INTRODUCTION

Over the last decades, a consensus has formed that the health benefits associated with a diet rich in fruit and vegetables may be derived, in part, from the intake of natural phytochemicals, some of which are potent antioxidants (Anon 2002). A theory has been proposed that antioxidant phytochemicals (mainly polyphenols, carotenoids and vitamin C), which are found in elevated levels in fruits especially berries (Machiex et al. 1990), augment natural anti-oxidant systems and protect against oxidative damage involved in the aetiology of cardiovascular disease, cancers and other diseases (Halliwell 1996). However, it is becoming clear that many classes of polyphenol compounds, such as anthocyanins, are poorly bioavailable and lack stability in vivo (Williamson and Manach 2005) and are therefore unlikely to provide antioxidant protection at the cellular level. Also, large proportions of ingested berry polyphenols remain in the gut and pass through to the large intestine where they may be fermented to support the indigenous microflora (Aura et al. 2005).

However, evidence continues to accrue that berries or polyphenol-rich berry preparations can influence the progression of neurodegenerative diseases, cancers, cardiovascular disease and diabetes in vivo (e.g. Ramassamy 2006; Erlund et al. 2008; Stoner et al. 2008; Tsuda 2008) even if an over-arching theory to explain their mechanism of action has not been formulated. This article illustrates biological activities of berry polyphenols that may be relevant to cardiovascular health, cancer and the modulation of glycaemic control.

MATERIALS AND METHODS

Plant material and extraction

Blackcurrants (Ribes nigrum L. breeding line 8982-6) were obtained from Bradenham Hall, Norfolk and blueberries (Vaccinium myrilllus L. cv. ‘Berkeley’) were grown at SCRi. Cloudberries (Rubus chamaemorus L.), lingonberries (Vaccinium vitis-idaea) and rowan berries (Sorbus aucuparia L. cv. ‘Sahlahama’) were a gift from Dr. Harri Kokko, University of Kuopio, Finland and arranged via the European Union Northberry Project. Strawberries (Fragaria ananassa cv. ‘Elksanta’), blackberries (Rubus fructicosus L.), pomegranates (Punica granatum L.) and red wine (Echo Falls, a Merlot variety wine from Mission Bell Winery, Madera, California, USA) were purchased from a local supermarket. Raspberries (Rubus idaeus L. cv. ‘Glen Ample’) were obtained from local farmers. Pure quercetin glucuronide (QG) and quercetin sulphate (QS) were gifts from Professor Alan Crozier, Division of Biochemistry and Molecular Biology, University of Glasgow. Polyphenol-rich extracts that lack sugars or ascorbic acid were extracted and used following solid phase extraction by the method described previously (McDougall et al. 2008a). Briefly, frozen fruit was homogenized in a Waring blender (6 × 20 s at full power) using an equal volume to weight of ice-cold 0.2% (v/v) formic acid in water. The extract was filtered through a glass sinter and applied to C18 solid phase extraction units (Strata C18-E, GIGA)
units, Phenomenex Ltd., U.K.) pre-washed in 0.2% (v/v) formic acid in acetonitrile and then pre-equilibrated in 0.2% (v/v) formic acid in water. Unbound material, which contained the free sugars, organic acids, and vitamin C, was discarded. After extensive washes, the polyphenol-enriched bound extracts were eluted with acetonitrile. The C18-bound extracts were evaporated to dryness in a Speed-Vac (Thermo Fisher, Basingstoke, U.K.). A sample of raspberry extract was put through an in vitro digestion procedure (GR) to simulate human gastrointestinal digestion, recovered by solid phase extraction (see McDougall et al. 2005a for method) and used in certain studies.

**Anthocyanin and phenol assays**

The total anthocyanin concentration was estimated by a pH differential absorbance method (Ribereau-Gayon and Stonestreet 1965). The absorbance value was related to anthocyanin content using the molar extinction coefficient calculated in-house for cyanidin-3-O-glucoside (purchased from ExtraSynthese Ltd., Genay, France). Phenol content was measured using a modified Folins-Ciocalteau method (Singleton and Rossi 1965) and, because all samples had passed through SPE treatment, we assume that they contain only phenolic components (George et al. 2005). Phenol contents were estimated from a standard curve of gallic acid.

