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Polyphenol–Polysaccharide Complex: Preparation, Characterization, and Potential Utilization in Food and Health

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Abstract

Polysaccharides and polyphenols coexist in many plant-based food products. Polyphenol–polysaccharide interactions may affect the physicochemical, functional, and physiological properties, such as digestibility, bioavailability, and stability, of plant-based foods. In this review, the interactions (physically or covalently linked) between the selected polysaccharides and polyphenols are summarized. The preparation and structural characterization of the polyphenol–polysaccharide conjugates, their structural–interaction relationships, and the effects of the interactions on functional and physiological properties of the polyphenol and polysaccharide molecules are reviewed. Moreover, potential applications of polyphenol–polysaccharide conjugates are discussed. This review aids in a comprehensive understanding of the synthetic strategy, beneficial bioactivity, and potential application of polyphenol–polysaccharide complexes.

1. INTRODUCTION

Polysaccharides and polyphenols have been reported to have some common bioactive properties, including anti-inflammatory, antidiabetic, antioxidant, and anti–cardiovascular disease (Halake & Lee 2017, González-Aguilar et al. 2017, Liu et al. 2018a, Lovegrove et al. 2017). Recently, polyphenol–polysaccharide interactions have attracted increasing attention (**Table 1**) because of their importance in understanding the functions and health benefits of whole food systems (Das et al. 2020). Interactions between polysaccharides and polyphenols (either physically associated or covalently linked) occur in many plant-based food materials and products (X. Liu et al. 2020). These interactions might alter food digestion, bioavailability, stability, and physiological properties (Nagar et al. 2020). Le Bourvellec & Renard (2012) reviewed the approaches and mechanisms of both noncovalent and covalent interactions between polyphenols and macromolecules. Zhu (2018) also described the factors that could influence the noncovalent and covalent interactions between polyphenols and cell wall polysaccharides. However, functional characteristics and bioactive properties of the complexes were not mentioned in his article. Cirillo et al. (2016) summarized the influences of both naturally occurring and synthesized polyphenol–polysaccharide conjugates on human health. The functional properties and structural information, however, were not clarified. This review summarizes the most recent information regarding the preparation and structural characterization of the polyphenol–polysaccharide conjugates, their structural–interaction relationships, and their effects on functional and physiological properties and applications as food and medicine. Furthermore, whole food systems rich in polysaccharides and polyphenols are discussed, aiding in a better understanding of the functions and health benefits of the conjugates as novel resolutions for functional food development.

2. POLYPHENOLS AND POLYSACCHARIDES

Polyphenols are bulky molecules that comprise hydroxyl groups in the form of catechol and other phenolic groups (Halake & Lee 2017). They exist widely in different plant-based food resources, including cereals, fruits, vegetables, tea, coffee, and wine (Gangopadhyay et al. 2016, Liu et al. 2017). More than 8,000 phenolic compounds have been identified (Singh et al. 2018) and categorized into simple phenolic acids, flavonoids, stilbenes, and lignans according to the number of phenol rings and the way they bond (Jakobek & Matić 2019). Phenolic acids and flavonoids are the two major categories, accounting for approximately 30% and 60% of the total phenolic compounds, respectively (Liu et al. 2018b). Polyphenols show many bioactive properties, including antioxidant, antimicrobial, antidiabetic, anti-inflammatory, anti–cardiovascular disease, anticancer, and other metabolic-regulation properties (Chatterjee et al. 2015; Hu & Luo 2016; Liu et al. 2017, 2018a). Polyphenol-rich diets have been well noted for their health-promoting effects (Hu & Luo 2016).

Polysaccharides distribute widely in botanicals, animals, algae, and microorganisms (Yang et al. 2020). Because of their unique functional properties, especially viscosity forming and gelling abilities, polysaccharides have been extensively used in many food products as thickeners, gelling agents, and film formers (Lovegrove et al. 2017). Nonstarch polysaccharides as dietary fibers contribute many health benefits, including reducing postprandial blood sugar and serum cholesterol levels and relieving constipation. Some bioactive polysaccharides possess specific health-promoting properties, such as antimicrobial, antioxidant, antitumor, and immunostimulating effects (Liu et al. 2018b). These bioactivities have been reported mainly by relying on their physicochemical and conformational properties (Wang et al. 2017).

Some phenolics may be bonded to the polysaccharide molecules in nature. However, most polyphenols and polysaccharides remain segregated in intact plant tissues (Jakobek 2015). When

Table 1 Examples of noncovalent and covalent interactions between polysaccharides and polyphenols

Types of polysaccharides	Types of phenols	Types of interactions	References
Noncovalent interaction			
Apple cell walls	Native apple polyphenols	Hydrogen bond; maybe hydrophobic interaction	Renard et al. 2001
	Epicatechin, phloridzin, chlorogenic acid	Hydrogen bond	D. Liu et al. 2019
	Procyanidin	Hydrophobic interaction, hydrogen bond	Le Bourvellec et al. 2005, 2009, 2019
Grape cell walls	Proanthocyanidin	Hydrogen bond	Bautista-Ortin et al. 2014, Ruiz-Garcia et al. 2014
Apple pectin, arabinoxylan, xyloglucan, apple cell wall	Ferulic acid, (+/−)-catechin	Electrostatic interaction	Phan et al. 2017
Pectic polysaccharides	Chlorogenic acid, phloridzin, procyanidins	Electrostatic interaction, hydrophobic interaction, hydrogen bond	A. Fernandes et al. 2020, P.A.R. Fernandes et al. 2020
Blueberry pectin	Anthocyanins	Electrostatic interaction, hydrophobic interaction, hydrogen bond	Koh et al. 2020, Lin et al. 2016
Sugar beet pectin	Anthocyanins	Hydrogen bond	Buchweitz et al. 2012
Pectins	Procyanidins	Hydrogen bond, hydrophobic interactions	Buchweitz et al. 2013b, Watrelot et al. 2014
Strawberry pectins	Anthocyanins	Hydrogen bond	Buchweitz et al. 2013a
Cellulose	Ferulic acid, gallic acid, catechin, cyanidin-3-glucoside	Hydrogen bond, hydrophobic interaction	Phan et al. 2015
Strawberry dietary fiber	Hydroxytyrosol, 3,4-dihydroxyphenylglycol	Hydrogen bond	Bermudez-Oria et al. 2019
Lotus root soluble dietary fiber	Gallic acid, catechin	Hydrogen bond, hydrophobic interaction	Li et al. 2020
Oat β-glucan	Flavonols, flavones, hydroxycinnamic acids, quercetin, hydroxybenzoic acids	Hydrogen bond	Jakobek et al. 2020, Wang et al. 2013
Oat β-glucans, guar galactomannan, xanthan mannoglucuronoglucan	Vanillin, ferulic acid, caffeic acid, ethyl gallate, (−)-epicatechin gallate, (−)-epigallocatechin gallate	Hydrogen bond	Tudorache & Bordenave 2019
Corn silk polysaccharides	Flavonoids	Van der Waals forces, hydrogen bond	Q.W. Guo et al. 2018
	Procyanidins	Hydrogen bond	Fernandes et al. 2014
Hohenbuehelia serotina polysaccharides	*Juglans regia* L. polyphenols	Electrostatic interaction	Zhou et al. 2020
Wine polysaccharides	Tannin protein	Hydrophobic interactions, hydrogen bonds	Watrelot et al. 2017

(*Continued*)

Table 1 (*Continued*)

Types of polysaccharides	Types of phenols	Types of interactions	References
Covalent interaction			
Pectin	Catechin, rutin quercetin, hesperidin	ECH-mediated coupling reaction	Ahn et al. 2017
	Ferulic acid	Laccase-mediated reaction	Karaki et al. 2016
	Ferulic acid	Free radical–mediated reaction	Wang et al. 2020
	Naringenin	DCC-mediated coupling reaction	Mundlia et al. 2019
Starch	Quercetin	Free radical–mediated reaction	Cirillo et al. 2012
		CDI-mediated reaction	Liu et al. 2018c, Yong et al. 2020
		EDC-mediated coupling reaction	Lv et al. 2016
	Ferulic acid	CDI-mediated coupling reaction	Wen et al. 2016
Dextran	Catechin	Laccase-catalyzed reaction	Vittorio et al. 2016
		Free radical–mediated reaction	Vittorio et al. 2012
		Functionalization with magnetic iron oxide nanoparticles	Vittorio et al. 2014
Arabinoxylan	Catechin	Free radical–mediated reaction	Guo et al. 2021
Hyaluronic acid	Catechin, quercetin, hesperidin	ECH-mediated coupling reaction	Halake & Lee 2017
	Green tea catechin	HRP-mediated reaction	Lee et al. 2015
	Catechin	EDC-mediated coupling reaction	Liang et al. 2016
Inulin	Catechin, tannin	Free radical–mediated reaction	Liu et al. 2014b; Spizzirri et al. 2010, 2011; Zeng et al. 2020
Chitooligosaccharides	Hydroxybenzoic acid, p-coumaric acid, protocatechuic acid, caffeic acid, vanillic acid, ferulic acid, syringic acid, sinapinic acid	DCC-mediated coupling reaction	Eom et al. 2012
Alginate hydrogels	Quercetin	EDC-mediated coupling reaction	Nam & Yeo 2016
Curdlan	Ferulic acid	Free radical–mediated reaction	Cai et al. 2019, Yu et al. 2021
Gum arabic	Ferulic acid	Laccase-mediated reaction	Vuillemin et al. 2020
Gellan gum	Curcumin, naringenin	DCC-mediated coupling reaction	Mundlia et al. 2020
Flax fibers	Syringaldehyde, p-coumaric acid, acetosyringone	Laccase-mediated reaction	Fillat et al. 2012

