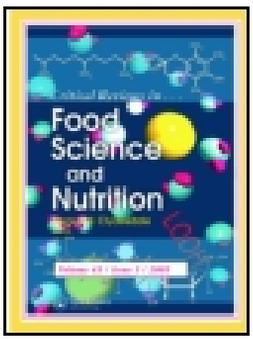

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REVIEW

Delivery of synergistic polyphenol combinations using biopolymer-based systems: Advances in physicochemical properties, stability and bioavailability

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ABSTRACT

When consumed at sufficiently high levels, polyphenols may provide health benefits, which is linked to their antidiabetic, antiinflamatory, antimicrobial, antioxidant, antitumor, and hypolipidemic properties. Moreover, certain polyphenol combinations exhibit synergistic effects when delivered together – the combined polyphenols have a higher biological activity than the sum of the individual ones. However, the commercial application of polyphenols as nutraceuticals is currently limited because of their poor solubility characteristics; instability when exposed to light, heat, and alkaline conditions; and, low and inconsistent oral bioavailability. Colloidal delivery systems are being developed to overcome these challenges. In this article, we review the design, fabrication, and utilization of food-grade biopolymer-based delivery systems for the encapsulation of one or more polyphenols. In particular, we focus on the creation of delivery systems constructed from edible proteins and polysaccharides. The optimization of biopolymer-based delivery systems may lead to the development of innovative polyphenol-enriched functional foods that can improve human health and wellbeing.

KEYWORDS

Synergism; multiple polyphenols; delivery systems; protein-polysaccharide complexes; bioavailability

Introduction

Polyphenols are secondary metabolites produced by many edible plants (Bao et al. 2016; Petti and Scully 2009; Xu et al. 2017). They may lessen oxidative damage of proteins, lipids, and carbohydrates in living cells and tissues, thereby reducing the risk of certain chronic diseases (Cirillo et al. 2016; Fernandez-Panchon et al. 2008; Scalbert et al. 2005). Polyphenols are, therefore, a good source of nutraceuticals for application in the food and supplement industries. Nevertheless, polyphenols are highly unstable to light, heat, and alkaline conditions due to the presence of multiple hydroxyl groups in their structure (Oliver et al. 2016). Moreover, many polyphenols have poor solubility characteristics, which restricts their incorporation into many food products (Ariyarathna and Karunaratne 2016; Rodriguez et al. 2016). The consumption of some polyphenol-enriched foods/matrix/ingredient is often limited because of their astringency, when the content of polyphenols is higher than a certain level, the astringency is linked to their ability to precipitate salivary proteins in the mouth (Cheynier 2012). After ingestion, polyphenols are often metabolized within the human gut, which impacts their absorption and bioactivity profile (Crozier et al. 2009). Specifically, during the process of entering the circulatory system through the small intestinal wall and transporting to the liver, polyphenols may undergo deglycosylation, glucuronidation, sulfation and methylation steps. There is therefore considerable interest in developing effective delivery systems to overcome these problems.

Delivery systems with a variety of different structures can be fabricated from range of food-grade components, including proteins, carbohydrates, lipids, surfactants, and minerals (McClements 2014). In this review, we focus on the encapsulation of polyphenols in delivery systems assembled from biopolymers, such as proteins and polysaccharides. Some polyphenols, especially those with large numbers of hydroxyl groups, have a high affinity for biopolymers (Bohn 2014), which means that they can easily be encapsulated and retained. Polyphenols may bind to biopolymers *via* either non-covalent or covalent interactions to form multifunctional complexes with synergistic functional attributes (Bordenave et al. 2014). Covalent binding of polyphenols to biopolymers leads to the formation of conjugates, which may have enhanced stability and bioavailability characteristics (Fang and Bhandari 2010). Similarly, non-covalent binding can lead to the formation of polyphenol-biopolymer complexes held together by physical interactions, which also have improved functional attributes (Liu et al. 2017b; Liu et al. 2019). Previous studies have shown that these conjugates and complexes can be used to encapsulate, protect, and deliver various polyphenols, including quercetin, resveratrol, curcumin, and epigallocatechin gallate (Li et al. 2015b; Wang et al. 2014a; Liu et al. 2017b). As well as being encapsulated in molecular-based delivery systems, such as

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conjugates and complexes, polyphenols can also be encapsulated in colloidal-based delivery systems, such as biopolymer nanoparticles or microgels (McClements 2014).

Encapsulation helps to improve the efficacy of polyphenols in food and biomedical applications (Chawda et al. 2017; Cirillo et al. 2016; Etxabide et al. 2018). Ideally, any polyphenol delivery system should have a high encapsulation efficiency, good retention, protection and release properties, a high oral bioavailability, and a good safety profile (Esfanjani and Jafari 2016; Liang et al. 2017a; Wang, Jung, and Zhao 2017).

Most previous studies have focused on the encapsulation of a single polyphenol but there is evidence that combinations of polyphenols may have synergistic effects when administered together. And, in general, the term 'synergy' means that a combination of two or more things creates an effect that is greater than the sum of their both acting separately. Studies have shown that bioactive food compounds can produce synergistic effects, particularly in traditional Chinese medicine research (Long et al. 2015). Agah and coworkers used an in vitro model of inflammatory pathways to investigate whether the different flavonoids in sorghum and cowpea could synergistically reduce inflammation, the results showed that combining the structurally related cereal flavones and legume flavonols elicits strong synergistic anti-inflammatory response in LPS-stimulated nonmalignant colonocytes, noticeably, the ratios of the different combined treatments significantly affected the magnitude of synergy (Agah et al. 2017). The concept of synergy is therefore of great significance in designing functional foods for promoting human wellbeing and preventing diseases. Consequently, there is interest in developing synergistic polyphenol delivery systems. For this reason, this review highlights recent advances in the development of molecular and colloidal delivery systems for encapsulating two or more polyphenols. Finally, the benefits and challenges of developing these types of biopolymer-based delivery systems are discussed, along with expected future trends.

Bioactive polyphenols

Various types of polyphenols are present in plant-based foods, which vary in their levels, physicochemical characteristics, and nutritional effects (Shahidi and Ambigaipalan 2015). Polyphenolic compounds are easily oxidizable because they contain a large amount of hydroxyl groups. For this reason, many of them are highly potent natural antioxidants that can be used in foods (Tomás-Barberán and Espín 2001). Chemically, phenolic compounds possess one or more aromatic rings with one or more hydroxyl groups attached, and are usually classified as flavonoids, phenolic acids, stilbenes, curcuminoids, coumarins, and tannins (Liu 2004). Figure 1 shows the chemical structures of some common polyphenolic compounds, while Table 1 summarizes some of their most important molecular and physicochemical properties.

