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Bioactive compounds in fruit and berries – effects on human health

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Bioactivity – bioactive compounds: definitions and limitation

- Effects in humans
- Effects of oral intake of compounds
- Effects on human health – direct effect in the primary body or indirectly through a prebiotic effect or antibacterial effect.
  - Medicine - pure compounds – against diseases – Medical Agency
  - Plant medicinal compounds – mild diseases – Medical Agency

  - Supplemental foods – nutritional and wellbeing, non-diseases - Food Agency
  - Functional foods – EFSA health claim – 'early diagnosed markers for physiological unbalance', claim for reduced risk of developing diseases by reducing risk factors
  - Food – general nutritional health from existing accepted safe foods in EU
  - Novel Foods – new food crops accepted as safe in EU.

Health: perception or documentation

- Perception as specifically healthy food – native medicine
- Epidemiological evidence – populations – diet/food type
- In vitro tests - isolated compounds or products (chemical reactions, cultivated human cells etc).
- Animal tests (pre-clinical) – feeding exp.
- Human clinical tests – exploratory
- Human clinical tests – confirmatory
- Double blinded – placebo controlled experiments

Plant phenolics

Dietary sources of plant phenolics (Naczk & Shahidi, 2006).

Phenolic compounds	Dietary sources
Phenolic acids	
Hydroxycinnamic acids	Apricots, blueberries, carrots, cereals, pears, cherries, citrus fruits, oilseeds, peaches, plums, spinach, tomatoes, eggplants
Hydroxybenzoic acids	Blueberries, cereals, cranberries, oilseeds
Flavonoids	
Anthocyanins	Bilberries, black and red currants, blueberries, cherries, chokecherries, grapes, strawberries
Chalcones	Apples
Flavanols	Apples, blueberries, grapes, onions, lettuce
Flavanonols	Grapes
Flavanones	Citrus fruits
Flavonols	Apples, beans, blueberries, buckwheat, cranberries, endive, leeks, lettuce, onions, olive, pepper, tomatoes
Flavones	Citrus fruits, celery, parsley, spinach, rutin
Isoflavones	Soybeans
Xanthones	Mango, mangosteen
Tannins	
Condensed	Apples, grapes, peaches, plums, mangosteens, pears
Hydrolysable	Pomegranate, raspberries

