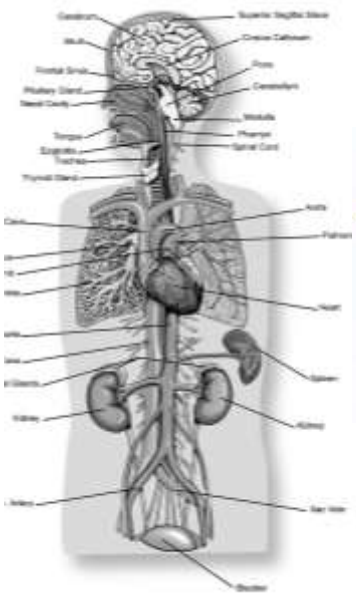
Blackcurrants and Human Health: An Update

The James Hutton Institute

Gordon McDougall



Blackcurrant Growers Conference 13th March 2013
Thatchers Cider, Sandford, Somerset

Outline of talk

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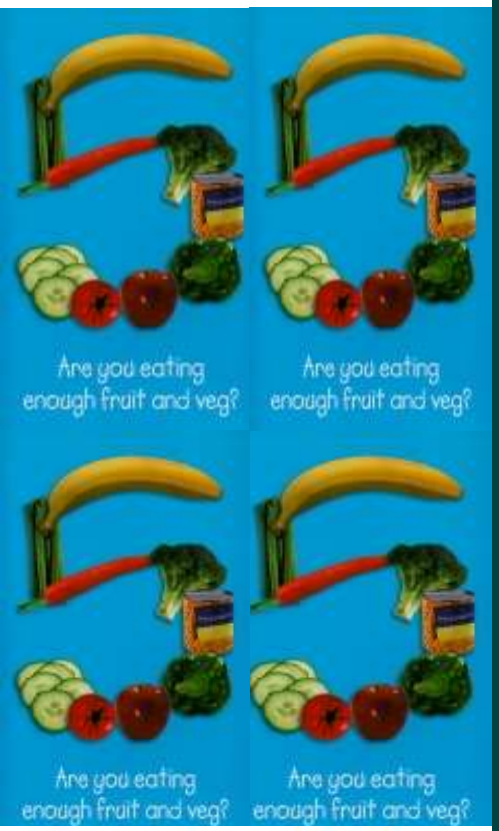
- Introduction
- Berries and antioxidants
- Possible health benefits?
- Examples of new JHI research
- Overview and future directions



healthier scotland
SCOTTISH GOVERNMENT

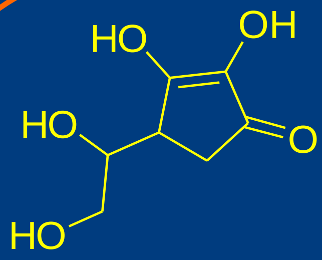
- "Insufficient intake of fruit and vegetables increases the chances of developing cancers, cardiovascular disease and strokes" - World Health Organisation (2003)
- The 3 main causes of premature death in Scotland

Led to the "5 a day" programme - Govern[illegible] to alter our die[illegible]

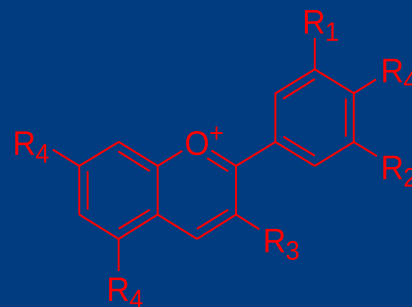
How do FAV affect health?

Minerals (Zinc)? Vitamins (C and E)?
Fibre? Displacement? Lower Fat?
Phytochemicals? Antioxidants?

Berries are a rich source of antioxidants – the two main types are **Polyphenols** and Vitamin C