Polyphenol types

Flavonoids

Flavonoids account for about two-thirds of the dietary phenolics found in food sources with the remaining one-third

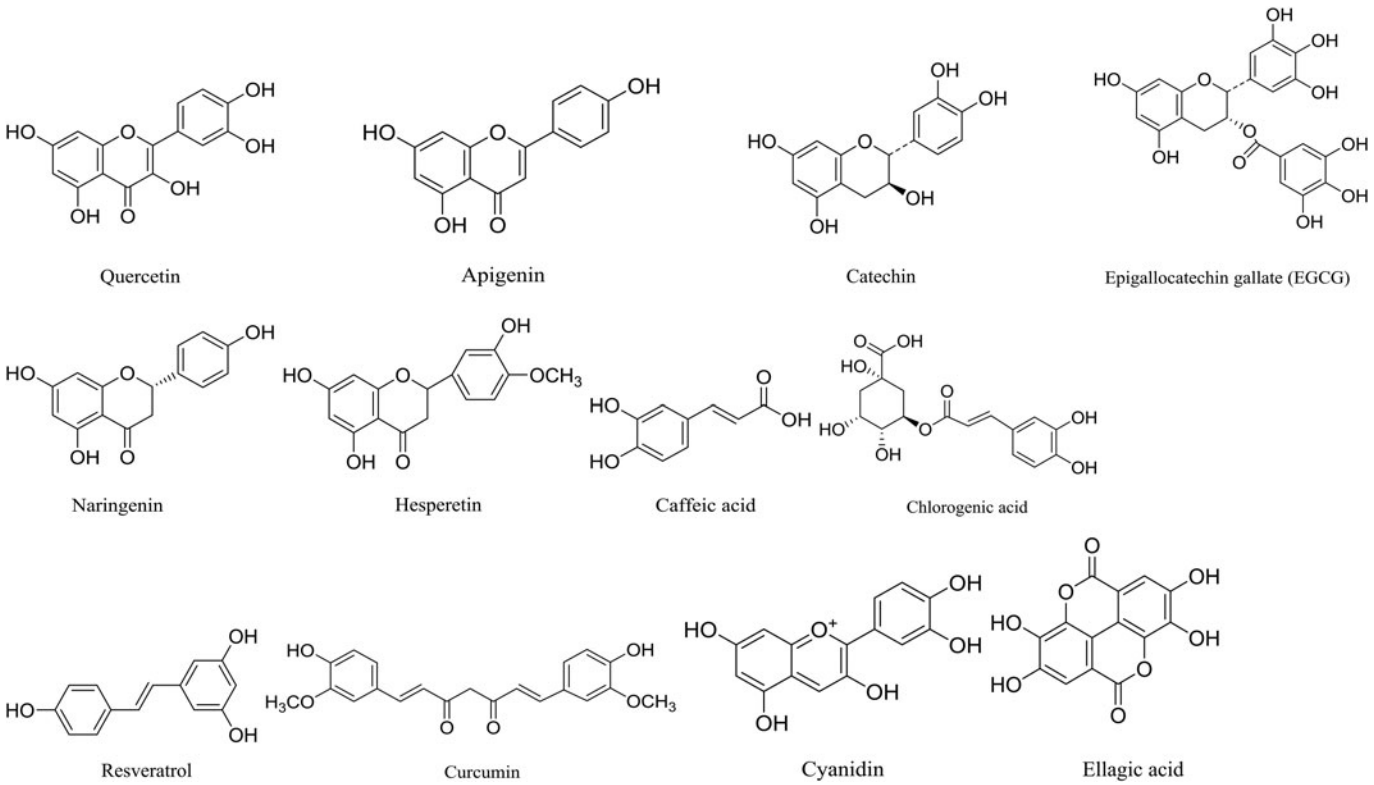

Figure 1. The chemical structures of some common polyphenols (resveratrol, curcumin, caffeic acid, chlorogenic acid, catechin, quercetin, hesperetin, naringenin, apigenin, cyanidin, ellagic acid, epigallocatechin gallate) present in plants.

Table 1. The physicochemical properties and stability of some common polyphenols (Some data were collected from http://www.chemspider.com).

Polyphenols	Molecular weight	log P	Solubility	Factors affecting stability
Quercetin	302	1.480	Almost insoluble in water, soluble in glacial acetic acid	Sensitive to oxidation, lights and pH
Apigenin	270.24	2.10	Almost insoluble in water, partially soluble in hot alcohol, soluble in dilute KOH solution	Sensitive to oxidation and pH
Catechin	290.27	0.49	Soluble in hot water, ethanol, acetic acid, acetone, slightly soluble in cold water and ether, almost insoluble in benzene, chloroform and petroleum ether	Sensitive to oxidation, lights and pH
EGCG	458.37	2.08	Soluble to 10 mM in water and to 100 mM in ethanol	Sensitive to oxidation, lights and pH
Naringenin	272.25	3.19	Almost insoluble in water, but soluble in acetone, ethanol, ether and benzene	Sensitive to oxidation, lights and pH
Hesperetin	302.28	2.90	Slightly soluble in water, chloroform and benzene, partially soluble in ether, soluble in dilute alkali solution, easily soluble in ethanol	Sensitive to oxidation, lights and pH
Caffeic acid	180.16	1.42	Slightly soluble in cold water, easily soluble in hot water and cold ethanol	Sensitive to oxidation and pH
Chlorogenic acid	354.31	−0.36	Water solubility was 4 wt% at 25 °C, soluble in ethanol and acetone, very slightly soluble in ethyl acetate	Sensitive to temperature, oxidation, pH, and lights
Resveratrol	228.24	3.139	Poorly soluble in water, soluble in ether, chloroform, methanol, ethanol, acetone, etc.	Sensitive to temperature, oxidation, pH, and lights
Curcumin	368.38	2.92	Insolubility in water, more soluble in alkaline	Sensitive to oxidation, lights and pH
Cyanidin	287.24	1.89	Easily soluble in water, methanol, ethanol, dilute alkali and dilute acid	Highly sensitive to temperature, oxidation, pH, and lights
Ellagic acid	302.19	0.52	Slightly soluble in water	Sensitive to oxidation and lights

being mainly phenolic acids (Robbins 2003; Liu 2004). Different flavonoids are classified according to the nature of the heterocycle unit in their molecular structure: flavonols (quercetin); flavones (apigenin); flavanols (catechins, epigallocatechin gallate); flavanones (naringenin, hesperetin); anthocyanidins (cyanidin, pelargonidin, delphinidin); and, isoflavonoids (genistein).