**Platelet aggregation**

Antecubital blood from healthy human volunteers (25 ml) was collected to investigate the effect of components on platelet aggregation. The blood was mixed with 3.15% (w/v) sodium citrate to obtain a ratio of 9:1 (blood:anti-coagulant) then centrifuged at 1000 rpm (MSE Mistral 2L centrifuge) for 18 min to obtain platelet rich plasma (PRP). The PRP was collected and the remainder was centrifuged at 2000 rpm for 10 min to obtain platelet poor plasma (PPP). The PPP was collected and the pellet containing the red blood cells discarded. Aliquots (450 µl) of PPP and PRP in a glass vial were placed in an aggregometer (Chrono-Log corporation). The rings were suspended between two wire hooks attached to an isometric force transducer and were stretched to achieve approximately 1 g of resting tension (determined from previous work to produce optimal length-tension of this tissue). The baths were maintained at 37°C and bubbled with 95% oxygen and 5% carbon dioxide during the experiment.

Equilibration of 30 min was allowed before exposing the tissues to a test dose of 3 µmol/l phenylephrine (PHE) (an α1 adrenergic receptor agonist) and to 3 µmol/l carbachol (CARB) (a muscarinic agonist). After washing out thoroughly, the tissues were contracted with 10 mmol/l KCL twice with a 20 min wash out in between. After the second constriction with KCl, another wash out was carried out and approximately 30 min was allowed for the tissues to return to resting tone before further studies were undertaken.

A cumulative does-response curve to PHE (0.01 to 10 µmol/l) was then constructed which allowed the vessel to reach a stable plateau, and from this point relaxation to CARB (0.01 to 10 µmol/l) was recorded. The tissues were then washed out thoroughly before the test compounds were added. The extracts were added to give the following final concentrations, RE 90, 18, 1.8, 0.36 and 0.036 µg/ml, GR 1.8 µg/ml, QG 50 µg/ml (100 µmol/l) and 10 µg/ml (21 µmol/l) and QS 60 µg/ml (157 µmol/l), 12 µg/ml (31 µmol/l) and 3 µg/ml (8 µmol/l). AA was studied at 18 µg/ml (100 µmol/l). Additional control rings were incubated with vehicle alone (Krebs buffer for BC, RE, GR and AA and DMSO for QS and QS). The artery rings were incubated with the extracts for one hour then concentration response curves to PHE (0.01 to 10 µmol/l) and CARB (0.01 to 10 µmol/l) were repeated. After wash out the vessels were incubated with 100 µmol/l N³-Nitro-L-Arginine methyl ester (L-NAME) a nitric oxide synthetase inhibitor. After 20 min incubation, another concentration response curve to PHE (0.01 to 10 µmol/l) was constructed.

The contractile responses to KCL at the start of the experiment allowed standardisation of the results obtained from the different rings in the different organ baths. The increase in tension caused by PHE in the presence of L-NAME compared to in the presence of the extracts provides a measure of basal NO bioavailability. NO bioavailability was calculated for each ring over the full PHE concentration-response curve and for each sample and was expressed as the area between the two curves (AUC g/g) using the calculation:

\[
\frac{\text{PHE} + \text{L} - \text{NAME}}{\text{KL}} - \frac{\text{PHE + extract}}{\text{KL}} = \frac{X}{2} = \text{AUC g/g}
\]

Unpaired t-tests using Minitab were carried out comparing NO bioavailability in the presence of extracts and the appropriate vehicle with Bonferroni correction tests for multiple comparisons. A value of P < 0.05 was regarded as significant. n = 6-10 per group results expressed mean ± S.E.M.

**Measurement of superoxide by xanthine/xanthine oxidase-lucigenin chemiluminescence**

The effect of extracts on O₂⁻ levels generated by xanthine/xanthine oxidase (XO) (White et al. 1996) was investigated by lucigenin chemiluminescence. AA was examined at final concentrations of 9 to 0.0009 µmol/l, RE at 9 to 0.0009 µmol/l, QS at 2 to 0.0002 µg/ml and QS at 3 to 0.0003 µg/ml. The extracts were added to 6 ml polyethylene (PE) vials containing 2 ml Krebs and XO (0.002 U), lucigenin (15 µmol/l) and xanthine (800 nM) were added to the PE vial and chemiluminescence read in a TRI-CARB 2100 TR liquid scintillation analyser (Packard BioSciences), set to count at 10-second intervals for three minutes beginning immediately after addition of XO. The results obtained in the presence of extracts were compared to standards in which no extract was present to determine if extract had reduced O₂⁻ levels. A blank containing only 15 µmol/l lucigenin was subtracted from all readings. The data obtained was expressed as a percentage of O₂⁻ inhibited in the presence of extract compared to the control, the calculation is:

\[
A = \frac{\text{extract - blank}}{\text{control - blank}} \times 100
\]

A = % O₂⁻ detected in presence of extracts

100 – A = % inhibition of O₂⁻ by extracts.

