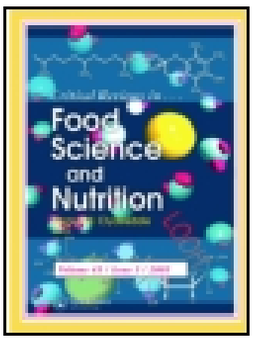

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

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To cite this article: Jian-Hui Ye & Mary Ann Augustin (2018): Nano- and micro-particles for delivery of catechins: Physical and biological performance, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2017.1422110

To link to this article: https://doi.org/10.1080/10408398.2017.1422110

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2017.1422110

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Nano- and micro-particles for delivery of catechins: Physical and biological performance

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ABSTRACT

Catechins, present in many fruits and vegetables, have many health benefits, but they are prone to degradation. Nano- and micro-particle systems have been used to stabilise catechins when exposed to adverse environments and to improve their bioavailability after ingestion. This review discusses the inherent properties of various catechins, the design of delivery formulations and the properties of catechin-loaded nano- and micro-particles. The protection afforded to catechins during exposure to harsh environmental conditions and gastrointestinal tract transit is reviewed. The bioavailability and efficacy of encapsulated catechins, as assessed by various *in vitro* and *in vivo* conditions, are discussed. Bioavailability based on uptake in the upper gut alone underestimates the bioavailability as polyphenols. The caveats with interpretation of bioavailability based on various tests are discussed, when taking into consideration the pathways of catechin metabolism including the role of the gut microflora. However, taken together, the weight of the evidence suggests that there are potentially improved health benefits with the use of appropriately designed nano- and micro-particles for delivery of catechins. Further systematic studies on the metabolism and physiological effects of encapsulated catechins *in vivo* and clinical trials are needed to validate the bioefficacy of the encapsulated catechins.

KEYWORDS

Catechins; microencapsulation; delivery; nano-particles; bioavailability; bioefficacy

1. Introduction

Catechins are a group of phenolic compounds present in a variety of fruits, vegetables, plant-based beverages and wines. The amounts of catechin compounds in selected products are given in Table 1. Tea leaves are a rich source of many catechin compounds including epigallocatechin gallate (EGCg), epigallocatechin (EGC), epicatechin gallate (ECg), epicatechin (EC), and their geometric isomers gallocatechin gallate (GCg), gallocatechin (GC), catechin gallate (Cg), and catechin (Braicu et al., 2013). Catechins have antioxidant and antimicrobial activity, making them useful additives for improving the quality of food products and as bioactive ingredients for functional foods and dietary supplements (Senanayake, 2013). Catechins also exhibit biological functionalities such as antioxidant, anti-proliferation and anti-inflammatory (Higdon and Frei, 2003; Zhong et al., 2012) and chemopreventive properties (Porath et al., 2005) and maintain cardiovascular and metabolic health (Wolfram, 2007). For example, EGCg is beneficial for alleviating a variety of conditions including Huntington's disease (Ehrnhoefer et al., 2006), obesity (Boschmann and Thielecke, 2007), diabetes (Waltner-Law et al., 2002), and breast and prostate cancer (Stuart et al., 2006).

However, many bioactives including catechins that have been extracted from the source material (e.g. plants, animal tissue) are no longer protected and are prone to degradation. Stabilisation of catechins is therefore desirable after extraction, and when they are processed into ingredients or incorporated into foods, until they reach the target site of action for maximum efficacy in the body (Fang and Bhandari, 2010; Hong et al., 2014). Encapsulation has the potential to protect catechins when they are incorporated into foods both during processing and in the final product as well as after ingestion when exposed to high pH environment after stomach transit in the gastrointestinal tract. Encapsulation entraps active agents within a carrier material to increase stability of bioactives and enable their targeted and timed delivery in specific environments at a specific site to improve the bioavailability of the bioactive (Augustin et al., 2005; Augustin and Hemar, 2009; Zhang et al., 2013; Roos and Livney, 2017).

This review considers the characteristics of catechins and the rationale for their encapsulation. It appraises the developments in nano- and micro-particles for the delivery of catechin compounds. The focus is on the design of delivery systems for catechins formulated using materials generally regarded as safe (GRAS). The encapsulation techniques, and functionality of particles by various methods used for assessment of the delivery system performance are examined. An evaluation of the suitability of the methods used for assessment of bioefficacy of ingested catechins, which requires consideration of the metabolism of catechins in the body as well as the role of the gut microflora, is also covered.

2. Properties of catechins

Belonging to flavan-3-ols subclass, the skeleton of catechin compounds consists of two aromatic rings (the A- and B-rings)

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Table 1. Catechin contents in selected foods.

Foods	Total catechins	Catechin	EC	Other catechins	Reference
Based on dry weight (mg/g)					
Green tea	51–300	0–1.3	4.4–21.2	EGC: 16.2–45 EGCg:20.3–104 ECG: 3.4–46	Cabrera et al., 2003; Harbowy and Balentine, 1997; Khokhar and Magnusdottir, 2002
Black tea	5–90	0–1.7	1.1–5.6	EGC:0.2–6.3 EGCg: 2.7–25.2 ECG:0.7–8.6	
Cocoa powder	0.18–1.07	0.08–0.45	0.12–0.73	ND[a]	Andres-Lacueva et al., 2008
Based on fresh weight (mg/kg)					
Chocolate, black	460–610	107–132	327–503	ND	Arts, van de Putte, and Hollman, 2000; Manach et al., 2004
Apple	20–120	2.8–17	48–103	ND	
Apricot	100–250	26–57	60–171	ND	
Blackberry	130–188	7	181	ND	
Blueberry	11	ND	11	ND	
Cherry	50–220	5–22	14–96	ND	
Grape, black	204	89	86	ECg: 28	
Peach	50–140	23–129	3–15	ND	
Beans	350–550	— [b]	—	—	

[a]ND, not detected.
[b]–, not determined.
Abbreviations: EGCg: epigallocatechin gallate; EGC: epigallocatechin; ECg: epicatechin gallate; EC: epicatechin.

and a dihydropyran heterocycle (the C-ring) with a hydroxyl group or a gallate moiety at C-3 position. Catechins can be classified into two groups according to the substitution of gallate moiety at C-3 position: gallated catechins (EGCg, GCg, ECg, and Cg) and non-gallated catechins (EGC, GC, EC, and catechin) (Braicu et al., 2013). The structures of the major catechins are given in Figure 1 A.

2.1. Physico-chemical properties

Pure catechin compounds are colorless crystalline substances with bitter or astringent taste. They are soluble in polar solvents such as water and methanol. Gallated catechins are more bitter and astringent than their non-gallated catechins counterparts (Hara, 2001). Catechins undergo isomerization, hydrolysis, oxidation and condensation reactions. Temperature and pH affect the degradation reactions of catechins, with the effects being dependent on the catechin and their form (Li et al., 2012a; Fan et al., 2016). Heat-induced catechin degradation occurs above 40°C, both in solution and solid state (Fan et al., 2016; Li et al., 2011). EC and EGC have lower thermostabilities at 90°C compared to other catechins (EGCg, GCg, ECg, Cg GC, C) (Fan et al., 2016). Catechins decompose by ~75% at 30 min in Krebs-Ringer bicarbonate buffer (pH = 7.4, 37°C) but are relatively stable in acidic solution (Zhu et al., 1997).

