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Dietary fiber-based colon-targeted delivery systems for polyphenols

Hsi-Yang Tang, Zhongxiang Fang, Ken Ng*

School of Agriculture and Food, Faculty of Veterinary and Agricultural Sciences, The University of Melbourne, Parkville, VIC, 3010, Australia

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ABSTRACT

Background: Natural polyphenols have potential therapeutic effects on colon-based diseases and gut microbial dysbiosis. However, the delivery of pure polyphenols to the colon has to overcome chemical instability, degradation, and metabolism in the upper gastrointestinal tract after oral ingestion. Dietary fibers have been exploited as microbiota-triggered release systems to protect polyphenols in the upper gut and specifically deliver them to the colon.

Scope and approach: This review focuses on the recent development of colon-targeted polyphenol delivery systems using encapsulation technologies based on dietary fibers for both food and pharmaceutical applications. The detailed characteristics and advantages of commonly used dietary fibers and the main mechanisms of encapsulation preparation are discussed. The challenges of targeting the colon and the colonic health benefits of polyphenols are elaborated. In addition, the scope for specific modulation of gut microbiota by the selective combination of polyphenol and dietary fiber is highlighted.

Key findings and conclusions: The microbial-triggered release mechanisms of dietary fiber-based delivery systems maintain the structural integrity and protect the polyphenols during passage through the harsh environment of the upper gastrointestinal tract to maximize their concentration in the colonic region. In addition, dietary fibers offer several advantages over other materials for polyphenol encapsulation and delivery, including strong dietary fiber-polyphenol binding interactions, high colonic mucoadhesion, and synergistic prebiotic effects from dietary fiber and polyphenol that result in health benefits for the colon and the body.

1. Introduction

Colon-targeted delivery systems have gained considerable interests in recent years for delivering drugs for the treatment of inflammatory bowel disease (IBD), a multifactorial intestinal disease with symptoms that include recurrent episodes of abdominal pain, severe diarrhea, bowel distension and vomiting, for which there is currently no permanent curative treatment (De Souza & Fiocchi, 2016; Kotla et al., 2018). The rationale of delivery systems that specifically target the colon is to prevent the loss of drug from chemical and biochemical degradation in the upper digestive tract and to allow for the delivery of high-concentration drug payload to the inflamed region of the colon to exert effective therapeutic outcomes (Amidon, Brown, & Dave, 2015; Kotla et al., 2018). In addition to pharmacotherapy that offers immediate relief from discomfort and symptoms, nutraceutical intervention has emerged as a promising strategy for the long-term treatment or prevention of IBD. These natural alternatives are expected to possess relatively less toxicity and fewer side effects than the pharmaceuticals used to treat the symptoms of the disease (Duda-Chodak, Tarko, Satora, & Sroka, 2015).

Polyphenols are a major group of phytochemicals found in various plants and plant-based products. These natural compounds have been an intense area of functional food research due to their potential health beneficial effects (anti-oxidative, anti-inflammatory, anti-carcinogenic properties, etc.) (Shahidi & Ambigaipalan, 2015). A significant number of studies have investigated the role of polyphenols specifically in colon health with an emphasis on the treatment of IBD and modulation of gut microbiota, as previously reviewed (Martin & Bolling, 2015; Serra, Almeida, & Dinis, 2018). Nonetheless, pure polyphenols can undergo extensive chemical degradation and modification in the upper gastrointestinal tract (GIT) after ingestion, which consequently reduce the final concentration of intact polyphenols that accumulate in the colon (Wang, Li, & Li, 2017). Therefore, developing suitable and safe delivery systems is essential to overcome these limitations. The colon-targeted delivery of polyphenols has several advantages, as follows: (i) the colon is the main region where IBD occurs, and the delivery of high concentrations of polyphenols with specific colonic bioactivity to the colon would ensure that they exert their intended therapeutic effects; (ii) colon-targeted delivery is considered a strategy for protecting the structural integrity of polyphenols to the target site; (iii) for

* Corresponding author.
E-mail address: ngkf@unimelb.edu.au (K. Ng).

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Abbreviations:

CD	cyclodextrin
CS	chitosan
DHPG	dihydroxyphenylglycol
EE	encapsulation efficiency
GI or GIT	gastrointestinal (GI) tract (GIT)
IBD	inflammatory bowel disease
IL:	interleukin
NF-κB	nuclear factor-kappa B
PEC	polyelectrolyte complexation
PEG	polyethylene glycol
PLGA	poly lactic-co-glycolic acid
SCFAs	short-chain fatty acids
TNBS	trinitrobenzene sulfonic acid
TNF-α:	tumor necrosis factor-α
TPP	tripolyphosphate
UC	ulcerative colitis

polyphenols that rely on microbial-mediated biotransformation in the colon to generate metabolites with stronger therapeutic potency, the protection of intact polyphenols in the upper digestive tract is desirable; and (iv) delivery systems can increase colonic polyphenol availability and permit decreases in the dose and dosing frequency in the treatment of IBD (Agüero, Zaldivar-Silva, Pena, & Dias, 2017; González et al., 2019; Martin & Bolling, 2015; Wang et al., 2017; Xiao, Cao, & Huang, 2017).

Nonetheless, the fact that the colon is located in the distal part of the digestive tract involves great challenges for colon-targeted delivery. In recent years, researchers have proposed several ideal formulations based on different release mechanisms, such as time-controlled, pressure/osmotic-controlled, and pH-sensitivity (Amidon et al., 2015). However, as some of these pharmaceutical materials are not considered food-grade, they may not be suitable for the use of dietary and nutritional supplements. In addition, these formulations are often associated with several limitations, such as highly variable interindividual differences in GI transit time, pH, and disease status (healthy *vs* intestinal disease condition), which may ultimately lead to imprecise and premature release or undesirably low local accumulation of encapsulated bioactive molecules in the colonic region (Kotla et al., 2018).

Dietary fibers are carbohydrate polymers with ten or more monomer units resistant to enzymatic hydrolysis in the human small intestine, and they are partially or completely fermented by colonic microflora (Jakobek & Matić, 2018). Dietary fibers can originate from either natural (both plant and animal origins) or synthetic sources that exhibit physiological health benefits, such as inulin, pectin, alginate, chitosan (CS), cyclodextrin (CD), and several gums (Jakobek & Matić, 2018; Padayachee, Day, Howell, & Gidley, 2017). These biodegradable biopolymers have high stability in the stomach, are low cost, and have abundant natural sources and may have the potential for the development of biocompatible oral delivery systems. Some dietary fibers have already been used as delivery materials to improve the *in vivo* bioavailability of poorly absorbed polyphenols, with an emphasis on absorption via small intestinal enterocytes (Fang & Bhandari, 2010; Liang et al., 2017). Considering their fermentable properties, the assembly of dietary fiber-based structures as encapsulation carriers may be used to construct microbial-triggered delivery systems that target the colonic region (Bermúdez-Oria, Rodríguez-Gutiérrez, Rubio-Senent, Lama-Muñoz, & Fernández-Bolaños, 2017). Dietary fibers offer several advantages over other materials for the encapsulation of polyphenols, including strong binding interactions with polyphenols, high colonic mucoadhesion, which would allow high concentrations of payload at the colonic surface, and potential synergistic prebiotic effects between fiber and polyphenols that may result in enhanced colonic health benefits (Debele, Mekuria, & Tsai, 2016; Fathi, Martin, & McClements, 2014; Jakobek & Matić, 2018; Xu, Xu, Ma, Tang, & Zhang, 2013).

The objective of this review is to summarize the recent advancements in colon-targeted polyphenol delivery systems using dietary fiber as an encapsulation carrier or as an enteric coating layer. The details of certain commonly used dietary fibers in delivery systems, their advantages and the main mechanisms for carrier fabrication are discussed. In addition, the challenges of targeting the colon and the colonic health benefits of polyphenols are elaborated.

2. Polyphenols and colon health

2.1. Polyphenols and inflammatory bowel disease (IBD)

IBD is a chronic and relapsing autoimmune disease of the human digestive tract that includes two primary variants of Crohn's disease and ulcerative colitis (UC). Typically, Crohn's disease is characterized by interrupted transmural inflammation located mainly in the ileum and colon, but it can occur in any region of the intestine, whereas UC is characterized by uninterrupted mucosal inflammation specifically in the colon (Abraham & Cho, 2009). The exact etiology of these recurring disorders remains largely unclarified, although Crohn's disease and UC are generally considered to result from the complicated interplay between personal genetic susceptibility, immune response, gut microbiota dysbiosis, and unfavorable environmental factors, such as poor diet and antibiotic use. Consequently, the loss of tolerance that characterizes the gut immune system induces uncontrolled inflammatory responses that lead to long-lasting mucosal injuries (De Souza & Fiocchi, 2016).

Polyphenols are major plant metabolites that possess potential preventive and therapeutic effects in the management of IBD (Valdés et al., 2015). Although direct evidence of positive effects from clinical intervention trials for the polyphenol-based treatment of human IBD is scarce, a large number of pilot studies have provided compelling evidence to support a positive role of specific polyphenols, such as curcumin, anthocyanins, resveratrol, quercetin and luteolin, or polyphenol-rich extracts in decreasing the risks of the disease and the onset and progression of IBD through numerous mechanisms (Martin & Bolling, 2015). One of these mechanisms involves the deactivation of crucial pro-inflammatory signaling cascades to downregulate the expression of several proinflammatory enzymes and cytokines, as well as an increase in the local antioxidant capacity in the colonic region to scavenge reactive oxygen species, neutralizing inflammation in colonocytes (Martin & Bolling, 2015; Serra et al., 2018). For example, proanthocyanidin-rich grape seeds reduced the incidence of colitis in a trinitrobenzene sulfonic acid (TNBS)-induced rat model by upregulating the anti-inflammatory activities of glutathione peroxidase and superoxide dismutase to defend the gut mucosa from attack and suppressing the levels of tumor necrosis factor-α (TNF-α), κB kinases and the nuclear factor-kappa B (NF-κB) pathway in colonic tissues (Wang et al., 2011). Curcumin and anthocyanins have also been shown to block NF-κB activity and to decrease the expression of the proinflammatory cytokine genes interleukin (IL)-12, TNF-α and interferon gamma in the mucosal cells of TNBS-induced mice (Piberger et al., 2011; Ukil et al., 2003). Luteolin decreased the activation of IL-8, cyclooxygenase-2, nitric oxide synthase, and the Janus kinase/signal transducer and activator of transcription pathway, which induced the expression of inflammatory genes in HT-29 cells (Nunes, Almeida, Barbosa, & Laranjinha, 2017).

