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Phenolic-enriched foods: sources and processing for enhanced health benefits

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Polyphenols are ubiquitous secondary products present in many plant foods. Their intake has been associated with health benefits ranging from reduced incidence of CVD, diabetes and cancers to improved neurodegenerative outcomes. Major dietary sources include beverages such as coffee, teas and foods such as chocolate. Fruits are also major sources and berries in particular are a palatable source of a diverse range of polyphenol components. There are a number of ways that polyphenol uptake could be increased and healthier polyphenol-rich foods could be produced with specific compositions to target-specific health effects. Firstly, we could exploit the genetic diversity of plants (with a focus on berries) to select varieties that have enhanced levels of specific polyphenols implicated in disease mitigation (e.g. anthocyanins, tannins or flavonols). Working with variation induced by environmental and agronomic factors, modern molecular breeding techniques could exploit natural variation and beneficially alter polyphenol content and composition, although this could be relatively long term. Alternatively, we could employ a synthetic biology approach and design new plants that overexpress certain genes or re-deploy more metabolic effort into specific polyphenols. However, such 'polyphenol-plus' fruit could prove unpalatable as polyphenols contribute to sensorial properties (e.g. astringency of tannins). However, if the aim was to produce a polyphenol as a pharmaceutical then 'lifting' biosynthetic pathways from plants and expressing them in microbial vectors may be a feasible option. Secondly, we could design processing methods to enhance the polyphenolic composition or content of foods. Fermentation of teas, cocoa beans and grapes, or roasting of cocoa and coffee beans has long been used and can massively influence polyphenol composition and potential bioactivity. Simple methods such as milling, heat treatment, pasteurisation or juicing (*v.* pureeing) can have notable effects on polyphenol profiles and novel extraction methods bring new opportunities. Encapsulation methods can protect specific polyphenols during digestion and increase their delivery in the gastrointestinal tract to target-specific health effects. Lastly we could examine reformulation of products to alter polyphenol content or composition. Enhancing staple apple or citrus juices with berry juices could double polyphenol levels and provide specific polyphenol components. Reformulation of foods with polyphenol-rich factions recovered from 'wastes' could increase polyphenol intake, alter product acceptability, improve shelf life and prevent food spoilage. Finally, co-formulation of foods can influence bioavailability and potential bioactivity of certain polyphenols. Within the constraints that certain polyphenols can interfere with drug effectiveness through altered metabolism, this provides another avenue to enhance polyphenol intake and potential effectiveness. In conclusion, these approaches could be developed separately or in combination to produce foods with enhanced levels of phenolic components that are effective against specific disease conditions.

