JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Review

pubs.acs.org/JAFC

Overview of Metabolism and Bioavailability Enhancement of Polyphenols

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Supporting Information

ABSTRACT: A proper diet is one of major factors contributing to good health and is directly related to general condition of the organism. Phenolic compounds are abundant in foods and beverages (fresh and processed fruits and vegetables, leguminous plants, cereals, herbs, spices, tea, coffee, wine, beer) and their pleiotropic biological activities result in numerous health beneficial effects. On the other hand, high reactivity and very large diversity in terms of structure and molecular weight renders polyphenols one of the most difficult groups of compounds to investigate, as evidenced by ambiguous and sometimes contradictory results of many studies. Furthermore, phenolics undergo metabolic transformations, which significantly change their biological activities. Here, we discuss some aspects of metabolism and absorption of phenolic compounds. On the basis of information reported in the literature as well as in summaries of clinical trials and patent applications, we also give an overview of strategies for enhancing their bioavailability.

KEYWORDS: *polyphenols, metabolism, absorption, bioavailability*

INTRODUCTION

Polyphenols are natural compounds characterized by a high structural diversity, and their common occurrence in plants renders them intrinsic dietary components. They are found only in plants and certain fungal species and are not synthesized neither by animals nor by humans.[1,2] At present, polyphenols are looked upon as secondary metabolites characterized by a wide spectrum of physiological functions.[1,3] The number of phenolic compounds identified in plant extracts has already exceeded 8000.[4]

The diversity of phenolic compounds structures results not only from a large variety of carbon backbone chains within this group of compounds but also from various modifications (e.g., acylation or glycosylation) of primary and secondary substituents.[1,5] On the basis of the number of carbon atoms and carbon chain structure, phenolic compounds are classified into the following subgroups: phenolic acids, cumarin derivatives, naphthoquinone derivatives, xanthone derivatives, stilbene derivatives, 2-phenylchroman-4-one derivatives (flavonoids), chalcone derivatives, and aurone derivatives.[1,3,5−8] Polyphenols also comprise complex compounds such as condensed tannins (proanthocyanidins), hydrolyzable tannins, lignans (monolignol dimers derived from phenylalanine; three main monolignols are *p*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol), lignins (monolignol polymers), as well as phenolic pigments found in black tea, namely, theaflavins and thearubigins (formed by oxidation and polymerization of catechins).[1,3,5,7,9]

Plant polyphenolic compounds are incorporated into a food matrix and are commonly consumed from tea, wine, fruits, vegetables, and legumes. Their bioavailability is still under discussion and depends on factors associated with food processing, with the host organism (sex, age, composition of intestinal microflora), as well as on interactions between polyphenols and other molecules (such as salivary proteins and digestive enzymes).[1,5,10−14] The majority of polyphenols occur in foods and beverages in the form of biologically unavailable polymers or glycosides that are degraded to low molecular weight compounds by intestinal enzymes originating from the host organism or secreted by colonic microflora.[14−17]

The bioavailability of phenolics depends largely on their dietary content; consistently, it could be significantly enhanced by supplementation with either polyphenol-rich extracts or individual compounds. The form of supplementation may considerably influence the polyphenol bioavailability and one could list such forms as, among others, polymeric capsules,[18] phospholipid−polyphenol complexes,[19] liposomes[20] and proliposomes,[21] micro-[22] and nanoemulsions,[23] micro-[24] and nanoparticles,[25] adjuvants,[26] solid dispersions,[27] inclusion complexes with cyclodextrins,[28] and cocrystals.[29] In this review, we focus on selected aspects of the metabolism and absorption of polyphenolic compounds and on strategies of enhancement of their bioavailability.

ABSORPTION AND METABOLISM OF POLYPHENOLIC COMPOUNDS

The concentrations of polyphenolic compounds in the bloodstream depend on their modifications during metabolism and absorption form the gastrointestinal tract. In the oral cavity, polyphenols (particularly flavanols and proanthocyanidins), partially released from the food matrix, are able to interact with salivary proteins rich in proline. Polyphenolic compounds interact with proline-rich proteins by hydrogen bonds or

Received: October 2, 2013
Revised: November 30, 2013
Accepted: December 2, 2013
Published: December 2, 2013

dx.doi.org/10.1021/jf404439b | J. Agric. Food Chem. 2013, 61, 12183−12199

hydrophobic interactions, thus forming soluble polyphenol−protein aggregates that can bind together forming bigger complexes that precipitate from the solution. Furthermore, the polyphenol−protein interactions alter proteins tertiary structure, which can affect their activity.[30] Polyphenolic compounds exhibit different affinities toward the proline-rich proteins. It was proved that (+)-catechin had a higher affinity toward the salivary proteins than (−)-epicatechin, whereas a proanthocyanidin dimer coupled by a C-4−C-8 bond exhibited a higher affinity toward those proteins than a dimer having a C-4−C-6 bond.[31] Interestingly, in spite of the formation of polyphenol−protein aggregates, availability of the polyphenolic compounds did not change significantly. Furthermore, Cai and Bennick[32] showed that the absorption of quercetin was unchanged despite the formation of quercetin−protein aggregates.

In the stomach, polyphenols are exposed to strong acidic conditions, which might influence their stability. However, the experiments carried out on several compounds from this group (i.e., resveratrol,[33] quercetin,[34] and catechin[35]) revealed that they were stable at low pH. Similarly, proanthocyanidins were also reported to be stable at such pH,[36,37] despite earlier results suggesting their degradation to monomers in an acidic environment.[38] Interestingly, some studies indicate that phenolic derivatives could be absorbed in the stomach. In vivo experiments carried out by Passamonti et al.[39] demonstrated that malvidin-3-glucoside appeared in the plasma of rats after only 6 min of anthocyanins administration. Probably, such a fast appearance of this compound in the bloodstream might result from the presence of transporters in the stomach wall. Presumably, such a function might be effected by a bilitranslocase (TC 2.A.65.1.1). This is an organic anion transporter, expressed in the liver, kidney, vascular endothelium, and gastric epithelium and responsible for the transport of bilirubin and biliverdin, as well as anthocyanins and flavonoid aglycons.[40−42] Moreover, phenolic acids (such as dimethoxycinnamic, chlorogenic, gallic, caffeic, and *p*-coumaric acids) could also be absorbed in the stomach.[43−45]

Flavonoids are usually glycosylated, and therefore, in the small intestine, the sugar unit is released and an aglycone is formed by an endogenic β-glucosidase. Two enzymes are particularly active at this stage, namely, lactase-phlorizin hydrolase (LPH) (EC 3.2.1.62) and cytosolic β-glucosidase (CBG) (EC 3.2.1.21). LPH is present on the luminal side of the brush border in the small intestine and is mainly responsible for the hydrolysis of lactose to glucose and galactose; however, it can also hydrolyze flavonoid-O-β-D-glycosides. The lipophilicity of aglycones released in this way is higher than that of glycosides and therefore the aglycones can enter the epithelial cells via passive diffusion. In the case of polar polyphenol glycosides, their transfer into enterocytes is carried out by an active sodium-dependent glucose transporter (SGLT1) and they can undergo the action of CBG.[46]

The small intestine is the main site of polyphenol glucuronidation mediated by enzymes belonging to the family of uridine diphosphate glucuronosyltransferases (UGT). Particularly, UGT1A8 and UGT1A10 isoforms are believed to be responsible for flavonoids glucuronidation on the A-ring at the positions C5 and C7.[47] High levels of O-methylated forms and O-methylated flavanol glucuronides are also observed; the enzymes that take part in the formation of those derivatives are catechol-O-methyltransferases (COMT). These enzymes are responsible for methylation of compounds containing a catechol residue, mostly at the position *m*-3′-O-. S-Adenosylmethionine is a donor of the methyl group.[48] After reaching the interior of enterocytes, polyphenolic compounds are transported by the portal vein to the liver where they undergo further coupling reactions, similarly to other xenobiotics. The main role of the coupling reactions is to limit the action of chemical compounds and to facilitate their elimination in bile and urine by causing an increment in their solubility. In the liver, the main coupling reactions are sulfation, methylation, and (to a lesser extent) glucuronidation.[46] The conjugation with sulfate occurs by the action of sulfotransferases (SULT) and requires sulfate residues coming from 3′-phosphoadenosine-5′-phosphosulfate. Particularly, SLUTA1 and SLUTA3 are responsible for sulfation of the B-ring of (−)-epicatechin at the positions C3′ and C4′ and of the A-ring at the positions C5 and C7.[49] The conjugation reactions are very efficient, as phenolic aglycones occur in the plasma at very low concentrations or are completely absent, except for epigallocatechin gallate and epicatechin gallate occurring in the blood in their unmodified forms.[50]

