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Gastrointestinal interactions, absorption, splanchnic metabolism and pharmacokinetics of orally ingested phenolic compounds

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The positive health effects of phenolic compounds (PCs) have been extensively reported in the literature. An understanding of their bioaccessibility and bioavailability is essential for the elucidation of their health benefits. Before reaching circulation and exerting bioactions in target tissues, numerous interactions take place before and during digestion with either the plant or host's macromolecules that directly impact the organism and modulate their own bioaccessibility and bioavailability. The present work is focused on the gastrointestinal (GI) interactions that are relevant to the absorption and metabolism of PCs and how these interactions impact their pharmacokinetic profiles. Non-digestible cell wall components (fiber) interact intimately with PCs and delay their absorption in the small intestine, instead carrying them to the large intestine. PCs not bound to fiber interact with digestible nutrients in the bolus where they interfere with the digestion and absorption of proteins, carbohydrates, lipids, cholesterol, bile salts and micronutrients through the inhibition of digestive enzymes and enterocyte transporters and the disruption of micelle formation. PCs internalized by enterocytes may reach circulation (through transcellular or paracellular transport), be effluxed back into the lumen (P-glycoprotein, P-gp) or be metabolized by phase I and phase II enzymes. Some PCs can inhibit P-gp or phase I/II enzymes, which can potentially lead to drug–nutrient interactions. The absorption and pharmacokinetic parameters are modified by all of the interactions within the digestive tract and by the presence of other PCs. Undesirable interactions have promoted the development of nanotechnological approaches to promote the bioaccessibility, bioavailability, and bioefficacy of PCs.

Introduction

Phenolic compounds (PCs) are a diverse group of plant-derived secondary metabolites. Thousands of unique PCs have been identified and classified into different groups including phenolic acids, flavonoids, stilbenes and lignans, although many subcategories exist. The complexity of their chemical structure ranges from simple phenolic acids with low molecular weights to condensed tannins with complex molecular structures and high molecular weights.[1] The diversity is increased by the presence of at least one sugar moiety covalently attached to the backbone of the PC. Data produced from decades of scientific research has shown that the consumption of PC-rich diets is associated with a reduced risk of a variety of non-communicable diseases, such as type 2 diabetes, cardiovascular diseases, certain cancers, *etc.*[2–5] However, prior to reaching circulation, PCs interact with a great number of micro- and macromolecules in the gastrointestinal (GI) lumen, enterocytes, and liver, *e.g.*, nutrients in co-consumed foods, digestive enzymes and cellular transporters. All of these interactions reciprocally affect the functionalities of the involved molecules and alter the pharmacokinetic parameters of PCs. The present work will

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discuss PC interactions within the GI tract, the effects of PCs on the molecules they interact with, and how these interactions alter PC absorption. We will also briefly discuss the novel nanotechnological methods currently being used to enhance PC bioefficacy.

1. Interactions of polyphenolic compounds in the gastrointestinal lumen

PCs are ubiquitously present in plant foods, including fruits, vegetables, whole grains, tree nuts, and spices. Dietary PCs are poorly absorbed mainly due to an array of actions within the GI tract that mediate their transformation and enteric efflux for elimination through stool. Furthermore, interactions with molecules of co-consumed foods interfere with their bioaccessibility for absorption. While the majority of ingested PCs do not reach target tissues at a concentration that allows them to exert bioactions, they can exert health-promoting effects within the GI tract through their interactions with co-consumed nutrients, digestive enzymes and transporters.

1.1. Interactions of phenolic compounds with other nutrients and the consequent health effects

1.1.1 Interactions with dietary fiber. PCs in plant foods, including fruits, vegetables, cereals, nuts, and legumes, are predominately present along with indigestible cell wall components, namely fibers. Most consumed PCs remain bound to components of the food matrix, predominantly fiber, and are not readily accessible for digestion and absorption in the upper GI tract.[6] The strength and type of binding between fibers and PCs varies widely, primarily depending on the composition of fibers. For example, anthocyanin extractability from grapes (*Vitis vinifera* L. cv. Tempranillo) differs depending on the composition of cell wall polysaccharides, *e.g.*, cellulose, lignin, *etc*., which suggests a varied degree of conjugation of PCs with fibers.[7] Some fibers, particularly pectin, can form secondary structures, *i.e.*, hydrophobic pockets, to encapsulate PCs.[8] Thus, PCs interact with fibers through a combination of hydrogen bonds formed between the hydroxyl groups of PCs and ether bonds of fibers and the hydrophobic interactions that occur within pockets.[9] However, due to the varied nature of PCs and fibers, their interactions are not universal and vary according to the chemical structures of both. An example of this has been described by Wang *et al.* who showed that the *in vitro* adsorption of flavonoids to oat β-glucan differs depending on the type of flavonoid (flavonol > flavone > flavanone > isoflavone), while structural modifications (hydroxylation, glycosylation, methylation, methoxylation, esterification or galloylation) can widely increase or decrease adsorption.[10] Furthermore, PCs can bind to fibers *via* non-covalent bonds when they are from different food sources. For example, cellulose can rapidly (<1 min) bind with catechin, ferulic acid, chlorogenic acid, gallic acid, and cyanidin-3-glycoside in *in vitro* studies.[11] Because these interactions are largely inevitable in plant foods consumed by individuals, approaches such as industrial food processing and cooking have been identified to make PCs more accessible for absorption in the upper GI tract by weakening these interactions or binding. *In vitro* cellulase treatment of oat (*Avena nuda* L.) is able to liberate PCs, significantly enhancing the PC content and antioxidant capacity (as determined by ABTS, DPPH, FRAP and inhibition of protein oxidation).[12] In a C57BL6/J mouse model with diet-induced obesity, pretreatment of wheat aleurone with xylanase and feruloyl esterase significantly increased the bioavailability of ferulic acid, which is normally tightly bound to the insoluble arabinoxylan fiber matrix.[13] Finally, in a study of healthy men, ferulic acid was found to be more bioavailable in bread made with flour that was pretreated with yeast, xylanase, cellulase, β-glucanase and feruloyl esterase.[14]

The majority of PCs contained in non-processed plant foods do not reach the circulation because of the previously mentioned interactions with the fibers that transport them to the large intestine. However, the reduced bioavailability of PCs caused by fibers is compensated for by the health benefits of the breakdown products derived from bacterial metabolism in the lower GI tract. For example, Saura-Calixto proposed that antioxidant compounds that are bound to dietary fibers could confer health benefits from their metabolites produced by bacterial metabolism.[15] Furthermore, some PCs have been found to possess probiotic characteristics by promoting the growth of

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The authors study the health-promoting effects of bioactive compounds from tropical fruits; dietary fiber and polyphenols found in mango pulp are of particular interest. They are currently analyzing the mechanism of action of an improvement in the serum lipid profile, modulation of hepatic and peripheral gene expression and lipoprotein metabolism in rats that is exerted by mango bioactives administered in their diets. The bioavailability, bioaccessibility, metabolism and tissue distribution of phenolics is also an active area of research. Their work is done in collaboration at the Autonomous University of Ciudad Juarez (UACJ), the Research Center for Food and Development (CIAD) and the University of Sonora (UNISON) in northwestern Mexico.

beneficial bacteria and inhibiting pathogenic bacteria.[16] The beneficial effects of PCs on microbiota are beyond the scope of this review, but they have recently been described by Duda-Chodak *et al.*[17]

1.1.2 Interactions with starch. The study of PC–starch interactions has revealed that starch can form complexes with different PCs.[18,19] The mechanism through which PCs interact with starch has been analyzed by X-ray diffraction and appears to depend on the chemical structure of the PC. In the case of catechins in tea, hydrogen bonding is the predominant force, while hydrophobic interactions seem unlikely.[20] Interestingly, tannins bind to starch through a combination of hydrogen bonds and hydrophobic interactions.[21]

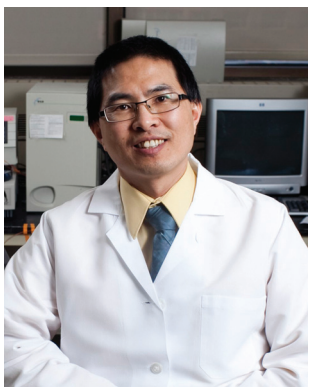
PC–starch complexes have been used to protect and transport PCs from various sources. For example, *in vitro* results suggest that genistein–starch complexes serve to protect genistein from the harsh gastric environment and deliver it to the small intestine where pancreatic amylase hydrolyzes starch to slowly release genistein.[18] Similarly, starch protects PCs extracted from yerba mate (*Ilex paraguariensis*) and preserves their antioxidant capacities.[22]

Notable consequences of the PC–starch interaction include a decrease in both rapidly digestible starch and slowly digestible starch and, as a consequent, an increase in resistant starch. Rapidly and slowly digestible starches are hydrolyzed by digestive enzymes, while resistant starch remains intact and reaches the large intestine. Accordingly, resistant starch that is produced by its interaction with PCs is functionally similar to dietary fiber and can carry PCs to the large intestine as previously described.[23] *In vitro* studies have shown that starches supplemented with blue corn anthocyanins,[24] sorghum tannins,[25] green tea PCs,[26] berry PCs,[27] and other sources are able to impede hydrolysis. In healthy men and women (n = 3 and 6, respectively), an inverse correlation was observed between PC content and the glycemic index of pigmented potatoes, thereby suggesting that the formation of complexes between PCs and starch significantly decreases starch digestibility.[28] The many health benefits of resistant starches include an increase in satiety, modulation of carbohydrate and lipid metabolism, and several others.[29] Bello-Pérez and Paredes-López[30] described in detail how resistant starches have various health benefits to consumers and can influence the digestibility of other starches.