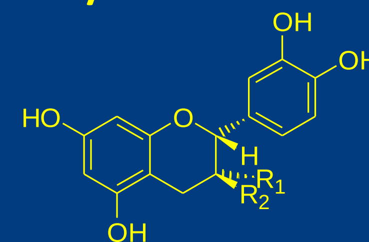


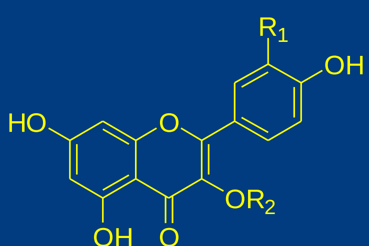
Vitamin C



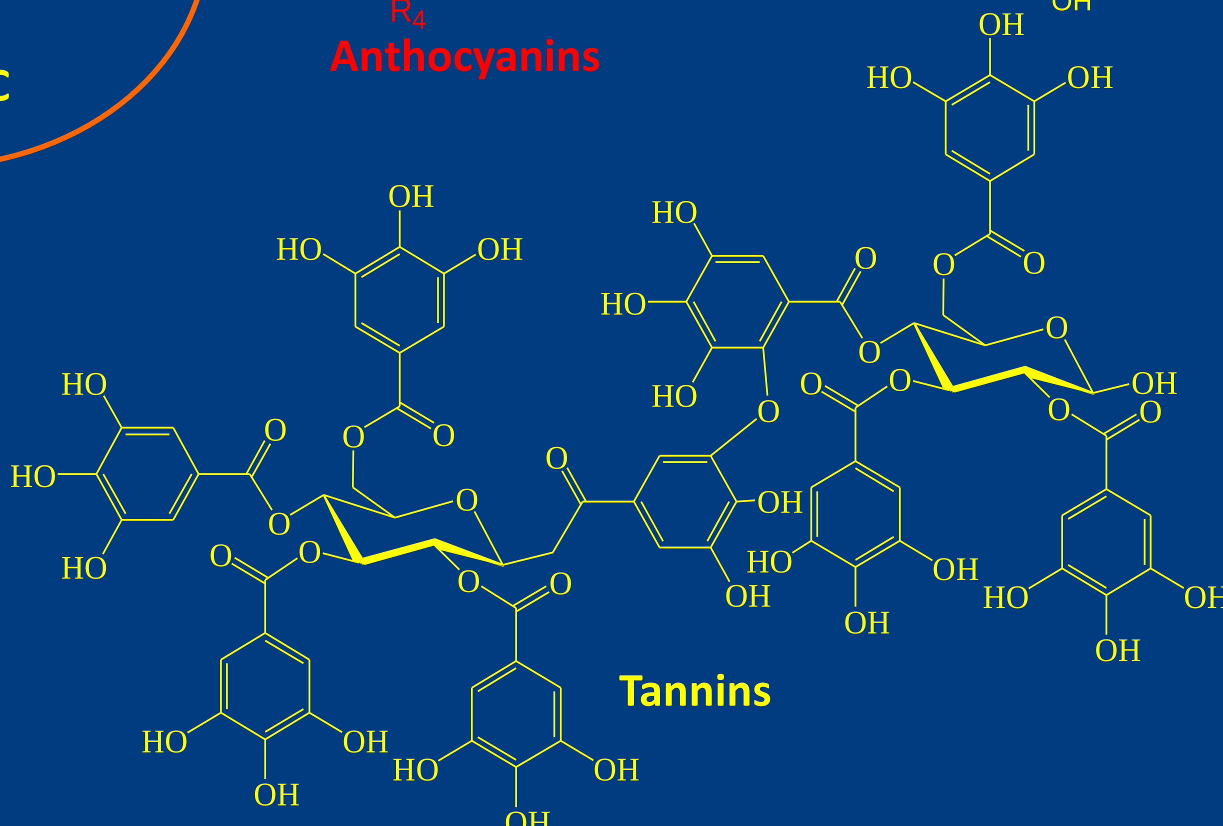
Anthocyanins

Flavanols/PACs





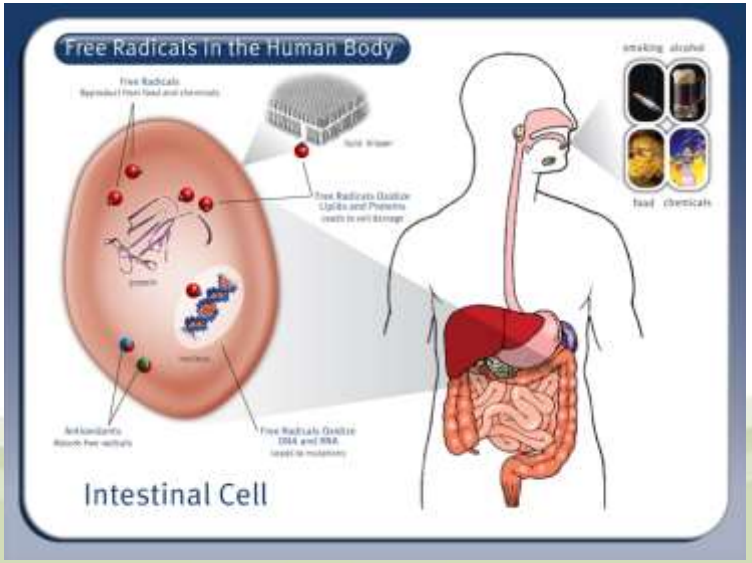
Flavonols



Tannins

Living with oxygen & free radicals

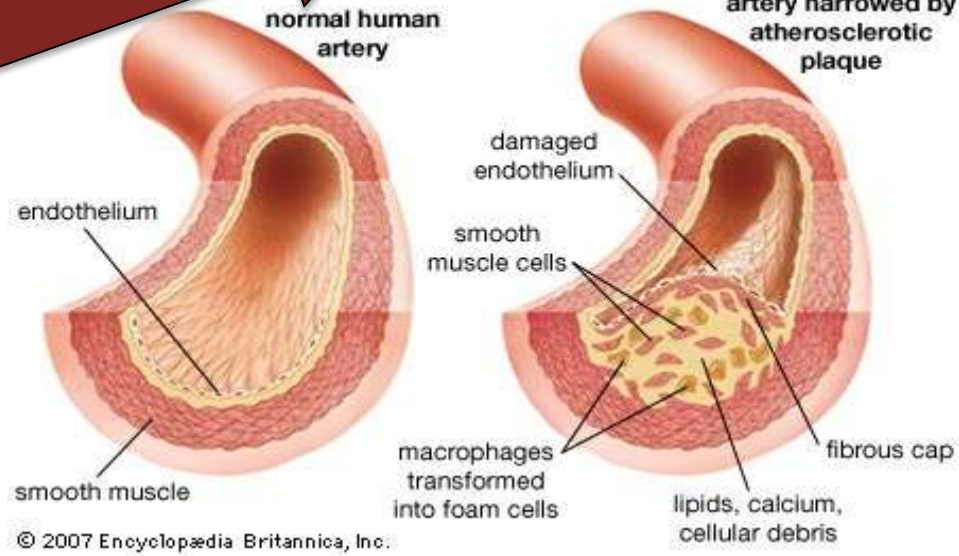
- We “burn” our food with oxygen to release energy
- By-products include free radicals which are ***VERY*** reactive. They can damage the body and cause disease.
- Our bodies work hard to remove these radicals and prevent damage
- Dietary antioxidants are proposed to “top-up” our protective systems



Free radicals are involved in the development of cardiovascular disease

Oxidative stress

Oxidative stress



- **Protein damage and lipid peroxidation leads to loss of membrane integrity, cell damage and cell death**
- **DNA damage leads to mutations**

Stroke, Atherosclerosis,

High Blood Pressure, Heart attack

A simplified version?

Polyphenols as antioxidants

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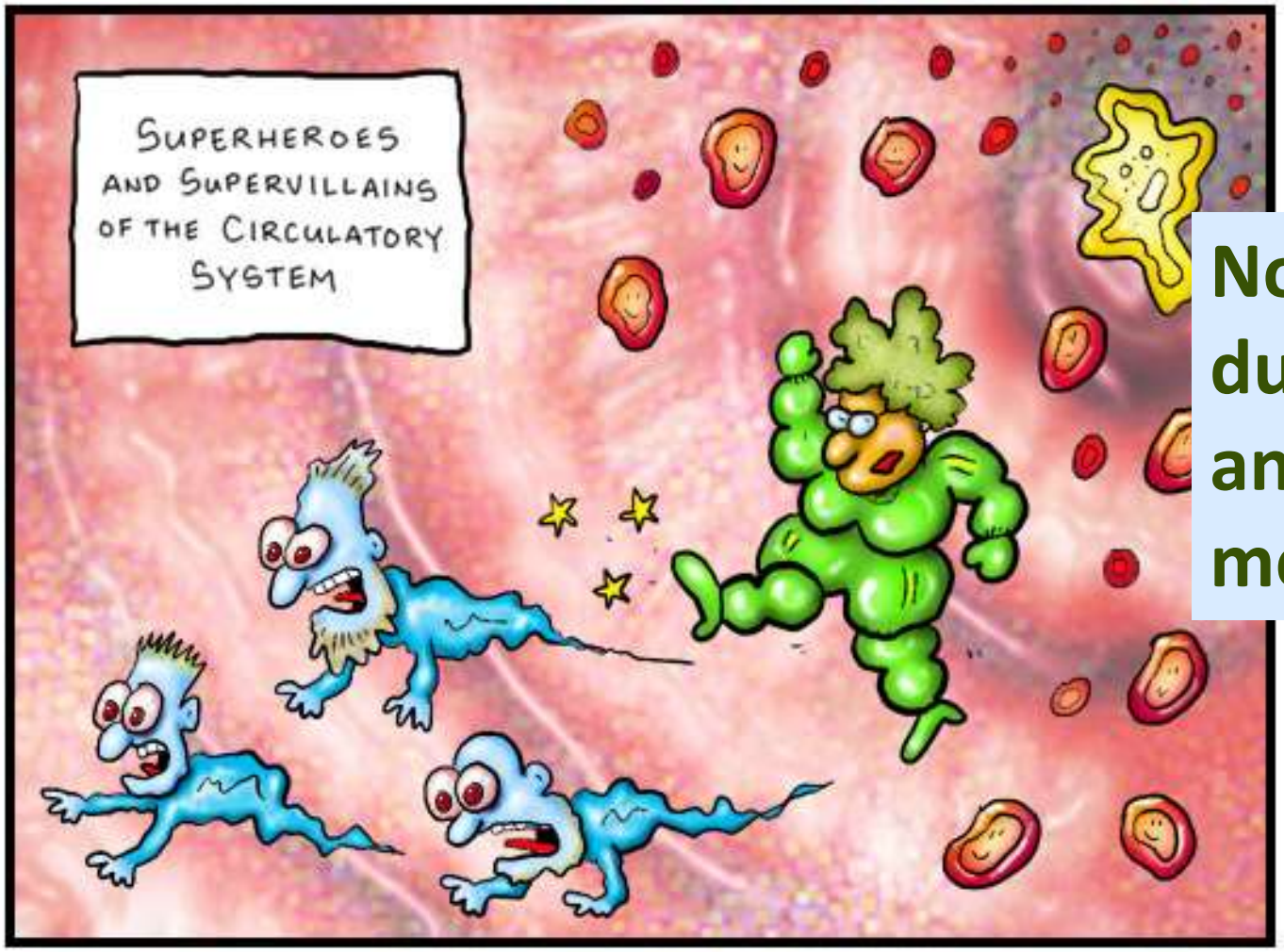

Auntie Oxidant kicks out the Free Radicals.

Not all effects due to antioxidant mechanisms?