In the liver phenolic compounds (similarly to other xenobiotics) undergo the reactions catalyzed by phase I enzymes (i.e. oxidation, reduction, hydrolysis, and hydration). Flavonoids are partially hydroxylated by cytochrome P450 (CYP). For example, genistein (5,7,4′-trihydroxyisoflavone) is transformed to orobol (5,7,3′,4′-tetrahydroxyisoflavone) as a result of mono-oxygenation by CYP1A1, CYP1A2, CYP1B1, or CYP2E1.[51] However, this process is not crucial in the metabolism of polyphenolic compounds because these substances contain hydroxyl groups in their structures. Phenolic compounds undergo conjugation reactions faster than oxidation.[52]

The large intestine is the main site of polyphenol absorption and colonic microflora play a major role in the catabolism of these compounds. *Clostridium orbiscindens* and *Eubacterium ramulus* producing enzymes able to execute the fission of the C-ring in quercetin and naringenin, as well as *Enterococcus casseliflavus* responsible for deglycosylation of quercetin-3-glucoside were identified in humans.[53] (−)-Epicatechin catabolism starts with the fission of the C-ring, which leads to the formation of 1-(3′,4′)-dihydroxyphenyl)-3-(2″,4″,6″-trihydroxy)propan-2-ol, which in turn is converted to 5-(3′,4′)-dihydroxyphenyl-valerolactone. In the next step, the valerolactone ring is degraded to 5-(3′,4′)-dihydroxyphenyl-valeric acid and then undergoes β-oxidation to 3-hydroxyphenylpropionic acid. α-Oxidation of this compound yields 3-hydroxyphenylacetic acid. In the degradation process of epigallocatechin gallate (EGCG) and epicatechin gallate (ECG), the galloyl moiety is eliminated by an esterase and the released gallic acid is decarboxylated to pyrogallol.[54] The metabolites formed by the colonic microflora are absorbed and transported by the portal vein to the liver, where they are subjected to the conjugation reactions resulting in monoglucuronides and monosulfates of 5-(3′,4′)-dihydroxyphenyl-valeric acid and hydroxyphenylpropionic acid. Then, the conjugated metabolites are transported to the bloodstream and are subsequently excreted in urine,[55,56] whereas the remaining (unabsorbed) metabolites are eliminated with faeces.[50]

Bile can also contain the conjugated metabolites. In the research carried out on rats, glucuronides and 3′-O-methylcatechin sulfate were found in bile.[57] Probably, the metabolites from the liver are transported back to the intestinal lumen by enterohepatic circulation and either are subjected to enzyme actions causing formation of less polar aglycones of polyphenolic compounds that can be reabsorbed or are eliminated with faeces.[58] Metabolism and absorption of polyphenols in humans are schematically represented in Figure 1.[14,31,39,43−46,59−65]

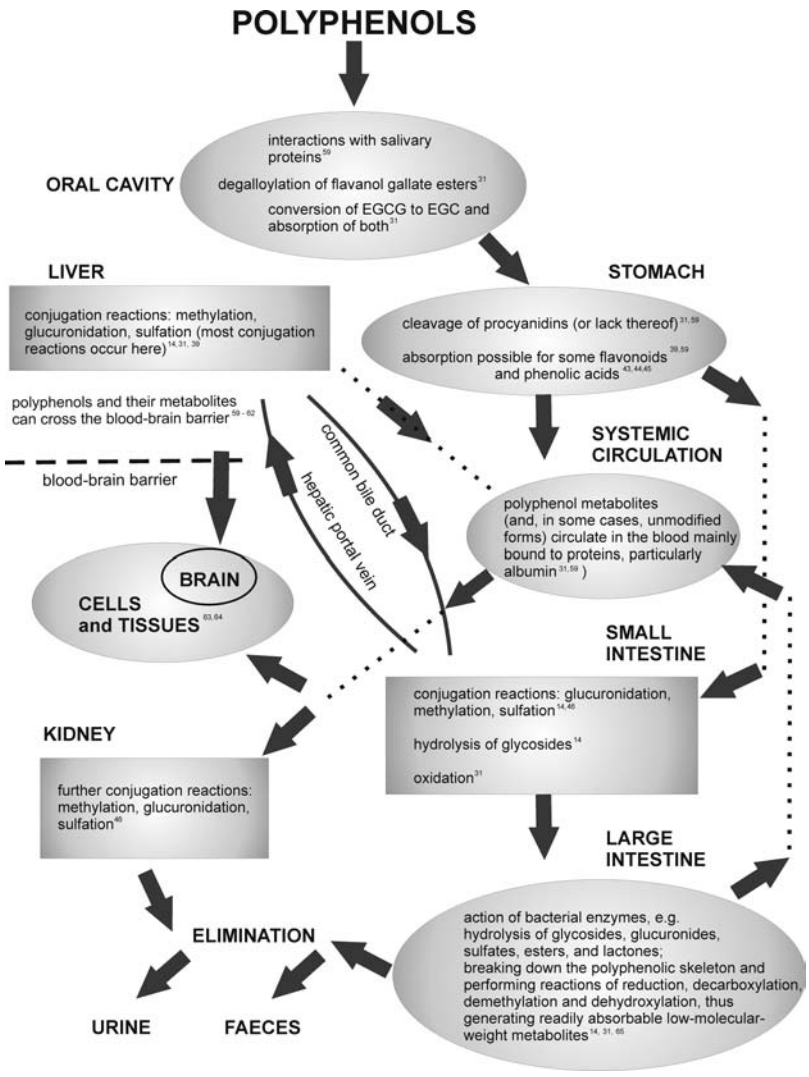

Figure 1. Schematic illustration of the metabolism and absorption of dietary polyphenols in humans.

TRANSPORT OF POLYPHENOLS FROM THE INTESTINAL LUMEN INTO CELLS

The transport of phenolic compounds to the cell is effected by a certain type of protein transporters. As it was mentioned earlier, hydrophilic compounds can be transported to the enterocytes by SGLT1. Glucuronides and sulfates of polyphenolic compounds are too hydrophilic to enter the cell by simple diffusion. Therefore, research revealed that proteins containing an ATP-binding cassette (ABC) are involved in this process.[65,67] These are membrane-type proteins containing one or more ATP-binding domains. Their expression occurs in the epithelial layers of the gastrointestinal tract, liver, kidney, placenta, and testes. All the proteins belonging to this family have a specific ABC domain, responsible for binding and hydrolysis of ATP. The energy released from ATP hydrolysis is used in the transport of different substances. The family of ABC transporters comprises multidrug resistance proteins (MRPs), breast cancer resistance protein (BCRP, ABCG2), and P-glycoprotein,[67] which are involved in the efflux of bioactive compounds from the intestinal cells either to the basolateral (blood) side or back into the intestinal lumen. These transporters show little specificity toward substrates; however, they play a crucial role in limiting the delivery of substances into cells.[68] MRP3 (ABCC3), localized in the basolateral membrane of the intestinal enterocytes, is responsible for the transport of trans-resveratrol glucuronide to the bloodstream.[69] Experiments carried out on Caco-2 cells indicated that MRP2 (ABCC2), localized in the apical membrane of the enterocytes, is responsible for the transport of polyphenols conjugated with glucuronide and/or sulfate.[70] Other experiments revealed that MRP2 also took part in the transport of naringenin and quercetin and its metabolites; it seems that P-glycoprotein (ABCB1) was also involved in naringenin transport.[71,72]

Moreover, glucose transporters (GLUT-1, GLUT-2, and GLUT-3) also participate in the transport of polyphenols. It was reported that GLUT-2 (SLC2A2) participated in quercetin 3-glucoside transport[73] while GLUT-4 (SLC2A4) was involved in the transport of genistein, myricetin, and quercetin;[74] the transport of quercetin was carried out not only by GLUT-4 (SLC2A4)[74] but also by GLUT-1 (SLC2A1).[75]

INFLUENCE OF POLYPHENOLIC COMPOUNDS ON EXPRESSION AND ACTIVITY OF ENZYMES PARTICIPATING IN XENOBIOTIC METABOLISM

Flavonoids not only are substrates for enzymes taking part in xenobiotic metabolism but also act as their regulators. Results of many experiments showed that flavonoids influence the