1.1.3 Interactions with fat. Dietary fat and micellization have been identified as key determinants of PC bioavailability and bioaccessibility. This notion has been particularly well documented in several models of quercetin absorption. In rats, quercetin bioavailability increases when it is administered alongside lipids and emulsifiers, and this increase is partially attributed to better quercetin solubility.[31] In pigs, an increase in dietary fat results in a concomitant increase in the bioavailability and half-life of quercetin.[32] In overweight adults, dietary fat increases quercetin absorption.[33] However, this effect may be extended to other flavonoids. The results of *in vitro* studies show that some, but not all, anthocyanins are affected by dietary fat.[34] Thus, the impact of dietary fat on PC absorption is probably dependent on the chemical structure of the PC. A common explanation for the dietary fat-mediated increased in PC bioavailability is the increase in micellization, which may exert a protective effect on PCs that is similar to fiber and starch.[35]

An increase in bioavailability can consequently increase the bioefficacy of PCs in target tissues other than the GI tract. This has been demonstrated in a rat model in which dietary fat increased the bioavailability of peanut skin PCs and in turn their plasma VLDL- and triacylglycerol-lowering abilities were potentiated.[36]

1.1.4 Interactions with cholesterol and bile. PC–cholesterol interactions may decrease cholesterol absorption. The interactions can occur within micelles where cholesterol molecules direct PCs toward the micelle membrane and PCs decrease cholesterol accumulation inside the micelles and its further enteric uptake.[37] For example, *in vitro* data shows that theaflavins decrease cholesterol incorporation into mixed micelles,[38]



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and black tea catechins,[39] apple PCs,[40] luteolin and quercetin[41] displace cholesterol from the micelle. In addition to diminishing cholesterol incorporation into micelles, PCs hinder cholesterol absorption by decreasing its solubility. For example, apple PCs can form insoluble precipitates with cholesterol oxidation products and consequently impede their uptake.[40] Tea catechins form hydrogen bonds with bile salts, which are then less available to facilitate cholesterol solubility in the intestinal milieu.[42] Dimeric and trimeric catechins from peanut skin can dose-dependently degrade intestinal micelles independently of bile.[43] Rat studies have also shown that black tea PCs decrease cholesterol micellar solubility, resulting in decreased lymphatic cholesterol recovery.[39] PCs can also hinder the enterohepatic circulation of steroids and favor fecal excretion. Catechins display an *in vitro* bile-binding capacity, with esterifiable catechins being more effective than unesterified ones.[44] These data support the lowering effects of PCs from the pecan nut (*Carya illinoinensis*) on total- and LDL cholesterol levels in rats fed high-fat diets.[45] Thus, PCs from diverse sources (red wine, green tea, grape seed and bilberry) have been favorably compared to hypocholesterolemic drugs.[46] Although a substantial amount of literature shows that PCs can decrease cholesterol absorption, studies examining the effects of cholesterol on PC absorption remains lacking.

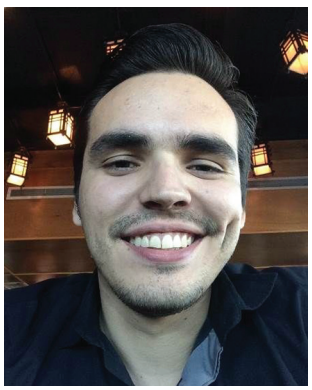
1.1.5 Interactions with dietary protein. Since proteins can form hydrogen bonds and hydrophobic interactions with PCs, they are remarkably good at binding to PCs of varied molecular structures and can reach colloidal-size aggregates.[47] One of the most commonly known effects of PC–protein interactions is protein precipitation by tannins that results in an astringent sensation.[48,49] Astringency due to PC–protein interactions is mediated by the combination of hydrogen bonding and hydrophobic interactions, but it is disrupted when certain carbohydrates (xanthan gum > pectin > gum arabic) strongly bind the PCs first.[50] PC–protein interactions with milk proteins have been thoroughly studied. For example, resveratrol, genistein and curcumin interact with α and β caseins through hydrophobic interactions and hydrogen bonds.[51] Furthermore, green and black tea catechins with low molecular weights have a strong affinity for casein micelles and alter the secondary structures of the proteins.[52]

PC–protein interactions are not random because the physicochemical characteristics of PCs and proteins can be used to predict their non-covalent interactions. Binding is stronger when PCs have a higher log *P* (a higher log *P* indicates hydrophobic nature), a double bond at position 2–3, and a keto group at position 4. Furthermore, the isoelectric point, number of acidic/basic amino acid residues, number of proline residues and secondary structures allow for similar predictions to be made for proteins.[53] For catechins, a gallate group increases protein affinity, whereas a pyrogallol group decreases it.[52] In the case of PCs binding to milk β-lactoglobulin, affinity increases with the number of hydroxyl groups in the PC.[54] However, this is not a general rule because the position of the hydroxyl group is more important than the number in most cases.

PC–protein interactions affect both compounds. *In vitro* digestion experiments have shown that green tea catechins, specifically epigallocatechin-3-gallate (EGCG), slow down milk protein digestion. The binding of EGCG to milk proteins does not decrease its antiproliferative activity, which suggests that the interaction does not impair EGCG bioactivity.[55] However, milk proteins can decrease the antioxidant capacity of green and black tea flavonoids,[56] particularly with α-casein which exerts a stronger impact on the antioxidant capacity of smaller PCs than larger ones.[57] These results suggest that when a protein binds to a PC molecule, the latter is unable to transfer electrons, hydrogen atoms or both. As previously mentioned, antioxidant capacity is one of the most recognized characteristics of PCs, but it also seems to be necessary to prevent the oxidation of essential nutrients before their uptake in the upper GI. Thus, a decrease in their antioxidant capacity can indirectly affect oxidation-labile nutrients. For example, green tea catechins incorporated into micelles prevent linoleic acid (ω-6 fatty acid) peroxidation[58] and regenerate α-tocopheroxyl radicals (oxidized α-tocopherol) into α-tocopherol,[59] when present within sodium dodecyl sulfate (SDS) micelles in both instances. The oxidation of ω-3 fatty acids (eicosapentaenoic and docosahexaenoic acid) is also decreased by PCs from grape seed extracts.[60] It is logical that PCs would be sacrificed to maintain tocopherols and ω-6/ω-3 fatty acids in a reduced state since both are indispensable and PCs are not.

PC–protein interactions confer protection to the PC. Therefore, dairy matrices such as yogurt and cheese have been used for these purposes.[61] For example, Cheddar,[62] Chihuahua,[63] Gouda,[64] Pecorino[65] and other[66,67] cheese types have been used as delivery vehicles for PCs. However, such incorporation also modifies the cheese-making ability of milk and alters sensory parameters.[66,68]

1.1.6 Interactions with metallic ions. PCs are able to chelate metallic ions in the GI, thereby decreasing metal-catalyzed free radical production. However, the decreased bioavailability of the PCs and the metals is a notable disadvantage. *In vitro* digestion experiments have shown that chlorogenic acid and



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rutin from potato and sweet potato form complexes with iron that result in the decreased bioavailability of both PCs.[69] Quercetin in synthetic wine forms complexes with iron that remain intact after the gastric phase of *in vitro* digestion. Presumably, the iron binds to at least two sites where the hydroxyl groups of quercetin are located.[70] Gallic acid, caffeic acid, catechin and rutin can chelate copper ions with higher affinities than iron.[71] Zinc chelation by sorghum PCs in healthy adults does not occur unless phytic acid is present,[72] while studies of Caco-2 cells show that grape seed extract hinders zinc uptake due to strong binding by procyanidins.[73] However, the ion chelation of PCs is strongly dependent on pH and varies between gastric and intestinal conditions.[74]

Although the micronutrient chelation properties of PCs can raise concerns of nutrient deficiencies, minimal effects on iron, copper and zinc status in the liver have been reported in piglets fed diets supplemented with PC-rich products (1% grape marc meal extract or spent hops).[75] A null effect on the status of serum zinc or copper in rats was reported when they were fed red wine, which is rich in PCs, for either a 3 or 28 d period.[76]

1.2 Effects on digestive enzymes. As previously discussed, PCs can strongly interact with proteins. Therefore, interactions with the main digestive enzymes are expected, resulting in delayed/decreased macronutrient digestion and absorption. However, it should be noted that not all PC–enzyme interactions will result in a marked inhibition of enzyme activities because PCs may not bind to the active site, or the molecular ratio of the PCs to enzyme may be too low to cause a significant reduction.[77]

1.2.1 Effects on amylase. In vitro[78–83] and *in vivo*[84–86] studies have shown that PCs can inhibit α-amylase, and this inhibition can delay the digestion of carbohydrates and/or decrease absorption. PC-rich extracts from finger millet inhibit the amylases developed during malting through mixed non-competitive inhibition, while individual PCs isolated from the extracts (gallic acid, vanillic acid, quercetin and *trans*-cinnamic acid) act through uncompetitive inhibition, thus showing that inhibition kinetics vary among different PCs.[87] Efforts to understand the underlying mechanisms through which PCs bind to and inhibit amylase have been reviewed elsewhere.[88] However, molecular characteristics such as hydroxylation, unsaturation, and ideal carbohydrate moiety positioning allow for optimal inhibition, whereas methylation, methoxylation, isomerism, conjugation and others hinder the amylase-inhibiting properties of PCs. In the case of catechins, the presence of a galloyl group rather than a non-galloylated group favors the inhibition of amylase.[89] A recent study has shown that only catechins with a galloyl moiety at position 3 exhibit significant α-amylase inhibition. Furthermore, the inhibition by some compounds (EGCG, theaflavin-3,3′-digallate and tannic acid) is competitive, while others (epicatechin gallate, theaflavin-3′-gallate and theaflavin) exhibit mixed-type inhibition.[90]

Because of the α-amylase-inhibiting properties of PCs, their antidiabetic potential has been compared to acarbose,[91,92] a commercially available medication that acts through α-amylase inhibition. In fact, flavonoids are considered to be glucose-lowering agents because they exert acarbose-like effects without negative side effects.[93] Most significantly, a synergistic effect has been demonstrated when administering acarbose alongside PCs from berries,[94] green tea,[78] black tea[95] and other[96] sources. The health benefits of PCs that inhibit α-amylase in the GI tract are related to a decrease in glucose absorption that in turn impacts insulin secretion, potentially improving glucose/insulin metabolism at the whole organism level.