2.2. Bioavailability and metabolism of catechins

The low bioavailability of catechins has been in part attributed to degradation and metabolism in the gastrointestinal tract, poor membrane permeability and pre-systemic hepatic elimination (Cai et al., 2002; Wu et al., 2014; Zhang et al., 2004). Catechins are stable in gastric fluid (pH 1.5–2) but are more unstable when exposed to intestinal fluids. Different catechins exhibit different stabilities under digestive conditions (Bhushani et al., 2016; Ferruzzi et al., 2009; Zou et al., 2014; Wu et al., 2014). Bhushani et al. (2016) reported that only 2.66% EGC and 0.91% EGCg were recovered after *in vitro* digestion of tea extract powder compared with 52.58% EC and 31.73% ECg. About 4.6% EGC, 6.1% EGCg, 8.2% EC and 8.4% ECg were recovered from commercial Ready-To-Drink green tea after *in vitro* digestion (Shim et al., 2012). The great difference in the recovery of EC and ECg in both studies might be due to different *in vitro* digestion models used regarding the concentration of enzyme and gastric digestion time (Bhushani et al., 2016; Shim et al., 2012). However, even if they are bioaccessible, the catechins are poorly absorbed across intestinal membranes due to their strong hydrophilicity (Zhang et al., 2004). Permeability studies in a Caco-2 cell model demonstrated that the apparent permeability (P_{app}) values for catechins were $0.8\sim3.5 \times 10^{-7}$ cm/s (Zhang et al., 2004), which were lower than that for the poorly permeable marker mannitol where the P_{app} values were $6–10 \times 10^{-6}$ cm/s (Stephens et al., 2002; Yang et al., 2003).

The recoveries of gallated catechins such as EGCg and ECg in plasma were lower than their non-gallated forms EGC and EC in human body (Warden et al., 2001). In a randomized, double-blind and placebo-controlled study, only 9628 ng EGCg was recovered from plasma after an oral administration of 1600 mg EGCg in a single dose (Ullmann et al., 2003). There was low plasma recovery of ingested catechins (0.158%) in free form and as glucoronidated or sulphonated derivatives after administration of black tea in humans (Warden et al., 2001). However, it should be noted that the recovery of catechins in the unchanged, glucoronidated and sulphonated forms in the plasma does not capture the full range of metabolites that are possible after ingestion of catechin, as there is

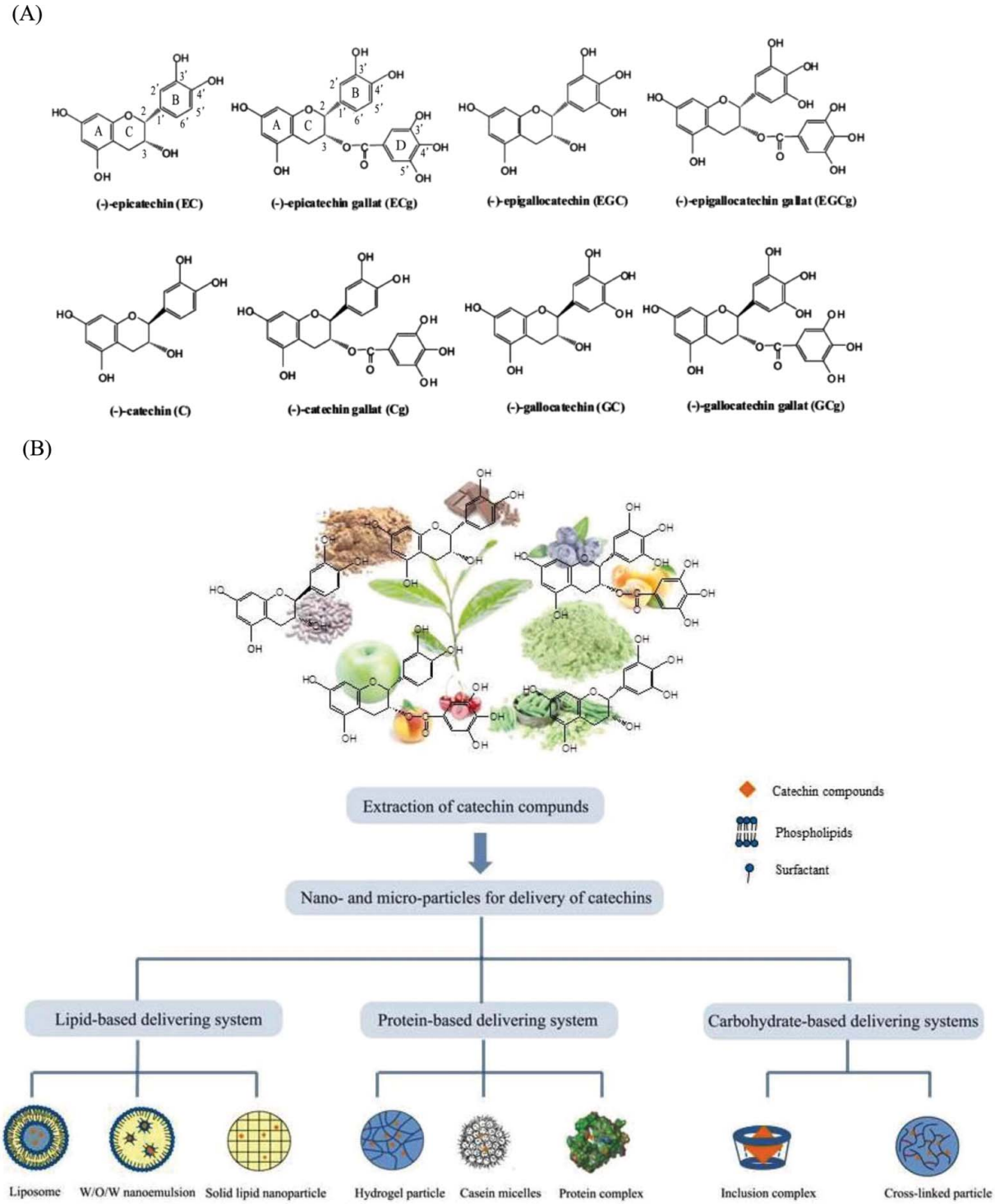

Figure 1. Delivery of catechin compounds: molecular structures (A) and delivery types (B).

modification of polyphenols occurring in the liver and by gut microflora (Clifford et al., 2013; Del Rio et al., 2010), as discussed below.

There are two distinct pathways for metabolism of catechins. One pathway is via biotransformation reactions within the living system through glucuronidation, methylation and sulfonidation reactions to form glucuronides, sulphates and O-methylated derivatives (Clifford et al., 2013). The other is degradation of catechins that escape the upper gut and are transferred into the lower gut by gut microflora (Roowi et al., 2010). Glucuronide, sulfate, and methyl metabolites of (epi) catechin and (epi) gallocatechin glucuronide in plasma reach peak after 1.6–2.3 h of intake, which is attributed to the absorption in the small intestine, and then decline to trace level around 8 h after ingestion (Clifford et al., 2013). Ottaviani et al. (2016) found that ~70% of the ingested (−)-epicatechin labelled by [2-^{14}C] was absorbed in the lower intestine following catabolism by the gut microbiome. Therefore, bioavailability based on uptake in the upper gut alone underestimates bioavailability as polyphenols that are not metabolized in the upper gut are transferred

in the lower gut and acted upon by the gut microflora (Ottaviani et al., 2012).

3. Formulation and design of delivery systems with food grade materials

The encapsulation of a bioactive is of value when it can improve the stability, mask an unpleasant taste or aroma or improve the bioavailability of the bioactive, or allow its transformation into a useful physical form e.g. from a liquid to a powder. At times, the encapsulation system is required to perform more than one of these functions for it to be effective.

