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Diet-Derived Phenols in Plasma and Tissues and their Implications for Health

Abstract

This paper seeks to catalyse a reappraisal of the nature, fate and biological significance in humans of phenols, polyphenols and tannins (PPT) consumed in normal diets, and in particular questions the primacy of PPT radical-scavenging mechanisms for the supposed health benefits of diets rich in fruits and vegetables. PPT are classified by structure and function. Arguments are presented to show that cinnamates and derived polyphenols make significantly larger contributions to the total PPT intake than the flavonols and flavones upon which the vast majority of attention has been focussed previously. Daily intakes of total PPT may range from less than 100 mg to in excess of 2 g, and the critical importance of coffee and black tea as the major dietary sources is shown. Only some 5% of the dietary PPT is absorbed in the duodenum, and of this only some 5%, mainly flavanols, reaches the plasma unchanged, the balance being mammalian conjugates. Over 95% of the intake passes to the colon and is fermented by the gut microflora. A fraction of the resulting microbial metabolites is absorbed and appears in the plasma primarily as mammalian conjugates. Even following high intakes of PPT, the plasma metabolites collectively make a very small (less than 5%) and transient contribution to the total concentration of redox active substances in plasma. This explains the failure of most studies that sought to detect an increase in plasma antioxidant power after consuming a PPT-rich meal or supplement. The powerfully antioxidant PPT aglycones, much used in *in vitro* studies, do not reach the plasma. The redox potential of those unchanged PPT and PPT metabolites that reach the plasma enables them to scavenge damaging radicals, but the endogenous plasma antioxidants, especially ascorbate, are required for disposal of the resultant phenoxyl radicals. Black tea and coffee, the major sources of PPT, are poor sources of ascorbate. It is suggested that if diets rich in fruits and vegetables are health-promoting, and if these effects are due to PPT, then alternatives to radical-scavenging mechanisms must be sought. Evidence is presented to show that some mammalian metabolites of PPT may indeed be able to protect the vascular endothelium and that diets rich in PPT may in humans at normal dietary levels have the ability to protect against Type II diabetes and the metabolic syndrome through effects on glucose absorption and associated hormones. Such effects are recommended for further investigation.

Key words

Absorption · antioxidants · black tea · chlorogenic acids · cinnamates · coffee · derived polyphenols · diabetes · flavonoids · fruit · GIP · GLP1 · gut microflora · hydroxycinnamates · insulin · metabolism · phenols · polyphenols · tannins · review · vegetables

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Introduction

Simple phenols, polyphenols and tannins (PPT) have been of great interest for many years, in part because of their impact on the colour, odour and flavour of foods and beverages [1], but more recently because of the possibility that these substances may have health-protecting properties [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13]. PPT may be classified in several ways, for example, by biosynthetic origin, occurrence, function or effect, or structure [1], [12], [14]. A classification based on structure and function will be used in this paper [15]. Simple phenols are substances containing only one aromatic ring and bearing at least one phenolic hydroxy group and possibly other substituents, whereas polyphenols contain more than one such aromatic ring. Phenols and polyphenols may occur as unconjugated aglycones or as conjugates, frequently with sugars, organic acids, amino acids, lipids, etc. [16].

The Diversity of Dietary Phenols, Polyphenols and Tannins

The commonest simple phenols are cinnamates that have a C_6-C_3 structure [17], [18] accompanied by C_6-C_2 and C_6-C_1 compounds, and a few unsubstituted phenols [19], [20], [21]. In general these occur as conjugates. Flavonoids are the most extensively studied polyphenols, all characterised by a C_6-C_3-C_6 structure, subdivided by the nature of the C_3 element into anthocyanins, chalcones, dihydrochalcones, flavanols, flavanones, flavones, flavonols, isoflavones and proanthocyanidins. The flavanols and proanthocyanidins generally occur unconjugated but the others normally occur as glycosides. Since the seminal paper of Hertog et al. [22] there has been a tendency to think of dietary PPT as encompassing only the flavonoids, and the flavonoids *per se* to consist only of the three flavonols and two flavones that featured in that study, but this is misleading and was never intended. It is not possible to say with precision just how many individual PPT occur regularly in human diets, but on present evidence a figure in excess of 200 seems reasonable [16].