(*Continued*)

Table 1 (*Continued*)

Types of polysaccharides	Types of phenols	Types of interactions	References
Carboxymethyl chitosan	Gallic acid, protocatechuic acid	EDC-mediated coupling reaction	Xu et al. 2021, Yu et al. 2011
	Caffeic acid, ferulic acid	Free radical–mediated reaction	Liu et al. 2013
Chitosan	Gallic acid	Laccase-catalyzed reaction	Li et al. 2019
		EDC-mediated coupling reaction	Liu et al. 2020; Pasanphan & Chirachanchai 2008; Rui et al. 2017b; Xie et al. 2014, 2016
		Free radical–mediated reaction	Curcio et al. 2009
	Vanillic acid, coumaric acid	Free radical–mediated reaction	Chatterjee et al. 2015
	Catechin	Laccase-mediated reaction	Chung et al. 2003, Kim et al. 2017
		Free radical–mediated reaction	Cho et al. 2013, Zhu & Zhang 2014
	Ferulic acid	Laccase-mediated reaction	Aljawish et al. 2012, 2014, 2016
		EDC-mediated coupling reaction	Wang et al. 2018, Woranuch & Yoksan 2013
	Proanthocyanidin	Free radical–mediated reaction	Jing et al. 2018
	Chlorogenic acid	EDC-mediated coupling reaction	Rui et al. 2017a, Wei & Gao 2016
	Caffeic acid, ferulic acid	Free radical–mediated reaction	Hu et al. 2016, Liu et al. 2014a
	Curcumin	Imine formation method	Saranya et al. 2018
	Protocatechuic acid	EDC-mediated coupling reaction	Liu et al. 2016b
	EGCG	Free radical–mediated reaction	Lei et al. 2014a, Mittal et al. 2021, Moreno-Vasquez et al. 2017
	Caffeic acid	EDAC-mediated coupling reaction	Lee et al. 2013

Abbreviations: CDI, *N*,*N*′-carbonyldiimidazole; DCC, dicyclo-hexylcarbodiimide; ECH, epichlorohydrin; EDAC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; EDC, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; EGCG, epigallocatechin gallate; HRP, horseradish peroxidase.

cells are ruptured during food processing or mastication, the two types of compounds start to associate and form an interaction complex (X. Liu et al. 2020, Renard et al. 2017), either covalently or noncovalently (Zhu et al. 2018). These interactions lead to vital influences on the sensory and nutritive qualities of many food ingredients and products (Liu et al. 2018b, Zhu et al. 2018).

3. NONCOVALENT COMPLEXES AND THEIR MECHANISMS

Polyphenol–polysaccharide complexes in foods mainly exist as noncovalent interactions. These complexes could alter polyphenolic bioavailability, improve food flavor, enhance polyphenolic stability, inhibit food oxidation, and disrupt other binary interactions, e.g., phenol–protein interactions (Zhu et al. 2018). For example, noncovalent interaction between anthocyanins/tannins and

yeast polysaccharides weakened astringency and promoted their color stability in wine (Zhang et al. 2017). For noncovalent interactions, polyphenols can be retained via surface adsorption (Le Bourvellec et al. 2005) or encapsulation by forming hydrophobic cavities through the chain alignment of polysaccharides (Zhou et al. 2020). Molecular forces, including hydrogen bonds, hydrophobic interactions, van der Waals forces, and electrostatic interactions, are involved in the physical complex formation (Domínguez Avila et al. 2017b, Lin et al. 2016, Padayachee et al. 2012).

The interactions between polyphenols and polysaccharides are influenced by their structural characteristics (Q.W. Guo et al. 2018, Zhu et al. 2018). Polyphenol compounds with hydrophobic groups and higher degrees of polymerization show a better tendency to interact with polysaccharide molecules, whereas polar groups, such as quinic acid moieties, compromise these interactions (Gonçalves et al. 2018). The chain conformation and hydrophobicity of polysaccharide molecules also strongly affect the retention of polyphenols (A. Fernandes et al. 2020). As per P.A.R. Fernandes et al. (2020), linear arabinans could retain eightfold and twofold chlorogenic acid and phloridzin, respectively, of that of the branched arabinans. In addition, environmental factors, including pH, temperature, mixing time, ionic strength, and substrate concentration, affected their interaction intensities (Zhang et al. 2017). For instance, the flavonoids bound per corn silk polysaccharide (CSP) mass unit (physically) increased with increases in the flavonoid concentration in the mixture (Q.W. Guo et al. 2018). The pH value not only influenced the stability of polyphenols but also affected their noncovalent interactions with polysaccharides (Jakobek & Matić 2019). Koh et al. (2020) reported that the pectin-anthocyanin adsorption was the highest at pH 3.0 and lowest at pH 4.0. Anionic pectin and cationic anthocyanins showed the strongest electrostatic interaction at pH 3.0 and anthocyanins are partially protonated at pH 4.0. Therefore, the influences of pH on the noncovalent interactions between polyphenol and dietary fiber molecules might be modulated by the amount of protonated and deprotonated functional groups or the ratio of protonated:deprotonated molecules (Jakobek & Matić 2019).

Various thermodynamic equations and isothermal models, such as Langmuir and Freundlich equations and the Clausius-Clapeyron equation, were used to quantify the physical interactions between polyphenols and polysaccharides (Q.W. Guo et al. 2018, Koh et al. 2020).

Both the Langmuir equation (Equation 1) and Freundlich equation (Equation 2) calculate the amount of adsorbed polyphenol per unit mass of polysaccharide (Q_e) as follows:

$$Q_e = Q_m K_L C_e / (1 + K_L C_e) \quad 1.$$

and

$$Q_e = K_L C_e^{(1/n)}, \quad 2.$$

where Q_e is the amount of adsorbed polyphenol per unit mass of polysaccharide (μg/mg), K_L is the apparent binding affinity constant, C_e is the free solute polyphenol concentration at equilibrium (mg/mL), $1/n$ is the adsorption driving force constant, and Q_m is the apparent maximum adsorption capacity (μg/mg).

The Clausius-Clapeyron equation calculates the Gibbs free energy change before and after absorption (ΔG) as follows:

$$\ln K_C = \Delta S/R - \Delta H/R \quad 3.$$

and

$$\Delta G = -RT \ln K_C, \quad 4.$$

where T is the temperature (K), K_C is the equilibrium distribution coefficient, ΔS is entropy change, R is the perfect gas constant (8.314 J/mol/K), ΔG is Gibbs free energy change, and ΔH is enthalpy change.

4. COVALENT INTERACTION COMPLEXES AND THEIR MECHANISMS

CS: chitosan

EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide

NHS: *N*-hydroxysuccinimide

HOBt: hydroxybenzotriazole

Naturally occurring covalently linked polyphenol–polysaccharide complexes have been found in the flowers/leaves of many medicinal plants and some food crops (**Table 2**). However, owing to structural complexity and challenges in isolation, the detailed structural features of the complexes and the distribution of polyphenols along the polysaccharide molecular chain have not been well clarified. As shown in **Table 2**, the polysaccharide portion of the complex mostly comprises up to six monosaccharide compositions containing a higher percentage of uronic acid. Ferulic acid has been reported to be covalently linked to psyllium arabinoxylan through an ester bond. This complex is regarded as the primary contributor for its strong gelling capacity (Yin et al. 2019). A similar arabinoxylan–ferulic acid complex was also identified in wheat bran. This structure, however, cannot be retained by the commonly used alkaline extraction method. The covalently linked ferulic acid could be easily removed by alkaline treatment under thermal processing conditions. Recently, efforts have been made to graft various polyphenols onto polysaccharide molecules (Liu et al. 2018b), as shown in **Table 1**. For example, phenolic acids, including caffeic, gallic, and ferulic acids, were reported to be covalently linked to chitosan (CS) (Liu et al. 2013, 2017), starch (Lv et al. 2016), curdlan (Cai et al. 2019), pectin (Wang et al. 2020), inulin (Liu et al. 2014a), dextran (Vittorio et al. 2016), and gum arabic (Vuillemin et al. 2020). These reactions were achieved by laccase-catalyzed polymerization (a free radical–mediated reaction) and carbodiimide-mediated coupling reaction. The covalently linked polyphenol–polysaccharide conjugates demonstrated improved or additional physicochemical and bioactive properties, which extended their applications compared with the unmodified polyphenols and polysaccharides (Liu et al. 2016b, 2018a). The detailed preparation methods and their corresponding mechanisms for covalent conjugates are summarized below.