Phenolic acids

As mentioned earlier, phenolic acids make up about one-third of the phenolic compounds found in plant-based foods (Robbins 2003; Liu 2004). The type and level of phenolic acids present in foods impacts their color, sensory qualities, nutritional attributes, and antioxidant activity (Maga and Katz 1978). Phenolic acids can be subdivided into two major groups: hydroxybenzoic acids (vanillic and syringic acids); and, hydroxycinnamic acids (caffeic and chlorogenic acids).

Stilbenoids

Stilbenoids are hydroxylated derivatives of stilbene. An common example of a stilbenoid with nutraceutical properties is resveratrol. Studies have shown that resveratrol may exhibit a range of health benefits (Jang et al. 1997).

Curcuminoids

Curcuminoids have two aromatic rings linked together by a 7-carbon chain (Manolova et al. 2014). This structure may have different substituents leading to different forms of curcuminoids. The most common curcuminoid used in foods is curcumin, which is a natural yellow pigment found in turmeric. Curcumin can exist in several tautomeric forms, including a 1,3-diketo form and two equivalent enol forms.

Tannins

Tannins consist of multiple phenolic groups covalently linked together. They are widely found in plant-based foods and have the ability to bind and precipitate proteins, which is responsible for their astringency. Ellagic and tannic acids are two common types of tannins found in foods.

Polyphenol health benefits

The polyphenols extracted from plants have been claimed to exhibit a broad range of different health benefits, including antioxidant, antitumor, antidiabetic, antiinflamatory, antimicrobial, and hypolipidemic properties (Bellion et al. 2010; Hollman et al. 2011; Le Bourvellec and Renard 2012). In general, the proposed mechanisms of action for polyphenols include: (i) *nonspecific mechanisms* – the presence of phenolic groups leads to free radical scavenging (Scalbert et al. 2005) and a reduction in oxidative stress (Tsao 2010); and, (ii) *specific mechanisms* – specific molecular motifs are able to interact with cellular signaling pathways and related machinery that mediate cell function (Fraga et al. 2010; Vauzour et al. 2010). For instance, potential mechanisms responsible for the proposed anticarcinogenic effects of polyphenols include: (i) blocking and suppressing the initiation stage; (ii) inhibiting NF-kB activation; and, (iii) inducing apoptosis of tumor cells (Scalbert et al. 2005).

Challenges to incorporating polyphenols in foods

Ideally, formulators of functional foods would like to enrich their products with bioactive polyphenols so as to enhance their health benefits. There are, however, a number of challenges to successfully incorporating polyphenols into many foods. As mentioned earlier, they are susceptible to chemical

degradation when exposed to light, heat, or alkaline conditions found in many foods, which means they may be lost prior to ingestion. They are often astringent, which leads to an undesirable taste profile, which reduces their consumption. If they are ingested, they often have a relatively low bioavailability and bioactivity because of their poor solubility in gastrointestinal fluids and their tendency to be rapidly metabolized by enzymes in the gastrointestinal tract (GIT). For these reasons, effective strategies are needed to encapsulate, protect, and delivery polyphenols in functional food applications.

Enhancing polyphenol stability, bioavailability and bioactivity

In general, the stability, palatability, bioavailability, and bioactivity of polyphenols can be improved during product development, storage, and consumption using several strategies:

- *Processing technologies*: Processing operatings such as freeze drying, spray drying, and microwave drying can be used to enhance the long-term storage stability of polyphenols by converting them into a powdered form (Wais et al. 2016). However, these approaches do not usually enhance the palatability, bioavailability, or bioactivity of polyphenols.
- *Excipient ingredients*: Digestible lipids can increase the bioaccessibility of polyphenols by forming mixed micelles in the aqueous phase that can solubilize and transport them (Pandita et al. 2014). Antioxidants can inhibit the oxidation of polyphenols within foods and inside the human gut, thereby increasing the amount that remains in a bioactive form (Almajano, Delgado and Gordon 2007; Spizzirri et al. 2009, 2010; Cirillo et al. 2010, 2012). Piperine, from black pepper, inhibits the metabolism of curcumin within the human gut, as well as retarding its efflux from the epithelium cells, thereby improving its oral bioavailability (Anand et al. 2007). Careful design of the food matrix surrounding polyphenols can therefore be used to enhance their performance.
- *Molecular complexation*: Polyphenols can be physically (complexation) or chemically (conjugation) linked to other molecules to improve their functionality (Le Bourvellec and Renard 2012; Prigent et al. 2003, 2007; Naczk et al. 2006; Kroll, Rawel, and Rohn 2003; Spizzirri et al. 2009). The most common physical interactions used to form complexes are hydrophobic, electrostatic, and hydrogen bonds, whereas a variety of different chemical reactions can be used to form conjugates by linking polyphenols to other molecules. Carefully designed complexes or conjugates can be created to overcome many of the challenges associated with incorporating polyphenols into foods.
- *Encapsulation*: The functionality of polyphenols can also be improved by encapsulating them in certain kinds of colloidal particles, such as those in emulsions, nanoemulsions, solid lipid nanoparticles, biopolymer nanoparticles, and microgels (Velikov and Pelan 2008; Chawda et al. 2017). The polyphenols are typically trapped inside small particles that are dispersed within water. As a result, they are isolated from components in the aqueous phase that can cause their degradation. Moreover, their encapsulation may reduce their tendency to cause astringency within the mouth. Finally, encapsulation may protect them from metabolism within the human gastrointestinal tract. For instance, Huang and coworkers fabricated the zein-pectin core/shell nanoparticles loaded with resveratrol, when the nanoparticles were exposed to a simulated gastrointestinal tract containing stomach and small intestine phases, and the bioaccessibility of the encapsulated resveratrol was higher than that of free resveratrol. Moreover, the *in vitro* $ABTS^{+\cdot}$ radical scavenging capacity and ferric ion reducing power of resveratrol was greatly enhanced when it was encapsulated inside the biopolymer nanoparticles. The gastrointestinal fluids collected after digestion of the encapsulated resveratrol also exhibited strong intracellular reactive oxygen species scavenging activity (Huang et al. 2019).

The focus of the current article is the design, fabrication, and utilization of delivery systems for polyphenols, which include molecular complexes and colloidal particles. We limit this review to the development of delivery systems fabricated from food-grade biopolymers, i.e. proteins and polysaccharides.