Estimated over 8000 polyphenolic compounds isolated

including over 4000 flavonoids

Ignat et al. 2010

Compounds in fruit and berries with potential health effect, examples

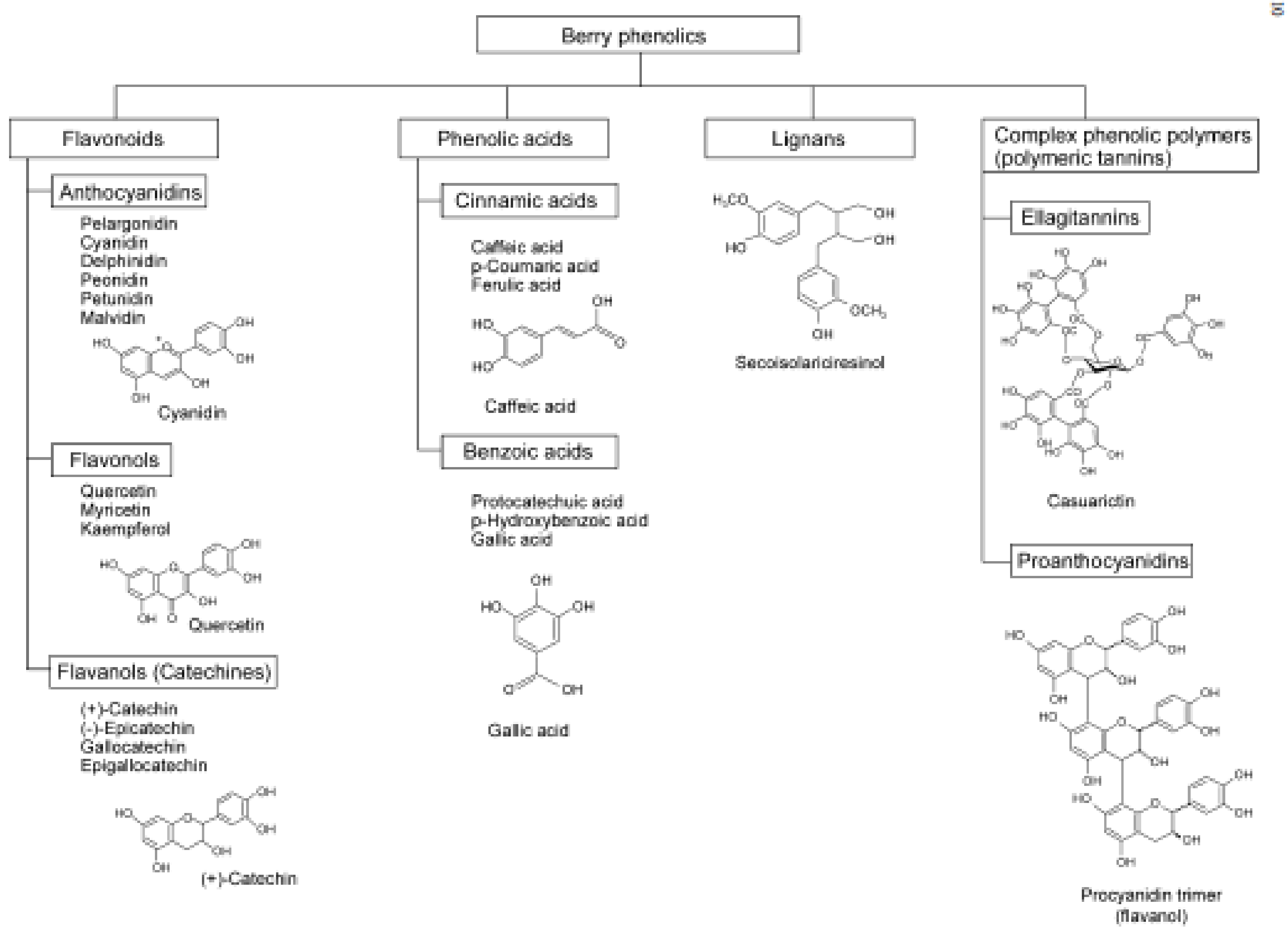


Fig. 1 Chemical structures of the main classes of phenolic compounds in berries

Puupponen-Pimiä et al. 2005

Potential health effect of fruit and berries in humans

- Anti-bacterial, direct bacteriostatic or b-cidal, pH, inhibit bacterial adhesion to epithelial cells
- Anti-viral
- Prebiotic, change bacterial profile in intestine, alter epithelial uptake
- Anti-oxidant, scavenger of free radicals, (induce increased body GSH, SOD),
- Anti inflammation, (arthritis, osteoarthritis), Metabolic syndrome (obesity),
- Anti- diabetic (improve insulin sensitivity and synthesis, blood glucose lowering, glycaemic index GI of food)
- Protective against CVD – cardio vascular diseases (LDL cholesterol lowering - bind and excrete bile acids from intestine, vaso-dilation of arteria, blood pressure lowering, inhibit platelet aggregation, anti-atherosclerosis)
- Anti-carcinogenic
- Anti-mutagenic
- Anti-toxic, detoxifying
- Vision, cognitive and neural function, sleep quality, immune defence etc.

Antioxidant capacity of fruit and berries

FRAP antioxidant capacity, mmol/100 g, examples avg. 3 samples	
Buckwheat flour	1.99
Ginger rhizomes	3.76
Red cabbage	1.88
Pomegranate	11.33
Apple (Gold del)	0.29
Dog rose	39.46
Blueberry, bilberry	8,23
Black currant	7,35
Sour cherry	5,53
Blackberry	5.07
Blueberry , corymbosum	3,64
Raspberry	3.06
Strawberry, cultiv	2.17
Sweet cherry	1.02

!! Different measurement methods, different preparations, quality of raw material, genetic variation

Halvorsen et al., 2002

Antioxidant effect of single compounds

Table 2. Antioxidant Activity of Phenolic Compounds and Vitamin C in Black Currants[a]

peak	t_R (min)	compound	quantity (nmol/g)	antioxidant activity (nmol of Trolox/g)	antioxidant activity (%)
	3.2	vitamin C	2328 ± 99	1094 ± 101	17.5 ± 1.6
1	12.9	caffeic acid-*O*-glucoside	80 ± 1	76 ± 12	1.2 ± 0.2
2	13.5	delphinidin-3-*O*-galactoside	52 ± 1	60 ± 14	1.0 ± 0.2
3	14.8	delphinidin-3-*O*-glucoside	839 ± 7	886 ± 158	14.2 ± 2.5
4	17.0	delphinidin-3-*O*-rutinoside	2233 ± 37	2049 ± 336	32.8 ± 5.4
5	18.3	cyanidin-3-*O*-glucoside	327 ± 5	261 ± 61	4.2 ± 1.0
6	20.3	cyanidin-3-*O*-rutinoside	1693 ± 1	1181 ± 236	18.9 ± 3.8
7	22.4	petunidin-3-*O*-rutinoside peonidin-3-*O*-galactoside	103 ± 2	77 ± 15	1.2 ± 0.2
8	24.0	malvidin-3-*O*-galactoside peonidin-3-*O*-glucoside	71 ± 1	nd	
9	25.9	peonidin-3-*O*-rutinoside	126 ± 17	nd	
10	31.3	myricetin-3-*O*-rutinoside	135 ± 3	119 ± 17	1.9 ± 0.3
11	31.8	myricetin-*O*-glucuronide	138 ± 2	116 ± 21	1.9 ± 0.3
12	35.0	myricetin-3-*O*-(6′′-malonyl)glucoside	29 ± 1	nd	
13	37.5	quercetin-3-*O*-rutinoside	77 ± 2	40 ± 7	0.6 ± 0.1
14	39.1	quercetin-3-*O*-glucoside	83 ± 3	40 ± 9	0.6 ± 0.1
15	40.5	delphinidin-3-*O*-(6′′-*p*-coumaroyl)glucoside	77 ± 1	43 ± 8	0.7 ± 0.1
16	42.5	quercetin-3-*O*-(6′′-malonyl)glucoside	17 ± 1	19 ± 3	0.3 ± 0.1
17	43.9	kaempferol-3-*O*-rutinoside	12 ± 0	nd	
18	45.2	kaempferol-3-*O*-galactoside	23 ± 1	nd	
		unidentified peaks		189 ± 8	3.0 ± 0.1

[a] Data expressed as mean values ± standard error ($n = 3$). t_R, retention time in minutes; nd, not detected. Peak numbers and retention times refer to HPLC traces in **Figure 1**. For identification of compounds see Table S1 and text in the Supporting Information.