1.2.2 Effects on lipase. Lipase hydrolyzes triacylglycerols in the GI prior to their uptake, and their inhibition results in delayed/decreased fatty acid absorption and reduced postprandial lipemia.[97,98] Several PC-rich sources have exhibited *in vitro* lipase-inhibiting properties, including black tea catechins,[99] oolong tea,[100] black chokeberries (*Aronia melanocarpa* L.),[101] kiwi fruit (*Actinidia chinensis* L.),[102] litchi flower (*Litchi chinensis* Sonn.)[103] and peanut shells.[104] Black tea catechins can also exert *in vivo* lipase inhibition in rats, which consequently decreases postprandial hypertriglyceridemia.[105]

Luteolin and chrysoeriol extracted from *Tacoma stans* (a medicinal plant used by some ethnic groups in Mexico to treat diabetes)[106] and acteoside from *Ligustrum purpurascens* (consumed in China as an infusion to aid in weight loss)[107] inhibit lipase *in vitro*, which may underlie the reported health effects of these and likely other medicinal plants.

The lipase-inhibition mechanism has been described as a competitive inhibition in the case of flavonoid and non-flavonoid PCs. For example, chlorogenic acid and caffeic acid exhibit a competitive inhibition against rice bran lipase activity *in vitro*, which occurs through a combination of hydrogen bonds and hydrophobic interactions.[108] Noble muscadine grape extracts, cyanidin and cyanidin-3,5-diglucoside competitively inhibit pancreatic lipase *in vitro*.[109] Mate tea also exhibits competitive inhibition against porcine and human pancreatic lipase.[110] Molecular characteristics such as the number and position of hydroxyl groups, the degree of polymerization and carbohydrate conjugation seem to be structural features that modulate the lipase inhibition activity mediated by PCs.[111] Furthermore, the presence of a galloyl moiety appears to strongly favor lipase inhibition.[105,112] PCs have been favorably compared to orlistat, a commercially available lipase inhibitor with numerous side effects.[111,113] However, the effectiveness of orlistat is significantly higher than most of the PCs evaluated, as is the case with PCs extracted from mango cv Ataulfo (tannic acid, penta-*O*-galloyl-β-D-glucose and mangiferin) that inhibit lipase activity to a lesser extent than orlistat (data not yet published).

1.2.3 Effects on proteases. PCs can bind to and inhibit pepsin, trypsin and chymotrypsin activity. The binding of EGCG to pepsin occurs through hydrophobic and electrostatic interactions, which result in non-competitive inhibition.[114] The inhibitory effect of EGCG on trypsin and α-chymotrypsin is attributed to alterations of their secondary structures that are triggered by high-affinity EGCG binding.[115] Catechins can also inhibit trypsin by binding to the active site, which alters the enzyme's 3D structure and activity.[116] Tannic acid exhibits modest trypsin inhibition through a combination of competitive and noncompetitive inhibition *via* hydrophobic and electro-

static interactions.[117] Other sources of PCs, such as acteoside, osmanthuside and ligupurpuroside A, B and C from the Kudingcha bitter tea (*Ligustrum purpurascens*), are also reported to be non-competitive inhibitors of pepsin, trypsin and α-chymotrypsin, but their mechanisms of action have not been described in detail.[118] Because of the inhibitory effects that PCs exert on digestive proteases and the previously mentioned binding to dietary proteins, protein digestion is delayed.[119]

1.3 Effects on intestinal nutrient transporters. Another mechanism through which PCs influence the digestive process is by interacting with nutrient transporters. Some PCs, such as tiliroside, inhibit glucose transport through both GLUT2 and SGLT1 in Caco-2 cells, having more of an effect on the latter.[120] Quercetin and isoquercetin inhibit GLUT2 expressed in *Xenopus laevis* oocytes through non-competitive kinetics, but they have no effect on GLUT5 or SGLT1.[121] Others have confirmed that there are no inhibitory effects of quercetin on either GLUT5 or SGLT1 in the same *X. laevis* oocyte model.[122] Green tea PCs inhibit SGLT1 in everted jejunal sacs from male Wistar rats through a competitive mechanism.[123] Quercetin-3-*O*-glucoside and quercetin-4′-*O*-glucoside inhibit SGLT1 in a brush-border-membrane vesicle model from pig jejunum, while quercetin-3-*O*-galactoside, quercetin-3-*O*-glucorhamnoside, quercetin aglycone, naringenin-7-*O*-glucoside, genistein-7-*O*-glucoside and cyanidin-3,5-*O*-diglucoside had no effect on SGLT1. These results highlight how the carbohydrate moiety and experimental models can produce contrasting results.[124]

PCs interact with Niemann-Pick C1-Like 1 (NPC1L1), the main intestinal cholesterol transporter, and directly prevent the uptake of dietary cholesterol and modulate its expression. Evidence obtained from a screening of several PCs indicates that liquiritigenin, sakuranetin, isosakuranetin, hesperetin, apigenin, luteolin, quercetin, daidzein, coumestrol, phloretin, and (−)-epicatechin gallate significantly inhibit cholesterol uptake in Caco-2 cells, while further experiments revealed that quercetin significantly decreases the mRNA expression of NPC1L1 in the same cell line.[41] Another study has shown that incubation of Caco-2 cells with curcumin significantly decreases NPC1L1 mRNA and protein expression,[125] an effect that is mediated by the modulation of transcription factor sterol regulatory element-binding protein 2 (SREBP2).[126] Other authors have observed similar results regarding NPC1L1 modulation using different foods such as black chokeberries (rich in anthocyanins)[127] and persimmon (*Diospyros kaki* L., rich in tannins).[128]

Taken together, the current literature points to PCs being important modulators of macronutrient digestion through direct binding, enzyme inhibition and transporter inhibition. However, no single molecule is capable of mediating all of these effects; therefore, ideally, dietary habits should include the consumption of PCs from various sources to accomplish the synergistic effect of the different PCs to maximize their potential health effects.

Fig. 1 shows a graphical depiction of the described luminal interactions between nutrients and enzymes.

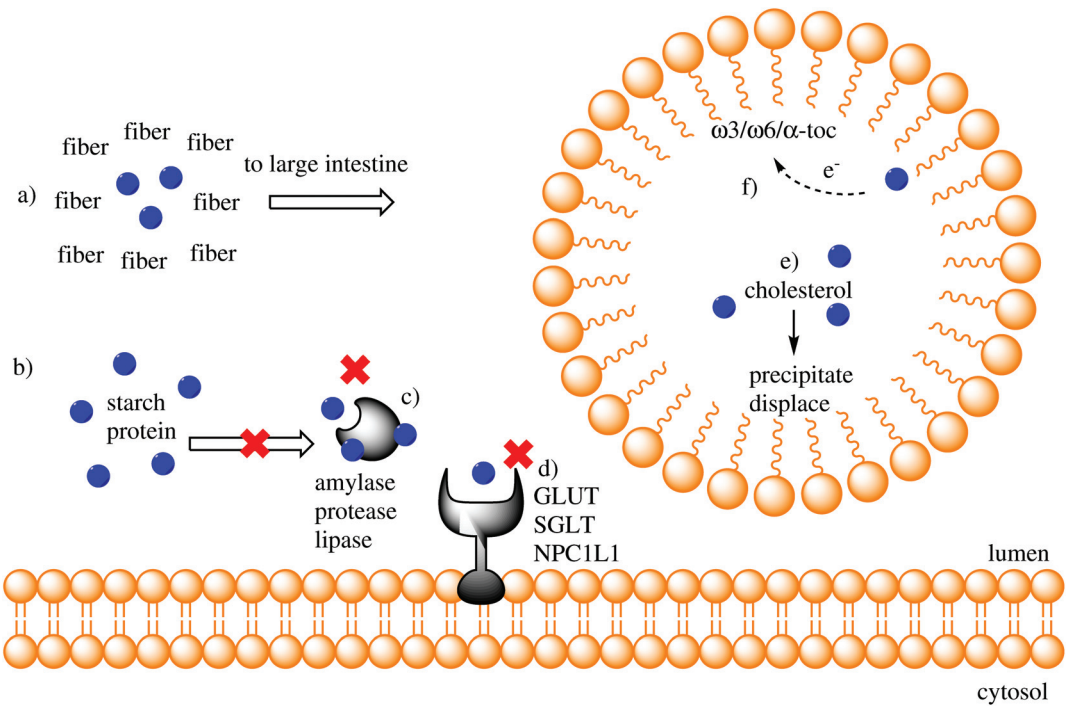

Fig. 1 Gastrointestinal interactions of phenolic compounds (PCs) with other nutrients, digestive enzymes and nutrient transporters. (a) PCs (blue spheres) bound to fiber material in the lumen of the small intestine are not bioaccessible and are carried with it to the large intestine where bacterial metabolism may take place; PCs may delay starch and dietary protein digestion by (b) directly binding to them, (c) inhibiting digestive enzymes or (d) inhibiting transporters; (e) when PCs bind to cholesterol, it will be displaced from the micelle or insoluble precipitates may form, which hinders cholesterol absorption; (f) PCs bound to the micelle membrane can act as antioxidants, aiding in reducing ω3/ω6 fatty acids or α-tocopherol.

2 Mechanisms of transport into the enterocyte

After the previously discussed interactions take place in the GI lumen, orally ingested PCs (and other xenobiotics) must pass through the gut epithelia before reaching the bloodstream and/or lymphatic system.[129] Bioaccessibility of PCs is critical for their enteric and systemic bioavailability,[129,130] which is determined by many factors including PC type, the amount in edible sources, the nature of its matrix and several host-related factors.[131] Once released, both hydrophilic (*e.g.*, phenolic acids or glycosylated PCs) and lipophilic (*e.g.*, procyanidin or prenylated PCs) PCs are transported by the various mechanisms that have been previously characterized for other xenobiotics and nutrients.[132] Transcellular mechanisms such as passive diffusion (PD), carrier-mediated active (AT) and facilitated (FT) transport and paracellular transport in tight junctions (TJ) are the most recognized,[133,134] and all of them make a particular contribution to PC transport and homeostasis, as presented in Fig. 2.