Polyphenols: Health: Intake: Berries: Breeding: Reformulation: Processing

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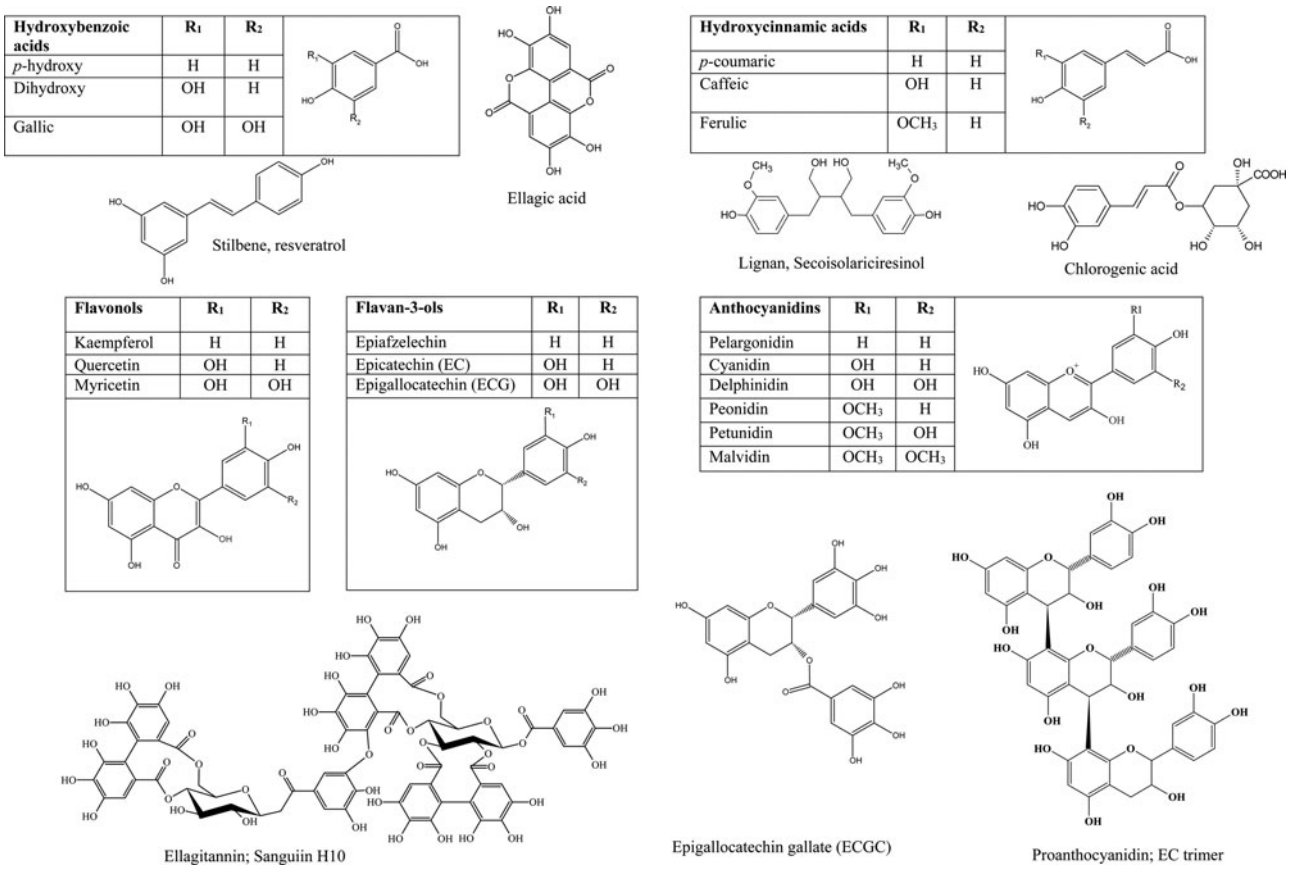

Fig. 1. Structures of common polyphenol groups.

There is mounting epidemiological evidence that intake of polyphenols in foods can have beneficial effects on various human health outcomes. For example, there is substantial evidence for an association between polyphenol intake and incidence of inflammatory responses and risk of colorectal cancer[1,2]. Many *in vitro* and animal studies have examined the potential mechanisms behind these benefits and have suggested effects ranging from reduced incidence of CVD, diabetes and cancers to improved neurodegenerative outcomes[3].

In the present paper, I will provide a brief overview of the sources of dietary polyphenols in foods and discuss means to increase overall dietary intake and the possible health benefits, with a focus on berries as a potential source.

Structural diversity of polyphenols and main dietary sources

Polyphenols are secondary plant metabolites and although they must contain a characteristic phenolic ring, they have very diverse structures[4–7] (Fig. 1). There are relatively simple structures with recognisable phenolic cores such as the phenolic acids (e.g. hydroxybenzoic acids and hydroxycinnamic acid derivatives) and stilbenes and lignans[4]. The flavonoids are a major sub-group based on a C_6–C_3–C_6 core structure with variations that lead to the most common groups, e.g. flavan-3-ols or catechins, flavonols and anthocyanidins. Other flavonoid groups such as flavanones, etc. are important in citrus fruits[5].