Table 1. Selected Strategies for Enhancing the Bioavailability of Phenolic Compounds Reported in the Literature: Inclusion Complexes with Cyclodextrins or with Dendrimers; Structural Analogues; Derivatives; Adjuvants as Absorption/Permeation Enhancers; Gastroretentive Floating Tablets; Soft Gelatin (Softgel) Capsule Technology; Subcutaneous Polymeric Implants; Nanodisks; Nanofibers; and Crystal Engineering (e.g. Cocrystallization)

means of enhancing bioavailability	study model	ref
Inclusion Complexes with Cyclodextrins		
inclusion complexes of a **soy isoflavone extract** with β-cyclodextrin	Sprague–Dawley rats	Lee et al., 2007[28]
cyclodextrin-based nanosponges (hyper-cross-linked cyclodextrin polymers nanostructured to form three-dimensional networks) loaded with **resveratrol**	hamster buccal mucosa carcinoma-derived cell line (HCPC-I); ex vivo studies with the use of buccal mucosa of rabbit and skin of pig	Ansari et al., 2011[93]
daidzein/hydroxypropyl-β-cyclodextrin/polyvinylpyrrolidone ternary system	chemical analysis	Borghetti et al., 2011[94]
Inclusion Complexes with Dendrimers		
inclusion complexes of **daidzein** with poly(amidoamine) (PAMAM) and poly(propylene imine) (PPI) dendrimers	in vitro studies on several cell lines	Zhao et al., 2011[95]
PAMAM dendrimers complexed with **puerarin**	rabbits (ocular absorption study)	Yao et al., 2011[96]
Structural Analogues		
EF-24 (a synthetic analogue of **curcumin**)	CD2F1 mice	Anand et al., 2007[97]
cyclohexyl-containing synthetic analogues of **bisdemethoxycurcumin**	BALB/c mice	Gagliardi et al., 2012[98]
Derivatives		
peracetylated **EGCG** derivative	human cell lines: esophageal cancer (KYSE150) and colon cancer (HCT-116); lipopolysaccharide-stimulated RAW264.7 murine macrophages; mice	Lambert et al., 2006[99]
several ester derivatives of **quercetin**	Madin–Darby canine kidney cell lines (MDCK-1 and MDCK-2); human colon cancer cell line (Caco-2)	Biasutto et al., 2007[100]
methyl capping of all free hydroxyl groups of **flavones**	human liver S9 fraction; human colon cancer cell line (Caco-2)	Walle, 2007[101]
Adjuvants as Absorption/Permeation Enhancers		
coadministration of **curcumin** and piperine	Wistar rats; **healthy volunteers**	Shoba et al., 1998[26]
cotreatment with **EGCG** and piperine	mice	Lambert et al., 2004[102]
transdermal delivery system for **quercertin** in Carbopol gel with dimethylformamide or L-menthol permeation enhancers	ex vivo study with the use of abdominal hairless pig skin	Olivella et al., 2007[103]
curcumin administered with piperine as absorption enhancer	Sprague–Dawley rats	Shaikh et al., 2009[25]
administration of quaternary ammonium–chitosan conjugate (N^+(60)-Ch) with **red grape skin and seed polyphenol extracts**	human endothelial progenitor cells (oxidative stress induced by hyperglycemia)	Felice et al., 2012[104]
Gastroretentive Floating Tablets		
gastroretentive floating tablets of **silymarin**	chemical analysis	Garg and Gupta, 2009[105]
floating stomach–retentive egg albumin tablets of several **polyphenols**	chemical analysis	Rosenzweig et al., 2013[106]
Soft Gelatin (Softgel) Capsule Technology		
softgel capsules containing **silybin** in a 1:2 complex with phosphatidylcholine	**healthy volunteers**	Savio et al., 1998[107]
soy isoflavone soft capsules	**healthy postmenopausal women**	Cheng et al., 2004[108]
Subcutaneous Polymeric Implants		
subcutaneous polymeric implants loaded with **polyphenon E** (a standardized green tea extract)	Sprague–Dawley rats; effect on benzo[a]pyrene (BP)-induced DNA adducts	Cao et al., 2011[109]
punicalagin-loaded subcutaneous polymeric implants	Sprague–Dawley rats; effect on benzo[a]pyrene (BP)-induced DNA adducts	Aqil et al., 2012[110]
Nanodisks		
incorporation of **curcumin** into nanodisks comprising a disk-shaped phospholipid bilayer whose edge is stabilized by a scaffold protein, recombinant human apoplipoprotein (apo) A-I	mantle cell lymphoma cell lines (Granta, NCEB, and Jeko); apoptosis assays	Singh et al., 2011[111]
Nanofibers		
curcumin-loaded poly(epsilon-caprolactone) nanofibers	wound healing model in streptozotocin-induced diabetic mice	Merrell et al., 2009[112]
Crystal Engineering (e.g., Cocrystallization)		
cocrystals of **quercetin**/ quercetin/caffeine, quercetin/caffeine/methanol, quercetin/isonicotinamide, and quercetin/theobromine dihydrate	Sprague–Dawley rats	Smith et al., 2011[29]
baicalein nanocrystal	Sprague–Dawley rats	Zhang et al., 2011[113]
seven previously undescribed crystal forms of **EGCG** (including the pure crystal structure of EGCG)	rats	Smith et al., 2013[114]

expression and the enzyme activity of phase I, II, and III detoxification systems.[76,77] On the molecular level, flavonoids may induce the expression of enzymes involved in phase I, II, and III xenobiotic metabolism. In the cytoplasm, phenolic compounds cause dissociation of nuclear factor erythroid 2-related factor 2 (Nrf2) from its inhibitor—Kelch-like ECH associating protein 1 (Keap1). Next, Nrf2 is translocated to the nucleus where it interacts with DNA in the region known as antioxidant response element (ARE). As a result, this translocation triggers the activation of *CYP*, *SULT*, *MRP*, and *BCRP* genes.[77]

Cytochromes P450 are enzymes belonging to the group of mono-oxygenases, playing a crucial role in the metabolism of many endogenic hydrophobic compounds (sterols, prostaglandins, fatty acids) and xenobiotics (drugs, carcinogens, food components). Their main role is the conversion of xenobiotics to less toxic substances. As mentioned earlier, flavonoids are substrates in the reactions catalyzed by cytochrome P450, but a number of studies indicate that polyphenolic compounds could also influence the synthesis and activity of these enzymes. The studies showed that 5 μM galangin, 0.5 μM diosmin, and 5 μM

Table 2. Selected Strategies for Enhancing the Bioavailability of Phenolic Compounds Reported in the Literature: Polyphenol-Phospholipid Complexes and Hybrid Systems Based on Those Complexes; Conventional (First-Generation) and Modified Liposomes; Proliposomes; Micelles and Micelle-Based Hybrid Delivery Systems; Nanosuspensions; Microemulsions; Self-emulsifying, Self-microemulsifying, and Self-nanoemulsifying Drug Delivery Systems (SEDDS, SMEDDS, and SNEDDS)

