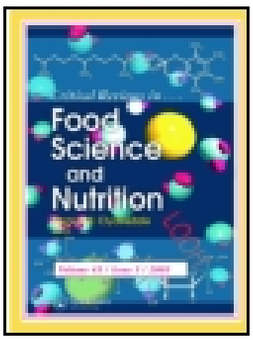

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REVIEW

Changes in bioactive compounds and antioxidant activity of plant-based foods by gastrointestinal digestion: a review

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ABSTRACT

Phenolic compounds, omnipresent in plants, are a crucial part of the human diet and are of considerable interest due to their antioxidant properties and other potential beneficial health effects, for instance, antidiabetic, antihypertensive, anti-inflammatory, and anticancer properties. The consumption of a variety of plant-based foods containing various phenolic compounds has increased due to published scientific verification of several health benefits. The release of phenolic compounds and change in their bioactivities examined through *in vitro* simulated gastrointestinal digestion could provide information on the biological potency of bioactive components, which will allow us to elucidate their metabolic pathways and bioactivities at target sites. This review reports on the recent research results focused on changes during the gastro and/or intestinal phase. The effect of digestive enzymes and digestive pH conditions during simulated digestion accounted for the variations in bioaccessibility and bioavailability of phenolic antioxidants as well as the corresponding antioxidant activities were also summarized and presented in the review.

KEYWORDS

Antioxidant activity; digestive enzymes; *in vitro* simulated gastrointestinal digestion; plant-based foods; pH; phenolic antioxidants

Introduction

Nowadays, consumers' increasing awareness of the benefits provided by plant-based foods beyond basic nutrition has led to numerous research studies aiming to investigate the many health-promoting effects associated with their high proportion of bioactive compounds. Among the bioactive compounds, the most common and important groups are natural antioxidants such as polyphenol groups. Diverse plant-based food categories contain various bioactive compounds that exhibit various antioxidant capacities, which, due to synergistic interactions, may contribute to more positive physiological effects than the consumption of synthetic antioxidants alone (Wang et al. 2011). It has been reported in various epidemiological and interventional studies that the ingestion of foods rich in phenolics is linked to a number of other effects for health sustenance, such as antioxidant activity, which could lower the risk of experiencing oxidative stress-associated degenerative, chronic, and pathological complications (Annunziata et al. 2018; Mrduljaš, Krešić, and Bilušić 2017; Shahidi and Ambigaipalan 2015; Shahidi and Peng 2018).

Aside from foods that are rich sources of bioactive compounds, effects of bioactive compounds on health nourishment bank on their stability of action, bioaccessibility, and bioavailability, which can vary according to various factors such as the processing of raw materials (Campos-Vega et al. 2015), the food matrix itself or that in which it is incorporated (Cai et al. 2020; Koehnlein et al. 2016; Reginio et al. 2020a; Thuengtung et al. 2018), digestion environments (Ketnawa, Suwannachot, and Ogawa 2020; Lucas-González et al. 2018b), and colon microbiota (Chait et al. 2020; Dou, Chen, and Fu 2019; Gullon et al. 2015; Mosele et al. 2016). In order to exert bioactivity, bioactive molecules must be driven out from the food matrix, metabolized in the gastrointestinal tract, and reach the blood circulation in a biochemically active state (Annunziata et al. 2018; Martínez-Las Heras et al. 2017; Shim et al. 2012). In the same context, bioactive molecules are required to be bioaccessible in order to demonstrate their bioactivity after biotransformation. The effect on health benefits is largely dependent on bioaccessibility and bioavailability, which can be measured regarding the change in the concentration and metabolites of solubilized components in the digestive tract, circulatory, or excretory systems.

Plant-derived foods, including vegetables, fruits, seeds, legumes, cereals, and grains, contain different miscellaneous bioactive compounds or phytochemicals, and their nutritional values generally depend on the class and concentration of these various bioactive substances; therefore, interest has been focused on assessing their quantitative effectivity in the human body. Bioactive compounds that have their origin in plant sources are produced as secondary metabolites, eliciting desired health beneficial effects in animals and humans (Zhao, Wu, and Wang 2015). Compatible documentation from cohort studies, through *in vitro* or *in vivo* investigations, suggests that plant bioactive compounds are an important source of therapeutic and preventive agents that downgrade the risk of developing aforementioned oxidative stress-associated

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

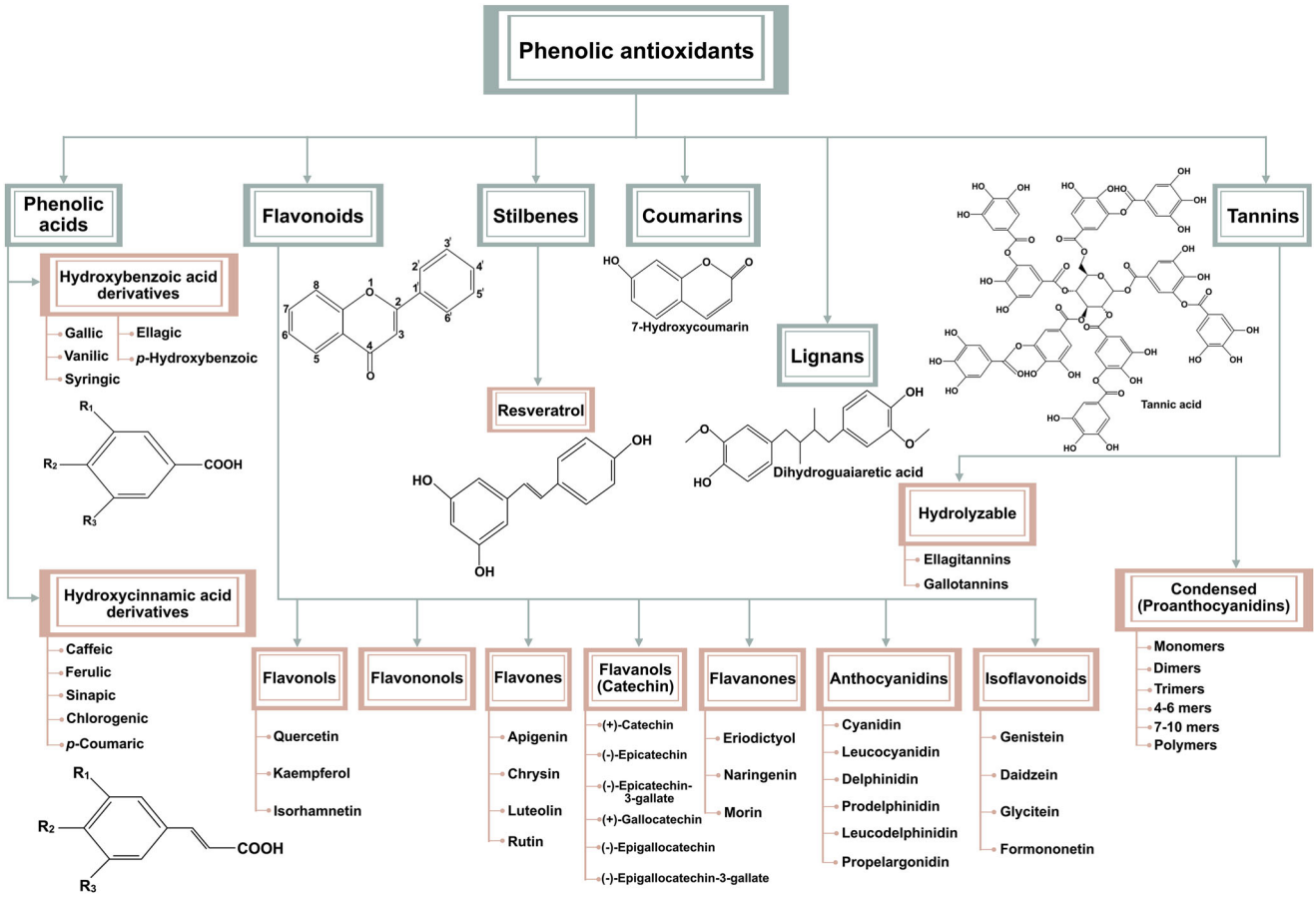

Figure 1. Groups of plant-derived phenolics, and some representative chemical structure and their substitution patterns, highlighted for phenolic acids and flavonoid groups. Reproduced and modified from Naczk and Shahidi (2004), Shahidi and Ambigaipalan (2015) and San Miguel-Chávez (2017).

degenerative complications (Zhao, Wu, and Wang 2015). Thus, dietary guidelines have always highlighted the intake of various plant-based foods to lessen the severity of such chronic diseases. The biological potency of these bioactive compounds has been associated with their synergistic and additive effects rather than the purified chemicals themselves (Shahidi and Ambigaipalan 2015; Zhao, Wu, and Wang 2015). The health benefits of polyphenols depend on class and type, the amount one must consume to obtain the effective dose, and their bioavailability (Shahidi and Ambigaipalan 2015). In addition, the biological activity of bioactive compounds varies as a result of structural and chemical modifications during the digestion process (Celep et al. 2015). Thus, it is necessary to monitor these changes during digestion, which include food matrices, enzymatic activity, and altered pH, to evaluate and fully understand the bioavailability and bioactivity of food components.

Principles of bioactive compounds: class, metabolism, and mechanism of antioxidant action

Classification of polyphenols arranges to phenolic acids, flavonoids, stilbenes, coumarins, lignans, and oligomeric-polymeric proanthocyanidins (tannin) (Mrduljaš, Krešić, and Bilušić 2017; Naczk and Shahidi 2004; San Miguel-Chávez 2017; Shahidi and Ambigaipalan 2015) as displayed in Figure 1 and Table 1, and have been used comprehensively as nutraceuticals or alternative components to provide a health nourishment other than primary nutritional properties (Naczk and Shahidi 2004; Shahidi and Naczk 2003; Zhao, Wu, and Wang 2015). Structurally, they are an array of non-complex phenolic molecules to complex-insoluble polymers with high molecular weight in size (Zhao, Wu, and Wang 2015). Depending on their chemical properties, polyphenols can be soluble in water or organic solvents; some are found in glycoside form (San Miguel-Chávez 2017). Categorization of polyphenols is defined as plant compounds consisting an aromatic ring attached directly to a hydroxyl group (-OH) (phenolic acids) or attached to several -OH groups (polyphenols) (Figure 1). Phenolics (C_6C_n) are substituted phenolic ring with different substitution groups include carboxylic acid, alcoholic, or aldehydic groups (Naczk and Shahidi 2004; Shahidi and Naczk 2003; Zhao, Wu, and Wang 2015). The bioactivities of these compounds are attributed to the arrangement of -OH groups, the hydroxylation patterns, and variations in the phenolic rings (Minatel et al. 2017; Naczk and Shahidi 2004). Moreover, antioxidant activity increases due to a second -OH at the ortho (*o*-) or para (*p*-) position existing on a phenol ring (Shahidi and Ambigaipalan 2015). Polyphenols are not only limited to compounds with the ability to scavenge free radical or reduce oxidization but also include those of *in vivo* antioxidant mechanism by enzymatic induction (Shahidi and Ambigaipalan 2015).

Table 1. Different classes of phenolic and flavonoids, their substitution patterns, and dietary sources.