The term "tannin" refers historically to crude plant preparations that are capable of converting hides to leather [23] and such preparations are not consumed as human food. However, the functional polyphenols contained therein at high concentrations may also occur in certain foods and beverages but at comparatively low concentrations that would render them totally ineffective for producing leather. These polyphenols may be subdivided into the flavonoid-derived proanthocyanidins (condensed tannins) [24] and the gallic acid-derived and ellagic acid-derived hydrolysable tannins, this latter subgroup being of more restricted occurrence in human food (but commoner in some animal feeds) [25]. The phloroglucinol-derived phlorotannins, while never used for preparing leather, also have a limited occurrence in human food [19]. The more recent term "phytoestrogen" refers to substances with oestrogenic and/or anti-androgenic activity at least *in vitro*, and encompasses some isoflavones, some stilbenes, some lignans and some coumarins [26]. The lignans are not oestrogen-active until transformed by the gut microflora [26], [27]. "Antioxidants" is a third function-based term much used to describe PPT, but individual compounds differ markedly in their ability to scavenge reactive oxygen species and reactive nitrogen species, and inhibit oxidative enzymes. Mammalian metabolites of PPT do not necessarily retain fully the antioxidant ability of the PPT found in plants and especially not that of their aglycones as commonly tested *in vitro* [28], [29].

The PPT discussed above are substances found in healthy and intact plant tissues, and in the main are of known structure. However, many traditional foods and beverages as consumed have been produced by more or less extensive processing of such plant tissues, resulting in biochemical or chemical transformations of the naturally-occurring PPT. In some cases, black tea, matured red wines, and coffee beverage, for example, these transformations may be substantial, generating large quantities of substances not found in the original plant material. Despite significant advances in the last decade [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], the structures of the majority of these novel compounds have yet to be elucidated. Although often described as tannins, these substances are not functional tanning agents, and should be referred to collectively as derived polyphenols until such time as their full structural characterisation permits a more precise nomenclature.

The Consumption of PPT

There have been several attempts to estimate the quantities of PPT consumed, either by using diet diaries or food frequency questionnaires and data on the typical composition of individual commodities [3], [8], [42], [43], [44], [45], [46], [47], [48], [49], [50], or by diet analysis [6], 22], [51]. In comparison with the comprehensive databases providing the content in the diet of the established micro- and macro-nutrients, data for the contents of PPT are much more limited. Those data available for PPT content have been obtained by many different methods of analysis, rarely take account of the effects of agricultural practice, season, cooking or commercial processing, are not necessarily just for the edible portion, and may be for varieties of fruit and vegetable different from those consumed in a particular diet under investigation [45], [46], [52].

These are potentially serious limitations since quantitatively cultivars may differ substantially in composition, and the non-edible parts of fruits and vegetables may differ greatly both quantitatively and qualitatively, compared with the flesh or juice [53]. In addition, domestic cooking and commercial processing may in some cases cause extensive leaching and destruction [54], [55], [56], [57], [58], [59], [60].

Data based upon analysis of particular diets avoid these limitations but are usually restricted to a few PPT because of the difficulties and cost associated with quantifying so many individual compounds of known structure, to say nothing of the serious difficulties associated with quantifying the uncharacterised derived polyphenols [61]. When such data are available, they are usually for PPT as aglycones released by hydrolysis (to simplify the analysis still further) and generally for the flavonols and flavones first studied by Hertog et al. [22] since these are amongst the easiest to determine [44], [47], [48], [51], [52], [62], [63], [64], [65], [66], [67], [68]. There are more limited data for flavanones [44], [64] and isoflavones after hydrolysis

[44], [52], and flavanols, and proanthocyanidins [6], [69] (which occur as aglycones).