There are also complex large molecular weight tannin derivatives[7], which are split into condensed tannins (e.g. proanthocyanidins composed of flavan-3-ol groups) and hydrolysable tannins (e.g. the ellagitannins which are composed of esters of ellagic acid derivatives). However, the enormous complexity of (poly)phenols lies in the potential for multiple decorations with other groups, including sugars, alcohols and acids[7]. In fact, most common flavonoids are rarely found in foods without attached sugars, acids or alcohols. For example, the hydroxycinnamic acid, caffeic acid, is most often found as chlorogenic acid, an ester with quinic acid, and anthocyanidins and flavonols are rarely found without attached sugars (i.e. as anthocyanins and flavonol glycosides)[4–7].

Plant-based foods are the primary source of polyphenols and excellent analytical work by various groups, including data on Finnish intake[8] has outlined the polyphenol contents of common foods (Fig. 2) Although the highest sources are clearly fruits, coffee and tea make a larger overall contribution to intake due to higher volume of intake. In fact, the major dietary sources of polyphenols vary with habitual diet with tea intake more

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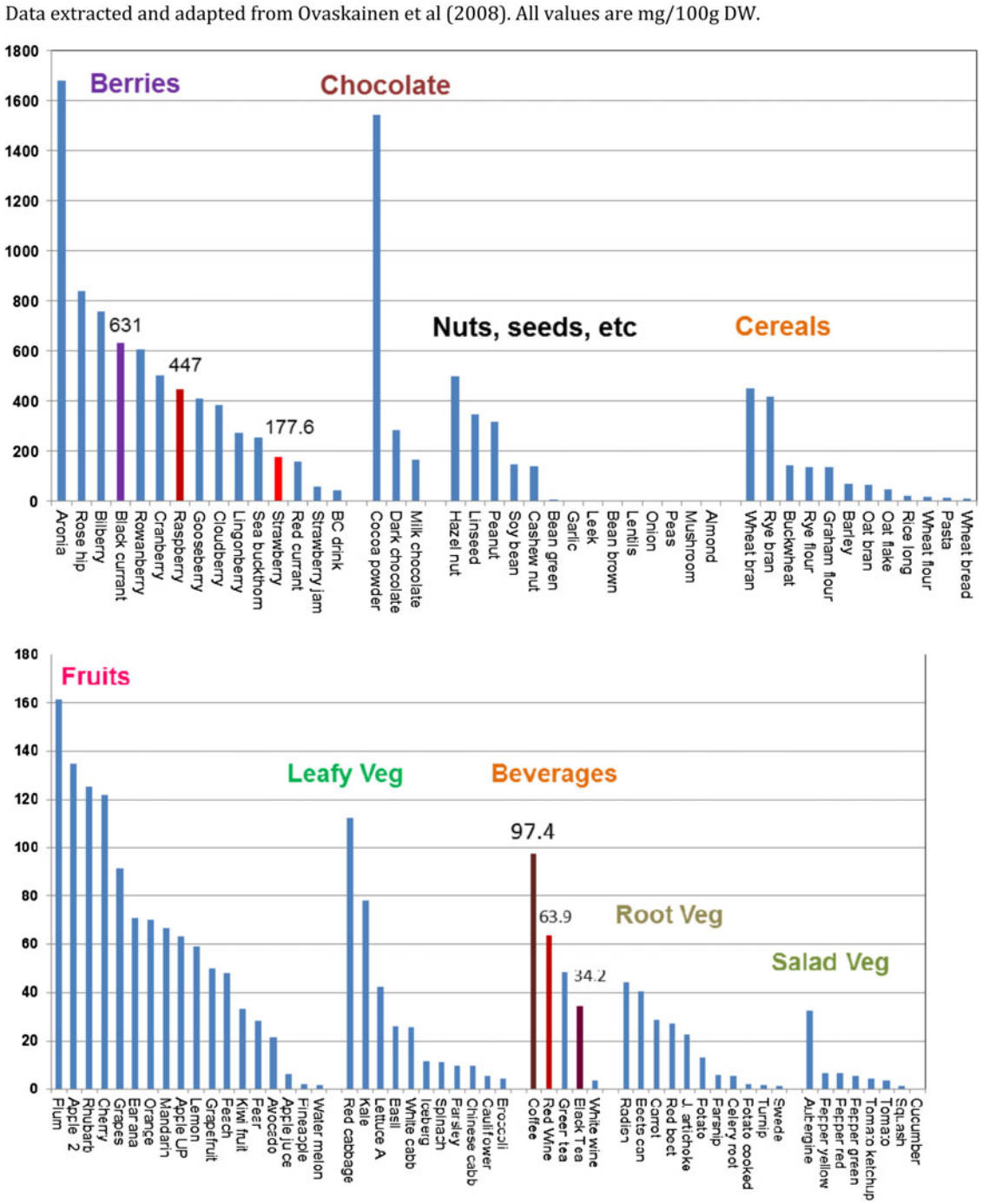

