Food Research International 107 (2018) 423–436

Contents lists available at ScienceDirect

Food Research International

journal homepage: www.elsevier.com/locate/foodres

Review

In vitro digestion models suitable for foods: Opportunities for new fields of application and challenges

Raquel Lucas-González, Manuel Viuda-Martos, José Angel Pérez-Alvarez, Juana Fernández-López*

IPOA Research Group, Agro-Food Technology Department, Escuela Politécnica Superior de Orihuela, Universidad Miguel Hernández, Orihuela, Alicante, Spain

ARTICLE INFO

Keywords:
In vitro digestion assay
Bioaccessibility
Bioactive compounds
Food matrix
Nano-delivery systems

ABSTRACT

In vitro digestion assays simulate the physiological conditions of digestion *in vivo* and are useful tools for studying and understanding changes, interactions, as well as the bioaccessibility of nutrients, drugs and non-nutritive compounds. The technique is widely used in fields such as nutrition, pharmacology and food chemistry. Over the last 40 years, more than 2500 research articles have been published using *in vitro* digestion assays (85% of which have been published in the last two decades) to elucidate multiple aspects such as protein digestibility, nutrient interactions or the viability of encapsulated microorganisms. The most recent trend in the use of this technique involves the determination of the antioxidant activity of bioactive compounds after digestion. However, the inability to reproduce certain *in vivo* digestion events, as well as the multiple models of *in vitro* digestion, point to a need to optimize and validate the method with *in vivo* assays to determine its limitations and uses. The purpose of this paper is to provide an overview of the current state of the art of *in vitro* digestion models through an analysis of how they have evolved in terms of the development of digestion models (parameters, protocols, guidance) and taking into consideration the boom in new fields of application.

1. Introduction

Food digestion is a complex process in which many factors are involved and that has actually aroused the interest of the food industry because of there is a growing relationship between food and health and therefore the reduction of development certain chronic diseases (Bornhorst, Gouseti, Wickham, & Bakalis, 2016). During human digestion, ingested foods are broken down into nutrients which are used by the body for energy, growth and cell repair. Food digestion implies two main processes that occur simultaneously: (*i*) mechanical transformation, whereby larger pieces of food get broken down into smaller pieces, starts in the mouth and continues into the stomach; and (*ii*) enzymatic transformation, whereby several different enzymes break down macromolecules into smaller molecules that can be absorbed into the bloodstream, starts in the mouth and continues into the intestines (Alminger et al., 2014; Guerra et al., 2012). Several organs, hormones and nervous stimuli are involved in the digestion process. The liver and the pancreas are also important players in the digestive system due to their function of secreting hydrolytic enzymes and biliary salts (Minekus et al., 2014).

Knowledge of the physicochemical changes that occur in foods during the digestion process and the various factors influencing nutrient bioaccessibility (the amount of a compound that is released from the matrix and is solubilized into the water phase (chyme) become available for absorption in the systematic circulation through the gut wall), bioavailability (the total amount of a compound that is released and absorbed, to reach the bloodstream, where it is delivered to the different body tissues) and digestibility (it applies specifically to the fraction of food components that is transformed into potentially accessible matter (present in the complete digesta, soluble and non-soluble fractions) through all physical and chemical processes that take place in the lumen) (Fernández-García et al., 2012; Hedren, Diaz, & Svanberg, 2002), would be helpful for designing functional foods since recommended daily nutrient ingestion and the processing conditions that would maximize the health benefits of bioactive compounds (Manach, Williamson, Morand, Scalbert, & Rémésy, 2005; Sengul, Surek, & Nilufer-Erdil, 2014) could be established. It is clear that the digestive system is central to numerous questions raised not only by researchers, but also by commercial companies in various fields such as nutrition, toxicology, pharmacology, and microbiology (Dean & Ma, 2007; McAllister, 2010).

Testing the efficacy of newly developed foods or delivery systems

* Corresponding author at: IPOA Research Group, Agro-Food Technology Department, Escuela Politécnica Superior de Orihuela, Universidad Miguel Hernández, Crta. Beniel km. 3,2, E-03312 Orihuela, Alicante, Spain.
E-mail address: j.fernandez@umh.es (J. Fernández-López).

https://doi.org/10.1016/j.foodres.2018.02.055
Received 3 December 2017; Received in revised form 19 February 2018; Accepted 25 February 2018
Available online 27 February 2018
0963-9969/

depends on the availability of digestion models that accurately simulate the complex physicochemical and physiological events that occur in the human gastrointestinal tract (Hur, Lim, Decker, & McClements, 2011). *In vivo* feeding methods, using as models animals or humans, generally offer the most precise results and as mentioned Marcano, Hernando, and Fiszman (2015) are still considered the "gold standard" for determined diet-related questions, but unluckily, analyse the complex multistage process that occurs during the human or animal digestion is technically difficult, costly, and limited by ethical issues when potentially harmful substances are involved (Augustin et al., 2014; Minekus et al., 2014). Consequently, there is a real need for use *in vitro* models that closely mimic the physiological processes occurring during human digestion (Minekus et al., 2014), taking into consideration several factors such as the occurrence and concentration of digestive enzymes, the pH values in gastric and intestinal phases, digestion time and salt concentrations, among other factors (Marcano et al., 2015). Such models should be flexible, accurate, and reproducible. As of now, *in vitro* digestion models provide a useful alternative to animal and human models by rapidly screening food ingredients (Hur, Lee, Kim, Chun, & Lee, 2013).

As, mentioned Coles, Moughab, and Darragh (2005) the perfect *in vitro* digestion technique (i) should provide precise results in a short time and (ii) might consequently help as a tool for quickly analysis of foods or food models with different compositions and structures. However, at this moment, any *in vitro* method is inevitably going to fail to match the precision that could be obtained by actually studying a food *in vivo*, basically by the inherent complexity of the digestion process (Coles et al., 2005; Fuller, 1991; Hur et al., 2011).

Few years ago, food and animal scientists across the world have used various *in vitro* digestion models to analyse the structural and chemical changes that happen in several food matrices when are submitted to simulated gastrointestinal conditions, enabling the explosion in the number of scientific works published on digestion studies in recent years.

The aims of this paper is to provide an overview of the current status of *in vitro* digestion models through an analysis of the evolution of these methods as regards the development of digestion models (parameters, protocols, guidance) and to study the boom in new fields of application.

2. Summary of survey

For the survey we have used Scopus® as a data base for the searches because it is the largest searchable citation and abstract source for searching the literature and because it is continually expanded and updated (Chadegani et al., 2013). The following items were introduced in the Scopus web page to refine the search: *Years*, from "all years" to "2016"; *Key words*, "*in vitro* digestion" and "foods"; *Type of document*, "paper" or "review"; The following "subject areas" were excluded: nursing, veterinary, environment sciences, physic and astronomy, materials, neuroscience, computer science, energy, business, psychology, earth and planet and undefined; The following "exact journal titles" were also excluded: Animal, Journal of Animal Science, Poultry Science, British Poultry Science, Journal of Allergy and Clinical Immunology, and Clinical and Experimental Allergy. With all these restrictions, a total of 2187 document results were obtained. Fig. 1 shows a diagram explaining the search criteria and process. Within this final result, different words were independently added to refine the search, depending on the information required.

3. Interest and evolution of *in vitro* digestion models over time

A simple analysis of the evolution of the number of publications (Fig. 2) is sufficient to appreciate the current interest of the scientific community in the *in vitro* digestion of foods. While the first published paper in this area dates from 1954 (DeBaun & Connors, 1954), which was followed by a trickle of papers every year, the most important efforts to simulated the human stomach and small intestine have been made in the past two decades, a period in which more than 85% of the papers published to date have appeared. In the four years preceding this review, more than 150 papers per year have been published related to *in vitro* digestion of foods, peaking in 2015 when 218 papers were published.

The survey also showed that although *in vitro* digestion models have been applied to all type of foods, the most common foods tested were: vegetables (26%), dairy foods (23%), bakery foods (17%), meat products (13%), marine foods (12%) and egg foods (7%).

3.1. Static/dynamic in vitro digestion models

A huge range of gastrointestinal models have been designed to simulate the food digestion process, ranging from single static systems to multi-compartmental and dynamic systems. In addition, *in vitro* digestion models differed from one another in various parameters. One of these is the number and type of step included in the digestion sequence; depending on the study purpose, simulated digestion models can include the oral, gastric or/and small intestinal phases, and in some cases, large intestinal fermentation (Polovic et al., 2008; Sek, Porter, & Charman, 2001). Another important variation between models is the chemical composition of the digestive solutions used in each phase - the type and enzyme concentrations, the salts and buffers used, the biological polymers, the surface-active components, and so on (Almaas et al., 2006; Boise & Eggum, 1991; Chattertona, Rasmussen, Heegaard, Sorensen, & Petersen, 2004; Hur et al., 2011; Hur, Decker, & McClements, 2009; Kitabatake & Kinekawa, 1998; Porter et al., 2004). Finally, the mechanical stresses as well as the fluid flows used in each phase in the digestion sequence flow geometries and profiles, magnitude and direction of applied stresses, *etc*. are also an important variation factor (Brandon et al., 2006; Hur et al., 2011; McClements, Decker, & Park, 2009). Different reviews have been published addressing these variation factors (Bornhorst et al., 2016; Guerra et al., 2012; Lefebvre et al., 2015). This only gives a brief idea about the sophistication that can be achieved with these systems, which, besides the varying conditions that can be applied, help understand the difficulties involved in comparing compare results between studies.

A wide number of these works have been accomplished using static models (89%), in which gastric and small intestinal digestion is imitated in three successive phases (oral, gastric and small intestinal). In each phase, the food product is incubated for a specific time and at a specific temperature with simulated artificial saliva and gastric and small intestinal digestive fluids, respectively while the pH is generally maintained at a fixed value by using a buffer. While this may seem a simple method, the lack of consensus concerning the physiological conditions applied has led to different models and hence results which cannot be compared across research teams. To minimize this problem, the COST INFOGEST network proposes a general standardized and practical static digestion method based on relevant conditions that can be applied for various ends (Minekus et al., 2014). The objective of this consortium was to harmonize *in vitro* static systems that simulate digestive processes by defining key parameters and conditions. The scientific community has shown great interest in this study, as can be seen from the numerous citations (345, by Scopus®) that it has received since 2014 (year of publication). This harmonized static *in vitro* digestion method for foods should contribute to the production of more comparable data in the future. During the application of this standardized method, several authors have reported some limitations, which much be taken into account. Rodrigues, Barros-Mariutti, and Zerlotti-Mercadante (2016) reported that this general method needs to be adapted in the case of studies applied to lipophilic compounds (carotenoids, plant sterols, among others). They concluded that two steps must be included (micelle separation by centrifugation and carotenoid exhaustive extraction from the micelles with diethyl ether) in the case of analysis on carotenoids from fruits. In spite of all these limitations, a

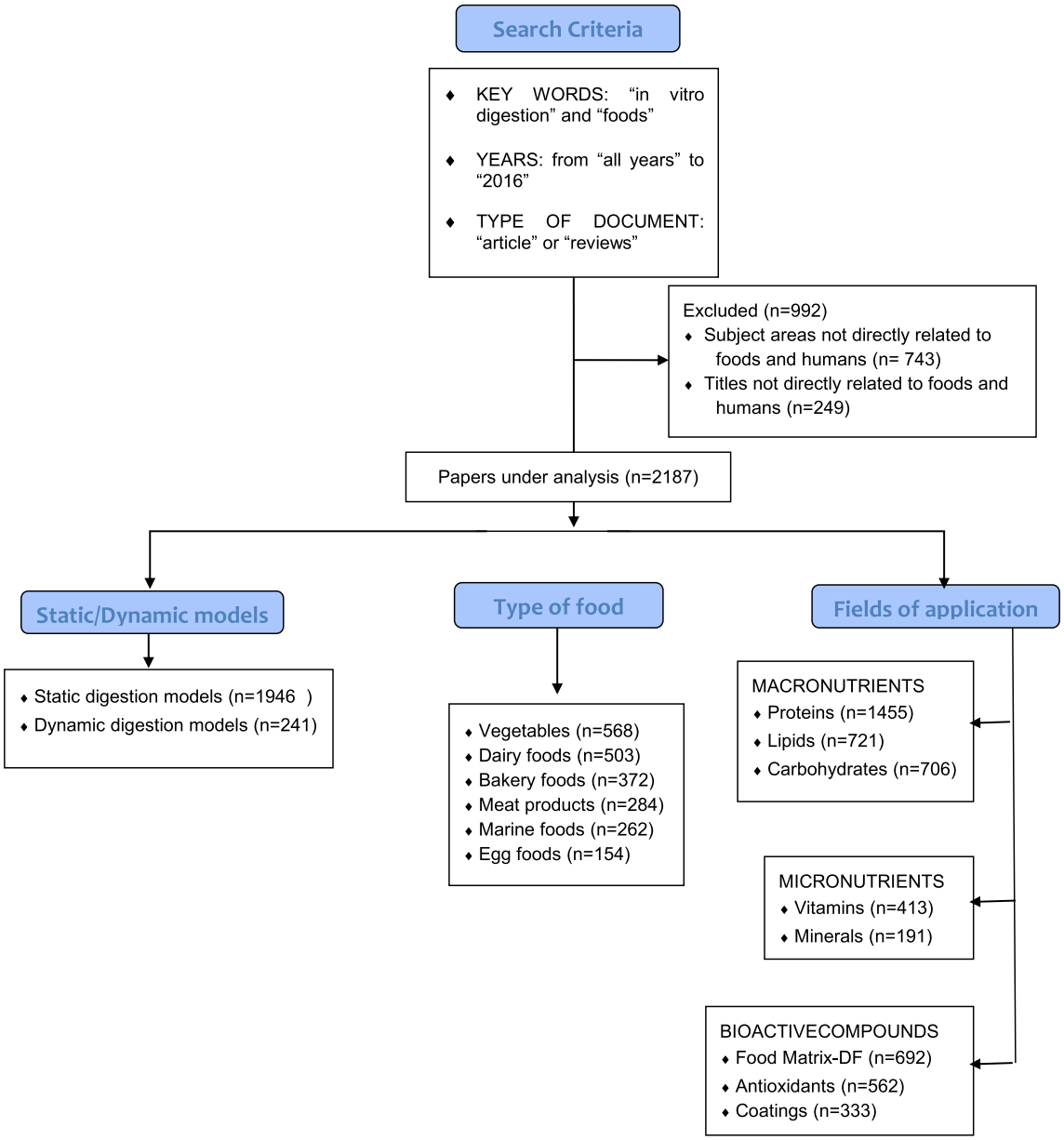

Fig. 1. Flow chart of the search criteria applied to select the papers used in this review (based on the CONSORT diagram for clinical research).

