adapted with permission from ref 277. Copyright 2012, Wiley−VCH.]

antioxidant and antibacterial activity, as well as fast cell attachment and enhanced osteogenesis, to a substrate.[287]

A promising direction in biomaterials is inclusion of polyphenols in hydrogels, which have been shown to have excellent properties for wound dressing and tissue engineering applications. GA-conjugated gelatin (GGA) was introduced to a gelatin-hydroxyphenyl propionic (GH) hydrogel to create an injectable in situ forming hydrogel with enhanced ROS/RNS scavenging properties. The GGA/GH hydrogel showed tunable mechanical and antioxidant properties, as well as effectively promoted tissue regeneration. Furthermore, shape-memory hydrogels, formed simply by soaking a polar polymer gel (e.g., PVA, gelatin, or methacrylic acid-functionalized ε-poly-L-lysine) in a TA solution, are attractive new biomaterials, because of strong antioxidant and antibacterial properties, as well as mechanical robustness.[288−290]

4.3.3. Capsules and Hydrogels for Targeted Drug Delivery. Polymeric materials that deliver simultaneous antioxidative activity and targeted drug release enable multifaceted therapeutic treatment of severe inflammatory disorders, such as rheumatoid arthritis, Crohn's disease, and lupus.[291] LbL assembly of TA with different hydrogen-bond acceptors on sacrificial templates enabled development of a new class of hollow hydrogen-bonded capsules useful for controlled drug delivery.[190] For example, LbL PVP/TA microcapsules, obtained by dissolution of an inorganic template material, can be used as doxorubicin (DOX) carriers with negligible leaking of the drug, even after long storage.[292] These microcapsules have low toxicity and are stable in near-physiological pH, making them a suitable candidate for targeted drug delivery. Interestingly, the PVP/TA LbL film can also form nonspherical microcapsules by geometric selection of the sacrificial core (Figures 13a−i).[293] Cuboidal microcapsules demonstrated better internalization by breast cancer cell lines.[293] Furthermore, the hollow polymer microcapsules were unrecognizable to macrophages, in contrast to their rigid counterparts with an intact core.[293] More recently, ultrasound stimulus was applied to provide on-demand, controlled release of DOX from PVP/TA capsules (Figure 13j).[294] In addition, intracellular protein delivery have been pursued using hollow protein/TA microcapsules.[295] These microcapsules showed long-term stability in an extracellular-mimicking environment but disintegrated in an intracellular-mimicking environment, because of the competitive interaction of TA with glutathione. It is important that assembly/disassembly of protein/TA microcapsules did not affect protein bioactivity, opening a pathway for controlled delivery of different biomacromolecules.[295]

Antioxidant polymers have also demonstrated their promise for treatment of ocular diseases. In particular, a novel, biodegradable, in situ gelling copolymer with antioxidant functionality—GA-functionalized gelatin-*g*-poly(*N*-isopropylacrylamide) (GNGA)—was developed to improve the total antioxidant status in glaucomatous eyes while simultaneously