Fig. 2. Total phenol contents of common foods.

important in the UK and wine and fruit intake in Mediterranean diets[8]. It is clear that berries can contribute high polyphenol content and there is evidence that increased berry intake has had beneficial effects on health in Scandinavian diets[9]. As berries are generally universally regarded as palatable, greater inclusion in the diet represents a plausible means to increase overall polyphenol intake. In addition, although coffee and tea are rich in specific polyphenols[10] (flavan-3-ols in teas and hydroxycinnamic acid derivatives in coffee), berry intake brings higher levels of specific components such as anthocyanins and ellagitannins[4,6,7]. Although other fruits and vegetables, nuts and certain breads can be reasonably good sources of polyphenols, the focus of the present paper is on berries given the long history of the Hutton Institute in berry cultivation and breeding.

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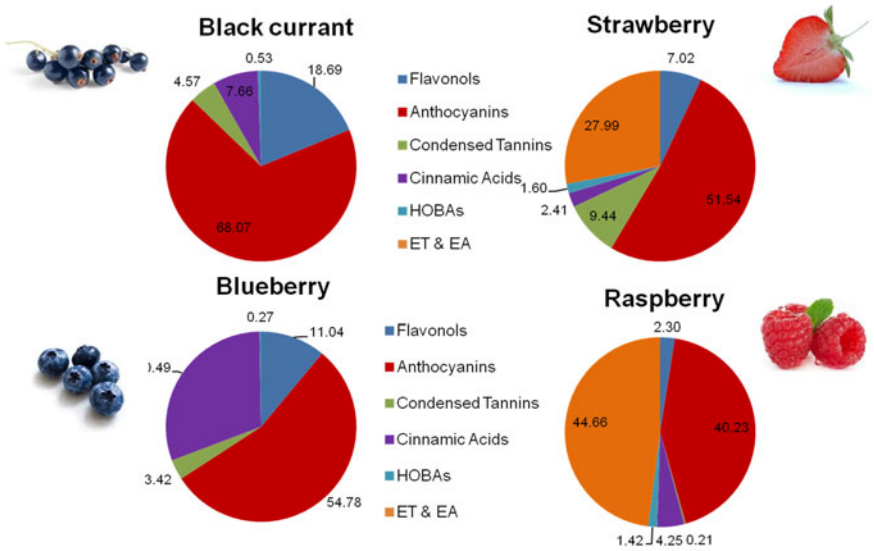

Fig. 3. Representative polyphenol composition of berry species.

Enhancing polyphenol content and composition in berries: breeding

There is substantial variation in polyphenol composition between different species of berries. Therefore as anthocyanins have been implicated as influencing human disease[1,11] then selecting anthocyanin-rich berry species such as black currant, blueberries and blackberries could be important (Fig. 3) for intervention trials. Within species, there is also great variation in polyphenol content but also in composition. Some of the most different material may arise from wild, unimproved varieties and provides another source of polyphenol variation. For example, anthocyanin composition in raspberry varieties can be markedly different (Fig. 4(a)), which may influence potential bioactivity. There are substantial differences in flavonol content and composition in black currant genotypes (Fig. 4(b)), which can be of importance as quercetin has been implicated in various health benefits[12]. The differences between genotypes are under genetic control and can be selected for in breeding programmes. The variations can be even more subtle. In blueberry, certain genotypes accumulate a higher proportion of acetylated anthocyanins which set them aside from other genotypes (Fig. 4(c)). This can be of biological relevance because acylated anthocyanins improve colour tone and stability in juices[13] but have been suggested to be less bioavailable than non-acylated anthocyanins[14].