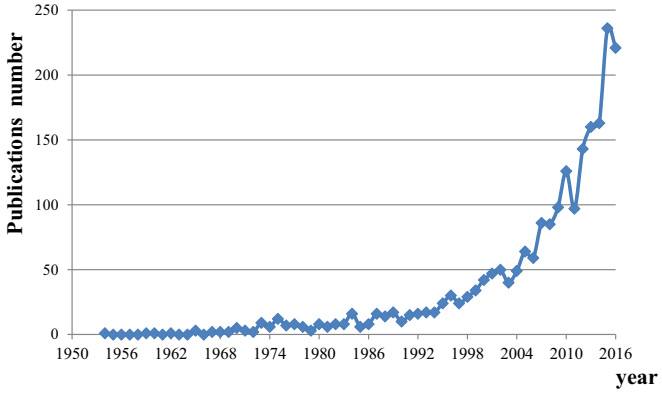

Fig. 2. Evolution of the number of publications on *in vitro* digestion studies.

recent review about the correlation between *in vivo* and *in vitro* data on food digestion concludes that although, *in vitro* static models are oversimplistic and do not reproduce all the dynamic aspects of the GIT, they are increasingly useful in predicting *in vivo* digestion in some cases (Bohn et al., 2017).

The *in vitro* gastrointestinal static models have numerous advantages, the principal purpose to imitate the biochemical processes that happen in the gastrointestinal tract and normally use a single set of initial conditions (pH, concentration of enzymes, bile salts, *etc.*) for each part of the gastrointestinal tract. Nevertheless, this simplistic method is frequently not an accurate reproduction of the more complex *in vivo* conditions, where the biochemical environment is continually changing and physical parameters such as shear and grinding forces can have a large impact on the breakdown of larger food particles and the release of nutrients (Golding & Wooster, 2010). The geometry (vertical alignment, horizontal alignment or beaker) (Campbell, Arcand, & Mainville, 2011; Tompkins, Mainville, & Arcand, 2011), the biochemistry (the different digestive secretions are added to the compartments of the model over time) (Marciani et al., 2001) and the physical forces

Table 1
Static *vs* dynamic *in vitro* human digestion models for food applications.

Static	Dynamic
Type of study	
Useful for limited digestions (gastric and/or intestinal step)	Applicable to total digestion studies
Type of food	
Homogenized/simple foods Isolated or purified food compounds	Complex foods
Major applications	
Macronutrients *Protein hydrolysis *Lipid hydrolysis *Starch resistance Bioactive molecules *Release from simple food matrices *Solubility and bioaccessibility	Foods & Pharmaceutical *Release and bioaccessibility of nutrients from complex food matrices *Protein digestion *Lipid separation *Peptide production
Main objectives	
Improve food properties Preliminary trials to justify possible nutrition and health claims	Effect of food structure on nutrient delivery, nutrient interactions, probiotic survival, prebiotic delivery, *etc*.
Main advantages	
Rapid and simple Cost-effective Need to be validated only in light of their intended use	Better accuracy the dynamic environment of the intestine: peristaltic movements, physical forces, shear forces, *etc*. Allow direct comparison with the results *of in vivo*/clinical studies
Main disadvantages	
Lack the mechanical forces that contribute to *in vivo* digestion and the constant changes in biochemical environment; excessive metabolite accumulation, which can interfere with digestion	Should be validated for their ability to reproduce the conditions of the gastrointestinal tract.

(simulated using Teflon rollers, flexible discs or water jackets) are the three most important factors that have been differently addressed in the design of these dynamic digestion models (Kong & Singh, 2010; Vardakou et al., 2011). Some of the more advanced dynamic digestion models have a geometry designed to represent the fundus and antrum of the stomach, and/or the duodenum (Thuenemann, 2015). These designs allow for the simulation of the physical forces exerted on the digesta during transit through the gastro-intestinal tract, which in turn allows simulation of the inhomogeneous nature of the digesta and localized biochemical environments, as *in vivo* (Kong & Singh, 2010; Marciani et al., 2001; Marciani, Gowland, Spiller, et al., 2001; Tompkins et al., 2011; Vardakou et al., 2011). Table 1 shows a general comparison between static and dynamic digestion models as a function of the type of study, type of food, major applications, main objectives and advantages and disadvantages.

3.2. Evolution and new fields of application

Of note, too, is how the specific aim of this technique has changed with time, taking into account that it can be applied to several scientific areas such as, nutrition, food chemistry, pharmacology, microbiology and toxicology. The greatest numbers of studies have been into the behaviour of macronutrients (mainly proteins) and drugs during digestion (Fig. 3). However, in the last decade (2006–2016), new fields of applications have appeared, among which the three most relevant are: (i) the effect of the digestion process on the bioaccessibility of bioactive compounds and on their antioxidant activity (of a total of 562 documents found, 92% were published in last decade), although in most cases the objective was (ii) the specific effect of the food matrix (mainly dietary fiber in vegetable foods) on these properties (of a total of 692 documents found, 70% were published in the last decade); and (iii) the effect of digestion on coating integrity (mainly focused on nanodelivery systems) of bioactive compounds (a total of 481 documents found, 85% were published in last decade). All of these are examples of new applications and the importance given to them in the last decade, because most did not exist in in the 1980s and very few existed in the 1990s (Fig. 3).

3.2.1. Effect of in vitro gastrointestinal digestion process on bioaccessibility and antioxidant properties of bioactive compounds

During recent years, several bioactive compounds (vitamins such as A, C, D and E, polyphenolic compounds, carotenoids and dietary fiber) have been studied for their potential health benefits in the development of functional foods, nutraceuticals, pharmaceuticals and other applications (Table 2) (Sotomayor-Gerding et al., 2016). Nevertheless, it should be borne in mind that any healthy effects of above mentioned compounds are determined by their bioavailability due to their chemical, thermal and shelf stability in the face of various processing conditions as mentioned Sotomayor-Gerding et al. (2016) and Cilla, Bosch, Barberá, and Alegría (2018). Furthermore, their lipophilic nature and insolubility present challenges for their delivery and absorption (Alminger et al., 2014). For these reasons, when the potential functionality of several bioactive compounds are analysed, their bioavailability in food matrix is more significant than the amount of that bioactive compound.

It is well known that fruits and vegetables are an important source of bioactive phytochemicals (mainly polyphenolic compounds) which could exert numerous beneficial effects *in vivo*, mainly related to their high antioxidant potential donating a hydrogen atom or an electron to other compounds, scavenging free radicals and quenching singlet oxygen as reported Oliveira et al. (2009) and Chen et al. (2014). This interest in the antioxidant properties of phenolic compounds has led to a high number of papers being published on their characterization (quantity and type of polyphenolic compounds) in all types of foods, and on the effect of processing on their antioxidant properties (Colle, Lemmens, Van Buggenhout, Van Loey, & Hendrickx, 2010; Karakaya & Yilmaz, 2007; Rosa, Dufour, Lullien-Pellerin, & Micard, 2013). Moreover, the potential availability of antioxidants compounds after digestion is important, and several works have indicated that the bioavailability of individual compounds with antioxidant activity is poor (Palafox-Carlos, Ayala-Zavala, & González-Aguilar, 2011). Because of this, the impact of *in vitro* gastrointestinal digestion on the stability of polyphenolic compounds, and hence on their antioxidant properties, has been one of the more widely examined topics during last decade. Such is the case with a wide variety of fruits including citrus (Chen et al., 2014; De Ancos, Cilla, Barberá, Sánchez-Moreno, & Cano, 2017; Rodrigo, Cilla, Barberá, & Zacarías, 2015), different types of berries (Bermúdez-Soto, Tomás-Barberán, & García-Conesa, 2007; Correa-Betanzo et al., 2014; Fazzari et al., 2008; Huang, Sun, Lou, Li, & Ye, 2014; Liang et al., 2012; Lucas-González et al., 2016), tomato (Svelander et al., 2010; Talens, Mora, Bramley, & Fraser, 2016), grape (Chen et al., 2014; Tagliazucchi, Verzelloni, Bertolini, & Conte, 2010), apple (Bouayed, Deußer, Hoffmann, & Bohn, 2012; Bouayed, Hoffmann, & Bohn, 2011) and figs (Kamiloglu & Capanoglu, 2013). But its impact has also been tested in different vegetables (Pugliese et al., 2014; Soriano-Sancho, Pavan, & Pastore, 2015), grains and cereals (Chitindingu, Benhura, & Muchuweti, 2015; Gong, Jin, Wu, & Zhang, 2013; Podio et al., 2015), fruit juices (Aschoff et al., 2015; Cilla et al., 2011; Cilla, González-Sarrías, Tomás-Barberán, Espín, & Barberá, 2009; Fawole, Opara, & Chen, 2015; Gil-Izquierdo, Gil, Ferreres, & Tomás-Barberán, 2001; Pérez-Vicente, Gil-Izquierdo, & García-Viguera, 2002; Rodríguez-Roque, Rojas-Grau, Elez-Martínez, & Martín-Belloso, 2013), vegetable juices (Wootton-Beard, Moran, & Ryan, 2011) and other types of processed foods (Colantuono, Ferracane, & Vitaglione, 2016; Dall'Asta et al., 2016; Dinnella, Minichino, D'Andrea, & Monteleone, 2007; Jiwan, Duane, O'Sullivan, O'Brien, & Aherne, 2010; Kamiloglu et al., 2015; Oliveira & Pintado, 2015; Vaghini, Cilla, Garcia-Llatas, &

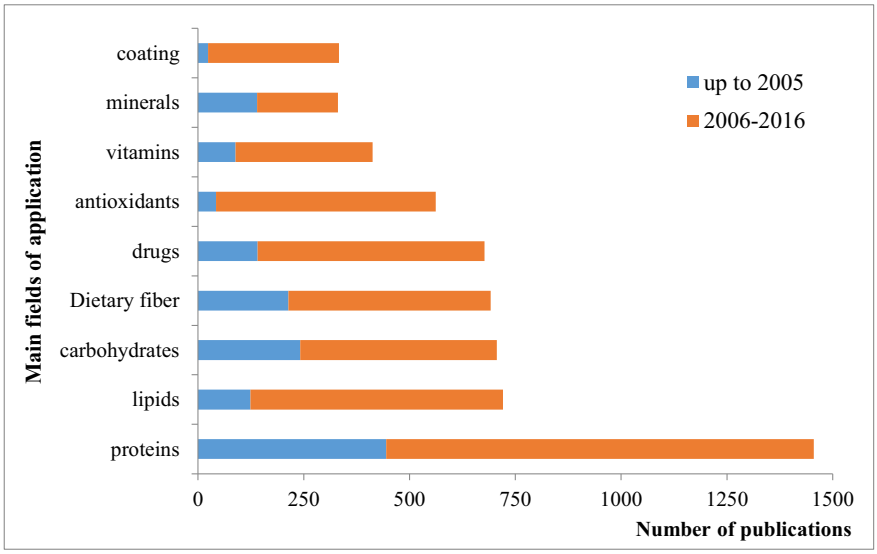

Fig. 3. Change in main fields of application of *in vitro* digestion studies with time.

Lagarda, 2016). Henning et al. (2014) studied the variability in the antioxidant activity of different dietary supplements commonly used as sources of antioxidant polyphenols (pomegranate, milk thistle, green tea, grape seed, goji and açai). In most of these studies, the stability of phenolic compounds was assessed by determining the total phenolic content (*e.g.* using the Folin-Ciocalteau method), which does not yield information on the recovery of specific phenolic classes or molecules, and by determining the antioxidant capacity (by methods such as DPPH, FRAP, ABTS or FIC). In this case, controversial results have been reported: in some cases, the total phenol content recovered and hence the antioxidant activities, after the gastric and intestinal phase of *in vitro* digestion was not reduced (compared with the gastric step) (Fazzari et al., 2008; Tagliazucchi et al., 2010; Tagliazucchi, Verzelloni, & Conte, 2012), but in other cases it was (Bermúdez-Soto et al., 2007). Also in some cases a high and positive correlation between total phenolic content and antioxidant activity was reported, but in some cases no such correlation was found. In conclusion, it seems that digestion may alter antioxidant properties of foods, depending partly on variations in the polyphenol content. Further analyses of specific phenolic compounds, especially their possible degradation products, should be carried out to clarify these conflicting results.

In an interesting work, Chen et al. (2014) analysed 33 fruits, evaluating their total phenolic content and antioxidant capacity before and after *in vitro* digestion. They also reported great variations among fruits; following the gastric phase of the *in vitro* digestion model, there was a significant increase in the total phenolic content of 8 fruits. After the duodenal phase of digestion, the total phenolic content of 25 fruits had increased compared with their initial total values, while the total phenolic content of 8 fruits had decreased. They also found that after the gastric phase of digestion, the DPPH, ABTS and FRAP values of some fruits had significantly increased (by up to 10.74 fold), but others decreased compared with their initial values. Compared with the values observed after the gastric phase of digestion, the DPPH, ABTS and FRAP values of some fruits were significantly lower after the duodenal phase of digestion, but others were higher. As can be seen, there is no overall pattern to the behaviour of these fruits during *in vitro* digestion. Previous studies found that a number of polyphenols increased after the gastric phase of the *in vitro* digestion process since polyphenols are highly sensitive to alkaline conditions. After the pancreatic digestion phase, the antioxidants are degraded by the alkaline pH, leading to an overall loss in the antioxidant capacity after *in vitro* digestion (Bermúdez-Soto et al., 2007). It is possible that when these compounds are exposed to such conditions, a proportion of the polyphenol compounds are transformed into different structural forms with different chemical properties, and different degrees of bioaccessibility, bioavailability and biological activity, which are undetectable by the individual HPLC and HPLC–MS polyphenol analyses. The presence of polyphenol derivatives has been described in some studies (Aura et al., 2005; Fleschhut, Kratzer, Rechkemmer, & Kulling, 2005).