Transcellular transport is mediated by transmembrane pumps, channels, and carriers expressed in a polarized fashion, while paracellular transport is driven by solute gradients.[133] Transport out of epithelial cells is further facilitated by serosal-facing (basolateral) membrane transporters[135] that deliver both free and vesicle-contained PCs into the bloodstream and lymphatic system or efflux them back to the lumen. However, the novel transporters and mechanisms for the intestinal handling of PCs and the inhibitory action of PCs on well-known transporters have been elucidated in recent years,[132] which has helped to complete our understanding of the first-pass metabolism of PCs.[136] In the following paragraphs, we will attempt to summarize the main transporting mechanisms involved in the transepithelial uptake and efflux of PCs in and out of the enterocyte.[137,138]

2.1 Passive diffusion (PD). PCs with small molecular weights that are hydrophobic ($\log P > 2.0$) or neutral are mainly transported by PD.[139,140] As in the case with dietary fats and fat-soluble vitamins,[141] the luminal processing of hydrophobic PCs such as alkylated-PCs or procyanidin heterodimers involves bile salt-emulsification, micellar formation and apical membrane translocation.[142] Experimental data using Caco-2 cells (TC7 cell line) has shown that several PCs in virgin olive oil (*e.g.*, hydroxytyrosol, tyrosol, *p*-coumaric acid, apigenin and luteolin) are partitioned in oil/water mixtures and their further absorption (mainly by PD) is different.[143] However, PD also depends on many other factors including the interaction of the PCs with the mucous-layer and their size.[133] For example, Rastogi and Jana[144] evaluated the possible bi-directional transport of caffeic and gallic acids, chrysin, quercetin, resveratrol and rutin in Caco-2 cells and observed a greater permeability in the absorptive direction; therefore, they were more likely to be absorbed for further first-pass metabolism than transported back (efflux) to the lumen. Additionally, free ferulic acid permeates by PD ($\log P = 1.5$) that is not dependent on its apical concentration, but it does not permeate by transcellular (*i.e.*, TJ) transport.[145]

Highly complex PCs such as hydrolyzable (*e.g.*, gallotannins and ellagitannins) and condensed (*e.g.*, EGCG and other oligomeric proanthocyanidins) tannins must be hydrolyzed to smaller molecules (tri, di and monomers) to be absorbed through any transporting mechanisms. Because the human small bowel is not prepared to hydrolyze them, they pass through intact to the large bowel and are fermented by the resident microbiota.[146,147] Once hydrolyzed (Fig. 2) and before

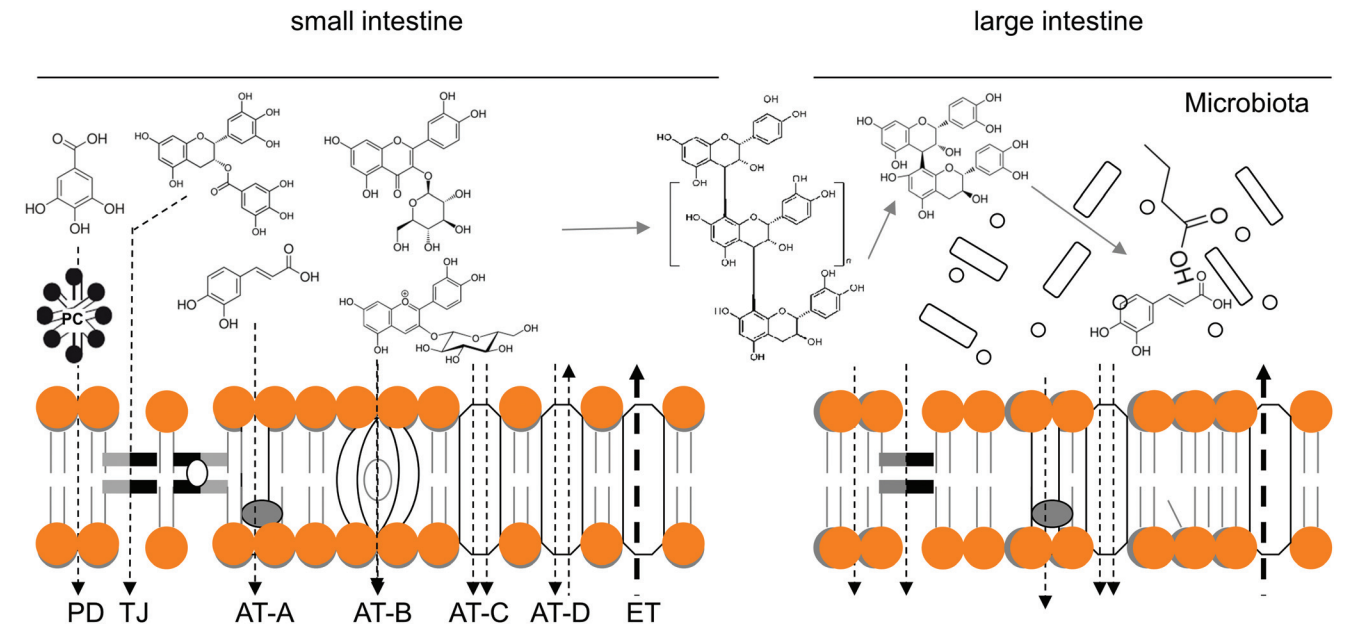

Fig. 2 Hypothetical transport mechanisms for phenolic compounds (PCs). Passive diffusion (PD), paracellular (TJ), single-solute (AT-A), translocase-type (AT-B) and co-solute symporter (AT-C) and antiporter (AT-D) active transporters, efflux transport (ET).

being metabolized by the gut microbiota, monomeric PCs are absorbed through PD by colonic cells.[148] Genistein and daidzein (isoflavones) are transformed by the colonic microbiota into dihydro metabolites that are transported by PD according to the pH-partition (proton-gradient) hypothesis and also by breast-cancer resistant protein (BCRP), a member of the ABC transporter proteins.[129,139]

2.2 Paracellular transport. Hydrophobic ($\log P > 2.0$) and neutral PCs and other nanoparticles can easily pass between the narrow gaps (*i.e.*, TJ) that separate the neighboring enterocytes[149] by certain proteins called claudins. These proteins are distributed along the apical-basal axis and confer to TJ a particular electrical resistance that varies by 100 000-fold between "tight" and "leaky" epithelia.[133] This is the reason why PCs with a small mass that are charged, such as chlorogenic, gallic and rosmarinic acids, can use this transport system, although their permeation rate is low (5 mM), and the non-absorbed molecules travel directly to the large bowel.[150,151] It seems likely that EGCG is also absorbed intact *via* TJ,[134] as its Caco-2 permeability (nmol min^{-1} mg^{-1} protein) is similar (0.22) to gallic acid (0.16). However, a low degree of discrimination for different-sized PCs suggests the presence of large aqueous spaces in TJ[133] that provide a more fluid media for their gradient transport.

TJ transport seems to compensate for the inadequate expression (region-dependent) of active transporters and epithelial damage. Stephens *et al.*[152] evaluated the *ex vivo* illeal transport of paclitaxel ($\log P = 3.96$), propranolol ($\log P = 3.0$) and digoxin ($\log P = 1.3$) in P-gp-deficient and wild-type mice. Their results suggest that differences in absorption between wild-type and knockout mice are at the level of transcellular permeability, and the ileum and distal colon are regions of relatively high transcellular permeability for xenobiotics that are compensated for by the enhanced expression of P-gp. Additionally, EGCG, myricetin, quercetin and genistein ($\log P$s ranging from 1.2 to 2.7) exhibit protective effects on intestinal TJ against oxidative stress, acetaldehyde, enteric bacteria and inflammatory cytokines;[153] therefore, their potential TJ transport is plausible.

2.3 Active (AT) and facilitated (FT) transport. Most pharmacokinetic studies aim to define the AT/FT of PCs to design efficient drug-delivery systems.[132] AT utilizes different energy-coupled mechanisms that create ion/solute gradients across membranes, while FT passes solutes across membranes (apical/basolateral) down their electrochemical gradient and does not use energy at all.[129] However, it is well recognized that the specificity of these particular substrates for individual transporters is not as specific as it is for enzymes.[129,141] In the case of PCs, most of them are either absorbed as glycosides or modified by the brush border and bacterial enzymes [*e.g.*, β-glycosidases (β-GS), lactase-phloridzin hydrolase (LPH)] before being absorbed as aglycones. From a structural stand point, AT/FT is divided into the following three categories: (A) glycosylated PCs, (B) cationic aglycones and (C) neutral or hydrophobic aglycones, as shown in Table 1.

The "classical model of sugar absorption" involves the high-affinity, sodium-dependent and phloridzin-sensitive sodium/glucose co-transporter 1 (SGLT1; depicted in Fig. 1 as AT-C) located on the apical side of the brush border membranes and also glucose transporters (GLUT, depicted in Fig. 1 as AT-B) 2 and 5, which can be translocated upon leptin signaling to either the apical or basolateral membrane.[135] AT is used by PC glycosides such as anthocyanins because their PD is less probable.[140,154] However, glucose transport by SGLT1 and GLUT-2 may be inhibited by flavonols and green tea catechins (Table 1) through competitive and non-competitive mechanisms; therefore, these PCs must be transported as glycosylated PCs[92] or otherwise supplemented with aglycones or unsweetened beverages rich in these PCs to exert antidiabetic effects.[92,135,155]

Organic cation (OC) translocases move positively and negatively charged molecules according to their electrochemical gradient, and most of them belong to the solute carrier (SLC) and amphiphilic solute facilitator (ASF) families. The influx (apical-basolateral) absorption of small anionic PCs in particular can be absorbed not only by PD but also by these transporters (Table 1) since the role that organic anion transporters (OAT) play in the intestinal absorption of xenobiotic substances is considered negligible.[129] Monocarboxylate (MCT) 1–4 transport OCs such as lactate and pyruvate by a proton-coupled transport mechanism. MCT1 (SLC16A1) and MCT4 (SLC16A3) are expressed in the small bowel (at low levels) and large bowel (at high levels)[156] and transport quercetin[137] and ferulic acid.[157] Under physiological conditions, ferulic (194 g mol^{-1}) and *p*-coumaric (164 g mol^{-1}) acids with a higher hydrophobicity ($\log P = 1.5$) are more readily absorbed by MCT1 in Caco-2 cells than gallic acid, which is mostly absorbed by PD (170 g mol^{-1}, $\log P = 0.7$ (ref. 150)). MATE1, which is highly expressed in the liver and intestine and located in the apical membranes, peroxisomes and endoplasmic reticulum, transports quercetin and enhances glucose uptake.[158] It is unknown whether MATE2, which is expressed at lower levels in the small bowel, performs the same duties.