Borges et al., 2010

Relative contribution to antioxidant effect in different berry species

Table 7. Total Content and Contribution to the Antioxidant Capacity of Vitamin C and Different Groups of Phenolics Detected in Berries[a]

compound	black currant	blueberry	raspberry	red currant	cranberry
vitamin C	2328 (18)	115 (0)	1014 (11)	313 (47)	1107 (23)
anthocyanins	5521 (73)	4810 (84)	885 (16)	328 (21)	725 (39)
ellagitannins			1352 (58)		
ellagic acid derivatives			34 (0)		
(−)-epicatechin					1121 (0)
procyanidin dimers					994 (12)
chlorogenic acid	80 (1)	8 (2)		89 (5)	119 (2)
flavonols	514 (5)	751 (14)	67 (0)	69 (4)	456 (10)
unidentified	(3)		(15)	(23)	(14)

[a] Data expressed in nmol/g of fresh weight; numbers in parentheses are percentages of the total antioxidant activity.

Borges et al., 2010

Causes of variation in concentration of single compounds – (ex anthocyanins)

- Genetic – determine specific compound profile and potential for high concentration
- Season – maturity
- Year to year – climate variation
- Cultivation methods, light exposure

- Processing – product manufactoring (pericarp - flesh)
- Storage – shelf life – compound stability

- Challenge to reproduce product quality and health effect

Bioavailability

- Anthocyanins and large polymeric tannins in general show low uptake and low concentrations in blood
- Anthocyanin metabolites found in blood reach maximum concentration after 1-2 hours and are depleted again after approx. 10-12 hours.

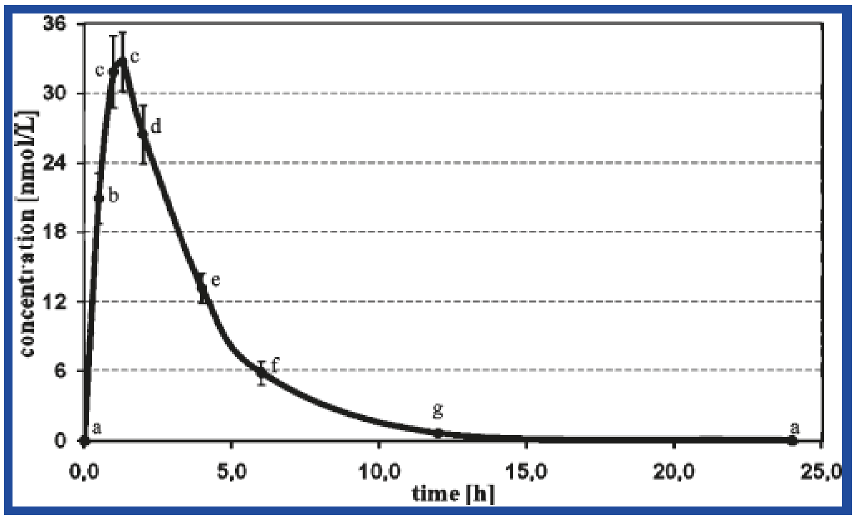


Figure 1. Plasma anthocyanin concentration in subjects who consumed chokeberry juice providing 0.8 mg of anthocyanins per kg body weight. Values are means ± SEM, $n = 13$. Values with different letters are significantly different at $P < 0.05$.

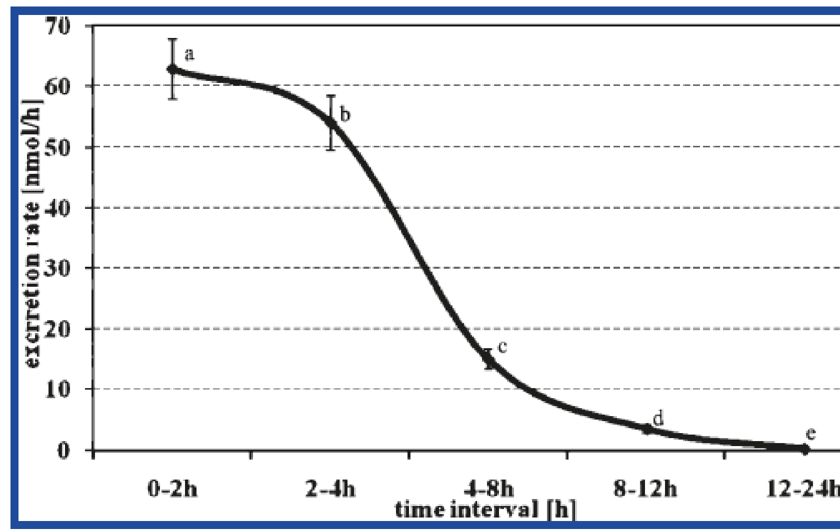


Figure 2. Urine excretion rate of anthocyanins in subjects who consumed chokeberry juice providing 0.8 mg of anthocyanins per kg body weight. Values are means ± SEM, $n = 13$. Values with different letters are significantly different at $P < 0.05$.