In the study by Henning et al. (2014) into the effect of *in vitro* digestion on the antioxidant capacity in some commercially available polyphenol-rich antioxidant dietary supplements (including extracts from pomegranate, green tea, grape seed, resveratrol, milk thistle, and acai, and goji berry), differential results were also reported. In some samples, the antioxidant activity after *in vitro* digestion remained unchanged, but in other samples it was increased by 50%, compared with non-digested controls. Such modifications were attributed to the hydrolysis of some of these compounds during digestion and the formation of other metabolites with higher or lower antioxidant activity (Bialonska, Kasimsetty, Khan, & Ferreira, 2009; Janisch, Ölschläger, Treutter, & Elstner, 2006).

In a study to assess the polyphenolic profile stability and changes in the antioxidant potential of maqui berry during *in vitro* digestion, Lucas-González et al. (2016) demonstrated that polyphenolic compounds present in maqui are released, mainly in the early phases of gastrointestinal digestion, where they might exert bioactivity as antioxidant compounds after their absorption in gastric digestion. However, their stability, especially that of anthocyanin compounds, is profoundly affected in the last phase of digestion, probably modifying their physicochemical properties which are reflected in their antioxidant properties and bioaccessibility.

In vitro digestion studies have been applied not only in fruits and vegetables but also their respective processed co-products (Table 2). Although the co-products resulting from plant food processing represent a major disposal problem for the industry concerned, they also represent a promising source of bioactive compounds. In this case, the bioaccessibility of some of these bioactive compounds found in fruit-processing (grape, mango, pomegranate, apple, *etc.*) (Blancas-Benitez et al., 2015; Colantuono et al., 2016; Gullón et al., 2015a; Gullón, Pintado, Fernández-López, Pérez-Álvarez, & Viuda-Martos, 2015b; Mosele, Macia, Romero, Motilva, & Rubio, 2015; Wang, Williams, Ferruzzi, & D'Arcy, 2013) and vegetable-processing co-products (cauliflower, black carrot, *etc.*) (Gonzales et al., 2015; Kamiloglu et al., 2016) is also being investigated. For example, Gullón, Pintado, Fernández-López, et al. (2015b) concluded that although the digestion process of pomegranate peel flour reduces the polyphenolic

Table 2
Recent studies about the effect of *in vitro* digestion process on antioxidant capacity and bioaccesssibility of bioactive compounds in foods.

Type of Food	Bioactive compound	Properties evaluated[a]	Reference
Whole foods			
Citrus fruits	Polyphenols	Bioaccesibility and antioxidant properties	Chen et al. (2014)
Mullberries	Anthocyanins	Bioaccesibility and antioxidant properties	Liang et al. (2012)
Maqui berries	Polyphenols	Bioaccessibility and antioxidant properties	Lucas-González et al. (2016)
Wild blueberries	Polyphenols	Bioaccessibility and antioxidant properties	Correa-Betanzo et al. (2014)
Chinese bayberries	Polyphenols	Antioxidant properties	Huang et al. (2014)
Raspberries	Polyphenols	Antioxidant properties	McDougall, Dobson, Smith, Blake, and Stewart (2005)
Chockeberries	Polyphenols	Antioxidant properties	Bermúdez-Soto et al. (2007)
Figs	Polyphenols	Bioaccessibility	Kamiloglu and Capanoglu (2013)
Grapes	Polyphenols	Bioaccessibility and antioxidant properties	Tagliazucchi et al. (2010); Chen et al. (2014)
Apples	Polyphenols	Bioaccessibility and antioxidant properties	Bouayed et al. (2011), Bouayed et al. (2012); Tenore, Campiglia, Ritieni, and Novellino (2013); Chen et al. (2014)
Chaenomeles fruits	Polyphenols	Stability and antioxidant properties	Miao et al. (2016)
Tomato	Polyphenols	Bioaccessibility	Svelander et al. (2010); Talens et al. (2016)
Sweet cherry	Polyphenols	Antioxidant properties	Fazzari et al. (2008); Chen et al. (2014)
Chilli peppers	Carotenoids	Bioaccessibility	Pugliese et al. (2014)
Bean seeds	Polyphenols	Bioaccessibility and antioxidant properties	Soriano-Sancho et al. (2015)
Cereals	Polyphenols	Antioxidant properties	Gong et al. (2013); Chitindingu et al. (2015); Masisi, Beta, and Maghadasian (2016)
Pomegranate juice	Polyphenols	Bioaccessibility and antioxidant properties	Pérez-Vicente et al. (2002); Fawole et al. (2015)
Orange juice	Carotenoids, flavonoids and Vitamin C	Bioaccessibility	Gil-Izquierdo et al. (2001); Aschoff et al. (2015)
Others fruit juices	Polyphenols	Antioxidant properties	Ryan and Prescott (2010); Rodríguez-Roque et al. (2013)
Vegetable juices	Polyphenols	Antioxidant properties	Wootton-Beard et al. (2011); Helal, Tagliazucchi, Verzelloni, and Conte (2014)
Extra virgin olive oil	Polyphenols	Antioxidant properties	Dinnella et al. (2007)
Black carrot jams and marmalades	Polyphenols	Bioaccessibility	Kamiloglu et al. (2015)
Soluble coffee	Polyphenols	Bioaccessibility and antioxidant properties	Podio et al. (2015)
Dietary supplements	Polyphenols	Antioxidant activity	Henning et al. (2014)
Strawberry and peach yogurt	Polyphenols	Bioaccessibility and antioxidant properties	Oliveira and Pintado (2015)
Different fortified foods	Carotenoids and retinoids	Bioaccesibility and antioxidant properties	Courraud et al. (2013)
Bread	Phenolic acids	Bioaccessibility	Dall'Asta et al. (2016)
Durum wheat pasta + barley flour enriched with β-glucan	Polyphenols	Antioxidant properties	Montalbano et al. (2016)
Pomegranate peels enriched cookies	Polyphenols	Bioaccessibility and antioxidant properties	Colantuono et al. (2016)
Spice enriched starchy foods	Thymol and carvacrol	Bioaccessibility and antioxidant properties	Aravena, García, Muñoz, Pérez-Correa, and Parada (2016)
Plant sterols enriched fermented milk beverages	Plant sterols	Bioaccessibility	Vaghini et al. (2016)
Organic and non-organic baby foods	Carotenoids	Bioaccessibility	Jiwan et al. (2010)
Coproducts from agrofood industries			
Grape coproducts	Polyphenols	Bioaccessibility	Wang et al. (2013)
Mango coproducts	Polyphenols	Bioaccessibility	Blancas-Benitez et al. (2015)
Pomegranate coproducts	Polyphenols	Bioaccessibility and antioxidant properties	Mosele et al. (2015); Gullón, Pintado, Fernández-López, et al. (2015b); Colantuono et al. (2016)
Apples coproducts	Polyphenols	Bioaccessibility and antioxidant properties	Gullón, Pintado, Barber, et al. (2015a)
Date palm coproducts	Polyphenols	Bioaccessibility and antioxidant properties	Gullón, Pintado, Barber, et al. (2015a)
Cauliflower coproducts	Polyphenols	Bioaccessibility and antioxidant properties	Gonzales et al. (2015)
Black carrot coproducts	Polyphenols	Bioaccessibility	Kamiloglu et al. (2015)

[a] Bioaccessibility is evaluated as bioaccessibility index, representing the proportion of the amount of the bioactive compound in the soluble fraction of the digested sample respect to its amount in the total digested sample (soluble + non-soluble fraction). Antioxidant properties are evaluated comparing the antioxidant activity in the undigested sample (using antioxidant methods such as DPPH, ABTS, FRAP, FIC, *etc.*) respect to the same values after each phase of *in vitro* gastrointestinal digestion. Stability of each bioactive compound is estimated as its amount after each digestion phase respect to the amount in the undigested sample.

concentration and the antioxidant properties, this co-product could be used in the food industry as potential ingredient to develop functional foods that promote health benefits. Kamiloglu et al. (2016) reported a significant decrease (23–83%) in the total phenolic content, total monomeric anthocyanin content and total antioxidant capacity in black carrot, peel and pomace as a result of *in vitro* gastrointestinal digestion. Nevertheless, the amount of pomace anthocyanins released at all stages of *in vitro* gastrointestinal digestion was higher than that of black carrot anthocyanins, suggesting that pomace may be a better source of bioaccessible anthocyanins.

It is important to highlight that although fruits, in general, are rich source of polyphenolic compounds, the quantity of compounds that are available for absorption under the environments of the small intestine, is possibly quite small. As mentioned Kamiloglu and Capanoglu (2013) this does not mean that the ingested insoluble compounds have no role in health protection, as these compounds, if they are not absorbed in the small intestine, can reach the large intestine, where they can be transformed and/or degraded by the colon microflora. Recent researches have focused on studying the metabolites obtained, which might have a beneficial effect on the large intestine cells and/or bacteria and also be absorbed to exert a biological action (Gullón, Pintado, Barber, et al., 2015a). In this way, Cilla, Alegría, Barberá, & Lagarda (2013, chap. 6) reported that the applications of combined systems, that include the fractions obtained from simulated human digestion (gastrointestinal and/or colonic fermentation) and the incorporation of cell culture-based models, allow to evaluate bioaccessibility and to conduct bioactivity studies, in order to gain better insight from a nutritional/functional point of view of the chemopreventive action derived from foods and bioactive compounds in cell models of disease.

Bohn et al. (2015) published a review about gaps of knowledge on the bioaccessibility of bioactive compounds in which the effect of food matrix and food processing was also commented; but this review was mainly focused on factors effecting micelle formation, co-constituents influencing influx and efflux *via* transporter systems or altering phase I/II metabolism, as these have often been overlooked or excluded from consideration.

3.2.2. Effect of food matrix on bioaccessibility of bioactive compounds during the in vitro digestion process

The bioaccessibility of bioactive compounds from solid matrices must also be taken into account since only the compounds released from the food matrix and/or absorbed in the small intestine are potentially bioavailable and able to exert their beneficial effects (Tagliazucchi et al., 2010; Tagliazucchi et al., 2012). The main food components are proteins, carbohydrates, fiber and fats, and their interactions with phytochemicals must also been considered. It is clear that the stability of bioactive compounds during gastrointestinal digestion depends on their structure and the food matrix. For this reason, different studies to investigate the effects of the food matrix and food components on the bioaccessibility of bioactive compounds from different sources, using *in vitro* gastrointestinal digestion models, have been proposed (Table 3).

Fruits and vegetables possess matrices rich in dietary fiber, whose association with phytochemicals modulates their relative bioaccessibility (Alminger et al., 2014). In a study comparing the stability and bioaccessibility of carotenoids in pure forms or from whole food, Courraud, Berger, Cristol, and Avallone (2013) demonstrated that vitamin A and carotenoid standards were unstable, whereas food carotenoids were generally better protected by the food matrix (30–100% recovery compared with 7–30% for standards). Podsędek, Redzynia, Klewicka, and Koziołkiewicz (2014) studied the stability and antioxidant capacity of anthocyanins present in raw red cabbage and in its anthocyanin-rich extract, to evaluate the effect of the cabbage composition. The results also demonstrated that the food matrix is an important factor influencing the stability of red cabbage acylated anthocyanins subjected to *in vitro* gastrointestinal digestion. The authors suggested that vegetable constituents (mainly dietary fiber) protect the labile anthocyanins from degradation under the physiological conditions simulated.

Although, it is clear that the susceptibility of phytochemicals to degradation increases after their release from the food matrix, other interactions with compounds released form the food matrix(including soluble fibers) and overall viscosity may also affect their bioaccessibility (Alminger et al., 2014; Schwiggert, Mezger, Schimpf, Steingass, & Carle, 2012). Several studies have reported that molecular interactions between dietary fibers and phenolic compounds could negatively affect their bioaccessibility (Bouayed et al., 2011; Palafox-Carlos, Ayala, & Gonzalez-Aguilar, 2011; Alminger et al., 2014), as fiber-entrapped polyphenols are both poorly extractable and barely soluble in gastrointestinal fluids. Some of these studies have even shown that this interaction may not only limit their absorption, but also prevent the hydroxyl groups from polyphenols from stabilizing free radicals. This effect limits the bioaccessibility and consequently lowers the antioxidant activity due to the fewer hydroxyl groups available to stabilize radicals (Palafox-Carlos et al., 2011). Velderrain-Rodríguez et al. (2016) also reported that this decrease in antioxidant properties could be related to its instability due to changes in pH during digestion. So, foods with a high amount of insoluble fiber and/or phytochemicals bound to dietary fiber or entrapped in the food structures had lower levels of bioaccessible phenolic compounds and so a lower antioxidant capacity after *in vitro* digestion. It should be noted that the greatest loss of these compounds takes place in the intestine and colon, not during gastric digestion (Podsędek et al., 2014). Moreover, recent studies have demonstrated that in this type of food, the action of bacterial enzymes dramatically increases the antioxidant potential of the food residues in the lower gastrointestinal tract (Azurra-Papillo, Vitaglione, Graziani, Gokmen, & Fogliano, 2014; Napolitano et al., 2008).These findings suggest the need to reconsider the correlations performed and it would be advisable to include such measurements after the enzymatic digestion procedure, including microbiota-like bacterial enzymes, to obtain a more reliable picture, particularly when the health effects of the foods within the gastrointestinal tract are being considered (Azurra-Papillo et al., 2014).