Black currant fraction	Cell line	Pharmacological effect	Reference
CARDIOVASCULAR SYSTEM			
Juice	J774A.1 macrophage cell line	Increased paraoxanase 1 expression, improving macrophage cholesterol attenuation	Rosenblat *et al.*, 2010[62]
Extract	Human umbilical vein endothelial cells	Increased activation of endothelial NO synthase and dilation of blood vessels	Edirisinghe *et al.*, 2011[69]
NERVOUS SYSTEM			
Extract	M1 transfected COS-7 cells	Increased recovery of calcium flux in type-1 muscarinic R's	Joseph *et al.*, 2004[70]
PULMONARY SYSTEM			
Extract (proanthocyanidin)	A549 alveolar epithelial cell line	Induced CCL26 secretion and amplified interferon-gamma	Hurst *et al.*, 2010[71]
TUMORS			
Whole fruit extract	HT29 colon cancer; MCF-7 breast cancer	Decreased the proliferation of cancer cells	Olsson *et al.*, 2004[72]
Whole fruit extract	HT29 colon cancer	Inhibited cancer cell growth	Wu *et al.*, 2007[73]
Whole fruit extract	HeLa cervical cancer	Reduced cell viability	McDougall *et al.*, 2008[74]
Juice	Caco-2 colorectal adenocarcinoma; MCF-7 and MDA-MB-231 breast cancer; AGS stomach adenocarcinoma; PC-3 prostate cancer	Suppressed cancer cell proliferation	Boivin *et al.*, 2007[75]
CAPS	Ehrlich ascites tumor	Exhibited cytotoxicity	Takata *et al.*, 2005[76]
Press residue extracts	Caco-2, HCT 116 and HT-29 colon cancer	Inhibited cell proliferation	Holtung *et al.*, 2011[77]
Skin extract	HepG2 liver cancer	Displayed antiproliferative effect	Bishayee *et al.*, 2010[78]

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There is considerable evidence for health effects of black currants

Model studies with cell lines

Gopalan et al (2012) Food and Function, **3**, 795-809

Black currant fraction	Animal model	Pharmacological effect	Reference
CARDIOVASCULAR SYSTEM			
Oil (GLA)	Spontaneously hypertensive rats	Decreased blood pressure values	Engler, 1993[79]
Olive-blackcurrant-fish oil mixture	Wistar rats	Decreased serum TXA-B2 prothrombotic factor	Pregnolato, 1996[80]
Anthocyanin fraction	Sprague-Dawley rats	Decreased relative amount of hepatic saturated fatty acids and increased plasma tocopherol levels	Frank *et al.*, 2002[81]
Black currant concentrate	Norepinephrine-precontracted thoracic aortas of rats	Induced vasodilation via H1 receptors to increase NO levels	Nakamura et al., 2002[82]
Oil	Wistar rats	Inhibited accumulation of n-3 PUFA in liver and significantly decreased plasma GSH	Vecera *et al.*, 2003[83]
Seed oil	Wistar female rat blood samples	Decreased plasma GSH and *t*-butyl hydroperoxide-induced lipoperoxidation; did not effect hepatic GSH levels	Breinholt *et al.*, 2003[84]
Anthocyanin fraction	Watanabe heritable hyperlipidemic rabbits	Increased LDL and cholesterol and decreased VLDL content	Nielsen *et al.*, 2005[56]
Anthocyanin component (delphinidin-3-*O*-rutinoside)	rod outer-segment membranes in frogs	Inhibited endogenous NO and cGMP release	Matsumoto *et al.*, 2005[85]
Concentrate (delphinidin)	Sprague-Dawley rats	Decreased peripheral vascular resistance	Iwasaki-Kurashige *et al.*, 2006[86]

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Animal model systems

Gopalan et al (2012) Food and Function, **3**, 795-809

NERVOUS SYSTEM			
Oil (GLA)	Streptozotocin-induced diabetes in mature Sprague-Dawley rats	Modulated TXA2 and increased motor nerve conduction velocity	Dines *et al.*, 1996[87]
OCULAR SYSTEM			
Juice extract (cyanidin)	Wistar rats and Japan White rabbits	Improved rhodopsin regeneration and dark adaptation by enhancing rhodopsin precursor formation	Matsumoto *et al.*, 2006[88]
Extract	1 day old white Leghorn chicks	Inhibited enlargement of the globe component dimensions in artificially induced myopia	Iida *et al.*, 2010[89]
PULMONARY SYSTEM			
Leaf extract (proanthocyanidin)	Saline-induced pleurisy and carrageenin-induced right hind limb edema in male Wistar rats	Decreased inflammation and inhibited neutrophilic cellular infiltration	Garbacki *et al.*, 2004[48]
SKELETAL SYSTEM			
Seed oil	Monosodium urate crystal-induced inflammation in subcutaneous air pouches formed in Sprague-Dawley rats	Inhibited formation of monosodium urate crystal formation	Tate *et al.*, 1994[90]
TUMORS			
Oil (GLA)	Metastatic 13762MAT:B breast tumor in the lungs of Fischer rats	Reduced the number of foci and tumor burden	Karmali *et al.*, 2004[91]
Juice	Xenografted Ehrlich ascites tumor in ICR mice	Inhibited tumor growth	Takata *et al.*, 2005[76]
Modified CAPS	Xenografted Ehrlich ascities tumor in ICR Mice	Reduced tumor weight	Takata *et al.*, 2007[92]
Skin extract	DENA-initiated and PB-promoted hepatocarcinogenesis in Sprague-Dawley rats	Suppressed the number, size, and volume of hepatocyte nodules	Bishayee *et al.*, 2011[93]
		Lowered the number and area of GGT-positive foci; reduced the expression of HSP70, HSP90, COX-2 and NF-κB	Bishayee *et al.*, 2012[94]
		Diminished lipid and protein oxidation; reduced the expression of iNOS, 3-NT, antioxidant enzymes and Nrf2	Thoppil *et al.*, 2012[95]

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Animal model systems 2

Black currant fraction	Clinical study	Clinical effect	Reference
CARDIOVASCULAR SYSTEM			
Seed oil (GLA)	23 cryptogenic ischemia stroke patients undergoing transesophageal echocardiography, 26 known-cause stroke patients, 57 non stroke controls	Inhibited platelet formation, decreased fibrin formation, and increased anti-coagulant effect	Stone *et al.*, 1995[96]
Concentrate (anthocyanin)	Right trapezius muscles in 20 healthy human subjects	Induced relief of shoulder stiffness and decreased muscle fatigue via improved blood flow	Matsumoto *et al.*, 2005[97]
Oil	Randomized, double- blind, crossover study of 15 healthy female subjects administered black currant seed oil supplements	Decreased LDL cholesterol levels when administered with fish oil	Tahvonen *et al.*, 2005[98]
Juice	Serum inflammatory markers in 48 peripheral artery disease patients	Reduced serum inflammatory markers such, e.g. C reactive protein	Dalgard *et al.*, 2009[99]
Seed press residue	Serum and stool tocopheral concentrations in 36 healthy female subjects	Increased alpha- and gamma-tocopherol serum concentrations	Helbig *et al.*, 2009[51]
Oil (soft capsule)	Observational study of 2154 dyslipidemic patients	Increased serum HDL-C protein and lowered triglyceride and total cholesterol in low BMI patients with hyperlipidemia	Fa-Lin *et al.*, 2010[100]
20% Juice (anthocyanin)	Randomized, cross-over, double-blind, placebo-controlled acute meal study in 11 female and 9 male healthy volunteers	Did not have significant effect on total plasma nitrate, nitrite, ICAM, or VCAM levels	Jin *et al.*, 2011[101]
anthocyanin	Cross-over study in 12 hypercholesterolemic patients	Increased NO-cGMP activation, improved serum lipid profile, decreased inflammatory markers	Zhu *et al.*, 2011[102]

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Human studies confirm potential health effects

A useful recent review

Berries and Health: A review of the evidence. Gordon J. McDougall and Derek Stewart

http://www.foodhealthinnovation.com/media/5637/berries_august_2012.pdf

So what's new?