In an attempt at modest cost to shed more light on the nature and quantity of PPT consumed by various populations we developed a computerised spreadsheet database beginning with the several hundred papers identified in the NEODIET reviews [16] with continued updating as more information has been published or found [17], [52], [70], [71], [72], [73], [74], [75]. The database covers 80 commodities, including five alcoholic beverages, six fruit juices and three other non-alcoholic beverages, and 14 PPT subgroups including derived polyphenols, with every entry labelled to show the paper(s) from which the information was taken. Data sources have been restricted to papers using specific methods of analysis: data for "total phenols by Folin-Ciocalteu" or "total antioxidant power as gallic acid equivalents" and similar, have been excluded. In order to reflect the variability in composition, data have always been entered as "high" and "low" values (mean ± 2σ wherever possible) and an overall mean for each commodity used in determining the amounts of PPT consumed.

While recognising the limitations (discussed above) of such an approach to estimating diet composition and the intake of PPT, using this database in conjunction with diet diaries available from our other studies [76], [77], [78] has produced interesting data (Table **1**) and insights.

From Table **1** it is clear that PPT intakes may vary substantially, and that the flavones and flavonols, upon which most emphasis has so far been placed [22], [44], [47], [48], [51], [52], [62], [63], [64], [65], [66], [67], [68], form a comparatively small part of the total intake for the populations studied. The relatively low consumption of chalcones and dihydrochalcones, isoflavones, anthocyanins, and stilbenes reflects the comparatively low consumption of apples and ciders, soya products, dark berries and red wines by these populations. The significant contributions made by the hydroxycinnamates (in these populations primarily reflecting coffee consumption [17], [18]) and derived polyphenols (in these populations primarily reflecting black tea consumption [79], [80], [81]) are striking. In this context "black tea" refers to the beverage prepared from the fermented leaf (as distinct from green tea) and not to the addition or otherwise of milk to the beverage prior to consumption. This domination by PPT from black tea and coffee indicates the importance also of considering the hydroxycinnamates and derived polyphenols whenever assessing the dietary significance of PPT, and clearly shows the limitations of looking only at flavonols and flavones after hydrolysis no matter how precise *per se* the data for these aglycones might be.

It is important to stress that data for the composition of black tea and coffee beverage reflect exactly what is consumed (with the exception of the dregs left in the cup) since all transformations associated with processing and domestic preparation have already taken place. Moreover, the NEODIET database is replete with analytical data from numerous sources for the composition of these beverages (thus better avoiding extreme values associated with any peculiarity of the material analysed or method of analysis) compared with data for many fruits and vegetables. Accordingly, the estimated consumption figures obtained using this database are likely to be more accurate than would have been the case if solid foods were the major sources of PPT, and data were for raw rather than after cooking/processing. This ar-

Table **1** Mean dietary intakes of 14 classes of PPT as determined from diet-diaries and a food composition data base

PPT	*103 UK females aged 20–30 years*[a]		*50 UK males aged 27–57 years*[b]	
	Estimated as conjugates	*Estimated as aglycones*[c]	*Estimated as conjugates*	*Estimated as aglycones*[c]
Total, range	100–2300		30–2200	
Total, mean	780	451	1058	598
Hydroxybenzoates	15		23	
Hydroxycinnamates	353	176	670	335
Total flavonoids	210	105	205	103
Anthocyanins	5		9	
Chalcones and dihydrochalcones	0.7			
Flavanols	64		58	
Flavanones	22		89	
Flavones	72		17	
Flavonols	35		26	
Isoflavones	9		0.13	
Proanthocyanidins	7		6	
Ellagitannins	23			
Derived polyphenols	170	170	160	160
Stilbenes	9			
Lignans	0.04			

[a] Ref. [49].

[b] Ref. [50].

[c] Aglycones are estimated approximately by taking rutin as a representative flavonoid and 5-caffeoylquinic acid as a representative hydroxycinnamate and adjusting for the relevant molecular masses.

gument applies also to the data for PPT delivered by wines and juices. Using this approach has led us to estimate typical mean intakes of PPT for the two populations so far studied to be in the range 450 to 600 mg as aglycones.