For the formulation of delivery systems intended for the improved delivery of catechins in food applications, only GRAS status materials may be used. Examples of these include oils and fats, low molecular weight emulsifiers (phospholipids, Tweens, mono- and diglycerides), proteins (caseins, whey proteins, plant proteins), sugars and syrups, and other carbohydrates (chitosan, gum arabic, alginate, pectin, carrageenan, emulsifying starches, cellulosic material, cyclodextrins). There are many examples of encapsulated delivery systems formulated with one or more GRAS components for formulation of nano- and micro-particles for delivering catechin compounds (Fangueiro et al., 2014; Gómez-Mascaraque et al., 2016a; Lestringant et al., 2014). Typical encapsulation techniques used for preparing micro- and nano-particulated delivery systems include spray drying, emulsion formation, extrusion, coacervation, crosslinking reactions, inclusion complexes, layer-by-layer (LbL) self-assembly, electrospraying and electrospinning (Augustin and Hemar, 2009; de Villiers et al., 2011).

The size of encapsulated particles and their functionality may be tailored depending on the formulation and the processing techniques used for their production. Nanoparticles are in the range of 10 to 100 nm while microcapsules are larger in the micron size range and can be up to 800 μm (Williams, 2008). Tables 2–5 list nano- and micro-encapsulated delivery systems of catechin compounds and their properties including the encapsulation efficiency, particle size, zeta potential, polydispersity index, loading amount, stability and release properties of the encapsulated core. Different types of delivery systems for catechin compounds are showed in Figure 1 B.

3.1. Lipid-based systems

Lipids are often used in the formulation of delivery systems. Many edible oils and fats (i.e. triacylglycerols) can serve as efficient carriers for lipid soluble bioactives and may be formulated with surface active lipids (e.g. mono- and di-glycerides, phospholipids) for the formulation of liposomes, solid lipid particles and emulsions (Table 2).

3.1.1. Liposomes

Liposomes consist of one or more concentric lipid bilayers that can entrap both hydrophilic and lipophilic actives. Uni-lamellar or multi-lamellar liposomes can be fabricated. Hydrophilic molecules are entrapped in the aqueous center while hydrophobic molecules can be inserted into the bilayer membrane (Sercombe et al., 2015). Emulsion, phase inversion emulsion and emulsion-solvent evaporation methods have been applied for liposome formation. Ultrasonication, extrusion and high-pressure homogenization have been employed to produce nanoscale liposomal delivery systems (Huang et al., 2011; Luo et al., 2014; Tsai and Chen, 2016).

Phospholipids from natural sources (soy or milk) and chemical surfactants (Tween 20, Tween 80, cetyltrimethylammonium bromide, dimethyldioctadecylammonium bromide) have been used for catechins encapsulation with various loading capacities (0.3∼10% w/w of EGCg, Table 2). The properties of the particles were as follows: particle size of 12 nm∼180 nm, encapsulation efficiency of 60∼99%. The zeta potential was negative as expected, except when a chitosan coating was applied (Table 2). Cholesterol addition improves the structural rigidity of liposomes and resistance of catechins to degradation under *in vitro* and *in vivo* conditions (Taylor et al., 2005).

There are different encapsulation efficiencies for various catechins due to their varied affinities for lipid bilayers. ECg shows higher affinity for the phosphatidyl choline derived from egg yolk compared to EGCg, EC and EGC (Hashimoto et al., 1999). Liposomes consisting of egg phosphatidylcholine and cholesterol have 99.6% encapsulation efficiency for EGCg compared with 39.5% and 31.9% for catechin and EC respectively (Fang et al., 2006).

3.1.2. Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) have a matrix of solid crystalline lipid whereas the matrix of nanostructured lipid carriers (NLC) consists of solid and liquid lipids. Compared to liposomes, these are cheaper to prepare than liposomes and have been found to be efficiency for carrying bioactive loads. Encapsulating efficiencies for EGCg have been reported to 80% and 90% respectively for SLN and NLC (Frias et al., 2016). The higher encapsulation efficiency of NLC compared to SLN is due to lower degree of crystallinity and a lower density due to the mixture of liquid and solid fat in NLCs.

3.1.3. Double emulsions

Water-in-oil-in-water (W/O/W) double emulsions entrap the hydrophilic bioactives in the inner water phase and delay the release of the encapsulated core when the emulsion droplet is in an aqueous environment. W/O/W double emulsions system have been used to encapsulate hydrophilic substances such as 1,3,6,8-pyrenetetrasulfonic acid tetrasodium salt (Adachi et al., 2003), L-ascorbic acid (Khalid et al., 2013), and resveratrol (Hemar et al., 2010). Food-grade W/O/W emulsions are usually prepared by two-step emulsification. Examples of W/O/W emulsion formulations containing catechins and their properties are given in Table 2.

3.2. Protein-based systems

Food proteins are attractive as ingredients in food industry because of their nutritional value. They have inherent physical functional properties (e.g. emulsification, gelation, foaming, and water binding capacity) and this combined with their ability to bind bioactives make them useful in formulating encapsulation systems (Augustin and Hemar, 2009). Table 3 summarises a selection of protein-based systems reported for carrying catechins.

Table 2. Lipid-based delivery systems for catechins.

Core	Coating Materials	Method	Loading capacity	Particle characteristics[a]	Stability/Releasing properties	Reference
EGCg	Lecithin/glyceryl tridecanoate /glyceryl tripalmitate /Kolliphor HS15 = 9.3/40/6.7/44 (w/w), with or without addition of 2 mg/mL chitosan as a coating material	Phase inversion emulsion	2.6% EGCg (%w/w)	PS: 43 nm∼54 nm EE: ∼99% PI: 0.19∼0.28 ZP: −9 mV∼ −13 mV for nanoparticles; 13 mV∼21 mV for chitosan-coated nanoparticles	In PBS (pH 7.4, 4°C and 1 d): %loss of encapsulated EGCg: <5% %loss of native EGCg: ∼100% *In vitro* release via dialysis (PBS, pH 5.0, 37°C and 2 h): %Release of encapsulated EGCg: ∼2% %Release of native EGCg: ∼100%	Zhang et al., 2013
EGCg	PC/kolliphor HS15/α-tocopherol acetate = 36.2/45/8.8 (w/w), with or without replacing 30 mol% of PC with KOdiA-PC	Phase inversion emulsion	10% EGCg (%w/w)	PS:100 nm∼110 nm EE: 96% PI: 0.18∼0.23 ZP: −20 mV ∼ −30 mV	In PBS (pH 7.4, 4°C and 2 d): %loss of encapsulated EGCg:<20% %loss of native EGCg:>90% *In vitro* release via dialysis (PBS, pH 5.0, 37°C and 2 h): %Release of encapsulated EGCg: ∼40% %Release of native EGCg: ∼100%	Zhang et al., 2016b
EGCg	PC/cholesterol = 4/1 (w/w) Tween 80 = 1.08 mg/mL	Emulsion-solvent evaporation	4.9 mg/mL EGCg	PS: 180 nm EE: 86%	In simulated gastric juice (pH 1.3, 37°C and 4 h): %Release of encapsulated EGCg: 21% In simulated intestinal juice (pH 7.5, 37°C and 4 h): %Release of encapsulated EGCg: >35%	Luo et al., 2014
EGCg	PL/cholesterol/Tween 80 = 16/2.4/4 (w/w)	Emulsion-solvent evaporation	2.5 mg/mL EGCg	PS: 72 nm EE: 92% PI: 0.29 ZP: −11 mV	*In vitro* release via dialysis (PBS, pH 5.5, 37°C and 6 h): %Release of encapsulated EGCg: 6% %Release of native EGCg: ∼92% In simulated gastric juice (pH 1.5, 37°C and 3 h): %loss of encapsulated EGCg: <10% %loss of native EGCg: <10% In simulated intestinal juice (pH 7.4, 37°C and 1.5 h): %loss of encapsulated EGCg: 69% %loss of native EGCg: 97%	Zou et al., 2014
Catechin	PC/cholesterol/Tween 80 = 6/1/1 (w/w)	A thin-film method and subsequent ultrasonication and extrusion.	0.3% catechin (%w/w)	PS: 37 nm EE: 80% PI: 0.16 ZP: −15 mV	In citrate-phosphate buffer via dialysis (pH 7.4, room temperature, 12 h): %Release of encapsulated EGCg: 56% %Release of native EGCg: ∼85% In simulated gastric juice (pH 1.2, 37°C and 2 h): %loss of encapsulated EGCg: ∼10% %loss of native EGCg: ∼10% In simulated intestinal juice (pH 7.5, 37°C and 2 h): %loss of encapsulated EGCg: ∼10% %loss of native EGCg: ∼45%	Huang et al., 2011