means of enhancing bioavailability	study model	ref
Polyphenol−Phospholipid Complexes and Hybrid Systems Based on Those Complexes		
green tea catechins complexed with phospholipids (Greenselect Phytosome)	**healthy volunteers**	Pietta et al., 1998[115]
	obese subjects	Di Pierro et al., 2009[19]
softgel capsules containing **silybin** in a 1:2 complex with phosphatidylcholine	**healthy volunteers**	Savio et al., 1998[107]
silibinin formulated with phosphatidylcholine (silipide)	**patients with confirmed colorectal adenocarcinoma**	Hoh et al., 2006[116]
silybin phytosome	**prostate cancer patients**	Flaig et al., 2007[117]
	subjects with localized prostate cancer planning a prostatectomy	Flaig et al., 2010[118]
Meriva, a lecithinized **curcumin** delivery system	**osteoarthritis patients** (3 months/50 patients and 8 months/100 patients)	Belcaro et al., 2010[119]
	symptomatic benign prostatic hyperplasia patients	Ledda et al., 2012[120]
	diabetic patients	Steigerwalt et al., 2012[121]
	patients with various chronic diseases (pain-relieving properties)	Di Pierro et al., 2013[122]
silybin combined with phosphatidylcholine and vitamin E	**patients with nonalcoholic fatty liver disease**	Loguercio et al., 2012[123]
phytosome-loaded chitosan microsphere system for **curcumin** delivery	rats	Zhang et al., 2013[124]
Conventional (First-Generation) and Modified Liposomes		
small unilamellar liposomal vesicles loaded with **silibinin**	carbon tetrachloride-induced hepatotoxicity (BALB/c mice and Wistar rats) and the pyloric ligation method (Wistar rats)	Maheshwari et al., 2003[125]
buccal liposomal delivery system of **silymarin**	ex vivo permeation study using excised chicken cheek pouches	El-Samaligy et al., 2006[20]
hybrid liposomes-encapsulated **silymarin**	carbon tetrachloride-induced oxidative stress in albino rats; hepatoprotective activity	El-Samaligy et al., 2006[126]
propolis liposomes	acetaminophen-induced hepatotoxicity in Wistar rats	Ambardekar et al., 2012[127]
liposome-in-hydrogel complex systems prepared by incorporating **quercetin and rutin**-loaded ceramide liposomes into cellulose hydrogel	ex vivo mouse skin permeation study	Park et al., 2013[128]
Proliposomes		
silymarin proliposomes	beagle dogs	Yan-yu et al., 2006[21]
dehydrosilymarin proliposomes	rabbits	Chu et al., 2011[129]
Micelles and Micelle-Based Hybrid Delivery Systems		
encapsulation of **curcumin** into monomethoxy poly(ethylene glycol)-poly(ε-caprolactone) micelles	transgenic zebrafish model (angiogenesis); murine colon carcinoma cell line (C-26); subcutaneous C-26 colon carcinoma model in BALB/c mice	Gou et al., 2011[130]
curcumin-loaded poly(d,l-lactide-co-glycolide)-b-poly (ethylene glycol)-b-poly(D,L-lactide-co-glycolide) (PLGA-PEG-PLGA) triblock copolymeric micelles	mice	Song et al., 2011[131]
self-assembled polymeric micelles loaded with **curcumin**	murine 4T1 breast tumor model	Liu et al., 2013[132]
monomethoxy poly(ethylene glycol)-poly(ε-caprolactone) micelles loaded with **curcumin**	human umbilical vein endothelial cells (HUVECs); transgenic zebrafish model (angiogenesis); subcutaneous and pulmonary metastatic LL/2 tumor models in C57BL mice	Gong et al., 2013[133]
in situ gel-forming hybrid delivery system composed of **curcumin**-loaded micelles and thermosensitive hydrogel	cutaneous wound repair models (linear incision and full-thickness excision wound models)	Gong et al., 2013[134]
Microemulsions		
microemulsions vs gels for topical application of ***Aloe vera* and *Arnica montana* extracts**	ex vivo permeation study on porcine skin	Bergamante et al., 2007[135]
nobiletin chitosan-based microemulsions	mice	Yao et al., 2008[136]
puerarin submicrometer emulsion	rabbits	Yue et al., 2008[137]
microemulsion for dermal delivery of **quercetin**	excised guinea-pig and Yucatan micropig skin	Kitagawa et al., 2009[138]
puerarin microemulsion	mice	Wu et al., 2009[22]
quercetin-loaded microemulsion	a murine model of airways allergic inflammation	Rogerio et al., 2010[139]
Nanosuspensions		
nanosuspension of ***Cuscuta chinensis* extract** rich in flavonoids and lignans	acetaminophen-induced hepatotoxicity in Wistar rats	Yen et al., 2008[140]
silybin nanosuspensions	beagle dogs	Wang et al., 2012[141]
Self-emulsifying, Self-microemulsifying, and Self-nanoemulsifying Drug Delivery Systems (SEDDS, SMEDDS, and SNEDDS)		
SMEDDS of ***Pueraria lobata* isoflavone extract**	rabbits	Cui et al., 2005[142]
SEDDS of **puerarin**	beagle dogs	Quan et al., 2007[143]
SMEDDS of **silymarin**	Sprague−Dawley rats	Woo et al., 2007[144]
SMEDDS of **daidzein**	Sprague−Dawley rats	Shen et al., 2010[145]
SNEDDS of **persimmon leaf extract**	beagle dogs	Li et al., 2011[146]
SNEDDS loaded with **morin**−phospholipid complex	Wistar rats	Zhang et al., 2011[147]
SMEDDS of **baicalein**	Sprague−Dawley rats	Liu et al., 2012[148]

Table 3. Selected Strategies for Enhancing the Bioavailability of Phenolic Compounds Reported in the Literature: Incorporation in Solid Dispersions; Solid Lipid Nanoparticles and Their Second Generation, i.e. Nanostructured Lipid Carriers; Micronization; Microencapsulation by Poly(lactic-co-glycolic acid) (PLGA) or by Polylactic Acid (PLA); Protein/Polyphenol or Pectin/Protein/Polyphenol Microcapsules; Other Delivery Systems Based on Micro- or Nanoparticles; and Topical/Transdermal Delivery by Means of Gels and Solutions

means of enhancing bioavailability	study model	ref
Incorporation in Solid Dispersions		
solid dispersion capsules of **hesperetin and naringenin**	**healthy volunteers**	Kanaze et al., 2007[149]
solid dispersion of **biochanin A**	Sprague–Dawley rats	Han et al., 2011[150]
		Han and Lee, 2011[151]
Solid Lipid Nanoparticles and Their Second Generation, i.e. Nanostructured Lipid Carriers		
quercetin-loaded solid lipid nanoparticles	Wistar rats	Li et al., 2009[22]
nanostructured lipid carriers for the intravenous delivery of **silybin**	New Zealand rabbits and Kunming mice	Jia et al., 2010[152]
quercetin-loaded nanostructured lipid carriers as a topical delivery system	mice	Chen-yu et al., 2012[153]
tocol nanostructured lipid carriers loaded with **baicalein**	Wistar rats	Tsai et al., 2012[154]
solid lipid nanoparticles and nanostructured lipid carriers loaded with **resveratrol**	in vitro simulation of gastrointestinal transit	Neves et al., 2013[155]
Micronization		
micronized purified flavonoid fraction (Daflon 500 mg), an oral phlebotropic drug consisting of **90% micronized diosmin** and 10% flavonoids expressed as hesperidin	**patients suffering from chronic venous insufficiency, venous ulcers, and hemorrhoids**	Lyseng-Williamson and Perry, 2003[156]
water-dispersible **hesperetin** obtained by micronization	**women volunteers with cold sensitivity;** effect on peripheral vasodilatation	Takumi et al., 2012[157]
Microencapsulation by Poly(lactic-co-glycolic acid) (PLGA) or by Polylactic Acid (PLA)		
microencapsulation of **puerarin** nanoparticles by PLA	chemical analysis	Chen et al., 2009[158]
curcumin-loaded PLGA nanoparticles	Sprague–Dawley rats	Shaikh et al., 2009[25]
subcutaneously injectable sustained release PLGA microparticles loaded with **curcumin**	BALB/c inbred mice; nude (BALB/c nu/nu) mice bearing MDA-MB-231 xenografts	Shahani et al., 2010[159]
PLGA nanoparticles loaded with **curcumin**	Sprague–Dawley rats	Xie et al., 2011[160]
Protein/Polyphenol or Pectin/Protein/Polyphenol Microcapsules		
EGCG/gelatin layer-by-layer assembled films and microcapsules	chemical analysis	Shutava et al., 2009[161]
EGCG-, tannic acid-, curcumin-, or theaflavin-loaded gelatin-based nanoparticles consisting of a soft gel-like interior with or without a surrounding layer-by-layer shell of polyelectrolytes	human breast cancer cell line MBA-MD-231; effect on hepatocyte growth factor-induced intracellular signaling	Shutava et al., 2009[162]
kafirin microparticle encapsulation of **catechin and sorghum condensed tannins**	chemical analysis	Taylor et al., 2009[163]
quercetin-loaded pectin/casein polymer microcapsules	a murine model of acetic acid-induced colitis	Guazelli et al., 2013[164]
Other Delivery Systems Based on Micro- or Nanoparticles		
lactose- or hypromellose-based tabletted microspheres containing fresh **artichoke (*Cynara scolymus*) extract**	chemical analysis	Gavini et al., 2005[165]
daidzein-loaded chitosan microspheres	Wistar rats	Ge et al., 2007[166]
polycaprolactone microspheres loaded with **quercetin**	rabbit synovial cells; Wistar rats	Natarajan et al., 2011[167]
EGCG-loaded Eudragit S100-based enteric microparticles with intestinal mucoadhesive property	isolated small intestine of rats	Onoue et al., 2011[24]
nanoparticle **curcumin** with increased water solubility (colloidal dispersion of curcumin nanoparticles)	Sprague–Dawley rats; **healthy volunteers**	Sasaki et al., 2011[168]
	healthy volunteers	Kanai et al., 2012[169]
	pancreatic or biliary tract cancer patients who failed standard chemotherapy	Kanai et al., 2013[170]
silymarin-loaded porous silica nanoparticles	beagle dogs	Cao et al., 2012[171]
		Cao et al., 2013[172]
quercetin-loaded poly(ethylene glycol) hydroxystearate-based nanosized emulsions	chemical analysis	Dora et al., 2012[173]
curcumin-loaded poly(ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) (PCL-PEG-PCL) triblock copolymeric nanoparticles	Wistar rats	Feng et al., 2012[174]
nanocarriers (transfersomes and ethanol-containing vesicles) for topical administration of **resveratrol**	human immortalized keratinocyte cell line (HaCaT); ex vivo permeation studies on porcine skin	Scognamiglio et al., 2013[175]
Topical/Transdermal Delivery by Means of Gels and Solutions		
EGCG transdermal gel	SKH-1 mice	Lambert et al., 2006[176]
gels vs microemulsions for topical application of ***Aloe vera* and *Arnica montana* extracts**	ex vivo permeation study on porcine skin	Bergamante et al., 2007[135]
solutions and hydrogels for delivery of **resveratrol** via the skin	ex vivo permeation and skin deposition studies with the use of mouse skin	Hung et al., 2008[177]

diosmetin induced CYP1A1 transcription,[78,79] while in rats treated with 80 mg/kg body weight tangeretin a modulation of CYP1A1/2 and (to a lesser extent) CYP2B1/2 transcription was observed.[80] Additionally, polyphenolic compounds interacting with CYP can influence the metabolism of drugs. CYP3A4, a cytochrome occurring mainly in the liver and in the intestine, is responsible for the metabolism of approximately 50% of compounds having therapeutic activities.[51] Studies indicate that flavonoids from grapefruit juice administered in the amount of 200 mL of the juice three times a day for two days inhibit the

