# Potential Health Benefits of Berries

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**Abstract:** Fruit and vegetable consumption is inversely related to the incidence of heart disease and several cancers. However, many people in countries in Northern latitudes do not eat the recommended "5-a-day" of fruit and vegetables. For such populations, a potentially important source of fruit may be locally grown soft fruits (eg. raspberries, blackberries, blueberries, blackcurrants). Such berries contain micronutrients such as vitamin C and folic acid which are essential for health. However, berries may have additional health benefits as they are also rich in phytochemicals such as anthocyanins which are glycosidic-linked flavonoids responsible for their red, violet, purple and blue colours. *In vitro* studies indicate that anthocyanins and other polyphenols in berries have a range of potential anti-cancer and heart disease properties including antioxidant, anti-inflammatory, and cell regulatory effects. Such experimental data has lead to numerous health claims on the internet implying that "berries are edible superstars that may protect against heart disease, cancers and ageing". However, the bioavailabilty of polyphenols such as anthocyanins would appear to be limited, thus compromising their nutritional relevance. Consequently the aim of the article is to assess the current scientific evidence for claims that berries may have additional health benefits to those normally associated with consuming fruit and vegetables.

**Keywords:** Berries, soft fruit, micronutrients, anthocyanins, cancer, heart disease.

## 1. INTRODUCTION

In the United Kingdom ischemic heart disease (31%), cancer (30%) and stroke (15%) were the principal causes of death during 2001 [1]. A major contributing factor to the aetiology of these chronic diseases is a poor diet [2-4]. Diet in the developed world is a complex mixture of foods with highly variable consumption patterns. For example, a review of the "Scottish diet" highlighted poor dietary habits and recommended reducing intake of cakes and pastries, fats, sugar and confectionery, while increasing fruit, vegetable and cereal consumption [5]. However, despite recommendations to eat an average of 400g of fruit and vegetables per day, actual daily consumption in Scotland between 1993 and 2000 only rose from 190g to 200g [6]. This is unfortunate as considerable evidence indicates that adequate fruit and vegetable consumption has a role in preventing many chronic diseases, including heart disease, stroke and several cancers, [3, 7-12], long term consumption also being associated with decreased premature mortality rates [13].

Reasons why some populations appear reluctant to increase intakes of fruit and vegetables are complex. However, the persistence of traditional dietary patterns may reflect, in part, the historical expense and lack of availability of fresh fruit and vegetables in Northern latitudes. For such populations, a potentially important source of plant-based food may be locally grown soft fruits (e.g. raspberries, strawberries, blueberries, cranberries and blackcurrants). As with other fruit and vegetables, berries are important dietary sources of fibre and essential vitamins and minerals. They also contain a vast number of other phytochemicals for which there are no known deficiency conditions but which may have marked bioactivities in mammalian cells of potential health benefit. These include effects on oxidative damage, detoxification enzymes, the immune system, blood pressure, platelet aggregation, and anti-inflammatory, anti-bacterial and anti-viral responses [14]. Compared with most fruit, berries are unusual in that they are rich in anthocyanins. These are glycosidic-linked flavonoids responsible for their red, violet, purple and blue colours. Therefore the aim of this review is to assess whether there is a putative role for berries and in particular the anthocyanins and other phytochemicals they contain, in the prevention of chronic diseases.

## 2. SOFT FRUITS (BERRIES AND CURRANTS)

The most commonly consumed berries are strawberries (*Fragaria x ananassa*), raspberries (*Rubus idaeus*), blackberries (*Rubus* spp.), blueberries (*Vaccinium corymbosum*), black currants (*Ribes nigrum*) and red currants (*Ribes rubrum*). There are also a number of crosses between raspberries and blackberries available such as the loganberry (*Rubus loganbaccuus*). Edible berries have been a part of man's diet for centuries. The modern cultivated strawberry, for example, is a descendent of a woodland variety grown by the Romans which was then subsequently crossed with American and Chilean varieties around 1750. Raspberries have been cultivated in Europe since the Middle Ages and blackberries may have been eaten since Neolithic times [15]. Despite this historical longevity most types of berries have never been developed beyond local markets [16], reflecting in part their susceptibility to decay post-harvesting. A

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notable exception is the American cranberry (*Vaccinium macrocarpon*) which is exported worldwide both as the berry and as a juice.

## 3. ESSENTIAL MICRONUTRIENTS IN BERRIES

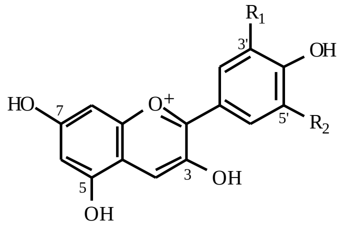
As with other fruits, berries contain a range of micronutrients which are essential for health. In particular, many types of berries contain a high level of vitamin C (ascorbic acid), so much so that often only a handful of the fruit can provide the recommended daily allowance (RDA). As this vitamin has antioxidant activity, acts as a cofactor in hydroxylation reactions which are required for collagen synthesis, has a role in hormone synthesis, the immune system, iron absorption, platelet aggregation, thrombus formation and may have a role in preventing heart disease, osteoporosis and a range of cancers, [17-22] berries are an obvious dietary source for populations with sub-optimal vitamin C status. The biological roles of vitamin C are reviewed in detail in [23].

Berries can also be significant dietary sources of folic acid, a water soluble B vitamin which as well as being essential to prevent neural tube defects in new-borne babies also may play a role in reducing risk of heart disease and cancer through a range of mechanisms including lowering homocysteine levels, catalysing nitric oxide formation and maintaining DNA stability [24, 25]. For a recent review of the physiology of folate and vitamin B12 in health and disease, see [26].

## 4. PHYTOCHEMICALS IN BERRIES

Phytochemicals are not required for normal functioning of the body and their absence does not result in a deficiency condition. However, they may have bioactivity in mammalian cells which could impact on health and disease. Berries are a rich source of such phytochemicals, in particular anthocyanins and flavonols. Concentrations in berries will be influenced by many factors including environmental conditions, degree of ripeness, cultivar, cultivation site, processing and storage of the fruit [27-29].

The anthocyanins are conjugated anthocyanidins, which provide the distinctive and vibrant palate of colours found in dark berries. There are six anthocyanidins distributed throughout the plant kingdom; cyanidin, malvidin, delphinidin, peonidin, petunidin and pelargonidin (Fig. **1**). They form conjugates with a number of sugars, in particular glucose, sophorose, rutinose, rhamnose, galactose, arabinose and xylose (Fig. **2**). The structures of the main anthocyanins in berries are summarised in Figure **2** and listed in more detail along with other phenolics in (Table **1**). There is much variety and while some fruits, such as cranberry (*Vaccinium macrocarpon*) and elderberry (*Sambucus nigra*), contain derivatives of only one type of anthocyanin (i.e. cyanidin), a wide array of anthocyanins is found in blueberry (*Vaccinium corymbosum*) and blackcurrant (*Ribes nigrum*). In general the anthocyanin profile of a tissue is characteristic, and it has been used in taxonomy, and for the detection of adulteration of juices and wines. Blackcurrants are characterised by the presence of the rutinosides and glucosides of delphinidin and cyanidin [30], with the rutinosides being the most abundant. Other anthocyanins and flavonol conjugates have been noted, but at much lower concentrations [31, 32]. Whilst redcurrants (*Ribes rubrum*) are very closely related to blackcurrants, they contain mainly cyanidin diglycosides with cyanidin monoglucosides present only as minor components [33]. Strawberries (*Fragaria x ananassa*), blackberries (*Rubus* spp.), and red raspberries (*Rubus idaeus*) are all from the Rosaceae family but they have a diverse anthocyanin content. The major anthocyanins in raspberries and blackberries are derivatives of cyanidin, while in strawberries pelargonidin glycosides predominate [33]. The major components in blueberries are delphinidin-3-galactoside and petunidin-3-glucoside, however, many minor anthocyanins are also present [34, 33]. Cranberries belong to the Ericaceae, the same family as blueberries, but have cyanidin-based compounds as their major anthocyanins [35]. As with cranberries, blackberries and raspberries, the major anthocyanins in elderberries are cyanidin-based, with cyanidin-3-sambubioside and cyanidin-3-glucoside predominating [36] (Table **1**, Fig. **2**).