However, not only dietary fibers affect the release of bioactive compounds during the *in vitro* digestion process, and several studies have highlighted the role of proteins and fats in this process. Mullen, Edward, Crozier, and Serafini (2008) reported a positive effect of the fat content on the bioavailability of pelargonidin 3-O-glucoside from strawberries; their bioavailability was higher when strawberries were consumed with cream due to positive effect of the fat in the cream on the absorption of strawberries in metabolism. Ortega, Reguant, Romero, Macia, and Motilva (2009) reported that during the *in vitro* digestion of cocoa food products, the extractability of phenolic acids, flavonoids and proanthocyanidins appeared to be improved in the presence of fat, increasing by a factor of1.2 to 3 in cocoa liquour (50% fat content) compared to cocoa powder (15% fat content). Other authors have also reported the preserving effect of fat/oil on the total phenolic content during digestion, an effect that could be related to the delay in absorption and metabolism of fatty foods that resulted in greater polyphenol absorption (Sengul et al., 2014).

The affinity of milk and egg proteins as well as gelatins for polyphenols depends on both the protein and phenolic structures (Bohin, Vincken, Van der Hijden, & Gruppen, 2012). For example, chlorogenic acid associated with milk caseins rather than with β-lactoglobulin, and this complexation was relatively stable in simulated gastric and intestinal steps (Dupas, Marset-Baglieri, Ordonaud, Ducept, & Maillard, 2006). Keogh, Mclnemey, and Clifton (2007) determined that the absorption of flavonoids in milk chocolate decreased due to double bonds formed between flavonoids and milk proteins.

Sengul et al. (2014) proposed an interesting study to understand how the food matrix and individual food components affect the bioavailability of phenolics, especially the anthocyanins found in

Table 3
Recent studies about the effect of food matrix on antioxidant capacity and bioaccesssibility of bioactive compounds during the *in vitro* digestion process.

Type of food matrix	Bioactive compound	Properties evaluated[a]	References
Plant foods matrix	Polyphenols	Antioxidant properties	Azurra-Papillo et al. (2014)
Dietary fiber	Polyphenols	Bioaccessibility	Carlos et al. (2011)
	Vitamin A and carotenoids	Bioaccessibility	Courraud et al. (2013)
	Phenolic compounds	Bioaccessibility	Velderrain-Rodríguez et al. (2016)
	Phenolics and anthocyanins	Bioaccessibility	Sengul et al. (2014)
	Polyphenols	Bioaccessibility	Palafox-Carlos et al. (2011)
	Polyphenols	Bioaccessibility and antioxidant properties	Bouayed et al. (2011)
	Carotenoid	Bioaccessibility	Schwiggert et al. (2012)
Soluble dietary fiber	Polyphenols	Bioaccessibility	Ortega, Macia, Romero, Reguant, and Motilva (2011)
Solid food matrices (peach, plums, prunes, walnuts and tomatoes)	Polyphenols, flavonoids, anthocyanins and carotenoids	Bioaccessibility	Tagliazucchi et al. (2012)
Red Cabbage	Anthocyanins	Stability and antioxidant properties	Podsędek et al. (2014)
Chocolate matrix (fats, proteins and dietary fiber)	Polyphenols	Digestibility and bioaccessibility	Serafini et al. (2003); Keogh et al. (2007); Ortega et al. (2009); Neilson et al., 2009Fogliano et al. (2011)
Coffe and milk	Polyphenols	Antioxidant properties	Dupas et al. (2006)
Fat matrix	Polyphenolic compounds	Bioaccessibility	Mullen et al. (2008)
Vegetable oil (hazelnut oil)	Polyphenols	Bioaccessibility	Ortega et al. (2011)
Blueberry, oat meal and milk	Polyphenols	Antioxidant properties and bioaccessibility	Cebeci and Sahin-Yesilcubuk (2014)
Carob flour	Polyphenols	Bioaccessibility	Ortega et al. (2011)
Dairy and egg	Polyphenols (grape extracts)	Bioaccessibility and antioxidant properties	Pineda-Vadillo et al. (2016)

[a] Bioaccessibility is evaluated as bioaccessibility index, representing the proportion of the amount of the bioactive compound in the soluble fraction of the digested sample respect to its amount in the total digested sample (soluble + non-soluble fraction). Antioxidant properties are evaluated comparing the antioxidant activity in the undigested sample (using antioxidant methods such as DPPH, ABTS, FRAP, FIC, *etc*.) respect to the same values after each phase of *in vitro* gastrointestinal digestion. Stability and digestibility of each bioactive compound is estimated as its amount after each digestion phase respect to the amount in the undigested sample.

pomegranate fruit (one of the richest sources of phenolics). Model systems composed of both commonly consumed foods - liquid foods (sunflower oil, skim milk, soy milk, honey, cream, skim plain yogurt, probiotic yogurt and lemon juice) and solid foods (minced lean meat, bread, read apple, soybean and wheat starch) - and food components (soy protein, casein, meat protein, gluten, stearic acid, linoleic acid, starch, lactose, galactose, fructose, glucose, pectin, cellulose, ascorbic acid, tocopherol, citric acid and salt) were developed. The results showed that the phenolic compounds from pomegranate were more stable to gastrointestinal digestion than anthocyanins and that they were mostly lost during pancreatic digestion rather than gastric digestion. By and large, the consumption of pomegranate with foodstuffs or food components exerted an inhibiting effect or no effect on the total phenolic content. The preserving effect of oil and carbohydrates on the total phenolic content during digestion was also observed in this study. By contrast, significant decreases during gastric digestion were evident in both the total phenolic and anthocyanin content of pomegranate when it was consumed with foods rich in protein, such as milk, bread, yogurt, soy protein, casein and meat protein.

In short, the application of *in vitro* simulated gastrointestinal digestion has demonstrated that food components or food matrices have different effects on bioactive compounds, and, in some cases, only a minor fraction of the total quantity of these compounds in foods is potentially bioaccessible. So, while developing or consuming a functional food product, the interaction of the bioactive compound with a food component in a given food matrix needs to be taken into consideration to increase their bioaccessibility.

Another interesting application that has emerged in the recent years is the use of *in vitro* digestion models in nanotechnology, more specifically for assessing the digestion and absorption of engineered nanomaterials (metal/mineral-based, soft lipid and solid biochemical macromolecules, including new proteins, polysaccharides and nucleic acids) released from food matrices. A recent review published on this aspect also highlighted the need to further adapt and standardize the available models and the corresponding analytical methods to allow quantification of the digestive fate of engineered nanomaterials, including their uptake across the gastrointestinal barrier (Lefebvre et al., 2015).

That the interest of these studies remains very high is clear; an example of this is the recent review published about their contribution for a better and extensive understanding of *in vivo* digestion conditions in different groups of the population (infants, elderly and patients of cystic fibrosis or gastric bypass surgery) which would offer better opportunities to develop relevant products with high bioefficacy (Levi et al., 2017). *Improved in vitro digestion stability of bioactive compounds by nano-delivery systems*

As can be seen above, the bioavailability of bioactive compounds contained in foods is affected by their solubility and stability, the food matrix in which they are included and the location in the human gastrointestinal tract where they are released, often in response to an environmental trigger, such as pH, ionic strength or enzyme activity. Therefore several approaches to increase the solubility, stability (mainly protection against oxidation) and bioaccessibility (biosorption) of these bioactive compounds, whether naturally present in foods or intentionally added, have been exploited in the last decade (Bakowska-Barczak & Kolodziejczyk, 2011; Çam, Içyer, & Erdogan, 2014; Jilani, Cilla, Barberá, & Hamdi, 2015, 2016; Li, Lee, Shin, Chen, & Park, 2015; Li, Shin, Chen, & Park, 2015; Li, Shin, Lee, Chen, & Park, 2016; Saenz, Tapia, Chavez, & Robert, 2009; Shin, Chung, Kim, Joung, & Park, 2013; Wang et al., 2015).

In order to better integrate some of these bioactive compounds into a food matrix or beverage system, nano-delivery systems made of food grade materials have attracted much attention (Fathi, Mozafari, & Mohebbi, 2012; Li et al., 2016). A delivery system is defined as one in which a bioactive material is entrapped in a carrier to control the rate of bioactive release. A nano-delivery system (smaller than 100 nm) may confer bioactive compounds with a rapid dissolution speed, higher stability, a tailored release pattern, higher permeation rates, higher bioavailability and other advantages compared with other similar delivery system (micro-sized or larger) (McClements, 2015; Weiss, Gaysinksy, Davidson, & McClements, 2009). Typically, food applicable nano-delivery systems can be carbohydrate, protein or lipid-based,

Table 4
Recent studies about the use of nanodelivery systems for coating bioactive compounds and their behaviour in the *in vitro* digestion process.

Type of nanosystem	Stabilization	Bioactive compounds	References
Nanoemulsions		Astaxanthin	Kim et al. (2012) Acevedo et al. (2014)
Nanoemulsions	β-lactoglobulin	Quercetin	Pool et al. (2013)
Nanoemulsions	Modified starches	B-carotene	Liang et al. (2013)
Nanoemulsions		Lycopene	Kim et al. (2014)
Nanoemulsions	Soy protein	Beetroot pomace extract	Tumbas-Šaponjac et al. (2016)
Nanoemulsions	Chitosan	Curcumin	Shin et al. (2013); Li et al. (2016)
		Curcumin	Ahmed, Li, McClements, and Xiao (2012)
Nanoemulsions	Lactoferrin and lactoferrin/alginate	Curcumin	Pinheiro, Coimbra, and Vicente (2016)
Nanoemulsions	Carotenoids (asthaxantin and lycopene)		Acevedo et al. (2014); Ha et al. (2015); Sotomayor-Gerding et al. (2016)
Nanoemulsions	Modified starch	β-Carotene	Liang et al. (2013)
Nanoemulsions	Binary emulsifiers and β-cyclodextrin complexes	Tocopherols and phenolic compounds	Cheong, Tan, and Nyam (2016a, 2016b)
Nanoemulsions	Different carrier oils	β-Carotene	Qian, Decker, Xiao, and McClements (2012)
Nanoliposomes		Epigallocatechin gallate from green tea	Zou et al. (2014)
Nanoliposomes	Alginate-Chitosan	Medium-chain fatty acids	Liu et al. (2013)
Nanoliposomes	Soy lecithin	Green tea catechins	Rashidinejad et al. (2016)
Nanoliposomes		Curcumine	Zou et al. (2016)
Nanoparticles	Witepsol and camauba	Rosmarinic acid	Madureira et al. (2016)
Nanoparticles	Pluronic F127 and lecithin	B-Carotene	Chuacharoen and Sabliov (2016)
Nanoparticles	β-Lactoglobulin-dextran	B-Carotene	Yi, Lam, Yokoyama, Cheng, and Zhong (2014)
Nanoparticles		Curcumin	Noack, Oidtmann, Kutza, and Mäder (2012)
Nanoparticles		Polyphenol compounds	Pool et al. (2012)

although the possibility of industrial production and the greater encapsulation efficiency and lower toxicity attributed to lipid-based systems have tended to attract more attention (Aditya et al., 2013; Fathi et al., 2012; Livney, 2015). As a consequence, various kinds of lipid-based nano-delivery systems have been evaluated to encapsulate bioactive compounds in order to better incorporate them into food and beverage systems, including nanoemulsions, nanoliposomes, nanoparticles and nanospheres (Table 4) However, the stability and the absorption efficiency of these carriers within the gastrointestinal tract is still a major barrier, which has led to growing interest in understanding the digestion process of food colloids.

3.2.2.1. Nanoemulsions. Oil in water (O/W) nanoemulsions are colloidal dispersion systems composed of small lipid droplets (50–100 nm) dispersed within an aqueous medium (McClements, 2012). This structure is particularly attractive for encapsulating, protecting and transporting lipophilic nutraceuticals for food and related applications. The relatively small size of the droplets in nanoemulsions provides them with a number of potential advantages over conventional emulsions: high optical clarity, good stability for gravitational separation and particle aggregation, and increased bioavailability (Liu, Sun, Li, Liu, & Xu, 2006; Shakeel & Ramadan, 2010; McClements & Rao, 2011). On the other hand, there is a limit to the amount of a bioactive component that can be successfully incorporated into a nanoemulsion before crystals are formed, which may lead to physical instability of the delivery system as well as a reduction in the bioaccessibility of the encapsulated component (Li, Du, Jin, & Du, 2012). These nanoemulsions can been prepared using different methods, including high-pressure homogenization, ultrasonication, emulsification-evaporation, *etc*. Kim, Hyun, Yun, Lee, and Byun (2012) used high pressure homogenization to prepare nanoemulsions of supercritical CO_2 extracted astaxanthin which were unaffected during storage under light and thermal conditions. Acevedo et al. (2014) found that these nanoemulsions also exerted a higher antioxidant protective effect against cellular oxidative stress and oxidative stability than free astaxanthin. Lycopene nanoemulsions (with linseed oil) were prepared by Kim, Ha, Choi, and Ko (2014) using an emulsification-evaporation method. Ha et al. (2015) and Sotomayor-Gerding et al. (2016) reported that such nanoemulsions protected the antioxidant activity and improved the bioaccessibility of lycopene-enriched tomato extract. Nanoemulsions are thermodynamically unstable and need certain emulsifiers or encapsulating methods on the oil-water interface to stabilize the colloidal system (Gonnet, Lethuaut, & Boury, 2010). Biopolymer is usually used for coating nanoemulsions to increase the stability and, absorption rate, as well as to modulate the payload release pattern (Abbas, Bashari, Akhtar, Li, & Zhang, 2014; Ozturk, Argin, Ozilgen, & McClements, 2015). Chitosan is a natural polysaccharide widely applied used in functional foods and recently studied as a coating for the encapsulation of several bioactive compounds (Shin et al., 2013). Li et al. (2016) reported that chitosan coatings inhibit the degradation of curcumin during thermal and UV irradiation treatment but may interfere with the lipolysis of nanoemulsions during *in vitro* digestion, which also slightly decreases its bio-accessibility. Liang, Shoemaker, Yang, Zhong, and Huang (2013) reported that, through *in vitro* digestion, the bioaccessibility of β-carotene was significantly improved after encapsulation in nanoemulsions stabilized by modified starches. Pool, Mendoza, Xiao, and McClements (2013) reported that quercetin dissolved in nanoemulsions stabilized by a globular protein (β-lactoglobulin) had higher bioaccessibility than quercetin dissolved in bulk oils or in bulk water.