Organic cation transporter 1 (OCT1) and 2 (OCT2) are localized to the basolateral membranes and transport small-mass, hydrophilic OCs and PCs. However, red and white wine and grapefruit juice, as well as naringin, naringenin, and bergamottin, interfere with the xenobiotic transport of OCs.[159,160] An acidic GI milieu may promote solute and taurocholate uptake by OATP2B1, but its substrate specificity is narrower than OATP1A2.[129] OCT1 is inhibited by fruit juice flavonoids such as phloretin and quercetin through non-competitive mechanisms.[161] It is noteworthy that ionic PCs may suffer a nucleophilic attack along the GI tract (*e.g.*, procyanidins); therefore, they must be protected from harsh GI conditions,[131] possibly through rapid AT by one or more of the above transporters. Lastly, micelle-driven PD is a well-known mechanism for lipophilic PCs, but the ongoing dilution of hydrophobic PCs (and other xenobiotics) rapidly reaches supersaturation of intestinal colloids, thereby promoting their absorption by many other mechanisms.[162] Transporters that have been previously identified and characterized for fatty acids [fatty acid translocase/cluster of differentiation 36 (FAT/CD-36)] and

Table 1 Intestinal transporters of PCs

Transporter	Expression	Direction	Area	Substrate specificity	PC	Ref.
Glycosylated-PCs						
GLUT2	High	AP-BA-SC	Basolateral	GPC	(I) quercetin, quercetin-3-*O*-glycoside, EGCG, fisetin, myricetin and gossypin	130 and 135
SGLT1	High	AP-BA	Apical	GPC	(I) catechin, EGCG	129, 130 and 226
Ionic aglycones						
MATE1/SLC47A1	Med	AP-BA	Apical	ION (cation)	(T) quercetin and metabolites	129, 130 and 158
MATE2	Low	AP-BA	Apical	ION (cation)	—	129 and 130
MCT1/SLC16A1	Low	AP-BA	Apical	AMP	(I) *p*-coumaric, ferulic, gallic, gentisic, 4-hydroxybenzoic, protocatechuic, sinapic, syringic and vanillic acids	129, 130, 150 and 156
MCT4/SLC16A3	—	AP-BA	Apical	AMP	—	129 and 130
OCT1	Med	AP-BA	Basolateral	ION (cation)	(I) red and white wine, grapefruit juice, naringin, naringenin, and bergamottin, phloretin and quercetin	129, 130, 159 and 160
OCT2	Med	AP-BA	Basolateral	ION (cation)	—	129 and 130
OCTN1	—	AP-BA	Apical	ION (cation)	(I) phloretin and quercetin	130 and 161
Efflux						
BCRP/ABCG2/MXR	Med	Efflux	Apical	BSE, ION (anion)	(I) quercetin, coumestrol and isoflavones	129, 130 and 139
MDR1/ABCB1/P-gp	Med	Efflux	Apical	BSE, ION, AMP, HPB, PCP	(T) flavonoids, (I) grapefruit juice	129 and 130
MRP1/ABCC1	Med-high	Efflux	Apical	ION (anion), PCP	(T) quercetin, naringenin, (I) grapefruit juice	129 and 130
MRP2/ABCC1	Med-high	Efflux	Apical	ION (anion), PCP	(T) quercetin, naringenin, (I) grapefruit juice	129 and 130

Abbreviations: amphipathic (AMP), broad specificity (BSE), phase II-conjugated PC (PCP), glycosylated PC (GPC), hydrophobic (HPB), inhibition (I), ionic PC (ION), systemic circulation (SC), transport (T).

cholesterol/fat-soluble vitamins [NPC1L1 and scavenger receptor class B member 1 (SRB1)] may be involved in the apical absorption of long-chain alkyl-PCs such as catechols or steroid-like PCs such as isoflavones[163] because it is well known that their dietary supplementation modifies the concentration of blood lipids in a structure-specific, competent way.[164] However, there are very few reports regarding this phenomenon. Nevertheless, as has been observed with other ionic transporters, significant competitive interactions for hydrophobic PCs that are similar to those between the fat-soluble vitamins A, D, E and K may occur.[141]

2.4 Efflux transport. Intracellular homeostasis and the deleterious accumulation of xenobiotic substances such as PCs are controlled by their influx (AT, FT) and efflux (AT). The most investigated efflux transporters in the intestine are P-glycoprotein (P-gp/MDRP1), multidrug resistance protein 1, 2 (MRP 1,2) and breast cancer resistance protein (BCRP), and these transporters are also involved in the efflux of the PC aglycone. P-gp transports hydrophobic, amphipathic and cationic molecules in the basal-to-apical and blood-to-lumen directions, and its secretion varies across different segments of the intestine.[129] It transports flavonoids back to the lumen,[165] but other fruit flavonoids such as those found in grapefruit juice[159] and monoglycerides[129] may affect P-gp pharmacokinetics. MDRP1 is highly expressed in the small and large intestine. It is localized to the basolateral membrane and transports substances from the enterocyte into the interstitial fluid rather than to the lumen. MDRP1 prefers anionic compounds, and its inhibition by PCs is poorly understood. MDRP2 is mainly located at the tip of jejunal enterocytes, and its substrate affinity overlaps with P-gp. It excretes flavonoids such as quercetin and naringenin back to the lumen[165] and is also inactivated by grapefruit flavonoids.

3 Splanchnic metabolism of phenolic compounds

Absorbed PCs (and other xenobiotics) are subjected to phase I and II metabolism and then either transported into circulation or excreted back into the intestinal lumen. This mechanism affects their bioactivity, their mRNA/protein expression and the activity of the enzymes that metabolized them, thereby regulating their own and other molecules' metabolism.[166,167]

3.1 Effects on phase I enzymes and pharmacokinetic parameters of other xenobiotics. Phase I enzymes are those of the cytochrome P450 (CYP450) superfamily that are expressed in the liver, small intestine, and other tissues,[168] and they increase the reactivity of their substrate through oxidation. CYP3A4 is one of the most abundant and relevant CYP450 members, and it is expressed in the small intestine where it accounts for approximately 80% of total CYP450. Other isoforms such as CYP2C9, CYP2C19, CYP2J2 and CYP2D6 are also expressed.[169] Because CYP450 metabolizes

ingested xenobiotics, a failure to maintain appropriate enzymatic activity can lead to potentially serious drug–drug or drug–nutrient interactions.[170,171]

Sixty PCs from different subcategories were analyzed for their potential CYP3A4 and CYP2C9 inhibitory activities *in vitro*. Anthocyanins, flavonoid glycosides and methylated catechins showed minimal inhibition, but several compounds (bergamottin, imperatorin, dicoumarol, proanthocyanidin A2, naringenin, phloretin, amentoflavone, chrysin, apigenin, luteolin, acacetin, galangin, kaempferol, quercetin, myricetin and isorhamnetin) significantly inhibited both enzymes.[172] Amentoflavone in particular had the lowest IC_{50} values for CYP3A4 (0.07 μM) and CYP2C9 (0.03 μM).[172] Others including quercetin, rutin, gallic acid and ellagic acid inhibited CYP3A4, and their inhibitory potential decreased according to the order listed. The following PCs are listed based on their decreasing inhibitory effects on CYP2D6: gallic acid, quercetin, ellagic acid and rutin. The inhibitory potential was assessed using *in vitro* assays in both instances.[173] Using human liver microsomes and a recombinant system, gallic acid has been shown to inhibit CYP3A4 activity (IC_{50} > 600 μM), mostly through its spontaneous oxidation products. Therefore, antioxidants that maintain a reduced state prevent gallic acid-mediated CYP3A4 inhibition.[174] Tea infusions prepared from the *Artemisia annua* (annual wormwood) plant contain rosmarinic acid and chlorogenic acid as its main PC content. Some but not all extracts prepared from *A. annua* inhibit CYP3A4 and CYP1A1 in Caco-2 cells, but neither rosmarinic acid nor chlorogenic acid produce the same inhibitory effects, which indicates that the PC content from *A. annua* does not inhibit these enzymes.[175]

Important pharmacokinetic effects have been documented due to the PC-induced inhibition of the intestinal (and/or hepatic) CYP450 system. One of the most recognized is the grapefruit effect in which bergamottin and other furanocoumarins present therein inhibit CYPs, which leads to altered therapeutic effects of drugs, such as prasugrel (platelet inhibitor),[176] statins (hypocholesterolemics),[177] fexofenadine (antihistaminic),[178] pirfenidone (antifibrotic)[179] and others. An IC_{50} of 1.97 μM for quercetin and 7.8 μM for myricetin on rat CYP3A4 has been reported with a consequent increase in area under the curve (AUC) and peak plasma concentration (C_{max}) of the antineoplastic doxorubicin.[180,181] Quercetin increases the C_{max}, AUC_{0-24} and half-life ($t_{1/2}$) of valsartan (antihypertensive) when both compounds are concomitantly administered to rats. The authors of this study suggest that the inhibition of P-gp and possibly CYP3A4 are responsible for the pharmacokinetic effects exerted on valsartan.[182] Mice fed 3% green tea PCs for four weeks show no difference in mRNA/protein expression or enzyme activity of CYP3A11, CYP3A13, CY3A16 and CYP3A25 in the small intestine, but a significant decrease was observed in liver. This decrease was reflected by the higher plasma concentration of triazolam (a CYP3A substrate) compared with the control.[183] Baicalein is a flavonoid present in *Scutellariae radix* that can inhibit CYP3A4 and P-gp in rats resulting in an increased C_{max} and AUC of orally administered nimodipine (a Ca^{2+} channel blocker). The same effect was not observed when the drug was administered intravenously.[184] Tea PCs and daidzein (but not caffeine) increase the AUC and $t_{1/2}$ of lansoprazole (a proton pump inhibitor) when administered to rats, a finding that the authors propose is due to CYP3A inhibition.[185]

The described alterations in drug metabolism can sometimes be considered beneficial, as the parallel consumption of CYP-inhibiting PCs will allow the patient to take a smaller dose, and in the case of doxorubicin, this can lessen side effects. However, potential toxicity can occur with any drug if the dose is not adjusted by the physician, especially for drugs with low therapeutic indexes. Although this concept has been considered extensively for drug–drug interactions over the past few decades,[186] it merits further study for nutrient–drug interactions because of the ubiquity of PCs in vegetables.