Absorption and Metabolism of PPT

Extensive studies in humans and animals have indicated that some PPT can be absorbed in the small intestine, for example, certain cinnamate conjugates [82], [83], flavanols [84] (that occur naturally as aglycones), and certain flavonoid glucosides [85], [86] (but not the corresponding flavonoid rutinosides [87]). The mechanisms of absorption have not been completely elucidated but involve *inter alia* interaction of certain glucosides with the active sugar transporter (SGlT1) and lumenal lactase-phloridzin hydrolase, passive diffusion of the more hydrophobic aglycones, and interaction with cytosolic β-glucosidase. Although varying with PPT subclass and matrix, when expressed relative to the total intake of PPT, only some 5 to 10% of the amount consumed is absorbed at this site. The major part of that absorbed (90 to 95% for every substance so far studied) enters the circulation as mammalian conjugates produced by a combination of methylation, sulphate conjugation, glucuronide conjugation and, in the case of some phenolic acids, also by glycine conjugation [29]. Only a very small amount of the total PPT consumed, maximally 5 to 10%, enters the plasma unchanged.

The 90 to 95% of the total PPT ingested, plus any mammalian glucuronides excreted through the bile, pass to the colon where they are metabolised by the gut microflora. Transformations may be extensive, and include the removal of sugars, removal of phenolic hydroxyl groups, fission of aromatic rings, and metabolism to carbon dioxide, possibly via oxaloacetate [88]. A substantial range of microbial metabolites has been identified, including phenols and aromatic/phenolic acids/lactones possessing 0, 1 or 2 phenolic hydroxyl groups and up to five carbons in the side chain [89], [90], [91], [92], [93], [94], [95], [96], [97], [98], [99], [100], [101], [102], [103], [104], [105], [106], [107], [108], [109], [110], [111]. *Eubacterium* is of particular interest since this species not only metabolises dietary (poly)phenols [99], [100], [105], [106], [112], [113], [114], [115], [116], but also produces butyrate [117], a preferred energy source for colonic epithelial cells thought to play an important role in maintaining colon health in humans. The yield of phenolic/aromatic acids is variable (up to × 10) between individuals, but can be substantial (up to 50%) relative to the intake of PPT substrates [95], [103], [104], [108], [109], [110].

There is evidence from cell culture studies that some of the aromatic/phenolic acids, e.g., benzoic, salicylic, *p*-coumaric and ferulic acids, are transported actively by the monocarboxylate transporter MCT1 [118], [119], [120], [121], [122]. A comparatively small percentage of these microbial metabolites may eventually appear unchanged in plasma or urine but the majority is subject to mammalian conjugation as described for intact PPT.

Table **2** summarises in a semi-quantitative manner so far as current knowledge allows the fate of a "typical" daily consumption of some 450 to 600 mg of PPT (as aglycones) previously defined in Table **1**.

Plasma Pseudo-Pharmacokinetics

Since for the majority of dietary PPT, neither the conjugates consumed, nor their free aglycones, are detectable in plasma, it is rarely possible to perform true pharmacokinetic analyses. Most so-called pharmacokinetic data that have been published relate to the concentrations of aglycones released after hydrolysis of mammalian conjugates in plasma or urine with commercial β-glucuronidase and/or sulphatase, and the data so obtained are better referred to as pseudo-pharmacokinetics. Published data are summarised in Table **3**. Although the maximum concentration achieved transiently varies to some extent with PPT subclass and matrix in which consumed, it is unlikely that plasma metabolite concentrations will routinely exceed 10 μM in total, and approximately 1 μM for total aglycones. The reported T_{max} values range from 1 to 2.5 hours for substances absorbed in the duodenum [85], [86], [87], [123], [124], [125], [126], [127], [128], [129], [130], up to 5 to 12 hours when microbial metabolism is a prerequisite [87], [104], [131]. Elimination half-lives are very variable, ranging from as low as 1 hour [132], [133] to values in excess of 20 hours [85], [6], [87]. The very low values may be artefacts of observation periods being less than the true half-life, whereas the very high values may be exaggerated because of a biphasic elimination reflecting significant entero-hepatic circulation of glucuronides. When studied explicitly, repeat dosing has failed to provide evidence of accumulation in plasma suggesting that, in general, significant elimination occurs in a time period shorter than the interval between repeat doses [123].