**Assessment of superoxide levels in SHRSP rat aorta**

Lucigenin chemiluminescence was also used to investigate O₂⁻ levels in the abdominal and thoracic arteries of SHRSP, in the presence and absence of extracts. The arteries were cleaned and cut in...
to 4 mm rings and placed into a PE vial containing 2 ml Krebs. The weight of the tissue was recorded and the artery ring was incubated for one hour with extracts. AA was used at a final concentration of 130 μg/ml (738 μmol/l), RE at 90 μg/ml, QG at 240 μg/ml (500 μmol/l) and QS at 310 μg/ml (809 μmol/l). After an hour’s incubation, O₂⁻ was quantified against a standard curve generated from xanthine and XO and 15 μmol/l lucigenin.

**Cell proliferation and measurements of cell viability**

Human cervical cancer (HeLa) cells were grown as a monolayer in Dulbecco’s Modified Eagle Medium (DMEM) as described previously (Ross et al. 2007). Cells were harvested by trypsin treatment, washed with phosphate buffered saline (PBS) and resuspended in growth medium. They were then seeded to a final density of approximately 250,000 cells in 5 ml growth media inclusive of the different treatment solutions. Berry extracts were diluted in PBS then filter-sterilised and checked for phenol content to adjust for losses due to filtration. Cells were harvested over a 7 day period and cell number was assessed by counting and viability was assessed using a kit according the manufacturers instructions (Dojindo CCK-8 kit, from NBS Biologicals, Cambridge, UK). The antiproliferative effectiveness was estimated using an extrapolation of % inhibition values to yield the median effective dose (EC₅₀) at day 4 when the cells were actively growing and contained the largest proportion of viable cells.

**α-Glucosidase assay**

The assay method has been described previously (McDougall et al. 2005b). Acetone powder from rat intestine (Sigma Chem Co. Ltd, product H3360) was used as a source of α-glucosidase. The release of p-nitrophenol from p-nitrophenyl α-D-glucopyranoside (Sigma Chem Co. Ltd, product N1377) was measured after incubation at 37°C for 2 hours in the presence or absence of 50 μg/ml phenol content with suitable controls for each sample. Assays were carried out in triplicate.

**RESULTS AND DISCUSSION**

Significant increases in nitric oxide (NO) bioavailability were seen from 90-0.36 μg/ml raspberry extract (RE) compared with the control buffer (Fig. 1). In contrast, blackcurrant extracts (BE) were not effective at 18 or 90 μg/ml. A raspberry extract that had been processed by an in vitro digestion procedure to simulate gastrointestinal digestion (GR) was similarly effective at 1.8 μg/ml. This suggests that the active ingredients of RE are not lost or that additional active compounds are formed during the digestion.

Ascorbic acid (AA) at 18 μg/ml (100 μmol/l) also increased NO bioavailability significantly compared to the control but to levels lower than 1.8 μg/ml or 0.36 μg/ml RE. Such comparisons of efficacy may be indicative but can only be valid if a full set of concentrations were performed for both components.

Both quercetin derivatives, QS and QG, significantly increased NO bioavailability compared to their vehicle DMSO (Fig. 1). However, the compounds showed different concentration effects. QG was more effective at the higher concentration (50 μg/ml than 10 μg/ml) but QS was equally effective at 60 and 12 μg/ml, which suggests that QS is more potent. However, it should be noted that RE at 1.8 μg/ml and 0.36 μg/ml was considerably more effective than QS at 1.5 μg/ml.