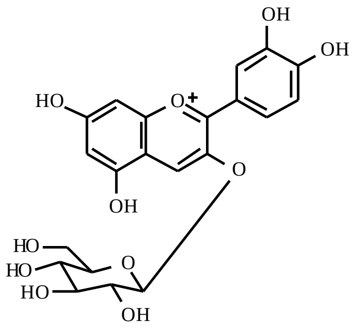


| Anthocyanidin | R₁ | R₂ | Colour |
|---|---|---|---|
| Pelargonidin | H | H | orang-red |
| Cyanidin | OH | H | red |
| Delphinidin | OH | OH | pink |
| Peonidin | $OCH_3$ | H | bluish purple |
| Petunidin | $OCH_3$ | OH | purple |
| Malvidin | $OCH_3$ | $OCH_3$ | redish purple |

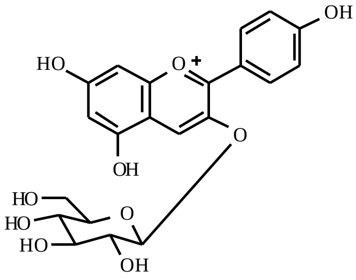
**Fig. (1).** Structures of the major anthocyanins

Flavonols and other flavonoids are commonly quantified as the aglycone after acid or enzyme hydrolysis to remove sugar residues [37, 38]. Using this approach the myricetin, quercetin and kaempferol content (Fig. **3**) of edible berries had been estimated [39]. Quercetin was found to be highest in bog whortleberry (*Vaccinium uliginosum*) (15.8 mg/100 g), bilberry (*Vaccinium myrtillus*) (1.7 – 3.0 mg/100 g) and in elderberries. In blackcurrant cultivars, myricetin was the most abundant flavonol (8.9 – 20.3 mg/100 g), followed by quercetin (7.0 – 12.2 mg/100 g) and kaempferol (0.9 – 2.3 mg/100 g) [40]. In comparison, the total anthocyanin content of red raspberries is ca. 60mg/100g [41]. Specific flavonol glycosides that have been identified in berries include quercetin-3-glucoside, quercetin-3-rutinoside quercetin-3-galactoside and quercetin-3-xylosylglucuronide, myricetin-3-glucoside, myricetin-3-galactoside and myricetin-3-rutinoside (Fig. **4**, Table **1**) [42-45].

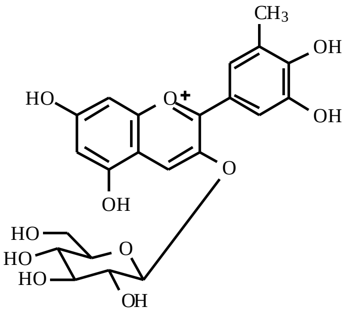
Berries can contain substantial amounts of the flavan-3-ol monomers (+)-catechin and (-)-epicatechin as well as dimers, trimers and polymeric proanthocyanidins (Fig. **5**). The



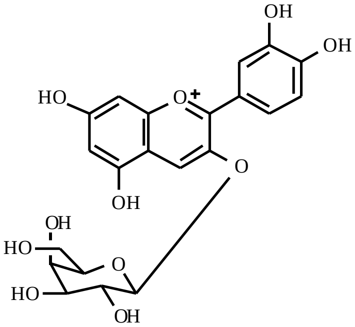
**Cyanidin-3-*O*-glucoside**
**(*Blackberry, Strawberry, Elderberry*)**



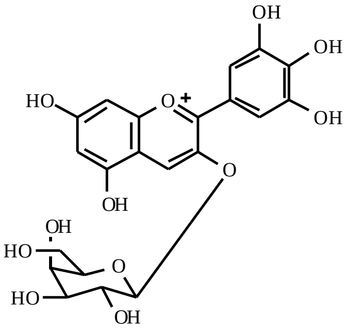
**Pelargonidin-3-*O*-glucoside**
**(*Strawberry*)**



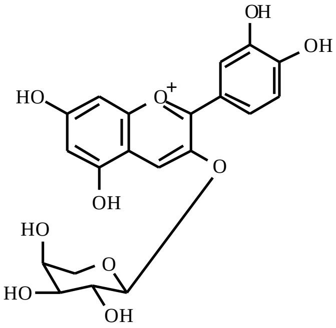
**Petunidin-3-*O*-glucoside**
**(*Blueberry*)**



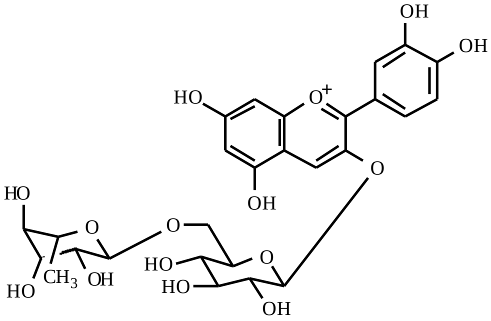
**Cyanidin-3-*O*-galactoside**
**(*Cranberry*)**



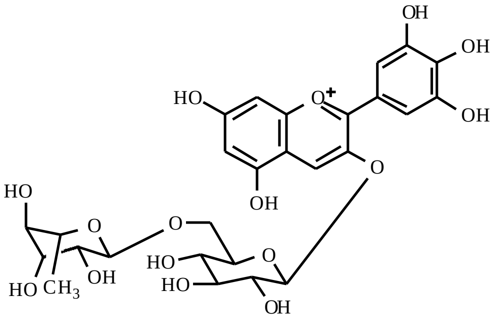
**Dephinidin-3-*O*-galactoside**
**(*Blueberry*)**



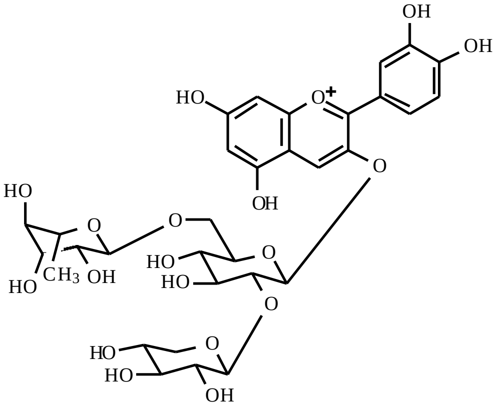
**Cyanidin-3-*O*-arabinoside**
**(*Cranberry*)**



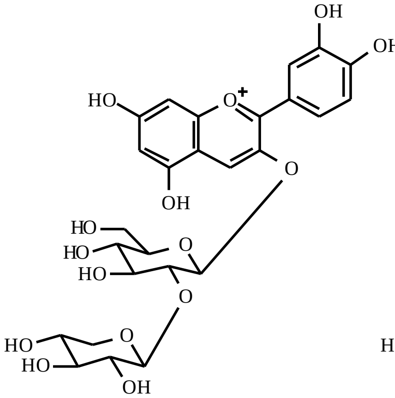
**Cyanidin-3-*O*-rutinoside**
**(*Blakcurrant,* Blackberry)**



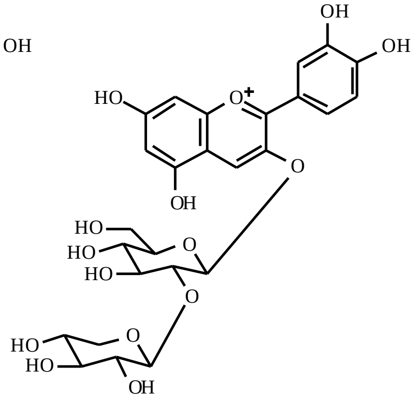
**Delphinidin-3-*O*-rutinoside**
**(*Blakcurrant*)**