Another proposed mechanism of action of polyphenols in IBD therapy is associated with the direct amelioration of gut microbiota derangement, which in turn, may normalize mucosal permeability and epithelial barrier function. Typically, gut inflammation is closely related to distinct alterations in the gut microbiota to some extent, either due to a change in diversity/population, the metabolic activity of the

microbiota or a combination of both (Danneskiold-Samsøe et al., 2019). Recent studies have reported that patients with IBD exhibit reductions in some Firmicutes and Bacteroidetes species, especially the Clostridium species *Faecalibacterium prausnitzii,* and an increasing level of Proteobacteria and Actinobacteria (Buttó & Haller, 2016). Polyphenols have been reported to possess a "prebiotic-like" effect due to their low host bioavailability and microbial metabolism in the colonic region, which promote the growth of specific anti-inflammatory gut microbial species while inhibiting the growth of pathogenic species (Duda-Chodak et al., 2015; Tomás-Barberán, Selma, & Espín, 2016). For instance, resveratrol supplementation in DSS-rat models increased the levels of beneficial bacteria of *Lactobacilli* and *Bifidobacteria* and reconstructed mucosal architecture, which was associated with enhanced mucosal permeability and epithelial barrier function (Larrosa et al., 2009). Several epigallocatechin gallate-rich teas increased the levels of *Lactobacillus* spp. and *Enterococcus* spp. while inhibiting the pathogen populations of *Bacteroides*, *Prevotella* and *Clostridium histolyticum* (Sun, Chen, Cheng, Zhang, Zheng, & Zhang, 2018).

2.2. Polyphenols and gut microbiota modulation

Polyphenols have long been known to possess high antioxidant activity and certain biological functions, such as anti-inflammatory effects, but recently, much attention has shifted towards their capacity to maintain gut microbial homeostasis (Valdés et al., 2015). As many studies have recently indicated a positive link between gut microflora and host health, the "actual" or "true" bioefficacy of polyphenols could be redefined because polyphenols not only exert biological functions at a systemic level but also are metabolized by colonic microbes. These resulting colonic metabolites alter the gut microbial profile, which can have a crucial role in human health through the newly appreciated effect of host-microbe interplay (Serra et al., 2018). As previously discussed, an imbalance in the profile and/or function of gut microflora, referred to as intestinal dysbiosis, is often correlated with a multitude of intestinal diseases (e.g., IBD and ulcers). Intestinal dysbiosis has also been found to link to the development of numerous systemic disorders, including obesity and related metabolic complications (Marques, Mackay, & Kaye, 2018), progressive neurological conditions, and other disorders associated with the gut-brain axis (Serra et al., 2018).

Upon reaching the colon, polyphenols are extensively degraded and metabolized by colonic microbiota (Tomás-Barberán et al., 2016). A large proportion of bacteria species beneficial to health, such as *Akkermansia* spp., *Prevotella* spp., *Roseburia* spp., and *Faecalibacterium* spp., have been found to be increased in response to the presence of polyphenols. As a result of colonic microbial biotransformation of polyphenols, the subsequently produced simple phenolic acids, including benzoic and vanillic acids, can be absorbed from colonocytes into the systemic circulation to exert their intended biological activities and increase overall antioxidant capacity in the colonic region (Cox & Blaser, 2013).

Polyphenol catabolic processes involve a series of microbial metabolic steps, including ring fission and cleavage, dehydroxylation, decarboxylation, racemization, and hydrogenation (Low, Hodson, Williams, D'Arcy, & Gidley, 2016). For instance, quercetin is metabolized and converted into protocatechuic acid by microbial dioxygenases via C-ring cleavage (Serra et al., 2012). *Clostridium coccoides* can metabolize ellagic acid via dehydroxylation to urolithins (García-Villalba, Beltrán, Espín, Selma, & Tomás-Barberá;n, 2013). Lunularin is the main colonic microbial metabolite of resveratrol, generated by *Slackia equolifaciens* and *Adlercreutzia equolifaciens* via a hydrogenation reaction (Bode et al., 2013).

In addition, polyphenols can influence the levels of microbial-

Table 1
Polyphenols with colon bioactivities and their stability and degradation in the GI system.

Polyphenol	Main colonic bioactivities	Chemical properties and gastrointestinal stability	Reference
Curcumin	Anti-colon carcinogenic effect Gut microbiota modulation Treatment of IBD	- Hydrophobic and water-insoluble - Low bioavailability - Rapid elimination from systemic circulation - Low chemical stability in GIT	(Beloqui et al., 2014; Davis and Brewster (2004)
Rutin	Gut microbiota modulation Treatment of IBD	- Hydrophilic (due to sugar moiety) and moderate water solubility - Low bioavailability (5.2–11.1% *in vitro*) - Relies on gut microbial biotransformation to liberate more bioactive quercetin aglycone	(Amaretti, Raimondi, Leonardi, Quartieri, & Rossi, 2015; D'Urso, 2017; Rabišková et al., 2012)
Icariin	Anti-colorectal cancer Therapy of ulcerative colitis	- Hydrophobic and water-insoluble - Low bioavailability (12% *in vivo* rat model) - Rapid elimination from systemic circulation - Relies on gut microbial biotransformation to liberate more potent metabolites including icarisde II, icaritin, *etc*	(Li et al., 2013; Shi et al., 2014; Wu, Kim, and Han (2016)
Anthocyanins	Anti-colon cancer activities Gut microbiota modulation Treatment of IBD	- Moderate solubility - Low bioavailability (5.1%; red wine) - Low chemical stability under neutral pH environment (small intestinal condition) - High chemical reactivity	(Flores et al., 2015; Lapidot, Harel, Granit, & Kanner, 1998)
Quercetin	Anti-proliferative effect on colon cancer cells Gut microbiota modulation Treatment of IBD	- Hydrophobic and water-insoluble - Low bioavailability (38%; shallots) - Undergoes extensive first-pass metabolism and rapid elimination in the upper GIT - Prone to auto-oxidation	(Park et al., 2005; Parkar, Trower, & Stevenson, 2013; Wiczkowski et al., 2008)
Oleuropein	Anti-colon carcinogenesis effect Treatment of IBD	- Hydrophilic and moderate water solubility - High bioavailability - Low chemical stability under acidic environment and rapid degradation by intestinal enzymes (lipase)	Carrera-González, Ramírez-Expósito, Mayas, and Martínez-Martos (2013)
Resveratrol	Anti-colon carcinogenesis effect Gut microbiota modulation Treatment of IBD	- Hydrophobic and water insoluble - Low bioavailability (< 1% *in vivo*) - Rapid systemic elimination - Undergoes dramatic metabolism in the enterocytes and hepatocytes after oral administration - Short biological half-life	(Bode et al., 2013; Cottart, Nivet-Antoine, Laguillier-Morizot, & Beaudeux, 2010; Matos et al., 2015; Samsami-kor, Daryani, Asl, & Hekmatdoost, 2015)

generated short-chain fatty acids (SCFAs) derived from the colonic fermentation of dietary fiber (Cox & Blaser, 2013). It is well documented that SCFAs are associated with human metabolic health and intestinal diseases, including IBD and microbial dysbiosis (Sun, Wu, Liu, & Cong, 2017). In addition to their role as a substrate for lipogenesis and gluconeogenesis, processes that promote energy harvest (SCFAs account for approximately 10% of the daily energy requirement), SCFAs such as butyrate are the preferred fuel utilized by colonocytes to promote the growth of healthy colonic cells. SCFAs also appear to play a vital role in regulating epithelial cell tight junctions, improving the mucosal permeability and epithelial barrier function (Cox & Blaser, 2013). Similar to some polyphenols, butyrate inhibits proinflammatory signaling pathways, including NF-κB and MAPK signaling, thereby suppressing inflammatory cytokine synthesis associated with IBD (Manco, Putignani, & Bottazzo, 2010). Furthermore, the acidic nature of SCFAs contributes to microbial homeostasis by maintaining a low lumen pH throughout the colon, which is unfavorable for the growth of some pathogenic bacteria such as enterohemorrhagic *Escherichia coli* (Cordonnier et al., 2017).

3. Factors affecting the delivery of polyphenols to the colon

Colon "targeting" generally refers to formulations that minimize the degradation, elimination and/or absorption of encapsulated compounds in the stomach and small intestine before reaching the lower parts of the digestive tract, which improves local delivery to the colonic region (Kotla et al., 2018). Nonetheless, since the colon is positioned at the distal region of the digestive tract, the development of a delivery system that survives the passage to this specific region is challenging. In the design of colon delivery systems for polyphenols, possible factors, including the GI stability of specific polyphenols, physiological barrier of the colon, and properties of the encapsulation material, need to be carefully considered.

3.1. Gastrointestinal stability of polyphenols

It is well established that polyphenols have low oral bioavailability, with only 5–10% absorption of the pure form in the upper GIT (Table 1); many promising solutions relying on nano/microencapsulation have been developed to increase the absorption efficiency of polyphenols by improving their dissolution rates and solubility (Fang & Bhandari, 2010). Conversely, colon-targeting formulations would need to be able to prevent or reduce the release and loss of polyphenols in the upper GIT, and the liberation of payload should be induced once the carrier enters the colon (Wang et al., 2017). Notably, although most polyphenols are largely unabsorbed and eventually accumulate in the colon as a result of their poor solubility, polyphenols can undergo extensive degradation and metabolism in the stomach and small intestine (Table 1), which significantly reduces the final concentrations of parent polyphenols that accumulate in the colon (Wen, Hu, Li, Zong, & Wu, 2018). For instance, β-glucosidases present on the small intestine brush border hydrolyze glucosidated phenolic compounds into more readily absorbable aglycones, which may then undergo further modifications by phase 1 and/or phase 2 metabolism inside the enterocyte (Chiou et al., 2014). Some pH-sensitive polyphenols may be rapidly eliminated or cleared upon consumption. For example, anthocyanins are rather stable under acidic conditions but are chemically unstable at higher pH. This leads to the early elimination or modification of anthocyanins due to the instant shift in pH from the stomach to the small intestine, and consequently to the low concentration of intact anthocyanins reaching the colon (Flores et al., 2015). Resveratrol is another easily oxidizable and eliminated phenolic compound in the upper GIT (Matos, Gutiérrez, Iglesias, Coca, & Pazos, 2015).