Work on neuroprotective effects
Research on colon cancer
Research relevant to Diabetes

Intake of blackcurrants influences mouse models of Alzheimer's disease

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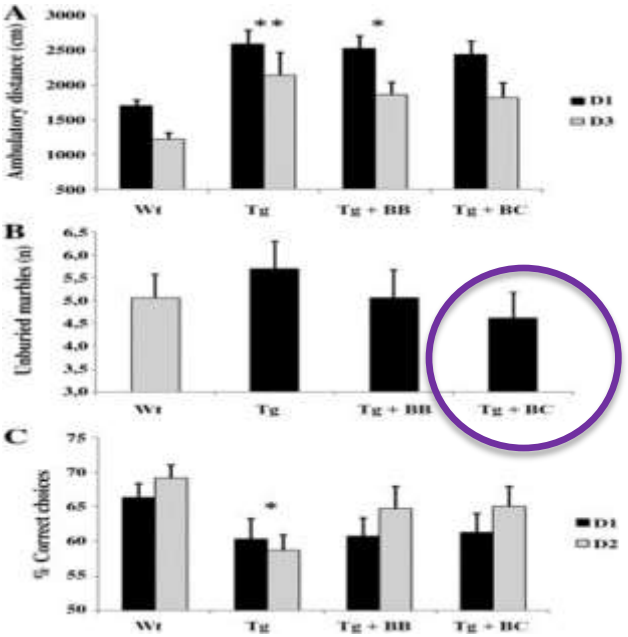

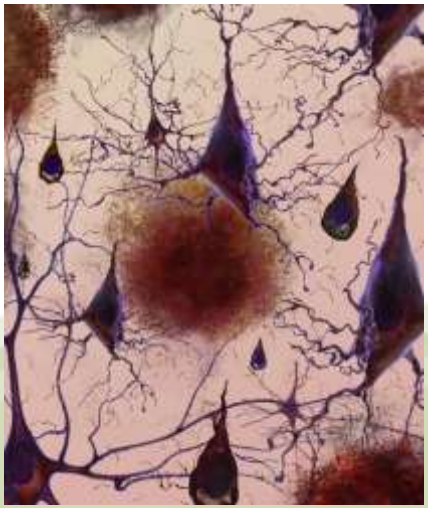

Berries improve cognitive function through neuroprotective effects

BrainHealthFood

Vepsäläinen, McDougall, Stewart et al. (2012). J Nutr Biochem. ***24****, 360-70*

Other ways berry polyphenols can affect human health?

Antioxidant theory? Low levels in serum!

Majority of polyphenols <u>remain in gut</u>

Are these components inactive?

Possible roles

Modulating colonic microbiota?

In-gut antioxidants?
Benefit gut epithelia function / colon cancer

Modulate digestive processes

Berry polyphenols inhibit growth of colon cancer cells

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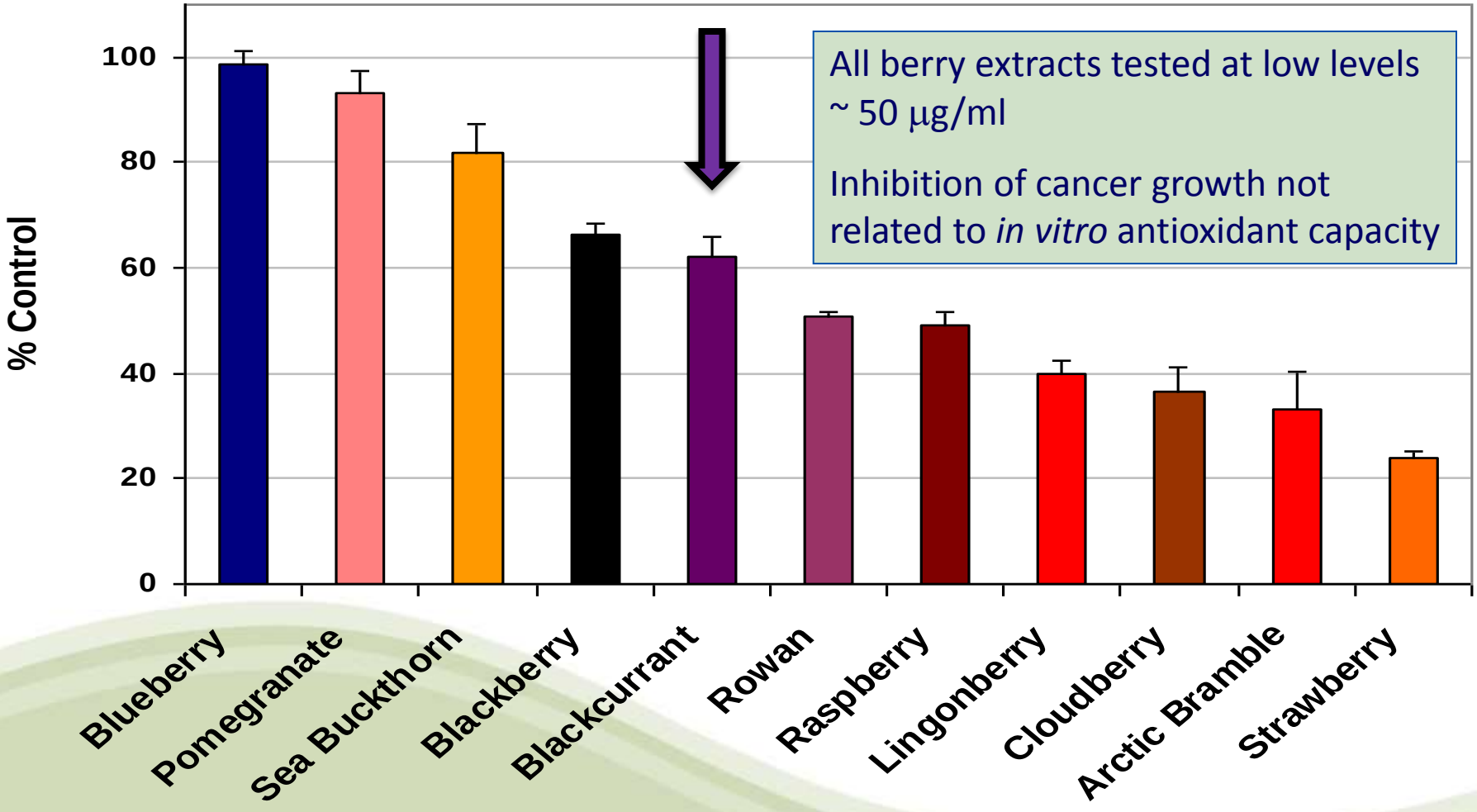

McDougall et al. (2008) J. Agric. Food Chem. 56; 3016-3023

Colon cancer and polyphenols

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Berry extracts protect against DNA damage in colon cancer cells; SB = BC > RB

Colonic metabolism of berry polyphenols

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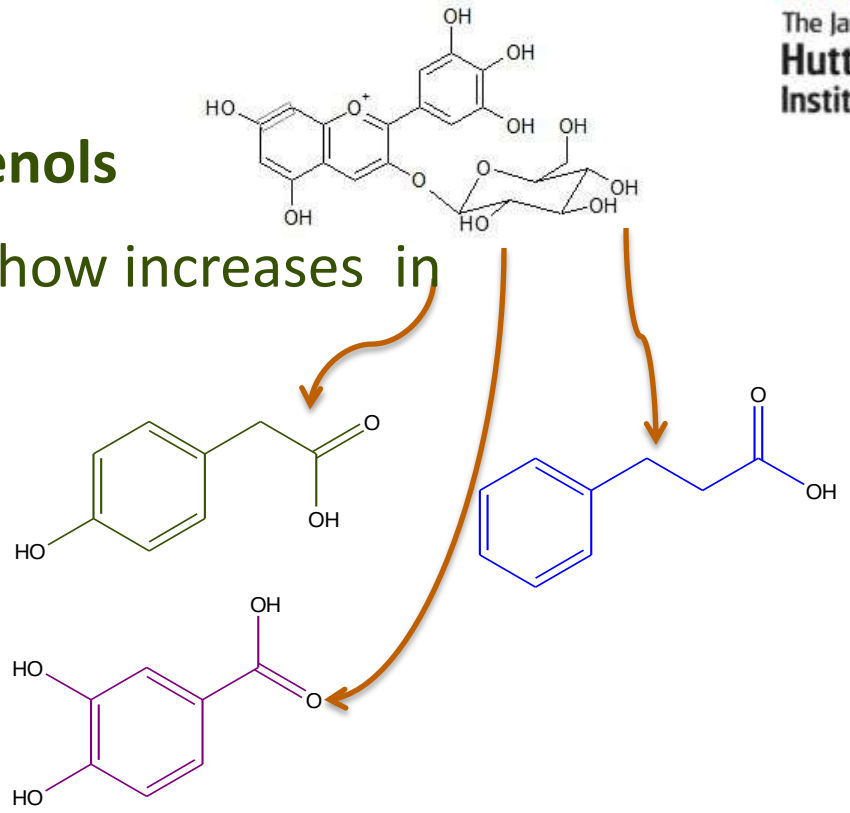
Colonic bacteria degrade polyphenols