**Cyanidin-3-*O*-($2^{G}$-*O*-xylosylrutinoside)**
**(*Redcurrant, Raspberry*)**



**Cyanidin-3-*O*-sophoroside**
**(*Raspberry*)**



**Cyanidin-3-*O*-sambubioside**
**(*Elderberry*)**

**Fig. (2).** Structures of the major anthocyanins in berries.

**Table 1. Endogenous Phenolics in Berries. Major Components Indicated in Bold Font**

| Common name | Genus and species | Family | Phenolics | Reference |
|---|---|---|---|---|
| **Blackcurrant** | *Ribes nigrum* | Grossulariaceae | **Del-3-Rut; Cy-3-Rut;** Del-3-Glc; Cy-3-Glc Peo-3-Rut, Mal-3-Rut Mal-3-Rut, Mal-3-Glc, Myr-3-Rut, Myr-3-Glc, Q-3-Rut, K-3-Glc | Matsumoto *et al*., 2001a<br>Frøytlog *et al*., 1998<br>Hakkinen and Auriola, 1998<br>Määttä *et al*., 2003 |
| **Redcurrant** | *Ribes rubrum* | Grossulariaceae | Cy-3-Glc-Rut, Cy-3-Soph, Cy-3-Glc, **Cy-3-Xyl-Rut,** Cy-3-Rut | Goiffon *et al*., 1999 |
| **Strawberry** | *Fragaria* × *ananassa* | Rosaceae | **Pel-3-Glc, Cy-3-Glc,** Pel-3-Ara **Ellagic acid** | Goiffon *et al*., 1999, Bridle and Garcia-Viguera, 1997<br>Amakura *et al*., 2000 |
| **Blackberry** | *Rubus spp.* | Rosaceae | Cy-3-Sop, Cy-3-Glc-Rut, **Cy-3-Glc, Cy-3-Rut,** Q-3-Gal, Q-3-Glc, Q-3-Rut, Q-3-XylGlcAC, **lambertianin C** | Hong and Wrolstad, 1990<br>Cho *et al*., 2004,<br>Degénéve 2004 |
| **Red raspberry** | *Rubus idaeus* | Rosaceae | Cy-3-Sop, Cy-3-Glc-Rut, Cy-3-Rut, Cy-3-Glc, Pel-3-Sop, Pel-3-Glc-Rut, Cy-3,5-DiGlc, Cy-3-Samb, Pel-3-Glc, Pel-3-Rut, **sanguiin H-6,** lambertianin C, Q-3-Rut, Q-3-Glc, Q-3-GlcAC | Boyles and Wrolstad, 1993<br>Mullen *et al*., 2002 |
| **Blueberry** | *Vaccinium corymbosum* | Ericaceae | **Del-3-Gal,** Del-3-Glc, Cy-3-Gal, Del-3-Ara, Cy-3-Glc, Pet-3-Gal, Cy-3-Arab, **Pet-3-Glc,** Peo-3-Gal, Pet-3-Arab, Peo-3-Glc, Mal-3-Gal, Peo-3-Arab, Mal-3-Glc, Mal-3-Arab, caffeoylquinic acids, **Q-3-Gal,** Q-3-Glc, Q-3-Rut | Kader *et al*., 1996;<br>Goiffon *et al*., 1999;<br>Prior *et al*., 2001,<br>Cho *et al*., 2004 |
| **Cranberry** | *Vaccinium macrocarpum* | Ericaceae | **Cy-3-Gal, Cy-3-Ara,** Cy-3-Gal, Cy-3-Ara, Myr-3-Gal, Q-3-Gal, Q-3-Rham | Huopalahti *et al*., 2000;<br>Prior *et al*., 2001;<br>Vvedenskaya *et al*., 2004 |
| **Elderberry** | *Sambucus nigra* | Caprifoliaceae | Cy-3-Samb-5-Glc, Cy-3,5-DiGlc, **Cy-3-Samb, Cy-3-Glc** | Bridle and Garcia-Viguera, 1997 |

Abbreviations: Cyanidin (Cy); Pelargonidin (Pel); Peonidin (Peo), Petunidin (Pet), Malvidin (Mal), Quercetin (Q), Myricetin (Myr), Kaempferol (K); Glucoside (Glc), Diglucoside (DiGlc); Sophoroside (Sop); Xyloside (Xyl); Acetylxyloside (XylAc); Arabinoside (Ara); Acetylarabinoside (AraAc); Glucuronide (GlcAC); Xylosylglucuronide (XylGlcAC); Acetylglucoside (GlcAc); Galactoside (Gal); Rhamnoside (Rham), Rutinoside (Rut); Sambubioside (Samb).

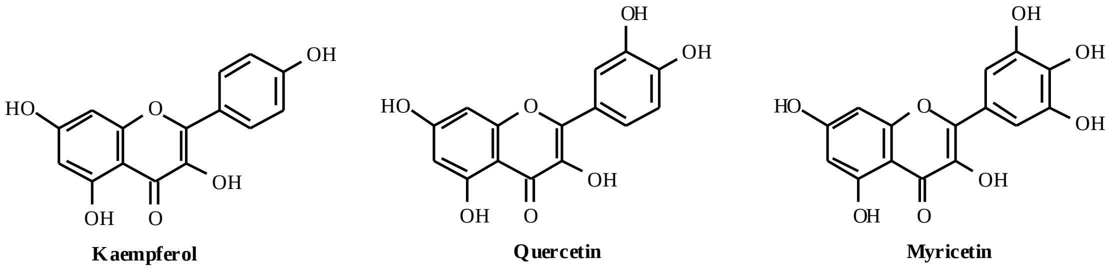
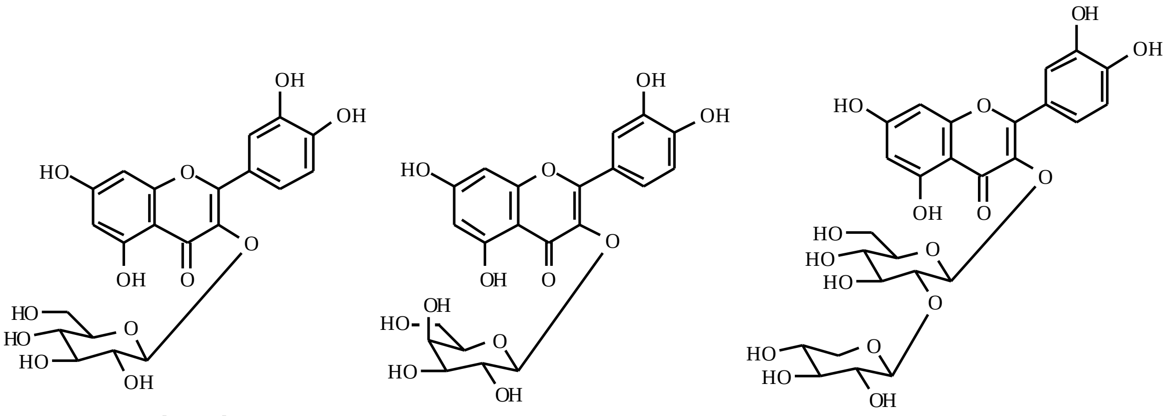


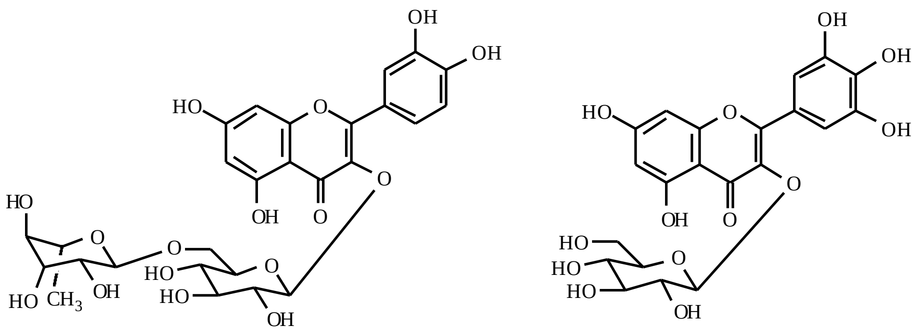
**Fig. (3).** Structures of the flavonol aglycones kaempferol, quercetin, isorhamnetin and myricetin.

concentration of the polymers is usually greater than the monomers, dimers and trimers and overall, cranberries are a particularly rich source of these compounds [46, 47] (Table **2**).

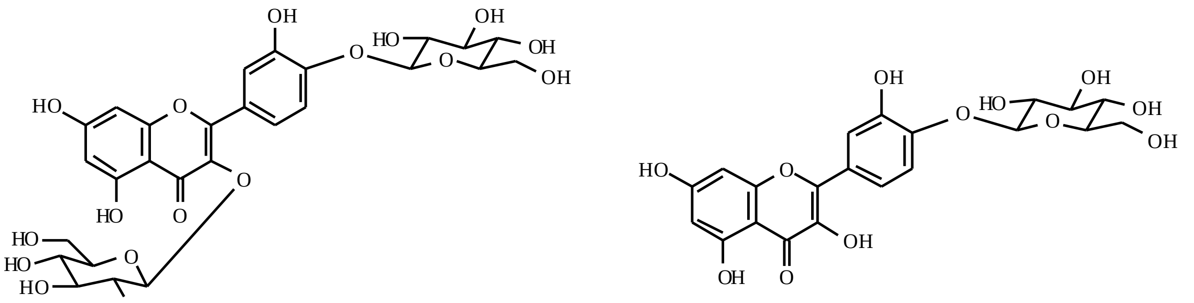
The hydroxybenzoate, ellagic acid (Fig. **6**) has been reported to be present in berries, particularly raspberries (0.58 mg/100 g), strawberries (1.8 mg/100 g) and blackberries (8.8 mg/100 g) [48]. Indeed ellagic acid has been described as being responsible for > 50% of total phenolics quantified in strawberries and raspberries [49]. In reality, however, free ellagic acid levels are generally low, although substantial quantities are detected along with gallic acid after acid hydrolysis of extracts as a product of ellagitannin breakdown (Fig. **6**). For instance, red raspberries, the health benefits of which are often promoted