Table 4. Selected Clinical Trials Focused on Enhancing Polyphenols Bioavailability[a]

ClinicalTrials.gov identifier enrollment	study title	tested means of enhancing polyphenol bioavailability
NCT00181662 6	Evaluation of Naturally Occurring Inhibitors of UDP-Glucuronyltransferase on the Oral Bioavailability of Curcumin in Normal Healthy Volunteers	addition of piperine or silybinin to curcumin
NCT00113841 42	Pilot Study of Curcumin (Diferuloylmethane Derivative) With or Without Bioperine in Patients With Multiple Myeloma	addition of bioperine to curcumin
NCT01199549 90	Phase 1 Bioavailability Study of Different Dietary Antioxidants in Volunteers	means of enhancing the bioavailability of resveratrol and soy isoflavones is not specified
NCT01331382 23	Effects of Resveratrol Alone or in Combination With Piperine on Cerebral Blood Flow Parameters and Cognitive Performance in Humans	addition of piperine to resveratrol
NCT01288859 10	Physiological Effects of New Polyphenol-enriched Foods in Healthy Humans	nut cream enriched with encapsulated cocoa polyphenols
		encapsulated curcumin-enriched bread
		addition of piperine, quercetin, and genistein to curcumin
NCT01324089 24	A Randomized, Double-Blind Pilot Trial of Resveratrol With or Without Piperine to Enhance Plasma Levels of Resveratrol	addition of piperine to resveratrol
NCT01490008 30	An Open-label, Single-center Trial to Evaluate Systemic Exposure of Catechins From Commercially Available, Topically Applied Veregen 15% Ointment in Patients With External Anogenital Warts and From Oral Intake of Green Tea Beverage in Healthy Volunteers	local application (on the defined anogenital administration area)
NCT01330810 12	Crossover, Multiple Dose Pharmacokinetics of Two Curcumin Formulations in Healthy Volunteers	addition of demethoxycurcumin and bisdemethoxycurcumin to curcumin
NCT01032031 95	The Effect of Dietary Bioactive Compounds on Skin Health in Humans in Vivo	addition of vitamin C to green tea catechins
NCT01564381 30	Effects of Resveratrol Supplements on Vascular Health in Postmenopausal Women	conjugation of resveratrol with arginine
NCT01294072 35	Phase I Clinical Trial Investigating the Ability of Plant Exosomes to Deliver Curcumin to Normal and Malignant Colon Tissue	conjugation of curcumin with plant exosomes
NCT01377961 450	Effect of Lycopene and Isoflavones on Glucose Metabolism	combination of isoflavones and lycopene
NCT01912820 30	A phase I Randomized, Double-Blind, Placebo-Controlled Two-Arm Study of Quercetin and Green Tea to Enhance the Bioavailability of Green Tea Polyphenols in Men Scheduled for Prostatectomy	combination of a green tea extract and quercetin

[a]http://clinicaltrials.gov; website accessed on September 6, 2013.

activity of CYP3A4, which metabolizes statins (e.g., simvastatin and lovastatin).[81] In this way, the flavonoids from grapefruit can lead to an increment in the statin concentration in the plasma.[82]

Polyphenols, to a certain extent, selectively regulate the expression of genes responsible for the metabolism of xenobiotics. For example, chrizin induced UGT1A1 in Caco-2 and HepG2 cells but did not influence UGT1A6, UGT1A9, and UGT2B7 expression. Also, 10 μM apigenin caused a 4-fold increase in the expression of UGT1A1 in Caco-2 cells; however, in combination with sulforaphane, the increase was even up to 12-fold.[83] In the experiments carried out on the same cell lines, genistein induced mRNA and protein expression of SLUT1A1 and SLUT2A1 in a dose-dependent manner. However, in Caco-2 the increase in SLUT2A1 mRNA level was observed already at the concentration of 0.2 μM.[84] Similarly, induction of SLUT1A1, SLUT2A1, and estrogen sulfotransferase SULT1E1 in a dose-dependent manner by biochanin A was observed in the liver and intestine of rats.[85]

Flavonoids can also significantly influence the drug's half-life by modulating the activity of ABC proteins.[86] Certain polyphenols present in grapefruit juice are able to inhibit the activity of P-glycoprotein (e.g., 0.7 μM 6′,7′-epoxybergamottin), which increases the absorption of talinolol (a beta blocker).[87] Furthermore, naringin (one of the components of grapefruit juice) inhibited organic anion-transporting polypeptide B (OATP-B), thus causing a decrease in fexofenadine absorption.[88]

SELECTED STRATEGIES FOR ENHANCING BIOAVAILABILITY OF POLYPHENOLS

In vivo, polyphenols do not reach as high concentrations as used in the majority of in vitro studies; their generally poor bioavailability likely contributes to poor outcomes of clinical trials.[89] A growing number of clinical trials are focused on bioavailability of phenolic compounds, polyphenol-rich extracts, or foods rich in phenolics (Tables 1S−6S in the Supporting Information). The influence of food matrix on the bioavailability of polyphenols has also been investigated in clinical studies (Table 6S in the Supporting Information). After a normal dietary intake, concentrations of particular metabolites of phenolic compounds in blood seldom exceed 1 nM,[14] and after the consumption of 10−100 mg of a single phenolic compound, its maximum concentration in plasma rarely reaches 1 μM.[90] Importantly, polyphenol concentrations in the gastrointestinal tract can reach and exceed 1 mM.[90] It is possible to reach even higher concentrations in colon when the compounds are administered in capsules made of polymers that undergo hydrolysis by bacterial glycosidases.[91] Examples of such polymers include guar gum, chondroitin sulfate, pectin, starch, amylose, dextran, chitosan, and inulin.

The low bioavailability of phenolics warrants a search for techniques for its enhancement. Novel, more bioavailable formulations of polyphenolic compounds and polyphenol-rich extracts are characterized by, among others, higher solubility and stability, more sustained delivery, enhanced pharmacological activities, and superior safety in comparison with conventional formulations; they are also better protected against degradation.[92] Among strategies for enhancing polyphenol bioavailability reported so far in the literature (Tables 1−3), in summaries of clinical trials (Table 4; Table 1S in the Supporting Information), or in patent applications (Tables 7S and 8S in the Supporting Information) are phospholipid−polyphenol complexes; formation of inclusion complexes with cyclodextrins or dendrimers; use of structural analogues; formation of derivatives (e.g., esterification); use of adjuvants (e.g., piperine) as absorption enhancers; transdermal delivery systems; polymeric

implants; nanodisks and nanofibers; and crystal engineering (e.g., cocrystallization).

Injections of small amounts of polyphenol-enriched serum were also proposed as a strategy for enhancement of phenolic compounds bioavailability.[178] However, a phase I clinical trial with quercetin administered by short intravenous infusion (in doses ranging from 60 to 1 700 mg/m^2 of body surface area) revealed nephrotoxicity as a side effect.[179] On the other hand, no clinical adverse effects were observed in a pilot study on prolonged intravenous administration of silibinin (20 mg/kg·day) as an anti-HCV agent.[180] The monotherapy started immediately before liver transplantation and the potent antiviral effect of the phenolic compound lasted as long as its intravenous administration; however, reinfection of the graft occurred after silibinin withdrawal.

Since polyphenols modulate the mechanisms that govern xenobiotic bioavailability, they could be used to design strategies to increase the limited bioavailability and thus bioactivity of some xenobiotics, including phenolic compounds themselves.[181] For instance, coadministration of polyphenol preparations with fruit juices (e.g., grapefruit juice[82,87]) could result in an enhancement of phenolics bioavailability. Interestingly, polyphenol-rich fruit juices were demonstrated not only to modulate the above-mentioned mechanisms but also to enhance the digestive recovery of phenolic compounds in vitro. In a study focused on the influence of common commercial beverage additives (such as citric acid, butylated hydroxytoluene, EDTA, ascorbic acid, milk, and citrus juices) on in vitro digestive recovery of tea catechins, the highest recovery of epigallocatechin (81−98%), epigallocatechin gallate (56−76%), epicatechin (86−95%), and epicatechin gallate (30−55%) was observed in the case of juice preparations (orange, grapefruit, lemon, and lime).[182] A marked increase in total catechin recovery was also observed for teas formulated with 50% bovine, soy, and rice milk.