3.2.2.2. Nanoliposomes. Nanoliposome is a new technology for the encapsulation and delivery of bioactive compounds (Zou et al., 2014). Liposomes (spherical bilayer vesicles resulting from the dispersion of polar lipids in aqueous solvents) have been widely studied for their ability to act as drug delivery vehicles by shielding reactive or sensitive compounds prior to release (Liu et al., 2011; Schroeder, Kost, & Barenholz, 2009). Nanoliposomes, measuring less than 100 nm, can be prepared using different methodologies such as extrusion, sonication and dynamic high pressure microfluidization among others (Zou et al., 2014). Compared with other delivery systems, liposomes have several benefits like (*i*) the option of large scale production, (*ii*) target ability, and (*iii*) the ability to transport water-soluble, water-insoluble and amphiphilic compounds (Chen, Han, Cai, & Tang, 2010; Fathi et al., 2012; Laye, McClements, & Weiss, 2008). Nevertheless, the applied of nanoliposomes have been limited by different factors such as their insufficient physical and digested stability (short release time) in the gastrointestinal tract, the disruption of liposome integrity and leakage of the encapsulated molecule (Liu, Jianhua, Wei, Ti, & Chengmei, 2013;

Reza, Johnson, Hatziantoniou, & Demetzos, 2008). To improve nanoliposomal stability a variety of surface modified systems have been developed, including poly-surface-conjugated nanoliposomes (Ramez & Palmer, 2011), chitosan coated nanoliposomes (Liu et al., 2013), silica external-layered nanoliposomes (Mohanraj, Barnes, & Prestidge, 2010) and protein site-specific modified nanoliposomes (Guo, Wu, & Guo, 2012).

Zou et al. (2014) successfully applied nanoliposome encapsulation to epigallocatechin gallate (from green tea) and they found that the degradation rate of their antioxidant activities during *in vitro* digestion was slowed by this method. Liu et al. (2013) developed an alginate-chitosan-coated nanoliposome to make better lipid membrane stability and avoid depletion of encapsulated food components (mainly medium chain fatty acids). These authors found that this delivery system might better resist lipolytic degradation and facilitate a lower level of encapsulated component release in simulated gastrointestinal conditions. Rashidinejad, Birch, and Everett (2016) encapsulated green tea catechins in nanoliposomes using soy lecithin and added them into a full-fat cheese; the authors reported a significant increase in the total phenolic content and antioxidant activity of the full-fat cheese and no effect on the pH or proximate composition. In the same way, these authors (Rashidinejad et al., 2016) found that individual catechins were recovered in different quantities comprised between 15 and 52% from cheese digesta after 6 h of gastrointestinal digestion; the authors also provided suggestion for the association of nanoliposomes with the surface of milk fat globules inside the cheese matrix.

3.2.2.3. Solid nanoparticles. Couvreur, Dubernet, and Puisieux (1995) defined nanoparticles as sub-micron solid particles, which may be used for the nano-encapsulation of compounds that showed bioactivity. However, it should be borne in mind that its possible obtained different nano-compunds like as nanoparticles, nanospheres or nanocapsules according on the method of preparation as mentioned Faridi-Esfanjani and Jafari (2016). Thus, Nanospheres can be considered matrix systems in which the bioactive compounds are physically and uniformly dispersed, while nanocapsules can be considered vesicular systems in which the bioactive compounds are confined in a cavity consisting of an internal liquid core enclosed in a polymeric membrane (Couvreur et al., 1995). To obtain the biodegradable polymeric nanoparticles, different compounds could be used for example (*i*) proteins like gelatin, whey or milk proteins, (ii) polysaccharides as chitosan, sodium alginate and starch, or (*iii*) synthetic polymers as reported Faridi-Esfanjani and Jafari (2016). At present, the use of biodegradable polymeric nanoparticles has attracted the attention of several scientific research groups mainly in food fields thanks to their favourable properties which include as mentioned Bae and Kataoka (2009) a good biocompatibility, easy design and preparation, structure variations and very interesting bio-mimetic characters. Especially in the field of smart bioactive carriers, polymer nanoparticles can deliver bioactive compounds directly to the intended site of action (Faridi-Esfanjani & Jafari, 2016). Conversely, natural nano-carriers have appeared as very attractive choices for controlled systems with bioactive compounds due to their resemblance to the extracellular matrix in the human body and various other favourable physicochemical properties. In this way, casein nanoparticles could be used to bind phenolic compounds throughout hydrophobic interactions between the phenolic rings and prolines, wrapping the casein around the phenolic compounds as reported Jöbstl, O'Connell, Fairclough, and Williamson (2004).

There are some reviews about the nano-encapsulation of bioactive compounds, most of them focused in the methods used for their preparation, and characterization, improving stability, and the suitability requirements for the bioactive compounds selected (Faridi-Esfanjani & Jafari, 2016; Fathi et al., 2012; Livney, 2015). However, the number of studies on the application of *in vitro* gastrointestinal digestion methods to evaluate the effect of these nanoencapsulation methods on the stability, bioavailability and bioaccessibility of the bioactive compounds is limited. Whatever the case, it is true that a greater number of such studies deal with nanoemulsions, followed by nanoliposomes while very few look at nanoparticles.

Some of these studies have compared the effectiveness of each encapsulation method in protecting the bioactive compound during the *in vitro* digestion process. Chuacharoen and Sabliov (2016) carried out a work with two different types of delivery system, such as nanoparticles and nanoemulsions and they analysed the capacity of these compounds to improve the physicochemical stability and the antioxidant properties of β-carotene in the presence of milk under *in vitro* gastrointestinal environments. They reported that nanoparticles enhanced the physicchemical stability and antioxidant properties of entrapped β-carotene compared with emulsions in the presence of milk under *in vitro* gastrointestinal environments. Zou et al. (2016) investigated the potential of three nanoparticle-based delivery systems to improve curcumin bioavailability. These authors found that the loading capacity of curcumin, the capacity to protect this compound from chemical degradation and its solubilisation inside intestinal fluids depended mainly on the nanosystem composition. These authors conclude that, in general terms, lipid nanosystems mainly nanoemulsions appeared to be the most effective at increasing the amount of curcumin available for absorption (Zou et al., 2016).

In view of the results of some of these papers, we conclude that each type of delivery nanosystem (nanoemulsions, nanoliposomes or nanoparticles) has their strengths and weaknesses to encapsulate, to protect and to release bioactive compounds and those specific studies need to be considered to improve the bioavailability and bioaccessibility of the same.

4. Conclusions

In vitro gastrointestinal digestion systems are a valuable tool for understanding the behaviour of food and food components during human digestion, as demonstrated by the large number of publications that they have generated. Their application has changed with time, not only as regards the process conditions (parameters, length scale, protocols and guidance) but also in the selection of new fields of application. In the last decade, for example, the greatest changes have tried to: (*i*) standardize and harmonize *in vitro* static and dynamic systems which gastrointestinal processes are simulate by defining critical parameters and setting that could be applied for various ends and that allow results to be compared across research teams; (*ii*) study the effect of the food matrix on the release, bioaccessibility and antioxidant properties of different bioactive compounds present in foods; and (*iii*) develop nano-delivery systems to increase the stability of these bioactive compounds and to evaluate their behaviour in each phase of gastrointestinal digestion.

The results obtained have contributed to understanding the behaviour of these compounds with bioactivity and hence to improve the development of new healthy foods.

References

Abbas, S., Bashari, M., Akhtar, W., Li, W. W., & Zhang, X. M. (2014). Process optimization of ultrasound-assisted curcumin nanoemulsions stabilized by OSA modified starch. *Ultrasonics Sonochemistry, 21*, 1265–1274.

Acevedo, F., Rubilar, M., Jofré, I., Villarroel, M., Navarrete, P., Esparza, M., & Shene, C. (2014). Oil bodies as a potential microencapsulation carrier for astaxanthin stabilization and safe delivery. *Journal of Microencapsulation, 31*, 488–500.

Aditya, N. P., Shim, M., Lee, I., Lee, Y., Im, M. H., & Ko, S. (2013). Curcumin and genistein coloaded nanostructured lipid carriers: In vitro digestion and antiprostate cancer activity. *Journal of Agricultural and Food Chemistry, 61*, 1878–1883.

Ahmed, K., Li, Y., McClements, D. J., & Xiao, H. (2012). Nanoemulsion and emulsion-based delivery systems for curcumin: Encapsulation and release properties. *Food Chemistry, 132*, 799–807.

Almaas, H., Cases, A., Devold, T. G., Holm, H., Langsrud, T., Aabakken, L., ... Vegarud, G. E. (2006). In vitro digestion of bovine and caprine milk by human gastric and duodenal enzymes. *International Dairy Journal, 16*, 961–968.

Alminger, M., Aura, A. M., Bohn, T. C., Dufour, S. N. E. L., Gomes, A., Karakaya, S., ... Santos, C. N. (2014). In vitro models for studying secondary plant metabolite digestion and bioaccessibility. *Comprehensive Reviews in Food Science and Food Safety, 13*, 413–436.

Aravena, G., García, O., Muñoz, O., Pérez-Correa, J. R., & Parada, J. (2016). The impact of cooking and delivery modes of thymol and carvacrol on retention and bioaccessibility in starchy foods. *Food Chemistry, 196*, 848–852.

Aschoff, J. K., Kaufmann, S., Kalkan, O., Neidhart, S., Carle, R., & Schwiggert, R. M. (2015). *In vitro* bioaccessibility of carotenoids, flavonoids, and vitamin C from differently processed oranges and orange juices [*Citrus sinensis* (L.) Osbeck]. *Journal of Agricultural and Food Chemistry, 63*, 578–587.

Augustin, M. A., Sanguansri, L., Rusli, J. K., Shen, Z., Cheng, L. J., Keogh, J., & Clifton, P. (2014). Digestion of microencapsulated oil powders: *in vitro* lipolysis and *in vivo* absorption from a food matrix. *Food & Function, 5*, 2905–2912.

Aura, A. M., Martin-Lopez, P., O'Leary, K. A., Willianson, G., Oksman-Caldentey, K. M., Poutanen, K., & Santos-Buelga, C. (2005). In vitro metabolism of anthocyaninsby human gut microflora. *European Journal of Nutrition, 44*, 133–142.

Azurra-Papillo, V., Vitaglione, P., Graziani, G., Gokmen, V., & Fogliano, V. (2014). Release of antioxidant capacity from five plant foods during a multistep enzymatic digestion protocol. *Journal of Agricultural and Food Chemistry, 62*, 4119–4126.

Bae, Y., & Kataoka, K. (2009). Intelligent polymeric micelles from functional poly (ethylene glycol)-poly (amino acid) block copolymers. *Advanced Drug Delivery Reviews, 61*, 768–784.

Bakowska-Barczak, A. M., & Kolodziejczyk, P. P. (2011). Black currant polyphenols: Their storage stability and microencapsulation. *Industrial Crops and Products, 34*, 1301–1309.

Bermúdez-Soto, M. J., Tomás-Barberán, F. A., & García-Conesa, M. T. (2007). Stability of polyphenols in chokeberry (*Aronia melanocarpa*) subjected to *in vitro* gastric and pancreatic digestion. *Food Chemistry, 102*, 865–874.

Bialonska, D., Kasimsetty, S. G., Khan, S. I., & Ferreira, D. (2009). Urolithins, intestinal microbial metabolites of pomegranate ellagitannins, exhibit potent antioxidant activity in a cell-based assay. *Journal of Agricultural and Food Chemistry, 57*, 10181–10186.

Blancas-Benitez, F. J., Mercado-Mercado, G., Quiros-Sauceda, A. E., Montalvo-Gonzalez, E., Gonzalez-Aguilar, G. A., & Sayago-Ayerdi, S. G. (2015). Bioaccesibility of polyphenols associated with dietary fiber and in vitro kinetics release of polyphenols in Mexican 'Ataulfo' mango (*Mangifera indica* L.) by-products. *Food & Function, 6*, 859–868.

Bohin, M. C., Vincken, J. P., Van der Hijden, H., & Gruppen, H. (2012). Efficacy of food proteins as carriers for flavonoids. *Journal of Agricultural and Food Chemistry, 60*, 4136–4143.

Bohn, T., Carriere, F., Day, L., Deglaire, A., Egger, L., Freitas, D., Golding, M., Le Feunteun, S., Macierzanka, A., Menard, O., et al. (2017). Correlation between in vitro and in vivo data on food digestion. What can we predict with static in vitro digestion models? *Critical Reviews in Food Science and Nutrition, 59*, 1307–1323.

Bohn, T., McDougall, G. J., Alegria, A., Alminger, M., Arrigoni, E., Aura, A. M., ... Santos, C. N. (2015). Mind the gap-deficits in our knowledge of aspects impacting the bioavailability of phytochemicals and their metabolites–a position paper focusing on carotenoids and polyphenols. *Molecular Nutrition & Food Research, 59*, 1307–1323.

Boise, S., & Eggum, B. O. (1991). Critical evaluation of in vitro methods for estimating digestibility in simple-stomach animals. *Nutrition Research Reviews, 4*, 141–162.

Bornhorst, G. M., Gouseti, O., Wickham, M. S. J., & Bakalis, S. (2016). Engineering digestion: Multiscale processes of food digestion. *Journal of Food Science, 81*, R534–R543.

Bouayed, J., Deußer, R., Hoffmann, L., & Bohn, T. (2012). Bioaccessible and dialysable polyphenols in selected apple varieties following *in vitro* digestion vs. their native patterns. *Food Chemistry, 131*, 1466–1472.