Biopolymer-based delivery systems

Many proteins are suitable for fabricating food-grade delivery systems because they have a high binding affinity for polyphenols, are biodegradable, and high good nutritional value (Elzoghby 2013; Elzoghby, Samy, and Elgindy 2012). Many polysaccharides are also suitable because of their high biocompatibility, biodegradability, and versatility (Fathi, Martin, and McClements 2014). A schematic representation of the co-delivery of multiple polyphenols using biopolymer-based delivery systems is depicted in Figure 2. Various

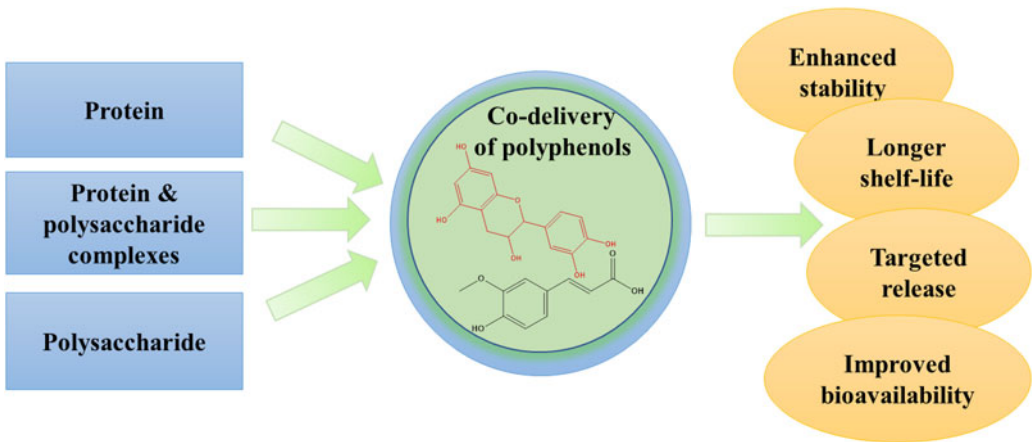

Figure 2. Schematic representation showing the composition of the co-delivery system for polyphenols and the potentially improved functions.

building components and construction techniques have been studied in co-delivering polyphenols to obtain synergistic effects.

Building blocks for assembling polyphenol delivery systems

Proteins and polysaccharides can be used in their natural form or physically, chemically or enzymatically modified to extend their functionality. The biopolymers may be linked to each other, or to the polyphenols, through either reversible or irreversible interactions. Reversible (physical) interactions are mainly combinations of non-covalent forces, such as hydrogen bonds, π-bonds, hydrophobic interactions, and electrostatic interactions. Irreversible (chemical) interactions are mainly covalent bonds, e.g. esterification (Liu et al. 2017a). Understanding the nature of the interactions between the molecules involved helps to rationally design delivery systems with improved functional properties. Protein-polysaccharide systems assembled using either non-covalent or covalent interactions have been used to encapsulate and deliver nutraceuticals (Foegeding et al. 2017). Attractive electrostatic interactions between oppositely charged groups are often used to assemble molecular complexes or colloidal particles from charged polysaccharides and proteins (Devi et al. 2017). Covalent bonds between the amino groups on proteins and the terminal reducing carbonyl groups on polysaccharides are often used to assemble molecular conjugates (Liu, Ru, and Ding 2012; Oliver, Melton, and Stanley 2006).

Interactions among polyphenols, proteins, and polysaccharides have been extensively described in the scientific literature (Swieca et al. 2013; Liu et al. 2016a Liu et al. 2017a). The formation of polyphenol-biopolymer complexes can be achieved in a number of ways, including: free radical grafting (Curcio et al. 2009; Spizzirri et al. 2009); enzyme-catalyzed reactions (Flanagan and Singh 2006; Kim and Cavaco-Paulo 2012); alkaline treatment (Kroll and Rawel 2001; Diftis et al. 2005); carbodiimide-mediated coupling reaction (Pasanphan and Chirachanchai 2008; Xie et al. 2014), and non-covalent interactions (Jakobek 2015). Figure 3 shows some of the main ways that functional foods may be created by utilizing interactions between proteins, polysaccharides, and polyphenols. These systems can be designed to improve the physical and chemical properties of polyphenols in foods, as well as to increase their palatability, bioavailability, and biological activity. The functional performance of these systems depends on the type and levels of proteins, polysaccharides, and polyphenols used, as well as their structural organization and the forces holding them together (Cho and McClements 2009).

Previously, researchers have used a variety of approaches to assemble biopolymer-based delivery systems for polyphenols. For instance, non-covalent complexes of soy protein and κ-carrageenan were prepared as delivery systems for quercetagetin (Wang, Liu, and Gao 2016). Soy protein–κ-carrageenan complexes were shown to be more effective than soy protein or κ-carrageenan alone for enhancing the light stability and radical scavenging ability of quercetagetin. The Maillard reaction and a grafting method were used to prepare ternary chlorogenic acid-lactoferrin-dextran conjugates (Liu et al. 2016b). The resulting ternary conjugates were shown to have better stability, bioaccessibility, and emulsification attributes than binary conjugates or lactoferrin alone. The same team also showed that covalent zein-EGCG compounds had better thermal stability, stronger antioxidant activity, and enhanced delivery properties than non-covalent ones (Liu et al. 2017b). In general, these