Wiczkowski et al., 2010

Uptake or excretion of specific anthocyanins

Table 1. Content of Cyanidin Derivatives in Chokeberry Juice

compound	content (mg/100 mL)
cyanidin-3-galactoside	12.60
cyanidin-3-glucoside	0.73
cyanidin-3-arabinoside	5.18
cyanidin-3-xyloside	0.59
total	19.10

Table 2. Anthocyanins Identified in Chokeberry Juice, Plasma and Urine

compound	retention time (min)	*m/z*	sample
cyanidin-3-galactoside	11.9	449, 287	juice, plasma, urine
cyanidin-3-glucoside	12.9	449, 287	juice, plasma, urine
cyanidin monoglucuronide	13.5	463, 287	plasma, urine
cyanidin-3-arabinoside	14.7	419, 287	juice, plasma, urine
peonidin-3-galactoside	16.6	463, 301	plasma, urine
peonidin monoglucuronide	18.6	477, 301	plasma, urine
peonidin monoglucuronide	19.1	477, 301	plasma, urine
peonidin-3-arabinoside	21.1	433, 301	plasma, urine
cyaniding-3-xyloside	22.3	419, 287	juice

Wiczkowski et al., 2010

Bioavailability cont..

Table 1. Daily Intake of Polyphenols from the Berry Products Consumed during the Intervention[a]

	day 1		day 2		
berry product	bilberries	lingonberries	black currant—strawberry purée	chokeberry—raspberry juice	av intake[b]
consumption/day (g)	100	50	100	70	160
total polyphenols (mg)	716	276	266	416	837
flavonols[c] (mg)	6.4	4.4	4.4	0.74	8.0
quercetin	4.6	2.2	2.2	0.72	4.9
flavanones[c] (mg)	0	0	0	0.36	0.18
anthocyanins[d] (mg)	550	48	192	240	515
procyanidins[e] (mg)	109	214	40	117	240
ellagitannins[f] (mg)	0	0	12.2	10.6	11.4
phenolic acids[c] (mg)	50.4	10	17.6	47	62.5
caffeic acid	11.9	2.5	3.4	35	26.4
protocatechuic acid	9.1	2.3	2.5	6.9	10.4
p-coumaric acid	7.9	0.77	5.5	1.8	5.5
vanillic acid	5.3	0.42	0.45	0.55	3.4
ferulic acid	0.95	0.77	0.94	0.80	1.7
gallic acid	2.6	0	2.5	1.3	3.2

[a] Intake calculations for polyphenols based on chemical analyses of berry products. [b] Average intake of polyphenols from two alternative days. [c] As aglycones. [d] Anthocyanins as cyanidin-3-glucoside. [e] Total procyanidins. [f] Ellagitannins as ellagic acid.

72 persons was given a berry diet with double amount of polyphenols/day compared to normal avg intake or a control diet without berries for 8 weeks