Although the majority of polyphenol aglycones are bioactive in the gut, some require gut microbial biotransformation to form derivatives with stronger bioactivities (Martin & Bolling, 2015). For example, clinical evidence shows that the bioefficacy of isoflavones is significantly related to the metabolism of isoflavones into the more potent equol by gut bacteria (Yuan, Wang, & Liu, 2007).

3.2. Gastrointestinal physiological factors

The large intestine in humans is physically arranged into the ascending, transverse, and descending colon located at the distal end of the digestive system, and the final segment is attached to the rectum (Date, Hanes, & Ensign, 2016). The primary function of the large intestine is to absorb remaining undigested nutrients and water coming from the small intestine and to store waste products until excretion. Physiologically, the colon is notably different from other parts of the digestive system; the colon possesses a neutral pH, a longer material transit time, higher material viscosity due to the low volume of luminal fluids, a thick mucus layer, and the presence of a large number of diverse gut microflora (Amidon et al., 2015). All these factors present obstacles in the preparation of delivery systems targeted to the colonic

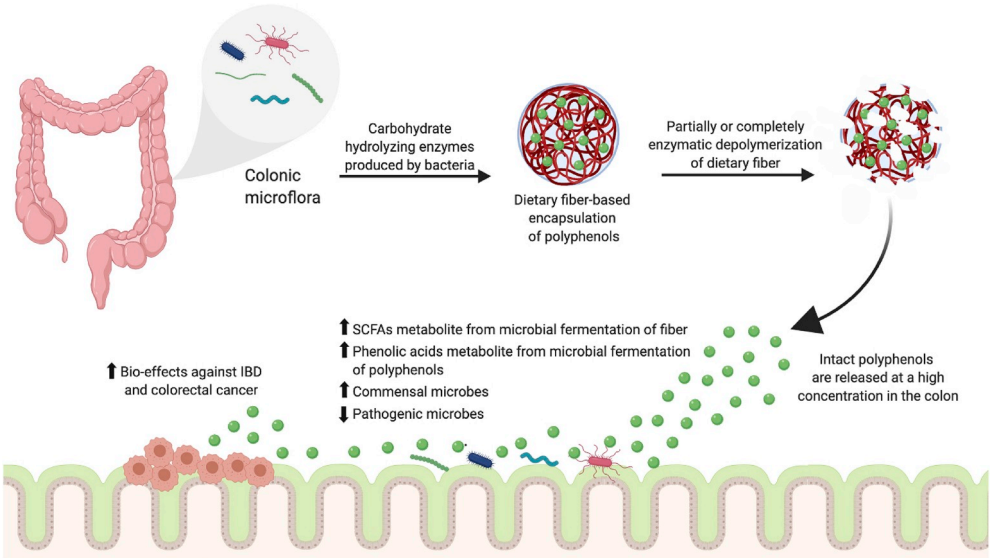
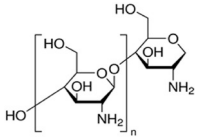
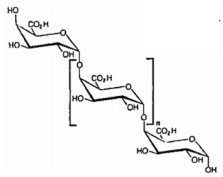
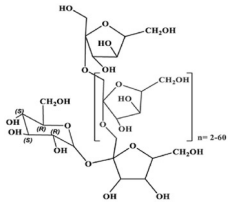
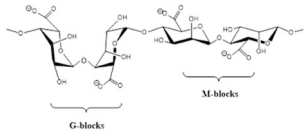
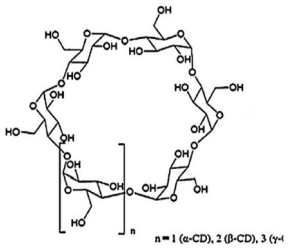
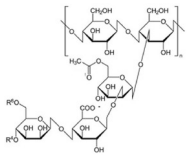
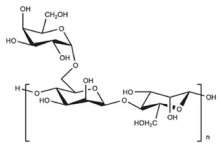


Fig. 1. Mechanism of colonic release of encapsulated polyphenol and biological effects based on a dietary fiber-based polyphenol delivery system. SCFAs: Short-chain fatty acids. IBD: Inflammatory bowel disease.

site. For example, when oral ingestion is chosen for IBD therapy, the encapsulation vehicles experience progressive pH variation as they pass through the GI systems, beginning with the highly acidic stomach (pH ~1–4) to the alkaline small intestine (pH ~6.5–7.5), and finally to the alkaline colonic (pH ~6–7.2) region (Kotla et al., 2018). Another obstacle for effective oral colon delivery is the thick mucus layer and highly viscous colonic luminal contents that may impede targeted delivery to the colonic surface and limit the penetration of nutrients through the absorption membrane (Date et al., 2016).

The formulation must withstand gastric environmental stress (physical agitation in the stomach, rapid change in pH between the stomach and small intestine, digestive enzymes, and emulsifying bile salts) and pass through the small intestine to reach the lower parts of the digestive tract. In this regard, to maintain the integrity of the formulation in the upper GIT and to allow for the precise delivery of encapsulated compounds to the colon, researchers have proposed several activation mechanisms of the formulations that respond to physiological variations and are specifically related to colon targeting. Nonetheless, many of these delivery systems, such as time-controlled, pressure/osmotic-controlled and pH-sensitive material release systems, are typically used for medical purposes and are therefore not suitable for the use of dietary and nutritional supplements. In addition, pharmaceutical systems are often associated with several limitations, such as highly variable interindividual differences in GI transit time, pH, and disease status, that may ultimately lead to imprecise/premature release or low local accumulation of drug payload in the colonic region (Amidon et al., 2015). Alternatively, researchers have developed microbial-induced delivery systems by considering the diverse gut microflora community. The colon is the predominant GI region for dietary interventions regarding gut ecology since the colon is the most heavily colonized region, with a total population of 10^{11}–10^{12} CFU/mL compared to 10^{1}-10^{2} and 10^{3}–10^{4} CFU/mL in the stomach and small intestine,

Table 2
Chemical, release and degradation properties of major dietary fibers used in colon-targeted polyphenol delivery systems.

Dietary fiber	Properties	Charge	Reference
Chitosan 	- Water-insoluble - Stable in alkaline environment - Partially degradable by colonic bacteria (especially by *Bifidobacterium* and *Lactobacillus* spp.)	Cationic	George and Abraham (2006)
Pectin 	- Water-soluble - High water holding property - Fully degradable by colonic bacteria (especially by Bifidobacteria, clostridia, and eubacteria)	Anionic	Liu, Fishman, Kost, & Hicks. (2003)
Inulin 	- Water solubility is associated with the polymer chain length - Stable in acidic environment - Fully degradable by colonic bacteria (especially by *Bifidobacterium* and *Lactobacilli*)	Non-ionic	Gupta et al. (2019)
Alginate 	- Water-soluble - Stable in acidic environment - High water holding property - Susceptible to chemical degradation at the higher pH of the small intestine and colon - Fully degradable by colonic bacteria	Anionic	Agüero et al. (2017)
Cyclodextrins 	- α-CD: soluble in water; β-CD and γ-CD: insoluble in water - Strong structural integrity - Neither hydrolyzed nor absorbed from upper GIT - Fully degradable by colonic bacteria (especially *Bacteroides*)	Non-ionic	(Fetzner et al., 2004; Zafar et al., 2014)
Xanthan gum 	- Water-soluble - High hydration and swelling property - Fully degradable by colonic bacteria (especially by *Bacillus* spp.)	Anionic	(Caddeo et al., 2014; Petri, 2015)
Guar gum 	- Water-soluble - High hydration and swelling property - Fully degradable by bacteria (especially by *Bacteroides*, *Bifidobacterium*)	Non-ionic	Kumar et al. (2018)

respectively. (Kotla et al., 2018). The gut microflora is mainly composed of strict anaerobes that express various hydrolytic and reductive metabolic enzymes to break down unabsorbed nutrients, mainly dietary fibers, resistant starch and protein (Amidon et al., 2015). In this view, dietary fibers have been found to be a novel biomaterial for colon-targeted delivery systems, as fibers can act as a "substrate" for enzyme-mediated degradation that predominately occurs in the colonic region (Fig. 1) and are not dependent on GI transit time or pH change as mechanisms to induce release.

4. Dietary fiber-based colon-targeted delivery systems for polyphenols

4.1. Advantages of dietary fiber for colon-targeted delivery

Substantial investigations have been conducted in the area of delivery systems for drugs, bioactive phytochemicals or nutraceuticals that target the lower parts of the digestive tract by using encapsulation carriers based on several natural and synthetic polymers (Amidon et al., 2015; De Vos, Faas, Spasojevic, & Sikkema, 2010). In particular, dietary fiber remains a promising biomaterial as a building block for oral delivery systems due to its many favorable characteristics, such as its stability in the stomach, biodegradability, biocompatibility, low toxicity, low cost, and abundance from natural resources (Debele et al., 2016; Fathi et al., 2014; Jakobek & Matić, 2018; Xu et al., 2013). The following section focuses on additional advantages that are particularly important for colon-targeted delivery systems for polyphenols, including strong binding interactions with polyphenols, remarkable crosslinking capacity (discussed in section 4.2), synergistic prebiotic effects, and mucoadhesion. The chemical and degradation properties of commonly used dietary fibers are summarized in Table 2.

4.1.1. Binding interaction with polyphenols

It is known that phenolics are tightly bound to dietary fibers in fruits and plants as solvent extractable (non-covalently linked) and non-extractable (covalently linked) phenolics (Padayachee et al., 2017). Most plant food phenolics are protected by dietary fiber, bypass the upper GIT regardless of the low pH and presence of various digestive enzymes, and reach the colon where colonic bacteria enzymes release these bound phenolics by unraveling the fiber structures (Pérez-Jiménez, Díaz-Rubio, & Saura-Calixto, 2013). Jakobek and Matić (2018) summarized the driving factors for the strong associations between extractable phenolics and fibers as mainly being due to non-covalent binding interactions that include hydrogen bonding, *van der Waals* forces, and hydrophobic interactions. Moreover, environmental influences (e.g., acidity, surrounding temperature, and ionic strength) can have a significant impact on the amount of polyphenols that bind to dietary fibers. The covalent bonds of esters also contribute to strong bonding (Bermúdez-Oria, Rodríguez-Gutiérrez, Rodríguez-Juan, González-Benjumea, & Fernández-Bolaños, 2018). Electrostatic interactions between plant cell wall fibers and polyphenols occur naturally (Padayachee et al., 2017). For example, negatively charged plant cell wall fibers have a strong binding affinity for positively charged cyanidin-3-glucoside (Phan, Flanagan, D'Arcy, & Gidley, 2017). Although the detailed structural relationship is still not fully clarified, it seems that the existence of certain functional groups (hydroxy, methyl, and galloyl moieties), molecular size, and the number of aromatic rings of polyphenols affect the strength of polyphenol-fiber binding interactions. For dietary fibers, the degrees of saturation and aggregation, configuration, and molecular size are essential characteristics in these interactions. These strong interactions may limit the accessibility of polyphenols from plant foods in the stomach and small intestine. This concept is known as bioaccessibility, which is defined as the amount of a specific compound released from the food matrix/delivery system in the GI system that becomes ready for absorption. The process of absorption includes transforming the compounds into material suitable for assimilation and presystemic metabolism (Carbonell-Capella, Buniowska, Barba, Esteve, & Frígola, 2014). The diminished bioaccessibility would thus decrease the quantity of phenolics absorbed by small intestinal enterocytes and prevent them from reaching the systemic circulation to be fully utilized in the body, which refers to their bioavailability (Jakobek & Matić, 2018).