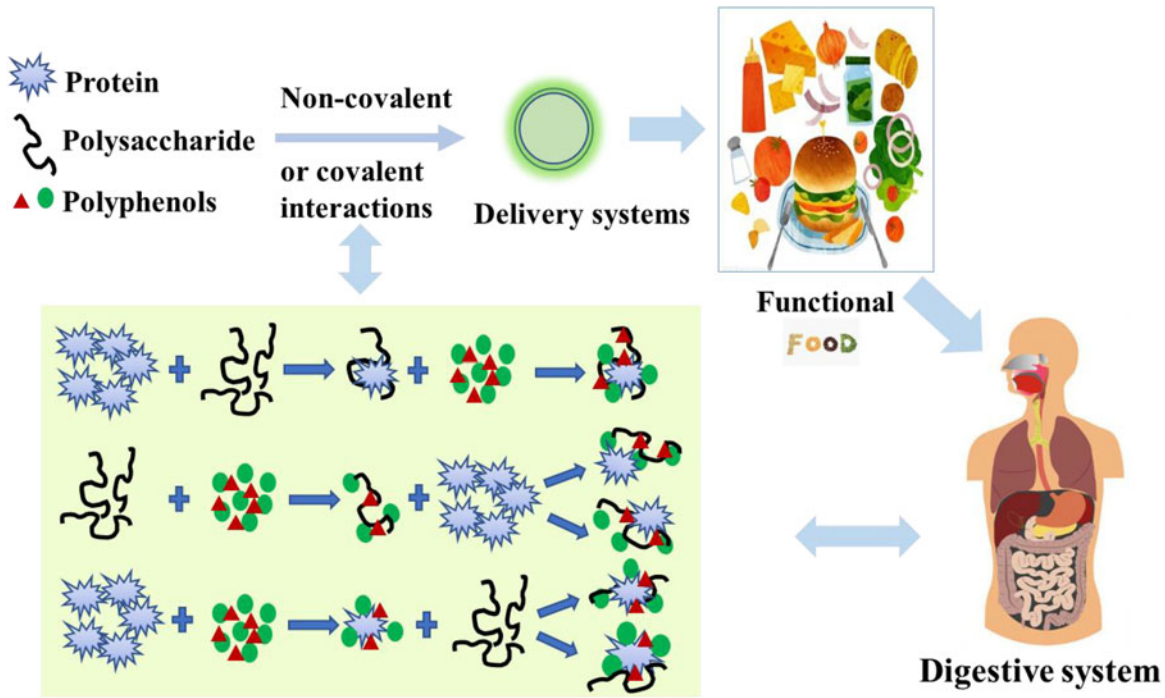

Figure 3. The schematic diagram of relationship between designing delivery systems using food-grade molecules and developing functional foods.

Table 2. Typical examples of constructing wall materials of delivery systems using interactions between food molecules.

Interactions type	Formation methods	Encapsulated polyphenols	Carrier materials	References
Noncovalent interaction (Physical crosslinking)	Electrostatic interaction	Tannins, Quercetagetin	Hyaluronan; Soy protein isolate-kappa-carrageenan	(Carn et al. 2012;Wang et al. 2016)
Covalent interaction (Chemical crosslinking)	Maillard reaction	Tea polyphenols; catechin	Bovine serum albumin -Chitosan; Beta-lactoglobulin-milk sugar lactose	(Kumar et al. 2016; Perusko et al. 2017)
	Free radical grafting	Catechin; EGCG; Gallic acid; Chlorogenic acid; Hydroxybenzoic and hydroxycinnamic acid derivatives	Ovotransferrin; Lactoferrin; Chitosan	(Liu et al. 2014; Liu et al. 2015b; Liu et al. 2015c; You, Luo and Wu 2014)
	Enzyme-catalyzed reactions	Phenolic compounds from *Hamamelis virginiana*	Chitosan-gelatins	(Rocasalbas et al. 2013)
	Alkaline treatment	Chlorogenic acid	Lactoferrin-polydextrose	(Liu et al. 2015a)
	Carbodiimide-mediated coupling reaction	Green tea catechin, quercetin; Gallic acid	Hyaluronic acid; Carboxymethyl chitosan, Chitosan	(Lee et al. 2015; Liang et al. 2016a; Liang et al. 2016b; Wang et al. 2014b; Yu et al. 2011)

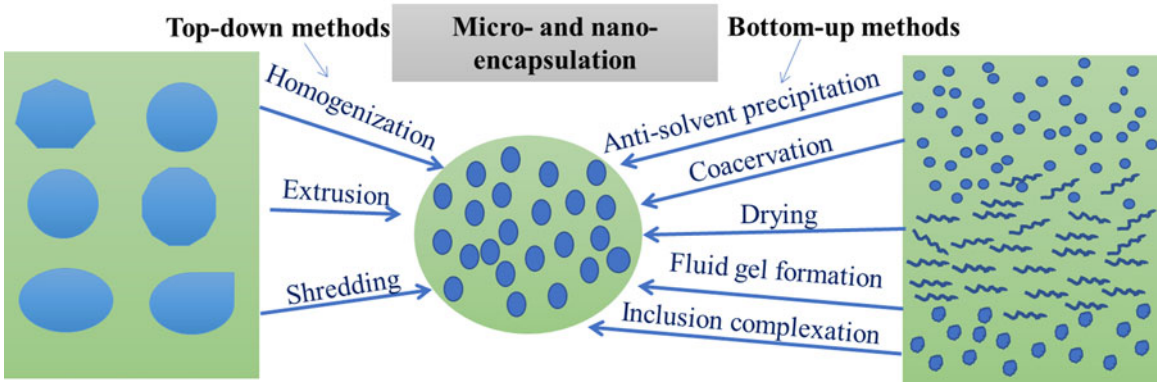

Figure 4. Schematic presentation of diverse methods used to construct delivery systems for bioactive components.

studies show that effective delivery systems for polyphenols can be created by careful selection of biopolymers and linking mechanisms. Some widely used food-grade complexes for constructing delivery systems to encapsulate polyphenols are summarized in Table 2.

Construction methods of multiple-polyphenol delivery system

In general, two basic methods can be used to produce delivery systems, i.e. 'top-down' and 'bottom-up' methods (Figure 4). For top-down methods, small particles are usually generated through a series of size-reduction processes, usually involving physical processing of foods using mechanical devices, e.g. by chopping, grinding, milling, spraying, or homogenization (Sanguansri and Augustin 2006; Joye and McClements 2014; Merisko-Liversidge, Liversidge, and Cooper 2003). For instance, polysaccharide-protein microgels can be formed by shredding larger particles in a commercial food processor (Yu et al. 2010) or by sonicating biopolymer solutions (Burey et al. 2008).

For bottom-up methods, small particles are usually produced by promoting the self-assembly of molecules that are attracted to each other (Inkyo et al. 2006; Inoue et al. 2007; Sanguansri and Augustin 2006; Shimomura and Sawadaishi 2001). Examples of this approach, include anti-solvent precipitation, coacervation, inclusion complexation, and micellization (Joye and McClements 2014). The antisolvent approach is one of the most widely used bottom-up approaches used to prepare delivery systems from biopolymers (Khan and Schneider 2013; Taheri, Jahanshahi, and Mosavian 2012; Wang et al. 2012). This approach has recently been used to prepare zein-hyaluronic acid nanoparticles for encapsulating quercetagetin (Chen et al. 2018b). The antisolvent approach has also been used to fabricate zein-tannic acid nanoparticles that can be used for encapsulation purposes (Zou et al. 2015b).