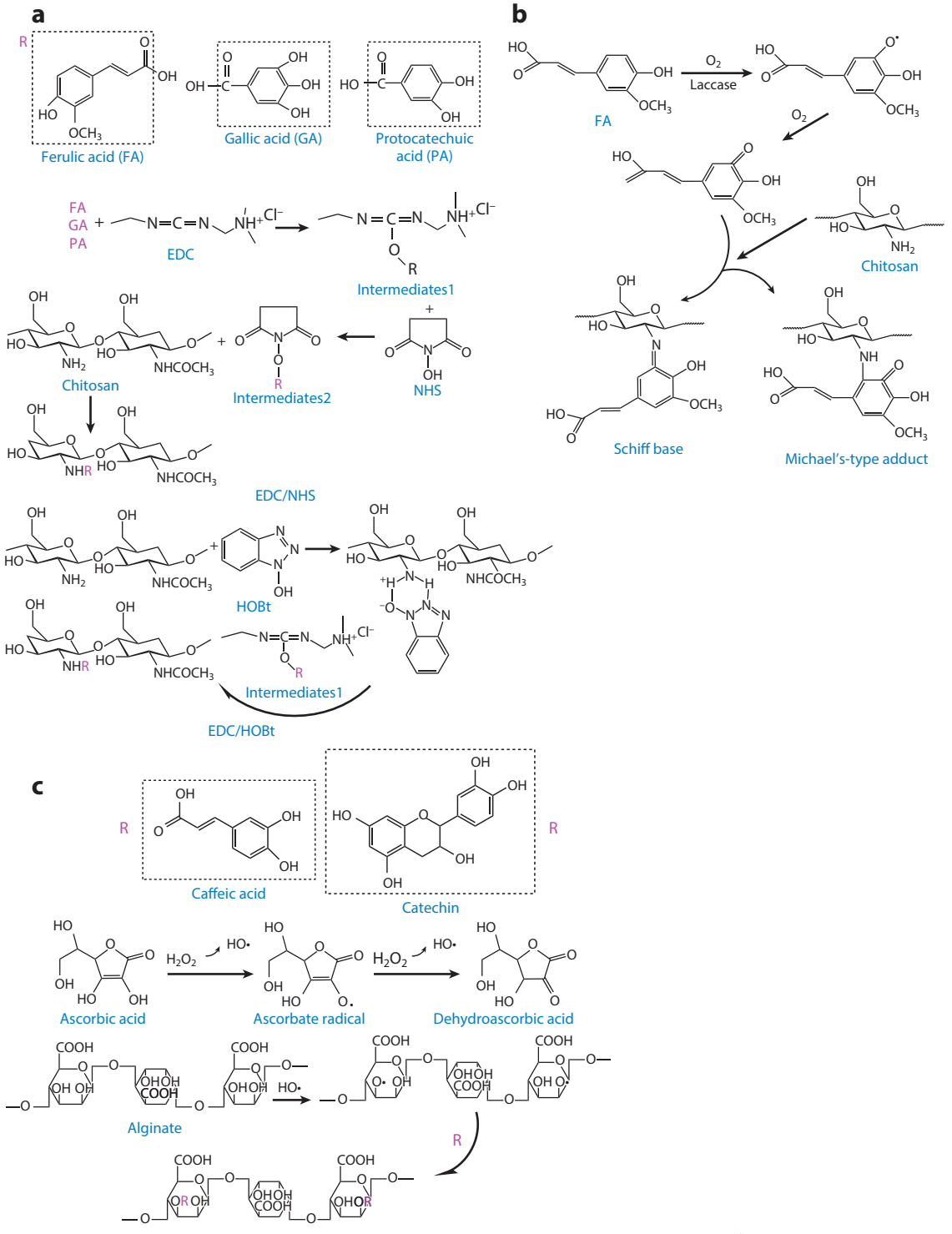
4.1. Polyphenol–Polysaccharide Conjugate Formation through the 1-Ethyl-3-(3-Dimethylaminopropyl) Carbodiimide Method

1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) is a water-soluble carbodiimide conjugating agent that induces the conjugation between polyphenols and polysaccharides. Theoretically, it can react with the carboxylic acid group and form highly reactive intermediates (**Figure 1*a***) (Wang et al. 2018). The intermediates are qualified to react with the amine and hydroxyl groups to form polyphenol–polysaccharide conjugates (Rui et al. 2017a). For polysaccharide (e.g., starch) or polyphenol (e.g., epigallocatechin gallate) molecules without carboxylic groups, their conversion into corresponding intermediates before the coupling reaction is necessary (Liu et al. 2018b). *N*-hydroxysuccinimide (NHS) or hydroxybenzotriazole (HOBt) are normally used to assist the reaction. NHS could improve the yield of the conjugates by inhibiting the side reactions such as hydrolysis of the intermediate, whereas HOBt can be used as a racemization suppressor. Relatively intense hydrogen bonds or ionic bonds can be formed between the hydroxyl groups of HOBt and the amino groups of CS (**Figure 1*a***) (Xie et al. 2014). Because of the simple operation procedure, high efficiency, and mild reaction conditions, the EDC/NHS method has been successfully applied for the conjugation of polysaccharides with many phenolic acids, e.g., gallic acid, caffeic acid, and ferulic acid (Liu et al. 2016b, 2018b; Wang et al. 2018; Yu et al. 2011). In addition to the EDC method, other chemical coupling reagents such as *N*,*N*′-carbonyldiimidazole (CDI), epichlorohydrin (ECH), and dicyclo-hexylcarbodiimide (DCC) have also been previously applied (Liu et al. 2016b, 2018c; Mundlia et al. 2020). The grafting efficiency ratio of polysaccharide–polyphenol conjugates is also greatly affected by the reaction conditions, including pH, temperature, reaction time, depolymerization degree, and structural features of polysaccharides and polyphenols (Hu & Luo 2016, Liu et al. 2017, Rui et al. 2017a, Wei & Gao 2016).

Table 2 Naturally occurring polysaccharide–polyphenol complexes

Plant substance isolated from	Used part	Yield (wt%)	Carbohydrate content (wt%)	Total phenols (GAE) (mM)	Monosaccharide composition (weight ratio)	Biological activity	References
Achillea millefolium L.	Flowers	6.6	21.1	0.9	Rha:Ara:Xyl:Gal:Glc:UA = 1.9:9.1:1.0:6.2:3.1:21.9	Antioxidative activity	Saluk-Juszczak et al. 2010
Agrimonia eupatoria L.	Aerial	3.1	30.4	2.7	Rha:Ara:Man:Gal:Glc:UA = 2.3:4.4:1.0:14.8:11.2:28.4	Anticoagulant activity	Tsirigotis-Maniecka et al. 2018
Arnica montana L.	Flowers	0.9	25.9	1.2	Rha:Ara:Gal:Glc:UA = 1.0:9.7:4.6:2.9:15.3	Antioxidative activity	Saluk-Juszczak et al. 2010
	Flowers	5.7	26	1.25	Rha:Ara:Gal:Glc = 1.0:2.8:2.1:1.4	Antitussive activity	Sutovska et al. 2014
	Flowers	0.9	11.3	4.83	Rha:Ara:Gal:Glc:UA = 1.0:6.0:6.5:6.0:8.5	Anticoagulant activity	Pawlaczyk et al. 2009
Chamomilla recutita L. Rauschert	Flowers	5.0	28.3	0.8	Rha:Ara:Xyl:Gal:Glc:UA = 1.0:2.1:2.5:1.4:1.2:10.7	Antioxidative activity	Saluk-Juszczak et al. 2010
Crataegus monogyna Jacq.	Flowers	2.8	36.2	0.72	Rha:Ara:Man:Gal:Glc:UA = 7.8:1.7:1.0:5.3:4.9:6.8	Anticoagulant activity	Pawlaczyk-Graja 2018
	Fruits	1.8	28.7	5.92	Rha:Ara:Man:Gal:Glc:UA = 2.0:6.5:1.0:6.1:10.6:5.1	Anticoagulant activity	Pawlaczyk-Graja 2018
Conyza canadensis L.	Flowers	0.9	34.1	1.6	Ara:Xyl:Man:Gal:Glc:UA = 5.9:1.0:1.5:2.8:6.75:44.0	Antioxidative activity	Saluk-Juszczak et al. 2010
Echinacea purpurea L.	Flowers	1.8	62.6	0.54	Rha:Ara:Xyl:Man:Gal:Glc:UA = 5.4:16.4:4.3:1.0:1.9:2.8:8.2	Antioxidative activity	Saluk-Juszczak et al. 2010
	Flowers	1.8	16.4	4.79	Rha:Ara:Man:Gal:Glc:UA = 1.8:11.9:1.0:9.8:3.3:13.6	Anticoagulant activity	Pawlaczyk et al. 2009
Erigeron canadensis L.	Flowers	~1.0	34.1	NA	Ara:Man:Gal:Glc:UA = 3.9:1.0:1.9:4.5:29.3	Anticoagulant and antiplatelet activity	Pawlaczyk et al. 2011
Fragaria vesca L.	Leaves	1.4	15.2	1.06	Rha:Ara:Gal:Glc:UA = 1.5:1.0:2.8:1.3:7.8	Radiation protection	Zbikowska et al. 2016
	Leaves	7.7	25.0	3.29	Rha:Ara:Xyl:Gal:Glc:UA = 5.1:3.4:1.0:5.3:2.4:24	Anticoagulant activity	Pawlaczyk-Graja et al. 2019
	Flowers	1.4	15.2	6.70	Rha:Ara:Gal:Glc:UA = 1.5:1.0:2.8:1.3:7.8	Anticoagulant activity	Pawlaczyk et al. 2009
Lythrum salicaria	Flowers	NA	74	0.10	Rha:Ara:Gal:UA = 2.8:1.0:1.4:5.4	Antitussive activity	Sutovska et al. 2012
Rubus plicatus W. et N.	Flowers	2.0	8.0	6.26	Rha:Ara:Xyl:Man:Gal:Glc:UA = 1.0:4.1:4.1:1.2:6.7:10.8:17.5	Anticoagulant activity	Pawlaczyk et al. 2009
	Leaves	2.0	8.0	1.55	Rha:Ara:Man:Gal:Glc:UA = 1.0:4.1:1.2:6.7:10.8:17.5	Radiation protection	Zbikowska et al. 2016
Sanguisorba officinalis L.	Flowers	1.8	21.0	1.37	Rha:Ara:Gal:Glc:UA = 1.3:3.1:2.4:1.0:19.6	Radiation protection	Zbikowska et al. 2016
Sambucus canadensis L.	Flowers	NA	43	0.7	Rha:Ara:Gal:Glc:UA = 1.6:1.4:1.0:1.2:1.4	Antitussive activity	Sutovska et al. 2013
Solidago virgaurea L.	Flowers	1.0	13.4	5.084	Rha:Ara:Gal:Glc:UA = 1.0:2.9:5.1:3.0:4.2	Anticoagulant activity	Pawlaczyk et al. 2009
	Flowers	1.0	24.7	1.34	Rha:Fuc:Ara:Xyl:Gal:Glc:UA = 8.6:1.9:7.4:1.0:5.4:5.0:8.7	Antioxidative activity	Saluk-Juszczak et al. 2010

Abbreviations: GAE, gallic acid equivalent; NA, not available.