Table **4** summarises the concentrations of a range of endogenous (i.e., non-dietary) simple phenols, including α-tocopherol, and ascorbate in plasma from healthy individuals. The total simple phenol and ascorbate concentration is between 159 and

Table **2** Fate of ingested PPT

	Aglycones (mg)
Estimated mean daily consumption (from Table **1**)	450 – 600
~ 5 – 10% of intake absorbed in duodenum and excreted in urine. Of this	22 – 60
5 – 10% unchanged plant (poly)phenols, and	< 6
90 – 95% mammalian conjugates	20 – 55
~ 90–95% fermented in colon (unabsorbed PPT+ enteric and entero-hepatic cycling of glucuronides, etc.)	400 – 570
Poorly-defined and very variable portion (5 to 50%?) absorbed depending on individual's flora and substrates. Mainly mammalian conjugates of microbial metabolites	20 – 285

Table **3** Plasma pseudo-pharmacokinetics after consumption of normal portions of rich sources

PPT Subclass	*C_{max} (nM) unchanged*[a]	*C_{max} (nM) mammalian conjugates*	*% urine excretion*
Anthocyanins	10 – 150	traces	N.D. - 0.1[b]
Flavanols, low fat	40 – 140	1000 – 2000	0.5 – 4.0
Flavanols, high fat	150 – 220	up to 6200	25 – 30
Flavonol glycosides	Minute traces	N.D.[b]	0.5 – 2.5
Flavonol aglycones	Minute traces	350 – 1100	
Flavanone glycosides	Minute traces	120 – 1500	4 – 10
Isoflavone glycosides	Minute traces	900 – 4000	20 – 55
Isoflavone aglycones	10 – 150	500 – 6500	
Cinnamates & chlorogenic acids	up to 120	up to 500	1 – 2
Phenolic gut flora metabolites		20 – 60	Up to 50
Hypothetical total if all consumed in one meal	**250 – 780**	**2890 – 21660**	

[a] C_{max} = maximum concentration achieved transiently in plasma.
[b] N.D. = not detected.

Table **4** Plasma concentrations (μM) of endogenous (non-dietary) phenols and other plasma antioxidants

	Plasma concentration, healthy individuals
Homogentisic acid	0.014 – 0.070[a]
p-Hydroxyphenyl lactate	40 – 90[b]
p-Hydroxyphenyl pyruvate	14 – 60[b]
Tyrosine	60 – 130[b,c]
Ascorbate	40 – 70[d,e]
α-Tocopherol	5 – 30[f]
Total endogenous phenols & antioxidants	**159 – 380**
Hypothetical total diet-derived phenols	3.1 – 22.4[g]
Averaged over three meals gives a transient increase of between 0.3 and 5%. Many people consume much less	≈ 1 – 7.5[g]

[a] Ref. [201], [b] Ref. [202], [c] Ref. [203], [d] Ref. [204], [e] Ref. [205], [f] Ref. [206], [g] From Table **3**

380 μM. The maximum additional concentration that is likely to be achieved from dietary sources, 3 to 22 μM, is marginal by comparison adding only between 0.3 and 5% if it is assumed, quite reasonably, that the "typical" mean intake is taken over three equal meals. Many people consume a much smaller quantity of dietary PPT and even those consuming double the average amount (450 to 600 mg aglycones) adopted in this paper will only achieve a transient 5 to10% increase in total plasma antioxidant content.