Therefore, approaches exploiting the strong binding affinity between dietary fibers and pure phenolic compounds have been used to prepare specific fiber-based controlled-release systems. The complexes derived from dietary fibers can be a type of control carrier to protect the encapsulated polyphenols during passage through the stomach and small intestine and to be released in the colon where the polyphenols can exert their biological effects and metabolic influence on the gut bacteria. The binding affinity between the encapsulation material and the bioactive compounds is a crucial parameter that directly influences the encapsulation efficiency (EE), loading capacity, and delivery performance of a formulation. The EE is defined as the percentage of compounds of interest that is successfully loaded into the particles, and the loading capacity reflects the quantity of compounds delivered per quantity entrapped (Zhang et al., 2012).

4.1.2. Prebiotic effect

Apart from strong binding interactions with polyphenols, dietary fibers as encapsulation biomaterials that are co-delivered to the colonic region can exert biological functions of their own to shape the gut microenvironment. Dietary fibers inherently function as prebiotics and generate metabolized products of SCFAs upon gut microbial fermentation (Xu et al., 2013). As previously discussed, the resulting SCFAs are associated with various aspects of human metabolic health and intestinal diseases, including IBD and dysbiosis, by regulating gut microbial homeostasis and epithelial cell tight junctions and by inhibiting several critical proinflammatory signaling pathways, thereby suppressing the inflammatory cytokine synthesis associated with colonic diseases (Cox & Blaser, 2013; Sun, Wu et al., 2017). Together with polyphenols, the formulation may mediate a synergistic effect in gut microbial modulation, which is another reason to consider dietary fibers as a biomaterial in the delivery of polyphenols to the colonic region.

4.1.3. Colonic mucoadhesion

It is crucial that the polyphenols delivered to the colon adhere to mucosal surfaces for an adequate period of time to maximize their oral effectiveness and bioactivities (Date et al., 2016). Some dietary fibers such as CS, alginate, and pectin are classified as excellent mucoadhesive agents, as they can facilitate the adhesion of delivery systems to the gut mucosal layer and therefore prolong the residence time of the corresponding polyphenols released in the colon. In most studies, the mucoadhesion strength of formulations is typically determined by their zeta potential value, an important parameter describing the electrostatic interactions between the mucoadhesive particle and intestinal mucosa (Bogataj et al., 2003). The inflamed mucosa in IBD is usually accompanied by a positively charged mucosal surface as a result of the accumulation of positively charged proteins (i.e., transferrin and antimicrobial peptides), providing a molecular target for a delivery system with an overall negative surface. The alginate-based system, for example, allows the release of polyphenols in response to microbial degradation of alginate in the region of inflammation (Zhang et al., 2015). The positive charge of CS, in contrast, permits contact with naturally occurring negatively charged protein groups that are expressed on the healthy epithelium (Madureira, Pereira, & Pintado, 2015). In all cases, the binding of the delivery system to the colonic mucosa should increase the local polyphenol availability and permit reductions in dose and dosing frequency. This advantage is particularly important when the formulation is used for the treatment of IBD because in most *in vivo* animal studies, a large dose of individual polyphenols is often required to be effective, but the finding may not be translatable or relevant to

human consumption, as it is not feasible to consume such a large quantity of polyphenols in a typical diet, even when a specific polyphenol is administered as a supplement (Martin & Bolling, 2015). The reason for the high dose may be due to the low colonic concentration of the bioactive parent polyphenol as a result of complex digestive factors (i.e., extensive metabolism or elimination) along the GIT. Delivering specific polyphenols to the colon with the minimum dosage required to be effective is necessary for an ideal delivery system, and dietary fibers are excellent candidates as materials to fulfill these requirements.

4.2. Main mechanism for the preparation of dietary fiber-based polyphenol encapsulation structures

Dietary fiber-based encapsulation structures with varying functional properties and sizes have been used to develop several biomaterials in different forms, including capsules, tablets, beads, fibers, sponges, and enteric coating layers with other formulations (e.g., the pharmaceutical Eudragit® formulation). Although the critical size that distinguishes microparticles from nanoparticles is still a debated concept, it is generally accepted that nanoparticles refer to a spherical particle diameter of 100 nm as the upper size limit, but the determination of micro/nanoparticle is also highly dependent on other factors, including the physicochemical and functional characteristics of the specific type of material (Joye & McClements, 2014). Terms such as micro/nanosphere, micro/nanohydrogel, micro/nanoemulsion, micro/nanoliposome and micro/nanomicelles are used according to the nature of the encapsulation vehicle, particle size, and bioactive agents involved in the delivery system. For further extensive discussion, we refer the reader to a more complete review of polyphenol encapsulation technology (Fang & Bhandari, 2010). Regardless of the encapsulation method used, the mechanisms underlying the synthesis of dietary fiber-based encapsulation structures are primarily classified as polyelectrolyte complexation, covalent crosslinking, ionotropic crosslinking, and self-assembly (Fig. 2) (Debele et al., 2016; Liu, Jiao, Wang, Zhou, & Zhang, 2008).

4.2.1. Polyelectrolyte complexation

Polyelectrolyte complexation (PEC) is primarily formed through direct electrostatic interactions between at least two oppositely charged groups of molecules (Fig. 2a). The common driving force of PEC formation can be induced between the charged components of polyphenols and an oppositely charged dietary fiber. Alternatively, neutral polyphenols may be entrapped or absorbed within a complex formed by the coacervation of positively and negatively charged dietary fibers (Fathi et al., 2014). Noncovalent interactions between polyphenol and dietary fiber, as previously discussed, may also strengthen the PEC process (Fathi et al., 2014). Unlike ionic crosslinking, the interaction in PEC is between two biopolymers with a “broad” molecular range. For instance, the amino group of positively charged CS can form a polyelectrolyte complex with the carboxyl group of alginates, in which polyphenols are encapsulated for delivery to the colon (Wen et al., 2018). Similarly, other negatively charged dietary fibers, such as pectin and some gums, are used for this purpose (Andishmand, Tabibiazar, Mohammadifar, & Hamishehkar, 2017; Udompornmongkol & Chiang, 2015). Polysaccharide-protein/peptide-derived complexes have also been prepared for the delivery of other bioactive compounds, as reviewed by Wei and Huang (2019).

4.2.2. Ionic crosslinking

Ionic crosslinking represents an advantageous alternative to PEC methods due to the simple and mild preparation using noncytotoxic and biocompatible crosslinkers. The main mechanism of particle synthesis is based on the electrostatic interactions between the dietary fiber and ionic crosslinkers with opposite charges, such as the polyanionic tripolyphosphate (TPP) and divalent cations (e.g., calcium and zinc), which have the tendency to form matrix gel structures via ionic

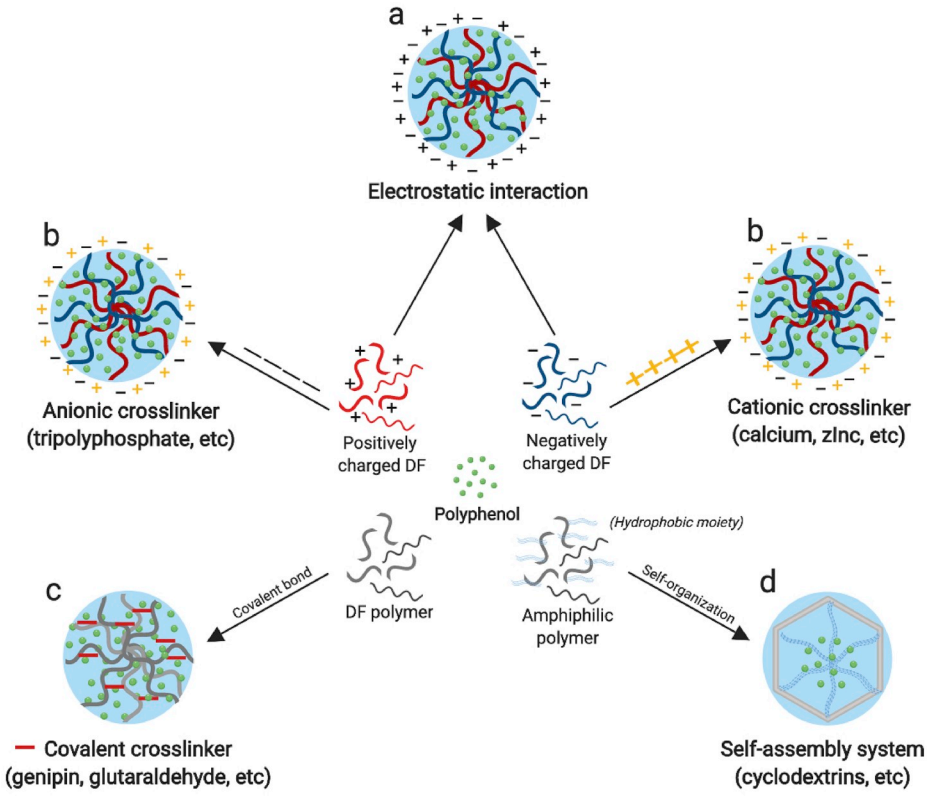


Fig. 2. Schematic representation of the formation of dietary fiber (DF)-based structures for polyphenol encapsulation: (a) Polyelectrolyte complexation, (b) Ionic cross-linking, (c) Covalent cross-linking, (d) Self-assembly system.