(Caption appears on following page)

Figure 1 (*Figure appears on preceding page*)

The schematic reaction mechanism for the synthesis of polyphenol–polysaccharide conjugates by (*a*) 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)-mediated, (*b*) enzyme-mediated, and (*c*) free radical–mediated methods. Abbreviations: HOBt, hydroxybenzotriazole; NHS, *N*-hydroxysuccinimide.

4.2. Enzyme-Mediated Polyphenol–Polysaccharide Conjugation Reactions

Enzymes, including laccase, tyrosinase, horseradish peroxidase, and chloroperoxidase, have been used to prepare polyphenol–polysaccharide conjugates (Aljawish et al. 2014, Hu & Luo 2016, Vuillemin et al. 2020). As presented in **Figure 1*b***, polyphenols are first converted into corresponding quinones through the enzymatic reaction and undergo nonenzymatic reaction to covalently connect to the nucleophilic amino groups of CS through either a Michael-type or Schiff-base reaction. Meanwhile, side reactions such as the quinone condensation may occur, resulting in phenolic oligomer formation during the conjugation reaction (Aljawish et al. 2014, Hu & Luo 2016).

The enzyme-mediated reaction has several advantages. Enzymes are safe and effective, low cost, and can be repeatedly utilized by adopting the immobilized technology (Vittorio et al. 2016). Of all the oxidation enzymes used for conjugation, laccase is the most promising. Laccase catalyzes the oxidation of aromatic substrates like polyphenols, polyamines, aminophenols, ortho- and paradiphenols, and aryl diamines (Kim et al. 2017).

However, enzymes catalyze the oxidation of phenol hydroxyl groups into quinones, which generate the colored polysaccharide derivatives with attenuated bioactivity, limiting their applications in food industries (Rui et al. 2017a). A lack of long-term stability and tendency for protein contamination in the final product also reduce the applicability of this method (Vittorio et al. 2016).

4.3. Free Radical–Induced Reactions

Polyphenol–polysaccharide conjugation could also be produced through free radical–induced reactions. Recently, many free radical initiator systems, including the ascorbic acid (Vc)–hydrogen peroxide (H_2O_2) redox pair, ceric ammonium nitrate, and potassium persulfate, have been developed to initiate the conjugation reactions between polyphenols and polysaccharides (Cai et al. 2019, Liu et al. 2017, Guo et al. 2021). The Vc–H_2O_2 redox system is a promising method that has been widely used (Liu et al. 2017). As shown in **Figure 1*c***, Vc can be oxidized by H_2O_2, inducing the formation of free hydroxyl radicals (Lei et al. 2014b, Wang et al. 2020). The formed hydroxyl free radicals abstract hydrogen atoms from the reactive amino group or hydroxyl groups (OH) of polysaccharide molecules, generating polysaccharide macroradicals (Cai et al. 2019, Jing et al. 2018). The polyphenols in close proximity to the reaction site become acceptors of polysaccharide macroradicals, which develop the conjugates (Liu et al. 2013). This reaction should occur in inert air, as oxygen could capture the free radical, decreasing the conjugation efficiency. The Vc–H_2O_2 redox pair–induced reaction has several advantages: (*a*) It is less expensive than carbodiimide and enzymes; (*b*) leads to higher reaction yields and less/no toxic compound generation, which is important in food and pharmaceutical applications (Pasanphan & Chirachanchai 2008); and (*c*) can be conducted at room temperature, which avoids the degradation and oxidation of polyphenols. Overall, Vc–H_2O_2 redox pair–induced conjugation is economical and ecofriendly. This method has been successfully utilized to synthesize many polyphenol–polysaccharide conjugates, including starch–quercetin, inulin–catechin, curdlan–ferulic acid, and dextran–catechin conjugates, to enhance their stability and biological activities (Cai et al. 2019, Cirillo et al. 2012, Liu et al. 2014a, Vittorio et al. 2012). Recently, our groups obtained arabinoxylan–catechin (AX-CA) conjugates by covalently tagging arabinoxylan [AX; molecular weight (Mw) 694 kDa] from wheat bran with catechin (CA), using a free radical reaction. AX-CA conjugates with different CA concentrations

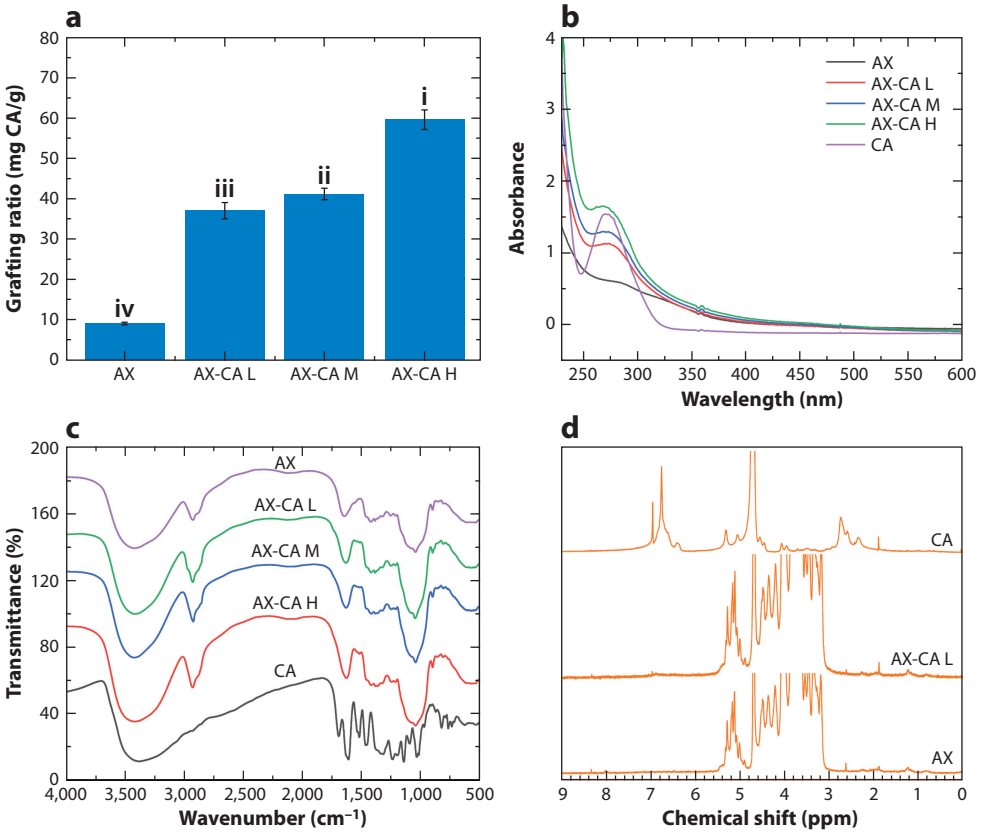


Figure 2

The (*a*) grafting ratios, (*b*) UV–vis spectra, (*c*) FT-IR spectra, and (*d*) 1H NMR spectra of arabinoxylan (AX), catechin (CA), and arabinoxylan-catechin conjugates (AX-CA L). Different letters (i–iv) within panel *a* indicate significant differences in grafting ratios of CA among various conjugates ($P < 0.05$). Adapted from Guo et al. (2021). Abbreviations: AX-CA H, AX-CA conjugate with high ratios of CA; AX-CA L, AX-CA conjugate with low ratios of CA; AX-CA M, AX-CA conjugate with medium ratios of CA; FT-IR, Fourier transform infrared; NMR, nuclear magnetic resonance; UV, ultraviolet.

were obtained, 37.06 (AX-CA L), 41.15 (AX-CA M), and 59.60 (AX-CA H) mg CA/g, by the Folin–Ciocalteu method (**Figure 2*a***). Grafting CA onto AX not only decreased the Mw, thermal stability, and apparent viscosity of AX but also enhanced its inhibition effects on starch digestibility in vitro, possibly because of synergistic enzyme inhibition effects between CA and AX (Guo et al. 2021).

4.4. Conjugate Purification Methods

After the conjugation reaction, the free polyphenols need to be removed from the mixture. The obtained conjugates need to be collected for further structural, functional, and bioactive property investigations. To achieve this, the reaction solution needs to be adjusted to pH 7.0 using an NaOH solution (Wei & Gao 2016), and the conjugates can be precipitated with three volumes of ethanol. The precipitates are washed twice with ethanol or other organic solvents (e.g., acetone) to remove the physically trapped polyphenols, which are once again dissolved and dialyzed

against distilled water to remove small molecular contaminants. The solution is condensed and lyophilized to obtain dry conjugates (Guo et al. 2021, Ahn et al. 2017, Halake & Lee 2017, Karaki et al. 2016, Wen et al. 2016, Zhou et al. 2020). High-performance size-exclusion chromatography (HPSEC) analysis coupled with refractive index and ultraviolet detectors can check whether the samples contain unconjugated polyphenols (Lv et al. 2016; Spizzirri et al. 2010, 2011). However, this method can only remove the unconjugated polyphenols if the unreacted or less reacted polysaccharides are still included in the samples, interfering with the followed sample evaluation. A column separation process may follow to remove the less conjugated polysaccharides.