Polyphenol content and composition can also be influenced by environmental or climatic conditions. For example, identical varieties of raspberries grown under identical agronomic conditions at different sites across Europe have different compositions but these compositions appear to be consistent at those locations across seasons (Fig. 4(d)). Given that predicted climatic changes envisaged under models suggest Europe will become generally warmer, varieties that are currently favoured in more southerly European locations may shift northward in future years. What is clear is that inter-genotype variation can be compounded by variation due to environmental and agronomic conditions and berries (or berry products) used in intervention studies must have their polyphenol content and composition closely defined.

Classical breeding usually involves selecting parents with useful suitable genotypic variation in polyphenol content and composition (and other favourable traits such as pest resistance, good yield, low fertiliser inputs, etc.) then screening for progeny with consistently elevated levels of specific components[15,16]. This essentially serendipitous gene-shuffling approach is often slow as many berry species require years before they reach sexual maturity and begin to set fruit. However, modern exploitation of increasing genetic and genomic resources (genetic maps, genome sequences, etc.) can provide gene-based markers for polyphenol traits that accelerate breeding by selecting for genotypes likely to have beneficially altered polyphenol composition well before sexual maturity and fruit set. Genetic maps and genome sequences are already available for some berry species[17,18] and our understanding of the biosynthesis of these polyphenol components is increasing rapidly.

Another means to obtain polyphenol-enriched berries would be to use a synthetic biology approach to modulate the biosynthesis of individual components by targeted alteration in the expression of specific genes. Techniques such as CRISPR (clustered regularly interspaced short palindromic repeats) are being developed that allow the surgical elevation of expression of endogenous genes that may modulate polyphenol

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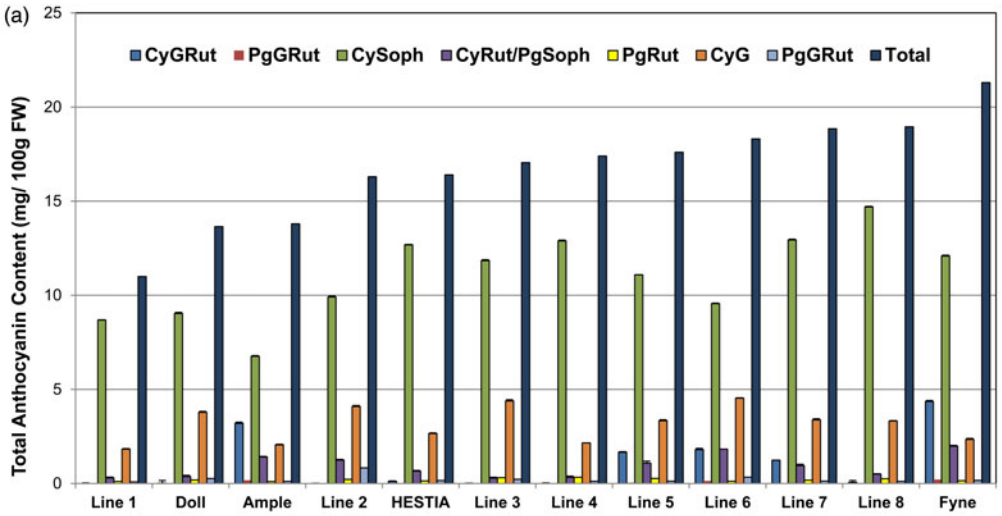
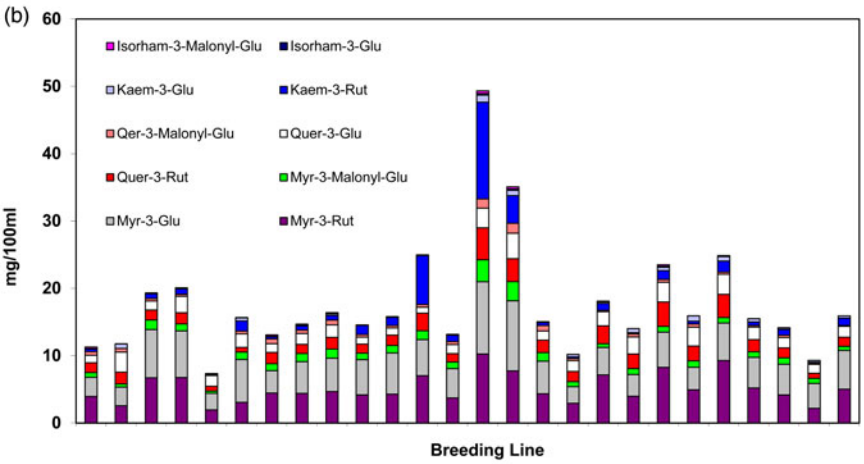