Many investigators have attempted to demonstrate increases in plasma antioxidant capability following the consumption of foods, beverages or supplements rich in PPT. Table **5** summarises the outcomes of 34 such studies [127], [130], [131], [132], [133], [134], [135], [136], [137], [138], [139], [140], [141], [142], [143], [144], [145], [146], [147], [148], [149], [150], [151], [152], [153], [154], [155], [156], [157], [158], [159]. The test substances included a range of fruit and vegetable products, including juices, alcoholic beverages, tea, and chocolate. In view of the calculations presented in Tables **3** and **4**, it is perhaps not surprising that increases in plasma antioxidant capacity were often undetectable, and at best, small and transient. Moreover, in four studies that produced increases in plasma antioxidant capability it could be attributed, at least in part, to increased plasma ascorbate [149], [156], [158].

In view of these observations, it is instructive also to consider the redox potentials of PPT-derived mammalian metabolites that are known to reach plasma, and to compare these with the corresponding values for the endogenous plasma antioxidants. The polyphenols with the lowest redox potentials are flavonoids with vicinal hydroxyl groups in the B-ring, and conjugation extending to the A-ring, e.g., quercetin aglycone (330 mV at pH 7) [160]. If the conjugation does not extend beyond the B-ring, then the redox potential is significantly higher even for (–)-epigallocatechin gallate (480 mV at pH 7) [161] with three vicinal hydroxyl groups. The value rises again when there are only two vicinal hydroxyl groups {e.g., (+)-catechin 570 mV [162] or caffeic acid 540 mV [162]}, a single *para* hydroxyl group (e.g., hesperidin 720 mV [162]) or isolated (*meta*) hydroxyl groups (e.g., resorcinol 810 mV [163]). These comparisons are extended to the endogenous (non-dietary) plasma antioxidants in Table **6**. Fig. **1** illustrates the marked effects of mammalian and microbial metabolism on the redox potential of PPT aglycones that are frequently examined in *in vitro* systems designed to demonstrate their potent antioxidant properties. When the aglycones of such powerful antioxidants are given intravenously to humans [164] or intraperitoneally to animals [165], [166], thus circumventing the protection

Table **5** The outcome of 34 studies[a] in which volunteers were given foods, beverages or supplements rich in PPT and plasma was analysed for total antioxidant activity

34 studies, (poly)phenol-rich diet compared with control
– 13 studies (3 high & 3 very high doses) showed no change in plasma antioxidant status *ex vivo*
– 21 studies (8 low & 7 moderate doses) showed small and transient increases in plasma antioxidant status *ex vivo*
– 1 showed reduction in plasma Vitamin E
– 1 showed reduction in plasma ascorbate and glutathione

[a] Refs: [127], [130], [131], [132], [133], [134], [135], [136], [137], [138], [139], [140], [141], [142], [143], [144], [145], [146], [147], [148], [149], [150], [151], [152], [153], [154], [155], [156], [157], [158], [159].

Table **6** A summary of published data for transient maximal plasma concentrations of diet-derived (poly)phenols, typical plasma concentrations of endogenous phenols and antioxidants, and associated redox potentials (pH 7)

Mammalian metabolite hydroxylation pattern	**Maximal transient concentration (μM)**	**Redox potential (mV) at pH 7**
1,2,3-*vic*	0.14[a]	400 – 600[d,e,f]
1,2-*vic*	0.8[a]	500 – 650[d,g,h,]
Single *para* or isolated *meta* hydroxy groups	10[a]	700 – 1050[d,e,g,i,j,k]
Blocked/inactive	?	Inactive
Damaging radicals		**Redox potential (mV) at pH 7**
Hydroxyl radical		2310[h]
Superoxide radical anion		1800[h]
Alkoxyl radical		1600[l]
Alkyl-peroxyl radical		1000 ± 60[h,l,m,]
PUFA (bis-allylic) radical		600[h]
Endogenous phenols and antioxidants in plasma	**Typical plasma concentration (μm)**	**Redox potential (mV) at pH 7**
Endogenous *p*-phenols	114, 280[a]	≈ 700[d,e,g,i,j,k]
α-Tocopherol	5 – 30	≈ 500[d,h]
Ascorbate	50 – 70[b]	≈ 280[e,h]
(depleted)	(≤ 11)[c]	
Glutathione		– 276[n]