5. STRUCTURAL CHARACTERIZATION

5.1. Fourier Transform Infrared Spectroscopy

Fourier transform infrared (FT-IR) spectroscopy can monitor the structural changes of polyphenol–polysaccharide complexes with various grafting ratios (Guo et al. 2021, Wei & Gao 2016). FT-IR spectra of polyphenols contain three characteristic peaks, attributing to −OH stretching and plane bending vibrations, C = C stretching vibrations of the aromatic ring, and C-O/C-C stretching vibrations (Liu et al. 2014a, 2016b; Woranuch & Yoksan 2013). Both physically and covalently linked complexes demonstrate all the characteristic peaks of polysaccharides and polyphenols. However, some new bands and peak shifts appear for covalently linked conjugates but not physical complexes (Ahn et al. 2017, Moreno-Vasquez et al. 2017, Wei & Gao 2016, Zhou et al. 2020). According to Wei & Gao (2016), FT-IR spectra of the CS–CA physical complex were similar to those of the control CS, but the covalent conjugates showed two new peaks at 1,730 and 1,640 cm^{-1}, attributed to C = O stretching in esters (connecting with OH group) and C = O stretching in CS amide (connecting with amide group), respectively. In our previous study (Guo et al. 2021), similar results have been reported for AX-CA complexes with different grafting ratios, as shown in **Figure 2*c***. Compared to AX, the spectrum of AX-CA conjugates exhibited a typical aromatic ring C = C stretching at 1,516 cm^{-1}. In summary, FT-IR could distinguish the covalently conjugated complex from the physical complex as well as conjugates of various grafting ratios by tracking the change of peak intensity or the presence of additional peaks when compared with polyphenol or polysaccharide alone.

5.2. Ultraviolet–Visible Spectroscopy

The ultraviolet–visible (UV–vis) spectra of pure polyphenols show one or two characteristic absorption bands, attributed to the π-system of the benzene ring (Ahn et al. 2017; Liu et al. 2013, 2014a,b, 2016b; Moreno-Vasquez et al. 2017; Wei & Gao 2016; Woranuch & Yoksan 2013; Xie et al. 2014). In contrast, polysaccharides show no absorption bands in a limited wavelength of UV–vis spectra. The UV–vis spectrum of polyphenol–polysaccharide physical complexes is similar to polyphenols (Wei & Gao 2016). However, peak shifts are commonly noticed for covalent conjugates, which might be due to the change of the electron states of phenolic chromophores (Ahn et al. 2017; Liu et al. 2013, 2014b; Moreno-Vasquez et al. 2017; Xie et al. 2014). Ahn et al. (2017) grafted polyphenols onto pectin molecules through a redox radical initiation method and observed that the pectin–polyphenol conjugates showed a new UV–vis absorbance at the frequency range of 200–600 nm compared with pure pectin. The maximum wavelengths (λ_{max}) for hesperidin, rutin, quercetin, and (+)-catechin appeared at 285, 265, 274, and 257 nm, respectively. After conjugation with pectin, the λ_{max} shifted to 283, 257, 258, and 277 nm, respectively (Ahn et al. 2017). Recently, Guo et al. (2021) compared the UV–vis spectra of AX, CA, and AX-CA conjugates (different grafting ratios). Both CA and AX-CA conjugates exhibited one characteristic absorption band at

274 nm, whereas AX showed no absorption peak in the range of 220–600 nm. In addition, the absorption intensity of UV–vis spectra of AX-CA conjugates increased with the increase of the grafting ratio at the same concentration (**Figure 2*b***).

5.3. Molecular Weight Changes

Mw changes have also been regarded as one of the indicators for conjugation reactions. For example, Jing et al. (2018) found that the conjugation reaction of CS–proanthocyanidin by a free radical method caused CS degradation. The Mw of proanthocyanidin–CS conjugates was approximately 50% lower than that of the original CS, which was likely caused by the ·OH attacking during the reaction (Jing et al. 2018). Similar results were also reported for the pectin–polyphenol conjugates created by an ECH-mediated coupling reaction (Ahn et al. 2017) and arabinoxylan-catechin created by free radical–mediated reactions (Guo et al. 2021). Given that a polysaccharide before reaction already exhibits Mw distribution and the change of Mw is highly affected by the reaction conditions, the Mw change can be used only as an additional indication of a conjugation reaction.

5.4. Nuclear Magnetic Resonance Analysis

The molecular structure of polyphenols grafted to polysaccharides can be characterized by ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy (Liu et al. 2013, 2014a, 2016b; Mundlia et al. 2020; Pasanphan & Chirachanchai 2008; Rui et al. 2017a; Wang et al. 2018; Woranuch & Yoksan 2013; Xie et al. 2014; Zhu & Zhang 2014). For a CS–gallic acid complex before conjugation, the full chemical shifts of CS are H-1 (4.6 ppm), H-2 (3.1 ppm), H-3–H-6 (3.6–3.9 ppm), and N-acetyl residue (2.0 ppm). After polyphenol tagging, several new peaks appear in the aromatic proton region (between 6.0 and 7.5 ppm) and are assigned to the methine protons of gallic acid (Xie et al. 2014). Our group also reported similar results for the AX-CA complex (Guo et al. 2021), which showed extra peaks at 6.5–7.5 ppm compared to AX (**Figure 2*d***). For an EDC-mediated coupling reaction, the signals at 7.4–8.0 ppm (HOBt) should not be observed, ensuring its inexistence in the conjugates (Rui et al. 2017a). ^{1}H NMR spectroscopy also delivers the degree of phenolic substitution through peak integration by which the substitution degree for proanthocyanidin–CS conjugation was obtained, which was 11.2% (Jing et al. 2018).

^{13}C NMR has been applied to characterize polyphenol–polysaccharide conjugates. For example, the ^{13}C NMR spectrum of CS shows signals at 105.5 ppm (C-1), 83.2 ppm (C-4), 75.5 ppm (C-3 and C-5), 61.0 ppm (C-6), and 57.9 ppm (C-2). Signals at 23.7 ppm and 174.2 ppm were attributed to the carbonyl and methyl groups, respectively, of *N*-acetylglucosamine. Compared with CS, phenolic acid–CS conjugates show additional peaks between 110 and 150 ppm and are assigned to the C = C double bond of phenolic groups (Liu et al. 2014b). The strengthened signal at 174.8 ppm was caused by the formation of carbonyl (C = O) groups between amino groups of CS and carboxyl groups of phenolic acid (Rui et al. 2017a). A new peak at 163 ppm was due to the formation of imine (C = N) (Saranya et al. 2018).

In addition to the 1D NMR (^{1}H and ^{13}C), 2D NMR spectroscopy, including homonuclear correlation spectroscopy (COSY), total correlation spectroscopy (TOCSY), heteronuclear single quantum coherence (HSQC), and heteronuclear multiple quantum correlation (HMBC), has also been widely used for polysaccharide (Q.B. Guo et al. 2018), polyphenol (Rouger et al. 2019), and polyphenol–polysaccharide complex analyses (Pawlaczyk-Graja et al. 2019). Therefore, NMR can be used to uncover the detailed information of polyphenol–polysaccharide conjugates, including the grafting positions between polyphenols and polysaccharides and the degree of substitution.

To summarize, FT-IR, UV spectroscopy, and NMR can characterize the structural features of polyphenol–polysaccharide conjugates and monitor structural changes before and after conjugation reactions by judging whether complexes contain the corresponding peaks of both polysaccharides and polyphenols. These spectroscopy methods can distinguish the noncovalent from the covalent conjugates, as the later normally demonstrate additional peaks caused by the covalent linkage between polysaccharide and polyphenol molecules, and they can compare conjugates of various grafting ratios by monitoring the corresponding peak intensity. In addition, Mw change of polysaccharides can be a supplementary indicator for the covalent conjugation reaction between polysaccharides and polyphenols.

6. PHYSICOCHEMICAL CHARACTERISTICS

6.1. Solubility

It has been summarized that "any structural character of polymers that hinder the intermolecular association leads to higher water solubility, such as branching structure and the number of charged groups, etc." (Guo et al. 2017). Tagging polyphenols onto polysaccharide molecules potentially hinders the intermolecular association and increases the solubility. Similarly, some water-insoluble phenolic compounds (e.g., quercetin) become water soluble after conjugation with polysaccharides. For instance, the solubility of CS is pH-dependent owing to the presence of an N-Ac group, which is almost insoluble at pH 7. However, the CS–polyphenol conjugates exhibited a better solubility, and the solubility of the phenolic acid-g-CS was related to the grafting ratio and reaction conditions (Rui et al. 2017a, Xie et al. 2014). The solubility increase was likely caused by the interruption of polyphenols on the intermolecular H-bond and crystalline structures of CS (Woranuch & Yoksan 2013). Furthermore, a study by Rui et al. (2017a) indicated that the water solubility of chlorogenic acid–CS conjugates was much higher than that of single chlorogenic acid or CS at pH $\geq$ 7.

6.2. Thermal Stability

Thermal stability of polysaccharides and polyphenol–polysaccharide conjugates can be evaluated by thermogravimetry (TGA) or differential scanning calorimetry (DSC) analysis. Parameters, including weight-loss stages, enthalpy change, and denaturation temperature, reflect thermal stability. For instance, using TGA analysis, both *Tremella fuciformis* polysaccharides (TPSs) and catechin-grafted TPSs show two main weight-loss stages (Liu et al. 2016b), which are attributed to the loss of absorbed and trapped water in polymers and depolymerization/combustion, respectively. Furthermore, the temperature for maximum weight-loss rate by the derivative thermogravimetric curve showed that TPS degraded more rapidly than catechin-g-TPS.