Phenolic acids					
Substitutions[a]			Common name	IUPAC name	Dietary sources
R1	R2	R3			
Hydroxybenzoic acid					
H	OH	H	*p*-Hydrobenzoic	4-Hydroxybenzoic	wine, vanilla, horse gram, carob, catechins, metabolites found in green tea
OH	OH	OH	Gallic	3,4,5-Trihydroxybenzoic	miscellaneous
OH	OH	H	Protocatechuic	3,4-Dihydroxybenzoic	olives, roselle, citrus calamondin, white wine, grapes, metabolites found in green tea
OCH3	OH	H	Vanillic	4-Hydroxy-3-methoxybenzoic	metabolites of caffeic, bark, ginseng root, açaí palm, wine, vinegar
OCH3	OH	OCH3	Syringic	3,5-Dimethoxybenzoic	several fruits olives, spices, pumpkin, palm, honey, red wine,
Hydroxycinnamic acids					
Substitutions[a]			Common name	IUPAC name	Dietary sources
R1	R2	R3			
H	OH	H	*p*-Coumaric	4-Hydromycinnamic	peanuts, navy beans, tomatoes, carrots, basil, garlic, wine
OH	OH	H	Caffeic	3,4-Dihydroxycinnamic	apples, artichoke, berries, pears
OCH3	OH	H	Ferulic	4-Hydroxy-3-methoxycinnamic	whole grains, spinach, parsley, grapes, rhubarb, wheat, oat, rye, barley
OCH3	OH	OCH3	Sinapic	4-Hydroxy-3,5-dimethoxycinnamic	spices, citrus and berry fruits, vegetables, cereals, oilseed crops
Flavonoids					
Class			Substitutions	Name	Dietary sources
Chalcones (ring c noncyclized)			2,4,3′,4′-OH	Butein	miscellaneous
			2,3,4,3′,4′-OH	Okanin	miscellaneous
Flavones			5,7-OH	Chrysin	fruit skin
			5,7,4′-OH	Apigenin	parsley, celery
Flavanones			5,4′-OH;7-rhamnoglucose	Naringin	citrus, grapefruit
			5,7,4′-OH	Narigenin	citrus
			3,5,7,3′,4′-OH	Taxifolin	citrus
			5,7,3′,4′-OH	Eriodictyyol	lemons
			3,5,3′-OH,4′-OMe;7-rutinose	Hesperidin	oranges
			5,7-OH;4′-OMe	Isosakuranetin	citrus
Flavonols			3,5,7,4′-OH	Kaempferol	leek, broccoli, endive, grapefruit, black tea
			3,5,7,3′,4′-OH	Quercetin	onion, lettuce, broccoli, tomato, tea, berries, apples, olive oil
			5,7,3′,4′-OH;3-rutinose	Rutin	buckwheat, citrus, red pepper, red wine, tomato skin
Flavononols			3,5,7,4′-OH;3-O-rhamnose	Engelertin	white grape skin
			3,5,7,5′,4′-OH;3-O-rhamnose	Astilbin	white grape skin
			5,4′-OH;7-glucose	Genistin	soybean
			3,5,7,3′,4′-OH	Taxifolin	fruits
Isoflavonoids			5,7,4′-OH	Genistein	soybean
			4′-OH,7-glucose	Daidzin	soybean
			4′,7-OH	Daidzein	soybean
Flavanols			3,5,7,3′,4′-OH	(+)-Catechin	tea
			3,5,7,3′,4′,5′-OH	(+)-Gallocathechin	tea
			3,5,7,5′,4′-OH	(-)-Epicatechin	tea
			3,5,7,3′,4′-OH	(-)-Epigallacatechin	tea
			3,5,7,3′,4′-OH;3-gallate	(-)-Epicatechin gallate	tea
			5,7,3′,4′,5′,3′′,4′′,5′′-gallate	(-)-Epigallocatechin gallate	tea
Anthocyanidins/Anthocyanins			5,7,4′-OH	Epigenidin	stored fruits
			3,5,7,4′-OH;3,5-OMe	Cyanidin	cherry, raspberry, strawberry
			3,5,7,3′,4′,5′-OH	Delphinidin	berries and Concord grapes
			3,5,7,4′-OH	Malvidin	berries, wine
			3,5,7,3′,4′,5′-OH	Delphinium	dark fruits
			3,5,7,4′-OH	Pelargonodin	dark fruits

[a]According to Figure 1. R1, R2, R3 represent substitution group in the structure of phenolic acids, and the substitution description of flavonoids group is also presented. The table was reproduced and adapted from Shahidi and Naczk (2003) and Naczk and Shahidi (2004).

Categories of phenolic acids divides into two major groups based on the constitutive carbon frameworks as shown in Figure 1 and Table 1. The first group is benzoic acid derivatives (i.e., hydroxybenzoic acids, C6-C1 derivatives) for example, gallic acid, ellagic acid, 4-hydroxybenzoic acids, protocatechuic acid, salicylic acid, and salicylaldehyde, which generally occur in low concentrations in foods (Lafay and Gil-Izquierdo 2008). The other is cinnamic acid derivatives (i.e., hydroxycinnamic acids, C6-C3 derivatives) that are much more general than the hydroxybenzoic acids, which are coumaric acid, caffeic acid, ferulic acid, and sinapic acid. However, hydroxycinnamic acids rarely occur in free form but glycosylated derivatives or esters combined forms; for instance shikimic acid, tartaric acid, quinic acid, and caffeic acid in which the last two acids are esters form of chlorogenic acid (CHA) (Zhao, Wu, and Wang 2015).

Flavonoids are a widely distributed group of plant phenolics and more than 3000 known structures that constitute an enormous class of phenolic compounds (Figure 1 and Table 1). The general structure of flavonoids consists of 15 carbon atoms in which the two C6 units are phenolic in nature and linked by a C3 group (C6–C3–C6). According to the oxidation state of the central pyran ring, flavonoids can be subdivided into flavonols, flavones, flavanones, flavanols (catechins), anthocyanins, isoflavonoids, and chalcones. Another member of flavonoid group, isoflavonoids, contain ring B attached to the C3 position of ring C, is naturally occurring phenolics with phytoestrogenic activity (Zhao, Wu, and Wang 2015). Among the flavonoids, anthocyanins are the largest and most important group of water-soluble vacuolar pigments found in abundance in fruits, flowers, vegetables, and grain sources. These are responsible for the purple, pink, red, and blue coloration and mainly exist in the conjugated form as glycosides (Naczk and Shahidi 2004). Anthocyanidins are the basic structures of anthocyanins, which are made up of two aromatic rings A and B bonded to a heterocyclic ring C that possesses an oxygen molecule. More than 23 different anthocyanidins have been found; the generic ones are pelargonidin, cyanidin, peonidin, delphinidin, petunidin, and malvidin (Zhao, Wu, and Wang 2015).

Tannins are widely distributed polyphenols with a wide diversity of structures that can bind and precipitate proteins from aqueous solutions. Tannins are categorized into condensed tannins (also known as proanthocyanidins) and hydrolyzable tannins according to their structures Figure 1. Coumarins are a large class of C6-C3 derivatives belonging to the benzo-α-pyrone group, which exist in free or combined forms as heterosides and glycosides. The simple coumarins encompass the hydroxylated, alkoxylated, and alkylated derivatives of the parent compound, along with their corresponding glycosides. Lignans, also identified as phytoestrogens, are a diverse group of bioactive phenolic compounds formed by a β-β-linkage between two phenylpropane units. These compounds are present in different parts of plant species in the free or combined form as glycoside derivatives (Zhao, Wu, and Wang 2015). Stilbenes share a similar chemical structure to flavonoids, which contain two phenyl moieties linked by a methylene bridge, however, occur in the human diet in low quantities. Quinones are compounds derived from aromatic compounds by the conversion of an even number of –CH = groups into –C(=O)– groups with any necessary rearrangement of double bonds resulting in a fully conjugated cyclic dione structure. The most general frame structures of plant quinones are *p*-quinone, *o*-quinone, anthraquinone, naphthoquinone, and naphtodianthrone (Naczk and Shahidi 2004; Shahidi and Ambigaipalan 2015; Shahidi and Naczk 2003; Zhao, Wu, and Wang 2015). The different phenolic molecules vary in their structure and chemical composition (Figure 1 and Table 1), they can display various bioactive properties, such as antioxidant, anti-diabetic, anti-cancer, antimicrobial, anti-inflammatory, anti-aging properties, etc. (Dou, Chen, and Fu 2019; Lucas-González et al. 2018b; Ortega-Vidal et al. 2019). Groups of plant-derived phenolics and some representative chemical structures are presented in Figure 1.

In general, free radicals are generated by the natural biological metabolism process with or without the support of endogenous enzymes, however, increase in number aroused by oxygen species existing environment. A free radical is an atom generated by the last level of energy that loses its stability by losing or gaining an electron showing an unpaired electron, and acts as intermediate electron acceptors/donors. Free radical species are typically known as reactive oxygen species (ROS), include superoxide anion ($O_2\bullet-$), hydroxyl radical (OH•), peroxyl radical (ROO•), hydroperoxyl radical (HOO•), hydrogen peroxide (H_2O_2), and hydrochlorous acid (HOCl). Furthermore, reactive nitrogen species (RNS) such as nitric oxide (NO•), nitrogen dioxide (NO_2), and peroxynitrite (ONOO−) also raise the risk of biological damage (Johansen et al. 2005). In addition, many biological factors and environment conditions, such as exposure to certain types of pollution, smoking, radiation, e.g., ultraviolet (UV) radiation from sunlight, ozone, and certain drugs, natural toxins, toxic chemicals, or pesticides, induce excessive of ROS and RNS in the biological system (Wang et al. 2011). With a drastic increase in ROS and RNS, biological defense mechanisms are disrupted by a decrease in defense mechanisms to protect against biological agents and are not able to neutralize them back to the normal redox state, the so-called oxidative stress state (Wang et al. 2011). Oxidative stress causes disturbances such as protein cross linking, lipid oxidation, DNA mutation as well as tissue damage at a later stage which may trigger aforementioned oxidative stress-associated degenerative complications as depicted in Figure 2 (Shahidi and Naczk 2003) because ROS and RNS react with other atoms and/or molecules present nearby and in the cellular environment (San Miguel-Chávez 2017; Wang et al. 2011).

Natural antioxidants that are obtained from plant phenolics, so-called phenolic antioxidants, which presumably act as safeguards against the accumulation of ROS and RNS and eliminate them from the system (Lucini Mas et al. 2020). The antioxidant properties of plant-based foods are mainly attributed to those polyphenolic compounds, the amount of which depends on the cultivar, variety, plant part, growing condition, harvest period, etc. Correlations from several

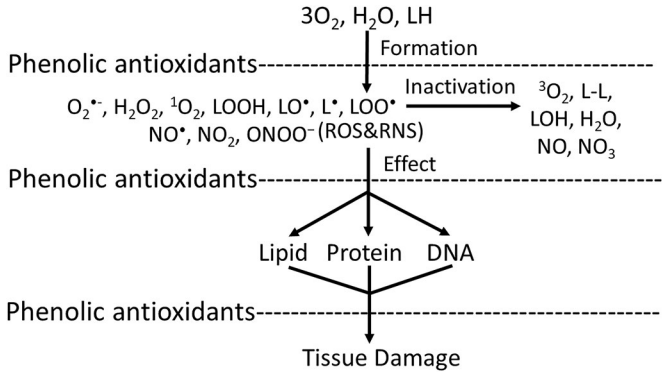

Figure 2. Consequences of reactive oxygen and nitrogen species in diseases and preventive role of phenolic antioxidants. Reproduced and modified from Shahidi and Naczk (2003).

previous studies indicated that the antioxidant capacities of certain plant-based foods mainly depends on phenolic antioxidant compounds (Carbonell-Capella et al. 2015; Chiang, Kadouh, and Zhou 2013; Ketnawa, Suwannachot, and Ogawa 2020; Koehnlein et al. 2016). Apart from plant sources, the antioxidant properties of phenolic antioxidants, which depend on the molecular structure–activity relationship (SAR), vary with the compositional characteristics and structures, particularly the number and positions of -OH groups and the nature of substitutions on the phenol ring as mentioned above (Miliauskas, Venskutonis, and van Beek 2004; Mrduljaš, Krešić, and Bilušić 2017). In general, phenolic antioxidants are capable of not only trapping singlet oxygen but also preventing first-chain initiation by scavenging initial radicals such as OH•, as well as binding metal ion catalysts (Fe^{2+} and Cu^{2+}). Apart from that capability, fundamental oxidation products was decomposed to non-radical species, and the breaking chain of hydrogen abstraction from substrates was prevented by phenolic antioxidants (Shahidi and Naczk 2003). Additionally, the mechanism of action of these phenolic antioxidants can be understood in two ways: (1) in a food system when different *in vitro* antioxidant method assays are usually applied and (2) in living systems, in which multiple radicals (ROS and RNS) and reactive chemical species and mechanisms are involved in generating an excessive amount of free radicals or an oxidative stress state (San Miguel-Chávez 2017).

In the food matrices, a free-radical chain reaction or autoxidation is initiated by the exposure of polyunsaturated lipids to light, heat, ionizing radiation, metal ions, or metalloproteins. Some enzymes, such as lipoxygenase, can also initiate oxidation. Natural antioxidants like phenolic antioxidants are considered as primary antioxidants that can prevent autoxidation by acting as free-radical scavengers, thus delaying or inhibiting the initiation step or interrupting the propagation step of lipid oxidation and bringing about the reduction of rancidity generated from volatile decomposition products (e.g., aldehydes and ketones) (Naczk and Shahidi 2004; Shahidi and Naczk 2003). Due to the low reduction potential of these phenolic antioxidants, they are capable of donating hydrogen atoms to lipid radicals, producing lipid derivatives and antioxidant radicals (Figure 3) that are more stable and promote autoxidation less readily (Bonnaire et al. 2008). Phenolic antioxidants may further terminate chain-propagation reactions by eliminating free radical intermediates (Shahidi and Ambigaipalan 2015).

For the second mechanism, in biological systems, phenols (ArOH) generally reduce the rates of organic matter oxidation by direct H atom transfer (from their OH groups) to the chain-carrying ROO• radicals involving a concerted proton-coupled electron transfer (O-H•••O•) (Foti, Daquino, and Geraci 2004). With this action, they successfully prevent lipid oxidation, protein cross linking, tissue damage from oxidative stress as mentioned above and displayed in Figure 2 (Shahidi and Naczk 2003).