All varieties grown at the Hutton Dundee in 2014 and harvested at full ripeness. Lines denote unnamed breeding lines and others are from the Glen series of Hutton varieties. Anthocyanin composition was determined by LCMS. All values are averages of triplicate ± SE. Cy = cyanidin; Pg = pelargonidin; G = glucose; Rut = rutinoside; Soph = sophoroside.



Breeding lines obtained from New Zealand Food and Health in 2008. Flavonol composition analysed by LCMS. Isorham – isorhametin, Quer = quercetin, Kaem = kaempherol, Myr = myricetin, Glu = glucose, Rut = rutinoside

Fig. 4. Polyphenol compositional diversity in different varieties of berry species. (a) anthocyanin diversity in raspberries; (b) flavonol diversity in black currant varieties; (c) anthocyanin diversity in blueberries; (d) anthocyanins in a raspberry variety grown in different locations in Europe.

content/composition[19]. However, in addition to concerns about genetic manipulation, various polyphenols are sensorially important; ellagitannins provide the astringency essential for the recognisable flavour profile of raspberries and flavonoids can influence bitterness[20]. Therefore, increasing the levels of certain polyphenols may lead to unpalatable fruits especially as domestication and concerted breeding programmes have consistently selected for fruits with reduced bitterness and astringency, as can be noted if wild berry varieties are tasted.

Another possibility would be to 'lift' biosynthetic pathways from plants into suitable microbial vectors such as yeasts and to produce polyphenols under large-scale *in vitro* conditions as envisaged in the European Union funded BACHBERRY grant. This approach has already been achieved for high-value plant metabolites (such as artemisinin)[21] or alkaloid precursors[22] and is probably better suited for the production of specific polyphenols as pharmaceuticals.

Processing methods for polyphenol-enriched products

Human subjects have been processing foods and altering their polyphenol composition for centuries. Fermentation of teas, cocoa beans and grapes, or roasting of cocoa and coffee beans has long been used and can massively influence polyphenol composition and potential