Koli et al. 2010

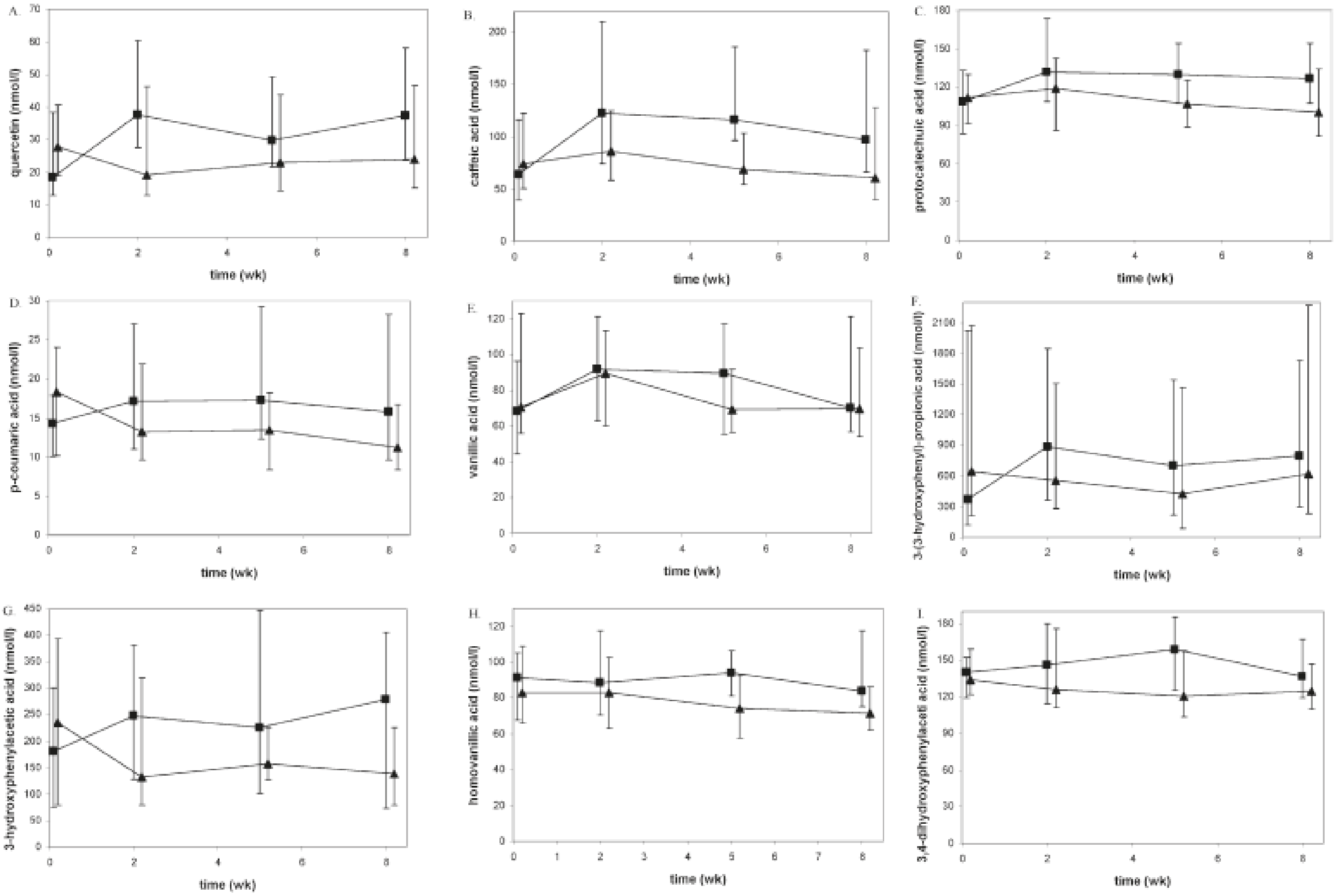


Figure 1. Plasma polyphenol concentrations (median ± 25th percentile) in middle-aged subjects consuming berries or control products as a part of their habitual diet for 8 weeks (■, berry group; ▲, control group): (**A**) quercetin; (**B**) caffeic acid; (**C**) protocatechuic acid; (**D**) *p*-coumaric acid; (**E**) vanillic acid; (**F**) 3-(3-hydroxyphenyl)propionic acid; (**G**) 3-hydroxyphenylacetic acid; (**H**) homovanillic acid (3-hydroxy-4-methoxyphenylacetic acid); (**I**) 3,4-dihydroxy-phenylacetic acid (DOPAC).

Koli et al. 2010

Clinical trials in Aronia - review

- 13 studies found up to 2009
- Extracts, concentrate or juices (27-45 mg anthocyanin/day)
- Studies indicate that chokeberry products may well be used as functional foods for disorders or diseases related to oxidative stress (MS, CVD, diabetes 2, - LDL cholesterol, TG, blood glucose, blood pressure, immunesystem, ROS protection).
- However most studies are of poor quality and of the exploratory type
- Confirmatory and rigorious clinical trials are needed before therapeutic recommendations can be given.

Chrubasik et al., 2010

Med Sci Monit, 2010; 16(1): CR28-34

Table 1. Mean values of the studied parameters after 1 (1 m) and 2 months (2 m) of aronia extract therapy in patients with MS.

Parameter	At baseline	After 1 m	After 2 m	Control group
SBP mmHg	143.40±7.87^{xxx}	136.00±12.33^{xxx,***}	131.83±12.24^{xxx,***}	115.32±8.98
DBP mmHg	87.20±9.90^{xxx}	84.24±9.57^{xxx}	82.13±10.33^{xx,*}	72.41±10.49
Body weight kg	84.32±12.53^{xxx}	83.66±12.46	84.40±12.33	68.18±12.14
Waist circumference cm	97.04±9.03^{xxx}	96.44±8.88	96.71±8.53	74.23±9.84
BMI kg/m^2	31.05±3.24^{xxx}	30.8±3.21^{xxx}	30.92±3.21^{xxx}	24.15±1.46
TC mg/dl	242.80±34.48^{xxx}	229.20±34.08^{xxx,**}	227.96±33.07^{xxx,***}	197.45±27.39
LDL-C mg/dl	158.71±35.78^{xxx}	150.00±34.63^{xxx,*}	146.21±34.63^{xxx,**}	119.94±14.02
HDL-C mg/dl	42.91±4.98^{xxx}	44.27±5.89^{xxx}	44.27±6.07^{xxx}	56.72±9.21
TG mg/dl	215.92±63.61^{xxx}	184.60±79.13^{xxx,*}	187.58±90.00^{xxx,*}	91.05±30.15
ET-1 pg/ml	2.44±0.51^{xxx}	1.92±0.39^{xx,***}	1.74±0.42^{xx,***}	0.98±0.38
CRP mg/dl	2.62±2.50	2.72±2.49	2.34±2.15	1.3±0.61
Fibrinogen mg/dl	249.20±27.17^{xx}	247.56±35.19^{x}	276.67±57.41^{xxx,*}	214.73±36.69
Fasting glucose mg/dl	92.92±11.03^{xxx}	90.12±11.16^{xxx}	93.92±10.48^{xxx}	77.95±7.36
Uric acid mg/dl	5.86±1.07^{xx}	5.93±1.21^{xx}	5.89±1.20^{xx}	4.91±0.88

*** $p<0.001$; ** $p<0.01$; * $p<0.05$ vs. baseline values; ^{xxx} $p<0.001$; ^{xx} $p<0.01$; ^{x} $p<0.05$ vs. the control group.
SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides, CRP – C-reactive protein; ET-1 – endothelin-1.

Table 2. Mean values of antioxidative enzymes and TBARS after 1 (1 m) and 2 months (2 m) of aronia extract therapy in patients with MS.

Parameter	At baseline	After I m	After 2 m	Control group
SOD (U/g-Hb)	2380.63±419.91^{xxx}	2860.11±508.27^{xxx,**}	3066.53±542.24^{xxx,***}	4458.87±761.01
CAT (U/mg-Hb)	261.30±59.78	208.55±48.09^{xxx,***}	213.34±47.36^{xxx,***}	265.96±30.27
GSH-Px (U/g-Hb)	12.60±5.97^{xx}	17.71±8.99*	19.18±9.09**	18.61±2.49
TBARS (μmol/g-Hb)	0.0712±0.0191^{xxx}	0.0529±0.019^{xxx,***}	0.0362±0.0135^{xx,***}	0.0237±0.00371

*** $p<0.001$; ** $p<0.01$; * $p<0.05$ vs. baseline values; ^{xxx} $p<0.001$; ^{xx} $p<0.01$; ^{x} $p<0.05$ vs. the control group.