Different evaluation assays are developed to measure antioxidant capacity depending on the mechanisms and properties of specific antioxidants: (1) free-radical scavenger [2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS)] radical-scavenging activities, the oxygen radical absorbance capacity (ORAC) assay, and hypochlorite (HOCl) scavenging capacity; (2) donating electrons or hydrogen atoms (ferric ion reducing antioxidant power (FRAP) assay); (3) chelation of metal cations (e.g., Fe^{2+} and Cu^{2+}), which decreases the catalytic formation of free radicals (metal ion chelating activity, MIC); and (4) effects on cell signaling pathways and gene expression (cellular antioxidant activity assay, inhibiting the oxidation of low-density lipoprotein (LDL) assay, the deoxyribose method, and the copper-phenanthroline-dependent DNA oxidation assays) (Carocho and Ferreira 2013; Fraga, Oteiza, and Galleano 2014; Huang et al. 2003; Miliauskas, Venskutonis, and van Beek 2004; Shahidi and Peng 2018; Soobrattee et al. 2005). To evaluate the antioxidant capacity of plant extracts regarding each distinctive mechanism, its specific target, reaction matrices, and dissolution solvents, the use of more than two antioxidant assay methods is important. Thus, the assessment of various bioactive compounds on antioxidant capacity through simulated digestion is commonly based on five *in vitro* antioxidant activity assays, for instance, scavenging activity on DPPH and ABTS radical and FRAP, MIC, and ORAC assays. Such assays mechanistically evaluate reaction kinetics between an oxidant and a free radical on the basis of either single electron transfer (SET) or a hydrogen atom transfer (HAT), and comparisons are made most appropriately between assays which utilize the same type of reaction kinetics (Huang, Ou, and Prior 2005). The SET relates to color change during the reduction of oxidants whilst HAT involves competition between substrate (probe) the antioxidant to trap free radicals (Huang, Ou, and Prior 2005). SET assays such as DPPH (Brand-Williams, Cuvelier, and Berset 1995), ABTS (Ozgen et al. 2006; Re et al. 1999), and FRAP (Benzie and Strain 1996) are simple, rapid, cost-effective, and easily interpreted as direct free radical inhibition or reduction capacity (FRAP). The DPPH assay is based on the reaction of antioxidants with transient nitrogen radicals, which used to refer to the peroxyl radical in a biological system (Huang, Ou, and Prior 2005). The ABTS assay is an electron transfer, whereby antioxidants donate one or two electrons to reduce the ABTS radical cation. FRAP results

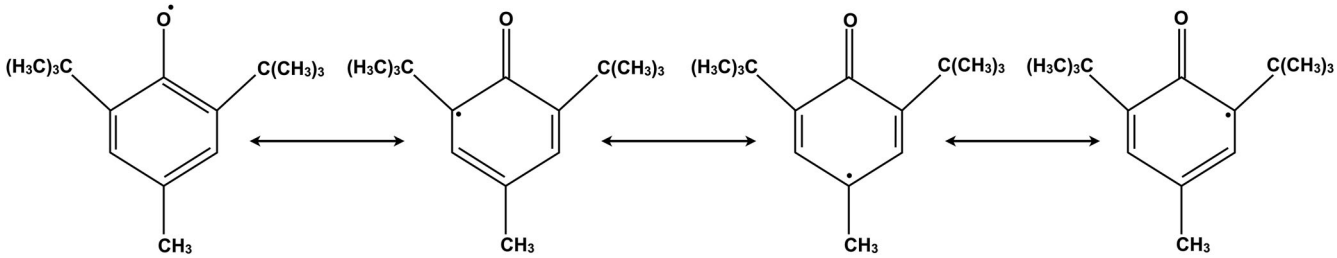

Figure 3. Resonance stabilization of phenoxyl radical based on transferring a H atom. Reproduced and modified from Shahidi and Ambigaipalan (2015).

reflect only the antioxidant reducing potential based on ferric ion instead of the antioxidant preventive effect (Ou et al. 2002). For MIC, transition metals, such as Fe^{2+} and Cu^{2+}, are well-known stimulants of lipid peroxidation, and their chelation may help to delay peroxidation and subsequently prevent food rancidity (Nasri 2017). Therefore, chelation of metal ions by bioactive compounds to the retardation of initiation stage and could retard the oxidative reaction. An ultraviolet-visible spectrometer can be used as an apparatus to measure the change in absorbance of either antioxidant or oxidant, the free-radical scavenging or reducing capability of the antioxidants can be calculated from the absorbance value (Ou et al. 2002). Concerning the chemical specificity of HAT assays, ORAC is one of the most commonly used (Huang et al. 2002); In the ORAC method, the activity of chain-breaking against peroxyl radicals is measured. It is chemically more relevant to evaluate substances able to directly trap peroxyl-radicals (Ou et al. 2002).

Change of phenolic antioxidants at digestive pathway and factors affecting antioxidant properties

In nature, bioactive compounds like phenolic antioxidants are present mainly as esters, glycosides, and polymers in water-soluble or insoluble forms as detailed in the above topics. Phenolic antioxidants need to undergo hydrolysis and metabolism through the environment and/or by the normal microflora of digestive tract before absorption as depicted in Figure 4. Liberation and activation of phenolic compounds are thus regulate by their bioaccessibility, and metabolized forms through the gastrointestinal tract after being transferred via the blood to the target organs (Karaś et al. 2017; Tarko, Duda-Chodak, and Zajac 2013). According to literatures, polyphenols are digested approximately 48% in stomach or gastric stage and small intestine or intestinal stage, whereas around 42% are bioaccessible in colon (Lafay and Gil-Izquierdo 2008; Saura-Calixto, Serrano, and Goñi 2007; Tarko, Duda-Chodak, and Zajac 2013). Remaining 10% of polyphenols is undigested and remains intact within the food matrix (Saura-Calixto, Serrano, and Goñi 2007; Tarko, Duda-Chodak, and Zajac 2013). Of all the polyphenols, only those in the aglycone form which presents strongly hydrophobic properties can pass through physiological membranes by diffusion. However, as the glycosidic form that presents the most in polyphenols have doubtlessly affected on absorption in the intestinal part (Karaś et al. 2017).

Due to the progress of analytical techniques such as high-performance liquid chromatography (HPLC), mass spectrometry (MS), gas chromatography (GC), and nuclear magnetic resonance spectrometry (NMR), the determination of the structure of single compounds from plant components during digestion or colon fermentation can be exploited. These techniques help to monitor and identify a wide range of those active biological compounds that change through digestion. The change in phenolic compounds and the antioxidant activity of plant-based foods during simulated digestion may derive from the corresponding change in individual phenolic structure (Goulas and Hadjisolomou 2019; Ma et al. 2020). This helps to understand the change of polyphenols during digestion by studying the conversions between polyphenolic compounds and metabolite forms.

Metabolism of polyphenols in humans was summarized by Shivashankara and Acharya (2010) and Karaś et al. (2017) and is depicted in Figure 4. Following the consumption of phenolic antioxidant-rich foods, the increase in the antioxidant capacity of the plasma or urine can be used as indirect evidence about absorption through the gut barrier (Castello et al. 2018; Chen, Milbury, and Blumberg 2019; Kurutas 2016; Stalmach et al. 2012; Tenore et al. 2015; Williamson and Clifford 2017). The recovery of some particular phenolic antioxidants in plasma and urine after ingestion allows a comparison of the bioavailability of the different phenolic compounds present in diets, and this was reviewed exclusively by Scalbert et al. (2002), which reported that the quantities of phenolic compounds found intact in urine varied from one phenolic compound to another. In summary, after ingestion of various flavonols and flavanols for 1–2 h, a post-prandial peak is observed, but it takes a longer time after isoflavone ingestion, and other phenolic compounds are only absorbed after partial degradation by the colon microflora in humans (Scalbert and Williamson 2000). For most flavonoids, absorption occurs in the small intestine; the plasma concentration increases then rapidly decreases (elimination half-life of 1–2 h) (Scalbert et al. 2002). It is also assumed that flavonoids can be metabolized through the action of phlorizin hydrolase (glycosylceramidase), an enzyme of the small intestinal brush-border membrane (Tarko, Duda-Chodak, and Zajac 2013). Some polyphenol can be oxidized yielding dehydrodimers derivatives of flavan-3-ols from oxidation of (+)-catechin and (–)-epicatechin. The recent results of human studies corroborate those findings from other *in vivo* studies in rats. Among the phenolic compounds in grape by-product extracts observed by Olivero-David et al. (2018), epicatechin had the fastest absorption with a maximum plasma concentration at

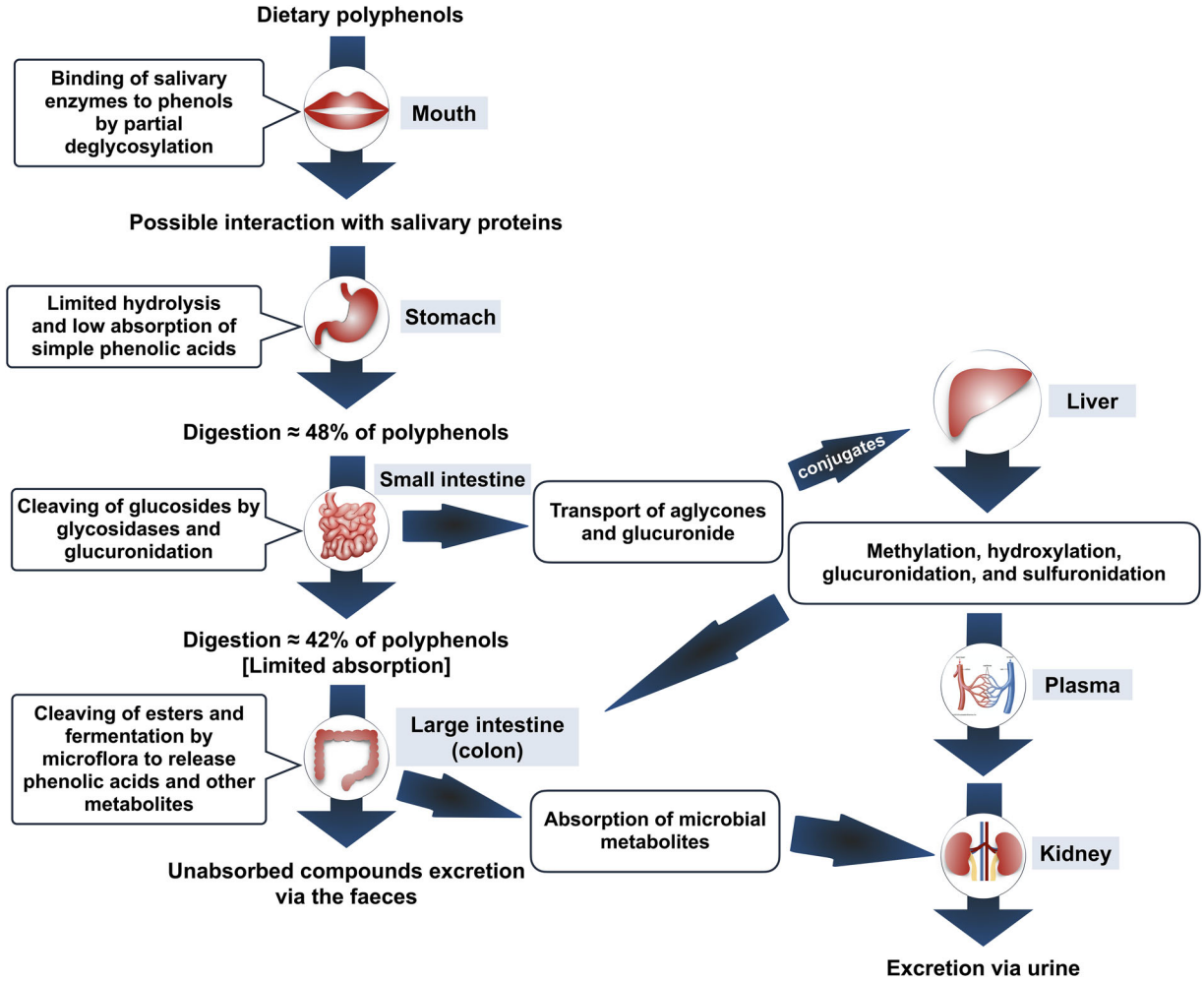

Figure 4. Scheme of a digestive pathway of polyphenols. Reproduced and modified from Karaś et al. (2017) and Shivashankara and Acharya (2010).

1 h after ingestion, while quercetin had the slowest excretion at 1.5 h maximum concentration. A more detailed investigation of the digestibility of proanthocyanidins was studied by Tourino et al. (2011) in rats fed with grape antioxidant dietary fiber. In terms of bioavailability, soluble proanthocyanidins was found to have higher digestibility (86 ± 2%) than soluble phenolics (38 ± 24%) and insoluble proanthocyanidins (25 ± 33%). Proanthocyanidin polymers were found to undergo two main processes in the intestinal tract. First was the depolymerization into epicatechin units with subsequent absorption in the small intestine. After conjugation, the compounds are either transferred directly to the bloodstream or excreted back to the colon via bile. Second was direct fermentation by the intestinal microbiota into phenolic acids such as caffeic acid and *p*-coumaric acid. Most products of fermentation were detected in both feces and urine, indicating that phenolics were absorbed and bioavailable before being excreted as metabolites (Tourino et al. 2011).