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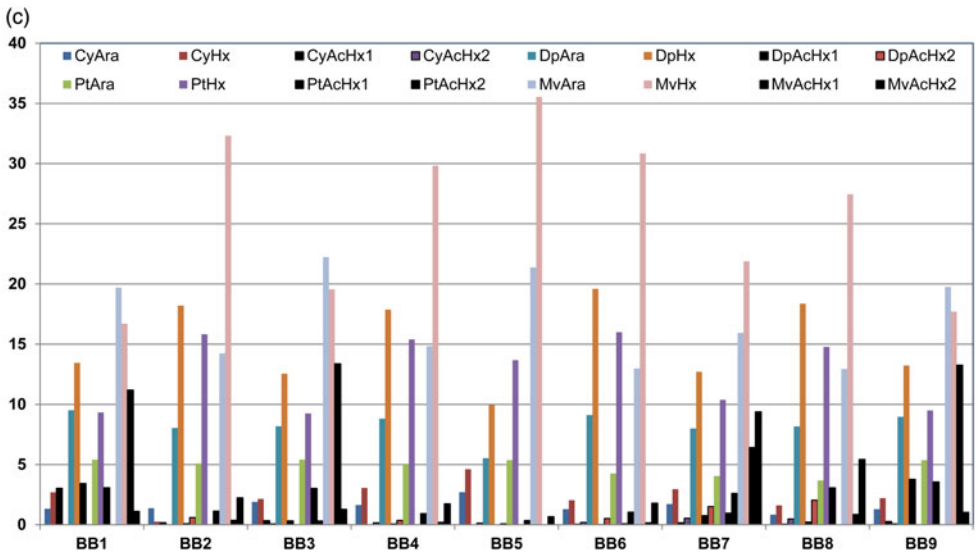

All blueberry varieties analysed at Hutton Dundee in 2011. 16 different anthocyanins were detected. All values are % of total anthocyanin content. Bars in black are acetylated anthocyanins.

Cy = cyanidin, Pt = petunindin, Dp = delphinidin, Mv = malvidin, HX = hexose, Ara = arabinose, AC = acetyl.

Nine anthocyanins were detected and are displayed as % of total anthocyanin content.

Fig. 4.

bioactivity. For example, oxidation during black tea processing leads to the formation of characteristic orange-brown theaflavin products from flavan-3-ols[23]. Fermentation during wine making often results in substantial degradation of grape anthocyanins, but can produce unusual anthocyanin derivatives. For example, Vitisin A derivatives are formed through reaction with pyruvate during red wine production[24]. These process-derived pigments alter the colour and tone of the wines and although they are more stable under gastrointestinal conditions[25], their uptake is less well understood[26]. Fruit wines made from Salal berries retain red colouration due to their high content of stable anthocyanin diglycosides containing pentoses[27].

The simplest way to reformulate to obtain polyphenol-enriched products may be to add berry juices to staple juices such as orange and apple juices. Berry juices, purees and 'wastes' or co-products (from juicing or pre-prepared fruit products) added to apple/citrus juices can easily double the polyphenol content and introduce specific novel polyphenol components (e.g. anthocyanins or ellagitannins). Studies on (e.g.) black currant-enriched apple juices and raspberry-enriched orange juices have illustrated that palatability is not reduced and the added colouration can enhance acceptability[28].

Another method to increase polyphenol intake is to use berry purees in products rather than clarified juices. The purees have the added benefits of the non-extractable polyphenols, which are either covalently attached to cell walls or embedded in the tissue matrix. These components have been called the 'neglected and underrecorded polyphenol content of foods, the missing polyphenols'[29]. As they are essentially antioxidant-rich dietary

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fibre, they can have positive effects through the gut such as enhancing lipid excretion, promoting chemopreventive effects throughout the gastrointestinal tract, encouraging growth of colonic microbiota and the release of systemic polyphenol metabolites through colonic degradation.

It is well known that techniques used to aid juicing such as addition of pectinolytic enzymes can have various effects on polyphenol composition and result in a balance of release of polyphenol from non-extractable polyphenols and degradation of flavonoid glycosides[30]. As novel extraction and processing methods (e.g. supercritical CO_2, pressurised water, microwave-enabled systems, pulsed electric fields, etc.) become available, their effects on polyphenol content and composition need to be defined.

Berry wastes or juicing residues could be used to improve nutrient stability in bakery[31] or meat products perhaps through inhibition of lipid oxidation. These could substitute for synthetic antioxidants currently used and have the added bonus of providing higher polyphenol content and dietary fibre.