The apparent effectiveness of the raspberry extract may be due to synergetic effects of a mixture of polyphenol components at lower levels as mixtures of QG and QS at concentrations well below those effective on their own caused significant increases in NO bioavailability (results not shown). Scavenging of superoxide has been postulated to protect NO bioavailability and maintain endothelial function by preventing NO conversion to peroxynitrile (Hamilton et al. 2001). Drugs such as Irbesartan that reduce superoxide levels, through blocking angiotensin II receptors, can influence hypertension (Brosnan et al. 2002). The raspberry extracts were effective scavengers of superoxide produced in vitro through xanthine/XO (Table 1). QG, RE and QS had the lowest EC₅₀ values but were not significantly different apart from being significantly more potent than ascorbic acid. The effective scavenging of superoxide by the extracts may partly explain their protection of NO bioavailability. However, in ex vivo studies with SHRSP rat aorta rings, all the extracts showed a slight tendency to reduce O₂⁻ levels compared to controls but these differences were not statistically significant (paired t-tests at p<0.05). The noted difference between the potent in vitro superoxide scavenging and the lack of effect in the ex vivo

### Table 1 Superoxide (O₂⁻) scavenging activity of extracts

<table>
<thead>
<tr>
<th>Extract</th>
<th>EC₅₀ μg/ml</th>
<th>Number per group (n)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quercetin glucuronide</td>
<td>0.012</td>
<td>4</td>
<td>0.006-0.022</td>
</tr>
<tr>
<td>GR extract</td>
<td>0.012</td>
<td>5</td>
<td>0.0055-0.024</td>
</tr>
<tr>
<td>Raspberry extract</td>
<td>0.026</td>
<td>6</td>
<td>0.012-0.059</td>
</tr>
<tr>
<td>Quercetin sulphate</td>
<td>0.047</td>
<td>5</td>
<td>0.020-0.103</td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>0.178</td>
<td>6</td>
<td>0.089-0.415</td>
</tr>
</tbody>
</table>

**Fig. 2 The effect of raspberry extracts on platelet aggregation.**

- Control RE 20 μg/ml
- RE 20 μg/ml
- Control RE 100 μg/ml
- RE 100 μg/ml

For data in Table insert, paired t-tests were carried out to test for significance, P<0.05 was regarded as significant.

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**Fig. 1 Effect of berry extracts on nitric oxide bioavailability in rat carotid artery.** * indicates a significant difference between the raspberry extracts and the control, using unpaired t-tests with Bonferroni correction tests for multiple comparisons using Minitab. P<0.05 was regarded as significant. AUC is the difference between the area under the curves for test and control samples as discussed in materials and methods.
system may be due to the inability of the components to reach the intercellular sites of superoxide generation.

Raspberry extract caused a significant reduction in ADP-dependent platelet aggregation (Fig. 2) at 100 µg/ml but not at 20 µg/ml. Although ascorbic acid at 235 µg/ml caused an apparent reduction in platelet aggregation, only the raspberry extracts caused a statistically significant effect (Table, inset Fig. 2). Quercetin derivatives are known not to inhibit platelet aggregation at these concentrations (Janssen et al. 1998) and the active components in the RE are unknown. In any case, the effective concentration of RE is unlikely to be encountered in vivo. Indeed, many studies suggest that anti-aggregation effects of flavonoids noted in vitro are due to concentrations that cannot be attained in vivo (Janssen et al. 1998).

Overall, it is apparent that raspberry extracts have considered cardio-protective potential and were noticeably more effective than blackcurrant extracts in vitro. Blackcurrant extracts are particularly rich in anthocyanins but raspberry extracts contain anthocyanins and ellagitannins (Machiex et al. 1990; Kalkonen et al. 2001; Maatta-Riihinen et al. 2004). Indeed, ellagitannins have already been shown to be effective vasodilatory agents in rat aorta (Mullen et al. 2002) possibly due to their high relative antioxidant capacity (Ross et al. 2007 and references therein).

Given their poor absorption and stability (Williamson and Manach 2005), it is unlikely that ellagitannins or anthocyanins would be sufficiently bioavailable to influence cardiovascular events in vivo. On the other hand, QG and QS have been reported in human plasma and urine at around 7-10 µM (Grafé et al. 2001) with a reported half-life of 20-72 hours (Walle et al. 2001). This level approaches the concentrations found to be effective in this study and the synergistic effects of QG and QS on NO bioavailability may occur in vivo as both components are present in plasma flowing exposure to dietary quercetin derivatives (Walle et al. 2001).