**Quercetin-3-glucoside** **Quercetin-3-galactoside** **Quercetin-3-xyloglucoside**



**Quercetin-3-rutinoside** **Myricetin-3-glucoside**



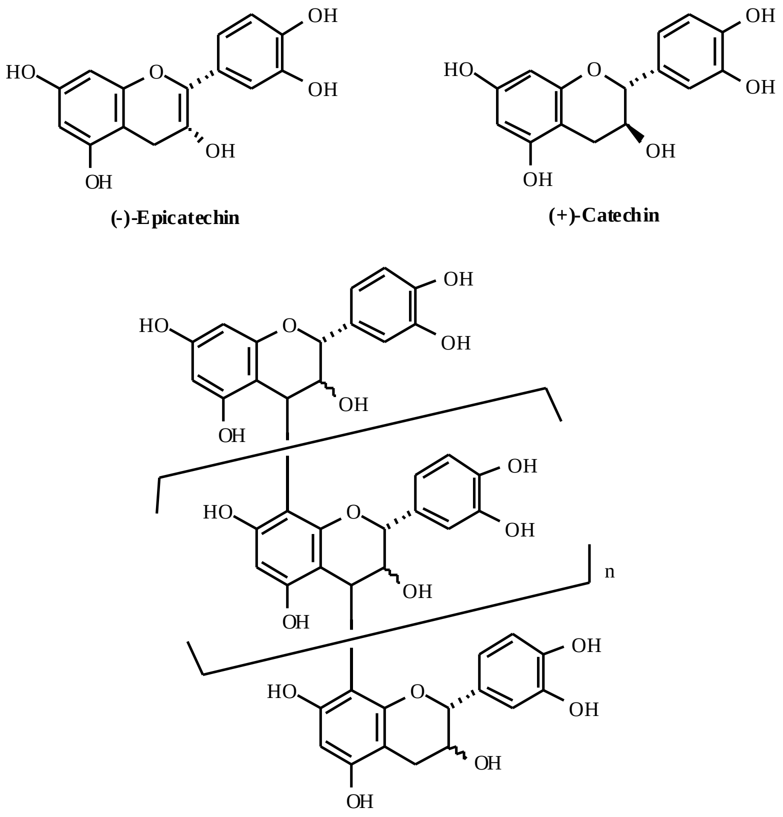
**Quercetin-3,4'-*O*-diglucoside** **Quercetin-4'-*O*-glucoside**

**Fig. (4).** Structures of flavonol glycosides.

on the basis of a high ellagic acid content, contain ca. 100 µg/100 g of ellagic acid compared to ca. 30 mg/100g of ellagitannins, mainly in the form of sanguiin H-6 and lambertianin C (Fig. **6**) [41]. Berries also contain a variety of hydroxycinnamates including caffeoyl/feruloyl esters but usually they are present in low concentrations [50] although in other fruits compounds such as 5-caffeoylquinic acid (chlorogenic acid) can accumulate in substantial concentrations.

## 5. POTENTIAL HEALTH PROPERTIES OF BERRY PHYTOCHEMICALS

There is a lack of epidemiological studies relating consumption of berries to disease risk. However, flavonoid intake and risk of CHD mortality was first investigated using the 7-Countries Study – a cross-cultural correlation study composed of 16 cohorts followed-up for 25 years after initial baseline measurements collected around 1960 [51]. The average intake of flavonols and flavones combined was found to be inversely associated with CHD mortality, statistically explaining 25% of the variability in CHD rates across the cohorts. There have subsequently been at least 7 epidemiological studies that appear to corroborate Hertog's original findings although weak but inverse relationships between intake and CHD have also been described [14]. Similarly, flavonoid intake has also been associated with decreased risk of cancer in some but not all studies [52, 53]. Numerous *in vitro* studies also indicate that plant secondary metabolites can potentially affect diverse processes in mammalian cells which, if also occurring *in vivo*, could have



**(-)-Epicatechin**

**(+)-Catechin**

**Oligomeric Procyanidins**
**n = 0, dimeric**
**n = 1, trimeric**
**n = 2, tetrameric**

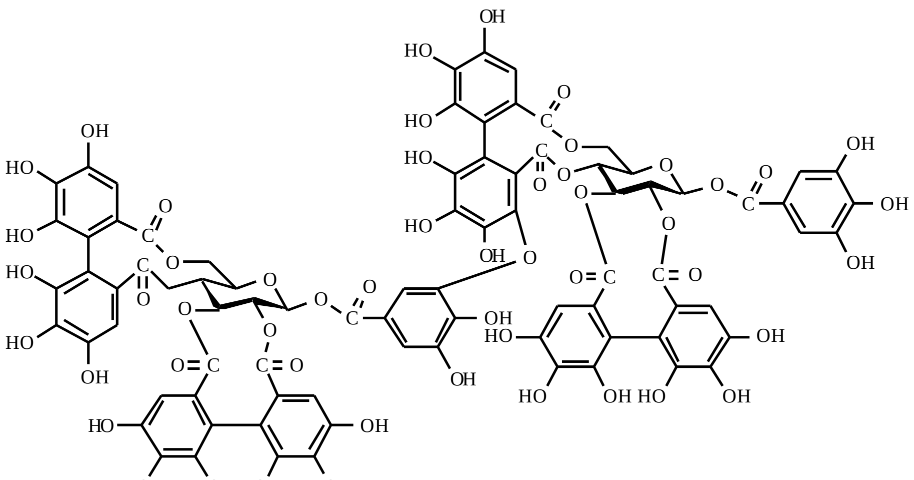
**Fig. (5).** Structures of the flavan-3-ol monomers (+)-catechin and (-)-epicatechin and oligomeric proanthocyanidins.

**Table 2. Concentration of Flavan-3-ol Monomers, Dimers and Trimers and Total Proanthocyanidins in Berries. Data Expressed as mg/100g Fresh Weight ± Standard Deviation. n.d. – Not Detected; n.a. – Not Analysed; PA – Proanthocyanidins**

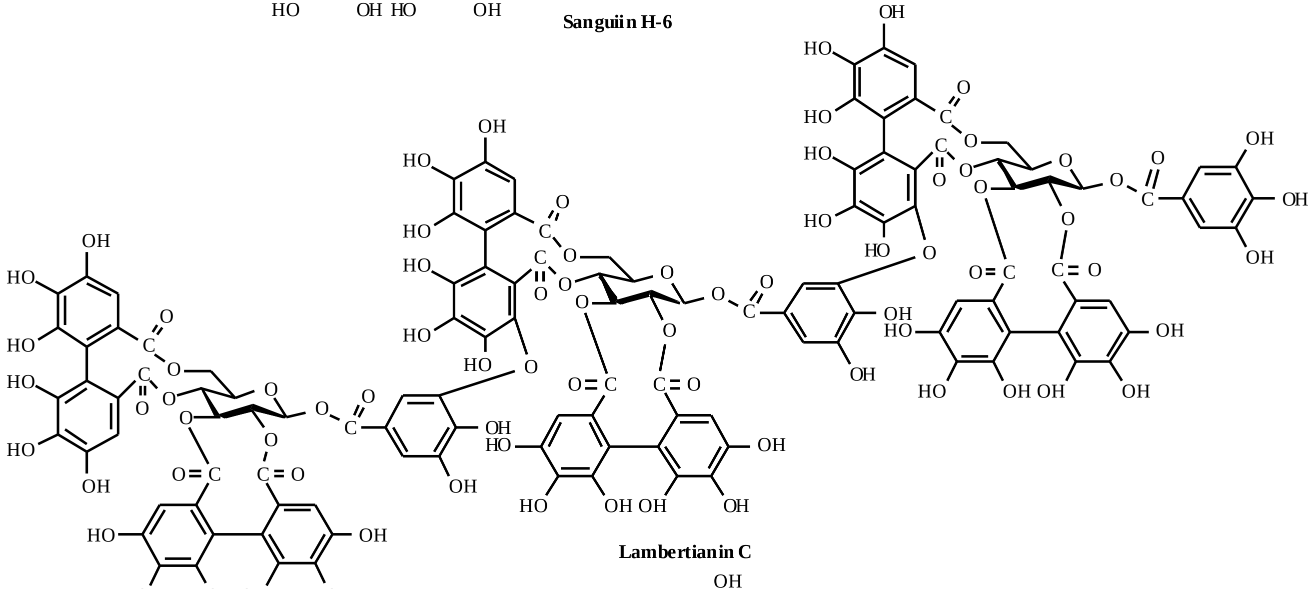
| Berry | Monomers | Dimers | Trimers | Total PAs | Source |
|---|---|---|---|---|---|
| Blackcurrant | 0.9 ± 0.2 | 2.9 ± 0.4 | 3.0 ± 0.3 | 122 ± 28 | Gu *et al.*, (2004) |
| Redcurrant | 3.2 | 1.9 | n.d. | n.a | de Pascual-Teresa *et al.*, (2000) |
| Strawberry | 4.2 ± 0.7 | 6.5 ± 1.3 | 6.5 ± 1.2 | 145 ± 25 | Gu *et al.*, (2004) |
| Blackberry | 3.7 ± 2.2 | 6.7 ± 2.9 | 3.6 ± 1.9 | 27 ± 17 | Gu *et al.*, (2004) |
| Red raspberry | 4.4 ± 3.4 | 11 ± 10 | 5.5 ± 5.7 | 30 ± 23 | Gu *et al.*, (2004) |
| Blueberry | 4.0 ± 1.5 | 7.2 ± 1.8 | 5.4 ± 1.2 | 180 ± 51 | Gu *et al.*, (2004) |
| Cranberry | 7.3 ± 1.5 | 26 ± 6.1 | 70 ± 13 | 419 ± 75 | Gu *et al.*, (2004) |