Co-administration with other components

How polyphenols are administered may influence their stability, overall uptake and potential bioactivity. Although the serum bioavailability of certain polyphenols are low (e.g. anthocyanins only reach up to μM levels[5,6]), there is some evidence other components of foods can influence their bioavailability. Co-administration with sugars may influence anthocyanin bioavailability. It was proposed that the sugar content in red grape juice increased anthocyanin uptake in human subjects through enhanced transit through intestinal brush border sodium-glucose-linked transporter 1 and GLUT2[32]. Malvidin glucoside uptake in human subjects was much higher from red grape juice than red wine but in this case the juice had higher original anthocyanin content[33]. However, anthocyanin uptake from blood oranges in rats was unaffected by the direct co-administration with glucose[34]. Alternatively, co-administration of sucrose with elderberry juice in human subjects led to a delayed and reduced amount of anthocyanins in urine suggesting uptake inhibition[35]. These differences may be due to the noted effect on flavonoid glycosides on sugar uptake and reflect the same proposed mechanisms whereby these polyphenols are thought to have positive effects on blood glucose levels[36].

Other food components can also have effects on polyphenol uptake. Anthocyanin uptake was similar from red wine or its dealcoholised form[33] but alcohol has been suggested to increase quercetin uptake from red wine[37].

Co-administration with fats may improve bioavailability of certain, more hydrophobic polyphenols through lipid phase absorption/micellarisation and uptake[38]. The presence of milk proteins markedly reduced apparent *in vitro* bio-accessibility of tea flavan-3-ols but subsequent uptake in intestinal cell models was increased[39]. In studies where subjects were given tea with or without milk the serum bioavailability of flavan-3-ols was unaffected[40]. This apparent disparity may arise as milk proteins bind and protect flavan-3-ols in the gastrointestinal tract but this does not prevent their subsequent active uptake.

The bioavailability of specific polyphenols may be influenced by the presence of other polyphenols. It is well established that piperine increases curcumin bioavailability by inhibition of glucuronidation in the liver and reduced phase I metabolism[41]. Indeed, other more common polyphenols can interfere with phase I metabolism and it is possible that specific polyphenols could alter clearance of other polyphenols by this mechanism.

Polyphenols are known to interfere with drug metabolism. For example, grapefruit polyphenols inhibit the effectiveness of cytochrome P450 3A4 and this can increase specific drug levels to potentially dangerous limits[42]. Inhibition of cytochrome P450 3A4 by polyphenols is well established[43], but whether one specific polyphenol class could selectively protect other polyphenols by this mechanism is less well established. However, quercetin increased bioavailability of green tea catechins in rats through inhibition of catechol-*O*-methyltransferase and multidrug resistance proteins[44]. Therefore it is possible that polyphenols could influence the bioavailability of other polyphenols by affecting clearance mechanisms. Alternatively, the flavonol quercetin-3-*O*-glucoside inhibited uptake of the structurally similar cyanidin-3-*O*-glucoside *in vitro*[45] probably through competitive inhibition of gut transporters. The interdependence of polyphenols on overall bioavailability requires further study and the effects of mixtures of polyphenol components in berry juices, or indeed in 'realistic food combinations' will be even more complex[38].

Finally, as more information becomes available about the potential bioactivities of polyphenols and the limits enforced by stability or bioavailability, other technological means to improve delivery can be developed[46,47]. For example, the use of nanoparticles to enhance delivery of bioactive polyphenol components across the blood–brain barrier[48,49] to improve neuroprotective effects is close to being a reality.

Conclusions

Berries have high polyphenol content and offer potential to enhance polyphenol intake, being a palatable source of unique and diverse polyphenols.

There is considerable natural variation in polyphenol content and composition between and within berry species and this variation can be exploited to breed new varieties with improved bioactivity and/or bioavailability. Composition and content may be also enhanced by processing methods or by re-formulation with other components.

As research uncovers new bioactivities and links specific polyphenols with potential underlying mechanisms, there is substantial potential to design berries or berry-enriched products with altered enhanced benefits for specific diseases or prevention strategies.

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Conflicts of Interest

None.

Authorship

The author had sole responsibility for all aspects of preparation of this paper.

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