(*Continued on next page*)

Table 2. (*Continued*)

Core	Coating Materials	Method	Loading capacity	Particle characteristics[a]	Stability/Releasing properties	Reference
TP	Lecithin/cholesterol = 4/1 (w/w)	A thin-film method and ultrasonication	TP/lecithin = 0.125/1 (w/w)	PS: 160 nm EE: 60% ZP: −67 mV	*In vitro* release via dialysis (PBS, 0.01M, 37°C and 6 h): %Release of encapsulated EGCg: >50%	Lu et al., 2011
Catechin extract	Lecithin/Tween 80 = 1/10	Emulsion	0.9 mg/mL	PS: ∼12 nm EE: 88% PI: ≦0.3 ZP: −66 mV	In aqueous solution (4°C and 120 d): %loss of encapsulated EGCg: 13.8%	Tsai and Chen, 2016
EGCg	Milk phospholipids (10%)	Emulsion	4 mg/mL EGCg	PS: 104 nm∼129 nm; EE: ∼60%; ZP: −4 mV ∼ −19 mV	In aqueous solutions (pH 3–7, 4°C or 25°C, presence of 5–15% hydrophobic peptides or sucrose) %loss of encapsulated EGCg: 40%∼70%	Gülseren and Corredig, 2013
EGCg	W_1: 1.2 wt% EGCg in 0.25 wt% of ascorbic acid solution O: glycerol (37.5 wt%), Softisan 100 (4.5 wt%), phosphatidylcholine (0.5 wt%), cationic lipid (0.5 wt%, CTAB or DDAB) W_2: P188 cooled solution	Double emulsion	∼14.5% (%w/w)	PS: 143 nm ∼184 nm; EE: >96% PI: 0.16∼0.30 ZP: = 20 mV∼26 mV		Fangueiro et. al., 2014
EGCg	W_1: EGCg dissolved in 2%w/v Pluronic F68 solution O: Lecithin/glycerol monostearate/stearic acid = 1/4/1 (w/w) W_2: 1%w/v Pluronic F68 solution	Double emulsion	5% EGCg (%w/w)	PS = 157 nm; EE = 67%; PI = 0.27; ZP = −37 mV	*In vitro* release via dialysis (sodium acetate buffer, pH 5, 37°C, 24 h): Cumulative %release of encapsulated EGCg: 10% at 1 h, 83.9% at 12 h and >90% at 24 h.	Radhakrishnan et al., 2016
Catechin/ curcumin	W_1: 750 μg/ml catechin, 3% gelatin, 2% NaCl, 0.2% ascorbic acid O: olive oil, polyglycerol polyricinoleate, 0.1% w/v curcumin W_2: 1% Tween 80, 0.2% ascorbic acid, 2% NaCl	Double emulsion	0.075% (%w/w)	PS = 2.8 μm∼3.1 μm; EE = ∼97%; ZP = −18 mV	*In vitro* release via dialysis (0.7 mg/mL porcine bile, 42.5 mM $CaCl_2$ and 40% ethanol, pH 5, 37°C, 2 h): %release of encapsulated catechin: ∼45% at 1 h, >90% at 6 h In simulated gastric juice (pH 2, 37°C and 6 h): %loss of encapsulated catechin: ∼17% %loss of native catechin: ∼40% In subsequent simulated intestinal juice (pH 7.2, 37°C and 6 h): %loss of encapsulated catechin:∼35% %loss of native catechin:∼74%	Aditya et al., 2015

Abbreviations: EE: encapsulation efficiency; PS: average particle size listed; ZP: Zeta potential; PI: polydispersity index. TP: tea polyphenols; PC: phosphatidylcholine; KOdiA-PC:1-(palmitoyl)-2-(5-keto-6-octene-dioyl) phosphatidylcholine; PL: phospholipid.; W1: inner aqueous phase; W2: secondary water phase; O: oil phase; P188: Poloxamer 188; CTAB: cetyltrimethylammonium bromide; DDAB: dimethyldioctadecylammonium bromide.

Table 3. Protein-based emulsion delivery systems for catechins.

Bioactive	Particle form	Method	Loading capacity	Particle characteristics[a]	Stability/ Releasing properties	Reference
Gelatin						
EGCg	EGCg-loaded gelatin A nanoparticle with. PSS/PAH shell	LbL assembly method.	∼30% (%w/w)	PS: ∼300 nm ZP: ∼−30 mV	*In vitro* release via 0.2 μm filter (pH 3, room temperature and 8 h): %release of encapsulated EGCg:∼60%	Shutava et al., 2009b
EGCg	(Gelatin A /EGCg)$_4$ capsule	LbL assembly method	30% (%w/w)	PS: 50 nm∼300 nm;	–	Shutava et al., 2009a
EGCg	Gelatin/EGCg capsule	Electrospraying	10% (%w/w)	PS: 470 nm; EE: 96%	In 96% ethanol (20°C, 100 h): %release of encapsulated EGCg: 4.2% In MES buffer (pH 6.1, 20°C, 100 h): %release of encapsulated EGCg: 8% In PBS (pH 7.4, 20°C, 100 h): %release of encapsulated EGCg: 8%	Gómez-Mascaraque et al., 2015
EGCg	Gelatin/EGCg capsule	Spraydrying	10% (%w/w)	PS: 4 μM; EE: 95%;	In MES buffer (pH 6.1, 20°C, 50 h): %release of encapsulated EGCg: 8%	Gómez-Mascaraque et al., 2016a
Milk proteins						
EGCg	EGCg/heated β-Lg nanoparticle (75°C, 20 min, 1 wt%)	Binding	Molar ratio of EGCg: heated β-Lg = 8:1	PS: <50 nm EE: 60%∼70% ZP: ∼-40 mV	In simulated gastric juice (pH 2, 37°C and 3 h): %Release of encapsulated EGCg:∼25%	Shpigelman et al., 2012
EGCg	EGCg/native β-Lg nanoparticle (1 wt%) EGCg/heated β-Lg nanoparticle (85°C, 20 min, 1 wt%) EGCg/desolvated β-Lg nanoparticle (ethanol desolvation, 1 wt%)	Binding	Molar ratio of EGCg: β-Lg up to 3:1	PS: <100 nm for three types of β-Lg EE: 54∼ 94% ZP: −17 mV ∼ −27 mV for native and heated β-Lg particles; 26 mV∼28 mV for desolvated β-Lg particles	—	Lestringant et al., 2014
EGCg	EGCg/heated β-Lg nanoparticle (85°C, 20 min, 0.5wt%)	Binding	Molar ratio of EGCg: heated β-Lg = 2:1	PS: ∼10 nm; EE: 78%; ZP: −40 mV	—	Li et al., 2012b
Other proteins						
Catechin	Catechin/Kafirin microparticle	Binding and comminution	20% (%w/w)	PS: 5–6 μm	In simulated gastric juice (pH 2, 37°C and 2 h): %Release of encapsulated antioxidant activity:∼40% In subsequent simulated intestinal juice (pH 7.6, 37°C and 2 h): %Release of encapsulated antioxidant activity:∼70%	Taylor et al., 2009
TP	TP/Soy protein/oil nanoemulsions	Emulsion	0.5% (%w/w)	PS: 268 nm ZP: ∼30 mV	In simulated gastrointestinal juice (gastric phase: pH 1.2, 37°C and 2 h; intestinal phase: pH 7.0, 37°C and 2 h): %recovery of EGC, EC, EGCg and ECg from nanoemulsion: 55%, 146%, 7% and 68% %recovery of unencapsulated EGC, EC, EGCg and ECg: 3%, 53%, 1% and 32%	Bhushani et al., 2016

Abbreviations: EE: encapsulation efficiency; PS: average particle size listed; ZP: Zeta potential; PI: polydispersity index. TP: tea polyphenols; β-Lg: β-lactoglobulin; LbL: layer-by-layer; PSS/PAH: polystyrene sulfonate/polyallylamine hydrochloride.