3.2 Effects on phase II enzymes. Phase II enzymes can conjugate several groups to their substrates, such as glucuronic acid (UDP-glucuronosyltransferase, UGT), sulfate (sulfotransferase, SULT), glutathione (glutathione-*S*-transferase, GST) and others. This will typically decrease the bioactivity and potential toxicity of the compounds, while also increasing their polarity and facilitating excretion.

UGT1A1 mRNA expression and glucuronidation activity are increased by resveratrol and resveratrol combined with either curcumin or chrysin in Caco-2 cells.[187] The glucuronidation of acacetin, a flavonoid aglycone, is significantly faster than its glycoside tilianin in enterocytes and hepatocytes from both genders of different species (humans, rats, mice, dogs and guinea pigs), thereby demonstrating that the carbohydrate moiety is a determining factor in how PCs are metabolized.[188] Quercetin and other flavonoids stimulate the expression of UGT mRNA through AhR (aryl hydrocarbon receptor) activation, a mechanism that evolved to prevent xenobiotic toxicity in animals.[189] Baicalein and 3-hydroxyflavone upregulate UGT1A1 mRNA expression in LS180 cells, while also increasing UGT1A protein expression and activity in a dose-dependent manner. The effect of baicalein was through AhR induction, and the effect of 3-hydroxyflavone was through pregnane X receptor (PXR) induction.[190] In healthy humans, perfused (−)-epicatechin is conjugated to (−)-epicatechin-3′-*O*-sulfate (and other sulfated conjugates) and shunted back into the intestinal lumen as a method of excretion that limits intestinal absorption.[191] Recent experiments have demonstrated that kaempferol, quercetin and resveratrol act as reversible competitive inhibitors of recombinant SULTs (SULT1A1, 1A3, 1B1, 1E1 and 2A1).[192] The effects of low doses of quercetin on UGT1 and GST were analyzed in different cell lines (Caco-2, HT-29, HuTu 80 and LT97) and revealed an induction effect.[193] Rosmarinic acid has a low inhibition constant (K_i) of 48.74 nM for GST when analyzed *in vitro*, suggesting a high capacity for inhibition.[194] Although phase I and II metabolism have been considered a barrier that inhibits absorption, favors excretion and decreases bioactivity, it has been recently proposed that in some cases covalent modifications can increase oral absorp-

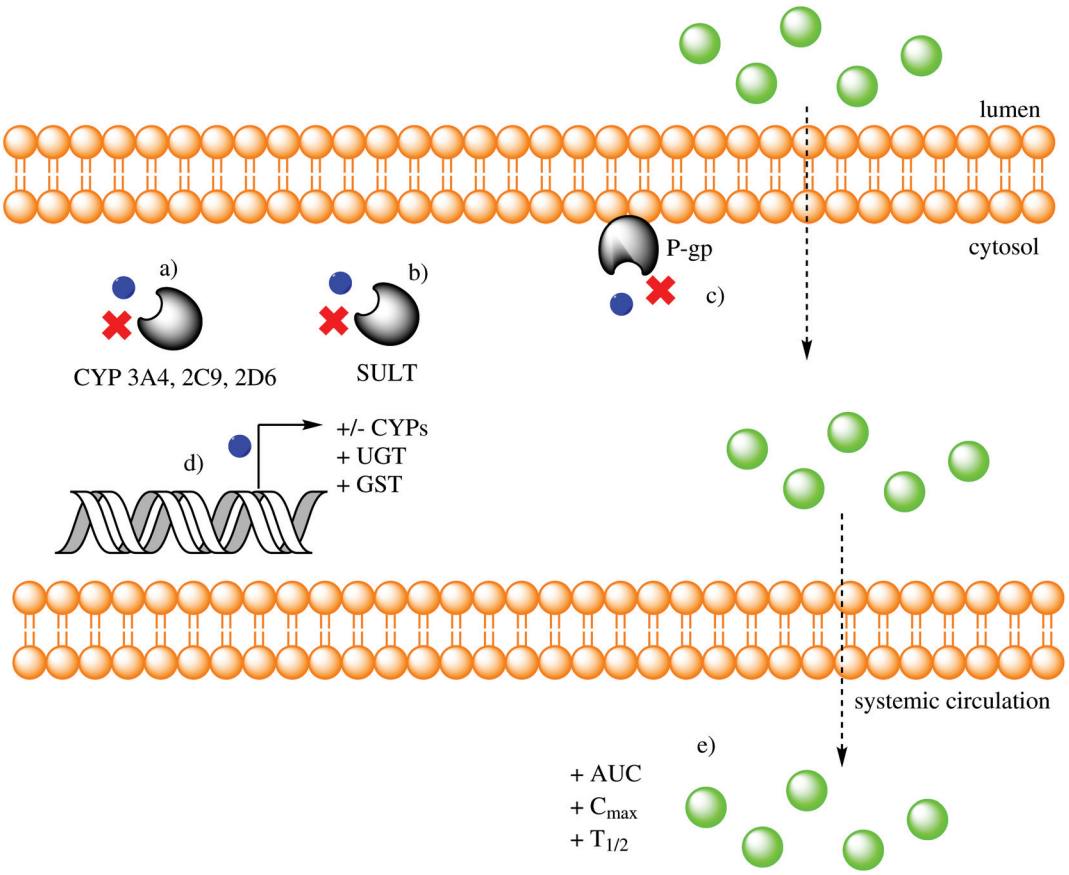

Fig. 3 Effect of phenolic compounds (PCs) on phase I/II enzymes and other xenobiotics. PCs (blue spheres) can inhibit (a) phase I enzymes (members of the cytochrome P450 superfamily, CYP), (b) phase II enzymes (sulfotransferases, SULT) or (c) efflux enzymes (P-gp); (d) they can also upregulate (+) or downregulate (–) mRNA transcription of phase I (CYP) or II (UDP-glucuronosyltransferase, UGT; glutathione-*S*-transferase, GST) enzymes; (e) net effect of phase I/II modulation is an increase (+) in area under the curve (AUC), maximum plasma concentration (C_{max}) and half-life ($t_{1/2}$) of other orally-ingested xenobiotics (green spheres).

tion and bioactivity.[195] Fig. 3 represents the effects that PCs exert on phase I and II metabolism.

4 Pharmacokinetics of phenolic compounds

As with any xenobiotic, orally ingested PCs are subjected to absorption, distribution, metabolism and excretion (ADME), which indicates that their pharmacokinetic profiles can be obtained.[196] Some parameters that have been utilized to evaluate their pharmacokinetic behavior include maximum concentration (C_{max}), time to reach maximum concentration (T_{max}), area under the plasma concentration curve (AUC), mean residence time (MRT) and elimination half-life ($T_{1/2}$). Table 2 summarizes the pharmacokinetic parameters for different PCs in plasma after oral administration.

Pharmacokinetic parameters vary for each compound and depend on different factors such as the molecular structure, dose, food matrix, localization in food, and study model, among others. For example, while the T_{max} of pure ferulic acid is 0.03–0.18 h, the T_{maxes} of puerarin and mangiferin are 0.55 and 0.83 h, respectively.[197–199] The oral co-administration of quercetin and rutin flavonoids, either pure or from herb extracts (*Hippophae rhamnoides*), has revealed differences in the C_{max}, T_{max}, $T_{1/2}$ and AUC in plasma.[200] The C_{max} and AUC of quercetin were higher than rutin when ingested together as pure compounds, which shows that quercetin affects the absorption of rutin. However, when both of the compounds naturally found in herb extracts were co-administered, the C_{max} and AUC of rutin were higher than quercetin.[200] In another study, puerarin was administered together with catechin, and the AUC and C_{max} for puerarin were 2.48- and 3.91-fold higher than when puerarin was administered alone. The opposite behavior was observed for catechin, which had lower AUC and C_{max} values than catechin administered alone. This behavior could be explained by the competitive efflux of catechin and puerarin by P-gp and MRP2 in the small intestine.[201]

Several studies have been developed using common Chinese herbs combined with Western drugs. Hongua and clopidogrel are often combined with ferulic acid-containing herbs to aid in cardiovascular disease treatment. Li *et al.* found that the C_{max} and AUC of plasma ferulic acid were significantly increased in rats when it was co-administered with clopidogrel