Inclusion complexation involves the encapsulation of a guest molecule into the cavity of a suitable host molecule. Some of the most commonly used host molecules are cyclodextrins, β-lactoglobulin, and starch, which all have hydrophobic pockets capable for incorporating non-polar bioactive agents (Zimet and Livney 2009). The bottom-up approach can also be used to form complex coacervates due to the electrostatic attraction between oppositely-charged biopolymers (Alvim and Ferreira Grosso 2010; Gan et al. 2011; Hedayati, Jahanshahi, and Attar 2012).

Each of these approaches has its own advantages and disadvantages in encapsulating, protecting, and delivering bioactive agents (Table 3). Thus, it is critical to select the most appropriate approach for a particular application, which depends on the nature of the bioactive agent, as well as the food matrix it will be incorporated into (McClements 2018).

Table 3. Strengths and weaknesses of each method to encapsulate.

Encapsulation methods	Strengths	Weaknesses	References
Anti-solvent precipitation	No need for specialized equipment and complex operating conditions, the associated costs is lower and the technique can easily be scaled up	Miscible solvent-antisolvent system is more difficult to choose; require recycling equipment to recover a large mixture of solvents and anti-solvents, which will increase production costs	(Joye, Davidov-Pardo, and McClements 2014; Thorat and Dalvi 2012)
Coacervation	High encapsulation efficiency	High costs; limited stability in aqueous matrices; be difficult to control particle size and prevent particle agglomeration	(Ezhilarasi et al. 2013; Joye and McClements 2014)
Inclusion complexation	Could be used to encapsulate volatile organic molecules for masking odors or flavors	Be difficult to find suitable biopolymers for cavities	(Ezhilarasi et al. 2013; Joye, Davidov-Pardo, and McClements 2014)
Drying	Reduce the sensitivity of biopolymers to hydrolysis; reduce capacity and costs for storage and transport	Require high amount of energy and the extended drying time	(Ezhilarasi et al. 2013; Joye, Davidov-Pardo, and McClements 2014)
Fluid gel formation	Flexible, heat-dissipating, capable of buffering and dispersing pressure	The particles produced can be easily deformed and have an irregular shape, and be difficult to characterize its properties; expensive	(Gabriele, Spyropoulos, and Norton 2009; Joye, Davidov-Pardo, and McClements 2014; Walther et al. 2002)
Shredding	Convenient	Require sophisticated equipment; heavy cost due to maintenance and running	(Jia, Dumont, and Orsat 2016; Joye, Davidov-Pardo, and McClements 2014)
Homogenization	Reduce the tendency to agglomerate or coalesce, break up the particles, improve the taste and look of the product, increase the viscosity, and prevent delamination	Require mechanical device; high energy consumption and not suitable for high viscosity	(Joye, Davidov-Pardo, and McClements 2014)
Extrusion	Be suitable for both hydrophilic and hydrophobic complexes	Require sophisticated equipment	(Augustin and Hemar 2009; Joye, Davidov-Pardo, and McClements 2014)

Properties of multiple-polyphenol delivery systems

In this section, some of the major physicochemical and functional properties of delivery systems containing a number of different polyphenols are highlighted.

Solubility

The solubility of polyphenols within food products and inside the gastrointestinal tract is one of the most important physicochemical properties affecting their impact on food quality and nutrition (Hu et al. 2017; Gleeson, Ryan, and Brayden 2016). The solubility of polyphenols depends on the physical and chemical properties of the solute and solvent, as well as the prevailing environmental conditions, such as pH, ionic strength, temperature, and matrix composition. For instance, the water-solubility of curcumin increases appreciably when the pH is raised above 8.0 because the molecule gains some negative charge, and therefore becomes more polar (McClements 2018). A main focus of researchers has therefore been to understand the major factors impacting the solubility of polyphenols and to use this knowledge to construct delivery systems to enhance their ability to be dispersed in aqueous products.

The formation and properties of polyphenol-biomacromolecule complexes is strongly influenced by the hydrophobicity/hydrophilicity characteristics of both the polyphenol and the biomacromolecule. For instance, when a polyphenol is highly water-soluble, the main driving force for protein complexation is relatively small (Le Bourvellec and Renard 2012; Haslam 1996) . In other words, the greater the water-solubility of the polyphenols, the weaker their affinity for proteins. Conversely, the more hydrophobic a polyphenol is, the greater is its tendency to bind to proteins, which is due to the presence of relatively strong hydrophobic interactions (Baxter et al. 1997, Richard et al. 2006). Protein–polyphenol complexes may be either soluble or insoluble after they have formed, which influences their impact on food quality, as well as their biological activities. Binding of polyphenols to polysaccharides can also improve their water-solubility. For instance, it has been shown that the conjugation of chitosan to catechol improves the polysaccharides water-solubility at neutral pH (Kim et al. 2013). This increase in solubility can be attributed to increased steric and electrostatic interactions between the conjugates compared to for chitosan alone (Ryu, Hong, and Lee 2015).

Curcumin, resveratrol and quercetin are plant-based polyphenols that are claimed to have a broad range of health benefits (Fan et al. 2018; Wang et al. 2015a; Ghayour et al. 2019). However, they both have limited water-solubility, which restricts their direct introduction into many foods and beverages. The water-solubility of curcumin can be enhanced by forming physical complexes with β-lactoglobulin (Li et al. 2015a). In this case, the non-polar curcumin molecules bind to hydrophobic patches on the surfaces of the globular proteins. The water-solubility of resveratrol has also been improved by encapsulating it inside carboxymethyl chitosan nanoparticles (Zu et al. 2016). In addition, when curcumin and quercetin were co-encapsulated in re-assembled casein micelles, their aqueous solubility could be significantly increased (Ghayour et al. 2019).

Recent studies have shown that tea polyphenols can increase the water solubility of soybean proteins by forming

physical complexes (Chen et al. 2019). Moreover, the binding of chlorogenic acid to milk proteins (whey protein or casein) has also been shown to enhance the solubility characersitics of the whole system (Jiang et al. 2018). In summary, there appears to be considerable scope in improving their solubility characteristics of both polyphenols and biomacromolecules by selecting the most appropriate pair for a particular application.

Stability

Many polyphenols are sensitive to chemical, enzymatic, and physical treatments used in foods. Chemical and enzymatic instability lead to changes in the molecular structure of polyphenols, which causes considerable alterations in their physicochemical and nutritional attributes (Joye, Davidov-Pardo, and McClements 2014). Physical instability leads to changes in the structural organization or location of the polyphenols in a system, such as conformational changes, aggregation, and gravitational separation, which can also impact their attributes (Joye, Davidov-Pardo, and McClements 2014). Figure 5 shows some of the major factors affecting polyphenol stability and their potential impact on polyphenol-containing systems. The instability of polyphenols can often be maintained or even improved by encapsulation in protein- and/or polysaccharides-based delivery systems. In the following section, EGCG, anthocyanin, curcumin and resveratrol have been selected as representative polyphenols to illustrate the stability of the polyphenol-loaded delivery systems. EGCG and anthocyanin are representive hydrophilic polyphenols, whereas curcumin and resveratrol are representive hydrophobic ones.