[a] From Table **3**, [b] From Table **4**, [c] Ref. [170], [d] Ref. [161], [e] Ref. [163], [f] Ref. [207], [g] Ref. [162], [h] Ref. [208], [i] Ref. [209], [j] Ref. [210], [k] Ref. [211], [l] Ref. [212], [m] Ref. [213], [n] Ref. [214]

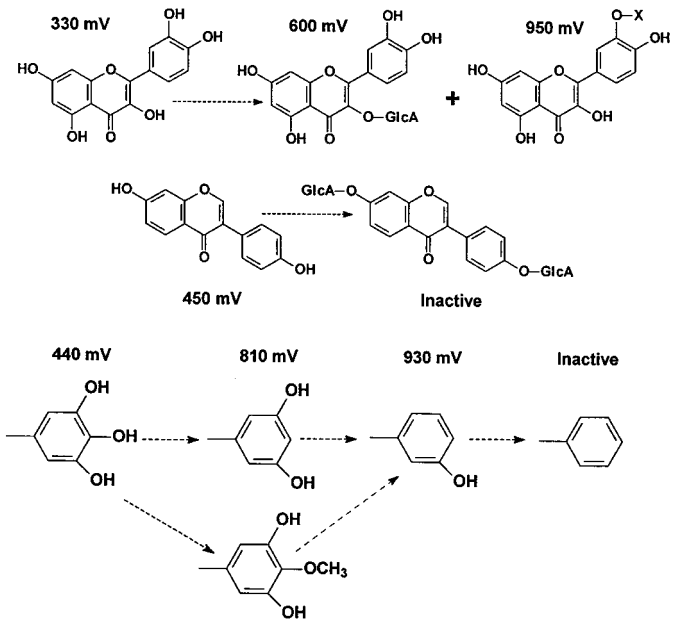

Fig. **1** Illustration of the effects of mammalian metabolism and microbial metabolism on the redox potential of (poly)phenols found in plasma compared with their precursors in the diet and the aglycones commonly used in *in vitro* studies.

offered by the gastric mucosa and Phase II conjugations, redox cycling causes serious and possibly fatal liver and kidney damage. One may conclude that it is better to avoid high plasma concentrations of the more potent PPT antioxidants (such as unconjugated quercetin), and that it might be ill-advised grossly to supplement normal diets with capsules and concentrates of such potent antioxidants.

Table **6** indicates that the diet-derived PPT metabolites are able thermodynamically to scavenge some or all of the damaging radicals should they come into contact. However, these metabolites are so hydrophilic {e.g., quercetin 3-glucuronide (K = 0.008) [167], [168] compared with quercetin (K = 66) [167], [168] and α-tocopherol (K = 550) [169]} that it is unlikely they will encounter lipid-derived radicals. However, any phenoxyl radicals generated will have to be removed either by transfer of the unpaired electron to an endogenous scavenger such as α-tocopherol, ascorbate, glutathione or serum albumin, or by dismutation or disproportionation although these latter mechanisms seem somewhat unlikely *in vivo* because of the relatively low phenoxyl radical concentrations. The implied demand for α-tocopherol and ascorbate is particularly interesting, since two of the supplementation studies (Table **5**) produced reductions in plasma ascorbate and α-tocopherol [150], and the major sources of dietary PPT identified from the NEODIET database (coffee and black tea) supply neither. Moreover, it is known that for approximately 14% of the over-65 population subgroup in the UK the mean plasma ascorbate value is below 11 μM [170], indicating biochemical depletion [171], suggesting that for heavy consumers of black tea or coffee within this population subgroup the transient concentration of PPT metabolites may approach or even exceed plasma ascorbate.

From the data assembled, it is difficult to envisage how diet-derived PPT metabolites can make a major contribution to radical scavenging in plasma compared with the contribution to be expected from the endogenous antioxidants in healthy individuals replete in ascorbate. It follows that if diets rich in fruits and vegetables are advantageous, at least in part, by virtue of their content of PPT then mechanisms other than radical scavenging are implicated.