3.2.1. Gelatin

Gelatin forms thermoreversible hydrogels in water due to the network formation below the helix-coil transition temperature (Peña et al., 2010). The gelling property makes gelatin a promising material for carrying bioactives. Gelatin A (pI 7–9) with a positive charge at neutral pH can be alternated with negatively charged EGCg. Both hydrophobic and electrostatic forces support the formation of uniform shells around the cores. In contrast, there is electrostatic repulsion between gelatin B (pI 4.7–5.4) which carries a negative charge at neutral pH and EGCg. Gelatin A is more widely used in the encapsulation of catechin compounds (Gómez-Mascaraque et al., 2015; Shutava et al., 2009a).

The LbL self-assembly technique has been used for preparation of particles (50–300 nm) containing gelatin and EGCg (Shutava et al., 2009a; Shutava et al., 2009b). With the electrospraying technique, gelatin particles (470 nm) with an EGCg loading of 10% (%w/w) are obtained at 100% encapsulation efficiency with preservation of antioxidant activity compared to a 30% antioxidant activity loss of free EGCg (Gómez-Mascaraque et al., 2015). Gelatin is superior for the encapsulation of EGCg compared with chitosan, achieving a higher encapsulation efficiency and bioaccessibility when spray drying is used (Gómez-Mascaraque et al., 2016a). The grafting reaction has also been employed to synthesize catechin−gelatin conjugate via a radical initiator, resulting in covalently bound catechin to the protein side chain (Spizzirri et al., 2009).

3.2.2. Milk proteins

The major milk proteins, caseins and whey proteins, have been used to carry a range of bioactive phenolic compounds (Livney, 2010). The ability of milk proteins to carry catechins is driven by the interaction between phenolics and milk proteins (Kanakis et al., 2011; Ye et al., 2013). The type of interaction depends on the size and structure of polyphenol molecules and the properties of proteins such as amino acid residues, hydrophilic and hydrophobic domains, leading to different affinities of catechins for milk proteins (Hasni et al., 2011; Ye et al., 2013). The interaction between catechins and proteins alters the protein conformation (Hasni et al., 2011), and also can mask the antioxidant activity of polyphenols (Zorilla et al., 2011).

The binding of catechins to casein micelles and whey proteins have been evaluated (Table 4). Different catechin compounds have different affinities for the various milk proteins. EGCg has the stronger affinity for the caseins and β-Lg compared to other catechins (Table 4), which is possibly due to the presence of more hydroxyl groups in EGCg resulting in an enhanced capacity to interact with proteins. The binding molar ratio of EGCg to heat-treated and un-treated β-Lg ranged from 2:1 to 8:1 respectively (Li et al., 2012b; Lestringant et al., 2014; Shpigelman et al., 2012), which corresponds to loading capacity of 5.0%∼19.9% (%w/w). Li et al. (2012b) and Shpigelman et al. (2012) considered heat-treated β-Lg as an effective natural vehicle for nanoencapsulation of EGCg, while Lestringant et al. (2014) found the binding efficacy of native β-Lg and heated β-Lg are comparable.

3.2.3. Other food proteins

Proteins from other sources (e.g. plants or seaweeds) have been used as delivery systems for catechins (Table 3). Zein (maize protein) has been used to produce nanometer fibers containing EGCg by electrospinning technology (Li et al., 2009). Kafirin encapsulated catechin, may be prepared through phase separation and freeze drying, where a mean particle size ranging from 5 μm to 6 μm was obtained (Taylor et al., 2009). Soy protein and rice bran protein isolate have been used to improve the stability, bioaccessibility and permeability of green tea catechins (Bhushani et al., 2016; Shi et al., 2017).

3.3. Carbohydrate-based systems

Table 5 lists selected carbohydrate-based systems have been used for the delivery of catechins.

3.3.1. Cyclodextrins

Cyclodextrins (CD) encapsulate both polar molecules and non-polar molecules (Fang and Bhandari, 2010). The ability of cyclodextrins to form complexes with catechins (1:1 complex) enables it to be used as a carrier for catechins (Ishizu et al., 2009; Jullian et al., 2007). Hydrophobic interactions, van der Waals interactions, hydrogen bonding, and release of ring strain in the CD cavity are the driving forces for the CDs complex formation (Xu et al., 2007).

EC forms a more stable complex with β-CD compared to catechin (Yan et al., 2007). γ–CD forms inclusion complexes with GCg but not with EGCg (Ishizu et al., 2009). Different effects of CD complexation on the functionality of catechins have been reported. Ishikawa et al. (2012) suggesting that it masks the free radical APPH scavenging ability of catechins using electron paramagnetic resonance (EPR) spin-trapping method, while Junior et al. (2017) who used the DPPH assay found that it did not. The incongruency is possibly due to different free radical scavenging assays used.

3.3.2. Chitosan

Chitosan (CS), α-(1–4)-2-amino-2-deoxy-β-D-glucan, is widely used as a wall material for biopolymeric nanoparticle delivery systems due to its cationic, biodegradable, biocompatible and non-toxic properties. Chitosan gels upon contact with polyanions, such as sodium tripolyphosphate (TPP), polyaspartic acid and poly-(ɣ-glutamic acid) (ɣ-PGA) and caseinphosphopeptides (CPPs), and forms cross-links with catechin compounds (Dube et al., 2010; Li and Fu, 2015; Wisuitiprot et al., 2011). Catechin-loaded chitosan nanoparticles have a particle size range of 102∼5000 nm and a positive surface charge of +25 mV ∼ +36.6 mV (Table 5). Carboxymethyl chitosan (CMC) and chitosan hydrochloride (CHC) are water soluble chitosan used for preparing folate-conjugated chitosan coated EGCg nanoparticles through the ionic cross-linking between folic acid-modified CMC and CHC (Liang et al., Table 5).

3.3.3. Other polysaccharides

Other types of polysaccharides used in the preparation of delivery systems for catechins include pectin (Yang et al., 2015), alginate (Kim et al., 2015; Kim et al., 2016), gum arabic (Peres et al., 2011; Rocha et al., 2011), inulin (Palma et al., 2014). Ca-alginate has been used to prepare catechin-loaded micro-particles with particle size >100 μm and encapsulation efficiency

Table 4. Interactions between milk proteins and catechins.