Bouayed, J., Hoffmann, L., & Bohn, T. (2011). Total phenolics, flavonoids, anthocyanins and antioxidant activity following simulated gastro-intestinal digestion and dialysis of apple varieties: Bioaccessibility and potential uptake. *Food Chemistry, 128*, 14–21.

Brandon, E. F. A., Oomen, A. G., Rompelberg, C. J. M., Versantwoort, C. H. M., Van Engelen, J. G. M., & Sips, A. J. A. M. (2006). Consumer product in vitro digestion model: Bioaccessibility of contaminants and its application in risk assessment. *Regulatory Toxicology and Pharmacology, 44*, 161–171.

Çam, M., Içyer, N. C., & Erdogan, F. (2014). Pomegranate peel phenolics: Microencapsulation, storage stability and potential ingredient for functional food development. *LWT- Food Science and Technology, 55*, 117–123.

Campbell, G., Arcand, Y., & Mainville, I. (2011). Development of a tissue mimicking stomach construct for in vitro digestive system. *Canada-UK gut and health workshop* (pp. 24–25). Canada: Saint-Hyacinthe, QC.

Carlos, H. P., Ayala, J. F., & Gonzalez-Aguilar, A. G. (2011). The role of dietary fiber in the bioaccessibility and bioavailability. *Journal of Food Science, 76*, R6–R15.

Cebeci, F., & Sahin-Yesilcubuk, N. (2014). The matrix effect of blueberry, oat meal and milk on polyphenols, antioxidant activity and potential bioavailability. *International Journal of Food Science and Nutrition, 65*, 69–78.

Chadegani, A. A., Salehi, H., Yunus, M. M., Farhadi, H., Fooladi, M., Farhadi, M., & Ebrahim, N. A. (2013). A comparison between two main academic literature collections: Web of science and Scopus databases. *Asian Social Science, 9*, 18–26.

Chattertona, D. E. W., Rasmussen, J. T., Heegaard, C. W., Sorensen, E. S., & Petersen, T. E. (2004). In vitro digestion of novel milk protein ingredients for use in infant formulas: Research on biological functions. *Trends in Food Science and Technology, 15*, 373–383.

Chen, C., Han, D., Cai, C., & Tang, X. (2010). An overview of liposome lyophilization and its future potential. *Journal of Controlled Release, 142*, 299–311.

Chen, G. L., Chen, S. G., Zhao, Y. Y., Luo, C. X., Li, J., & Gao, Y. Q. (2014). Total phenolic contents of 33 fruits and their antioxidant capacities before and after in vitro digestion. *Industrial Crops and Products, 57*, 150–157.

Cheong, A., Tan, C. P., & Nyam, K. L. (2016a). *In vitro* evaluation of the structural and bioaccessibility of kenaf seedoil nanoemulsions stabilised by binary emulsifiers and b-cyclodextrin complexes. *Journal of Food Engineering, 189*, 90–98.

Cheong, A., Tan, C. P., & Nyam, K. L. (2016b). In-vitro gastrointestinal digestion of kenaf seed oil-in-water nanoemulsions. *Industrial Crops and Products, 87*, 1–8.

Chitindingu, K., Benhura, M. A. N., & Muchuweti, M. (2015). *In vitro* bioaccessibility assessment of phenolic compounds from selected cereal grains: A prediction tool of nutritional efficiency. *LWT- Food Science and Technology, 63*, 575–581.

Chuacharoen, T., & Sabliov, C. (2016). The potential of zein nanoparticles to protect entrapped β-carotene in the presence of milk under simulated gastrointestinal (GI) conditions. *LWT- Food Science and Technology, 72*, 302–309.

Cilla, A., Alegría, A., Barberá, R., & Lagarda, M. J. (2013). Foods or bioactive constituents of foods as chemopreventives in cell lines after simulated gastrointestinal digestion: A review. In J. A. Morales-González (Ed.). *Oxidative stress and chronic degenerative diseases - A role for antioxidants* (pp. 131–151). U.K.: Intech.

Cilla, A., Bosch, L., Barberá, R., & Alegría, A. (2018). Effect of processing on the bioaccessibility of bioactive compounds – A review focusing on carotenoids, minerals, ascorbic acid, tocopherols and polyphenols. *Journal of Food Composition and Analysis*. http://dx.doi.org/10.1016/j.jfca.2017.01.009 in press.

Cilla, A., González-Sarrías, A., Tomás-Barberán, F. T., Espín, J. C., & Barberá, R. (2009). Availability of polyphenols in fruit beverages subjected to in vitro gastrointestinal digestion and their effects on proliferation, cell-cycle and apoptosis in human colon cancer Caco-2 cells. *Food Chemistry, 114*, 813–820.

Cilla, A., Perales, S., Lagarda, M. J., Barberá, R., Clemente, G., & Farré, R. (2011). Influence of storage and in vitro gastrointestinal digestion on total antioxidant capacity of fruit beverages. *Journal of Food Composition and Analysis, 24*, 87–94.

Colantuono, A., Ferracane, R., & Vitaglione, P. (2016). *In vitro* bioaccessibility and functional properties of polyphenols from pomegranate peels and pomegranate peels-enriched cookies. *Food & Function, 7*, 4247–4258.

Coles, L. T., Moughab, P. J., & Darragh, A. J. (2005). In vitro digestion and fermentation methods, including gas production techniques, as applied to nutritive evaluation of foods in the hindgut of humans and other simple-stomached animals. *Animal Feed Science and Technology, 123–124*, 421–444.

Colle, I., Lemmens, L., Van Buggenhout, S., Van Loey, A., & Hendrickx, M. (2010). Effect of thermal processing on the degradation, isomerization, and bioaccessibility of lycopene in tomato pulp. *Journal of Food Science, 75*, C753–C759.

Correa-Betanzo, J., Allen-Vercoe, E., McDonald, J., Schroeter, K., Corredig, M., & Paliyath, G. (2014). Stability and biological activity of wild blueberry (*Vaccinium angustifolium*) polyphenols during simulated in vitro gastrointestinal digestion. *Food Chemistry, 165*, 522–531.

Courraud, J., Berger, J., Cristol, J. P., & Avallone, S. (2013). Stability and bioaccessibility of different forms of carotenoids and vitamin A during *in vitro* digestion. *Food Chemistry, 136*, 871–877.

Couvreur, P., Dubernet, F., & Puisieux, F. (1995). Controlled drug delivery with nanoparticles: Current possibilities and future trends. *European Journal of Pharmaceutics and Biopharmaceutics, 41*, 2–13.

Dall'Asta, M., Bresciani, L., Calani, L., Cossu, M., Martini, D., Melegari, C., ... Scazzina, F. (2016). *In vitro* bioaccessibility of phenolic acids from a commercial aleurone-enriched bread compared to a whole grain bread. *Nutrients, 8*, 42–51.

De Ancos, B., Cilla, A., Barberá, R., Sánchez-Moreno, C., & Cano, M. P. (2017). Influence of orange cultivar and mandarin postharvest storage on polyphenols, ascorbic acid and antioxidant activity during gastrointestinal digestion. *Food Chemistry, 225*, 114–124.

Dean, J. R., & Ma, R. (2007). Approaches to assess the oral bioaccessibility of persistent organic pollutants: A critical review. *Chemosphere, 68*, 1399–1407.

DeBaun, R. M., & Connors, W. (1954). Nutritional assay, relationship between in vitro enzymatic digestibility and in vivo protein evaluation of powdered wey. *Journal of Agricultural and Food Chemistry, 2*, 524–526.

Dinnella, C., Minichino, D., D'Andrea, A. M., & Monteleone, E. (2007). Bioaccessibility and antioxidant activity stability of phenolic compounds from extra-virgin olive oils during *in vitro* digestion. *Journal of Agricultural and Food Chemistry, 55*, 8423–8429.

Dupas, C. J., Marset-Baglieri, A. C., Ordonaud, C. S., Ducept, F. M. G., & Maillard, M. N. (2006). Coffee antioxidant properties: Effect of milk addition and processing conditions. *Journal of Food Science, 71*, S253–S258.

Faridi-Esfanjani, A., & Jafari, S. M. (2016). Biopolymer nano-particles and natural nano-carriers for nano-encapsultion of phenolic compounds. *Colloids and Surfaces B: Biointerfaces, 146*, 532–543.

Fathi, M., Mozafari, M. R., & Mohebbi, M. (2012). Nanoencapsulation of food ingredients using lipid based delivery systems. *Trends in Food Science and Technology, 23*, 13–27.

Fawole, O. A., Opara, U. L., & Chen, L. (2015). Bioaccessibility of total phenolic concentration and antioxidant capacity of pomegranate fruit juice and marc after *in vitro* digestion. *Acta Horticulturae,* (1079), 285–290.

Fazzari, M., Fukumoto, L., Mazza, G., Livrea, M. A., Tesoriere, L., & Di Marco, L. (2008). In vitro bioavailability of phenolic compounds from five cultivars of frozen sweet cherries (*Prunus avium* L.). *Journal of Agricultural and Food Chemistry, 56*, 3561–3568.

Fernández-García, E., Carvajal-Lérida, I., Jarén-Galán, M., Garrido-Fernández, J., Pérez-Gálvez, A., & Hornero-Méndez, D. (2012). Carotenoids bioavailability from foods: From plant pigments to efficient biological activities. *Food Research International, 46*, 438–450.

Fleschhut, J., Kratzer, F., Rechkemmer, G., & Kulling, E. S. (2005). Stability and biotransformation of various dietary anthocyanins *in vitro*. *European Journal of Nutrition, 45*, 7–18.

Fogliano, V., Corollaro, M. L., Vitaglione, P., Napolitano, A., Ferracane, R., Travaglia, F., ... Gibson, G. (2011). *In vitro* bioaccessibility and gut biotransformation of polyphenols present in the water-insoluble cocoa fraction. *Molecular Nutrition & Food Research, 1*, S44–S55.