Studies with humans fed berries show increases in

- Phenylacetic acid derivatives
- Phenylpropionic acid derivatives
- Hydroxybenzoic acid derivatives

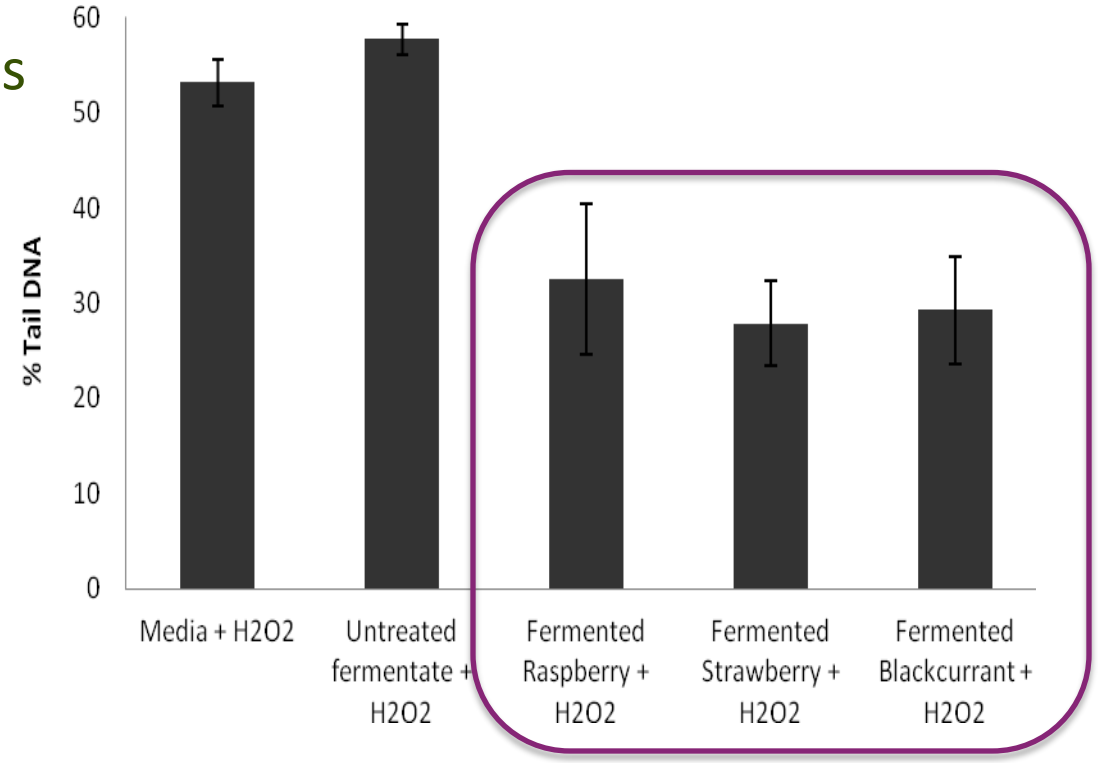


Laboratory fermentations with faecal bacteria gave similar products

Gill et al, J. Agric. Food Chem. (2010) 58, 10389–10395

Faecal products as effective as berry extracts

Berry polyphenols retain effectiveness as they undergo metabolism in the colon

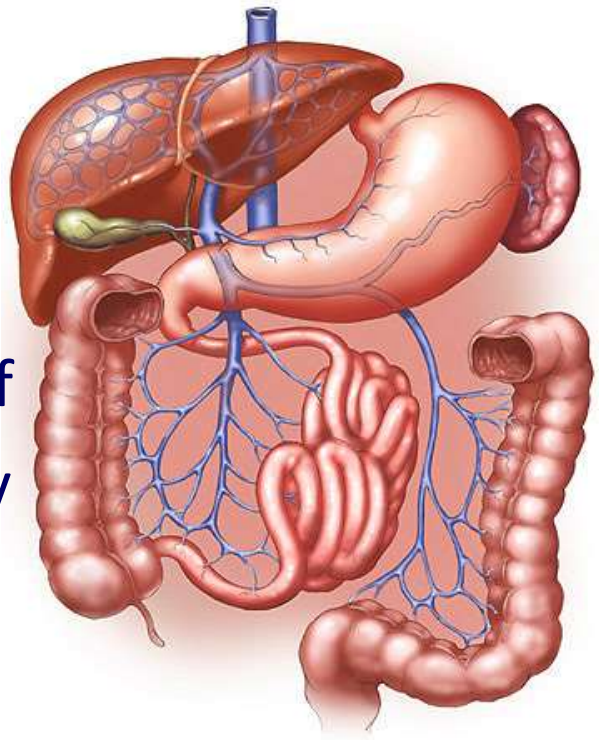


Berries contribute anticancer activity as they pass through the colon

Brown et al. (2012). PLoS ONE 7: e49740. doi:10.1371/journal.pone.0049740

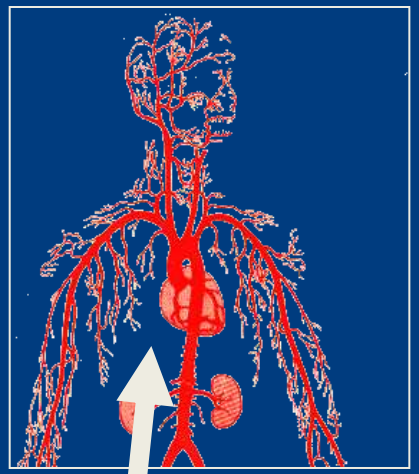
Control of nutrient availability

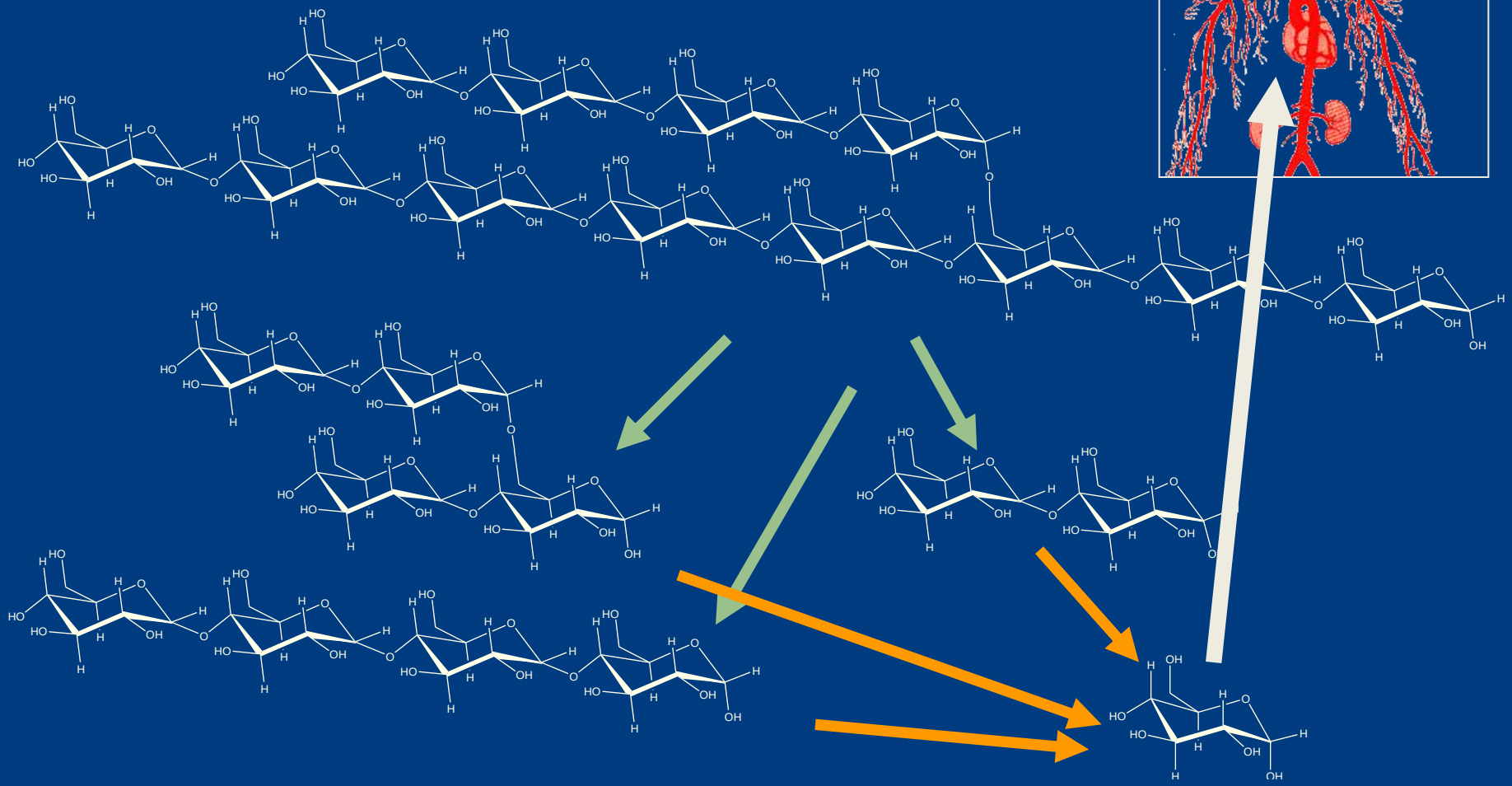
- Polyphenols can inhibit digestive processes and slow or modulate nutrient release from food



- Inhibition of lipid digestion – control of blood lipids, CVD, diabetes and obesity
- **Inhibition of starch digestion – blood glucose control and type 2 diabetes**