Milk protein	Equation	Catechin	EC	EGC	EGCg	Reference
Casein micelle	Scatchard plot				1^{st} portion: $K = 3.7 \times 10^3$ M 2^{nd} portion: $K = 1.5 \times 10^3$ M 3^{rd} portion: $K = 1.5 \times 10^3$ M	Haratifar and Corredig, 2014
α-casein	Equilibrium equation [a]	K[b] $= 1.8 \times 10^3$ M^{-1} (n [b] = 1.1)	$K = 1.8 \times 10^3$ M^{-1} (n = 0.9)	$K = 2.4 \times 10^3$ M^{-1} (n = 1.1)	$K = 7.4 \times 10^3$ M^{-1} (n = 1.5)	Hasni et al., 2011
β-casein	Equilibrium equation	$K = 2.9 \times 10^3$ M^{-1} (n = 1.0)	$K = 2.5 \times 10^3$ M^{-1} (n = 1.0)	$K = 3.5 \times 10^3$ M^{-1} (n = 1.1)	$K = 1.59 \times 10^4$ M^{-1} (n = 1.5)	
β-Lg	Langmuir-type model				$K = 1.05 \times 105$ M^{-1} (assuming n = 1)	Shpigelman et al., 2010
Heated β-Lg (75°C, 20 min)	$K_H = 3.7 \times 10^5$ M^{-1} (assuming n = 1)					
β-Lg	Equilibrium equation	$K = 2.2 \times 10^3$ M^{-1} (n = 1.1)	$K = 3.2 \times 10^3$ M^{-1} (n = 0.9)	$K = 1.1 \times 10^4$ M^{-1} (n = 0.9)	$K = 1.3 \times 10^4$ M^{-1} (n = 1.3)	Kanakis et al., 2011
β-Lg	Equilibrium equation				$K = 1.09 \times 10^5$ M^{-1} (n = 1.05)	Wu et al. (2013)
Heated β-Lg (120°C, 30 min)	$K_H = 3.26 \times 10^6$ M^{-1} (n = 1.14)					
Heated β-Lg in presence of 0.4% sucrose fatty acid ester	$K_{H+S} = 5.62 \times 10^6$ M^{-1} (n = 1.23)					
β-Lg	Equilibrium equation				$K = 4.3 \times 10^4$ M^{-1} (n = 1.2)	Lestringant et al., 2014

[a]Equilibrium equation for binding-related fluorescence quenching.
[b]K: overall binding constant; n: binding site.

Table 5. Carbohydrate-based emulsion delivery systems for catechins.

Core	Wall Materials (w/w)	Method	Loading capacity	Particle characteristics[a]	Stability/Releasing properties	Reference
Catechin or EGCg	Chitosan/TPP = 2.2/1	Crosslinking technique	3.7∼4.0 μg/mg	PS: 430∼440 nm ZP: 25 mV	—	Dube et al., 2010
Catechin	Chitosan/TPP = 2.5/1∼7.5/1	Crosslinking technique	10% (%w/w)	PS: 2.0 μm∼4.7 μm EE: 36%∼40% PI: 0.31∼0.39	In simulated gastrointestinal juice (the US pharmacopoeia): The cumulative %release of encapsulated catechin: 15.2%∼40.2%	Zhang and Kosaraju, 2007
EGCg	Chitosan (3–5 kDa)/PAA (30–50 kDa) = 1/1	Crosslinking technique	348 mg/g	PS: 102 nm PI: 0.22 ZP: 34 mV	In aqueous solutions (pH 2.5–7.4, 37°C, 1–5 h): %Release of encapsulated EGCg: ∼25% for pH 2.5 (0–1 h) and pH 4.0 (1–2 h); 41% for pH 6.6 (2–3 h); >80% for pH 7.0 (3–4 h) and pH 7.4 (4–5 h) In simulated gastric juice (pH 2.1, 37°C and 2 h): %loss of encapsulated EGCg: <10% %loss of native EGCg: ∼15% In simulated intestinal juice (pH 7.2, 37°C and 2 h): %loss of encapsulated EGCg:∼25% %loss of native EGCg: ∼80%	Hong et al., 2014
EGCg	Chitosan/TPP•6 H_2O = 5/1	Crosslinking technique	∼10% (%w/w)	PS: 150 nm∼200 nm PI: 0.1	In simulated gastric juice (pH 1.5, 25°C and 24 h): %release of encapsulated EGCg: ∼10% In simulated intestinal juice (pH 6.8, 25°C and 24 h): %release of encapsulated EGCg:∼50%	Khan et al., 2014
EGCg	CHC/FA-CMC = 1/1	Crosslinking technique	∼18 mg/g	PS: 407 nm EE_{max}: 75% ZP: +36.6 mV	*In vitro* release via dialysis (hydrochloric acid buffer, pH 1.3, 37°C and 1 h): %Release of encapsulated EGCg: ∼70% *In vitro* release via dialysis (PBS, pH 7.4, 37°C and 1 h): %Release of encapsulated EGCg: ∼37%	Liang et al., 2014
TP or TP-Zn complex	β-chitosan/TPP = 6/1	Crosslinking technique	45 μg TP or TP-Zn complex /mL	PS: 383 nm for TP; 85 nm for TP-Zn complex PI: 0.7 for TP; 0.15 for TP-Zn complex; EE: >97% for both ZP: ∼ +30 mV for both	*In vitro* release via dialysis (PBS, pH 7.4 and 5.5 h): %Release of encapsulated TP from TP and TP-Zn complex loaded nanoparticles: >80% *In vitro* release via dialysis (PBS, pH 4.5 and 5.5 h): %Release of encapsulated TP from TP and TP-Zn complex loaded nanoparticles: >80%	Zhang and Zhao, 2015
TP	Chitosan/TPP = 1/6	Emulsion and Crosslinking technique	10% (%w/w)	PS: <5 μm; EE: 24%∼60% for individual catechins EGC, EC, EGCg and ECg at pH 5.5;	*In vitro* release in PBS (pH 5.5, 2 h): %Release of encapsulated EC, EGC, EGCg and ECg: 100%, 65%, 65%, 70% *In vitro* release in PBS (pH 7.4, 2 h): %Release of encapsulated EC, EGC, EGCg and ECg: 100%, 52%, 62%, 75% In PBS (pH 5.5, 45–80°C and 24 h): %loss of encapsulated EC, EGC, EGCg and ECg: 40∼90% %loss of native EC, EGC, EGCg and ECg: >85% In o/w emulsion (1% w/w; 50°C and 30 d): %loss of encapsulated EC, EGC, EGCg and ECg: 35∼82% %loss of native EC, EGC, EGCg and ECg: >90%	Wisuitiprot et al., 2011

TP (EGCg>65%)	Chitosan/ɣ-PGA = 3/1∼6/1	Crosslinking technique	16.3∼74.6 μg/mg	PS: 134 nm∼147 nm; EE: 13.8%∼23.5%; ZP: 24.7 mV∼33.5 mV	Subsequent *in vitro* release in different buffers (pH 2.5–7.4, 1–7 h): Cumulative %Release of encapsulated catechins: 40% at pH 2.5 (1 h), 45% at pH 6.6 (1 h), 65% at pH 7.0 (1 h) and 100% at pH 7.4 (2 h)	Tang et al., 2013
EGCg	Chitosan/CPPs = 1/1	Crosslinking technique	0.25 mg/mL	PS: 150 nm; PI: 0.05∼0.14; ZP: +32.2 mV	—	Hu et al., 2012
Catechin	Sodium alginate/ $CaCl_2$ = 3/4	Absorption	49∼382 μg/mg	PS: 114 μm; EE: 10.6%–51.6%	In simulated gastrointestinal juice (gastric phase: pH 1.5, 37°C and 1 h; intestinal phase: pH 6.8, 37°C and 1 h): %release of encapsulated catechin: 55–57%.	Kim et al., 2015
EGCg	Gum arabic/maltodextrin = 3/2	Emulsion and spray drying	5% (%w/w)	PS: 40 nm, 400 nm PI: 0.58 EE: 96% ZP: −36 mV	—	Peres et al., 2011
TP	Maltodextrin or gum arabic or maltodextrin/gum arabic = ∼1/3, 1/1, 3/1, with or without adding 1 wt% chitosan as a coating material	Spray drying	193–249 mg gallic acid/g	PS: 40∼226 μm EE: 71%∼88%	In aqueous solutions (40°C, 84 d): %loss of encapsulated TC: 18.2%∼32.6% %loss of native TC: 32.6% In simulated gastric juice (pH 2.3, 37°C and 2 h): %release of encapsulated TC: 100% In simulated intestinal juice (pH 7.4, 37°C and 2 h): %release of encapsulated TC: 100%	Zokti et al., 2016