Polyphenol–polysaccharide conjugates normally demonstrate better thermal stability compared to the free polysaccharide, which is likely due to the increased crystallinity after conjugation (Liu et al. 2016b). For instance, catechin-g-inulin and four polyphenol-conjugated pectins all demonstrated higher stability than free inulin and pectin, respectively (Ahn et al. 2017, Liu et al. 2014a). Liu et al. (2018c) also suggested that the thermal stability of quercetin-g-starch was better than the *Cynanchum auriculatum* starch and quercetin. However, linking polyphenol to CS molecules decreased their thermal stability. Moreover, thermal stability was associated with grafting rate and the types of polyphenols (Liu et al. 2014b, 2017; Moreno-Vasquez et al. 2017; Pasanphan & Chirachanchai 2008; Woranuch & Yoksan 2013; Zhu & Zhang 2014). For example, Wang et al. (2018) evaluated the thermal property of CS and CS–ferulic acid conjugates by DSC. The thermal stability of CS decreased after grafting with ferulic acid, likely attributed to reduced

hydrogen bonding due to the interference of ferulic acid and relatively lower decomposition temperature of ferulic acid (Wang et al. 2018).

6.3. Crystallinity Analysis

X-ray diffraction (XRD) is a rapid analytical tool for the identification of crystalline material. In general, a spectrum with sharp narrow diffraction peaks indicates crystalline material and broad peaks reflect amorphous components (Liu et al. 2016b, Yong et al. 2020). Liu et al. (2014a) measured the crystallinity of catechin, inulin, and catechin-g-inulin by XRD, revealing that the catechin-g-inulin showed the highest degree of crystallinity. Catechin-g-TPS also demonstrated a higher crystallinity than TPS using XRD analysis (Liu et al. 2016b). However, grafted starch exhibited a decreased crystallinity compared to the original starch and polyphenols (Liu et al. 2018c, Yong et al. 2020). According to Liu et al. (2018c), *C. auriculatum* starch showed two intense diffraction peaks, suggesting a C-type crystallinity, whereas quercetin demonstrated a highly crystalline nature with numerous diffraction peaks. However, the crystalline peaks of both *C. auriculatum* starch and quercetin disappeared after the conjugation reaction, likely due to the starch gelatinization (Liu et al. 2018c). A similar phenomenon was found in the XRD patterns of the phenolic acid–grafted CS (Jing et al. 2018, Liu et al. 2016a). In brief, as a supplementary method, XRD can validate whether polysaccharides and polyphenols are covalently linked and investigate the crystallinity situation of the conjugated complex.

6.4. Rheological Properties

Introducing polyphenols into polysaccharides influences the overall rheological properties of polysaccharides in solutions. According to previous reports, pectin, starch, and CS grafted to phenolic acid all demonstrated shear-thinning flow behavior, with the flow behavior index (n) lower than 1 (Karaki et al. 2016, Lv et al. 2016, Wei & Gao 2016). The shear-thinning properties are attributed to the chain entanglements of polysaccharide molecules and are determined by their molecular structure and conformation (Wang et al. 2020, Xie et al. 2016). For example, native pectin showed slightly higher viscosities than the pectin–polyphenol complex, which was possibly caused by the decreased Mw and reduced intermolecular association due to the steric effect of bulky polyphenols (Ahn et al. 2017). However, opposite results were reported for CS, starch, and their conjugates. The conjugates showed much higher viscosity than the CS or starch under the same weight concentration (Lv et al. 2016, Wei & Gao 2016). The authors claimed the increased Mw and the formation of chlorogenic acid dimers or trimers were the main reasons. This still needs verification, as the Mw test was not conducted in that study (Wei & Gao 2016). Furthermore, the types of substituted polyphenols and the grafting ratio also affect the apparent viscosity. For instance, the apparent viscosity of CS decreased with an increasing degree of substitution (DS), but the apparent viscosity of carboxymethyl sweet potato starch solution increased with DS, which might be attributed to the presence of hydrophobic segments that favored intermolecular association, forming multimolecular aggregates (Lv et al. 2016, Xie et al. 2014).

A small-strain oscillation test can evaluate the dynamic flow behavior of the polysaccharides before and after polyphenol conjugations. Storage modulus (G′) and loss modulus (G″) are the two commonly used indicators. For instance, the dynamic flow behavior of gallic acid-g-CS showed gelling properties (G′ > G″). However, G″ of CS and octyl gallic acid-g-CS were higher than G′, and both exhibited liquid-like flow behavior. These differences were likely caused by their distinct macromolecular side chain as well as different solution conditions and concentrations (Xie et al. 2016).

6.5. Other Functional Properties

Many studies have confirmed that biopolymer–polyphenol conjugates endow better emulsifying capacity and emulsion stability (Lei et al. 2014b, Yu et al. 2021). The conjugates have also been reported to more effectively inhibit lipid oxidation than do the biopolymers alone (Wang et al. 2018). Lei et al. (2014a) found that the low-molecular-weight CS–epigallocatechin-3-gallate conjugates could better improve the physical stability of a β-carotene emulsion and inhibit the deterioration of β-carotene than could native CS.

7. BIOACTIVE PROPERTIES

7.1. Antioxidant Activity

Antioxidants could attenuate oxidative stress by scavenging reactive oxygen species such as free radicals that cause cell injury, which showed health benefits against many diseases such as diabetes, aging, atherosclerosis, cancer, and rheumatoid arthritis (Xu et al. 2021). Phenolic compounds have been widely studied for their antioxidant properties, which are associated with the number and arrangement of hydroxyl groups in the phenolic molecules (Liu et al. 2017). However, the limitations of phenolic compounds, including low water solubility, low bioavailability, rapid catabolism in the upper gastrointestinal tract and liver, and fast excretion through the urinary system, all compromise their health benefits when orally ingested (Paini et al. 2015). These challenges might be at least partially alleviated by their physical or chemical binding with polysaccharides.

The in vitro antioxidant activity of polyphenols, polysaccharides, and polyphenol–polysaccharide conjugates can be evaluated by the lipid peroxidation inhibition capacity, reducing power, radical scavenging, and β-carotene–linoleic acid assays (Liu et al. 2013, 2017; Yong et al. 2020). Conjugation of polyphenols with polysaccharides enhances the antioxidant property of polysaccharides, which is attributed to the action of polyphenols. The antioxidant property of conjugates was reported to be less than polyphenols at the same molecular concentrations (Rui et al. 2017a).

7.2. Anticancer Activity

Polyphenols demonstrated antiproliferative activity against colon, breast, liver, lung, leukemia, prostate, cervical, and skin cancer cells. The antiproliferative activity could be generally related to the cytotoxic effects of the polyphenols, leading to cell cycle arrest followed by apoptosis of the cancer cells (Liu et al. 2017). The antitumor activity of polyphenol–polysaccharide conjugates, especially CS–phenolic acid conjugates, has been widely studied. Lee et al. (2013) studied the anticancer effects of caffeic acid and CS-g-caffeic acid using CT26 colorectal carcinoma cells. Both caffeic acid and CS-g-caffeic acid conjugates revealed a dose-dependent inhibition of cell viability and antiproliferative effects against CT26 colorectal carcinoma cells. In comparison to caffeic acid, CS-g-caffeic acid conjugates also stimulate the apoptosis of tumor cells and showed high anti-invasive efficacy against tumor cells, as determined by a Matrigel Ò invasion assay (Lee et al. 2013). In addition to CS–phenolic acid conjugates, the dextran–catechin conjugates, synthesized by immobilized laccase, demonstrated antitumor activity in the cultured neuroblastoma cells (Vittorio et al. 2016). The polysaccharides and polyphenols isolated from plants demonstrated synergistic inhibition against many different cancer cells, e.g., the combination of oolong tea polysaccharides and polyphenols showed synergistic inhibition against hepatocellular carcinoma (HCC) in vitro and in vivo, which not only inhibited SMMC7721 cell proliferation but also significantly increased the antioxidant activity and immune function of the mice, suggesting that the conjugates might be functional supplements for the treatment of HCC (Wang et al. 2017).

7.3. Antibacterial Activity

MICs: minimum inhibitory concentrations

To prevent food contamination by microorganisms, antimicrobial agents have been used in the food industry. Given that some commonly used antimicrobial agents, including benzoic acid, sorbic acid, and sodium benzoate, may be toxic, developing natural antimicrobial agents is urgently needed (Atta et al. 2017, Yong et al. 2020). Some polyphenol–polysaccharide conjugates are currently used as efficient antimicrobial agents to prevent food contamination. Compared to pure polysaccharides, the polyphenol–polysaccharide conjugates showed enhanced antimicrobial effects on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas* spp., *Bacillus subtilis*, *Enterococcus faecalis*, and *Listeria monocytogenes* bacteria (Chatterjee et al. 2015, Cho et al. 2013, Li et al. 2019, Moreno-Vasquez et al. 2017, Mundlia et al. 2019, Pasanphan & Chirachanchai 2008, Vittorio et al. 2016, Yong et al. 2020). According to Jing et al. (2018), the minimum inhibitory concentrations (MICs) of CS–catechin conjugates were 64 μg/mL for *B. subtilis*, *E. faecalis*, *and L. monocytogenes* compared to 128 μg/mL for that of unmodified CS. However, when comparing the antimicrobial effects of conjugates with pure polyphenol, contradicting conclusions have been drawn. According to Yong et al. (2020), a starch aldehyde–quercetin conjugate exhibited stronger antimicrobial activity than the starch aldehyde but weaker antimicrobial activity than quercetin. The antimicrobial activity of the conjugate was mainly attributed to the quercetin moiety. However, Mundlia et al. (2019) reported that a naringenin–pectin conjugate exhibited MIC values of 2.5, 12, 11.5, 12.5, and 12.5 μg/mL for *Staphylococcus aureus* (MTCC 7443), *Staphylococcus epidermis* (MTCC 435), *B. subtilis* (MTCC 441), *E. coli* (MTCC 1652), and *Pseudomonas aeruginosa* (MTCC 424), respectively, compared to 6.5, 24.5, 12.5, 12.5, and 23.5 μg/mL of naringenin alone. The authors speculated that the better antibacterial activity of the amphiphilic naringenin–pectin conjugate compared to lipophilic naringenin was likely due to the greater aqueous solubility and penetration of the colloidal naringenin–pectin conjugate over the hydrophobic naringenin. As can be seen in the above-mentioned studies, the inhibitory capacity varied with bacterial strains and types of grafted polyphenols (Jing et al. 2018). It has been reported that the inhibitory effects of the complexes on, e.g., *S. aureus* were stronger than that on *Pseudomonas aureus* and *E. coli* (Li et al. 2019, Moreno-Vasquez et al. 2017). Antibacterial activity of polyphenol–polysaccharide conjugates could be achieved through irreversible damage to the bacterial cell wall and cytoplasmic membrane owing to hydrophobic properties enhanced by phenol grafting. This property favors the interaction with the phospholipid layer, one major component of the bacterial membrane, which subsequently increases membrane permeability (Aljawish et al. 2014, Li et al. 2019, Mundlia et al. 2019).