Subcutaneously Injectable Sustained Release Polymeric Microparticles. The low absorption of polyphenols from the gastrointestinal tract may be overcome by the use of subcutaneously injectable sustained release polymeric microparticles loaded with those compounds.[159] After a subcutaneous injection of a single dose of curcumin-loaded microparticles, sustained levels of this polyphenol were observed in mice blood and other tissues for nearly a month. It is worth emphasizing that curcumin levels in the lungs and brain were 10- to 30-fold higher than in the blood, which implies its accumulation in tissues. In an earlier study by Henning et al.,[63] green and black tea polyphenols were detected in the small and large intestine, liver, and prostate of mice in conjugated and free forms. Interestingly, the relative prostate bioavailability of the black tea theaflavin was 70% higher than that of the green tea EGCG. Similarly, after daily ingestion of three doses of soy milk or soy supplements by healthy women for five days before an esthetic breast reduction, soy isoflavones genistein and daidzein were detected in hydrolyzed breast tissue at concentrations (expressed as aglycone equivalents) ranging from 0.09 to 0.49 nmol/g and from 0.02 to 0.77 nmol/g, respectively.[64] At the same time, the concentrations of genistein and daidzein in hydrolyzed serum ranged from 0.14 to 2.83 μmol/L and from 0.10 to 1.40 μmol/L, respectively.

In contrast to systemic injections of curcumin, the above-mentioned curcumin-loaded subcutaneously injectable microparticles inhibited tumor growth in nude mice bearing MDA-MB-231 xenografts.[159] A pronounced antiangiogenic effect was observed, as evidenced by a decrease in vascular endothelial growth factor expression and poorly developed tumor microvessels. In another study, subcutaneous polymeric implants loaded with a standardized green tea extract (polyphenon E) significantly protected rats exposed to a continuous low-dose of benzo[a]pyrene (administered by a subcutaneous polymeric implant) against the formation of DNA adducts compared with administration of the extract via drinking water.[109] Importantly, the total dose of polyphenon E administered by implants was >100-fold lower than in the drinking water group. Similarly, in the study by Aqil et al.,[110] the total dose of punicalagin administered to rats through subcutaneous polymeric implants was approximately 38-fold lower than in the diet group. However, the level of ellagic acid (punicalagin hydrolysis product) in the implant group was over 2 orders of magnitude higher than in the diet group (589 ± 78 ng/mL vs 4.36 ± 0.83 ng/mL). Consistently, after a subsequent exposure of the rats to a continuous low-dose of benzo[a]pyrene (administered by a subcutaneous polymeric implant), the animals from the punicalagin-loaded implant group had almost 2-fold lower number of DNA adducts than in the diet group. Thus, the effective dose of punicalagin was substantially lower in the implant group than in the diet group, as in the case of polyphenon E in the study by Cao et al.[109]

Nanofibers and Nanodisks. As far as the micro- and nanobased strategies for enhancing polyphenol bioavailability are concerned, it is worth underlining that the limit between micro- and nanosizing is still a matter of debate.[183] Tubes and fibers with only two dimensions below 100 nm are looked upon as nanoparticles,[173] and they have been investigated as delivery systems for phenolics. Merrell et al.[112] reported an increased rate of wound closure in streptozotocin-induced diabetic mice when curcumin-loaded poly(caprolactone) nanofibers were used as a wound dressing. The fibers released curcumin in a sustained manner for 72 h. Importantly, the effective dose of the phenolic compound was not cytotoxic, with more than 70% viability of human foreskin fibroblast cells on the curcumin-loaded nanofibers. This polyphenol delivery system was demonstrated to maintain the viability of the fibroblasts under conditions of oxidative stress as well as to reduce inflammation by inhibiting interleukin-6 release from murine monocyte-macrophages seeded onto the fibers following stimulation by *Escherichia coli*-derived lipopolysaccharide. In another study, incorporation of curcumin into nanodisks also enhanced its biological activity (in vitro apoptosis induction in mantle cell lymphoma cells) compared with free curcumin.[111] The nanodisks comprised a disk-shaped phospholipid bilayer whose edge was stabilized by a scaffold protein, recombinant human apoplipoprotein (apo) A−I.

Microspheres vs Microcapsules. Microspheres[124,165−167] differ from microcapsules[161,164] in that the former are microparticles of spherical shape without membrane or any distinct outer layer, which leads to first-order diffusion phenomena[183] (Table 9S in the Supporting Information). In contrast, diffusion is zero order in the case of microcapsules, which are hollow microparticles composed of a solid shell surrounding a core-forming space available to permanently or temporarily entrapped substances.

Microspheres or microcapsules were tested as controlled release delivery systems for oral delivery of, among others, a polyphenol-rich *Cynara scolymus* (artichoke) extract;[165] daidzein;[166] EGCG;[161] quercetin;[164,167] and curcumin (in the form of phytosomes).[124] In the above-mentioned studies, the microspheres were based on lactose,[165] polycaprolactone,[167] or chitosan,[124,166] while microcapsules were based on gelatin[161]

Table 5. Complexation of Polyphenols with Phospholipids Has Been Used To Enhance Their Bioavailability, As Exemplified by Indena's Products Obtained with the Use of the Phytosome Technology[a]

plant's latin name; common name; and part of plant used	phenolics content; commercial name of standardized polyphenol-rich extracts combined with phospholipids
Aesculus hippocastanum L.; horse chestnut; bark	≥31.0% ≤ 37.0% of proanthocyanidin A2 by HPLC; proanthocyanidin A2 phytosome
Camellia sinensis (L.) Kuntze; green tea; young leaf	≥19.0% ≤ 25.0% of polyphenols expressed as (−)-epigallocatechin-3-O-gallate, ≥ 13.0% of (−)-epigallocatechin-3-O-gallate by HPLC; ≤0.1% of caffeine by HPLC; greenselect phytosome, green tea
Curcuma longa L.; tumeric; rhizome	≥18.0% ≤ 22.0% of curcuminoids by HPLC; meriva, turmeric phytosome
Crataegus spp.; hawthorn; flowering top	≥3.0% of vitexin-2″-O-rhamnoside by HPLC, ≥28% ≤ 34% of hawthorn typical constituents; hawthorn phytosome
Ginkgo biloba L.; ginkgo (or gingko); leaf	≥10.0% of total biflavones expressed as ginkgetin by HPLC; ginkgo biloba dimeric flavonoids phytosome
	≥7.0% of ginkgoflavonglucosides, ≥2.0% of ginkgoterpenes, ≥ 0.8% of bilobalide, ≥0.8% of ginkgolides by HPLC; ≤5 ppm of total ginkgolic acids by HPLC; ginkgoselect phytosome, ginkgo biloba
	≥5.0% of ginkgoflavonglucosides, ≥0.5% of ginkgoterpenes, ≥12.0% of phosphatidylserine by HPLC; virtiva, ginkgo biloba phosphatidylserine phytosome
Polygonum cuspidatum Sieb. and Zucc.; Japanese knotweed; rhizome	≥30% of resveratrol by HPLC; rexatrol, resveratrol phytosome
Silybum marianum (L.) Gaertn.; milk thistle; fruit	≥29.7% ≤ 36.3% of silybin by HPLC; siliphos, silybin phytosome
	≥15.0% ≤ 20.0% of silybin like substances calculated as silybin by HPLC; silymarin phytosome
Vitis vinifera L.; common grapevine, seed	≥25% ≤ 30% of proanthocyanidins by GPC; leucoselect phytosome, grape seed

[a]http://www.indena.com/index.php/phytosome.html; website accessed on September 5, 2013.

or pectin/casein polymer.[164] The release of polyphenols from the microspheres lasted from approximately 24 h (in vitro)[165] to more than 30 days (in vitro and in vivo, after intra-articular injection to rats)[167] or almost 35 days (in vitro and in vivo, after intramuscular injection to rats).[166] Bioavailability of polyphenols administered in the microspheres increased significantly, for instance, up to 39% for daidzein in rats after intramuscular injection.[166] Curcumin absorption after oral administration to rats through a hybrid system (curcumin phytosome-loaded chitosan microspheres) increased 1.67- and 1.07-fold compared with curcumin phytosomes and curcumin-loaded chitosan microspheres, respectively.[124] The half-life of curcumin administered through the hybrid system (3.16 h) was longer than for curcumin phytosomes (1.73 h) and curcumin-loaded chitosan microspheres (2.34 h). In acetic acid-induced colitis in mice, oral administration of quercetin-loaded microcapsules exhibited more pronounced anti-inflammatory and antioxidant effects than nonencapsulated quercetin.[164]