Abbreviations: EE: encapsulation efficiency; PS: average particle size listed; ZP: Zeta potential; PI: polydispersity index; TP: total polyphenols; TC: total catechins; TPP: sodium tripolyphosphate; PAA: polyaspartic acid; CHC/FA-CMC: carboxymethyl chitosan/ folate conjugated chitosan hydrochloride; ɣ-PGA: poly(ɣ-glutamic acid); CPPs: caseinophosphopeptides.

<52% (Kim et al., 2015; Kim et al., 2016). A mixture of gum arabic and maltodextrin has been used to incorporate EGCg through homogenization and spray drying, achieving encapsulation efficiency close to 96% (Peres et al., 2011). Inulin has been used for preparing catechins delivery systems through sonication and spray drying (Palma et al., 2014). The grafting reaction between −OH of inulin (C–6) and H-6/H-8 of catechin (A ring) produces a catechin grafted inulin complex (Liu et al., 2014).

3.4. Multi-biopolymers systems

Interactions between polysaccharides and proteins (including peptides) and catechins may be capitalized in the design of delivery systems (Zhao et al., 2013). A macromolecular conjugate of chitosan and whey protein isolate, prepared through the ionic crosslinking technique using TTP, was employed to encapsulate catechin, produces particles (1200 nm diameter) with encapsulation efficiency ranging from 29% to 42% (Zhang et al., 2009). Composite nanoparticles of EGCg/chitosan/β-lactoglobulin have been produced with particle size of 100∼300 nm and zeta potential of 20∼30 mV (Liang et al., 2015). Ternary aggregates for delivering EGCg fabricated with lactoferrin and high methylated pectin have a particle size of ∼500 nm and zeta potential of −34 mV ∼ −28 mV (Yang et al., 2015). Spray dried green tea extracts carried by combinations of maltodextrin, gum arabic and chitosan, have particles of 40–226 μm with encapsulation efficiencies of 71%–88% (Zokti et al., 2016).

4. Considerations for comparing delivery system performance

The choice of the encapsulant material and processing method should be guided by retro-designing the formulation once the environment exposure and the trigger for release of the bioactive has been defined (Ubbink and Krueger, 2006). This makes it difficult to make direct comparisons about the performance between the various systems without knowing the end application, as the performance of a system has to be considered in terms of fitness-for-purpose for the intended performance of the microcapsule in the target application. However, comparisons are possible where similar methods of assessment have been used to assess efficiency of encapsulation.

The encapsulation efficiency, catechin loading, stability and release properties are important considerations for evaluating delivery systems. Comparisons between various studies are compounded by the fact that there have been various methods used for quantification of the extracted catechins to provide evidence of catechin incorporation in the delivery formulation or the properties of the catechin-loaded capsules. Some authors use the Folin-Ciocalteu colorimetric assay to analyze free catechins including the total, un-entrapped, extracted or released catechins (Liang et al., 2014; Zhang et al., 2007), while others measure antioxidant capacities of these free catechins (Gómez-Mascaraque et al., 2016b; Taylor et al., 2009) as well as the whole catechin-loaded capsules (Shutava et al., 2009b). UV-vis spectroscopy was also applied to determine catechins (e.g. the total, un-entrapped, extracted or released) based on the specific UV absorbance of catechins (Gómez-Mascaraque et al., 2016a; Lestringant et al., 2014; Zhang et al., 2016). Fourier transform infrared spectrum of the whole delivery system was recorded to provide evidence of incorporation of catechins into various matrices (Gómez-Mascaraque et al., 2015; Gómez-Mascaraque et al., 2016a). Others employ HPLC-based methods for quantification of catechins (Gülseren and Corredig, 2013; Shpigelman et al., 2012; Tsai and Chen, 2016; Wu et al., 2014; Zhang et al., 2013; Zhang et al., 2016) after extraction of catechins with an appropriate solvent. The extract of catechin from catechin-loaded particles is often a challenge as polyphenols have varying affinities for the encapsulation material (e.g. proteins, polysaccharides). In addition, components other than catechin in the delivery formulation may be co-extracted by the solvent and interfere with the determination of catechin compounds when spectrophotometric methods are used for quantification. Some of these limitations have been overcome with the use HPLC-MS for quantification of catechins (Tsai and Chen, 2106).

There have also been different *in vitro* digestion models used to evaluate the release of catechins form the encapsulation system in terms of pH, digestive juice composition (e.g. enzyme, salt), digestion time and digestion stages (e.g. gastric digestion only, intestinal stage, or sequential gastric and intestinal digestion stages). For example, simulated gastrointestinal digestion model (gastric phase: pH 1.5, 37°C and 1 h; intestinal phase: pH 6.8, 37°C and 1 h) was used to evaluate the bioaccessibility of catechin delivered by calcium alginate microparticles with a final %release of 55–57% (Kim et al., 2015). The bioaccessibility of EGCg-loaded chitosan nanoparticles was measured by separate simulated gastric digestion (pH 1.5, 25°C and 24 h) and intestinal digestion (pH 6.8, 25°C and 24 h), with % release of encapsulated EGCg being ∼10% and ∼50% respectively (Khan et al., 2014). It will be necessary to develop and apply a standardized *in vitro* digestion models to assess the release profiles of catechins in order to appreciate the performance of variously formulated and processed nano-/micro-particles (Corstens et al., 2017).

5. Bioavailability of encapsulated catechins

The composition, particle size and interfacial properties of delivery systems are important influencing factors on the bioavailability of encapsulated catechins (Oliveira and Pintado, 2015). Encapsulated catechins were more stable and achieved improved sustainable release in digestive fluids compared with native catechins (Aditya et al., 2015; Bhushani et al., 2016; Lee et al., 2009; Zou et al., 2014). Dube et al. (2011) demonstrated the administration of EGCg-loaded chitosan nanoparticles enhances the plasma exposure of total EGCg by a factor of 1.5 relative to that of an EGCg solution, and attributed this to the enhanced exposure of liberative EGCg to the jejunum. Smith et al. (2010) also reported an improved oral bioavailability of EGCg-loaded nanolipidic particles in rats compared to free EGCg. Higher concentrations of catechin metabolites, including catechin sulphates and catechin glucuronides, were found in plasma when subjects consumed the phenol-enriched wines (non-encapsulated and nano-encapsulated) that was enriched with the same amount of phenolic extract, compared with the control wine (Motilva et al., 2016).

6. Potential health benefits with encapsulated catechins

To date most studies have been carried out on cell lines and animals. However it should be noted that as the gut microflora is significant in the metabolism of catechins, cellular assays for estimation of catechin bioavailability may be of limited utility as they do not account for the adsorption, distribution, metabolism and excretion of bioactive compound from oral intake of catechins. In addition, there are also inter-species differences on the metabolism of catechins (Clifford et al., 2013). This is an important consideration when assessing the relative importance of the various studies to the understanding of the effects in humans. Noting the caveats above, a review of the literature on use of cellular assays and animal studies is included as within limits, they do provide a comparison between the effects on specific aspects studied between the deliveries of free (unencapsulated) and encapsulated catechins.