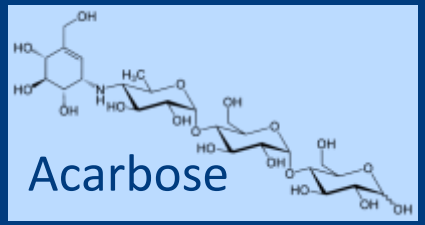
Inhibition of starch digestion



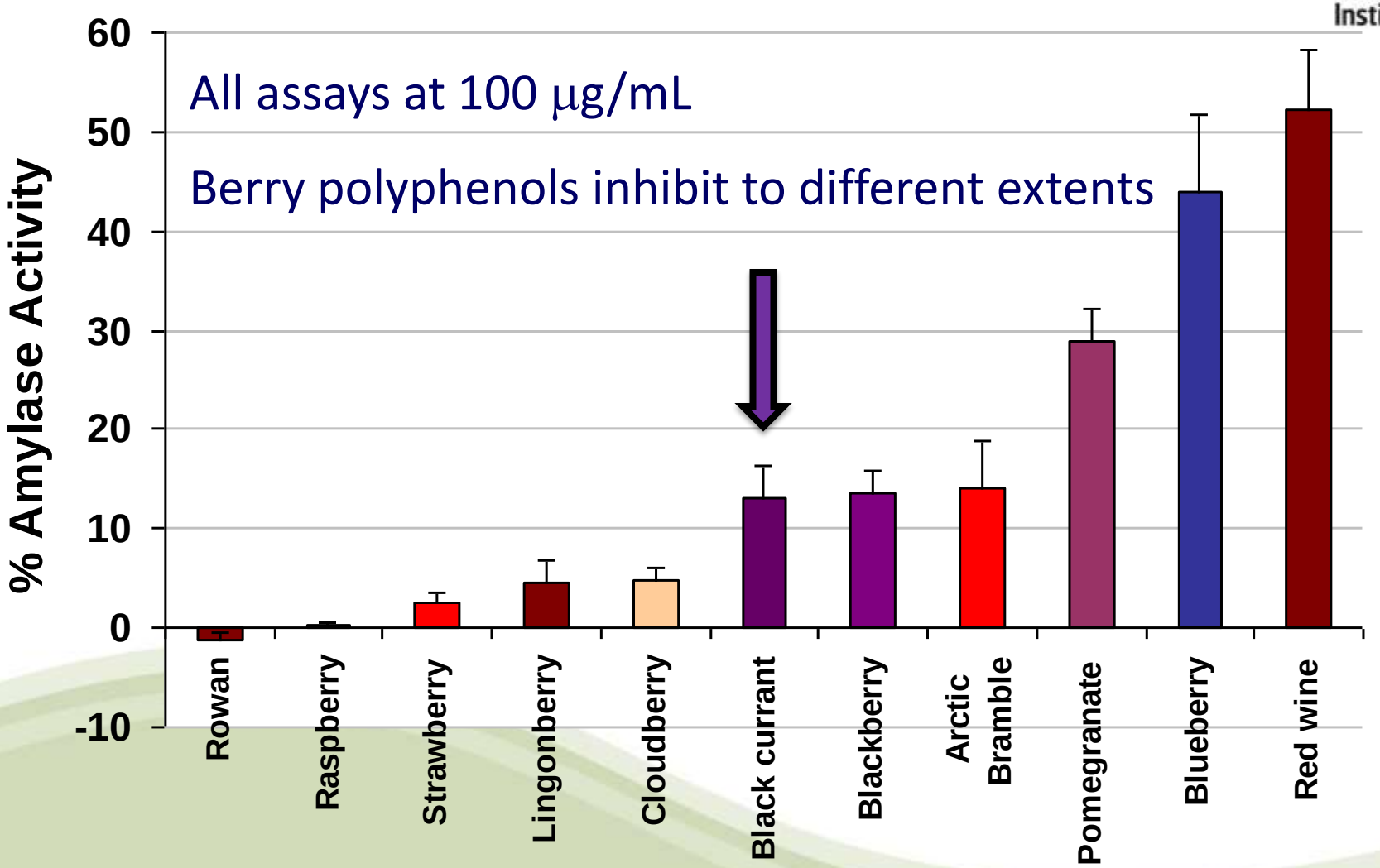


Amylase chops into fragments

α-glucosidase nibbles off glucose

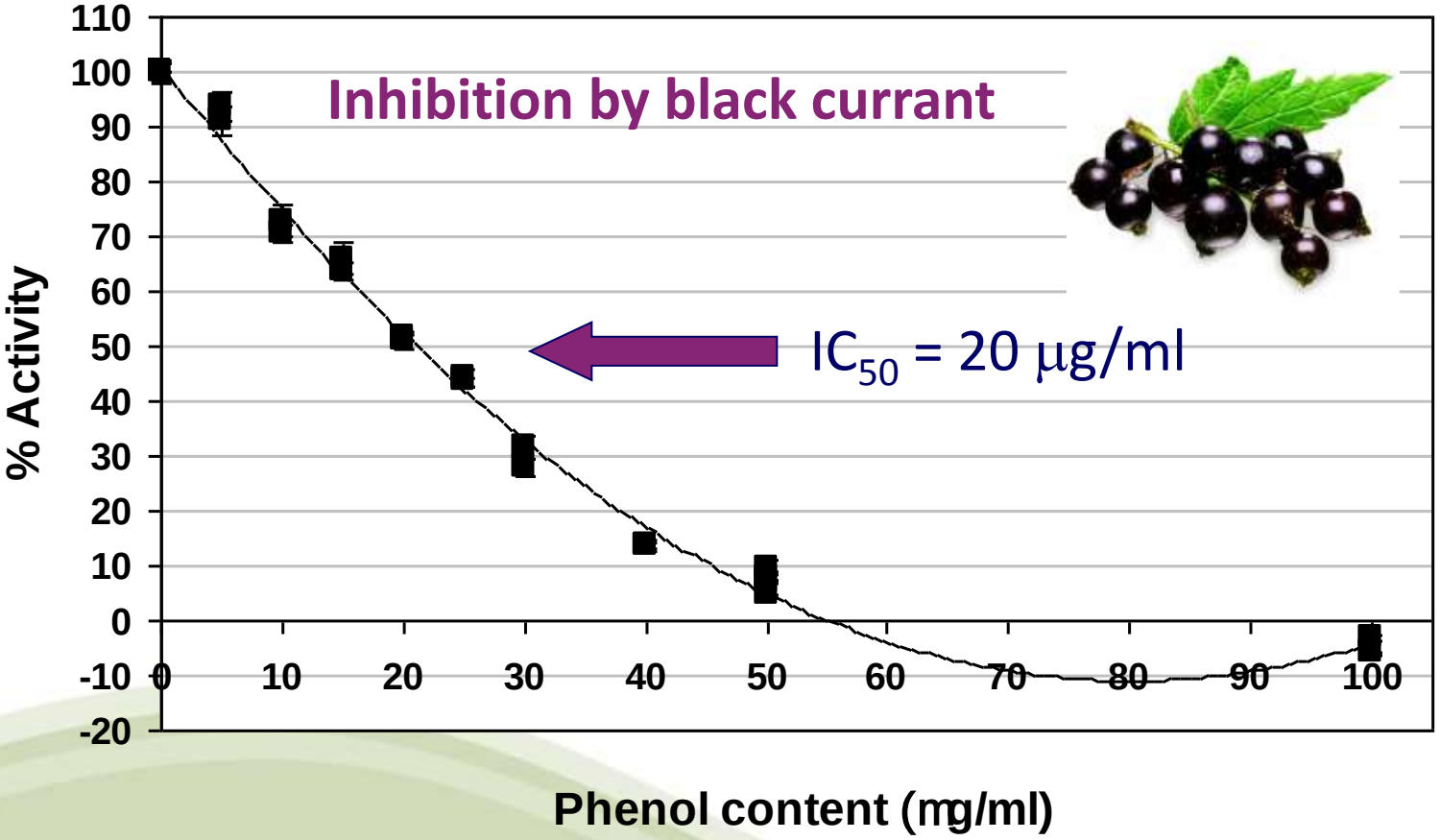


α-amylase inhibition



Grussu et al (2010) JAFC 53, 2760-2766