Class and structure

The bioavailability of phenolics is strongly influenced by their chemical structure and affected by the digestion conditions (Goulas and Hadjisolomou 2019). In addition, it is suggested that antioxidant activities count on the type of phenolics much more than total phenolic amounts (Carbonell-Capella et al. 2015; Pinto et al. 2017). Overall, isoflavones and gallic acid are best absorbed in the human digestive tract, followed by catechin, quercetin glycosides and flavanones; however, tea epicatechin gallate, anthocyanins and proanthocyanidins represent the weakest absorption (Fang 2014; Karaś et al. 2017). Gallic acid is very well absorbed in the stomach and small intestine (Karaś et al. 2017) and occurs in the form of the 4-*o* methylated and *o*-glucuronidated in plasma and urine (Lafay and Gil-Izquierdo 2008). Also, Quiros-Sauceda et al. (2015) reported on the identification of gallic and protocatechuic acids in mango (cv. Ataulfo) at all stages of digestion. When the free-form hydroxycinnamic acids, namely caffeic acid, ferulic acid, sinapic acid, or *p*-coumaric acid, are ingested, they are conjugated by the intestinal and/or hepatic detoxification enzymes after being absorbed from the stomach or the small intestine, besides, mostly esterified with quinic and tartaric acids or carbohydrate derivatives and are digested in the colon in esterified form (Lafay and Gil-Izquierdo 2008). A significant reduction of two hydroxycinnamic acids was observed in carob fruit products during *in vitro* digestion according to a study by Goulas and Hadjisolomou (2019). The recoveries of caffeic acid and syringic acid were lower than 17% and 49%, respectively, at the intestinal digestion

(Goulas and Hadjisolomou 2019). According to Dall'Asta et al. (2016), the less bioaccessible phenolics in aleurone-rich whole-grain bread were ferulic acid and *p*-coumaric acid while those with higher bioaccessibility were caffeic and sinapic acids.

It is also assumed that flavonoids can be metabolized through the action of enzymes of the small intestinal brush-border membrane, namely phlorizin hydrolase, glycosylceramidase (Crozier, Del Rio, and Clifford 2010; Fraga et al. 2010). Flavonoid metabolism begins in the mouth with hydrolysis of the glycosidic bond by *β*-glycosidase action, and it depends on the type of substituted sugar moiety in the molecule. The hydrolysis of glucose conjugated flavonoids is more expeditious than rhamnose conjugated ones. This may happen continuously in the lumen of the intestine or in enterocytes directly before absorption. Polyphenols containing glucose, arabinose, and xylose can be hydrolyzed by the human endogenous enzyme cytosolic *β*-glucosidase (Karaś et al. 2017). Except for catechins and proanthocyanidins, most flavonoids in food are glycosylated, and this glycosylation influenced absorption, distribution, and metabolism to a certain degree. In general, the absorption of polyphenols by the epithelial cells mainly depends on their permeability. However, flavonoid glycosides are highly polar molecules and should be hydrolyzed to their aglycone forms in order to diffuse across the cellular membrane (Kottra and Daniel 2007). Deglycosylation is considered a critical step in the absorption and metabolism of flavonoid glycosides (Walle et al. 2005). If a flavonoid glycoside is not absorbed in the small intestine, colonic microflora is the key hydrolase source that can metabolize the compound into its aglycone form in the large intestine (Xiao 2017). In the study of Inada et al. (2020), quercetin in jaboticaba peel and seed powder was released after gastric digestion due to the hydrolysis of quercetin glycosides, such as quercetin-3-*o*-glucoside and quercetin-3-*o*-rhamnoside. In a study by Carbonell-Capella et al. (2015), steviol glycosides were reported to have glycosidic bonds which were possible sites of action of the enzyme α-amylase and could thus result in an increase in these compounds after salivary digestion. Additionally, after intestinal digestion, rebaudioside F became highly bioaccessible because of important spatial separation of glycosidases from steviol glycosides occurring during *in vitro* and *in vivo* metabolism (Carbonell-Capella et al. 2015). According to Scalbert et al. (2002), many enzymes from the human digestive tract, either endogenous or produced by the microflora, play a role in polyphenol metabolism. The hydrolysis of many polyphenol glycosides, particularly quercetin-3-*o*-glucoside, is governed by the function of endogenous enzymes, namely cytosolic *β*-glucosidase (EC 3.2.1.21, predominantly in the liver) and lactase (EC 3.2.1.108, in the intestine). During absorption, phenolic compounds are subject to conjugation in the liver and enterocytes by various endogenous enzyme functions: (1) methylation of polyphenol catalyzed by catechol methyltransferase (EC 2.1.1.6), (2) conjugation of glucuronide conjugates by UDP-glucuronidase (EC 2.4.1.17), and (3) transformation of aglycones in sulfate derivatives by phenol sulfotransferase (EC 2.8.2.1). Beyond the absorption, polyphenolic compounds further metabolized in the organism are excreted metabolites in the urine or bile (Scalbert et al. 2002).

Literature data have suggested that anthocyanidins are less efficiently absorbed than other flavonoids in the gastrointestinal tract. Anthocyanidin catabolism mainly leads to the formation of glucuronide and methylated derivatives under the functions of enzymes, namely UDP-glucuronic transferase, UDP-glucose dehydrogenase, or sulfonated catechol methyltransferase (present in the small intestine, liver, and kidney). In the form of anthocyanidin glycosides, they are transported through gastric mucosal cells by (1) Na+-dependent glucose transporters and (2) bilitranslocase (TC 2.A.65.1.1) both are membrane transporters of organic anions (Scalbert et al. 2002). Several factors may affect anthocyanidin sorption, including (1) the aglycone structure (e.g., transport efficacy: malvidin and peonidin > delphinidin forms), (2) the type and number of substituted sugar moieties (bioavailability: glucose-based anthocyanidins or anthocyanidin glycosides > galactose-based anthocyanidins), (3) polymeric structure (absorption: monomeric > polymeric anthocyanidins), and (4) the presence of other food components (Fang 2014; Karaś et al. 2017). Mono-, di-, and triglycosides of cyanidin, peonidin, and delphinidin that are found both in the plasma and the urine may confirm this hypothesis (Lucas-Gonzalez et al. 2016). A recent study by Peixoto et al. (2016) confirms that anthocyanidins are absorbed in the glycosidic form, namely diglycoside anthocyanidins; delphinidin-3,5-*o*-diglucoside and cyanidin-3,5-*o*-diglucoside.

Molecular weight or size

Polyphenol molecular weight or size also has a crucial impact on intestinal absorption. Because of the high molecular weight of tea theaflavins (MW = 568), low recovery in the urine can be observed according to Scalbert et al. (2002). Moreover, another class of high- molecular-weight polyphenols is flavonoid polymers, for example, proanthocyanidins (syn. condensed tannins) presented with varying degrees of polymerization and molecular weights above 578. It is understandable that they are not practically absorbed in the gut (Scalbert et al. 2002). Furthermore, Pavan, Sancho, and Pastore (2014) demonstrated that some phenolics were predominantly diminished to unstable smaller molecules e.g. gallic acids after simulated digestion.

Food matrices

Firstly, bioactive substances must be released from food matrices. Only those that are liberated from food matrices in the digestive system are digested. One of the early factors responding to the bioavailability of polyphenols is the nature of the food matrix itself (Giusti et al. 2019). The other is the food matrix when consumed together with other kinds of foods (Annunziata et al. 2018; Carbonell-Capella et al. 2015; Tenore et al. 2015). The release of phenolics from the sample matrix is facilitated by interactions with dietary

constituents (proteins, carbohydrates, lipids, fibers, polysaccharides, or minerals) and digestive enzymes (Bouayed, Hoffmann, and Bohn 2011; Chiang, Kadouh, and Zhou 2013; Gullon et al. 2015). The structures of food components can be modified during digestion, and this may affect their absorption and bioaccessibility and thus, their bioavailability. Interlinkage between phenolic compounds and other food components (food matrices) was reviewed exclusively by Karaś et al. (2017).

The changes in phenolic antioxidants and their activities showed different trends during the digestion phase. Giusti et al. (2019) reported that phenolics may be released from the matrix of legumes in a limited amount during digestion due to physical interaction between free phenolics and cell wall material, thus low amount being available for absorption in intestinal part. Moreover, the covalent bond between cell wall polysaccharides and phenolic acids (mostly ferulic acid) prevents phenolics bonded with them from being cleaved by human pancreatic enzymes (Giusti et al. 2019). However, when tissues are finely ground, i.e., in the ground coat and cotyledon of legumes, the bioaccessibility of the same phenolic compounds is improved, which suggests a higher leaching rate of phenolic compounds from different food matrices (Giusti et al. 2019). The lower quantity of gallic and ellagic acids of jaboticaba (*Plinia jaboticaba*) peel and seed mixed powder may also be explained by the same phenomenon, which reduces their bioaccessibility after gastric digestion (Inada et al. 2020). The decrease in anthocyanin content (TAC) in chokeberry juice studied by Stanisavljević et al. (2015) is provoked by destroying the complexation with matrix proteins, carbohydrates, fibers and cell wall through hydrogen bonding and hydrophobic interactions. The addition of complex food matrix to the juice immediately decreased the total phenolic content, DPPH scavenging capacity, and total reducing power of chokeberry juice (Stanisavljević et al. 2015). The low bioavailability of anthocyanins from peel powder of jabuticaba, jamelão, and jambo fruits results from incomplete leaching of anthocyanins out of the fruit matrix due to possible interlinkage with other compounds, such as fiber and lipids, leading to lower accessibility of enzymes according to Peixoto et al. (2016). Previous studies suggested that interactions of phenolic acids and anthocyanins with polysaccharides, cellulose, and pectin greatly limit phenolic bioavailability (Bouayed, Hoffmann, and Bohn 2011; Carbonell-Capella et al. 2015; Giusti et al. 2019; Ti et al. 2015). Koehnlein et al. (2016) compared the phenolic contents of the popular Brazilian foods (36 types) treated by simulated digestion. After simulated digestion, cereals, legumes, vegetables, tuberous vegetables, chocolates, and fruits showed higher phenolic contents. In contrast, simulated digestion caused a reduction in the phenolic contents of different beverages, such as red wine, tea, coffee, and yerba mate. Unlike in liquid food matrices, phenolics in solid and complex matrices were protected from enzymatic action as well as pH alteration during digestion (Koehnlein et al. 2016). Apart from that, the extended extraction time along with the effect of intestinal enzymes could facilitate the release of additional phenolics from the matrix (Liyana-Pathirana and Shahidi 2006; Ortega et al. 2011). According to Ortega et al. (2011), soluble dietary fiber in a simulated digestion model enhanced the stability of phenolic compounds during intestinal digestion phase. Mosele et al. (2016) reported the presence of pectin in *Arbutus unedo* fruit causes gastric stage to hamper but intestinal stage to promote the liberation of bioactive compounds. The solubilization of phenolic compounds during gastric stage was limited because of the presence of pectin. Then, pectin-gel was degraded during intestinal digestion, which favored the release of phenolic compounds to the media (Mosele et al. 2016). Thuengtung et al. (2018) reported changes in antioxidant activity of pigmented rice in grain and slurry forms. DPPH and FRAP value for slurry was higher than those of grain during simulated digestion. In addition, Reginio et al. (2020b) reported a similar result in a simulated digestion study of Saba banana pulp using two forms of pulp: intact structure (cut) and a structure-less state (slurry). A continuous increase was found in TPC with comparatively faster release in slurry than that in cut. The trend of antioxidant activities in slurry > cut, which was increased in the gastric phase and then decreased at the onset of the intestinal phase, which confirms the effect of the food matrix on the release of bioactive compounds. Additionally, Cai et al. (2020) studied citrus (*Citrus unshiu*) peel tissue with different particle sizes and found that the digested fluid of the larger particle sizes comparatively retained more antioxidant compounds and greater activity than smaller ones during the simulated gastric stage due to a less damage cell surface. These studies can confirm about the effect of food structure/matrix, especially cellular structure disruption boost up the excretion of bioactive compounds.