Raspberry (Fig. 3A) and cloudberry extracts (Fig. 3B) inhibited the proliferation of HeLa cervical cancer cells in a dose-dependent manner. The raspberry extract gave an EC50 of 21.0 µg/ml GAE whereas the cloudberry extract gave an EC50 of 34 µg/ml GAE. Although the absolute value varied slightly with different experiments, the raspberry extracts were consistently more effective. Raspberry and cloudberry are closely related members of the Rubus family and have a similar polyphenol composition, differing mainly in the content of anthocyanins (Machiex et al. 1990; Kalkonen et al. 2001; Maatta-Riihinen et al. 2004). Previous work showed that an ellagitannin-rich raspberry sub-fraction was considerably more effective than the original extract or an anthocyanin-rich sub-fraction (Ross et al. 2007) which suggested that the ellagitannins were the predominant anti-proliferative agents in raspberry. However, if we consider that the cloudberry extract is effectively similar to an anthocyanin-depleted (and therefore relatively ellagitannin-enriched) raspberry extract, this suggests that the nature of the other anti-proliferative ingredients is much more complex. Indeed, in a separate study of the anti-proliferative effects of other Rubus species (McDougall et al. 2008a), we found that raspberry and arctic bramble extracts (which both contain anthocyanins and ellagitannins) were more effective than cloudberry extracts. Although cloudberry and raspberry contain similar ellagitannin profiles, they differ in the relative abundance of certain components (McDougall et al. 2008b) and it is intriguing to speculate that this may influence their biological activity or indeed their stability (Ross et al. 2007). Of course, cervical tissues are unlikely to come in contact with these components in vivo (Williamson et al. 2005) but colon cancer cells can be in direct contact with high levels of ingested polyphenols (e.g. Coates et al. 2007).

Berry extracts were screened to assess their ability to inhibit α-glucosidase activity in vitro (Fig. 4). Raspberry, lingonberry, rowan and pomegranate extracts showed significant inhibition whereas strawberry, cloudberry, blackcurrant and blueberry had no effect at the test concentration (50 µg/ml). Red wine extracts caused a significant increase in activity. Inhibition of α-glucosidase by drugs such as aca-
bose is a therapeutically proven means of controlling post-prandial blood glucose levels in patients with poor glycaemic control due to type 2 diabetes (Toeller 1994). Polyphenolic extracts from plants have been reported as effective inhibitors of intestinal α-glucosidase activity with K-values similar to acarbose (Matsui et al. 2001). Inhibition of α-glucosidase has been reported for isolated anthocyanins (Matsui et al. 2002) and anthocyanin-rich extracts (McDougall et al. 2005). Inhibitory activity by anthocyanins acylated with hydroxybenzonic acids (Matsui et al. 2002) may be related to the inhibition of α-glucosidase by chlorogenic acid derivatives (e.g. Matsui et al. 2004). The wide distribution of chlorogenic acid derivatives may explain the ubiquitous discovery of varying extents of α-glucosidase inhibition in plant extracts and in certain berry extracts (Machieux et al. 1990).

In addition, elevated chlorogenic acid or anthocyanin content does not explain the pattern of α-glucosidase inhibition noted in this screen. Rowan and lingonberry extracts contain high levels of anthocyanins but do so blueberry and blackcurrant, which, like rowan, also have high levels of chlorogenic acids (Machieux et al. 1990; Kahkonen et al. 2001; Maatta-Rihinen et al. 2004; Hakkinen et al. 2006). Raspberry and the pomegranate extract contain lower levels of chlorogenic acids and substantial amounts of ellagitannins (Gil et al. 2000; Ross et al. 2007). However, ellagitannin-rich cloudberry, strawberry and blackberry extracts were ineffective. This initial screen suggests that α-glucosidase inhibition may be due to a combination of different components but further work is required to identify the active components. It is clear from model studies (McDougall et al. 2007) that considerable amounts of a wide range of berry polyphenols survive gastric digestion and could be available to modulate α-glucosidase activity in the small intestine and influence blood glucose levels in vivo.

CONCLUSIONS

Polyphenol-rich extracts from berries have bioactivities that influence model systems for cardiovascular disease, cancers and glycaemic control. Although antioxidant capacity may be involved in the mechanisms of sparing NO bioavailability and glycaemic control. Although antioxidant capacity may influence model systems for cardiovascular disease, cancers and the metabolic syndrome. Polyphe-

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