Table 2 Pharmacokinetic parameters of selected orally ingested PC

PC	Condition/dose (per kg of body weight)	C_{max}	T_{max} (h)	$T_{1/2}$ (h)	AUC	Model/reference/units
Ferulic acid (FA)#	14.75 mg pure FA per kg	0.7 ± 0.1	0.1 ± 0.0	3.81 ± 1.0	1.11 ± 0.2	Sprague-Dawley rats[198]
FA#	*Rhizoma chuanxiong* extract/14.75 mg FA per kg	0.4 ± 0.1	0.3 ± 0.1	16.3 ± 4.1	0.77 ± 0.1	C_{max} μg L^{-1}
FA#	Nao-De-Sheng decoction/14.75 mg FA per kg	0.5 ± 0.1	0.1 ± 0.0	13.4 ± 3.5	1.02 ± 0.1	$AUC_{0-\infty}$ μg h L^{-1}
Puerarin (P)#	Pure compound/100 mg P per kg	0.2 ± 0.0	0.5 ± 0.3	6.0 ± 3.3	1.24 ± 0.1	
P#	*Radix puerariae* extract/100 mg P per kg	0.1 ± 0.0	0.9 ± 0.1	10.8 ± 1.9	0.33 ± 0.1	
P#	Nao-De-Sheng decoction/100 mg P per kg	0.2 ± 0.1	0.9 ± 0.1	4.05 ± 1.9	1.01 ± 0.1	
FA#	FA pure compound/10 mg FA per kg	8.1 ± 1.0	0.03 ± 0.00	1.7 ± 0.7	2961.7 ± 166.5	Sprague-Dawley rats[197]
FA#	FA with Honghua/10 mg FA per kg + 700 mg Honghua per kg	9.7 ± 1.9	0.09 ± 0.05	1.0 ± 0.6	4794.9 ± 663.2	C_{max} μg ml^{-1}
FA#	FA with clopidogrel/10 mg FA per kg + 7 mg clopidogrel per kg	1.4 ± 1.53	0.1 ± 0.1	0.8 ± 0.5	4843.6 ± 1121.8	$AUC_{0-\infty}$ h ng per mL
Quercetin (Q)**	Beverage (500 mg Q + 26.9 g Tang®)/500 mg	354.4 ± 87.6	4.7 ± 0.3	8.3 ± 1.4	3845.9 ± 689.8	Men and women[227]
Q**	Bar (Q fortified First Strike™ bar)/500 mg	698.1 ± 189.5	2.3 ± 0.5	8.0 ± 1.3	5314.8 ± 1432.4	C_{max} μg L^{-1}
Q**	Chews (Q in 2 chews)/500 mg	1051.9 ± 393.1	3.3 ± 0.8	5.5 ± 0.9	4147.1 ± 671.8	AUC_{total} μg L^{-1} h^{-1}
Q#	2.5 mg pure Q per kg with R	165.3 ± 31.9	3.37 ± 0.5	7.7 ± 1.1*	972.1 ± 85.8	Wistar rats[200]
Q#	2.5 mg Q per kg from polyherbal formulation	90.8 ± 21.4	3.27 ± 0.9	12.2 ± 1.5*	406.6 ± 24.8	C_{max} ng mL^{-1}
Rutin (R)#	2.5 mg pure R per kg with Q	61.1 ± 29.3	4.17 ± 1.2	11.9 ± 1.5*	456.6 ± 29.8	$AUC_{0-\infty}$ ng mL^{-1} h^{-1}
R#	2.5 mg R per kg from polyherbal formulation	121.7 ± 19.2	4.43 ± 0.8	7.4 ± 1.1*	731.4 ± 31.1	
Naringenin (NG)**	7 g raw tomatoes per kg (0.50 ± 0.03 μg NG per g)	ND	ND	ND	ND	Men and women[208]
NG**	3.5 g cooked tomato sauce per kg (3.39 ± 0.1 μg NG per g)	11.9 ± 2.7	0.3 ± 0.1	1.0 ± 0.2*	979 ± 360	C_{max} nmol L^{-1}
NG**	3.5 g tomato sauce + olive oil cooked/kg (3.82 ± 0.22 μg NG per g)	12.8 ± 3.1	0.7 ± 0.1	0.9 ± 0.2*	1459 ± 159	AUC nmol L^{-1} min^{-1}
NG glucuronide**	7 g raw tomatoes per kg	17.4 ± 3.8	2.1 ± 1.0	3.6 ± 0.3*	5330 ± 1105	
NG glucuronide**	3.5 g cooked tomato sauce per kg	427.9 ± 59.0	0.6 ± 0.1	1.7 ± 0.1*	49.7 ± 7.8	
NG glucuronide**	3.5 g cooked tomato sauce + olive oil/kg	353.1 ± 55.3	0.9 ± 0.1	2.4 ± 0.3*	58.6 ± 12.1	
Caffeic acid (CA) glucuronide**	Raw tomato/7 g raw tomatoes per kg	6.2 ± 1.5	1.6 ± 0.7	2.6 ± 0.4*	1141 ± 56	
CA glucuronide**	3.5 g cooked tomato sauce per kg	5.0 ± 2.7	2.5 ± 0.5	2.7 ± 0.8*	835 ± 138	
CA glucuronide**	3.5 g cooked tomato sauce + olive oil/kg	4.1 ± 0.5	1.5 ± 0.5	2.3 ± 0.0*	689 ± 122.8	
FA glucuronide**	Raw tomato/7 g raw tomatoes per kg	389.0 ± 82.6	3.0 ± 1.1	4.6 ± 0.8*	134.6 ± 32.1	
FA glucuronide**	3.5 g cooked tomato sauce per kg	343.9 ± 77.6	3.0 ± 1.1	7.5 ± 1.4*	184.1 ± 34.3	
FA glucuronide**	3.5 g cooked tomato sauce + olive oil/kg	351.5 ± 72.0	6.4 ± 3.7	5.8 ± 1.7*	139.1 ± 46.8	
Cichoric acid (CiA)#	*E. purpurea* extract/10 g per kg extract (2.4 mg CiA per g)	1263.6 ± 114.5	0.2 ± 0.0	8.4 ± 0.3	2426.5 ± 178.8	Sprague-Dawley rats[228]
Chlorogenic acid (ChlA)#	*E. purpurea* extract/10 g per kg extract (0.99 mg ChlA per g)	307.9 ± 24.5	0.2 ± 0.0	7.7 ± 1.4	692.5 ± 140.2	C_{max} ng mL^{-1}
Quinic acid (QnA)#	*E. purpurea* extract/10 g per kg extract (0.12 mg QnA per g)	612.7 ± 48.3	1.4 ± 0.1	6.6 ± 1.6	6723.6 ± 485.2	$AUC_{0-\infty}$ ng h per mL
CA#	*E. purpurea* extract/10 g per kg extract (0.58 mg CA per g)	558.4 ± 25.0	6.0 ± 0.0	4.9 ± 1.6	3976.1 ± 266.6	
Mangiferin (Mn)#	Pure compound/270 mg Mn per kg	0.4	0.8	14.1	5.4	Wistar rats[199]
Mn#	Zhi mu tablet (*Anemarrhenae rhizoma*)/270 mg Mn per kg	1.3 ± 0.4	5.0 ± 0.6	4.9 ± 2.6	11.3 ± 4.1	C_{max} μg ml^{-1}
						$AUC_{0-\infty}$ μg h L^{-1}
Delphinidin-3-*O*-G**	350 mL of 100% grape juice (58 ± 1 μmol)	1.4 ± 0.3	1.4 ± 0.4	0.9	3.5 ± 0.5	Men and women[229]
Delphinidin-*O*-GN**		1.5 ± 0.4	3.3 ± 0.3	1	6.9 ± 2.2	C_{max} nmol L^{-1}
Petunidin-3-*O*-G**	350 ml (6.8 ± 0.1 μmol)	1.0 ± 0.5	1.3 ± 0.5	NR	2.0 ± 0.6	AUC nmol h L^{-1}
Petunidin-*O*-GN**		2.0 ± 0.5	2.6 ± 0.2	1.4	7.6 ± 2.9	
p-Coumaric acid**	350 ml (1.9 ± 0.1 μmol)	64 ± 14	0.7 ± 0.1	NR	88 ± 27	
m-Dihydrocoumaric acid**		355 ± 57	5.8 ± 0.5	NR	4080 ± 968	
Dihydrocoumaric acid-*O*-S**		27 ± 1	6.0 ± 2.0	NR	388 ± 92	
CA**	350 ml (0.7 ± 0.1 μmol)	178 ± 53	0.5 ± 0.2	NR	1306 ± 312	
CA-3′-*O*-S**		47 ± 11	1.0 ± 0.0	NR	90 ± 23	

Table 2 *(Contd.)*

PC	Condition/dose (per kg of body weight)	C_{max}	T_{max} (h)	$T_{1/2}$ (h)	AUC	Model/reference/units
Dihydrocaffeic acid-3′-*O*-S**		161 ± 37	3.9 ± 0.4	NR	1164 ± 368	
Dihydroferulic acid-4′-*O*-S**		42 ± 9	4.4 ± 0.7	NR	359 ± 164	
FA**	350 ml (0.4 ± 0.0 μmol)	63 ± 13	1.8 ± 0.9	NR	468 ± 215	
FA-4′-*O*-S**		63 ± 9	1.2 ± 0.2	NR	370 ± 115	
Onion supplement#	Onion stewed and homogenized/100 mg	2.3 ± 1.4	0.6 ± 0.2	10.9 ± 4.1	9.7 ± 6.9	Men and women[230]
Q-4′-*O*-G#	Isolated from onions/100 mg	2.1 ± 1.6	0.7 ± 0.3	11.9 ± 4.0	8.4 ± 9.1	C_{max} μg mL^{-1}
Buckwheat tea#	Buckwheat tea/200 mg	0.6 ± 0.6	4.3 ± 1.8	10.3 ± 3.5	3.8 ± 3.9	AUC_{0-24h} h μg mL^{-1}
Q-3-*O*-R#	Q-3-*O*-R (tablet)/200 mg	0.3 ± 0.3	6.9 ± 2.9	11.8 ± 3.1	2.5 ± 2.2	
Q aglycone**	Q aglycone + 3% fat/30 μmol Q per kg	0.51 ± 0.05	1.7 ± 0.1	NR	117.3 ± 18.5	Pigs[32]
Q aglycone**	Q aglycone + 17% fat/30 μmol Q per kg	0.58 ± 0.06	1.1 ± 0.1	NR	184.5 ± 19.8	C_{max} μmol L^{-1}
Q aglycone**	Q aglycone + 32% fat/30 μmol Q per kg	0.56 ± 0.05	0.8 ± 0.1	NR	176.0 ± 18.5	AUC_{0-24h} min μmol L^{-1}
Q-3-*O*-G**	Q-3-*O*-G + 3% fat/30 μmol Q per kg	0.90 ± 0.08	1.1 ± 0.1	NR	205.5 ± 19.8	
Q-3-*O*-G**	Q-3-*O*-G + 17% fat/30 μmol Q per kg	0.89 ± 0.08	0.8 ± 0.1	NR	270.9 ± 19.8	
Q-3-*O*-G**	Q-3-*O*-G + 32% fat/30 μmol Q per kg	0.64 ± 0.08	0.7 ± 0.1	NR	249.7 ± 19.8	

ND not detected; NR not reported; ** standard error of the mean; # standard deviation; C_{max} maximum concentration; T_{max} time maximum concentration; $T_{1/2}$ elimination half-life; AUC area under the plasma concentration curve; * MRT mean residence time; *O*-S (*O*-sulphate); *O*-G (*O*-glycoside); *O*-GN (*O*-glucuronide); *O*-R (*O*-rutinoside).