Gastrointestinal digestion environments

It is well known that phenolic antioxidants, for example, in the class of phenolic acids and flavonoids, are metabolized extensively after gastrointestinal absorption, being transformed into plasma metabolites with higher or lower antioxidant activity than the corresponding raw materials (Boaventura et al. 2015; Correa et al. 2017; Gonçalves et al. 2019). The content, structure and activity of bioactive compounds are modified when they pass through the digestive tract as a consequence of enzymatic actions, pH alterations, and the metabolic activity of the innate normal flora in digestive tract (Boaventura et al. 2015; Correa-Betanzo et al. 2014). These variations may result from the simulated digestion environment or combination with the sample itself, i.e., form (solid/liquid, whole grain, slurry, structure, matrices), cooking/processing conditions, other food compositions, types, cultivars, parts (fruit, peel, pulp, leaves, bark, branch, stem, seed, root), maturity, environments, and extraction solvents (Celep et al. 2015; Koehnlein et al. 2016). The absorption of phenolics from the plant food matrix follows multistep pathways following (1) release of specific phenolics from the plant or food matrix, (2) solubilization of phenolics in the gut lumen, (3) hydrolysis or metabolism of phenolics, (4) uptake by small intestinal absorptive epithelial cells, (5)

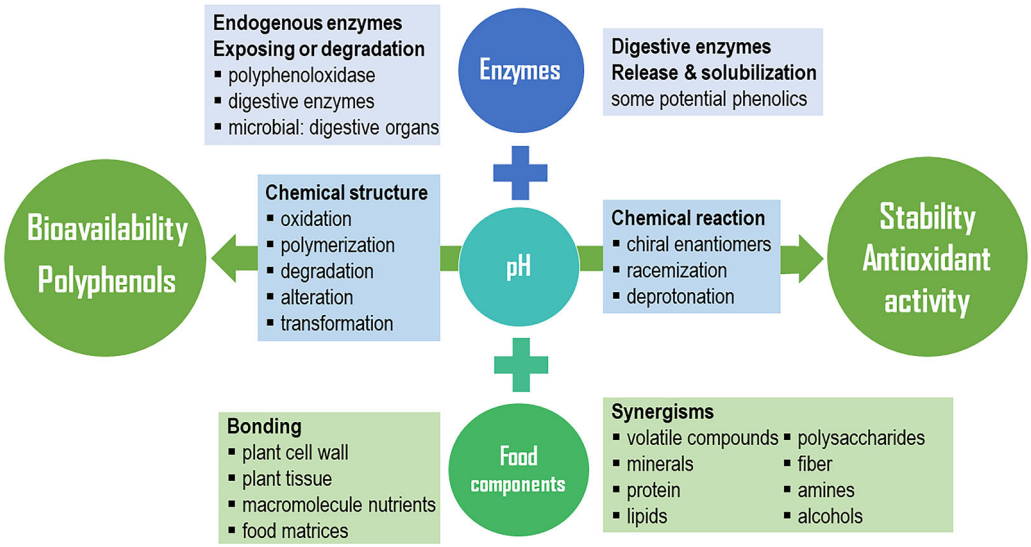

Figure 5. Factors affecting the bioavailability of polyphenols and stability of antioxidant activity during *in vitro* stimulated gastrointestinal digestion.

metabolism in intracellular tissues and secretion into the blood stream, (6) transfer of undigested phenolics to the colon, and (7) excretion of inessential metabolites in urine or bile (Carbonell-Capella et al. 2015).

Factors affecting the bioavailability of polyphenols and stability of antioxidant activity during *in vitro* stimulated gastrointestinal digestion are displayed in Figure 5. The increment, stability, or loss of bioactive compound content during simulated digestion can be influenced by the following factors: (1) synergistic effects of dietary components such as proteins, carbohydrates, lipids, fiber, and minerals (Alminger et al. 2014; Ortega et al. 2011), (2) chemical reactions that promote the oxidation and polymerization of bioactive compounds, resulting in the generation of other complex phenolic metabolites such as chalcones and quinones (Altunkaya, Gökmen, and Skibsted 2016), (3) enzymatic actions causing molecular transformations in the compounds based on their solubility behavior (Kroll, Rawel, and Rohn, 2003) and exposing water-soluble polyphenols from food matrices or broken chemical bonds in phenolics and proteins, carbohydrates, and lipids with cell wall tissues, thus promoting the release of phenolics, especially the phenolic acids, which are major constituents of the cell wall (Ti et al. 2015). Furthermore, (4) polyphenol oxidase (PPO) in plants can play a part because it shows maximum activity at or near neutral pH values, resulting in higher phenol degradation or polyphenols cross-linked with other polyphenols, carbohydrates, or proteins, as well as oxidation of certain phenolic compounds such as chlorogenic acid and catechin (Altunkaya, Gökmen, and Skibsted 2016; Ketnawa and Ogawa 2019). Additionally, (5) different pH conditions could possibly influence a proportion of the polyphenol compounds by degradation, alteration or transformation of bioactive compounds by their chemical structure (Ghosh, Chakraborty, and Raychaudhuri 2015) into dissimilar structural forms with various chemical properties, and various bioaccessibility, bioavailability, and biological activities, which may render polyphenol compounds detectable or undetectable by individual HPLC and HPLC-MS-MS polyphenol analyses. In addition to the enzymatic activity, low pH conditions could enhance softening of cell wall tissues (Lucas-Gonzalez et al. 2016) or increase the reactivity of phenolic compounds toward Folin-Ciocalteu reagent (Goulas and Hadjisolomou 2019). Moreover, in previous simulated digestion studies, the changes in the content of active biological compounds in the absence of digestive enzymes, marked as control (CT), indicated that the release and stability of compounds were strongly affected by both pH change and various digestive enzymes, i.e., gastric enzymes (pepsin, trypsin, and chymotrypsin) and pancreatic enzymes (mixtures of lipase, protease, and amylase). To be a bioaccessible and potentially bioavailable compound, the action of digestive enzymes is an essential physiological requirement of the digestion process specifically. Digestive enzymes aid in the hydrolysis of matrix macronutrients and contribute to degradation of the food matrix, which leads to greater polyphenol and flavonoid release, thus resulting in higher antioxidant activity (Carbonell-Capella et al. 2015; Giusti et al. 2019; Stanisavljević et al. 2015). Thus, health problems associated with insufficient secretion of digestive enzymes, such as exocrine pancreatic insufficiency, could contribute to maldigestion of nutrients and possibly lead to low release and stability of polyphenolic compounds in people with such disorders (Lucas-González et al. 2018b).

Apart from the released amount, a change in the response of antioxidant activities during simulated digestion essentially depends on several factors as follows: (1) the constancy of the antioxidant molecules in the presence of digestive enzymes and pH elevation; (2) the synergistic effect of food matrix components such as minerals, volatile compounds, etc. (Celep et al. 2015), as well as sugars, cell wall polysaccharides, pectin, alcohols, or amines (Masisi, Beta, and Moghadasian 2016); and (3) chemical reactions, for example, (a) the formation of chiral enantiomers with assorted activities, (b) an increase in racemization of molecules with increasing pH renders antioxidants more reactive at acidic pH in gastric stage than at pH 6.8–7.4 in intestinal stage (Jamali et al. 2008; Wootton-Beard, Moran, and Ryan

Table 2. Recent studies about bioactive compounds and bioactivity changes during *in vitro* simulated digestion.

Plant based foods	Digestive conditions	Phenolic compounds	Antioxidant activity	References
Rice, grain and legumes				
Red, black, and purple rice grains and slurries	**GT:** pepsin, HCl, pH 1.2, 0.5 h **IT:** pancreatin, amyloglucosidase and invertase, pH 6.8, 2 h (slurry), 24 h (grain)	**GT:** TPC+, TAC+ **IT:** TPC+, TAC-	**GT:** DPPH+, FRAP+ (grain and slurry) **IT:** DPPH+, FRAP+ (grain), DPPH-, FRAP- (slurry)	Thuengtung et al. (2018)
Brown and polished rice (TianYou 998)	**GT:** pepsin, HCl, pH 1.2, 1 h **IT:** Pancreatin, bile extract, $NaHCO_3$ pH 7.0, 2 h	**GT:** TPC+, TAC+ **IT:** TPC+, TAC- **HPLC-UV profiles:** gallic, protocatechuic, chlorogenic, caffeic, syringic, coumaric and ferulic acids	**GT and IT:** ORAC+	Ti et al. (2015)
Purple rice	**GT:** pepsin, HCl, pH 1.2, 2 h **IT:** Pancreatin, bile salts, $NaHCO_3$, pH 7.5, 2 h	**GT:** TPC+, TAC↔ **IT:** TPC+, TAC- **HPLC-UV profiles:** cyanidin-3,5-diglucoside, cyanidin-3-glucoside, cyanidin-3-rutinoside, peonidin-3-glucoside	**GT and IT:** DPPH+, ABTS+	Sun et al. (2015)
Quinoa seeds	**OL: α-amylase,** $CaCl_2$, $NaHCO_3$, pH 6.9, 5 min **GT:** pepsin, HCl, pH 2, 2 h **IT:** Pancreatin, NaOH, $NaHCO_3$, pH 7.0, 2 h	**OL:** TPC +, TFC+ **GT:** TPC ++, TFC++ **IT:** TPC ++, TFC- LC-ESI-MS/MS profiles: 4-hydroxyphenylacetic; *p*-coumaric; ferulic; vanillic; 4-hydroxybenzoic, neohesperidin	**OL:** DPPH+, ABTS+. FRAP+, MIC+ **GT:** DPPH++, ABTS++, FRAP++ and MIC++ **IT:** DPPH++, ABTS++, FRAP++, MIC+++	Pellegrini et al. (2017)
Fermented soybean	**GT:** pepsin, HCl, pH 1.2, 2 h **IT:** pancreatin, amyloglucosidase and invertase, pH 6.8, 2 h	**GT:** TPC+ **IT:** TPC++	**GT:** DPPH+, ABTS+, FRAP+, MIC+ **IT:** DPPH++, ABTS++, FRAP++, MIC++	Ketnawa and Ogawa (2019)
Legumes	**GT:** pepsin, HCl, pH 3.0, 2 h **IT:** Pancreatin, electrolyte solution, $NaHCO_3$, NaOH, pH 7.0, 2 h	**GT and IT:** TPC-, TAC- **HPLC-DAD profiles:** chlorogenic acid pelargonidin 3,5-diglucoside, delphinidin 3-glucoside	n/a	Giusti et al. (2019)
Vegetables				
Crisphead lettuce	**GT:** pepsin, HCl, pH 1.2, 2 h **IT:** pancreatin, amyloglucosidase and invertase, pH 6.8, 2 h	**GT:** TPC+ **IT:** TPC-	**GT:** DPPH+, ABTS+, FRAP+, MIC+ **IT:** DPPH-, ABTS-, FRAP-, MIC-	Ketnawa, Suwannachot, and Ogawa (2020)
Prickly Pear Cactus Cladodes (*Opuntia ficus-indica*)	**GT:** pepsin, HCl, pH 3.0, 2 h **IT:** pancreatin, NaOH, pH 7.0, 2 h	**GT and IT:** TPC-, TFC- **IT:** TPC- **UHPLC-PDA-HR-MS. Profiles:** isorhamnetin derivatives, quercetin, kaempferol derivatives 3,4-dihydroxybenzoic, 4-hydroxybenzoic, salicylic,chlorogenic, malic, sinapic, gallic acids, isoquercitrin, myricetin-hexoside	**GT and IT:** DPPH-	De Santiago et al. (2018)
Fruits				
Saba banana (*Musa 'saba'*, ABB Group)	**GT:** pepsin, HCl, pH 1.2, 0.5 h **IT:** pancreatin, amyloglucosidase, invertase, pH 6.8, 20.6 h (slurry), 24.6 h (cut)	**GT:** TPC+ **IT:** TPC-	**GT:** DPPH+, ABTS+, FRAP+, MIC- **IT:** DPPH-, ABTS+, FRAP-, MIC+	Reginio, Qin, Ketnawa, and Ogawa (2020b)
Chilean white strawberry (*Fragaria chiloensis* spp. *chiloensis f. chiloensis*)	**GT:** pepsin, HCl, pH 1.2, 30 min **IT:** amyloglucosidase, α-amylase, NaOH, pH 6.9, 45min	**GT and IT:** TPC-, TFC- HPLC-DAD-ESI-MS/MS Profiles: (epi)catechin hexoside, kaempferol, ellagic acid, protocatechuic acid	**GT and IT:** DPPH-, ABTS-, FRAP-, MIC-, SOA-	Thomas-Valdés et al. (2018)
Arbutus unedo fruit	**OL: α-amylase**, artificial saliva, pH 6.9, 5 min **GT:** pepsin, HCl, pH 2, 1 h **IT:** Pancreatin, bile extract, $NaHCO_3$, pH 6.5, 2 h	**OL:** TPC↔ **GT:** TPC- **IT:** TPC↔ **UPLC-MS/MS profiles:** p-hydroxybenzoic acid,catechol, gallic and ellagic acids, Dihydroxyphenyl-γ-valerolactone, trihydroxyphenyl-γ-valerolactone	n/a	Mosele et al. (2016)
Juices and beverages				
Jasonia glutinosa D.C. (Asteraceae) (rock tea)	**GT:** pepsin, mucin, HCl, pH 2, 2 h **IT:** Pancreatin, lipase, bile salts, $NaHCO_3$, pH 7, 2 h	**GT and IT:** TPC- **HPLC MS/MS profiles:** dicaffeoylquinic acids, 5-O-caffeoylquinic acid, 3-O-caffeoylquinic acid, 4-O-caffeoylquinic acid	**GT and IT:** DPPH-, ABTS-	Ortega-Vidal et al. (2019)

(*continued*)

Table 2. Continued.