α-glucosidase inhibition by berries



Boath et al. Food Chemistry (2012) ***135****; 929-936*

Co-incubation with acarbose

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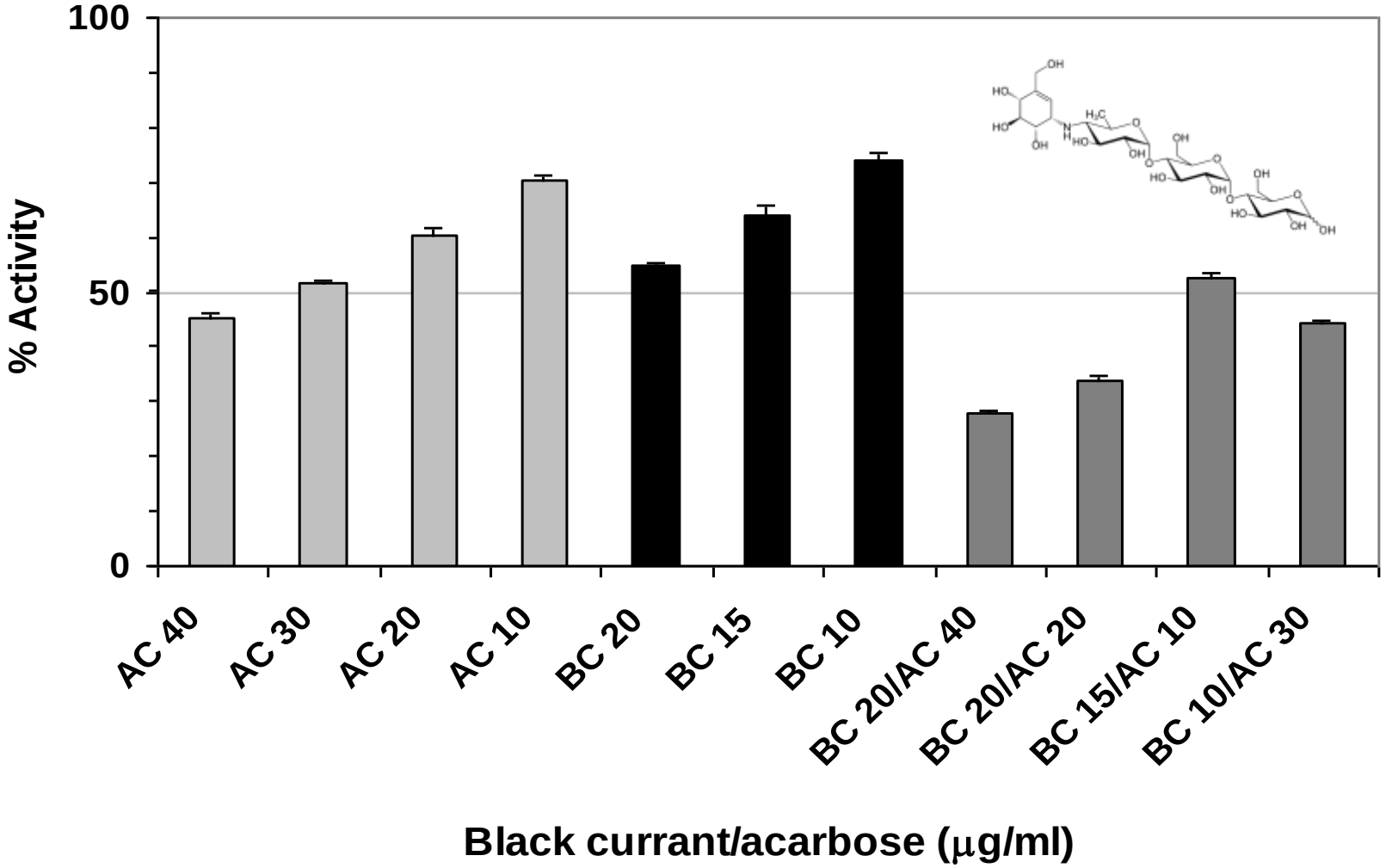
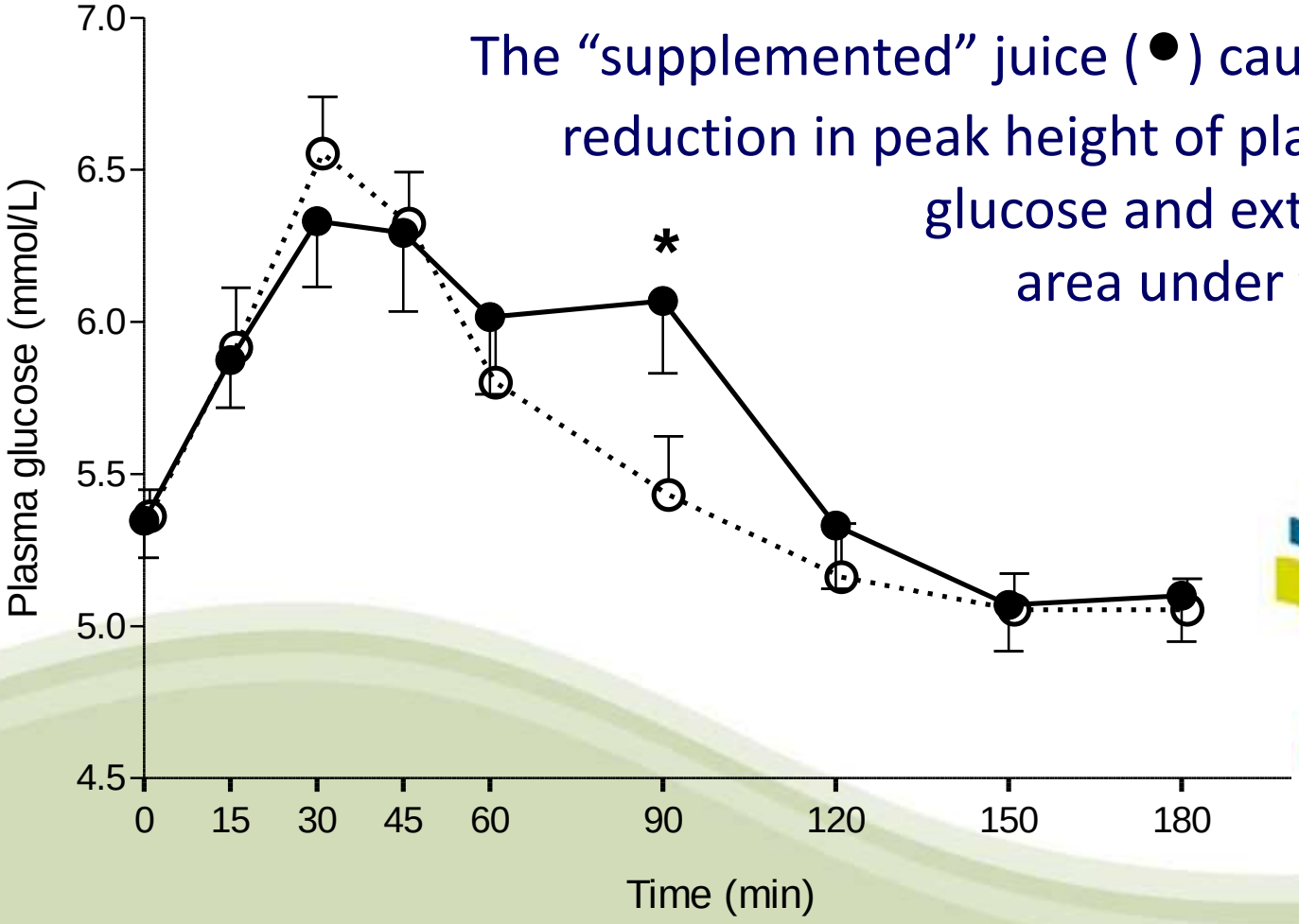