Solid Dispersions. Solid dispersions are multiphasic mixtures with at least one polymer component dominating.[183] A solid dispersion of biochanin A prepared with Solutol HS15 and hydroxypropylmethylcellulose enhanced its solubility (up to 60-fold) and bioavailability in rats.[150] The authors suggested that the increase in the flavonoid solubility may result not only from the solubilizing effect of hydrophilic carriers but also from biochanin A transition from crystalline to amorphous state.[150] Consistently, after oral administration of the flavonoid to rats in the form of a solid dispersion, there was approximately 13- and 5-fold increase in peak plasma concentration and area under the curve (the integral of the concentration−time curve), respectively. Moreover, both in vitro and in vivo effectiveness of biochanin A as a P-glycoprotein inhibitor was also improved by formulation into a solid dispersion.[151]

Co-administration with Absorption Enhancers. Piperine, an alkaloid isolated from fruit of *Piper nigrum* L. (black pepper) or *Piper longum* L. (long pepper) and a known inhibitor of hepatic and intestinal glucuronidation,[26] was reported to inhibit CYP3A4[184,185] and P-glycoprotein.[184] Several clinical trials have focused on the influence of piperine on the bioavailability of curcumin (ClinicalTrials.gov identifiers: NCT00181662; NCT00113841; NCT01288859) and resveratrol (NCT01331382; NCT01324089) (Table 4; Table 1S in the Supporting Information). When piperine was coadministered with curcumin, the bioavailability of this phenolic compound was increased by 154% in rats and by 2000% in humans.[26] The alkaloid was also reported to enhance the bioavailability of EGCG after intragastric coadministration of 164 μmol/kg EGCG and 70 μmol/kg piperine to CF-1 mice.[102] A 1.3-fold increase in peak plasma concentration and area under the curve was observed compared with mice treated with EGCG only, and the appearance of the flavanol in the colon and the feces of piperine-cotreated mice was slower than in mice treated with EGCG alone. At the concentration of 100 μM, piperine inhibited EGCG glucuronidation in mouse small intestine (by 40%) but not in hepatic microsomes.

Phospholipid−Polyphenol Complexes. Some methods of increasing polyphenol bioavailability have already been applied in dietary supplements present on the market. For instance, the Indena company offers products obtained with the use of the phytosome technology (Table 5) that takes advantage of the affinity of phenolics to phospholipids. This affinity results in the formation of supramolecular adducts having a definite stoichiometry and characterized by a higher rate and extent of solubilization into aqueous intestinal fluids, as well as by an enhanced capacity to cross biomembranes.[89,186] A substantial improvement in bioavailability (and thus in clinical applicability) resulting from the use of phytosomes as molecular delivery vehicles was demonstrated for, among others, green tea flavan-3-ols, grape seed proanthocyanidins, curcumin, and its related diphenolic curcuminoids from turmeric,[89] as well as for silybin and other silymarin flavonolignans from milk thistle.[89,186] Phospholipid−polyphenol complexes have already been tested in preclinical studies and clinical trials focused on, among others, prostate cancer and nonalcoholic fatty liver disease (silybin/silibinin phytosome); benign prostatic hyperplasia, diabetic microangiopathy, retinopathy, osteoarthritis, and acute pain in patients with various chronic diseases (curcumin phytosome); and obesity (green tea extract phytosome) (Table 4; Table 1S in the Supporting Information).

When in complexes with phospholipids, nonphenolic compounds were also demonstrated to be more bioavailable than their free forms. Such results were obtained for, among others, anti-inflammatory boswellic acids from *Boswellia serrata* gum resin extract[187,188] and for ginkgolides A and B and

bilobalide from *Ginkgo biloba*.[189,190] However, according to a recent paper by Liu et al.,[191] a superior absorption of steroidal saponins from *Rhizoma paridis* (the roots and rhizomes of *Paris polyphylla* var. *yunnanensis*) occurred for a solid dispersion compared with phytosomes. Recently, Zhang et al.[124] developed curcumin phytosome-loaded chitosan microspheres, thus combining polymer- and lipid-based delivery systems. Such hybrid systems appear to be a promising solution to the bioavailability problem of poorly soluble drugs (including polyphenols), as both oral absorption and retention time of curcumin were improved in the above-mentioned drug delivery system compared with its single components (i.e., phytosomes and chitosan microspheres).

Selected Strategies for Enhancing Resveratrol Bioavailability. The RevGenetics company (http://www.revgenetics.com/store/c-4-micronized-resveratrol.aspx; Web site accessed on September 5, 2013) uses two main approaches to enhance the bioavailability of resveratrol. One of them is capsules with a liquid fill protected from oxidation with the use of gaseous nitrogen (Licaps technology, "nitrogen bubble");[192] another is micronization of resveratrol. A preparation of resveratrol elaborated by RevGenetics is being tested in a clinical trial focused on the effect of this polyphenol in older adults with impaired glucose tolerance (ClinicalTrials.gov identifier: NCT01375959; the trial is currently recruiting participants). Micronization was reported to increase bioavailability of, for instance, hesperetin.[157] A single dose of this micronized flavonoid exhibited a peripheral vasodilatation effect in a study involving women with cold sensitivity. Many symptoms of chronic venous insufficiency, venous ulcers, and acute or chronic internal hemorrhoids were reported to be improved by Daflon, an oral phlebotropic drug consisting mainly of micronized diosmin (90%; other flavonoids expressed as hesperidin constitute 10% of the drug).[156] Importantly, in clinical trials Daflon had a tolerability profile similar to that of placebo.

In the case of resveratrol, one of strategies of increasing its bioavailability is to administer a natural glucosidic derivative of this stilbene (i.e., resveratrol 3-beta-mono-D-glucoside, known as piceid or polydatin) instead of the aglycone. In vivo studies in humans confirmed that most of the oral dose of resveratrol was recovered in urine, mainly in the form of sulfate and glucuronic acid conjugates.[193] Therefore, hydrolysis of the glucosidic derivative in small intestine and liver would enhance the amount of the biologically active trans-resveratrol.[194]

Use of Structural Analogues. As far as structural analogues and derivatives are concerned, the latter retain the essential characteristics of the parent compound (including its basic chemical structure) and can be obtained from the parent compound, while the former have a close structural relationship to the parent compound but are not considered as derivatives. Replacement of certain functional groups or atoms in the ring by others, as well as hydrogenation/dehydrogenation lead to the formation of an analogue of the parent compound. For instance, a synthetic structural analogue of curcumin (designated EF-24) was reported to be rapidly absorbed in CD2F1 mice, with the bioavailability of oral and intraperitoneal EF-24 estimated as 60% and 35%, respectively.[97] The maximum tolerable dose of the analogue following intravenous administration to mice was 32 mg/kg. Intraperitoneal injection of such a dose resulted in EF-24 concentration in plasma close to 1 μM. In BALB/c mice, the plasma molar concentrations of cyclohexyl-containing synthetic analogues of bisdemethoxycurcumin (BDC) were compared to those of the parent compound (BDC) after oral or intraperitoneal administration, and for cyclohexyl-valine-BDC, they were 55- and 73-fold higher, respectively, than for BDC.[98] Bioavailability-focused studies are underway on structural analogues of other phenolic compounds.[195]

Formation of Derivatives. Taking into account that elimination of residual acyl groups is expected to take place in vivo, Biasutto et al.[100] suggested that administration of ester derivatives of polyphenols may result in higher systemic levels of those compounds in their free forms compared with administration of free phenolics which undergo phase II conjugation reactions and subsequent elimination from the organism. For instance, some of ester-based precursors of quercetin were able to cross supported tight monolayers of Madin−Darby canine kidney (MDCK) cells or some clones of human colon cancer Caco-2 cell line.[100] They underwent partial deacylation but no phase II conjugation was observed during their transport in these models of transepithelial absorption. However, in other Caco-2 clones complete deacylation of the derivatives occurred and was followed by quercetin metabolism.

Lambert et al.[99] prepared a peracetylated derivative of EGCG, which not only increased in vitro biological activities of the flavanol (growth inhibitory activity toward human esophageal cancer KYSE150 cells and human colon cancer HCT116 cells; inhibition of nitric oxide production and arachidonic acid release from lipopolysaccharide-stimulated RAW264.7 murine macrophages) but also enhanced its bioavailability in vivo. In the in vitro studies, this precursor was rapidly converted to EGCG by HCT116 cells, and its administration led to 2.8- to 30-fold higher intracellular concentration of EGCG compared with treatment with nonacetylated flavanol at different time points (1, 2, 5, and 24 h). EGCG was detected within 5 min during in vitro incubation of the derivative with mouse plasma or mouse microsomes at 37 °C. In the in vivo studies on CF-1 mice, EGCG was more bioavailable when administered intragastrically in its acetylated form or if nonacetylated form was administered after the acetylated precursor.