Plant based foods	Digestive conditions	Phenolic compounds	Antioxidant activity	References
Yerba mate (*Ilex paraguariensis* A. St. Hil.) beverages	**OL:** α-amylase, artificial saliva, pH 6.75, 10 min **GT:** pepsin, HCl, pH 1.2, 2 h **IT:** Pancreatin, bile extract, $NaHCO_3$ pH 6.0, 1 h	**GT and IT:** TPC- **HPLC-DAD-ESI/MSn profiles:** salvianolic acid I (caffeic acid trimer), 5-O-caffeoiquinic acid (5CQA), 4-O-caffeoylquinic acid (4CQA), 3-O-caffeoylquinic acid (3CQA) and 3,5-O-dicaffeoyquinic acid (3,5 diCQA).	**GT and IT:** DPPH-, ABTS+, FRAP-, ORAC-, TBARS-	Correa et al. (2017)
Turkish fruit wines form Papazkarası blueberry, black mulberry and cherry	**GT:** pepsin, HCl, pH 2, 2 h **Post-GT:** $NaHCO_3$, pH 7.0, 2 h	**GT and post GT:** TPC+ **HPLC-DAD profiles:** gallic acid, chlorogenic acid, caffeic acid, vanillin, p-coumaric acid, rutin, quercetin	**GT and post GT:** DPPH+, MIC+, ABTS+, H_2O_2+	Celep et al. (2015)
Herb and spices				
Rosemary (*Rosmarinus officinalis* L) dried leave	**OL:** α-amylase, artificial saliva, pH 6.75, 10 min **GT:** pepsin, HCl, pH 1.2, 2 h **IT:** Pancreatin, bile extract, $NaHCO_3$ pH 6.0, 1 h	**GT and IT:** TPC- **LC-DAD-ESI/MSn profiles:** yunnaneic acid F, rosmarinic acid, Luteolin-O-glucuronide, salvianolic acid A, acetylluetolin-O-glucuronide sagerinic acid isomer, prolithospermic acid, caffeic acid and derivatives	**GT and IT:** DPPH-, ABTS-, ORAC-, FRAP+	Gonçalves et al. (2019)
Oregano (*Hedeoma patens*, *Lippia graveolens*, *Lippia palmeri*)	**OL: α-amylase,** artificial saliva, pH 6.5, 5 min **GT:** pepsin, mucin, HCl, pH 2.0, 1 h **IT:** Pancreatin, lipase, bile extract, $NaHCO_3$ pH 7.5, 1 h	**GT and IT:** TPC-, TFC- **UPLC-PDA profiles:** apigenin-7-glucoside, scutellarein, luteolin, luteolin-7-glucoside, phloridzin and chlorogenic acid	**GT:** ORAC+, DPPH+, ABTS+ **IT:** ORAC-, DPPH↔, ABTS↔	Gutiérrez-Grijalva et al. (2017)
Melissa officinalis, *Lavandula latifolia* and *Origanum vulgare* dried leaves	**OL: α-amylase, artificial** saliva, pH 6.75, 2 min **GT:** pepsin, HCl, pH 2.5, 2 h **IT:** Pancreatin, bile extract, $NaHCO_3$ pH 7.5, 2 h	**GT and IT:** TPC- **HPLC-DAD andUPLC-MS profiles:** coumaric acid-O-glycoside, −4-(3,4-dihydroxybenzoyloxymethyl)-phenyl-β-D-glycopyranoside, rosmarinic acid, luteolin-7-O-glucoside	**GT and IT:** DPPH-, ABTS-	Gayoso et al. (2018)
By-products				
Jaboticaba (*Plinia jaboticaba*) peel and seed	**GT:** pepsin, HCl, pH 2, 2 h **IT:** Pancreatin, bile extract, $NaHCO_3$ pH 6.5, 2 h	**GT:** TPC –, TAC + **IT:** TPC —, TAC - **HPLC-DAD:** Cyanidin-3-O-glucoside, ellagic acid and gallic acid	n/a	Inada et al. (2020)
Spent coffee (*Coffea arabica* L.)	**OL: *human salivar,* 15** sec. **GT:** pepsin, HCl, pH 2, 2 h **IT:** Pancreatin, Krebs–Ringer buffer pH 7.0, 2 h	**OL:** TPC –, TFC - **GT:** TPC +, TFC + **IT:** TPC ++, TFC- **HPLC-UV profiles:** tannin, chlorogenic acid, vanillin and (+)-catechin	**OL:** DPPH+, ABTS+ **GT:** DPPH++, ABTS++ **IT:** DPPH+++, ABTS+++	Campos-Vega et al. (2015)
Flours from persimmon (*Diospyros kaki*) co-products Var. 'Triumph' and 'Rojo Brillante'	**OL: α-amylase, $CaCl_2$,** $NaHCO_3$, pH 6.9, 5 min **GT:** pepsin, HCl, pH 2, 2 h **IT:** Pancreatin, NaOH, bile salt, $NaHCO_3$ pH 7.0, 2 h	**OL:** TPC+, TFC+ **GT:** TPC++, TFC++ **IT:** TPC-, TFC- **HPLC-UV profiles:** 4-hydroxybenzoic acid, quercetin-o-hexoside, quercetin-o-pentoside, kaempferol-o-rhamnoside, ellagic acid	**OL, GT and IT:** DPPH-, ABTS-, FRAP-, MIC+	Lucas-González et al. (2018a).

(+): increase, (–): decrease, (↔): stable, (OL): oral phase digestion, (GT): gastric digestion phase, (IT): intestinal digestion phase, (TPC): total phenolic content; (TFC): total flavonoid content; (TAC): total anthocyanin content; (ABTS): 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) radical scavenging, (DPPH): 2,2-diphenyl, 1-picryl hydrazyl radical scavenging, (ORAC): oxygen radical absorbance capacity, (H_2O_2): hydrogen peroxide radical scavenging, (SOA): superoxide anion scavenging capacity, (FRAP): ferric reducing antioxidant property, (MIC): metal ions chelating activity, (TBARS): inhibition of the production of thiobarbituric acid reactive substances.

2011), and (c) deprotonation in digestive fluid with increasing pH levels (Altunkaya, Gökmen, and Skibsted 2016) (Figure 5). The higher antioxidant capacity after simulated digestion is due to partial phenolic compounds hydrolysis that generates new compounds which may expose antioxidant activity but are considered as "undetected" derivatives by HPLC during simulated digestion (Pinacho et al. 2015).

To study the effect of digestive enzymes (i.e., amylase, pepsin, pancreas, trypsin, lipase, and invertase) on food digestion, simulated digestion without the addition of digestive enzymes (referred to as control; CT) or inactivation of the enzymes was applied in several studies, for example, gooseberries (Chiang, Kadouh, and Zhou 2013). Chiang, Kadouh, and Zhou (2013) reported the improved release and accessibility of TPC in two European gooseberries (*Ribes uvacrispa*): Tixia and Invicta. The samples treated with active digestive enzymes had higher TPC than their inactivated enzyme-treated counterparts. Total phenolic

content (TPC) seems to improve with increased release and shows higher bioaccessibility in simulated digestion with vs without digestive enzymes by this study.

Recent studies of bioactive compounds in the digestion

Recent studies of bioactive compounds and bioactivity change during *in vitro* simulated digestion were summarized in Table 2 and discussed below.

Oral digestion phase (oral stage)

It has been established that the bioavailability of some hydrophobic and some polar compounds is promoted by the oral mucosa. According to a study by Tenore et al. (2015), tea catechins, ranging from 74.8% to 99.5%, were detected in the salivary phase under *in vitro* oral conditions, indicating good consistency. Some phenolics, like catechin, are gastro-sensitive or poorly absorbed by the gastrointestinal tract. From salivary extraction studies, the dispensation of catechin to target specific tissues or organs occurs directly via absorption through the oral mucosal epithelium without undergoing potential degradation in the GI tract and/or excretion in the feces (Tenore et al. 2015). All three phenolic acids (gallic, caffeic, and syringic acids), flavonols (quercetin, rutin, and myricetin), and flavan-3-ols (catechin and epigallocatechin gallate) of Carob fruit were relatively stable during oral digestion, as their recoveries in the digestive fraction were higher than 83% according to Goulas and Hadjisolomou (2019). Phenolic acids of ground spent coffee were more stable under oral digestion as indicated by the decrease of main phenolics such as neochlorogenic acid (10.64%), cryptochlorogenic acid (17.54%), chlorogenic acid (24.89%), and isoorientin (45.74%) (Campos-Vega et al. 2015). Apart from the chemical structure, anthocyanins was deteriorated in the mouth by partial mediation of oral microbiota metabolism (Kamonpatana et al. 2014; Kamonpatana et al. 2012), of which glycosylated chalcones are some of the possible metabolites (Kamonpatana et al. 2012). The concentrations of all detected anthocyanins in maqui berry decrease in the oral stage by reduction of delphinidin-3-glucoside content by 54.40%, delphinidin-3-sambuboside content by 54.30%, and cyanidin-3-sambuboside by 80.61%. However, some studies suggested that phenolics were less effectively released during the oral phase due to the shorter contact time with the enzyme compared with gastrointestinal digestion (Lucas-Gonzalez et al. 2016).

Gastric digestion phase (gastric stage)

The release of phenolics (TPC) and flavonoids (TFC) from crisphead lettuce (*Lactuca sativa* L.) increased during 1 h of gastric stage (Ketnawa, Suwannachot, and Ogawa 2020) It was found that when running a simulated digestion without addition of digestive enzymes, TPC and TFC showed lower and higher values, respectively, at the stage of gastric stage for 1 h and gastric, indicating that polyphenols were driven out (Ketnawa, Suwannachot, and Ogawa 2020). The variations in TPC and TFC of five maturity stages of Saba banana were examined by Reginio et al. (2020b). In this study, TPC increased continuously during gastric stage. Bouayed, Hoffmann, and Bohn (2011) reported that approximately 65% of apple TPC and TFC were released in the stomach and only 10% in the small intestine. In a study by Dutra et al. (2017) about the bioaccessibility of rutin in mangaba frozen pulp, a change in rutin up to 125.37 mg was observed after exposure to simulated gastric conditions. The increase may be because rutin could be generated from quercetin, which is its aglycone form, through rupture of the linkage with the sugar during exposure to acidic conditions in gastric stage (Celep et al. 2015). Due to the low pH in gastric stage, flavonoid oligomers are degraded into smaller units. Of all the flavonoids, flavon-3-ols exist as aglycones and pass intact into the duodenum. In Carob flour, flavonols and flavon-3-ols decreased under gastric conditions (Goulas and Hadjisolomou 2019).

Peixoto et al. (2016) found that the gastric mucosa plays an important role in anthocyanin absorption from peel powder of jabuticaba, jamelão, and jambo fruits. Lucas-Gonzalez et al. (2016) also reported all anthocyanins in maqui berry increased in concentration. Regarding individual compounds, delphinidin-3-glucoside and delphinidin-3-sambuboside contents increased by 49.08% and 32.59%, respectively. The partial degradation of proanthocyanin oligomers into cyanidins leads to an increment of anthocyanins in the gastric fraction (Stanisavljević et al. 2015). The degradation of anthocyanins into smaller compounds was also observed in various legumes (Giusti et al. (2019), e.g. cyanidin 3-glucoside is degraded to protocatechuic acid during gastric stage. In addition, the most part of polyphenols appears to be released in the stomach, as confirmed by several studies. Correa-Betanzo et al. (2014) showed high stability of TPC and TAC (only 7% and 1% reductions, respectively) during gastric stage, while intestinal stage caused significant 49% and 15% loss, respectively, compared with non-digested wild blueberry samples. Thuengtung et al. (2018) reported changes in TAC of both pigmented rice grain and slurry forms during simulated digestion and revealed that the contents increased sharply during gastric stage but decreased at the beginning of the intestinal stage. Intestinal stage was concluded that anthocyanins are unstable in the small intestine and absorbed with low bioavailability (Thuengtung et al. 2018). The same trend was observed by Sun et al. (2015), which reported that gastric stage caused little change in the amount of anthocyanins (92.34 ± 3.37 (gastric stage) whereas 90.44 ± 5.65 (undigested sample) as reported of cyanidin 3-glucoside equivalents mg/g dry extract). However, TAC in the intestinal stage sample decreased significantly to 21.86 ± 4.06 cyanidin 3-glucoside equivalents mg/g dry extract ($p < 0.05$). Thus, about 76% of TAC were degraded during intestinal stage (Sun et al. 2015). In fruits like wild blueberry, TAC was highly stable during gastric stage and decreased by nearly 50% in comparison with the undigested sample when subjected to intestinal stage (Correa-Betanzo et al. 2014). Another study also found

that gastric stage did not significantly influence wild blueberry anthocyanins, but about 42% of TPC were degraded during intestinal stage (Liu et al. 2014). Similar results were obtained by Bermúdez-Soto, Tomás-Barberán, and García-Conesa (2007), which reported a significant reduction of anthocyanins (43%) and flavonols (26%) after intestinal stage of chokeberry, whereas CHA increased (24%) (Stanisavljević et al. 2015). The researchers assumed that the stable form, flavylium cation, of anthocyanins could be generated due to acidic pH and thus provided higher bioaccessibility of anthocyanins in the gastric stage (Lucas-Gonzalez et al. 2016).