6.1. Cardioprotective effects

The cardioprotective effects of catechins-loaded delivery system have been evaluated in cell culture and animal studies (Zhang et al., 2013; Hong et al., 2014). In a cell culture of THP-1-derived macrophages, nanoencapsulated EGCg in a lipid carrier and chitosan-coated nanostructured lipid carrier both exerted higher inhibitory effect on the development of atherosclerotic lesion compared to free EGCg, mainly through decreasing macrophage cholesterol content and MCP-1 expression (Zhang et al., 2013). Nanoemulsification of green tea extract significantly enhanced hypocholesterolemic effects of green tea catechins *in vivo*. A greater reduction of total and low density lipoprotein was observed in nanoemulsified EGCg-fed mice compared with green tea extract-fed mice, which was attributed to increased bioavailability of the tea polyphenols in nanoemulsified particles (Kim et al., 2012). EGCg-loaded nanoparticles prepared from chitosan and polyaspartic acid were administered orally to rabbit, and the effectiveness of EGCg against rabbit atherosclerosis was significantly improved by encapsulation (Hong et al., 2014).

6.2. Increasing cellular uptake, antioxidant and antiviral activities

High cellular uptake of catechins may lead to their higher cellular antioxidant abilities and antiviral activities. Hu et al. (2013) reported the EGCg-loaded nanoparticles assembled from chitosan and caseinophosphopeptide have stronger activity of scavenging free radical than free EGCg, using a cellular antioxidant activity assay. This is possibly due to the higher cellular uptake, which was confirmed by the green fluorescence inside the human hepatocellular caricinoma cells. Electrosprayed chitosan capsules of EGCg show prolonged *in vitro* antiviral activity and antibacterial activity against murine norovirus compared to the free EGCg, due to the sustained release of EGCg (Gómez-Mascaraque et al., 2016b). Encapsulation in chitosan nanoparticles improves the antibacterial activity of catechins and catechins-Zn complex against the growth of *Escherichia coli* and *Listeria innocua* (Zhang et al., 2016a). Gonçalves et al. (2016) developed three encapsulation formulations of EGCg comprising modified *n*-octenyl succinate anhydride (OSA)-starch, soybean lecithin and β-glucan through gas saturated solution drying, and found EGCg/lecithin and EGCg/β-glucan presents around 1.5-fold higher values of cellular antioxidant activity in Caco-2 cells than free EGCg at the same concentrations.

6.3. Anti-tumorigenic effects

The inhibitory effects of polyphenols in tumorigenesis and tumor growth include modification of the redox status and interference with basic cellular functions such as apoptosis, cell cycle, angiogenesis, invasion and metastasis (Kampa et al., 2007). At low concentrations of 1∼2 μM EGCg, a delivery matrix of gum arabic and maltodextrin enhances the inhibitory effect of EGCg on the proliferation of Du145 prostate cancer cells by 10–20%, compared with free EGCg (Rocha et al., 2011). The cytotoxicity of EGCg lipid nanoparticles was found to be higher against MDA-MB 231 human breast cancer cells and DU-145 human prostate cancer cells compared to native EGCg (Radhakrishnan et al., 2016). Luo et al. (2014) demonstrated that encapsulated EGCg in nanoliposomes exerts enhanced inhibitory effect on the viability of Caco-2 tumor cells as EGCg concentration was above 5.5 mM compared to free EGCg. An animal study showed that chitosan nanoparticles of EGCg inhibits proliferation-related protein expression of Ki-67 and PCNA and induces apoptosis-related protein expression of Bax and PARP in tumors harvested from the treated mice (Siddiqui et al., 2014). A nanoemulsion of catechin composed of lecithin, Tween 80 and deionized water induces a significant increase in the apoptosis of prostate cancer cell PC-3 compared with catechin extract, through decreasing B-cell lymphoma 2 (bcl-2) expression and increasing cytochrome c expression for activation of caspase-3, caspase-8, and caspase-9 (Tsai and Chen, 2016). However, Lestringant et al. (2014) and Haratifar et al. (2014a) demonstrated encapsulated catechins in milk proteins, e. g. β-Lg and casein micelles, have comparable anti-proliferation effect respectively on Caco-2 and HT29 cell lines, to their corresponding native forms.

Catechins may exert different inhibitory effect on different cells. For instance, catechins potently induce apoptotic cell death and cell cycle arrest in tumor cells but not in their normal cell counterparts (Haratifar et al., 2014b). There is significant inhibition on the proliferation of tumor cell line (D/v-src) for both EGCg and encapsulated EGCg in casein micelles whereas no obvious inhibition is exerted in the counterpart normal cell line (4D/WT) (Haratifar et al., 2014b). Folate conjugated chitosan coated EGCg nanoparticles showed differential antitumor activity towards different cancer cells (H1299, HeLa, and Capan-1), with the greatest inhibitory effect on the viability of HeLa cancer cells that had higher expression of folic acid receptors compared with H1299 and Capan-1 (Liang et al., 2014).

Nanoparticle-encapsulated EGCg may also induce apoptosis of cancer cells through intracellular signaling. Layer-by-layer-coated gelatin nanoparticles of EGCg retained its biological activity and blocked hepatocyte growth factor (HGF)-induced intracellular signaling in the breast cancer cell line MBA-MD-231 as potently as free EGCg (Shutava et al., 2009b). In tumor tissues of athymic nude mice subcutaneously implanted with

22Rγ1 tumor xenografts, the EGCg-loaded chitosan nanoparticles, compared with free EGCg and controls, significantly induced poly (ADP-ribose) polymerases cleavage, increase of Bax protein expression and concomitant decrease of Bcl-2 protein expression, activation of caspases as well as reduction of Ki-67 and proliferation of cell nuclear antigen (Khan, et al., 2014).

7. Future challenges

Food-grade delivery systems are gaining increasing attention as potential natural and cost-effective tools for improvement of the bioavailability of bioactives and the promotion of human health. They may be used as supplements or incorporated into functional foods and be alternative offerings to consumers who are interested in maintaining health and wellness. The bioefficacy of catechins may be improved by the use of appropriately designed delivery systems that are retro-fitted for the final application. This needs to take into consideration the formulation (i.e catechin loading, type and ratio of wall material to catechin) and the processing techniques required to obtain the desired functionality. The functionality is influenced by many factors including particle size, encapsulation efficiency and stability of nano-/micro-particles of catechins in various environments.

In vitro and *in vivo* studies done to date show positive benefits of encapsulation on the bioavailability and bioefficacy of catechins compared with free catechins, Conclusions based on *in vitro* trials and even *in vivo* experiments in Caco-2 cells or upper gastrointestinal track uptake need to have caveats placed around their interpretation, as the effects of catechins may be underestimated when the effects of transformations by gut bacteria are not taken into account. Bioactivities *in vitro* and *in vivo* research have not always been confirmed by or are not compatible with the results of epidemiological study (Mereles and Hunstein, 2011). The confusion in the literature may be related to the limited availability of fundamental information on the absorption, distribution, metabolism and excretion (ADME) of polyphenols (Clifford et al., 2013). Therefore it is essential to further complement the results of *in vitro* studies with more work on the appropriate biomarkers and in-body effects afforded by different delivery systems for catechins, which take into the account the metabolism of the delivered catechins by microbiota. Testing in human is critical for the unequivocal evidence for benefits for the condition of interest which makes further confirmatory evidence from human clinical trials essential to substantiate the benefits of catechin encapsulation.

Funding

This work was funded by the Fundamental Research Funds for the Central Universities (2017QNA6021) and the 111 Project (B17039).

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