Fuller, M. F. (1991). *In vitro digestion for pigs and poultry*. Wallington, UK: CAB International.
Gil-Izquierdo, A., Gil, M. I., Ferreres, F., & Tomás-Barberán, F. A. (2001). *In vitro* availability of flavonoids and other phenolics in orange juice. *Journal of Agricultural and Food Chemistry, 49*, 1035–1041.
Golding, M., & Wooster, T. J. (2010). The influence of emulsion structure and stability on lipid digestion. *Current Opinion in Colloid & Interface Science, 15*, 90–101.
Gong, L., Jin, C., Wu, X., & Zhang, Y. (2013). Relationship between total antioxidant capacities of cereals measured before and after in vitro digestion. *International Journal of Food Science and Nutrition, 64*, 850–856.
Gonnet, M., Lethuaut, I., & Boury, F. (2010). New trends in encapsulation of liposoluble vitamins. *Journal of Control Released, 146*, 276–290.
Gonzales, G. B., Smagghe, G., Mackie, A., Grootaert, C., Bajka, B., Rigby, N., ... Van Camp, J. (2015). Use of metabolomics and fluorescence recovery after photobleaching to study the bioavailability and intestinal mucus diffusion of polyphenols from cauliflower waste. *Journal of Functional Foods, 16*, 403–413.
Guerra, A., Etienne-Mesmin, L., Livrelli, V., Denis, S., Blanquet-Diot, S., & Alric, M. (2012). Relevance and challenges in modeling human gastric and small intestinal digestion. *Trends in Biotechnology, 30*, 591–600.
Gullón, B., Pintado, M. E., Barber, X., Fernández-López, J., Pérez-Álvarez, J. A., & Viuda-Martos, M. (2015a). Bioaccessibility, changes in the antioxidant potential and colonic fermentation of date pits and apple bagasse flours obtained from co-products during simulated *in vitro* gastrointestinal digestion. *Food Research International, 78*, 169–176.
Gullón, B., Pintado, M. M., Fernández-López, J., Pérez-Álvarez, J. A., & Viuda-Martos, M. (2015b). *In vitro* gastrointestinal digestion of pomegranate peel (*Punica granatum*) flour obtained from co-products: Changes in the antioxidant potential and bioactive compounds stability. *Journal of Functional Foods, 19*, 617–628.
Guo, X., Wu, Z., & Guo, Z. (2012). New method for site-specific modification of liposomes with proteins using sortase a-mediated transpeptidation. *Bioconjugate Chemistry, 23*, 650–655.
Ha, T. V. A., Kim, S., Choi, Y., Kwak, H. S., Lee, S. J., Wen, J., & Ko, S. (2015). Antioxidant activity and bioaccessibility of size-different nanoemulsions for lycopene-enriched tomato extract. *Food Chemistry, 178*, 115–121.
Hedren, E., Diaz, V., & Svanberg, U. (2002). Estimation of carotenoids accessibility from carrots determined by an in vitro digestion method. *European Journal of Clinical Nutrition, 56*, 425–430.
Helal, A., Tagliazucchi, D., Verzelloni, E., & Conte, A. (2014). Bioaccessibility of polyphenols and cinnamaldehyde in cinnamon beverages subjected to in vitro gastropancreatic digestion. *Journal of Functional Foods, 7*, 506–516.
Henning, S. M., Zhang, Y., Rontoyanni, V. G., Huang, J., Lee, R. P., Trang, A., ... Heber, D. J. (2014). Variability in the antioxidant activity of dietary supplements from pomegranate, milk thistle, green tea, grape seed, goji, and acali: Effects of in vitro digestion. *Journal of Agricultural and Food Chemistry, 62*, 4313–4321.
Huang, H., Sun, Y., Lou, S., Li, H., & Ye, X. (2014). *In vitro* digestion combined with cellular assay to determine the antioxidant activity in Chinese bayberry (*Myrica rubra* Sieb et Zucc.) fruits: A comparison with traditional methods. *Food Chemistry, 146*, 363–370.
Hur, S. J., Decker, E. A., & McClements, D. J. (2009). Influence of initial emulsifier type on microstructural changes occurring in emulsified lipids during *in vitro* digestion. *Food Chemistry, 114*, 253–262.
Hur, S. J., Lee, S. J., Kim, D. H., Chun, S. C., & Lee, S. K. (2013). Onion extract structural changes during in vitro digestion and its potential antioxidant effect on brain lipids obtained from low- and high-fat-fed mice. *Free Radical Research, 47*(12), 1009–1015.
Hur, S. J., Lim, B. O., Decker, E. A., & McClements, D. J. (2011). *In vitro* human digestion models for food applications. *Food Chemistry, 125*, 1–12.
Janisch, K. M., Ölschläger, C., Treutter, D., & Elstner, E. F. (2006). Simulated digestion of *Vitis vinifera* seeds powder: Polyphenolic content and antioxidant properties. *Journal of Agricultural and Food Chemistry, 54*, 4839–4848.
Jilani, H., Cilla, A., Barberá, R., & Hamdi, M. (2015). Biosorption of green and black tea polyphenols into *Saccharomyces cerevisiae* improves their bioaccessibility. *Journal of Functional Foods, 17*, 11–21.
Jilani, H., Cilla, A., Barberá, R., & Hamdi, M. (2016). Improved bioaccessibility and antioxidant capacity of olive leaf (*Olea europaea* L.) polyphenols through biosorption on *Saccharomyces cerevisiae*. *Industrial Crops and Products, 84*, 131–138.
Jiwan, M. A., Duane, P., O'Sullivan, L., O'Brien, N. M., & Aherne, S. A. (2010). Content and bioaccessibility of carotenoids from organic and non-organic baby foods. *Journal of Food Composition and Analysis, 23*, 346–352.
Jöbstl, E., O'Connell, J., Fairclough, J. P. A., & Williamson, M. P. (2004). Molecular model for astringency produced by polyphenol/protein interactions. *Biomacromolecules, 5*, 942–949.
Kamiloglu, S., & Capanoglu, E. (2013). Investigating the in vitro bioaccessibility of polyphenols in fresh and sun-dried figs (*Ficus carica* L.). *Journal of Food Science and Technology, 48*, 2621–2629.
Kamiloglu, S., Capanoglu, E., Bilen, F. D., Gonzales, G. B., Grootaert, C., Van de Wiele, T., & Van Camp, J. (2015). Bioaccessibility of polyphenols from plant-processing by-products of Black Carrot (*Daucus Carota* L.). *Journal of Agricultural and Food Chemistry, 64*, 2450–2458.
Kamiloglu, S., Capanoglu, E., Bilen, F. D., Gonzales, G. B., Grootaert, C., Van De Wiele, T., & Van Camp, J. (2016). Bioaccessibility of polyphenols from plant-processing by-products of black carrot (*Daucus carota* L.). *Journal of Agricultural and Food Chemistry, 64*, 2450–2458.
Karakaya, S., & Yilmaz, N. (2007). Lycopene content and antioxidant activity of fresh and processed tomatoes and in vitro bioavailability of lycopene. *Journal of the Science of Food and Agriculture, 87*, 2342–2347.
Keogh, J. B., Mclnemey, J., & Clifton, P. M. (2007). The effect of milk protein on the bioavailability of cocoa polyphenols. *Journal of Food Science, 72*, S230–S233.
Kim, D. M., Hyun, S. S., Yun, P., Lee, C. H., & Byun, S. Y. (2012). Identification of an emulsifier and conditions for preparing stable nanoemulsions containing the antioxidant astaxanthin. *International Journal of Cosmetic Science, 34*, 64–73.
Kim, S. O., Ha, T. V. A., Choi, Y. J., & Ko, S. (2014). Optimization of homogenization evaporation process for lycopene nanoemulsion production and its beverage applications. *Journal of Food Science, 79*, N1604–N1610.
Kitabatake, N., & Kinekawa, Y. I. (1998). Digestibility of bovine milk whey protein and β-lactoglobulin in vitro and in vivo. *Journal of Agricultural and Food Chemistry, 46*, 4917–4923.
Kong, F., & Singh, R. P. (2010). A human gastric simulator (HGS) to study food digestion in human stomach. *Journal of Food Science, 75*, 627–635.
Laye, C., McClements, D., & Weiss, J. (2008). Formation of biopolymer-coated liposomes by electrostatic deposition of chitosan. *Journal of Food Science, 73*, N7–N15.
Lefebvre, D. E., Venema, K., Gombau, L., Valerio, L. G., Raju, J., Bondy, G., ... Stone, V. (2015). Utility of models of the gastrointestinal tract for assessment of the digestion and absorption of engineered nanomaterials released from food matrices. *Nanotoxicology, 9*, 523–542.
Levi, C. S., Alvito, P., Andrés, A., Assunçao, R., Barberá, R., Blanquet-Diot, S., Bourlieu, C., Brodkorb, A., Cilla, A., Deglaire, A., et al. (2017). Extending in vitro digestion models to specific human populations: Perspectives, practical tools and bio-relevant information. *Trends in Food Science & Technology, 60*, 52–63.
Li, B., Du, W., Jin, J., & Du, Q. (2012). Preservation of (−)-epigallocatechin-3-gallate antioxidant properties loaded in heat treated beta-lactoglobulin nanoparticles. *Journal of Agricultural and Food Chemistry, 60*, 3477–3484.
Li, J., Lee, I. W., Shin, G. H., Chen, X., & Park, H. J. (2015). Curcumin-Eudragit® E PO solid dispersion: A simple and potent method to solve the problems of curcumin. *European Journal of Pharmaceutics and Biopharmaceutics, 94*, 322–332.
Li, J., Shin, G. H., Chen, X. G., & Park, H. J. (2015). Modified curcumin with hyaluronic acid: Combination of pro-drug and nano-micelle strategy to address the curcumin challenge. *Food Research International, 69*, 202–208.
Li, J., Shin, G. H., Lee, I. W., Chen, X., & Park, H. J. (2016). Soluble starch formulated nanocomposite increases water solubility and stability of curcumin. *Food Hydrocolloids, 56*, 41–49.
Liang, L., Wu, X., Zhao, T., Zhao, J., Li, F., Ye, Z., ... Yang, L. (2012). *In vitro* bioaccessibility and antioxidant activity of anthocyanins from mulberry (*Morus atropurpurea* Roxb.) following simulated gastro-intestinal digestion. *Food Research International, 46*, 76–82.
Liang, R., Shoemaker, C. F., Yang, X., Zhong, F., & Huang, Q. (2013). Stability and bioaccessibility of β-carotene in nanoemulsions stabilized by modified starches. *Journal of Agricultural and Food Chemistry, 61*, 1249–1257.
Liu, W., Jianhua, L., Wei, L., Ti, L., & Chengmei, L. (2013). Improved physical and in vitro digestion stability of a polyelectrolyte delivery system based on layer-by-layer self-assembly alginate-chitosan-coated nanoliposomes. *Journal of Agricultural and Food Chemistry, 61*, 4133–4144.
Liu, W., Liu, W. L., Liu, C. M., Liu, J. H., Yang, S. B., Zheng, H. J., ... Song, X. Y. (2011). Medium-chain fatty acid nanoliposomes for easy energy supply. *Nutrition, 27*, 700–706.
Liu, W., Sun, D., Li, C., Liu, Q., & Xu, J. (2006). Formation and stability of paraffin oil-in-water nano-emulsions prepared by the emulsion inversion point method. *Journal of Colloid and Interface Science, 303*, 557–563.
Livney, Y. D. (2015). Nanostructured delivery systems in food: Latest developments and potential future directions. *Current Opinion in Food Science, 3*, 125–135.
Lucas-González, R., Navarro-Coves, S., Pérez-Álvarez, J. A., Fernández-López, J., Muñoz, L. A., & Viuda-Martos, M. (2016). Assessment of polyphenolic profile stability and changes in the antioxidant potential of maqui berry (*Aristotelia chilensis* (Molina) Stuntz) during in vitro gastrointestinal digestion. *Industrial Crops and Products, 94*, 774–782.
Madureira, A. R., Campos, D. A., Oliveira, A., Sarmiento, B., Pintado, M. M., & Gomes, A. M. (2016). Insights into the protective role of solid lipid nanoparticles on rosmarinic acid bioactivity during exposure to simulated gastrointestinal conditions. *Colloids and Surfaces B: Biointerfaces, 139*, 277–284.
Manach, C., Williamson, G., Morand, C., Scalbert, A., & Rémésy, C. (2005). Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *American Journal of Clinical Nutrition, 81*, 230S–242S.
Marcano, J., Hernando, I., & Fiszman, S. (2015). *In vitro* measurements of intragastric rheological properties and their relationships with the potential satiating capacity of cheese pies with konjac glucomannan. *Food Hydrocolloids, 51*, 16–22.
Marciani, I., Gowland, P. A., Fillery-Travis, A. J., Manoj, P., Wright, J., Smith, A., ... Spiller, R. C. (2001). Assesment of antral grinding of a model solid meal with echo-planar imaging. *American Journal of Physiology - Gastrointestinal and Liver Physiology, 280*, G844–G849.
Marciani, I., Gowland, P. A., Spiller, R. C., Manoj, P., Moore, R., Young, P., & Fillery-Travis, A. J. (2001). Effect of meal viscosity and nutrients on satiety, intragastric dilution, and emptying assessed by MRI. *American Journal of Physiology - Gastrointestinal and Liver Physiology, 280*, G1227–G1233.
Masisi, K., Beta, T., & Maghadasian, M. H. (2016). Antioxidant properties of diverse cereal grains: A review on in vitro and in vivo studies. *Food Chemistry, 160*, 90–97.
McAllister, M. (2010). Dynamic dissolution: A step closer to predictive dissolution testing? *Molecular Pharmaceutics, 7*, 1374–1387.
McClements, D. J. (2012). Nanoemulsions versus microemulsions: Terminology, differences and similarities. *Soft Matter, 8*, 1719–1729.
McClements, D. J. (2015). Nanoscale nutrient delivery systems for food applications: Improving bioactive dispersibility, stability, and bioavailability. *Journal of Food Science, 80*, N1602–N1611.
McClements, D. J., Decker, E. A., & Park, Y. (2009). Controlling lipid bioavailability trhough physic-chemical and structural approaches. *Critical Reviews in Food Science*