Intestinal digestion phase (intestinal stage)

Several researchers reported that the escalation in phenolic compounds in intestinal stage may be due to the action of intestinal digestive enzymes, which facilitate the release of phenolics those bound to the matrix and the food together with longer digestion time (Bouayed, Hoffmann, and Bohn 2011; Dutra et al. 2017; Lucas-Gonzalez et al. 2016; Peixoto et al. 2016). Chait et al. (2020) found that gallic (647.4%) and chlorogenic (485.4%) acids were the two most bioaccessible phenolic acids after simulated digestion of carob pod. Celep et al. (2017) also reported an increment of gallic and chlorogenic acid concentrations in *Hypericum perfoliatum* medicinal plant after intestinal stage due to the hydrolysis of galloylated molecules of tannins (gallotannins). Likewise, the highest bioaccessibility of phenolic compounds was observed in intestinal stage for umbu-cajá frozen pulp, among which the highest levels were those of *trans*-cinnamic acid (127.58%), followed by gallic acid (73.92%) and catechin (69.94%) (Dutra et al. 2017). The increase in the amounts of flavonoids in the intestinal digestion phase may be related to the hydrolysis of complex compounds such as galloylated catechins from their glycoside to their aglycone forms; for example, the free flavonoids, (+)-catechin and rutin of carob pod showed the highest bioaccessibilities of 558.3% and 267.2%, respectively (Chait et al. 2020; Ortega et al. 2011). In the case of Jamelão fruits, high bioavailability of anthocyadinins was found after intestinal stage. Jamelão matrix was able to promote the highest values of bioaccessibility (~65% and 45%), respectively, according to the diglycoside anthocyadinin forms represented, i.e., delphinidin-3,5-*o*-diglucoside; cyanidin-3,5-*o*-diglucoside; petunidin-3,5-*o*-diglucoside; peonidin-3,5-*o*-diglucoside; and malvidin-3,5-*o*-diglucoside, that could positively impact on anthocyanin stability in intestinal stage (Peixoto et al. 2016). On the other hand, Lucas-Gonzalez et al. (2016) reported cyanidin-3-sambubioside and cyanidin-3-glucoside were detected in maqui berry digested at the intestinal phase. Moreover, HPLC-ESI-TOF/MS analysis showed that the major phenolic compounds during small intestinal digestion of *Moringa oleifera* Lam. leaves were quercetin-3-*o*-*β*-D-glucoside and ferulic acid (Dou, Chen, and Fu 2019). The higher stability of diglucosides can be explained by the reduction of the nucleophilic character of the C6 and C8 positions by glycosyl substitution at C5, which contributed to less electrophilic attack in anthocyanin 3,5-diglucosides than 3-glucosides (Sengul, Surek, and Nilufer-Erdil 2014). After simulated digestion, TPC and TFC had increased by 195.6% and 34.6% in cooked brown rice, and by 403.3% and 13.1% in cooked polished rice, according to a work of Ti et al. (2015). Thuengtung et al. (2018) observed the same increasing trend that TPC increased continuously during simulated digestion of both pigmented rice grains and slurries. Ketnawa and Ogawa (2019) reported a change in TPC at different stages of simulated digestion of fermented soybeans (Natto). The level of free phenolics increased dramatically from 10.41 to 25.65 mg gallic acid equivalents/g protein after simulated digestion. Campos-Vega et al. (2015) demonstrated the same trend for spent coffee (*Coffea arabica* L.) with two different roasting processes regarding higher release of certain polyphenols and other bioactive compounds like chlorogenic acid, vanillin, and (+)-catechin. The chemical bonds between phenolic compounds and proteins can be broken down by digestive enzymes, leading to the release from tissues of plant-based foods during simulated digestion (Mosele et al. 2016; Ti et al. 2015).

In another aspect, several authors reported that the changeover from gastric stage to intestinal stage causes a reduction in all the analyzed classes of polyphenols especially anthocyanidins (Ma et al. 2020; Tagliazucchi et al. 2010). During the gastric stage, the levels of soluble phenolic acids and flavonoids were not altered. However, a good proportion of most polyphenols was lost during incubation with pancreatin-bile salts at neutral or slightly basic pH regarded as under intestinal condition. This can be considered that the majority of the phenolics were degraded or transformed into new compounds (Dutra et al. 2017; Goulas and Hadjisolomou 2019; Ma et al. 2020; Peixoto et al. 2016). The reduction in the amount of polyphenols like TPC, TFC, TAC and CHA after intestinal stage has been reported extensively, e.g., for rice (Sun et al. 2015; Thuengtung et al. 2018; Ti et al. 2015), grape (Tagliazucchi et al. 2010), apples (Bouayed, Hoffmann, and Bohn 2011), berry fruit family (Chiang, Kadouh, and Zhou 2013; Correa-Betanzo et al. 2014; Lucas-Gonzalez et al. 2016), persimmon juice (Martínez-Las Heras et al. 2017), persimmon peel flours (Lucas-González 2018a), carob flour (Ortega et al. 2011), commercial tea infusions (Chen et al. 2013), and soy milk (Rodríguez-Roque et al. 2013).

There are some reports highlighting that TPC increased in gastric stage but decreased after intestinal stage in gooseberries (*Ribes uva-crispa*:Tixia and Invicta) (Chiang, Kadouh, and Zhou 2013). After gastric stage, there was a significant decrease in the TPC of jasmine tea, Longjing tea, and oolong tea infusions (Chen et al. 2013). Tenore et al. (2015) demonstrated that native catechin in tea infusions were lost due to gastric digestion (~44%) and after intestinal digestion (~91.8%). Tagliazucchi et al. (2010) also reported that grape phenolics were stable at the acidic pH of the gastric environment, but some of those were degraded in the mildly alkaline intestinal condition. The drop in pure caffeic and gallic acids and pure resveratrol was found to be as great as 24.9%, 43.3%, and 69.5%, respectively during

incubation in a mildly alkaline condition (Tagliazucchi et al. 2010). A number of polyphenols decreased after the gastric stage because they were sensitive to alkaline intestinal conditions, possibly due to structural transformation of polyphenols (Chen et al. 2013). When conditions turn from acidic to alkaline, the pH change can alter the chemical structure, molecular weight, or chemical composition of phenolic compounds (Olennikov, Kashchenko, and Chirikova 2015). In a study by Chen et al. (2014), following the gastric stage of simulated digestion, there was a significant ($p < 0.05$) decrease in the TPC of such foods as apple (read delicious), banana (general), grape (black, green, USA), grapefruit, mango (Hinan, Shuxian), mangoteen, nectarine, peach, pear (Hubei), plum (green), followed by an increase in the intestinal stage. Zorić et al. (2016) reported that the stability of rosmarinic acid was not significantly affected by slightly alkaline medium (pH = 7.5), although it presented a significant reduction (≥50%) when it was in acidic medium (pH = 2.5). Annunziata et al. (2018) found that TPC in green tea (Chun Mee 41022) was reduced in the intestinal stage to 62.51 ± 2.25 from the non-digested value of 1,005.70 ± 28.78 (mg gallic acid equivalents/g extract). In contrast, the study of Chen et al. (2014) monitoring the TPC of 33 different fruit extracts after simulated digestion, it was observed that the TPC of some fruits showed an increment, while others showed the opposite trend (Chen et al. 2014). Moreover, Ah-Hen et al. (2018) reported that total phenolics in the fruits are less bioaccessible in the gastric phase but increased in the intestinal phase. In the intestinal and complete digestion stages, the three main phenolic acids decreased by at least 80%, whereas isoorientin was hardly detected in digested ground spent coffee (Campos-Vega et al. 2015). Similar results were also reported in the digestion study of some herbal teas (Ortega-Vidal et al. 2019), implying that phenolics were unstable toward high pH in the simulated intestine. These results confirmed that the change in phenolics during simulated digestion may mainly come from the effect of pH. An escalation of the relative release of ellagic acid (74%), quercetin-3-*o*-rutinoside (53%), quercetin (34%), and gallic acid (17%) was observed after intestinal digestion of Jabotica peel and seed powder (Inada et al. 2020). It was observed that exposure to acid and alkaline conditions, hydrolysis of the ester bonds of ellagitannins takes place and leads to rearrangement into ellagic acid (Alminger et al. 2014). The increase in the release of ellagic acid by depolymerization of insoluble ellagitannins happened in the intestinal pH, and was also found in pomegranate (Inada et al. 2020; Mosele et al. 2015).

In another study, Ghosh, Chakraborty, and Raychaudhuri (2015) reported that the TPC and TFC of palm wine were the highest at pH 6.5, and were decreased in descending order of pH as follows: 6.5 > 5.5 > 4.5 > 3.5. Significant decreases in the TPC of various plant-based foods after simulated digestion were reported by several authors. Correa et al. (2017) and Boaventura et al. (2015) investigated the stability of yerba mate (*Ilex paraguariensis* A. St. Hil.) beverages and reported reductions of TPC 20%–33% after simulated digestion. In another study, rosmarinic acid from rosemary (*Rosmarinus officinalis* L.) leaf water extract underwent the most significant transformation during simulated digestion, which amounted to 60% compared to the 26% degradation of TPC (Gonçalves et al. 2019). In addition, there were significant decreases ($p < 0.05$) in TPC for some Turkish fruit wines made from native grape varieties (Papazkarasi), as well as blueberry, black mulberry, and cherry, according to the study of Celep et al. (2015). All polyphenolic compounds from Maqui berry [*Aristotelia chilensis* (Molina) Stuntz] decrease in concentration after simulated digestion and principally TAC, which was severely affected and showed bioaccessibility of 78.19% and 14.20% for TPC and TFC, respectively (Lucas-Gonzalez et al. 2016). The study of Pavan, Sancho, and Pastore (2014) also described that the TPC in araticum and papaya extract was dominantly diminished after simulated digestion. Therefore, the decrease in TPC during digestion may be correlated with pH changes in the digestion medium, especially the alkaline pH of the intestines.

Correa-Betanzo et al. (2014) reported that the absorbance peaks from anthocyanidins in blueberry extracts were disappeared because of the ring cleavage of most anthocyanidins when the pH of the medium shifted from acidic (pH 2) to alkaline (pH 8). Anthocyanidins are structurally transformed, especially under the elevated pH conditions of the digestion model, would render to form monomeric derivatives and thus imperceptible by spectrophotometry and HPLC-based methods. Stanisavljević et al. (2015) observed partial degradation of proanthocyanidin oligomers into monomeric units like cyanidins in Chokeberry (*A. melanocarpa*) Nero cultivar juice after gastric and pancreatic digestion. In a study of six legume varieties by Giusti et al. (2019), delphinidin 3,5-diglucoside, cyanidin 3-glucoside, and cyanidin 3,5-diglucoside were absent in the intestinal phase, probably due to their instability at intestinal pH. Carbonell-Capella et al. (2015) showed that carotenoids and anthocyanins diminished significantly during gastric digestion for the *Stevia rebaudiana* addition functional beverages, while the TPC showed a slight loss after the gastric digestion. Because of the low pH in gastric phase, a significant loss of carotenoids and anthocyanins occur since oxidized species may be reduced back to the native compounds (Carbonell-Capella et al. 2015).

Furthermore, most researchers reported insignificant changes in the phenolic profiles in the oral and gastric stage, but considerable disappearance of some main phenolics was observed in the intestinal stage and after the complete digestion stage (Dutra et al. 2017; Goulas and Hadjisolomou 2019; Ma et al. 2020; Peixoto et al. 2016). Several previous studies also described that simulated digestion caused a reduction of TPC, mainly catechins, in white and green tea, and brought out new compounds, which were flavonoid aglycones such as quercetin, kaempferol and myricetin, and ellagic acid from tannin degradation (Correa et al. 2017; Okello, Leylabi, and McDougall 2012). Sun et al. (2015) reported regarding four main peaks in undigested pigmented rice samples, which were tentatively identified as cyanidin-3,5-diglucoside, cyanidin-3-glucoside, cyanidin-3-rutinoside,

and peonidin-3-glucoside, respectively. After simulated digestion, the chromatograms indicated similar trend that of an undigested sample; however, intestinal digested samples showed significantly reduction of the peak height of anthocyanidins (all four peaks) which infers that anthocyanidins were unstable and extensively degraded at intestinal digestion phase. Other major anthocyanidins were either lost in those fractions or converted into other compounds (Sun et al. 2015). The intestinal absorption also influenced the esterification of catechins with gallic acid and caffeic acid with quinic acid (Coe, Fraser, and Ryan 2013; Ferruzzi 2010; Ortega-Vidal et al. 2019). Several studies have shown that the degradation of quercetin and kaempferol derivatives during intestinal digestion is different depending on whether they are incubated as pure compounds or as compounds in the form of an extract (Zorić et al. 2016). For example, about 33% of the chlorogenic acid content is absorbed in the small intestine, while around 67% reaches the colon and is transformed by the colonic microbiota (Correa-Betanzo et al. 2014; Stalmach et al. 2010).