Effect of Aronia

Aronox extract 3 x 100 mg/day in 25 Metabolic Syndrome humans compared to 22 healthy humans

Broncel et al. 2010

Cholesterol lowering by fruit and berries by their ability to bind and excrete bile acids in intestines, tested in vitro.

In vitro bile acid binding by blueberries (*Vaccinium* spp.), plums (*Prunus* spp.), prunes (*Prunus* spp.), strawberries (*Fragaria X ananassa*), cherries (*Malpighia punicifolia*), cranberries (*Vaccinium macrocarpon*) and apples (*Malus sylvestris*) on equal weight, dry matter (DM) basis[A,B]

Treatment	Bile acid binding	
	(μmol/100 mg DM)	Relative to Cholestyramine, %
Blueberries	0.73 ± 0.02^{b}	7.1 ± 0.2^{b}
Plums	0.60 ± 0.01^{c}	5.8 ± 0.1^{c}
Prunes (plums, dried)	0.53 ± 0.06^{cd}	5.1 ± 0.6^{cd}
Strawberries	0.52 ± 0.03^{cd}	5.1 ± 0.3^{cd}
Cherries	0.49 ± 0.03^{d}	4.8 ± 0.3^{d}
Cranberries	0.43 ± 0.04^{d}	4.1 ± 0.4^{d}
Apples	0.12 ± 0.01^{e}	1.2 ± 0.1^{e}
Cholestyramine	10.29 ± 0.05^{a}	100.0 ± 0.4^{a}
Cellulose	0.07 ± 0.02^{e}	0.7 ± 0.2^{e}

[A] Mean ± SEM within a column with different superscript letters differ significantly ($P \leqslant 0.05$), $n = 6$.
[B] The dry matter used for incubation was all the fruits was 103–107 mg, cholestyramine and cellulose 24–26 mg.

Bile acids are acidic steriods syntesized in the liver from cholesterol. Partly reabsorbed in intestines. Avoiding reabsorption may reduce cholesterol concentration in blood. Binding effect is not explained by TDF or PCH content in fruit.

Kahlon and Smith, 2007

Cranberry – health effects

- Suggested active compounds
  - Anthocyanins, flavonols, flavan-3-ols, proanthocyanidins phenolic acid derivatives
- Suggested effect in diseases and health:
  - CVD, cancers, urinary tract infections, dental health, Helicobacter pylori-induced stomach ulcers and gastric cancers.
- Suggested mechanisms of action
  - Antioxidant, radical scavenging, anti-bacterial, antimutagen anti carcinogen. Binding of toxic compounds, inhibiting bacteria adhesion to cells.

  - Intake of cranberry juice with dosis of 36 mg of proanthocyanidins/day help reduce the adhesion of certain E. coli bacteria to epithelial cells of the urinary tract – functional food claim in France (Heionen 2007). Adhesion of other disease bacteria are inhibited with similar type mechanisms.
  - Especially epicatechin tetramers and pentamers with at least one A type linkage seems most active in inhibiting fimbriae mediated adhesion of bacteria.

Côté et al., 2010

Vaccinium - Blueberries

Table 2 Chemical composition of *V. myrtillus*, and other selected *Vaccinium* species.

Quality parameter	*V. myrtillus* Norway[1]	*V. myrtillus* references[2]	*V. corymbosum* references[3]	*V. angustifolium* references[4]
Berry weight (mg f.w.)	457 ± 81	328 ± 63	1635 ± 346	326 ± 67
Dry matter (g/ 100 g f.w.)	15.0 ± 1.6	15.2 ± 3.2	16.4 ± 4.1	22.1 ± 13.1
Soluble solids content (Brix value in %)	10.8 ± 1.6	9.8 ± 1.1	12.7 ± 2.1	15.4 ± 1.6
pH	2.7 ± 0.1	3.1 ± 0.1	3.2 ± 0.2	2.7 ± 0.1
Titratable acidity (g/ 100 g f.w.)	1.4 ± 0.2	2.4 ± 1.5	1.4 ± 0.6	0.9 ± 0.1
Total anthocyanins (mg/ 100 g f.w.)	275 ± 72	364 ± 189	145 ± 54	181 ± 152
Total phenols (mg GAE/ 100 g f.w.)	612 ± 75	472 ± 164	289 ± 105	546 ± 255
Antioxidants FRAP (mmol/ 100 g f.w.)	5.7 ± 1.2	5.3 ± 2.2	2.6 ± 1.1	9.8 ±
Fructose (mg/ 100 g f.w.)	5290 ± 1027	3687 ± 1092	6171 ± 3150	3900 ±
Glucose (mg/ 100 g f.w.)	5348 ± 1074	3380 ± 988	3296 ± 852	5150 ±
Sucrose (mg/ 100 g f.w.)	578 ± 270	411 ± 187	180 ±	
Citric acid (mg/ 100 g f.w.)	1321 ± 150	683 ± 171	427 ± 168	
Malic acid (mg/ 100 g f.w.)	298 ± 95	261 ± 195		
Quinic acid (mg/ 100 g f.w.)	1703 ± 476	1370 ±	46 ± 73	
Catechins (mg/ 100 g f.w.)	45 ± 24	5.0 ±	5.3 ±	
Chlorogenic acid (mg/ 100 g f.w.)	32 ± 18		59 ± 82	
Ascorbic acid (mg/ 100 g f.w.)	3.0 ± 2.5	18.6 ± 24.6	9.2 ± 3.8	12.1 ± 6.9
Gallic acid (µg/ 100 g f.w.)	834 ± 235	1760 ±		
Quercetin (µg/ 100 g f.w.)	473 ± 262	2263 ± 966	3824 ± 2764	