(74.3 and 79.7%, respectively) compared with pure ferulic acid. Likewise, the average T_{max} was reduced 3 and 3.76 times when ferulic acid was co-administered with Honghua and clopidogrel, respectively. This behavior was the opposite of what was observed with pure ferulic acid administration and was associated with local interactions of ferulic acid with Honghua and clopidogrel in the intestine and/or an alteration in phase I/II metabolism (as previously discussed).[197] Ouyang *et al.* observed that the AUC, T_{max} and C_{max} of pure ferulic acid and ferulic acid from a Nao-De-Sheng decoction were higher than ferulic acid from the aqueous extract of *Rhizoma chuanxiong*. Similar behavior was observed when pure puerarin was orally administered, and the AUC, T_{max} and C_{max} were higher than when *Radix puerariae* extract was used as a source of puerarin.[198]

Another study compared the pharmacokinetics of isorhamnetin, quercetin and kaempferol after the oral administration of three different *Hippophae rhamnoides* preparations (TFH) in beagle dogs. The results showed that the C_{max} and AUC of isorhamnetin and quercetin in TFH-solid dispersion (TFH-SD) and TFH-self-emulsifying (TFH-SE) preparations were significantly enhanced compared to the TFH preparations, which represents a new alternative for the oral administration of flavones from TFH. Additionally, a double-peak phenomenon was observed with isorhamnetin (three TFH preparations), while this was only observed with quercetin in the TFH-SD preparations. This behavior revealed that quercetin and isorhamnetin have two sites of absorption, the stomach and gut. These PCs also exhibited different behaviors in different TFH preparations.[202] These results indicate that the source of PC, the interactions between them and their interactions with other molecules in the matrix alter their pharmacokinetic parameters.

All of the previously discussed interactions of PCs with fiber and other nutrients will be reflected in the pharmacokinetic behavior of PCs. In cereals such as corn, sorghum and wheat, the majority of PCs (>75%) are bound to indigestible cell wall polysaccharides.[203] The linkage of ferulic acid to xylans from wheat results in the low bioaccessibility of this compound in the small intestine (0.5%).[204] Additionally, the presence of hydroxyl groups on PCs favors hydrogen bond formation between PCs and cellulose or xylans.[205] The consequent decrease in absorption is reflected by a decrease in pharmacokinetic values. However, other studies have shown that PC–fiber interactions in fruits such as mango, papaya or pineapple have no impact on the bioaccessibility or antioxidant capacity of PCs.[206] PC–protein and PC–lipid interactions show that the pharmacokinetic behaviors of PCs can be affected.[207,208] Rosmarinic acid can form complexes with whey proteins in bovine milk (α-lactalbumin, β-lactoglobulin and lactoferrin) by hydrophobic, hydrogen bonding and dipole–dipole non-covalent interactions, and these complexes are more stable than proteins alone in *in vitro* digestion models.[207]

The pharmacokinetic behavior of PCs can also be altered by other compounds that may be generated as a result of their metabolism (phase I/II and/or bacterial).[209] For example, caffeic acid can be metabolized to dihydrocaffeic acid (reductase), caffeic acid-3-*O*-sulfate (SULT), ferulic acid or iso-

ferulic acid (catechol-*O*-methyltransferase), which can result in an overestimation of caffeic acid levels and disturb its pharmacokinetics.[209,210] Thus, pharmacokinetic profiles are a result of all of the previous GI interactions and metabolism.

5 Nanotechnology to improve the bioefficacy of phenolic compounds

Different techniques are currently being developed to minimize or bypass the previously described PC interactions in favor of chemical protection and targeted delivery. Nanotechnology is a novel and promising way to manipulate several metabolic processes to prevent or treat specific health-related problems.[211] Encapsulation allows for the controlled released of PCs and can be achieved at a nanoscale level, such as with liposomes and polymeric nanoparticles.[212] Also, loading biocompatible and biodegradable nanoparticles with PCs can enhance their aqueous solubility, chemical stability, bioavailability, circulation time and target specificity.[213] In that sense, nanoparticles have been proposed as carriers for PCs to improve their bioavailability and bioefficacy.

Haratifar *et al.*[214] used casein micelles as encapsulating material to protect tea EGCG from oxidation at the intestinal level. They found that EGCG encapsulation with casein micelles did not diminish its bioefficacy on proliferation inhibition in a cancerous colonic epithelial cell line (D/v-src), whereas the proliferation of the normal cell line (4D/WT) was maintained. A similar study performed by Guri *et al.*[215] reported that a PC–casein complex had similar effects as free PCs and did not decrease the viability of HT29-MTX, which mimics the presence of a mucus barrier in the intestine, whereas it did decrease the cell viability of adenocarcinoma cells (HT-29) proportional to the EGCG concentration. However, Jain *et al.*[216] have reported that the co-encapsulation of tamoxifen and quercetin in poly-(lactic-*co*-glycolic acid) nanoparticles results in a 5- and 3-fold increase in the oral bioavailability of tamoxifen and quercetin, respectively.

The use of nanosystems could facilitate the passage of PCs or other bioactive compounds through biological barriers and protect them from the metabolic modifications that result in lower absorption rates.[217] The most common biocompatible and biodegradable nanoparticles include nanoliposomes, nanoemulsions, lipid nanocarriers, micelles and poly-(lactic-*co*-glycolic acid) nanoparticles.[211]

Nanoliposomes, or nanometric liposomes, are colloidal structures that are commonly composed of phospholipids. These nanomaterials have been shown to enhance the bioefficacy of bioactive compounds. Due to their natural composition, they should be able to overcome regulatory hurdles to be readily attainable, and newly developed food products or nutraceutical formulations could be quickly implemented. Zou *et al.*[218] studied the stability of PCs from tea in nanoliposomes and reported that relatively favorable sustained release properties could be achieved with only 29.8% of the released PCs after 24 h of incubation. However, the use of nanoliposomes improved the chemical stability of PCs under alkaline pH conditions. These results suggest that further studies must be performed to enhance the use of nanoliposomes in food products with long shelf lives and improve bioefficacy.

Nanoemulsions consist of 10–100 nm oil droplets dispersed within an aqueous continuous phase, with each oil droplet surrounded by surfactant molecules.[219] Either micro- or nanoemulsions have been commonly developed to encapsulate lipophilic components so they can be dispersed into an aqueous medium. However, it is also possible to prepare water-in-oil micro- and nanoemulsions.[220] In that sense, nanoemulsions can also be successfully applied to PC entrapment. Baccarin *et al.*[221] showed that a PC-rich ethyl acetate fraction from pomegranate seeds entrapped in oil nanoemulsions was internalized as nanodroplets by the cells, but a higher proportion was detected along the cell membrane, which results in protection against UVB-induced DNA damage in the keratinocyte HaCaT cell line. Recently, a study performed by Nasr[222] focused on developing a mucoadhesive lipid nanoemulsion based on hyaluronic acid and co-encapsulated resveratrol and curcumin for the transnasal treatment of neurodegenerative diseases. This nanoemulsion was safe for use on the nasal mucosa, and it improved the brain delivery of PCs with a 7- and 9-fold increase for resveratrol and curcumin, respectively. Likewise, Rocha *et al.*[223] reported that polysaccharide nanoparticles can be successfully applied to enhance the chemical stability of EGCG while retaining its bioactivity, thereby reducing cell viability and inducing apoptosis in Du145 prostate cancer cells.

Nanotechnology can be applied to enhance the bioefficacy of certain types of PCs and combinations of them. Singh *et al.*[224] studied the antiproliferative effects of EGCG and theaflavin nanoparticles on diverse human cancer cell lines such as A549 (lung carcinoma), HeLa (cervical carcinoma) and THP-1 (acute monocytic leukemia) cells. They reported that EGCG and theaflavin enhanced the potential benefits of cisplatin. However, the nanoparticles containing EGCG-theaflavin and cisplatin were 20-fold more effective than the free compounds.

By using liposomes or other nanoparticles, nanotechnology can increase the bioavailability and cellular uptake of these compounds.[225] Hence, nanoparticle material should be selected based on the desired effect or the specific tissue to which PC delivery is required, and the chemical stability of both the nanoparticles and PCs along the GI tract should be taken into consideration.

Conclusion

Phenolic compounds interact with several macro- and micronutrients and host proteins (digestive enzymes, nutrient transporters and xenobiotic-metabolizing enzymes) within the gastrointestinal tract, and these interactions result in delayed or decreased nutrient digestion and absorption. Their absorption and pharmacokinetic parameters depend on their size, molecular complexity, charge, the food matrix, and the presence of other phenolic compounds or drugs. They can inhibit phase I and II enzymes and regulate their expression, which can lead to

potential drug–drug or drug–nutrient interactions. Knowledge of all of the mentioned interactions has inspired novel nanotechnological approaches that are currently under development to avoid undesired interactions, protect PCs from harsh chemical environments and allow for targeted delivery. The study of the specific molecules that are able to transport and protect these compounds is necessary to complement and provide an alternative to the therapies that are commonly used to treat different types of cancers and vascular disorders. The mechanism and mode of action of most PCs require further study due to their complex structures that affect their molecular interactions with other biomolecules, minerals, vitamins and enzymes.

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