Table 3
Overview and biological activities of common dietary fiber-based colon-targeted polyphenol delivery systems.

Polyphenol	Dietary fiber(s) involved	Delivery forms	Main colon targeted performance and bioactivities	Reference
Quercetin	Chitosan/Alginate	Electrospun nanofiber mat	- Efficient controlled release of ~73% loaded quercetin in simulated colonic fluid - Antioxidant activity of loaded quercetin was as effective as free quercetin - Formulation demonstrated anti-proliferation of colorectal cancer Caco-2 cells	Wen et al. (2018)
	Guar gum	Matrix tablet	- *In vitro* study showed retarded liberation of quercetin (12.4–15.4%) in upper GI conditions after 5 h of incubation - After 24 h, up to 94.27% of encapsulated quercetin was released	Singhal et al. (2011)
	Chitosan/Xanthan gum	Microparticle tablet	- Low protective effect under acidic environment (60% quercetin released at pH 2) - Additional Eudragit®-coated tablet: 27% released at pH 7.4 after 24 h	Caddeo et al. (2014)
Icariin	Chitosan/Alginate	Microspheres	- 10% icariin was released in simulated upper GI fluid after 2 h; 65.6% was released in colonic fluid after 24 h *in vitro* - *In vivo* study showed an improved colonic residence time of icariin - TNBS-rats treated with the formulation showed a reduction in the expression of TNF-α, IL-6 and IL-1β	Wang et al. (2016)
Anthocyanins	Chitin/Ethyl cellulose	Microspheres	- Effective protection for anthocyanins in the gastric environment (less than 30% was released) - 85% anthocyanins were released in the colonic condition *in vitro*	Wang et al. (2017)
	Cyclodextrins	Inclusion	- Partially slowed down the degradation of anthocyanins in the upper GI conditions *in vitro* - Improved the growth of domain bacteria and inhibited the growth of C. *histolyticum* group after 24 h of incubation	Flores et al. (2015)
	Pectin amide/ Maltodextrin	(1) Ca-pectin hydrogel; (2) Shellac-coated pectin/ maltodextrin capsule	- Both systems showed controlled release of anthocyanins in colonic conditions by approximately 20% compared to the non-encapsulated anthocyanins *in vitro*	Oidtmann et al. (2012)
	Pectin amide	Shellac-coated pectin amide beads	- Formulation showed a slightly retarded release of anthocyanins in a simulated upper GI condition and restarted release in the colon, as compared to the non-coated system	Oehme et al. (2011)
Curcumin	Guar gum	Eudragit®-coated liquisolid tablet	- Majority of curcumin released (86.4%) in the colon conditions *in vitro* - Liquisolid technology improved the dissolution of curcumin - *In vitro* cytotoxicity study showed that the curcumin-loaded formulation showed more potent anti-colon cancer effects on HCT-15 compared to free curcumin - *In vivo* pharmacokinetic model showed that the curcumin-loaded formulation delayed t_{max} and prolonged residence time of curcumin in colonic region	Kumar et al. (2018)
	Chitosan/Alginate	Hyaluronic acid-PLGA nanoparticle embedded in hydrogel	- 57.6% curcumin released after 24 h; 89.7% released after 48 h *in vitro* - Protected against mucosal damage; reduced expression of CD98 and TNF-α *in vitro* - Hyaluronic acid-functionalized system increased the cellular uptake of nanoparticles and helped relieve DSS-induced UC in mouse model	Xiao et al. (2016)
	Chitosan/Gum Arabic	Nanospheres	- Less than 2% and 76% of curcumin was released in simulated upper GI and colonic medium, respectively - Curcumin-loaded nanoparticles showed more potent anti-colon cancer activities against HCT116 and HT29 than free CU due to improved cellular uptake - Curcumin-loaded nanoparticles efficiently induced cell apoptosis, suggesting that the system might be beneficial in colorectal cancer therapy - MTT assay indicated the non-toxicity of the carrier	Udomporn mongkol and Chiang (2015)
	Alginate	Eudragit®-coated beads	- Prevented early release in the upper GI condition; over 60% loaded curcumin was released in the colonic region within 12 h *in vitro* - Effective cytotoxic activity against HT-29 cells with an IC_{50} of 10 μg/mL	Sookkasem et al. (2015)

(*continued on next page*)

Table 3 (*continued*)

Polyphenol	Dietary fiber(s) involved	Delivery forms	Main colon targeted performance and bioactivities	Reference
Resveratrol	Pectin	Ca-pectinate beads	- Lowest disease activity index (assessment of the severity of UC) was recorded in rats treated with the formulation	Abdin (2013)
	Chitosan/Pectin	Nanoparticles	- Slightly controlled release of resveratrol in the simulated colonic region (~49%)	Andishmand et al. (2017)
	Pectin	Ca-pectinate beads	- ~97% loaded resveratrol retained in the system after 6 h of incubation in simulated gastric fluid *in vitro* - Polyethyleneimine was found to strengthen the crosslinking capacity of the system with higher encapsulation efficiency and showed controlled release properties (more than 80%) in the colon *in vivo*	(Das et al., 2011a; Das & Ng, 2010; Das & Ng, 2010a)
	Pectin	Zn-pectinate beads	- Zinc was a better ionic crosslinking agent than calcium, which influenced the overall resveratrol EE (up to 98%) - Glutaraldehyde was found to be an excellent crosslinking agent to prepare delivery systems with higher stability and controlled release properties in both *in vitro* and *in vivo* models	(Das et al., 2010, 2011; Das & Ng, 2010b)
	Chitosan/Pectin	Zn-pectinate beads	- *In vivo* pharmacokinetics showed a high plasma concentration of resveratrol after ingestion for 9 h, indicating a successful delivery to the colon	Das et al. (2011b)
Oleuropein	Sodium alginate	Nanoparticles	- The single-unit system decreased the bioaccessibility of oleuropein in the upper GI condition and controlled release in the colonic region (90%) - Potential higher colonic bioavailability of oleuropein	González et al. (2019)
	Inulin	Nanoparticles	- The formulation showed the diminished bioaccessibility of oleuropein in simulated upper GI conditions	Pacheco et al. (2018)
Hydroxytyrosol (HT); 3,4-dihydroxy Phenylglycol (DHPG)	Pectin/Alginate	Hydrogel beads	- Amidated pectin showed the highest binding capacity with polyphenol, especially HT, which influenced the encapsulation efficiency - DHPG was highly immobilized by system (70–80%) after 2 h of incubation *in vitro*, indicating a successful delivery to the colon	Bermúdez-Oria et al. (2017)
3,4-dihydroxy phenylglycol	Pectin/Alginate	Hydrogel beads	- Molecular studies showed that both covalent and noncovalent bonds contributed to the strong interactions between dietary fibers and polyphenols - Antioxidant activity of the loaded DHPG remained effective	Bermúdez-Oria et al. (2018)
Rutin	Chitosan/Alginate	Pellets	- The system showed a low release of rutin in the upper GI condition (12–14%) and controlled release in the lower GI condition (87–89%) *in vitro* - *In vivo* administration of formulated rutin (10 mg/kg) showed a reduction in neutrophil infiltration from the inflamed colons of TNBS control rats	Rabišková et al. (2012)

interactions between the charged dietary fibers (both cations and anions) from the polymer-polymer interactions mediated via the crosslinkers (Fig. 2b). For instance, TPP has been used to crosslink CS, and calcium and zinc have been used to crosslink pectin polymers for the colon-specific delivery of quercetin and resveratrol, respectively (Das, Ng, & Ho, 2010; Wen et al., 2018). Alginate-based gels are generated via the guluronic acid blocks of adjacent polysaccharide chains with cationic crosslinkers (Debele et al., 2016). However, the instability and reversible nature of ionic-induced particles are major problems that hinder their use in colon-targeted delivery systems. The unexpected loss or outward flux of crosslinking ions as a result of the dissolution and swelling of particles may lead to the structural collapse of the delivery carrier in the upper GIT. Unlike covalently crosslinked particles, ionically induced complexes are typically pH-sensitive, a welcome characteristic for systems aiming to deliver polyphenols to the stomach or small intestine but not for specific delivery to the colonic site. Nonetheless, this limitation can be overcome by using combination strategies with additional PEC or crosslinkers to form a more stable and rigid matrix structure that can withstand the mechanical and swelling properties of ionic crosslinkers. In fact, most reported colon-controlled delivery systems for polyphenols often involve more than one mechanism to reinforce high yield and encapsulation capacity. For instance, the quality of icariin-loaded microspheres prepared by calcium-induced gelation of alginate was further improved by a PEC technique with CS using glutaraldehyde as a covalent crosslinker prior to freeze-drying dispersion (Wang, Wang, Zhou, Gao, & Cui, 2016).

4.2.3. Covalent crosslinking

Another method to form dietary fiber-based structures for polyphenol encapsulation is through covalent crosslinking, which takes place upon the introduction of covalent crosslinkers such as genipin, glutaraldehyde, and formaldehyde to bond with polymeric chains of fiber (Fig. 2c). In covalently crosslinked structures, covalent bonds are the primary driving force in the formation of matrix structures, although naturally occurring noncovalent interactions may also be present (Debele et al., 2016). This mechanism of formation may be particularly suitable for colon-targeted delivery systems due to their capacity to form a rigid matrix structure where polyphenols can be efficiently encapsulated without being dissolved in the marked variation in pH and the long transit time from the upper to the lower parts of the GIT. For example, colon-targeted pectin-glutaraldehyde microparticles allow for the relatively robust encapsulation of resveratrol because of the stronger reactivity and higher crosslinking efficiency of the crosslinker than microparticles synthesized by ionic crosslinking methods (Das & Ng, 2010b). However, the use of such covalent bond-forming crosslinkers is often avoided in many food applications due to potential undesirable reactions with bioactive substances and the potential toxicity that may result in adverse health consequences. For example, glutaraldehyde is highly toxic and may have irritating effects (Wang et al., 2017).