[1]Based on experimental data from Norwegian trials in 2009 (Nestby *et al.*, unpublished data)
[2]Data compiled from 27 references
[3]Data compiled from 24 references
[4]Data compiled from 4 references

Nestby et al 2011

Blueberries (NA spp)

- Bacterial anti-adhesion like in cranberries (in vitro)
- Anti cancer effect in vitro: colon, breast, prostate, leukemia
  - (quercetin, proanthocyanindins, anthocyanins and ursolic acid)
- Cardiovascular – reduces oxidative stress and inflammation
  - LDL cholesterol reduction (pterostilbene reduce by 29 % in animal model)
- Neuroprotective effects
  - Improve cell signalling and neuronal communication, protect against accumulation of harmfull compounds in brain and improve cognitive function in aged animals (protect against induced Alzheimer).
- Vision improvements, digestion, anti-diarrhea, anti-diabetic

Howell 2009, Neto 2007

Vaccinium - Blueberries

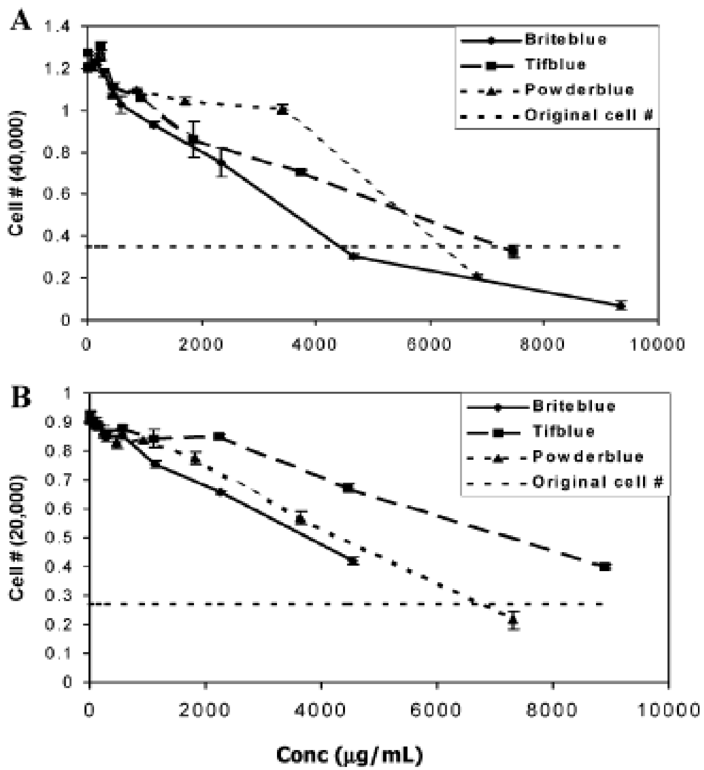


Figure 3. Inhibition of HT-29 (**A**) and Caco-2 (**B**) cancer cell proliferation by crude extracts of blueberries (mean ± SD, $n = 8$). The x-axis gives the concentration (μg/mL) of extracts in the culture medium. Original cell # is the cell number after 24 h of incubation and before treatments were applied.

Effect of three Vacc. ashei (rabbiteye) blueberry cultivars extracts on proliferation of two colon cancer lines in vitro

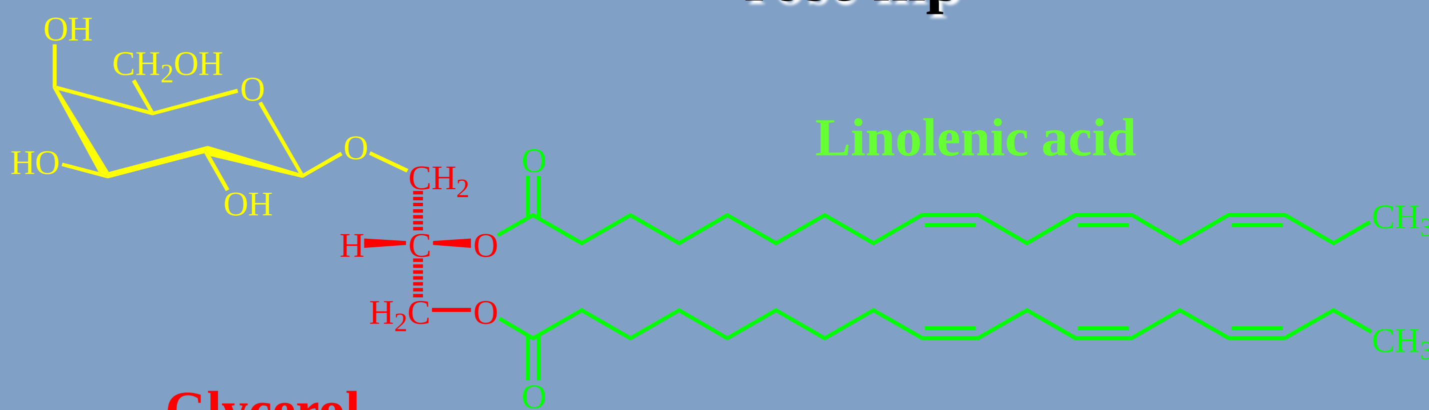
Anthocyanin fraction most potent inhibitor of tested phenolic compounds