Recent studies of antioxidant activities on digestion

It can be observed that antioxidant activity was either stable, increased, or decreased in the gastric or intestinal digestion phase, depending on the bioactive compounds. The antioxidant activities of certain types of plant-based foods decrease in the gastric and increase again in the intestinal digestion stage or vice versa. However, some of those decreases in activity occur from the beginning of simulated digestion. The reasons for those changes are discussed above. An increase in bioactive compounds is expected to improve their bioavailability at target sites, which will further improve the beneficial effects such as the antioxidant properties associated with them.

Some studies indicated that the antioxidant capacities of several plant-based foods were significantly higher after simulated digestion: as the simulated digestion progressed, the antioxidant activity increased. Chen et al. (2014) reported that only four fruits (two types of plum, red bayberry, and mango) out of 33 tested fruits had an improvement of antioxidant capacity after simulated digestion. A study of corn-cooked common bean chips showed that the antioxidant activity of both DPPH and ABTS increased significantly after simulated digestion ($p < 0.05$) (Luzardo-Ocampo et al., 2017). An increase in bioaccessibility as well as ABTS, DPPH, and ORAC values when the *Stevia rebaudiana* concentration increased was observed in newly developed functional beverages (Carbonell-Capella et al. 2015). Rodríguez-Roque et al. (2013) reported an increase of 30% at gastric stage of DPPH inhibition attributed to phenolic compound release from the food matrix related to the acidic condition of the stomach for soymilk. Campos-Vega et al. (2015) also reported the highest values of antioxidant activities after simulated digestion for spent coffee by two different roasting processes (medium and dark-roasting). The increment in DPPH, ABTS for the effect of simulated digestion on fermented soybean digestion was reported by Ketnawa and Ogawa (2019). After simulated digestion, ORAC had increased by 185.7%, in brown rice, and 293.4% in polished rice, compared with cooked samples before digestion (Ti et al. 2015). Chiang, Kadouh, and Zhou (2013) also reported that the simulated digestion improved the DPPH and ORAC of gooseberries.

In contrast, simulated digestion can cause a reduction in the antioxidant activities of certain types of plants or plant-based beverages. For example, rosemary (*Rosmarinus officinalis* L.) leaf water extract showed that, overall, simulated digestion decreased the antioxidant activity estimated by DPPH, ABTS, ORAC, causing reductions of 34.7%, 22.1%, and 41.7%, respectively, but an increase of 31.3% in the FRAP assay (Gonçalves et al. 2019). Correa et al. (2017) assessed the antioxidant activity of yerba mate beverages during simulated digestion, found that simulated digestion a decrease in the antioxidant capabilities of their samples, except for the ABTS assay. In the study according to Lucas-Gonzalez et al. (2016), simulated digestion of maqui berry (*Aristotelia chilensis* (Molina) Stuntz) decreased the reducing power (74.1%) as well as the scavenging properties of DPPH (89.9%) and ABTS (84.2%) with respect to a non-digested sample. However, the chelating activity was increased (126.8%). A more pronounced decrease in antioxidant activity in leaves (35%–67%) than in berries (24%–54%) after simulated digestion for the Madeiran elderberry (*Sambucus lanceolata*) was demonstrated by Pinto et al. (2017). Ketnawa, Suwannachot, and Ogawa (2020) reported that *in vitro* antioxidant activity in crisphead lettuce digesta increased in the gastric and intestinal phase during simulated digestion for 1 h and subsequently decreased, except for DPPH. ABTS exhibited the highest residual activity in crisphead lettuce during digestion, accounting for 61%–95%, followed by FRAP (70%–86%), DPPH (24%–52%), and MIC (32%–73%), respectively. The low antioxidant activity of the digested samples agrees with the degradation of phenolics that was also observed during simulated digestion of *Jasonia glutinosa* herbal tea infusions (Ortega-Vidal et al. 2019) and green tea (Donlao and Ogawa 2018). In another study, a significant decrease in antioxidant activity was found for bamboo soup after intestinal stage as comparison with the control, and DPPH and FRAP were decreased by 67.29% and 62.05%, respectively. After complete digestion, the DPPH and FRAP of the soup decreased by 89.66% and 74.26%, respectively (Ma et al. 2020). The sharp loss of antioxidant activity after intestinal stage also occurred in some Brazilian native fruits implying that the majority of antioxidants may be degraded in this stage (Vinholes et al. 2018). However, there are several reports that describe the MIC shows a significant increment after simulated digestion (Cai et al. 2020; Reginio et al. 2020b). In a study according to Cai et al. (2020), citrus (*Citrus unshiu*) peel tissue showed the values obtained in the DPPH and FRAP assays were decreased during simulated digestion, but the MIC assay showed an increasing trend. According to Ketnawa, Suwannachot, and Ogawa (2020), the antioxidant capacity of the lettuce digested fractions was lower than those of fresh extract, but higher than those of the digested fraction from

simulated digestion without adding digestive enzymes. These results showed that digestive enzymes support the digestion and can cause the release of polyphenols from associated compounds as mentioned above. The higher MIC activity could be related to fully disclosure of the high-affinity metal-binding groups (imidazole and carboxylic groups) which formed by intestinal digestion, and the enforcement of electrostatic and ionic interactions with metal ion (Luzardo-Ocampo et al., 2017). It can be shown that the relationship between pH and the flavonoid moieties responsible for metal chelation, for example, the *o*-dihydroxyl group in quercetin takes part in Fe^{2+}, Cu^{2+} and Al^{3+} chelation in alkaline solutions by inducing of metal ion binding to the catechol group in 1:1 ligand/metal ratio (Kasprzak, Erxleben, and Ochocki 2015).

Advantages, limitations of *in vitro* gastrointestinal models and challenge

In the recent years, *in vitro* food digestion systems have been increasingly popular and prevalently used for food nutritional or pharmaceutical studies. Theoretically, *in vivo* food digestion studies should be performed, however, this is limited by technical, ethical and financial prospects. Thus, *in vitro* digestion models have been preferably adopted to simulate food digestive behaviors within the GI tract. Generally, *in vitro* or static food digestion models are rapid and simple methods, since they only need scientific equipment that are commonly available in the laboratory leading to relatively affordable and cost-effective and no ethical restrictions compared to *in vivo* tests on animals or humans (Alegría, Garcia-Llatas, and Cilla 2015; Li et al. 2020; Mulet-Cabero et al. 2020). Their advantages of being better reproducibility, less labor and maintenance cost, and no ethical restrictions compared to *in vivo* tests on animals or humans have driven more attention and made them be adequately validated and standardized, whereas the reference material can be used if needed. Additionally, sample aliquots can be taken at various digestion times for the resulting digested micronutrient test thus can evaluate relative bioaccessibility comparing the solubility of a component in different foods (Alegría, Garcia-Llatas, and Cilla 2015). Furthermore, *in vitro* models allow a reduction or modification of the sample size, texture and structure. Hence, all above advantages allow *in vitro* models better control of the experimental variables than animal or human studies (Alegría, Garcia-Llatas, and Cilla 2015; Li et al. 2020; Mulet-Cabero et al. 2020).

The worldwide applications and significant scientific progress have been done on improving the *in vitro* digestion systems for assessing the digestibility of various food components, however, they oversimplify the digestive physiological, anatomical and geometrical factors (Li et al. 2020). *In vitro* models are failed to mimic the dynamic aspects of the digestive process especially the mechanical forces, fluid dynamics and motility biochemical conditions. Furthermore, solubilized digest is recognized that not all soluble or dialyzable compounds are absorbable (Alegría, Garcia-Llatas, and Cilla 2015; Li et al. 2020) since specific hydrolytic processes occurring at the brush border are not simulated (Wojtunik-Kulesza et al. 2020). Moreover, static *in vitro* digestion methods have more limitations which cannot mimic the complex dynamics of the digestion process continuously from oral to colon digestion or the physiological interactions with the host. For instance, for the gastric phase, the pH is kept constant, and there is a lack of the real time gradual addition of gastric fluid and an absence of gradual gastric emptying like in the human. In addition, the enzyme activity in each digestive phase is kept constant, regardless of the type of food and whether the food contains high or low amounts of proteins, lipids, and carbohydrates. The intestinal phase is treated as one phase rather than as sequential duodenal, jejunal and ileal phases, which exhibit different dilutions, mineral content, pH, enzyme activities and microbial content (Wojtunik-Kulesza et al. 2020). It is of importance that the upper GI anatomy and morphology along with the related biochemical environments and peristaltic movements occurring *in vivo* should be considered in the development of more advanced and biologically relevant *in vitro* digestion systems. Human digestive physiology (i.e. transit time, digestion and gastric emptying rate), gastrointestinal motility (i.e. peristaltic contraction frequency and force) and biochemical environment (such as pH, secretion rate of digestive juice and enzyme activity) are influenced by many biological factors including age, gender, posture, diseased states and etc. which *in vitro* models cannot simulated. The parameters that need to take them into consideration mainly include pH and duration of each digestion step, amount and type of digestive enzymes used, stirring/agitation speed, amount of food sample and etc. As a consequence, these limitations limit the possibility to compare results across research-groups and to deduce general findings (Li et al. 2020).

There is still significant amount of work needed to be performed in the future because none of the current *in vitro* digestion models reported in literature has been fully validated against *in vivo* data and recognized with widespread applications in scientific community. This is mainly due to the inherently complex anatomy, motility biochemical conditions and physiological functions of human GI tract. Especially, hormone and nervous system, mucosal cell activity, complexity of peristaltic movements, and involvement of the local immune system are extremely difficult and even impossible to generate *in vitro* (Li et al. 2020). These physiological factors are undoubtedly of significance in food digestion and may be investigated using Caco-2 cellular models in the future. Colonic fermentation, an important step in the metabolic action of several phytochemicals, would further enhance the physiological circumstances (Wojtunik-Kulesza et al. 2020).

However, even the *in vivo* models, specifically clinical trials, which is considered as the gold standard for observing certain perspectives of food digestion and nutrition studies (Mackie, Mulet-Cabero, and Torcello-Gómez 2020), also have limitations such as poor repeatability due to individual differences (Li et al. 2020). It is recommended that careful

evaluations of the study purposes are required for selection of the most appropriate digestion system owing to advantages and limitations. Given the limitations of both *in vitro* and *in vivo* experiments, a logistic way is that correlations should be established and compared based on data from *in vivo*/human cohort studies (Dupont et al. 2019) before considering the publication of such protocols. Recently, various *in vitro* digestion models has been extensively developed and designed and continuously modified to resemble the physiological reality happening in the gastrointestinal tract, predicting the possible outcomes or trends of *in vivo* digestion (Bohn et al. 2018; Li et al. 2020). If combined with the appropriate functional assays, there is a good hope to have the potential to provide reasonable and reliable understanding into physico- and biochemical changes when the food is digested.

Conclusion

Extrinsic factors of plants, for example, variety, cultivar, plant part, maturity, the growing-harvesting environment, cooking and processing method, food matrices as well as the digestion process (e.g. digestive enzymes, pH conditions and digestion environment) can influence the bioaccessibility and bioavailability of existing bioactive compounds. Additionally, intrinsic factors e.g. native phenolic classes, structures and molecular size, their metabolic pathway, and their metabolite forms responding to digestion condition also empower bioaccessibility and bioavailability. Thus, the use of plant-based food for direct consumption or in production as functional food or components should take into account the bioaccessibility and bioavailability of the contained bioactive compounds. From the reviewed studies, the effect of simulated digestion on changes of bioactivity, bioaccessibility and bioavailability of bioactive compounds also benefit further studies which include protection of those substances, i.e., microencapsulation techniques to ensure the delivery of these bioactive compounds to target site, the design and production of functional ingredients/foods as well as an effective dose. Additionally, there is evidence that after simulated digestion, colon normal flora can generate several derivatives displaying different bioactivities from undigested phenolic compounds.

Suggestions for future studies

It is necessary to further confirm the toxicity of such natural bioactive compounds. In future studies, most trends in research should focus on structurally transformed bioactive compounds as well as their relationships with bioactivity properties and colonic fermentation are necessary. Finally, the requirement of further *in vivo* studies (e.g. dietary interventions and effective dose) need to be observed for the purpose of unraveling and confirming the bioactivities at target sites.

Disclosure statement

No potential conflict of interest was reported by the authors.

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ThomasUnited States clockmaker who introduced mass production (1785-1859)More (Definitions, Synonyms, Translation)