anti-carcinogenic and anti-atherogenic implications. These processes include gene expression, apoptosis, platelet aggregation, LDL oxidation, blood vessel dilation, intercellular signalling, P-glycoprotein activation and the modulation of enzyme activities associated with carcinogen activation and detoxification (reviewed in [54]). For example, extracts of bilberry, rich in delphinidin and malvidin glycosides induce apoptosis in human leukaemia HL60 cells, the former also inhibiting the growth of colon cancer HCT116 cells [55]. Similarly, anthocyanins and hydroxycinnamic acids from blueberry and cranberry protect endothelial cells against TNFα induced inflammatory responses [56].

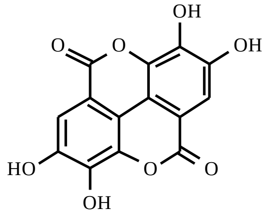
Other flavonols found in fruit including berries, such as quercetin, have been shown to inhibit cyclooxygenase and lipoxygenase activities [57]; both enzymes are involved in the release of arachidonic acid, the initiator of a general inflammatory response. Quercetin also exerts a preferential



**Sanguiin H-6**



**Lambertianin C**



**Ellagic acid**

**Fig. (6).** Raspberries contain high concentrations of two ellagitannins, sanguiin H-6 and lambertianin C. When extracts are treated with acid the ellagitannins are hydrolysed releasing substantial quantities of ellagic acid.

cytotoxic effect on dividing colon carcinoma HT29 and CACO2 cells [58] and induces apoptosis in human leukaemia HL60 cells following inhibition of growth. Possible mechanisms of action could include, increased expression of wild type p53 [59], reduction of Ki ras levels [60] or p21 upregulation [61]. Quercetin also inhibited DNA synthesis in human leukaemia HL60 cells [61, 62] and animal studies indicate that the incidence of carcinogen induced mammary tumours and lung tumours were decreased by dietary administration of quercetin [63, 64]. Extensive research has been carried out on the potential anti-cancer properties of ellagic acid, mediated in a number of mechanisms [65] such as the inhibition of metabolic activation of carcinogens [66], protection of DNA from alkylation by binding sites that may react with carcinogens [67] and the regulation of cell cycle progression and cell death (apoptosis) in cancer cells.

Potential cardiovascular protective effects of ellagitannins have also been reported as vasorelaxation assays on rabbit aorta found that sanguin H-6 and lambertianin C, were the active components of raspberry extracts responsible for vasorelaxation activity [68]. The flavonols quercetin and catechin were found to act synergistically to inhibit platelet aggregation and adhesion to collagen [69], atherosclerotic lesions being reduced by 46% in apolipoprotein E deficient mice when added to the diet [70].

Much attention has focussed on the ability of compounds such as anthocyanins and flavonols to act as antioxidants. This is possibly unsurprising as there is a substantial body of epidemiological and experimental literature suggesting that inadequate intakes of recognised nutritional antioxidants such as vitamin E, vitamin C and carotenoids can lead to oxidative damage of proteins, lipids and DNA *in vivo.* This, in turn, may predispose the development of many chronic diseases [71]. The antioxidant effectiveness of anthocyanins and other polyphenols *in vitro* is essentially due to the ease with which a hydrogen atom from an aromatic hydroxyl group is donated to a free radical [72]. In addition, their ability to chelate transition metal ions involved in radical-forming processes such as Fenton reactions [73, 74] and the induction of endogenous antioxidants [75] could also contribute to antioxidant efficacy of the compounds. Consequently, numerous studies have shown that many phenolic compounds found in fruits and vegetables, including berries, inhibit the oxidation of LDL and DNA *in vitro* e.g. [76, 77].

## 6. ABSORPTION OF BERRY PHYTOCHEMICALS

Although phytochemicals found in berries may exert numerous effects *in vitro*, they have to be absorbed from the gut if they are to exert a similar effect in systemic cells and tissues. This absorption will depend on numerous factors including molecular structure, the amount consumed, the food matrix, degree of bioconversion in the gut and tissues, the nutrient status of the host and genetic factors. Ingestion of fresh strawberries (240g), freeze dried blueberries (100g) and berry juices have all been reported to increase the antioxidant capacity of blood plasma by 14-30%. [78, 79] [80-82] which suggests that some phytochemicals with antioxidant properties are absorbed [83, 84]. However, this view has recently been challenged as any change in plasma antioxidant capacity after fruit consumption may be mainly due to fructose mediated increases in uric acid rather than fruit-derived antioxidants [85]. This is compatible with the observation that the absorbtion of anthocyanins and other flavonoids from the diet is relatively low.

### Anthocyanins

A variety of anthocyanins appear in urine after supplementation with berries or berry extracts but in very low concentrations, usually 0.1%, or less, of the ingested dose [86]. Anthocyanins have also been found in human plasma in very low concentrations 0.5-1 h after consumption, falling to near baseline levels within 6-8 h. After the consumption of an elderberry extract by elderly women, the main elderberry anthocyanins, cyanidin-3-glucoside and cyanidin-3-sambubioside, were detected in plasma. [87]. Thus, glycosylated anthocyanins, unlike flavonol glycosides, appear in the bloodstream. This may be a consequence of the fact that, in contrast to quercetin glucosides, anthocyanin glucosides are not hydrolysed by human small intestine β-glucosidases [88]. Studies with rats indicate that anthocyanin absorption occurs in the stomach as well as the small intestine [89-91].

Although only unmodified anthocyanins have been usually detected in urine after supplementation [86], improved analytical techniques are now beginning to reveal the presence of lower levels of methylated, glucuronidated and sulphated metabolites. For instance after consumption of elderberries, as well as cyanidin-3-glucoside and cyanidin-3-sambubioside, urine was found to contain four metabolites, peonidin-3-glucoside, peonidin-3-sambubioside, a peonidin glucuronide and a cyanidin-3-glucosylglucuronide. This demonstrates that methylation of the 3'-hydroxyl group had occurred as well as glucuronidation at an as yet undetermined position (Fig. **8**) [92]. In a study with strawberries, which contain pelargonidin-3-glucoside, the predominant anthocyanin to appear in urine was not the parent glucoside but three pelargonidin glucuronides, a pelargonidin sulphate and the aglycone pelargonidin [93].

### Flavonols

The absorption and excretion of flavonols in humans and model animal systems has been studied extensively. Although these investigations have not involved berries, flavonols that occur in berries such as quercetin-3-glucoside and the disaccharide quercetin-3-rutinoside (Fig. **5**) have been extensively investigated. Flavonol aglycones, such as quercetin (Fig. **3**) are hydrophilic and can passively diffuse across biological membranes. Flavonol glycosides, in contrast, are more water-soluble molecules which greatly limits their rate of diffusion through cell membranes. Thus, if the glycosides, which occur in berries and are the major components in other fruits and vegetables, are to be absorbed into the circulatory system some form of transport system is likely to be involved. On the basis of indirect evidence it has been proposed that flavonol glucosides, such as quercetin-3-glucoside, can be absorbed intact into the small intestine using the sodium-dependent glucose transporter (SGLT1) [94]. There is evidence that supports the involvement of SGLT1 in the uptake of flavonol glucosides [95] [96]. However, other studies with human intestinal Caco-2 cell monolayers have shown that quercetin-4'-glucoside is not absorbed despite the operation of SGLT1 which was demonstrated by the active transport of glucose [97]. Further research is required to determine the mechanism(s) by which flavonols and other flavonoids are transported from the lumen of the gastrointestinal (GI) tract into the bloodstream.