4.2.4. Self-assembly system

In this method, each element (i.e., molecules, polymers, and atoms) spontaneously connects in a manner that leads to the self-organization of these elements into a complex structure (Fig. 2d). This self-assembly process occurs through intramolecular and/or intermolecular interactions between the hydrophobic and hydrophilic components of the polymers. When hydrophilic polymers are grafted onto hydrophobic moieties, an amphiphilic copolymer is generated. In an aqueous environment, amphiphilic polysaccharides typically form self-assembled structures featuring hydrophobic center cores surrounded by a hydrophilic outer shell (Park, Saravanakumar, Kim, & Kwon, 2010). CD, a type of dietary fiber obtained from the intramolecular transglycosylation of starch, is an example of a self-assembly system that has been widely used in the fields of medicine and functional foods (Ryzhakov et al., 2016). In particular, the hydrophobic inner cavity of β-CDs has been recognized as a promising delivery carrier for hydrophobic/amphiphilic compounds such as anthocyanins; the pH-sensitive polyphenols included in the complexes are protected by the surrounding hydrophilic outer shell from the adverse environment in the upper GIT, allowing the polyphenols to be released intact in the colonic region (Flores et al., 2015; Layre, Volet, Wintgens, & Amiel, 2009).

4.3. Characterization of dietary fiber-based polyphenol delivery systems and their bioactivities in the colonic region

4.3.1. Chitosan

CS, derived mainly from chitin via alkaline deacetylation, is a linear polymeric fiber of animal origin with a high molecular weight. CS-derived encapsulation structures have been prepared as oral delivery vehicles for natural nutraceuticals, especially polyphenols, to enhance bioavailability (Fang & Bhandari, 2010; Liang et al., 2017). Briefly, the cationic polyelectrolyte property of CS offers a robust electrostatic interaction with the negatively charged mucosal surface. This interaction allows the nanoparticles to adhere to the small intestinal mucosal surface for a prolonged time, which improves the targeted polyphenol release and local concentration that enhances absorption and bioavailability upon oral administration. CS has acetyl, hydroxyl and amino functional groups that provide strong noncovalent interactions with polyphenols to improve the EE. For example, apple polyphenols have a strong binding affinity with CS mainly through hydrogen bonding (with hydroxy and amino groups) and hydrophobic interactions (with acetyl

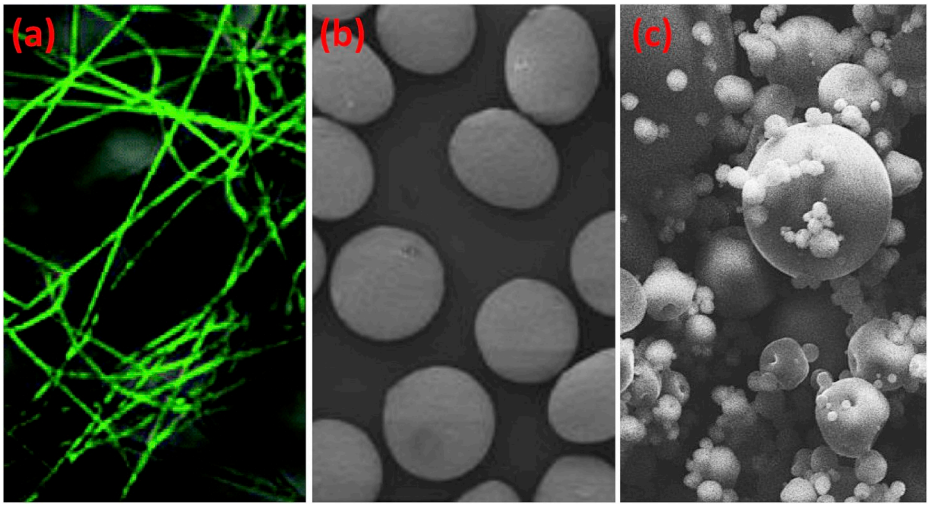


Fig. 3. Encapsulation structures prepared by the following different methods: (a) CLSM image of electrospun fibers by electrospinning (modified from Wen et al., 2018. With permission), (b) SEM image of chitin microspheres by freeze-drying (modified from Wang et al., 2017. With permission), and (c) SEM image of olive lead extract-sodium alginate particles by spray-drying (modified from González et al., 2019. With permission).

group) (Sun, Sun, Chen, Niu, Yang, & Guo, 2017). Furthermore, CS alone has therapeutic effects on IBD and colon cancer, another welcome trait for colon-targeted formulations (Azuma, Osaki, Minami, & Okamoto, 2015). Despite these advantages, CS is inherently pH-sensitive and soluble only at low pH. The application of CS for colon-controlled delivery often involves a multilayered strategy that protects the encapsulated polyphenols in the acidic conditions of the stomach. The degradation of CS occurs in the colon due to the actions of microbial enzymes, mainly glucuronidases, glycosidases, chitosanase, and chitin deacetylase (George & Abraham, 2006; Zhang & Neau, 2002).

Currently, several CS-based encapsulation nanocarriers (i.e., hydrogels, pellets, or spheres) have been prepared by employing different protocols for the colon-targeted delivery of polyphenols (Table 3). PEC is one of the most commonly used methods, and a PEC composed of CS and negatively charged alginate was employed as an outer coating layer for pellets loaded with rutin with an EE of 93–95% (Rabišková et al., 2012). The formulation prevented the premature liberation of rutin under conditions simulating the upper GIT, followed by an abrupt release of the payload (87–89%) in the colonic condition. The mechanism by which rutin was protected in the gastric environment was through the swelling of hydrophilic sodium alginate in the low pH condition, which formed viscous hydrogels that minimized its release from the pellets. Additionally, CS is not dissolved in the upper GIT and is sensitive to microbial degradation in the colonic region. The mucoadhesive nature of CS was able to promote the effectiveness of rutin at the site of inflammation in the colon, as evidenced by the ameliorated clinical activity score in TNBS-induced colitis rats (Rabišková et al., 2012).

In addition to preparation with PEC alone, CS-alginate complexes have also been prepared by the combination of ionic crosslinking and PEC (so-called layer-by-layer or multilayer systems) for IBD or colon cancer therapy. Recently, Wen et al. (2018) investigated the use of CS-alginate nanofibers (Fig. 3a) constructed by coaxial electrospinning in the colon-specific delivery of quercetin, a flavonoid with strong colon carcinogenic effects but low oral bioavailability due to its low water solubility and rapid elimination from the body due to first-pass metabolism. The authors first prepared sodium TPP ionic crosslinked CS microstructures to encapsulate quercetin. Afterwards, the structure was further improved by the PEC method with additional sodium alginate to form electrospun fiber mats. *In vitro* experiments demonstrated that electrospun fiber mats released quercetin in a controlled manner in the simulated colonic environment (73%) by the enzymatic action of bacterial glucosidases that degraded the fibers. The delivery system exhibited a strong mucoadhesive property due to CS, which aided in prolonging the residence time of the carriers and in the release of quercetin at a specific region in the GIT. These effects contributed to a marked inhibitory effect on colon carcinogenesis in this study using Caco-2 cells. Notably, the EE of the system was determined to be 92.2%, with a particle size, zeta potential and loading efficiency of 188.3 nm, +33.2 mV and 11.53%, respectively (Table 4). In addition, it is important to note that the encapsulation system should not affect the antioxidant activity of loaded polyphenols, as the local antioxidant activity at the colonic site is one of the primary mechanisms directly against the inflamed mucosal tissue or colon cancer cells. In this regard, the antioxidant activity of encapsulated quercetin in electrospun fiber mats was unaltered, and fluorescence microscopy analysis confirmed an improved anti-colon carcinogenic effect of the quercetin released from the system (Wen et al., 2018). Chitin microspheres (Fig. 3b), used as a single unit system, have been prepared by freeze-drying to deliver anthocyanins to simulated colonic environments (Wang et al., 2017).

For the treatment of the TNBS-induced rat model, CS-alginate microspheres loaded with icariin, a prenylated and glycosylated flavonol with the parental kaempferol structure, were orally administered (Wang et al., 2016). In this study, microspheres were synthesized by Ca-induced gelation with alginate followed by PEC with CS using glutaraldehyde as a covalent crosslinker. Although the association of icariin with the encapsulation vehicle was relatively low, with an EE of only

Table 4
Characterization of common dietary fiber-based colon-targeted polyphenol delivery systems.

Polyphenol	Dietary fiber(s) involved	Morphology	Particle size	Zeta potential (mV)	Encapsulation efficiency (%)	Loading efficiency	Reference
Quercetin	Chitosan/Alginate	Core-sheath fiber (electrospinning)	188.3 nm	+33.2	92.2	11.53%	Wen et al. (2018)
	Chitosan/Xanthan gum	Spherical (spray-drying)	5.3 μm	+33	63	-	Caddeo et al. (2014)
Icariin	Chitosan/Alginate	Spherical (emulsification-internal gelation)	101 μm		37.3	25–37%	Wang et al. (2016)
Anthocyanins	Chitin/Ethyl cellulose	Spherical (by solvent dissolution)	80 μm	~ +25–37.5	-	2718 mg/g	Wang et al. (2017)
	Ca-pectin hydrogel	Spherical (ionotropic gelation)	1800 μm	-	99	-	Oidtmann et al. (2012)
Curcumin	Chitosan/Gum Arabic	Spherical (emulsification solvent diffusion)	136 nm	+48	95.02	3.57%	Udompornmongkol and Chiang (2015)
	Chitosan/Alginate	Spherical (double emulsion solvent technique)	240–260 nm	− 13.7 ~ − 17.9	53-64 for curcumin	52.9–142.6 ng/mg 39.4–51.5 μg/mg	Xiao et al. (2016)
Resveratrol	Alginate	Spherical (ionotropic gelation)	120–202 nm	+29.8	85–98	-	Sookkasem et al. (2015)
	Chitosan/Pectin	Spherical	399 nm	+25	~63	-	Andishmand et al. (2017)
	Pectin	Beads (ionotropic gelation)	2200 μm	-	59–97	19–32%	(Das et al., 2011a; Das & Ng, 2010; Das & Ng, 2010a)
	Pectin	Beads (ionotropic gelation)	900–950 μm	-	96–98	-	(Das et al., 2010, 2011; Das & Ng, 2010b)
	Inulin	Spherical (spray-drying)	10 μm	-	70.5	-	Pacheco et al. (2018)
Hydroxytyrosol (HT); 3,4-dihydroxy Phenylglycol (DHPG)	Pectin/Alginate	Beads (ionotropic emulsion-gelation)	-	-	45–57	1–14%	Bermúdez-Oria et al. (2017)

37.3%, both *in vitro* and *in vivo* release studies showed the significant controlled release of icariin in the colon after 24 h of incubation or administration. As shown in Fig. 4, the microspheres released only 10% of icariin in the simulated gastric environment in first two hours, followed by a sudden release of 65.6% in the simulated colonic environment. The avoidance of icariin loss in the upper and middle GI regions can be attributed to the strong complex formed by additional covalent crosslinking with glutaraldehyde that enhanced the stability of the encapsulation structure. Furthermore, *in vivo* treatment resulted in dramatic reductions in proinflammatory cytokine expression, including TNF-α, IL-6, and IL-1β, suggesting the potential of the colon-targeted delivery system of icariin in the therapy of inflamed tissues in ulcerative colitis.