and Nutrition, 49, 48–67.
McClements, D. J., & Rao, J. (2011). Food-grade nanoemulsions: Formulation, fabrication, properties, performance, biological fate, and potential toxicity. *Critical Reviews in Food Science and Nutrition, 51*, 285–330.
McDougall, G. J., Dobson, P., Smith, P., Blake, A., & Stewart, D. (2005). Assessing potential bioavailabiliy of raspberry anthocyanins using an in vitro system. *Journal of Agricultural and Food Chemistry, 53*, 5896–5904.
Miao, J., Zhao, C., Li, X., Chen, X., Mao, X., Huang, H., ... Gao, W. (2016). Chemical composition and bioactivities of two common chaenomeles fruits in china: *Chaenomeles speciosa* and *Chaenomeles sinensis*. *Journal of Food Science, 81*, H2049–H2058.
Minekus, M., Alminger, M., Alvito, P., Balance, S., Bohn, T., Bourlieu, C., Carriére, F., Boutrou, R., Corredig, M., Dupont, D., et al. (2014). A standardised static in vitro digestion method suitable for food - An international consensus. *Food & Function, 5*, 1113–1124.
Mohanraj, V. J., Barnes, T. J., & Prestidge, C. A. (2010). Silica nanoparticle coated liposomes: A new type of hybrid nanocapsule for proteins. *International Journal of Pharmaceutics, 392*, 285–293.
Montalbano, A., Tesoriere, L., Diana, P., Barraja, P., Carbone, A., Spanò, V., ... Cirrincione, G. (2016). Quality characteristics and *in vitro* digestibility study of barley flour enriched ditalini pasta. *LWT- Food Science and Technology, 72*, 223–228.
Mosele, J. I., Macia, A., Romero, M. P., Motilva, M. J., & Rubio, L. (2015). Application of *in vitro* gastrointestinal digestion and colonic fermentation models to pomegranate products (juice, pulp and peel extract) to study the stability and catabolism of phenolic compounds. *Journal of Functional Foods, 14*, 529–540.
Mullen, W., Edward, C. A., Crozier, A., & Serafini, M. (2008). Bioavailability of pelargonidin-3-O-glucoside and its metabolites in humans following the ingestion of strawberries with and without cream. *Journal of Agricultural and Food Chemistry, 56*, 713–719.
Napolitano, A., Costabile, A., Martin-Pelaez, S., Vitaglione, P., Klinder, A., Gibson, G. R., & Fogliano, V. (2008). Potential prebiotic activity of oligosaccharides obtained by enzymatic conversion of durum wheat insoluble dietary fibre into soluble dietary fibre. *Nutrition, Metabolism, and Cardiovascular Diseases, 19*, 283–290.
Neilson, A. P., George, J. C., Janle, E. M., Mattes, R. D., Rudolph, R., & Matusheski, N. V. (2009). Influence of chocolate matrix composition on cocoa flavan-3-ol bioaccessibility in vitro and bioavailability in humans. *Journal of Agricultural and Food Chemistry, 57*, 9418–9426.
Noack, A., Oidtmann, J., Kutza, J., & Mäder, K. (2012). In vitro digestion of curcuminoid-loaded lipid nanoparticles. *Journal of Nanoparticle Research, 14*, 1113–1132.
Oliveira, A., & Pintado, M. (2015). Stability of polyphenols and carotenoids in strawberry and peach yoghurt throughout in vitro gastrointestinal digestion. *Food & Function, 6*, 1611–1619.
Oliveira, A. C., Valentim, I. B., Silva, C. A., Bechara, E. J. H., Baroos, M. P., Mano, C. M., & Goulart, M. O. F. (2009). Total phenolic content and free radical scavenging activities of methanolic extract powders of tropical fruit residues. *Food Chemistry, 115*, 469–475.
Ortega, N., Macia, A., Romero, M. P., Reguant, J., & Motilva, M. J. (2011). Matrix composition effect on the digestibility of carob flour phenols by an in-vitro digestion model. *Food Chemistry, 124*, 65–71.
Ortega, N., Reguant, J., Romero, M. P., Macia, A., & Motilva, M. J. (2009). Effect of fat content on the digestibility and bioaccessibility of cocoa polyphenol by an in vitro digestion model. *Journal of Agricultural and Food Chemistry, 57*, 5743–5749.
Ozturk, B., Argin, S., Ozilgen, M., & McClements, D. J. (2015). Formation and stabilization of nanoemulsion-based vitamin E delivery systems using natural biopolymers: Whey protein isolate and gum arabic. *Food Chemistry, 188*, 256–263.
Palafox-Carlos, H., Ayala-Zavala, J. F., & González-Aguilar, G. A. (2011). The role of dietary fiber in the bioaccessibility and bioavailability of fruit and vegetable antioxidants. *Journal of Food Science, 76*, R6–R15.
Pérez-Vicente, A., Gil-Izquierdo, A., & García-Viguera, C. (2002). *In vitro* gastrointestinal digestion study of pomegranate juice phenolic compounds, anthocyanins, and vitamin C. *Journal of Agricultural and Food Chemistry, 50*, 2308–2312.
Pineda-Vadillo, C., Nau, F., Dubiard, C. G., Cheynier, V., Meudec, E., Sanz-Buenhombre, M., ... Dupont, D. (2016). *In vitro* digestion of dairy and egg products enriched with grape extracts: Effect of the food matrix on polyphenol bioaccessibility and antioxidant activity. *Food Research International, 88*, 284–292.
Pinheiro, A. C., Coimbra, A., & Vicente, A. A. (2016). *In vitro* behaviour of curcumin nanoemulsion stabilized by biopolymer emulsifiers-effect of interfacial composition. *Food Hydrocolloids, 52*, 460–467.
Podio, N. S., López-Froilán, R., Ramirez-Moreno, E., Bertrand, L., Baroni, M. V., Pérez-Rodríguez, M. L., ... Wunderlin, D. A. (2015). Matching in vitro bioaccessibility of polyphenols and antioxidant capacity of soluble coffee by boosted regression trees. *Journal of Agricultural and Food Chemistry, 63*, 9572–9582.
Podsędek, A., Redzynia, M., Klewicka, E., & Koziołkiewicz, M. (2014). Matrix effects on the stability and antioxidant activity of red cabbage anthocyanins under simulated gastrointestinal digestion. *BioMedical Research International, 2014*, 1–14.
Polovic, N. D., Pjanovic, R. V., Burazer, L. M., Velickovic, S. J., Jankow, R. M., & Velickovic, T. D. C. (2008). Acid-formed pectin gel delays major incomplete kiwi fruit allergen Act c 1 proteolysis in in vitro gastrointestinal digestion. *Journal of Agricultural and Food Chemistry, 89*, 8–14.
Pool, H., Mendoza, S., Xiao, H., & McClements, D. J. (2013). Encapsulation and release of hydrophobic bioactive components in nanoemulsion-based delivery systems: Impact of physical form on quercetin bioaccessibility. *Food & Function, 4*, 162–174.
Pool, H., Quintanar, D., Figueroa, J. D., Mano, C. M., Bechara, J. E. H., Godınez, L. A., & Mendoza, S. (2012). Antioxidant effects of quercetin and catechin encapsulated into PLGA nanoparticles. *Journal of Nanomaterials, 2012*, 1–12.
Porter, C., Kaukonen, A. M., Taillardat-Bertschinger, A., Boyd, B. J., O'Connor, J. M., Edward, G. A., & Charman, W. N. (2004). Use of in vitro lipid digestion data to explain the in vivo performance of triglyceride-based oral lipid formulations of poorly water-soluble drugs: Studies with halofantrine. *Journal of Pharmaceutical Sciences, 93*, 1110–1121.
Pugliese, A., O'Callaghan, Y., Tundis, R., Galvin, K., Menichini, F., O'Brien, N., & Loizzo, M. R. (2014). In vitro assessment of the bioaccessibility of carotenoids from sun-dried chilli peppers. *Plant Foods for Human Nutrition, 69*, 8–17.
Qian, C., Decker, E. A., Xiao, H., & McClements, D. J. (2012). Nanoemulsion delivery systems: Influence of carrier oil on b-carotene bioaccessibility. *Food Chemistry, 135*, 1440–1447.
Ramez, S., & Palmer, A. F. (2011). Simple method for preparing poly(ethylene glycol)-surface-conjugated liposome-encapsulated hemoglobins: Physicochemical properties, long-term storage stability, and their reactions with O2, CO, and NO. *Langmuir, 27*, 8829–8840.
Rashidinejad, A., Birch, E. J., & Everett, D. W. (2016). A novel functional full-fat hard cheese containing liposomal nanoencapsulated green tea catechins: Manufacture and recovery following simulated digestion. *Food & Function, 7*, 3283–3294.
Reza, M. M., Johnson, C., Hatziantoniou, S., & Demetzos, C. (2008). Nanoliposomes and their applications in food nanotechnology. *Journal of Liposome Research, 18*, 309–327.
Rodrigo, M. J., Cilla, A., Barberá, R., & Zacarías, L. (2015). Carotenoid bioaccessibility in pulp and fresh juice from carotenoid-rich sweet oranges and mandarins. *Food & Function, 6*, 1950–1959.
Rodrigues, D. W., Barros-Mariutti, L. R., & Zerlotti-Mercadante, A. (2016). An *in vitro* digestion method adapted for carotenoids and carotenoid esters: Moving forward towards standardization. *Food & Function, 7*, 4992–5001.
Rodríguez-Roque, M. J., Rojas-Grau, M. A., Elez-Martínez, P., & Martín-Belloso, O. (2013). Soymilk phenolic compounds, isoavones and antioxidant activity as affected by in vitro gastrointestinal digestion. *Food Chemistry, 136*, 206–212.
Rosa, N. N., Dufour, C., Lullien-Pellerin, V., & Micard, V. (2013). Exposure or release of ferulic acid from wheat aleurone: Impact on its antioxidant capacity. *Food Chemistry, 141*, 2355–2362.
Ryan, L., & Prescott, S. L. (2010). Stability of the antioxidant capacity of twenty-five commercially available fruit juices subjected to an *in vitro* digestion. *International Journal of Food Science and Technology, 45*, 1191–1197.
Saenz, C., Tapia, S., Chavez, J., & Robert, P. (2009). Microencapsulation by spray drying of bioactive compounds from cactus pear (*Opunia ficus-indica*). *Food Chemistry, 114*, 616–622.
Schroeder, A., Kost, J., & Barenholz, Y. (2009). Ultrasound, liposomes, and drug delivery: Principles for using ultrasound to control the release of drugs from liposomes. *Chemistry and Physics of Lipids, 162*, 1–16.
Schwiggert, R. M., Mezger, D., Schimpf, F., Steingass, C. B., & Carle, R. (2012). Influence of chromoplast morphology on carotenoid bioaccessibility of carrot, mango, papaya and tomato. *Food Chemistry, 135*, 2736–2742.
Sek, L., Porter, C. J. H., & Charman, W. N. (2001). Characterisation and quantification of medium chain and long chain triglycerides and their in vitro digestion products, by HPTLC coupled with in situ densitometric analysis. *Journal of Pharmaceutical and Biomedical Analysis, 25*, 651–661.
Sengul, H., Surek, E., & Nilufer-Erdil, D. (2014). Investigating the effects of food matrix and food components on bioaccessibility of pomegranate (*Punica granatum*) phenolics and anthocyanins using an *in vitro* gastrointestinal digestion model. *Food Research International, 62*, 1069–1079.
Serafini, M., Bugianesi, R., Maiani, G., Valtuena, S., De Santis, S., & Crozier, A. (2003). Plasma antioxidants from chocolate. *Nature, 424*, 1013.
Shakeel, F., & Ramadan, W. (2010). Transdermal delivery of anticancer drug caffeine from water-in-oil nanoemulsions. *Colloids and Surfaces B: Biointerfaces, 75*, 356–362.
Shin, G. H., Chung, S. K., Kim, J. T., Joung, H. J., & Park, H. J. (2013). Preparation of chitosan-coated nanoliposomes for improving the mucoadhesive property of curcumin using the ethanol injection method. *Journal of Agricultural and Food Chemistry, 61*, 11119–11126.
Soriano-Sancho, R. A., Pavan, V., & Pastore, G. M. (2015). Effect of in vitro digestion on bioactive compounds and antioxidant activity of common bean seed coats. *Food Research International, 76*, 74–78.
Sotomayor-Gerding, D., Oomahc, B. D., Acevedo, F., Morales, E., Bustamante, M., Shene, C., & Rubilar, M. (2016). High carotenoid bioaccessibility through linseed oil nanoemulsions with enhanced physical and oxidative stability. *Food Chemistry, 199*, 463–470.
Svelander, C. A., Tibäck, E. A., Ahrnè, L. M., Langton, M., Svanberg, U. S. O., & Alminger, M. A. G. (2010). Processing of tomato: Impact on in vitro bioaccessibility of lycopene and textural properties. *Journal of Food Science and Agricultural, 90*, 1665–1672.
Tagliazucchi, D., Verzelloni, E., Bertolini, D., & Conte, A. (2010). *In vitro* bio-accessibility and antioxidant activity of grape polyphenols. *Food Chemistry, 120*, 599–606.
Tagliazucchi, D., Verzelloni, E., & Conte, A. (2012). The first tract of alimentary canal as an extractor. Release of phytochemicals from solid food matrices during simulated digestion. *Journal of Food Biochemistry, 36*, 555–568.
Talens, P., Mora, L., Bramley, P. M., & Fraser, P. D. (2016). Antioxidant compounds and their bioaccessibility in tomato fruit and puree obtained from a DETIOLATED-1 (DET-1) down-regulated genetically modified genotype. *Food Chemistry, 213*, 735–741.
Tenore, G. C., Campiglia, P., Ritieni, A., & Novellino, E. (2013). *In vitro* bioaccessibility, bioavailability and plasma protein interaction of polyphenols from Annurca apple (*M. pumila* Miller cv Annurca). *Food Chemistry, 141*, 3519–3524.
Thuenemann, E. C. (2015). Dynamic digestion models: General introduction. In K. Verhoeckx, P. Cotter, I. López-Expósito, C. Kleiveland, T. Lea, A. Mackie, T. Requena, D. Swiatecka, & H. Wichers (Eds.). *The impact of food bio-actives on gut health* (pp. 33–36). Springer International Publishing.
Tompkins, T. A., Mainville, I., & Arcand, Y. (2011). The impact of meals on a probiotic during transit through a model of the human upper gastrointestinal tract. *Beneficial*

Microbes, 2, 295–303.
Tumbas-Šaponjac, V., Čanadanović-Brunet, J., Ćetković, G., Jakišić, M., Djilas, S., Vulić, J., & Stajčić, S. (2016). Encapsulation of beetroot pomace extract RSM: Optimization, storage and gastrointestinal stability. *Molecules, 21*, 584. http://dx.doi.org/10.3390/molecules21050584.
Vaghini, S., Cilla, A., Garcia-Llatas, G., & Lagarda, M. J. (2016). Bioaccessibility study of plant sterol-enriched fermented milks. *Food & Function, 7*, 110–117.
Vardakou, M., Mercuri, A., Barker, S. A., Craig, D. Q. M., Faulks, R. M., & Wickham, M. S. J. (2011). Achieving antral grinding forces in biorelevant in vitro models: Comparing the USP dissolution apparatus II and the dynamic gastric model with human *in vivo* data. *AAPS PharmSciTech, 12*, 620–626.
Velderrain-Rodríguez, G., Quirós-Sauceda, A., Mercado-Mercado, G., Ayala-Zavala, J. F., Astiazarán-García, H., Robles-Sánchez, R. M., ... González-Aguilar, G. A. (2016). Effect of dietary fiber on the bioaccessibility of phenolic compounds of mango, papaya and pineapple fruits by an in vitro digestion model. *Food Science and Technology, Campinas, 36*, 188–194.
Wang, D., Williams, B. A., Ferruzzi, M. G., & D'Arcy, B. R. (2013). Microbial metabolites, but not other phenolics derived from grape seed phenolic extract, are transported through differentiated Caco-2 cell monolayers. *Food Chemistry, 138*, 1564–1573.
Wang, L. J., Hu, Y. Q., Yin, S. W., Yang, X. Q., Lai, F. R., & Wang, S. Q. (2015). Fabrication and characterization of antioxidant pickering emulsions stabilized by zein/chitosan complex particles (ZCPs). *Journal of Agricultural and Food Chemistry, 63*, 2514–2524.
Weiss, J., Gaysinksy, S., Davidson, M., & McClements, J. (2009). Nanostructured encapsulation systems: Food antimicrobials. In G. V. Barbosa-Cánovas, A. Mortimer, D. Lineback, W. Spiess, & K. Buckle (Eds.). *IUFoST world congress book: Global issues in food science and technology* (pp. 425–479). Amsterdam: Elsevier Inc.
Wootton-Beard, P. C., Moran, A., & Ryan, L. (2011). Stability of the total antioxidant capacity and total polyphenol content of 23 commercially available vegetable juices before and after in vitro digestion measured by FRAP, DPPH, ABTS and Folin-Ciocalteu methods. *Food Research International, 44*, 217–224.
Yi, J., Lam, T. I., Yokoyama, W., Cheng, L. W., & Zhong, F. (2014). Cellular uptake of β-carotene from protein stabilized solid lipid nanoparticles prepared by homogenization-evaporation method. *Journal of Agricultural and Food Chemistry, 62*, 1096–1104.
Zou, L., Zheng, B., Zhang, R., Zhang, Z., Liu, W., Liu, C., ... McClements, D. J. (2016). Enhancing the bioaccessibility of hydrophobic bioactive agents using mixed colloidal dispersions: Curcumin-loaded zein nanoparticles plus digestible lipid nanoparticles. *Food Research International, 81*, 74–82.
Zou, L. Q., Peng, S. F., Liu, W., Liu, Z., Gan, L., Liu, W. L., ... Chen, X. (2014). Improved *in vitro* digestion stability of (−)-epigallocatechin gallate through nanoliposome encapsulation. *Food Research International, 81*, 492–499.