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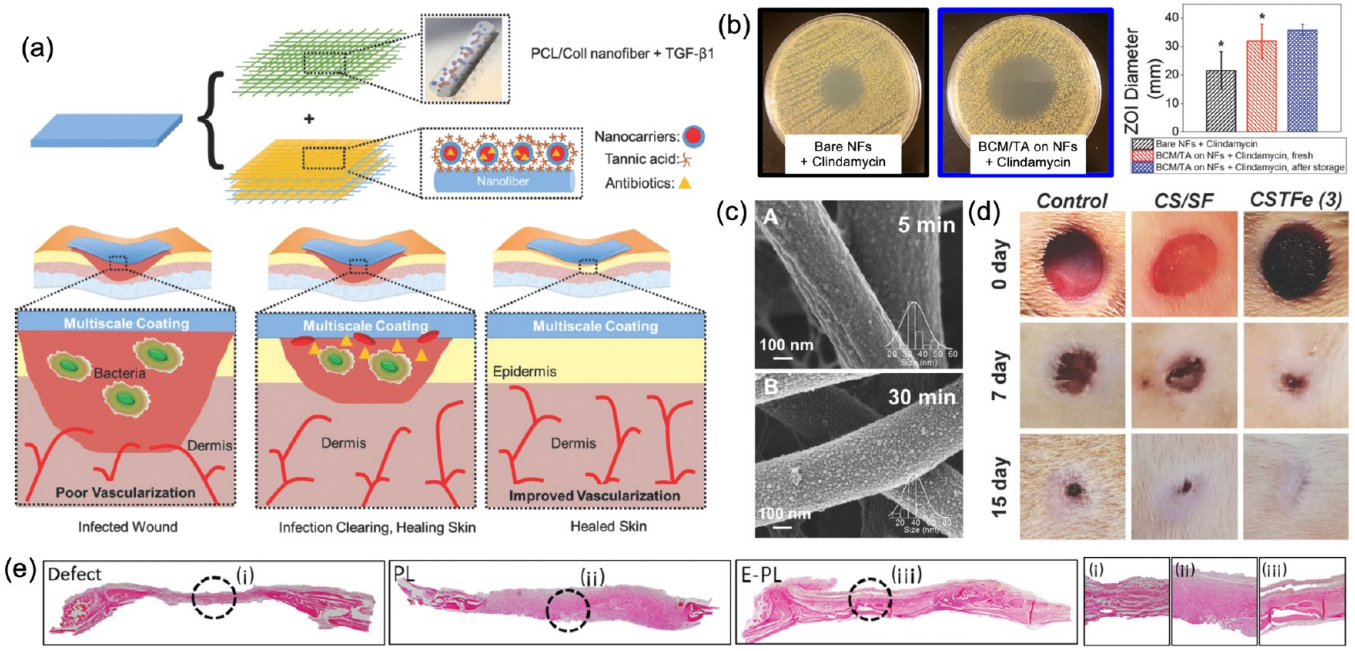

Figure 12. Polyphenolic antioxidant materials for accelerated tissue regeneration and wound healing. (a) Schematic representation of block copolymer micelles (BCM)/TA coatings on poly(caprolactone)/collagen nanofibers (PCL/Coll NFs) with transforming growth factor (TGF-β1). (b) Zones of inhibition (ZOI) for bare and BCM/TA-coated PCL/Coll NFs loaded with clindamycin as-deposited and after 20-week storage. (c) Surface coverage of $(BCM/TA)_{1.5}$ on PCL/Coll NFs deposited for (A) 5 min or (B) 30 min. [Adapted with permission from ref 283. Copyright 2018, Wiley–VCH.] (d) Temporal wound healing for chitosan (CS)/silk fibroin (SF) cryogels with and without incorporated TA/Fe^{3+} complexes (CSTFe (3) and CS/SF, respectively). [Reproduced with permission from ref 285. Copyright 2019 Wiley–VCH.] (e) Enhanced in vivo bone regeneration of a mouse calvarial defect 2 months after EGCG-coated nanofiber implantation. [Adapted with permission from ref 286. Copyright 2019, Wiley–VCH.]

releasing an antiglaucoma drug, pilocarpene.[296] In solution, the GNGA gel was twice as effective as GA in inhibiting DPPH$^{\bullet}$ (Figure 13k). Furthermore, the GNGA gels were shown to reduce H_2O_2-induced intracellular ROS in human lens epithelial (HLE) cells, while also significantly decreasing nitrite levels in glaucomatous rabbit eyes (Figure 13l).