Other anionic dietary fibers have also been used to prepare CS-based structures for the encapsulation of polyphenols. Gum Arabic-CS PEC was applied in the colonic delivery of curcumin to increase its bioactivity against colorectal cancer (Udompornmongkol & Chiang, 2015). The nanoparticles, which were synthesized based on an emulsification solvent diffusion method, had an average size of 136.3 nm with a high EE of 95% (Table 4). This formulation demonstrated excellent controlled performance, in which less than two percent of the loaded curcumin was released under simulated gastric conditions after five hours, followed by a high release rate of 76% under the colonic conditions after eight hours. Furthermore, the authors examined *in vitro* cancer cell viability using human colorectal carcinoma HCT116 and HT29 cell models. Curcumin-loaded nanoparticles showed a more potent reduction in cell viability than free curcumin. These results were mainly attributed to the improved mucoadhesion of the system, which enhanced the cellular uptake of curcumin and therefore resulted in additional cell apoptosis. Xanthan gum, another anionic dietary fiber, has also been utilized to form microparticles with CS by spray-drying to deliver quercetin to the colon (Caddeo et al., 2014). The microparticles were 5 μm in size and were compressed into tablets with a moderate EE of ~63% (Table 4). *In vitro* release studies showed that the tablets exhibited only a minor release of entrapped quercetin (approximately 60%) under an acidic environment. However, the sustained release of polyphenol from encapsulation carriers is a crucial prerequisite for the therapy of IBD. Conversely, after the authors applied the Eudragit pharmaceutical formulation to the tablet as an outer coating layer, the release in the simulated upper GI conditions was found to be significantly decreased (~13%), and the release in the colon was controlled by the non-Fickian diffusion of quercetin out of the tablets.

Multiparticulate systems including more than one formulation are highly suitable for colon-targeted delivery because of their reproducible and predictable transit time within the GIT, consistent release performance, and diminished potential local irritation. Furthermore, multiparticulate systems can be formulated to be more responsive to bacterial degradation for one of the components to achieve accurate release of payload at the target site. Xiao et al. (2016) designed CS-coated poly lactic-co-glycolic acid (PLGA) nanoparticles embedded in CS-alginate hydrogel for the colonic delivery of curcumin. The formulation was also prepared with hyaluronic acid and siCD98, which showed a synergistic therapeutic effect against UC by protecting the mucosa and relieving inflammatory sites in dextran sulphate sodium-induced colitis mice.

4.3.2. Pectin

Pectins are heterogeneous water-soluble dietary fibers with a high molecular weight and are found mainly in plant cell walls. Similar to other dietary fibers, pectins are anionic biopolymers resistant to enzymatic degradation in the upper GIT but can be enzymatically degraded by beneficial gut bacteria, mainly *Bacteroides* species, bifidobacteria, clostridia, and eubacteria (Dongowski, Lorenz, & Anger, 2000). Several review articles have been published summarizing the use of pectins in pharmaceutical applications over the past decade (Munarin, Tanzi, & Petrini, 2012; Sriamornsak, 2011). Regarding oral delivery systems for natural bioactives, pectins offer high affinity with polyphenols and are also mucoadhesive. For example, a strong interaction between tannins and pectin can be formed through hydrogen bonding and hydrophobic interactions (Mamet, Ge, Zhang, & Li, 2018). Procyanidins have a strong affinity for the cell wall, which is composed mainly of pectin (Le Bourvellec, Watrelot, Ginies, Imberty, & Renard, 2012). The direct use of pectin for polyphenol delivery specifically targeting the colon is not suitable because of the ease of dissociation of the formulation in gastric and small intestinal fluids. Nonetheless, this shortcoming can be controlled by the selection of an appropriate type of pectin with a high degree of methylation that reduces water solubility and by structural modifications via the formation of matrix structures with other cationic dietary fibers or food additives.

In most cases, low methoxy pectins (25–50% methoxylation) are desirable for the colon-targeted delivery of polyphenols because low methoxy pectins contain many available carboxylic groups that are prone to form a rigid matrix structure that can efficiently entrap polyphenols and protect them from degradation in the harsh upper GI environment. Pectins can be crosslinked by PEC with positively charged dietary fiber (e.g., CS), ionic crosslinking with divalent cations (e.g., calcium or zinc), or covalent crosslinking with dialdehydes such as glutaraldehyde. For example, early work describing pectin-based encapsulation structures of anthocyanins for colonic delivery was based on ionically crosslinking pectin with calcium and an additional shellac coating layer (Oehme, Valotis, Krammer, Zimmermann, & Schreier, 2011; Oidtmann et al., 2012). Nonetheless, the loading capacity of anthocyanins in these systems is relatively low, which may be attributed to the less rigid matrix structure constructed by a calcium-induced ionotropic mechanism or the high aqueous solubility of the anthocyanins that are associated with low encapsulation in insoluble pectinate systems.

Resveratrol is a stilbene with potent antioxidant properties that has been investigated for its therapeutic bioactivity on colon tumor cells

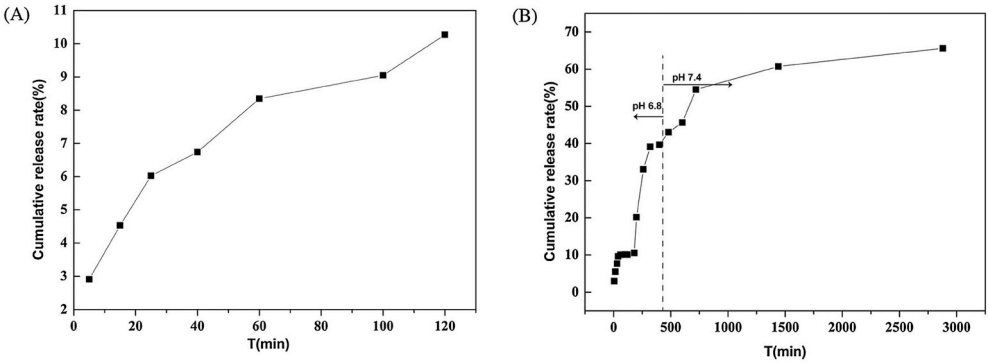


Fig. 4. (A) Controlled release of icariin from chitosan-alginate microspheres in the simulated gastric environment (120 min, pH 1.2), followed by (B) a sudden release in the simulated colonic fluid (500 min, pH 6.8) (Wang et al., 2016. With permission).

and colitis. However, resveratrol is rapidly absorbed and extensively metabolized in enterocytes once ingested, which limits the amount of resveratrol in the inflamed area of the colon. Das and Ng (2010) evaluated a series of resveratrol-loaded pectinate beads based on calcium- or zinc-induced gelation. It was observed that resveratrol was highly associated with Ca-pectinate beads, with an EE of up to 98%, and the beads obtained had an average size of approximately 1 mm. The *in vitro* release results showed that the system almost entirely preserved the loaded resveratrol (97% retention) after 6 h of incubation in media simulating gastric and intestinal conditions, and more than 80% reached the colon environment intact. Nonetheless, these Ca-pectinate beads failed to show colon-targeted release *in vivo*. This group further tested other ionic crosslinkers, and zinc was revealed to be a better ionic crosslinking agent than calcium mainly because zinc is more prone to form a rigid pectinate matrix structures due to its larger atomic radius (Das et al., 2010). These pectinate beads were further optimized by additional PEC with polyethyleneimine (Das, Chaudhury, & Ng, 2011a; Das & Ng, 2010a), CS (Das, Chaudhury, & Ng, 2011b) and covalent interaction with glutaraldehyde (Das & Ng, 2010b; Das, Ng, & Ho, 2011). Abdin (2013) subsequently used the system for UC therapy. Rats with oxazolone-induced UC treated with either intact resveratrol (non-encapsulated formulation) and resveratrol pectinate beads (encapsulated formulation) exhibited significant reductions in sphingosine kinase 1 and myeloperoxidase activities, indicators for inflammation and neutrophil infiltration in the colonic mucosa. Notably, the lowest disease activity index (assessment of the severity of UC) was recorded in rats treated with resveratrol pectinate beads, suggesting the importance of delivering intact resveratrol to the inflamed colonic region.

Recently, a multiparticulate system based on pectin-zinc–CS–polyethylene glycol (PEG) nanoparticles has been developed for the colon-specific delivery of resveratrol (Andishmand et al., 2017). The covalent bond of PEG enforced the entrapment of insoluble resveratrol, which was evidenced by the higher EE (63%) in the PEG-containing formulation than in the physically loaded resveratrol (26%) without PEG (Table 4). In addition, PEG remarkably reduced the particle size, which contributed to the successful delivery of resveratrol (~50%) to the colon. This result was attributed to the exceptional adhesion to the colon mucus due to the larger surface area of the nanoparticles, which prolonged the residence time and allowed microbial enzymes to degrade the carrier and subsequently release a high concentration of the resveratrol. Bermúdez-Oria et al. (2018) and Bermúdez-Oria et al. (2017) reported delivery systems that were based on the use of only dietary fibers as building blocks for encapsulation; in these delivery systems, hydroxytyrosol and 3,4-dihydroxyphenylglycol (DHPG) were encapsulated in pectin/alginate beads formed by calcium crosslinking and were successfully delivered to the colonic region.

4.3.3. Inulin

Inulin is a water-soluble dietary fiber found mainly in garlic, asparagus, chicory, and onion. Structurally, inulin contains a β-(2-1) linked D-glucopyranose, usually with an α-d-glucopyranose terminal group (Bonnema, Kolberg, Thomas, & Slavin, 2010). Inulin is fermented by beneficial colonic bacteria, mainly *Lactobacilli* and *Bifidobacterium* (accounting for up to 25% of the healthy gut flora in humans), which preferentially degrade it to generate a number of SCFAs (Bakker-Zierikzee et al., 2005). In addition, inulin inherently possesses significant therapeutic potential, including the inhibition of tumor growth, enhancement of calcium absorption and strong prebiotic properties (Gupta, Jangid, Pooja, & Kulhari, 2019). Because of these properties, inulin has been specifically applied to the construction of oral delivery systems in the form of nanoparticles and hydrogels for the localized targeting of certain pharmaceuticals related to colon diseases (Sun et al., 2018; Van den Mooter, Vervoort, & Kinget, 2003).