Protective Mechanisms other than Radical Scavenging

Although classically, mammalian conjugates of drugs are viewed as biologically significantly less active than the parent drug, this is not inevitably the case when PPT are considered. Some quercetin conjugates are able to inhibit lipoxygenase and xanthine oxidase. Quercetin 3-glucuronide, one of the three major human conjugates of dietary quercetin glycosides,

has been shown *in vitro* to protect the vascular endothelium [172], [173] and suppresses peroxynitrite-induced consumption of lipophilic antioxidants in human LDL [174]. Another human metabolite, quercetin 4′-glucuronide, inhibits xanthine oxidase *in vitro* at a concentration in plasma that on normal diets can realistically be approached (K_i = 0.25 μM) [175]. As these observations are more widely appreciated, and mammalian metabolites become more readily available, it is quite possible that other biologically interesting properties will be identified for mammalian conjugates of PPT.

Effects occurring in the gastro-intestinal tract prior to absorption also deserve greater consideration. For example, there is a growing body of evidence suggesting that diets rich in PPT may influence the absorption and metabolism of glucose, resulting in a lower glycaemic index [176] than would otherwise be expected. Red wine [177], coffee [178] and apple juice [179] have all been shown in controlled volunteer studies to slow glucose absorption and reduce the post-prandial surge in plasma glucose, an event known to be an independent risk factor for CHD [180]. Studies in which volunteers consumed normal portions of PPT-rich foods [178] have also produced reductions in the post-prandial concentrations of plasma insulin and glucose-dependent insulinotropic polypeptide and elevation in the concentration of glucagon-like polypeptide-1. A prospective study of 17,000 people suggested that the mean relative risk of developing Type II diabetes was only 0.5 (0.35 – 0.72) in those individuals habitually consuming six or more cups of coffee per day compared with those consuming two or less (p = 0.0002) [181], and a polyphenol-enriched diet has been reported to reduce the incidence and severity of nephropathy in Type II diabetics [182].

The reduced glycaemic index has been attributed to PPT-mediated inhibition of α-amylase [183], [184], maltase [185] or α-glucosidase (sucrase) [184], [186], but this mechanism would not operate with preformed glucose as observed in our studies [178], [179]. In studies using bolus doses of glucose, the observation is more conveniently explained by an effect on the active glucose transporter (SGLT1) in the duodenum. Phloridzin, a dihydrochalcone glucoside characteristic of apples and apple products [53], but now known to be more widely distributed [187], competes for the active site both *in vitro* and *in vivo* when given intraperitoneally [188], [189], [190], [191]. Other dietary PPT [(–)-epigallocatechin gallate, (–)-epigallocatechin and 5-caffeoylquinic acid] have been shown *in vitro* to dissipate the sodium gradient essential to the operation of SGLT1 [192], [193], and several quercetin glucosides have been shown to interact with it and thus to have the potential to interfere in glucose transport [194], [195], [196], [197], [198], [199], [200]. While these effects on glucose absorption and the associated hormones are modest, they have been achieved in volunteers consuming sensible quantities of common dietary components (as distinct from effects seen only *in vitro* with high levels of PPT aglycones never seen in the diet). Such effects repeated daily, or even several times daily for say 30 years, might in part explain the reduced incidence of chronic disease, especially Type II diabetes and the metabolic syndrome, in later life associated with diets rich in fruits and vegetables.

Conclusions

Evidence has been presented to indicate that very little of the dietary PPT consumed reaches human plasma, and that this transient fraction contains only weak antioxidants able to make little contribution to the total antioxidant activity of the plasma. This suggests that radical scavenging by PPT is unlikely to be the mechanism by which diets rich in fruits and vegetables protect against chronic diseases. Instead, it is proposed that modulation of glucose absorption in the duodenum prior to the absorption of PPT, with protection by PPT metabolites through mechanisms other than radical scavenging, might over a lifetime offer modest protection against chronic diseases, especially Type II diabetes and the metabolic syndrome.

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