5. CONCLUSIONS AND OUTLOOK

Techniques for imparting antioxidant activity to polymers are continuously growing in their strength as promising approaches to preserve the integrity of polymer materials, protect food from oxidative degradation, or consume ROS/RNS species in biological environment. However, the molecular principles of integration of antioxidant materials within a polymer matrix are insufficiently understood. Yet interactions of antioxidant molecules with other components of a polymer material are critically important for the development of materials in which antioxidant moieties are designed to be retained within or migrate from a functional matrix (i.e., nonmigratory and migratory materials). To emphasize the importance of building a better understanding and control of such interactions, this Review first introduced the structures, classifications, and physicochemical properties of polyphenol molecules and linked the intrinsic polyphenol properties to their interactions in a polymer matrix. The resultant antioxidant materials were then discussed in the context of applications in food packaging and biomedical engineering.

The main challenge for rational designing of antioxidant materials is to establish a correlation between strength and type of antioxidant–polymer interactions, materials' functionality and migratory versus nonmigratory behavior. Polyphenols are particularly versatile in their ability to bind to polymers via a variety of interactions, including hydrogen-bonding, electrostatic, π–π interactions, or by pH-dependent oxidative cross-linking. Detailed understanding of action of these interactions in different material preparation conditions, including pH, solvent, temperature, or application of a vacuum, can enable control of localization and antioxidant performance of these materials in food packaging and biomedical applications. Moreover, different ways of integrating antioxidants with polymers, such as simple blending of polyphenols with an inert matrix for migratory release, development of hydrogen-bonded nanofibers and layer-by-layer films for tunable release, as well as covalent attachment of polyphenols for nonmigratory scavenging, each have their specific advantages and challenges. For example, achieving homogeneous mixing of antioxidant components with a polymer matrix remains a major challenge in the development of robust migratory films. Solutions likely lie in a combined attention to tuning weak interactions between antioxidant and polymer matrix molecules and rational selection of processing paths (melt or solution mixing). On the other hand, for antioxidant materials, which are based on stronger hydrogen-bonded or electrostatic interactions, matching the chemistry of an antioxidant to that of a polymer component can be even more important. Hydrogen-bonded and electrostatic interactions can be efficiently controlled by assembly conditions, such as selection of a solvent, solution pH, or ionic strength, and these parameters should be more actively explored and exploited for the development of new antioxidant assemblies. For all types of antioxidant films, studies of multiple orthogonal properties (antioxidant activity and mechanical, optical, antimicrobial, antiviral, oxygen and/or water barrier proper-