Studies with human volunteers have been carried out following consumption of lightly fried onions, which contain especially high concentrations of flavonol conjugates, principally quercetin-4'-glucoside and quercetin-3,4'-diglucoside (Fig. **4**). Aziz *et al.* (1998) [98] reported that following ingestion of 300g of lightly fried onions by human volunteers, conjugatedquercetin (quercetin released by acid hydrolysis, therefore probably originating from quercetin glucuronide and sulphate metabolites – see below) appeared in plasma. A peak plasma concentration of almost 2 µM was reached after 1 h and levels declined *ca.* 3-fold over the next 4 hours and only trace quantities remained at 24 hours (Fig. **10A**).

Subsequently Day *et al.* (2001) [99] used HPLC with MS and diode array detection to analyse human plasma collected 1.5 h after ingestion of onions. A mixture of glucuronidated and sulphated conjugates of quercetin and methylquercetin were identified. In total 12 quercetin conjugates were detected, the major components being quercetin-3-*O*-glucuronide, its 3'-methylated derivative, isorhamnetin-3-glucuronide, a quercetin diglucuronide and quercetin-3'-sulphate (Fig. **7**). There was, therefore, extensive metabolism of the parent flavonol glucosides involving deglycosylation, glucuronidation, sulphation and methylation. In a further study a total of twenty three flavonol metabolites, comprising a mixed range of sulphate, methyl, glucuronide and glucoside derivatives of quercetin, were detected in plasma and urine after the consumption of onions [100].

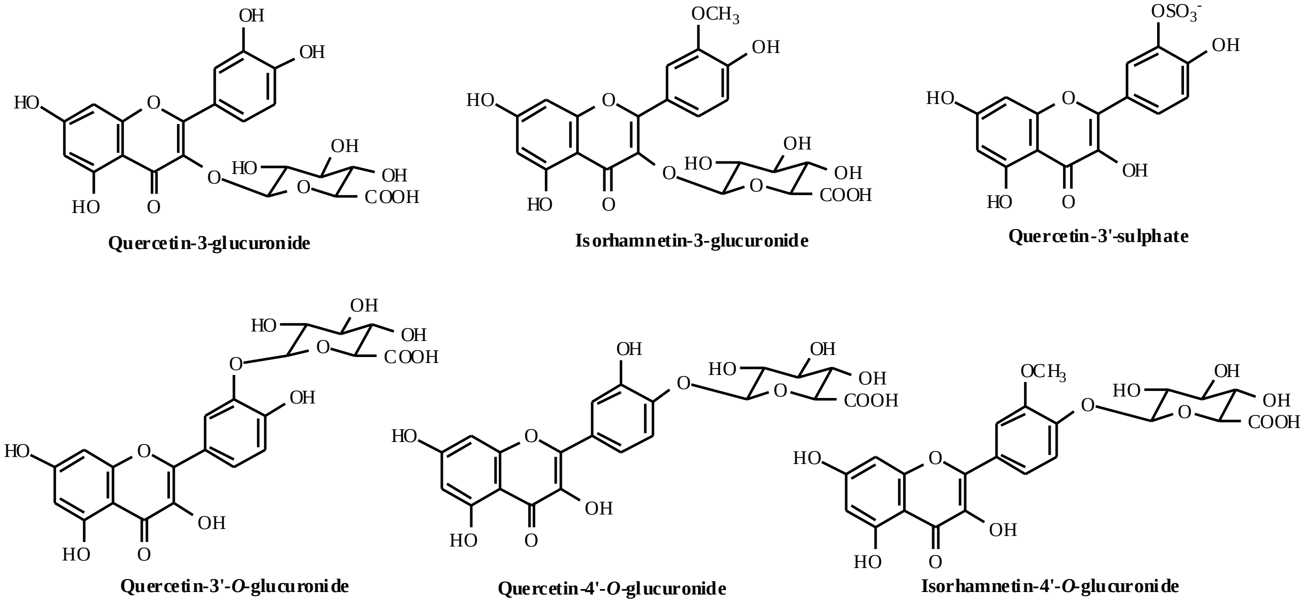
Quercetin glucosides are deglycosylated by β-glucosidases in the small intestine, namely broad specific cytosolic β-glucosidase (CBG) and lactase phloridzin hydrolase (LPH) [101]. The aglycone does not accumulate but is metabolised by uridine-5'-diphosphate glucuronyl-transferases, sulphotransferases and/or catechol-*O*-methyltransferases [102]. Studies with rats following ingestion of [2-$^{14}$C]quercetin-4'-glucoside indicate that as well as transport in the bloodstream there is a substantial efflux of the various quercetin metabolites back into the lumen of the GI tract [103]. Quercetin metabolites which do enter the circulatory system and gain access to the liver may then be further methylated, glucuronidated or sulphated [102]. Although there is evidence that enterohepatic circulation returns quercetin metabolites to small intestine, the extent to which this occurs is as yet unknown. The disaccharide, quercetin-3-rutinoside, which is found in berries, as well as apples and tea, is not a substrate for either LPH or CBG. In addition, it has a lower and delayed peak plasma concentration than quercetin-4'-glucoside [104] indicating that it may be absorbed in the distal section of the small intestine and/or the large intestine where it is probably degraded by colonic bacteria [88].

## Flavan-3-ols

Monomeric flavan-3-ols as well as dimers, trimers and oligomers are present in berries (Table **2**) but information on the absorption and metabolism of these compounds comes primarily from studies with (-)-epicatechin, (+)-catechin, procyanidin-rich chocolate and grape seed extracts. (-)-Epicatechin and (+)-catechin are absorbed in humans and animals appearing in plasma and urine primarily as glucuronidated, methylated and sulphated metabolites [105] [106-110]. Peak plasma concentrations typically occur 1-2 h after ingestion. Identified human plasma and urinary metabolites include (-)-epicatechin-3'-glucuronide, 4'-methyl-(-)-epicatechin-3'-glucuronide while in rats formation of 3'-methyl-(-)-epicatechin, (-)-epicatechin-7-glucuronide, 3'-methyl-(-)-epicatechin-7-glucuronide occurs (Fig. **9**) [111].

There is conflicting evidence on the absorption and metabolism of the oligomeric and polymeric flavan-3-ols in humans and animals. Koga *et al.* (1999) [112] observed the presence of (+)-catechin and (-)-epicatechin and an absence of dimers in the plasma of rats following ingestion of a grape seed extract. Extending this study, Donovan *et al.* (2002) [113] fed rats a GSE, (+) catechin and procyanidin $B_3$ meals. While conjugated metabolites of (+)-catechin were detected in plasma and urine after both the (+)-catechin and GSE meals there was no evidence of absorption for the procyanidins. However, in another study (-)-epicatechin and (+)-catechin and trace amounts of procyanidin dimer $B_2$ were detected in sulfatase- and β-glucuronidase-treated human plasma collected 30 min after ingestion of a cocoa beverage rich in flavan-3-ol monomers and procyanidins [114]. In keeping with this report, it has been shown that after oral administration of $B_2$ to rats, the dimer was absorbed and excreted in urine with a portion of the procyanidin being converted to (-)-epicatechin which undergoes post-ingestion conjugation and methylation [109]. On balance, however, the available evidence indicates that flavan-3-ol dimers, trimers and oligomers are, at best, poorly absorbed [115].