The loading of EGCG into nanoparticles constructed from either proteins (zein) or polysaccharides (chitosan) has been shown to enhance its stability in gastrointestinal fluids (Hong et al. 2014; Liang et al. 2017b). This is probably because the biopolymers protected the EGCG from reactive substances in the surrounding aqueous phase. The loading of the EGCG into the nanoparticles was mainly a result of electrostatic interactions and hydrogen bonds. EGCG has also been encapsulated within glycosylated casein nanoparticles, which improved its physical stability during storage (Xue et al. 2014). A hydrophilic anthocyanin-rich extract from *Hibiscus Sabdariffa* has been shown to form a complex with whey protein-arabic gum (Pimentel-Moral et al. 2018). This complex was then trapped within the inner phase of a water/oil/water emulsion, which improved its physical and chemical stability during storage at pH 4.5.

The stability of hydrophobic polyphenols can often be improved by embedding them within molecular complexes or colloidal particles. For example, curcumin encapsulated within α-lactalbumin or α-lactalbumin-dextran conjugates had better chemical stability than free curcumin (Yi et al. 2016). Similarly, zein-caseinate nanoparticles improved the stability of curcumin against UV irradiation and thermal treatment compared with free curcumin, which mainly due to the disordered structure of caseinate, it provided desirable thermal stability by generating both electrostatic and steric repulsion between the zein particles, thus preventing the particle disintegration or aggregation, and subsequently protecting the encapsulated curcumin inside the particles (Xue et al. 2018).

There has also been increasing interesting in encapsulating combinations of polyphenols into delivery systems because of their potential for synergistic interactions. For instance, studies have shown that curcumin and resveratrol have similar mechanisms of action in inhibiting tumor cell growth, anti-oxidation, and anti-inflammatory effects. Therefore, the combination of these two functional factors may exert a synergistic antioxidant effect. Curcumin and resveratrol have been encapsulated within the hyaluronic-coated lipid droplets in nanoemulsions formed by spontaneous emulsification (Nasr 2016). The encapsulated polyphenols were shown to have better chemical stability than the non-encapsulated ones. Another study found that encapsulation of both curcumin and catechin in gelatin-based emulsions increased their stability (Aditya et al. 2015).

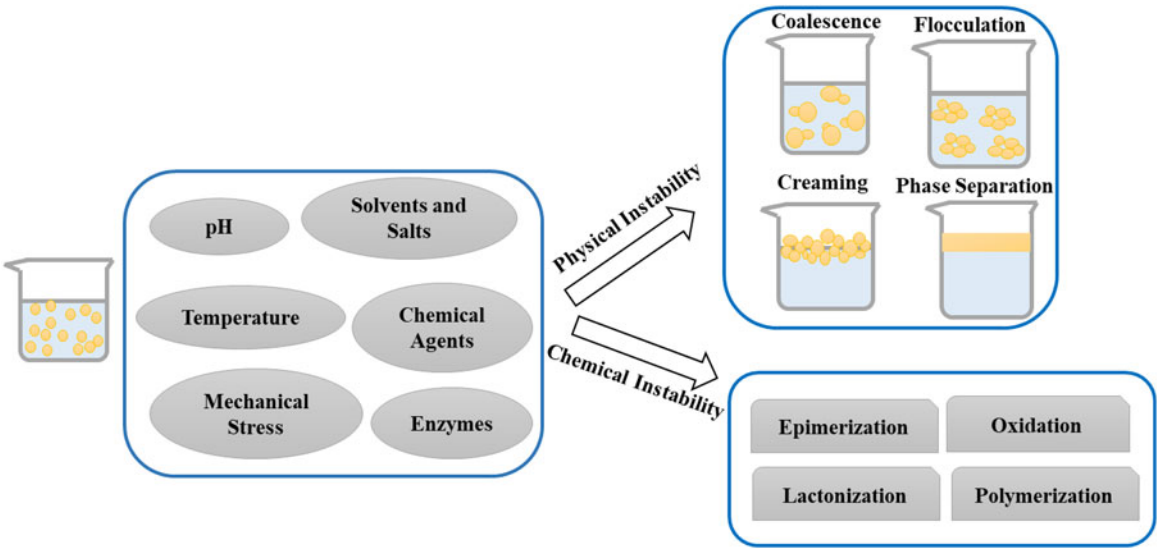

Figure 5. Schematic diagram of delivery systems instability change.

Table 4. Components, encapsulation efficiency, biological activity and stability of representative polyphenols-loaded delivery systems.

Bioactive polyphenols	Food matrix	Encapsulation efficiency	Observations	References
Quercetin	Pea protein isolate and mesquite gum	89.83 ± 0.24%	ABTS+· scavenging activity of 36.09 ± 1.38%, exhibited high physical stability during 28 days at 4 °C	(Cuevas-Bernardino et al. 2018)
Quercetagetin	Hyaluronic acid and zein	93.22%	After 8 months of storage (4 °C), the retention rate of quercetagetin was 77.93%; Improved the thermal and photochemical stability	(Chen et al. 2018b)
Tea polyphenol	Soy protein and pectin	None	Improved antioxidant activity, and physicochemical stability	(Jin et al. 2018)
EGCG	Caseinophosphopeptide and chitosan	Range from 70.5% to 81.7%	Enhanced its antioxidant activity	(Hu et al. 2013)
EGCG	Fucose-chitosan and gelatin	58 ± 6%	Effectively reduced gastric inflammation	(Lin et al. 2014)
Polyphenols extracted from dandelion	Alginate and pectin	77.35%	Good retention of hydroxycinnamic acids; Reveal a preferred-prolonged release profile	(Belščak-Cvitanović et al. 2016)
Curcumin, resveratrol	Zein and rhamnolipid	71% for curcumin and 85% for resveratrol	Preserved antioxidant activity; Improved stability and bioaccessibility	(Liu et al. 2018)