Unlike some dietary fibers that may require the combined use of other dietary fibers to form a robust encapsulation matrix, inulin has been used as a single-unit system for the delivery of secoiridoid to the colon (Table 3). Pacheco, González, Robert, and Parada (2018) encapsulated oleuropein into inulin microparticles by spray-drying and studied precolonic bioaccessibility *in vitro*. The bioaccessibility of oleuropein in the colon with the encapsulated system was higher than with the non-encapsulated system. Therefore, it is reasonable to speculate that under *in vivo* conditions, inulin would provide a protective effect for encapsulated oleuropein and enter the colon for fermentation by gut microbiota to release the payload at a high concentration, retaining its bioefficacy.

4.3.4. Alginate

Alginate is a linear and anionic biopolymer derived from brown seaweed. Alginate offers several attractive properties including non-toxicity, pH-sensitivity in alkaline conditions and high mucoadhesion. Importantly, the gel-forming capacity of alginate in the presence of divalent cations makes it favorable for oral delivery systems (Agüero et al., 2017). Alginate-based delivery systems with regard to colon specificity have been developed in the form of beads, fibers, and micro/nanoparticles in either single or multilayer units (Table 3).

As previously discussed, alginate is often used in combination with CS to form encapsulation particles via the PEC method. Only a few studies have reported the successful use of a single alginate system in the delivery of polyphenols. However, González et al. (2019) prepared olive leaf extract-loaded sodium alginate microparticles (Fig. 3c) by spray-drying and examined the digestion of oleuropein in the GIT. The EE of olive leaf extract was found to increase when the sodium alginate content was amplified due to a large number of hydroxyl moieties available for hydrogen bonding with oleuropein. *In vitro* results showed that compared with non-encapsulated olive leaf extract, alginate microparticles dramatically reduced the release rate (decreased bioaccessibility) of oleuropein in simulated upper GI conditions, suggesting a promising protective effect in these regions. The study addressed concerns regarding the susceptibility of alginate to the alkaline environment of the small intestine and the long transit time to the colon, which could be overcome by manipulating the concentration of alginate and encapsulation method. At higher concentrations, alginate as a single-unit system still had the tendency to form a rigid matrix structure to avoid the early release of oleuropein in the small intestine and to allow intact release towards the lower parts of the GIT.

In another study, Sookkasem, Chatpun, Yuenyongsawad, and Wiwattanapatapee (2015) developed self-emulsifying curcumin-coated calcium alginate beads with Eudragit S100 for colon-targeted delivery. The authors also explored the potential cytotoxic capacity against colonic cell lines and the antioxidant activity of encapsulated curcumin. The EE of the system varied from 85% to 98% depending on the combination (ratio/concentration) of sodium alginate and calcium chloride. Interestingly, the beads produced by the high concentrations of sodium alginate and calcium chloride showed no difference in EE among formulations, suggesting that the ratio of sodium alginate and calcium chloride is more critical to the crosslinking density and thus the overall EE than the contents of these substances. Nonetheless, the MTT cytotoxicity assay against HT-29 cells and a Fe^{3+}-reducing antioxidant assay showed that the activities of this system were slightly lower than those of uncoated curcumin.

4.3.5. Cyclodextrins

CD-containing biopolymers have been utilized in pharmaceutical applications since the early 1980s (Davis & Brewster, 2004). Recently, CD-based biopolymers have been used to form encapsulation structures for the controlled release of drugs at target sites (Zafar, Fessi, & Elaissari, 2014). Structurally, CDs are cyclic oligosaccharides comprising 6, 7, or 8 (namely, α-CD, β-CD, or γ-CD, respectively) glucose units through α-(1,4') glycosidic linkages, and CDs form macrocycle cages that appear as a torus-shaped complex with hydrophilic outer surfaces and adaptable hydrophobic inner cavities, which allow them to form reversible inclusion structures with numerous polyphenols

(usually hydrophobic polyphenols). These dietary fibers are fermented by beneficial colonic bacteria, especially *Bacteroides,* into small saccharides (Fetzner, Böhm, Schreder, & Schubert, 2004).

β-CD has been used in colon-targeted delivery systems, owing to the relatively low solubility of its outer surface and an appropriate cavity size that fits the broadest range of bioactive compounds (Table 3). Flores et al. (2015) fabricated a colon-targeted system using β-cyclodextrins for the delivery of anthocyanins and examined their release properties and potential impacts on gut microbiota regulation. In an *in vitro* batch culture model that mimicked the stomach to the colon, the CD-anthocyanin complex showed a significantly low release rate, indicating a successful protective effect and strong binding association in the cavity. Delphinidin-3-glucoside, with three B-ring hydroxyl moieties, showed the lowest release rate among the individual anthocyanins studied, including cyanidin-3-glucoside and malvidin-3-glucoside, with only two and one hydroxyl moieties in the B-ring, respectively. It can be concluded that hydrogen bonding is the main driving force of the interaction between CDs and anthocyanins and that it is crucial for overall EE. Encapsulation with β-CD improved the thermal stability under acidic conditions while enhancing the stability of anthocyanins in the digestive system, which might reinforce the release of anthocyanins in the colonic region (Fernandes et al., 2018). The delivery of intact anthocyanins to the colon increased the growth of *Bifidobacteria* and *Lactobacilli* while decreasing the growth of pathogenic species (*C. histolyticum*), demonstrating a specific polyphenol microbial modulation effect (Flores et al., 2015).

4.3.6. Gums

Natural gums have several food/additive applications, including as thickening, stabilizing and emulsifying agents (Mudgil, Barak, & Khatkar, 2014). In parallel to food applications, many studies have been carried out to examine the pharmaceutical potential of various gums due to their complex and branched polymeric structures, which exhibit marked mucoadhesive properties (Petri, 2015). Edible gums can originate from plant sources (e.g., guar gum and gum Arabic) or microbial sources (e.g., xanthan gum and gellan gum) (Caddeo et al., 2014; Udompornmongkol & Chiang, 2015).

Guar gum has been used for the colon-targeted delivery of polyphenols due to its controlled release characteristics and high fermentability by colonic bacteria, especially *Bacteroides*, *Ruminococcin*, and *Bifidobacteria*. Additionally, a hydrophilic matrix formed in the cold water of guar gum can carry polyphenols with varying solubility. Guar gum-based matrix tablets are promising carriers of quercetin for colon-targeted delivery in the therapy of colorectal cancer (Singhal, Jain, Singhal, Elias, & Showkat, 2011) (Table 3). The release rate of quercetin into the colonic site from the matrix tablet (after 24 h of incubation) was positively associated with the guar gum content used in the system. Over 80% of quercetin was liberated from the matrix containing 50% guar gum after incubation. Kumar, Rijo, and Sabitha (2018) prepared curcumin-loaded liquisolid tablets based on guar gum and Eudragit L100 for anticancer activity against HCT-15 cells. *In vitro* release studies reported that 42.21–86.4% and 10% of curcumin was released from the coated and uncoated matrix tablets, respectively, at the end of 24 h under simulated GI environments. *In vitro* cytotoxicity studies revealed that curcumin encapsulated in liquisolid tablets exhibited more potent anticancer activity against HCT-15 cells than free curcumin. As previously discussed, Arabic gum and xanthan gum have been used as building blocks to prepare complexes with CS to deliver curcumin and quercetin, respectively (Caddeo et al., 2014; Udompornmongkol & Chiang, 2015).

5. Conclusion and future perspectives

Studies using *in vitro* methods or animal models have shown that the microbial-triggered mechanisms of dietary fiber-based polyphenol delivery systems successfully maintain the structural integrity and have the potential to protect phenolic cargo during the passage through the harsh environment of the upper GIT to maximize the concentration of parent polyphenols in the colonic region. Specific properties, including strong bonding association with polyphenols and prolonged colonic mucoadhesion, make dietary fibers excellent candidates to deliver polyphenols to the colon. In addition, both dietary fibers and polyphenols benefit colon health and may display a synergistic effect on gut microbial homeostasis with potentially enhanced clinical utility in the treatment of IBD. However, challenges remain in the development, assessment and application of these systems. Issues such as those related to inconsistent EE, the influence of dietary fiber on the colonic bioactivities of polyphenols, and microbial degradation mechanisms need to be further addressed. Food scientists and formulation chemists need to work together towards developing advanced colon-targeted polyphenol delivery systems with improved overall efficiency and bioactivity.

From our understanding, some future research trends might be:

- The in-depth investigation of the molecular interactions between specific polyphenols and dietary fibers, as this relationship may influence the overall EE and release performance of the delivery system. No individual delivery system is suitable for the delivery of all polyphenols. The EE of previously reported attempts are variable (from 37 to 98%), and this variability can be improved by understanding the specific molecular characteristics that contribute to polyphenol-dietary fiber binding interactions and to selecting the most suitable combination (Jakobek & Matić, 2018). Other factors, such as processing methods, environmental influences (pH, temperature and crosslinking), and the nature of the encapsulation carrier (e.g., liposome, emulsion) can also be manipulated to optimize the overall efficiency of the systems.
- Investigate the potential negative influence of dietary fiber on the bioactivities of polyphenols, such as antioxidant and antiproliferative activities. It is important that the delivery system does not affect the intended potency of the polyphenol after release in the colon. Only a few studies address this subject (Bermúdez-Oria et al., 2018; Kumar et al., 2018; Udompornmongkol & Chiang, 2015; Wen et al., 2018). In addition, it would be beneficial for studies that focus on the treatment of IBD to assess changes in the gut microbiota profile and the production of SCFAs, as enhanced gut microbial homeostasis has recently been associated with the improvement of intestinal diseases.
- To understand the physiological influence of the gut microflora profile on the release performance of delivery systems in different disease states (healthy *vs* inflamed conditions). This topic is particularly important when the formulation is used to treat IBD. Individuals with IBD often exhibit altered gut microbial diversity/populations and enzymatic secretions, and these factors do not guarantee that the release function of the delivery systems will be induced, ultimately leading to imprecise liberation and decreased accumulation of polyphenols at the inflamed site.
- To expand the potential use of the combination of other natural polymers, such as proteins, to construct colon-targeted delivery systems with greater biocompatibility, biosafety and more precise targeting performance than currently existing systems (Wei & Huang, 2019).

Declaration of Competing Interest

None.

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