Human trial – modified glycemic response

Volunteers given sucrose-loaded black currant (BC) juice or sucrose-loaded high polyphenol BC juice

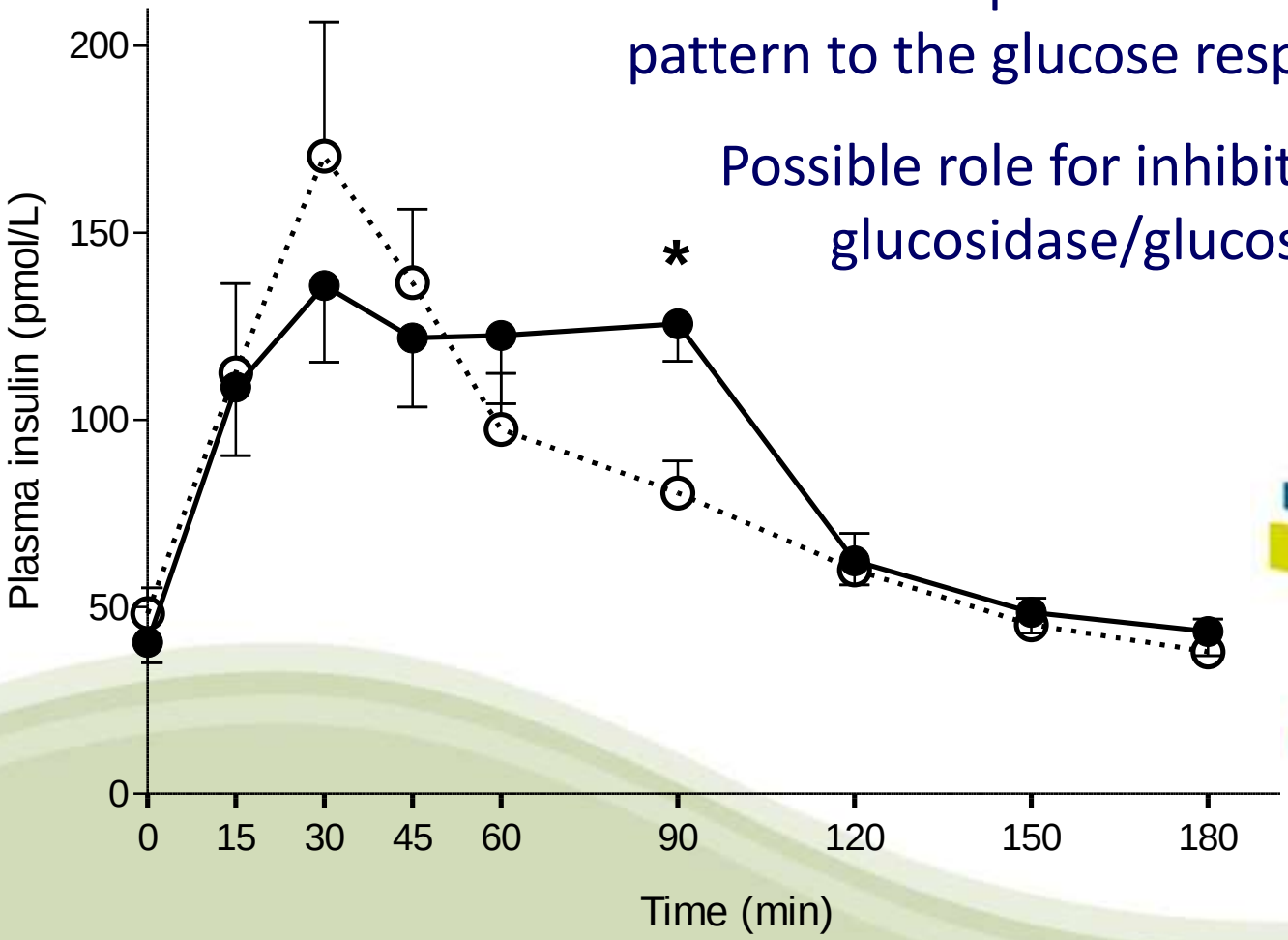


The "supplemented" juice (●) caused a reduction in peak height of plasma glucose and extended the area under the curve

Human trial – insulin response

The insulin responses showed a similar pattern to the glucose response

Possible role for inhibition of glucosidase/glucose transport?



*Törrönen et al. J. Functional Foods **4**, 746–756*

Summary

- Berry polyphenols inhibit enzymes involved in starch degradation *in vitro*
- The inhibition occurs at concentrations easily reached in the gut
- The active components are unknown but differ between amylase and glucosidase (↑ synergy?)
- Berry components can potentiate inhibition by acarbose at low levels
- **Initial** human studies show promise

Where now?

- Source of polyphenols – Wastes, by-products etc
- BrainHealthFood bioactive components from pomace
- Confirm effects at physiologically-relevant doses* and with *in vivo* metabolites (*includes product format)
- **Health Claims?**
- Effects of mixtures of components – synergies with pharmaceuticals
- Effects of climate, location, agronomy and variety on levels of active components

Future-proofing berryfruit CLIMAFRUIT

SEVENTH FRAMEWORK PROGRAMME EUBerry

EUBerry

healthier scotland SCOTTISH GOVERNMENT

Acknowledgements

Staff at the James Hutton Institute

Thank you for your attention

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JHI at Invergowrie on the north bank of the River Tay

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