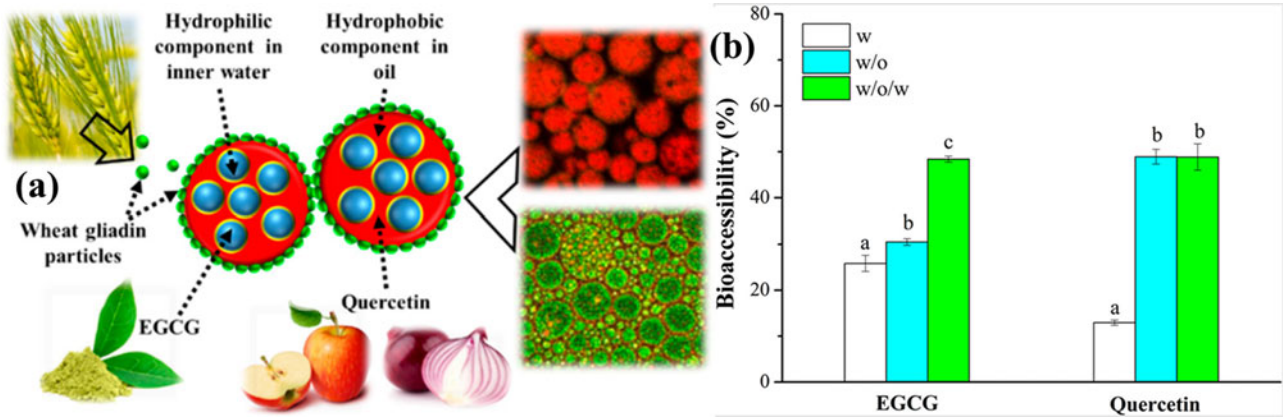

Figure 6. (a) Design of W/O/W emulsion gels to co-encapsulate EGCG and quercetin. (b) Bioaccessibility of EGCG and quercetin after simulated gastrointestinal digestion. W = Suspension of EGCG and quercetin dispersed together in water (pH 5.5); W/O = W/O emulsions containing EGCG in inner water and quercetin in oil; W/O/W = EGCG and quercetin coloaded W/O/W emulsion gels. Adapted from Chen et al. (2018b).

In summary, there appears to be considerable potential to use biopolymer-based delivery systems to enhance the chemical and physical stability of polyphenols in foods. A number of other representative studies on the utilization of biopolymer-based delivery systems for this purpose are summarized in Table 4.

Antioxidant activity

The encapsulation of polyphenols in biomacromolecule-based delivery systems may also impact their antioxidant activity in foods. Both resveratrol and curcumin have the ability to scavenge free radicals, to inhibit lipid peroxidation and DNA damage as well as to enhance endogenous antioxidants defenses (Ishrat et al. 2009; Leonard et al. 2003). Curcumin encapsulated in α-lactalbumin or α-lactalbumin-dextran conjugates exhibited a higher free radical scavenging activity and antioxidant activity than free curcumin (Yi et al. 2016). Previous studies showed that curcumin and resveratrol together make for a synergistic antioxidant effect than individual (Aftab and Vieira 2010). The antioxidant and photostability of both resveratrol and curcumin were improved when encapsulated by lipid-core nanocapsules, and co-encapsulation did not change the properties of formulation containing each polyphenol individually (Coradini et al. 2014; Friedrich et al. 2015). In addition, encapsulation of both curcumin and resveratrol in hyaluronic acid-based lipidic nanoemulsion has been shown to lead to delivery systems with good antioxidant activity and better brain targetability than the solution form of the polyphenols (Nasr 2016). Co-encapsulation of curcumin and resveratrol could exhibit a higher ability of reducing free radicals compared the single formulation, which could be explained by the synergic effect between curcumin and resveratrol (Guo, Yin, and Chen 2018). Other representative studies that have used biopolymer-based delivery systems to improve the functional performance of polyphenols are summarized in Table 4.

Bioavailability of polyphenols in the delivery system

Bioavailability can be defined as the fraction of a food component that is actually absorbed by the body in an active form (Carbonell-Capella et al. 2014). The bioavailability of polyphenols depends on their molecular structure and physicochemical properties (D'Archivio et al. 2010). Overall, the potential health benefits exhibited by a polyphenol depend on its stability, bioavailability, and bioactivity (Fang and Bhandari 2010).

Encapsulation of polyphenols in biopolymer-based nanoparticles has been shown to be an effective means of improving the bioavailability of EGCG, resveratrol, and

curcumin (Hu et al. 2017). Encapsulation of EGCG in biopolymer-coated-nanoliposomes improved its stability to degradation in gastrointestinal fluids (Zou et al. 2015a). In a recent study, W/O/W emulsion gels were designed using saccharose, gelatin, and wheat gliadin to codeliver EGCG and quercetin (Figure 6). EGCG was loaded in the internal aqueous phase while quercetin was loaded in the oil phase. The emulsion gels improved EGCG stability and quercetin solubility under simulated gastrointestinal conditions, leading to a 2- and 4-fold increase in their bioaccessibility, respectively (Chen et al. 2018a). Another study found that curcumin and resveratrol could be co-encapsulated within zein nanoparticles prepared using an antisolvent precipitation method, which led to an improvement in their bioaccessibility under simulated gastrointestinal conditions (Liu et al. 2018). In addition, curcumin loaded in zein-caseinate composite nanoparticles coud improve its absorption in the intestine, and exhibited greater bioavailability by cellular uptake studies (Xue et al. 2018). However, an improvement in the bioaccessibility or bioavailability of polyphenols after encapsulation is not always the case. For instance, some studies have shown that the bioavailability of polyphenols can be decreased by forming non-digestible complexes (Dueik and Bouchon 2016). Hence, it is important to carefully design any delivery system to behave optimally during processing, storage, and digestion. This depends on identifying the most appropriate biopolymer-based delivery system for the specific polyphenols and food matrix used.

Summary and outlook

Natural proteins and polysaccharides can be used to construct delivery systems for polyphenols that are suitable for incorporation into functional foods and beverages. Biopolymer-based delivery system can be designed to enhance the physicochemical properties, stability, bioavailability, and biological activity of single or multiple polyphenols. The inclusion of more than one type of polyphenol within a delivery system may lead to more effective functional foods due to the possibility of creating synergistic effects. However, there are still numerous challenges to consider when designing and applying these co-delivery systems, such as improving undesirable tastes and flavors caused by the astringency of some polyphenols. *In vitro* cell culture studies and *in vivo* animal feeding studies should also be performed to explore the efficacy and potential toxicity of polyphenol combinations. In addition, the behavior of polyphenol-loaded delivery systems in commercial foods and beverage products should be systematically studied. A more comprehensive understanding of the design and performance of delivery systems containing single or multiple polyphenols could lead to new products for application in the food, supplement, and medical industries.

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