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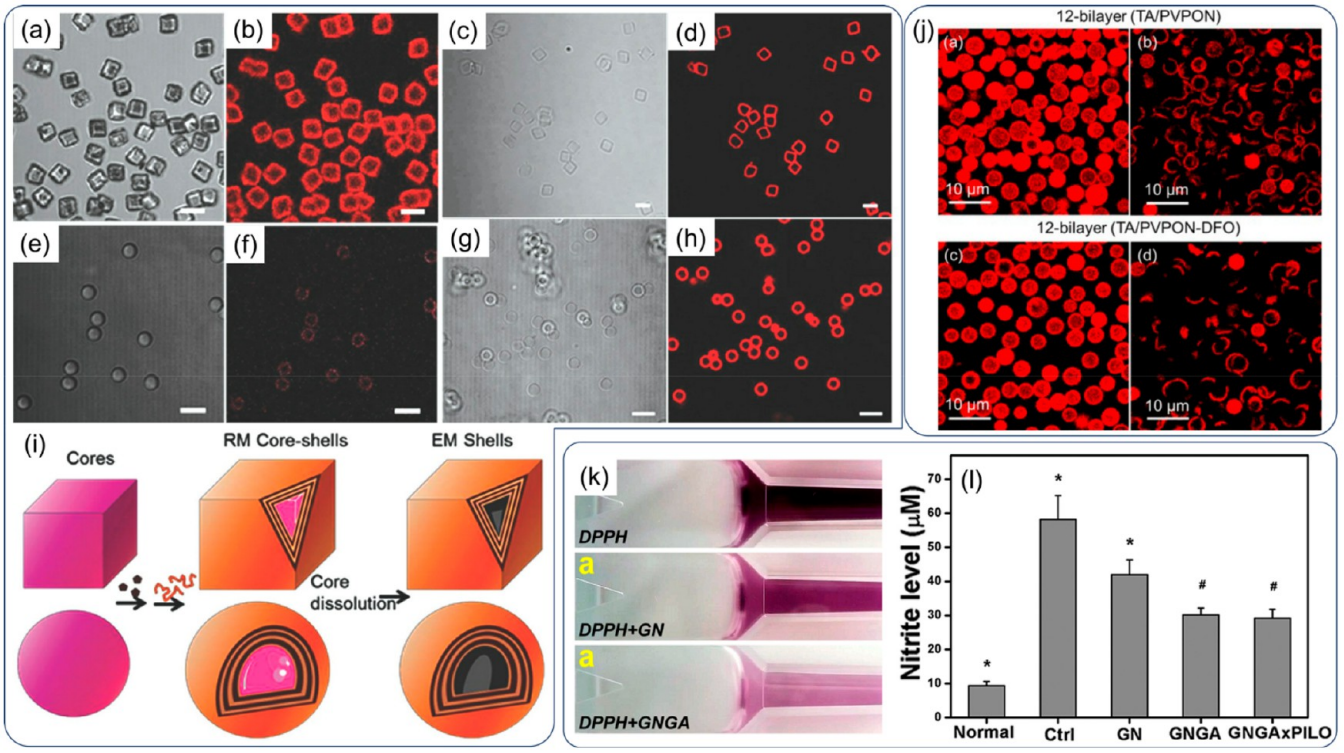

Figure 13. LbL assembly of PVP/TA on (a, b, e, f) rigid core−shell and (c, d, g, h) hollow shell geometries. Images are of PVP/TA coatings on cuboidal (panels (a)−(d)) and spheroidal (panels (e)−(h)) sacrificial templates, schematically shown in panel (i). [Reproduced with permission from ref 293. Copyright 2015, Wiley−VCH.] Confocal microscopy images of the encapsulation (left) and ultrasound-assisted release (right) of doxorubicin (DOX) for 12-bilayer TA/PVP (top) and TA/PVP-deferoxamine (DFO) (bottom) capsules. [Reproduced with permission from ref 294. Copyright 2020, American Chemical Society, Washington, DC.] (k) DPPH•-scavenging abilities of GA-functionalized gelatin-*g*-poly(*N*-isopropylacrylamide) (GNGA) in comparison to a control and nonfunctionalized GN. (l) Nitrite levels in normal and glaucomatous (ctrl) eyes after injection of polymer solutions of GNGA and GNGA loaded with pilocarpine (GNGAxPILO). [Reproduced with permission from ref 296. Copyright 2015, American Chemical Society, Washington, DC.]

ties) for a single material are still rare and should be more vigorously pursued.

Another future trend the area might see is a stronger focus on material multifunctionality. Recently reported synergistic enhancement of antiviral[297] and anticancer[298] performance of therapeutic agents by polyphenols opens exciting opportunities for incorporating these agents in materials.

Finally, future technologies will see an increased focus on sustainability, and antioxidant polymer materials are already seeing a considerable amount of such research. One example includes edible films made of proteins for food packaging applications,[299] and the use of polyphenols (tannic acid) as an efficient cross-linking agent to improve their functional properties.[300] In the case of antioxidant polymer materials for biomedical applications, more work should be done for achieving biodegradable polymer assemblies with antioxidant properties, as well as mitigating possible toxicity of the assemblies in biological environments.

In future sustainable and multifunctional polymer materials, controlled integration of antioxidant functionalities through a concerted effort in rational manipulation of chemical interactions and processing conditions is likely to eventually achieve performance that is highly sought-after in food packaging and biomedical applications.

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Notes

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