Sanguiin H-6 and lambertianin C (Fig. **6**) occur in high concentrations in raspberries [68] and both blackberries and



**Quercetin-3-glucuronide**

**Isorhamnetin-3-glucuronide**

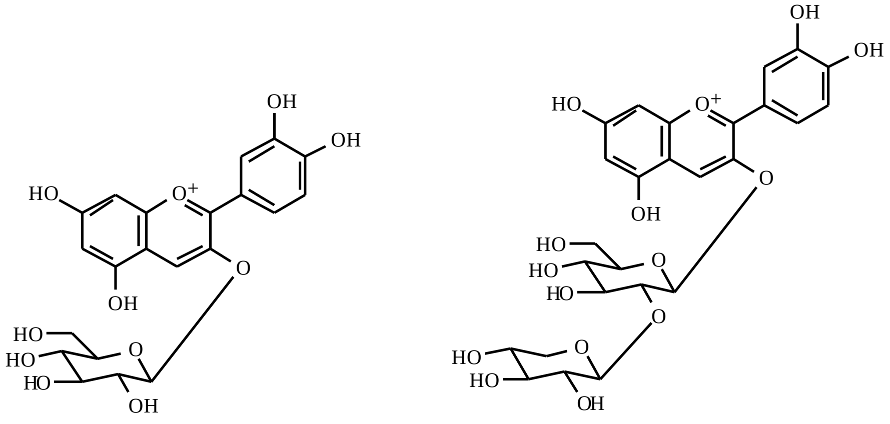
**Quercetin-3'-sulphate**

**Quercetin-3'-*O*-glucuronide**

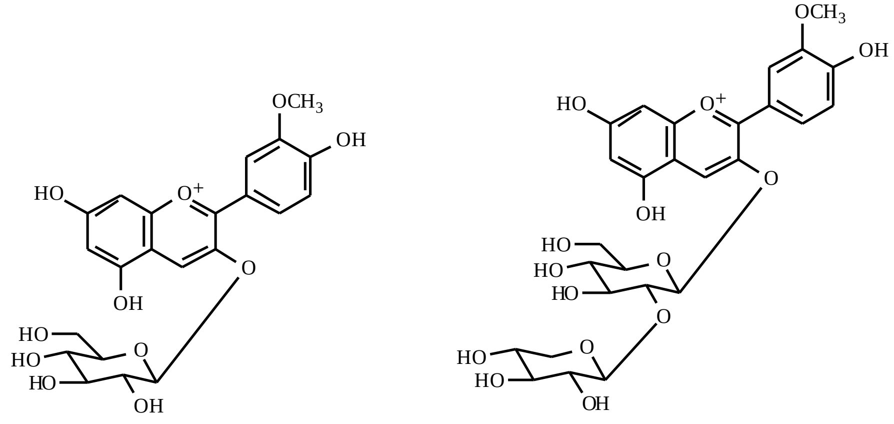
**Quercetin-4'-*O*-glucuronide**

**Isorhamnetin-4'-*O*-glucuronide**

**Fig. (7).** Flavonol metabolites detected in human plasma.



**Cyanidin-3-glucoside** **Cyanidin-3-sambubioside**



**Peonidin-3-glucoside** **Peonidin-3-sambubioside**

**Fig. (8).** Elderberrries contain cyanidin-3-glucoside and cyandidn-3-sambubioside which are converted to a number of metabolites including peonidin-3-glucoside and peonidin-3-sambubioside prior to excretion in urine.

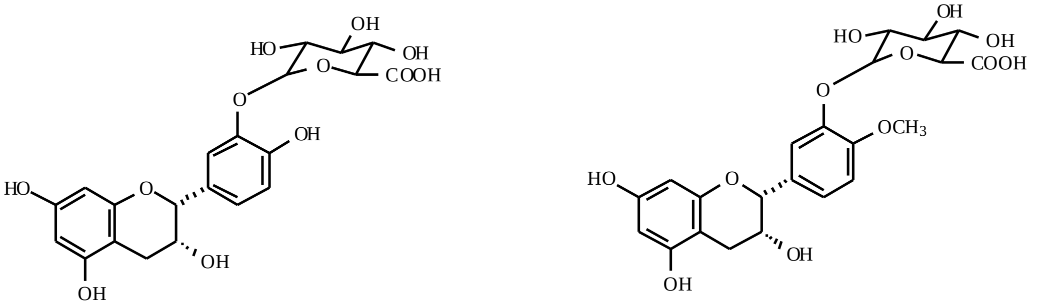
strawberries also contain substantial amounts of ellagitannins [116]. These compounds which have a molecular weight in excess of 1000 Da would appear to be too large to be absorbed into the circulatory system. They are, however, strong antioxidants [103] [116] and could exert protective effects as they pass through the GI-tract. In addition, they could also be depolymerised to some degree releasing gallic acid and ellagic acid which would be absorbed more readily.

## 7. BIOAVAILABILITY OF BERRY PHENOLICS

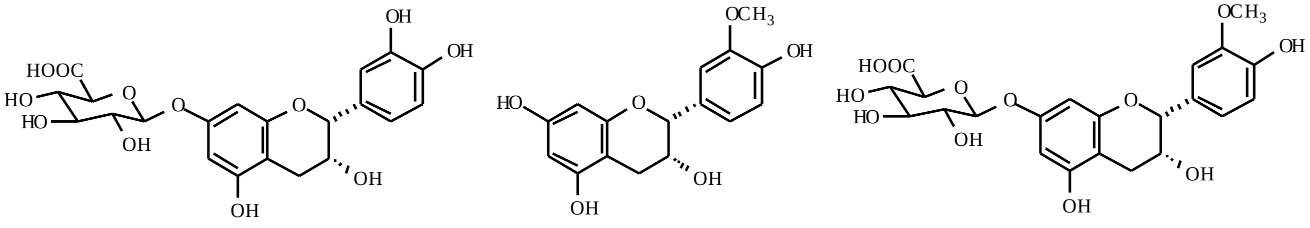
In addition to absorption, the activity of phytochemicals *in vivo* will also depend on the extent and manner of their metabolism by liver and kidney, their rate of excretion and the degree they are sequestered in body tissues. However, generally the bioavailability of dietary flavonoids has been difficult to assess. Quantitative analysis of quercetin in acid hydrolysed urine collected over a 24 h period after ingestion of onions accounted for 0.8% of the amount ingested and extrapolations from the amounts present in the bloodstream at peak plasma concentration also yielded a figure of 0.97% (Fig. **10A**) [98]. However, studies with ileostomy volunteers in which ileal fluid was analysed after ingestion of onions indicate that 50-75% of the onion flavonol glucosides are absorbed [94] [117]. To what extent and in what form the "missing" flavonols are bioavailable and sequestered in body tissues remains to be determined.

Dietary phenolics and their metabolites which are not absorbed in the small intestine pass into the large intestine and there is currently much interest in their possible catabolism by colonic bacteria resulting in ring fission and the formation of low molecular weight catabolites such as hippuric acid, benzoic acid and hydroxyphenylacetic acids [118]. Some of these acidic urinary catabolites are also products of other metabolic pathways unrelated to either flavonoid or hydroxycinnamate breakdown and they are present in substantial quantities in urine before supplementation. The assumption that relatively minor changes in the levels of these compounds are a direct consequence of the breakdown of the ingested phenolic compound is somewhat premature especially when, in the absence of studies using isotopically labelled substrates, detailed catabolic pathways are proposed [119-121].

Anthocyanins appear in plasma and are excreted in urine in far smaller concentrations than flavonols. This is evident in Figure **10** where the peak plasma concentration of the cyanidin-3-glucoside and cyanidin-3-sambubioside was *ca.* 100 nM which is *ca.* 20-fold lower than the conjugated quercetin that accumulated in plasma after eating onions.



**(-)-Epicatechin-3'-glucoronide (H)** **4'-Methyl-(-)-epicatechin-3'-glucuronide (H)**



**(-)-Epicatechin-7'-glucuronide (R)** **3'-*O*-Methyl-(-)-epicatechin (R)** **3'-Methyl-(-)-epicatechin-7-glucoronide (R)**

**Fig. (9).** (-)-Epicatechin metabolites that are produced in humans (**H**) and rats (**R**).

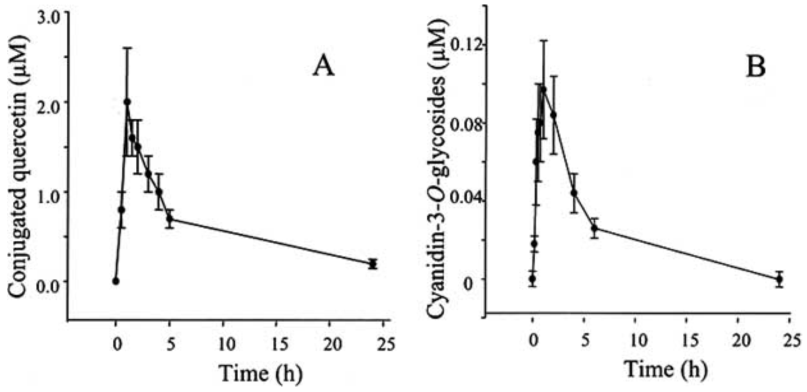


**Fig. (10).** Pharmacokinetics of (A) conjugated quercetin levels in plasma after the consumption of onions by human volunteers (n = 5) (Aziz *et al.* 1998) and (B) cyanidin-3-*O*-glycosides after the ingestion of an elderberry extract by elderly women (n = 4) (Cao *et al.* 2001). Data presented as mean values ± standard error.