A study with the use of human liver S9 fraction with cofactors demonstrated that methyl capping of all free hydroxyl groups of flavones dramatically increased their hepatic metabolic stability due to a metabolic shift to less efficient CYP-mediated oxidation.[101] The intestinal transport of flavones in Caco-2 transwell cultures was also enhanced as a result of methylation. One methylated flavones was administered orally to rats and proved to be highly bioavailable, while its unmethylated analogue was undetectable in tissues. Similarly, Henning et al.[196] observed that methylation of epigallocatechin increased its stability at neutral pH.

Complexation with Cyclodextrins. Another means of increasing water solubility of polyphenols is the formation of inclusion complexes with cyclodextrins. Borghetti et al.[94] developed a ternary system aimed at enhancing the solubilizing effect of cyclic oligosaccharides toward phenolic compounds and demonstrated its effectiveness using daidzein (a soy isoflavone). When cyclodextrins were used alone at the concentration of 6 mM, the highest solubilizing effect (a 9.4-fold increase in daidzein solubility in water) was observed for hydroxypropyl-β-cyclodextrin. Association of daidzein/cyclodextrin complexes to hydrophilic polymers (1%, w/w) resulted in a further increase in the isoflavone solubility, with the best result (a 12.7-fold increase) obtained for daidzein/hydroxypropyl-β-cyclodextrin/polyvinylpyrrolidone ternary system.

Crystal Engineering. A relatively new approach to improving bioavailability of active pharmaceutical ingredients is

cocrystallization.[197] Cocrystals are characterized by higher in vitro dissolution rate and in vivo bioavailability than other solid forms of drugs, as reported by Smith et al. for quercetin[29] and EGCG.[100] Insolubility of quercetin in water was overcome (to various extents) by all four tested cocrystals, namely, quercetin/caffeine, quercetin/caffeine/methanol, quercetin/isonicotinamide, and quercetin/theobromine dehydrate.[29] The most pronounced solubilizing effect was observed for quercetin/caffeine and quercetin/caffeine/methanol cocrystals, with a 14- and 8-fold increase, respectively, compared with quercetin dihydrate. Consistently, the cocrystals were up to 10-fold more bioavailable than quercetin dihydrate after oral administration to Sprague−Dawley rats. In a later study by Smith et al.,[114] after administration of four new cocrystals of EGCG to rats in the dose of 100 mg of EGCG per kg of body weight, a moderate improvement in relative bioavailability was observed for two of the cocrystals. The pharmacokinetic profile of the flavanol was markedly modulated as a result of cocrystallization. Furthermore, oral administration of nanocrystals of baicalein (a flavone isolated from the root of *Scutellaria baicalensis* Georgi) resulted in a 1.67-fold increase in its relative bioavailability in Sprague−Dawley rats compared with crystals.[113] Pulmonary administration of the nanocrystals resulted in rapid and extensive absorption and almost identical pharmacokinetic parameters as after intravenous injection of baicalein.

Examples of Achieved Concentration Levels. The in vitro concentrations of phenolic compounds mentioned in the section regarding the influence of polyphenols on expression and activity of enzymes participating in xenobiotic metabolism (e.g., 10 μM apigenin,[83] 5 μM galangin,[78] and 5 μM diosmetin[79]) are not likely to be achieved by normal diet.[14,90] Some of the enhanced delivery systems discussed in the present work render it possible to achieve plasma polyphenol concentrations exceeding 1 μM. For instance, coadministration of 2 g/kg of curcumin and 20 mg/kg of piperine (an inhibitor of hepatic and intestinal glucuronidation) to Wistar rats resulted in a short (1−2 h after ingestion) increase in the serum concentration of the phenolic compound (1.80 μg/mL = 4.9 μM) when compared with curcumin alone at the same dose (1.35 μg/mL = 3.7 μM).[26] Interestingly, the enhancing effect of piperine was much stronger in humans than in rats. When curcumin alone was administered to healthy human volunteers in the dose of 2 g, the polyphenol was either undetectable in serum or its concentrations were very low (0.006 μg/mL = 0.02 μM). However, coadministration of 2 g of curcumin and 20 mg of piperine resulted in much higher concentrations of the former (0.18 μg/mL = 0.49 μM) from 0.25 to 1 h after ingestion.

In Sprague−Dawley rats the efficacy of punicalagin (a hydrolyzable tannin)-loaded subcutaneous polymeric implants (two implants per animal; 40 mg of the tannin per implant) proved to be superior to a punicalagin-enriched diet (approximately 19 mg of the tannin/day·animal).[110] Although the polyphenol was undetectable in plasma, the product of its hydrolysis (ellagic acid) was readily detected. Importantly, ellagic acid plasma concentration was over 2 orders of magnitude higher in the implant group than in the diet group (589 $\pm$ 78 ng/mL = 1.9 μM vs 4.36 $\pm$ 0.83 ng/mL = 0.01 μM, respectively).

Smith et al.[29] reported that administration of cocrystals of quercetin and caffeine (1), or theobromine dihydrate (2), or isonicotinamide (3), or caffeine/methanol (4) to Sprague−Dawley rats resulted in higher plasma concentration of the flavonol when compared with a dihydrate crystal of quercetin (5), namely, 2.2 μM (1), 2.8 μM (2), 4.6 μM (3), and 8.6 μM (4) vs 0.9 μM (5).

Hormetic Effect. It is worth mentioning that increased concentrations of phenolic compounds in blood (resulting from the artificial enhancement of their bioavailability, as exemplified above) are not always equivalent with more pronounced health effects. One should take into account the occurrence of a hormetic effect which is characterized as opposite biological effects at low and high concentrations of a tested agent.[198] In other words, hormesis is defined as a biphasic response to a tested agent (e.g., cell growth stimulation at low concentrations and inhibition at high concentrations).[198,199] The hormetic effect is looked upon as an adaptive response of cells or organisms to a slight (usually transitory) stress such as, for instance, physical exercises, calorie-restricted diet, or exposition to low concentrations of some natural or synthetic compounds, including phenolics. Interestingly, hormetic effects were reported for polyphenols, for instance for quercetin,[200] garcinol,[201] and xanthohumol.[202] Therefore, some of the chemopreventive effects of polyphenol-rich diets observed in epidemiological and preclinical studies as well as in clinical trials[203−206] may result from hormesis, that is, an adaptive response of an organism to a slight stress associated with relatively low systemic levels of poorly bioavailable phenolics. For this reason, more human dose−response studies regarding phenolic compounds and polyphenol-rich extracts are needed in order to detect the hormetic effect, if present, and to assess its implication in terms of chemoprevention.

In conclusion, although the number of reports on the health beneficial effects of polyphenols is increasing rapidly and the evidence confirming their antioxidant activities is abundant, the knowledge on their metabolism and bioavailability in humans is still incomplete. It is worth emphasizing that metabolic transformations frequently change biological activities of polyphenols, which may be a reason for ambiguous or even contradictory results of studies regarding the influence of phenolic compounds on human organism. Such inconsistency in results across studies may also be caused by considerable differences in polyphenol content in food products as well as by a very large diversity in terms of structure and molecular weight among phenolics. Therefore, there is a need for determination of bioindicators for metabolism of particular polyphenols and standardization of bioassays is essential. A number of solutions to the problem of poor bioavailability of phenolic compounds have already been proposed; the present work includes a brief overview thereof. Importantly, some of the designed polyphenol delivery systems (e.g., phytosomes) seem to be very promising, as evidenced in preclinical studies and clinical trials.

Not all of the enhanced delivery systems discussed in the present work are designed for dietary applications. Some of them are aimed at topical (including ocular), subcutaneous, or intravenous administration. Among the means of enhancing delivery of nutraceuticals (including polyphenols) one could list phytosomes, liposomes, cyclodextrins, derivatives, adjuvants, solid dispersions, nanoemulsions, micronization, and microencapsulation, among others.[23,207,208] Oral safety studies have been performed on dendrimers,[209] and they could be used for dietary applications in future. In general, toxicity problems arise particularly in the case of nonbiodegradable particles that accumulate in tissues.[210] Efficacy and safety of any enhanced delivery system that has not yet been in use has to be assessed by the relevant regulatory authorities before it can be adopted for disease prevention or therapy in humans.

■ ASSOCIATED CONTENT

Supporting Information

Additional tables of selected clinical trials. This material is available free of charge via the Internet at http://pubs.acs.org.

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Funding

The study was supported by Grant NN 312-446-840 from the Polish Ministry of Science and Higher Education.

Notes

The authors declare no competing financial interest.

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