7.4. Antidiabetic Activity

Diabetes mellitus is attributed mainly to the defects in insulin secretion (Type I), insulin action (Type II), or both, inducing abnormalities in the metabolism of carbohydrates, lipids, and proteins. Diabetes mellitus may lead to atherosclerosis, nephropathy, retinopathy, cardiovascular diseases, infections, adverse drug reactions, and early mortality (Anyanwu et al. 2019, Peng et al. 2019).

Recently, the antidiabetes (Type II) activities of polysaccharides and polyphenols have been widely studied. These effects are partially due to their postprandial blood glucose–reducing effects due to enzyme inhibition activity and enzyme accessibility related to starch digestion. Moreover, they are related to increased secretion of glucagon-like peptide-1 (GLP1) from intestinal L-cells; inhibition of dipeptidyl peptidase-4 (DPP4), which increases GLP1 half-life; increased insulin secretion via (direct or indirect) β-cell stimulation; and increased insulin sensitivity on peripheral tissues (an effect that may be mediated by the PPARγ transcription factor) (Domínguez Avila et al. 2017a). However, the effects of polyphenol–polysaccharide conjugates have rarely been

NO: nitric oxide

PGE2: prostaglandin E2

reported. An in vitro assay by Zhu & Zhang (2014) found that the α-glucosidase inhibitory effects decreased in the order of conjugates > polyphenols > acarbose > polysaccharides; the α-amylase inhibitory effect decreased in the order of acarbose > conjugates > polyphenols > polysaccharides at the concentration of 1 mg/mL (Zhu & Zhang 2014). Zeng et al. (2020) also reported that the fluorescence of the α-amylase and α-glucosidase could be quenched by tannin–inulin conjugates through a static quenching mechanism. Although different types of polysaccharides and polyphenols showed different antidiabetic activities, the overall antidiabetic activity of their conjugates was generally stronger than that of the corresponding polysaccharides and polyphenols alone on a molecular concentration basis. For example, the dose-dependent inhibition activity of CSPs and CSP–luteolin complexes against α-amylase and α-glucosidase have been previously reported (Q.W. Guo et al. 2018). The IC_{50} values of CSPs and CSP–luteolin complex for α-amylase were estimated to be 6.11 and 5.75 mg/mL, respectively, whereas those for α-glucosidase inhibition were 9.01 and 4.66 mg/mL, respectively (Q.W. Guo et al. 2018). Overall, polysaccharide and polyphenol conjugates can be potentially treated as functional ingredients for developing novel food products to reduce the risk of type II diabetes.

7.5. Anti-Inflammatory Activity

Inflammation is considered a protective process initiated by the organism to eliminate the harmful stimuli for tissue healing, which can be regarded as an innate immune response. The inflammation process correlates with the release of chemical mediators like prostaglandins, tumor necrosis factors, and interleukins (Shehata et al. 2018). However, excessive secretion of inflammatory cytokines, such as nitric oxide (NO), prostaglandin E_2 (PGE_2), interleukin 6, and tumor necrosis factor-α, causes adverse effects on human health (Zhang et al. 2019). The prolonged use of conventional anti-inflammatory steroidal or nonsteroidal drugs leads to side effects such as cognitive dysfunction, depression, kidney damage, myocardial infarction, and gastrointestinal tract bleeding (Yao et al. 2019). Therefore, polyphenol–polysaccharide conjugates as potential anti-inflammatory agents have attracted increasing attention. For example, gallic acid–grafted CS could decrease the expression of inducible NO synthase and cyclooxygenase-2 and inhibit the production of NO and PGE_2 in lipopolysaccharide-stimulated RAW264.7 macrophages (Ahn et al. 2016). The anti-inflammatory action of gallic acid–CS conjugates can be achieved by downregulating transcriptional factors (nuclear factor κB and activator protein-1) through mitogen-activated protein kinase signaling pathways (Ahn et al. 2016). Saranya et al. (2018) studied the anti-inflammatory potential of curcumin-conjugated CS microspheres. This conjugate demonstrated similar anti-inflammatory effects to that of the free curcumin, and both showed dose-dependent inhibitions (Saranya et al. 2018).

7.6. Intestinal Fermentability

Ingested polyphenols are poorly bioavailable in the upper gut. Up to 90% of them enter the colon and are metabolized by bacterial microflora into absorbable metabolites. Dietary fibers play a crucial role in delivering the polyphenols from the gastrointestinal tract to the colon through forming complexes with polyphenols preventing their degradation (Bermudez-Oria et al. 2019, Dobson et al. 2019, Le Bourvellec et al. 2019, Lin et al. 2016, Liu et al. 2019, Zhu et al. 2018). Mercado-Mercado et al. (2015) reported that the bioaccessibility of polyphenols in complete calyces and decoction residues of Roselle was 26.68% and 71.72%, respectively. It can be deduced that the interaction of polyphenols and cell wall polysaccharides in Roselle improved the bioavailability of polyphenols after the gastric and duodenal phases. Solari-Godiño et al. (2017) conducted an in

vitro digestion test of grape pomace–fortified anchovy (*Engraulis ringens*) mince and found a positive correlation between the amount of polyphenol entering the large intestine and the amount of dietary fiber added. Therefore, the interaction of a polyphenol and a polysaccharide may increase the bioavailability of polyphenols.

When they enter the colon, dietary fibers as prebiotics affect the diversity of the microbiota and are converted into metabolites such as short-chain fatty acids and reabsorbed by the human body for health benefits (Porter & Martens 2017). The presence of polyphenols could modify the profiles of generated short-chain fatty acids (Guo et al. 2021). For example, tea polyphenols added to the fermentation system, containing resistant starch and konjac glucomannan fermented by fecal extract, could facilitate lactic acid production but inhibit acetic, propionic, and butyric acid production. The inoculated probiotics could weaken the inhibitory effects of tea polyphenols on acid production, which would result in enhanced acetic, propionic, and butyric acid production but decreased lactic acid production (Geng 2014). Geng (2014) also indicated that polyphenols degraded into three major metabolites [phenyl propionic acid, 3-hydroxyphenyl acetic acid, 5-(3-hydroxyphenyl) valeric acid] and two minor metabolites (benzoic acid, phenyl lactic acid). However, the degradation of the polyphenols by microbiota was reduced when they interacted with cell wall polysaccharides of apple matrices. This was due to steric hindrance between bacterial enzymes that target procyanidins (hitherto unknown enzymes) and many bacterial sugar active enzymes that target cell wall polysaccharides. Le Bourvellec et al. (2019) reported that conjugating procyanidins with cell wall polysaccharides, noncovalently or covalently, significantly reduced procyanidin degradation in the large intestine. Moreover, plant polyphenols in the complex could inhibit the growth of *Bacteroidetes* and *Firmicutes*, which changes the way other prebiotics and energy metabolism in vivo are degraded by changing the composition of the intestinal flora (Padayachee et al. 2017, Xue et al. 2016).

Overall, after conjugation with polysaccharides, the bioavailability of polyphenols can be significantly improved, which in turn modifies the in-colon fermentability of polysaccharides in several ways when compared to pure polysaccharides: (*a*) It delays the overall degradation speed during fermentation; (*b*) changes the profile of generated short-chain fatty acids; and (*c*) modifies the gut microbiota profile and level.

8. APPLICATIONS

8.1. Application for Food Preservation and Packaging

Finding a safe and degradable food packaging material to satisfy the requirements of green packaging is urgently required with the increasing concern of consumers toward environmental issues and food safety (J. Liu et al. 2020). At present, owing to their biodegradable and edible properties, some carbohydrate polymers, such as starch, cellulose derivatives, CS, and pectin, are extensively used in packaging materials to extend the shelf life of food products (Riaz et al. 2018, Ye et al. 2018). In addition, active packaging, as an innovative packaging technology, not only exhibits remarkable biocompatibility and edibility but also extends the quality and shelf life of food by gradually releasing the active factors and adsorbing compounds that contaminate or oxidize food from the surrounding atmosphere (J. Liu et al. 2019, Rui et al. 2017b). For example, adding natural antioxidants to biodegradable materials to improve the biological, physical, and mechanical properties of thin films has attracted increasing attention (J. Liu et al. 2017, 2019; Mittal et al. 2021; Riaz et al. 2018; Rui et al. 2017b; Ye et al. 2018). J. Liu et al. (2019) investigated the changes in the enzyme activities and physicochemical parameters of *Agaricus bisporus* packaged with CS, polyethylene, and gallic acid-g-CS film during cold storage. Gallic acid-g-CS film could maintain the postharvest quality of mushrooms, possibly because of the antioxidant nature of gallic acid-g-CS. Likewise,

Ye et al. (2018) found that a composite membrane with the mass ratio of tea polyphenols to CS of 3:7 could significantly postpone the consumption of vitamin C and soluble solids, decrease the mass loss rate and rotting rate, and extend the shelf life from 2 to 8 days at room temperature. Therefore, the composite film of polyphenol–polysaccharide conjugates shows a great application potential in food preservation and packaging.