Conjugated quercetin excreted after eating onions corresponded to 0.98% of the amount ingested [98] while figures for anthocyanins are typically 0.1% or less [86] with one exception, the urinary excretion of anthocyanins from strawberries which corresponded to 1.8% of the amount consumed [93]. This was accredited to analysing the urine immediately after collection as opposed to after storage of frozen samples. However, studies with urine collected after dosing with raspberries have failed to detect any differences in the anthocyanin content of fresh or thawed frozen urine with the recovery in both instances being *ca.* 0.1% (Borges and Crozier, unpublished). The higher urinary recovery of anthocyanins occurring after the ingestion of strawberries may, therefore, be a special feature of pelargonidin-3-glucoside.

It is unclear why plasma and urinary levels of anthocyanins are usually much lower than those of flavonols after supplementation. There are two possible factors that may have an influence on absorption. As mentioned earlier, anthocyanins are not hydrolysed by GI tract β-glucosidases [88] and this may reduce the amounts that pass through the gut wall into the bloodstream. However, a recent study in which anthocyanin absorption was investigated after *in situ* perfusion of the jejunum + ileum found that absorption ranged from 10.7% for malvidin-3-glucoside to 22.4 % for cyanidin-3-glucoside [90]. This is much higher than indirect estimates of anthocyanin absorption based on either plasma content or urinary excretion levels. A further factor to consider, in addition to catabolism to hydroxyphenylacetic acids and related compounds, is that at low pH anthocyanins exist as flavylium cations but can undergo pH-dependent structural changes [122]. They will be at *ca.* pH 6 in the GI tract, the circulatory system and body tissues so there may be conversion to other forms such as chalcones which are not so readily detected as the red coloured flavylium ion.

Flavan-3-ol monomers appear to be efficiently absorbed into the bloodstream as Donovan *et al.* (2002) [113] fed rats a single 20 mg (+)-catechin supplement and observed that urinary excretion of (+)-catechin metabolites over a 24 h period corresponded to 37% of the ingested dose. This is much higher than equivalent figures obtained with flavonols and anthocyanins and indicates that flavan-3-ol monomers are efficiently absorbed from the GI-tract into the circulatory system.

Although the term bioavailability is used freely in the literature, information is only beginning to emerge on the levels and identity of phenolic compounds and their *in vivo* metabolites that appear in the circulatory system after ingestion of berries and other fruits and vegetables. Saturation of metabolic pathways by "pharmacological" doses appear to be required to obtain the free form in the blood [123]. Ingestion of nutritionally relevant amounts results in extensive deglycosylation, glucuronidation, sulphation and methylation reactions mediated by a range of enzymes in the small intestine, liver and colon. The extent and identity of these *in vivo* metabolites that accumulate in body tissues is very poorly understood although information is beginning to be obtained from feeding radiolabelled flavonoids to model animal systems [103]. It is, however, clear that in most instances once flavonoids and other phenolics enter the circulatory system they undergo extensive metabolism. Thus, if physiological studies, with cell cultures and *in vitro* test systems, investigating potential protective effects are to be of any relevance they should be making use of genuine *in vivo* metabolites, like quercetin-3-glucuronide and quercetin-3'-sulphate, and not aglycones or glycosides which do not accumulate in the body [124]. This should be borne in mind in relation to the following section on possible health benefits of consuming berries.

## 8. STUDIES SUGGESTING HEALTH BENEFITS OF BERRIES

### 8.1. Cancer

Cancer development is commonly recognised as a microevolutionary process that requires the cumulative action of multiple events. (1) initiation: induction of DNA mutation in a somatic cell, (2) promotion: stimulation of tumourigenic expansion of the cell clone, (3) progression: malignant conversion of the tumour into cancer [125]. *In vitro* studies suggest that certain berry extracts can moderate such processes in particular by inhibiting the growth and proliferation of cancer cells, inducing cell death [126], [55] and impairing angiogenesis through inhibition of expression of vascular endothelial growth factor VEGF [127]. Results from animal models, however, are equivocal. For example, inclusion of freeze dried black raspberries and strawberries [128] in the diets of rats given a tumour initiator resulted in decreased progression, incidence and multiplicity of oesophageal tumours. However, similar effects were not observed with blueberries [129]. A human intervention study did find that after 5 weeks consumption of berry juice (aronia, blueberry and boysenberry), there was a decrease in oxidised DNA bases in peripheral blood mononuclear cells [81] although whether this implies a decrease in risk of developing cancer is uncertain.

### 8.2 Heart Disease

Uptake of oxidised low density lipoprotein cholesterol by monocytes and macrophages in the vascular endothelium may be a key event in the development of the plaque which occludes the coronary arteries [130, 131]. Although *in vitro* studies have shown that extracts from blackberry, cherry, raspberry, blueberry and bilberry can inhibit LDL oxidation [132, 133], results from intervention studies have been disappointing. For example, no significant inhibition of LDL oxidation was observed after volunteers had consumed 100g of berries per day (blackcurrants, bilberries and lingonberries) for 8 weeks [134]. Similarly, consumption of berry juice did not affect plasma lipids, LDL oxidation, platelet aggregation and adhesion molecule concentration in a healthy population [135].

### 8.3. Immune System

Consumption of 330ml berry juice per day for 2 weeks is reported to increase lymphocyte responsiveness to mitogen activation, enhanced natural killer cell lytic activity and T-lymphocyte specific cytokine secretion by human volunteers suggesting enhanced immune function [81]. Whether such potentially beneficial effects are specific to berries or reflect a more general response to increased fruit intake is unclear.

### 8.4. Neurological Function

Diet may play a role in improving age-related neurological dysfunction [136] and studies with aged rats have reported that dietary berry extracts can protect against and even reverse certain age-induced declines in brain function such as those in learning, memory, motor performance and neuronal signal transduction [137, 138], [139, 140].

### 8.5. Urinary Tract Health

The effects of cranberries on urinary tract health have been widely investigated since the 1920's. It was previously thought that acidification of the urine as a result of consuming cranberries was responsible for the ameliorative effects on urinary tract infections (UTI). However cranberries contain proanthocyanidins which appear to prevent adherence of p-fimbriated *E.coli* to the uroepithelial cells [141], [142]. Other types of berries may have similar properties e.g. the blueberry, which is also a *Vaccinium* species. Several clinical trials of cranberry juice and cranberry tablets have been published. Although a Cochrane review [143], [144] found insufficient evidence to recommend cranberry juice for treatment or prevention of UTI, there are now more trials suggesting that cranberry juice or tablets do have some protective effect [145]. For example, women who consumed 50ml of a cranberry-lingonberry concentrate for 6 months had a UTI recurrence rate of 16% compared with 36% in the control group [146] and Stothers (2002) [147] found absolute risk reductions of 12% for cranberry juice and 14% for cranberry juice tablets for recurrence of UTI.

## 9. EFFECTS OF FOOD PROCESSING ON BERRIES

Advances in horticultural techniques and international trade means it is often possible to obtain fresh berries out of the traditional summer and autumn seasons. However, berries generally have a short shelf life and as a result, they are often preserved before eating. In addition, they are widely used in juices, wines, liquors, jam, ice-cream yoghurt and confectionery. Therefore, the effects of processing and storage methods on micronutrient and phytochemicals content needs to be considered when assessing potential health benefits.

In general, vitamin C content of berries declines during storage by up to 56% depending on duration and temperature. However, concentrations of other phenolics such as anthocyanins and ellagic acid remain relatively unchanged and ellagitannin levels may actually increase possibly indicating some endogenous metabolism post-harvest [41, 148, 149]. However, losses in vitamin C (36%) and flavonols (6-50%) have been reported during jam-making and subsequent storage [29, 150-152]. In contrast, concentrations of free ellagic acid initially increase after manufacture due to thermal decomposition of the ellagitannins in the berries [150]). Large losses in flavonols and vitamin C may also occur during the manufacture of berry juices although cold pressing methods may be less destructive than those involving steam extractions [29].

## 10. CONCLUSIONS

Berries are rich sources of essential micronutrients, particularly vitamin C and folic acid. They also contain numerous phytochemicals. These have diverse effects *in vitro* which suggest potential health benefits. However, until more is known about the absorption and metabolic fate of berry anthocyanins and flavonols *in vivo*, it would be unwise to ascribe additional health promoting properties to berries beyond those recognized for fruit and vegetables in general. However, in populations with habitually low intakes of plant-based foods, locally grown fresh or frozen berries are an underused and potentially valuable dietary resource.

## ACKNOWLEDGEMENTS

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