8.2. Effects of Polyphenol–Polysaccharide Complex on Wine Astringency

Astringency is an important index for the sensory evaluation of wine. Astringency is attributed to the interaction between concentrated tannins and saliva proteins, leading to aggregate formation and subsequent precipitation (Bautista-Ortin et al. 2014, Quijada-Morin et al. 2014, Renard et al. 2017, Watrelot et al. 2017). Perception of astringency can transform with tannin structure and interactions with other macromolecules. For example, polysaccharides compete with salivary proteins for concentrated tannin substrates, inhibiting protein–tannin interaction, thereby reducing the astringency of red wine (Quijada-Morin et al. 2014, Watrelot et al. 2017). Quijada-Morin et al. (2014) compared the influences of proanthocyanidins, oligosaccharides, and polysaccharides on astringency perception of Tempranillo wines and showed that rhamnogalacturonan-II and mannoproteins could significantly reduce the astringency perception compared to oligosaccharides. The interactions between polysaccharides and tannins were strongly associated with the structure of polysaccharides. For example, the degree of methylation in homogalacturonans of pectin, monosaccharide composition, and linkage patterns of the hairy region of pectin all affected the noncovalent attachment of tannins (Quijada-Morin et al. 2014, Watrelot et al. 2017).

8.3. Nanoparticles for Delivery of Active Ingredients

Nanoencapsulation has been widely used for delivering nutraceutical molecules to desired target sites. It shows multiple favorable properties such as excellent stability, good biocompatibility, large specific surface area, easy preparation, and preferable sustained release characteristics (Janesirisakule et al. 2013, Jung et al. 2013, Zhou et al. 2020). Given that many nutraceutical molecules are oxidation sensitive during their storage and/or transportation, nanocarriers with an antioxidative property can be a possible solution for this problem (Binsi et al. 2017, Hu et al. 2016).

Binsi et al. (2017) found fish oil encapsulates, including gum arabic and sage extract, exhibited significantly higher encapsulation efficiency, good sphericity and smooth surfaces, and a lower rate of lipid oxidation during storage when compared to gum arabic alone. Hu et al. (2016) reported that nanocomplexes from the phenolic acid–grafting CS could improve the encapsulation efficacy and stability under alkaline and neutral environments. Similarly, according to Soliman et al. (2014), hydrocaffeic acid–CS nanoparticles did not show any sign of aggregation or precipitation over a pH range of 4–10 and maintained their size compared with CS nanoparticles, which aggregated when pH $>$ 6.5. To extend the biomedical application of polyphenol–polysaccharide complexes as active nanocarriers, more research regarding their toxicological effects needs to be conducted.

9. DISCUSSION AND FUTURE PERSPECTIVES

Polysaccharides and polyphenols are both diversified and show various bioactive properties. The combination of polysaccharide and polyphenol into complexes, either physically or chemically linked, can be used to develop food products targeting consumers with a high risk of human health problems, e.g., type II diabetes, obesity, cardiovascular disease, etc. Therefore, conjugation shows great potential for functional food development. As shown in **Table 3**, some polyphenol–polysaccharide complex–related products or techniques have already been patented

Table 3 Polysaccharide–polyphenol complex–related patents

Field	Application	Information about the patent	Title of the patent	Patent numbers
Food	Beverage	A substantially clear ambient-temperature beverage comprising tea polyphenols and anionic polysaccharides (iota carrageenan, kappa carrageenan, lambda carrageenan, etc.), which are used to inhibit the precipitation of polyphenols and caffeic acid and keep the solution clear	Beverage containing a polymeric polyphenol	WO2010097255A2
	Antimicrobial composition	An antimicrobial composition comprising polyphenols extracted from Chinese medicine; polysaccharides (cellulose, carboxymethyl cellulose, dextran, etc.) are added to enhance the solubility of polyphenols	Antimicrobial composition based on polyphenols and polysaccharides; method for preparing use of the same	WO2019221642A1
	Suppressing the unpleasant odor and unpleasant taste of low methoxyl (LM) pectin	An aqueous liquid beverage containing LM pectin; polyphenols are added to cover up the unpleasant odor and taste of LM pectin	Aqueous liquid beverage	WO2016084887A1
	Antioxidant compositions	A combination of sulfated polysaccharides and polyphenols derived from the fruit of *Solanum melongena*	Antioxidant compositions and methods of use thereof	WO2005084452A1
	Alleviating astringency derived from polyphenols contained in a food/drink product and inhibiting return of astringency	Polysaccharides extracted from the yeast are used to alleviate astringency derived from tannins	Novel yeast and polysaccharide; astringency alleviation method of food/drink product using the same	JP2017120342
	Improving stability and water solubility for polyphenols that have poor stability and poor water solubility	Pectin and gum arabic are used to improve the water solubility of polyphenols with hypoglycemic activity extracted from raphuma (*Apocynum venetum* L.)	Polyphenol-containing extract, polyphenol-containing composition, and food composition as well as producing method thereof, method for improving stability, and method for improving water solubility	JP2018118544
	Beverage	A beverage containing tea polyphenols; water-soluble soybean polysaccharides are used to inhibit the precipitation of polyphenols to keep the solution clear	Improved beverage comprising tea polyphenols	EA201791131
	Antioxidant composition that is useful for the preservation of foodstuffs	The antioxidant composition comprises polyphenols and polysaccharides extracted from soapbark tree	Composition, method of application, and use of a natural additive from soapbark tree extracts to improve the quality of meat products	US201313872326
Medical	Food additives	By joining a quercetin-containing solution to starch to support quercetin with starch, a polyphenol-containing composition usable as an additive for food and drink can be obtained	Method for producing a polyphenol-rich composition	US30106607
	Viscosupplement, antiadhesion film, or dermal filler	EGCG is covalently attached to hyaluronic acid via thiol linkages	Polymer-flavonoid conjugates and hydrogels for biomedical applications	WO2015034436A1

(*Continued*)

Table 3 (*Continued*)

Field	Application	Information about the patent	Title of the patent	Patent numbers
	Lipid-lowering and hypoglycemic agent	A combination of tea polysaccharides and tea polyphenols extracted from *Camellia nitidissima* Chi with lipid-lowering and hypoglycemic activities	Method for preparing a *Camellia nitidissima* Chi lipid-lowering and hypoglycemic agent	US201514940160
	Use in prophylactic treatment of upper respiratory tract infections	Arabinogalactan and polyphenols extracted from larch trees are used in this patent	Composition comprising arabinogalactan and polyphenols from larch trees	US201313848487
	Hemostatic and diuretic compounds	Compounds related to the polysaccharide–polyphenol complex are extracted from the shoots of the European dewberry with 50% ethanol	Method for production of polyphenol complex possessing predominantly hemostatic and diuretic activities	UAA200607844
	Treating diabetes	The degraded galactomannan (tara gum, guar gum, and locust bean gum) and the polyphenol compounds extracted from hot-water extraction fraction of Theaceae plants	Composition for preventing, ameliorating, or treating diabetes	JP2004236811
	Drug delivery	Chitosan is electrostatically bonded to the tannin to form a chitosan–tannin composite material	Chitosan–tannin composites	US201615380754
Medical/ cosmetic	Medical or cosmetic compounds	A process for the production of cosmetic or medical dermatological compositions in the form of a gel; polysaccharides (gum arabic, tragacanth gum, alginic acid, guar gum, or xanthan gum) are used as the vehicle of the active ingredients (glycolic acid, mandelic acid, gallic acid, etc.) to regulate the rheological properties of the gel	Medical or cosmetic compounds and composition thus obtained	WO2019215592A1
Cosmetic	Dermocosmetic compositions	Cosmetic compositions containing a combination of functional ingredients of vegetal origin, one consisting of tamarind gum polysaccharides and the other consisting of polyphenols extracted from beech tree buds	Dermocosmetic compositions based on tamarind seed polysaccharides and vegetable extracts	WO2009040847A2
	Personal care composition that provides enhanced intercellular tight junction in skin cells	A personal care composition that comprises the polyphenols extracted from *Aloe vera* and a hyaluronic acid polymer with a molecular weight of 5–60 kDa	Personal care compositions	WO2015158550A1

for potential utilization in the food, drug, and cosmetic categories. However, many challenges still exist.

First, structural characterization of naturally occurring covalently linked polyphenol–polysaccharide conjugates remains challenging because of the structural complexity of polysaccharides and the relatively small percentage of conjugated polyphenols. The detailed structural features, e.g., linkage position and distribution pattern of polyphenols, are still unclear, which significantly hinders the establishment of structure–activity relationships.

Second, for synthetic polyphenol–polysaccharide conjugates, CS-grafted polyphenols have been the most studied conjugate compared to the other polysaccharide-based complexes because of the reactive amino groups. In contrast, the research on other polysaccharides is still limited.

Moreover, the current synthetic methods still cannot satisfy the requirement for large-scale production. The complex produced is not consistent among batches, which restricts their commercial applications.

Third, it should be noted that most evidence collected regarding the bioactive properties of the conjugates is from in vitro studies. Also, the novel polyphenol–polysaccharide covalently linked conjugates might have safety concerns and need to be examined before commercialization. Overall, more animal and/or clinic trials are urgently needed to illustrate the toxicology, bioavailability, and metabolism of the conjugates.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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