Weiguang, 2005

Rose hip fruit – pain reduction in osteoarthritis by active compounds Galacto lipid (GOPO) and two triterpene acids oleanolic acid and ursolic acids*

Anti-inflammatory galactolipid isolated from rose hip

Galactose



Glycerol

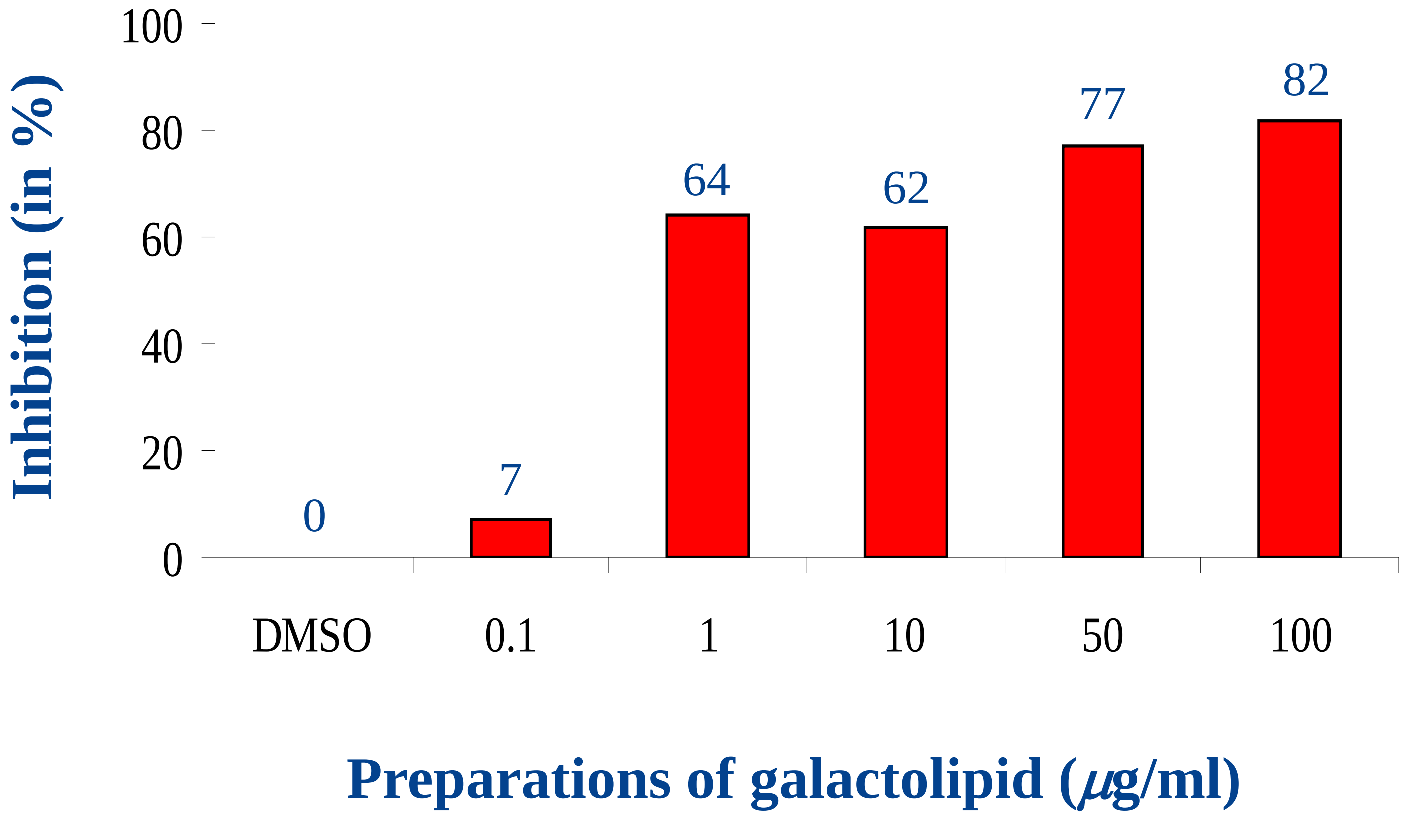
DOTGG

(2*S*)-1,2-**D**i-*O*-[(9*Z*,12*Z*,15*Z*)-**o**ctadeca-9,12,15-**t**rienoyl]-3-*O*-*β*-D-**g**alactopyranosyl **g**lycerol

Larsen et al. 2003

* Saaby et al, 2011

Effect of the isolated galactolipid on chemotaxis of human peripheral blood PMN's



Larsen *et al*. (2003). *Journal of Natural Products* **66**, 994–995.

Conclusion

- Fruit and berry constitute a large resource of bioactive compounds with diverse biological actions that may be exploited for preserving human health

- Great promise for future more concise knowledge and understanding of effects, mechanisms, effective compounds, relevant species, relevant products and doses.

- Preserving health and preventing diseases will improve life quality and may reduce health costs of society dramatically.

- Much more rigorious experiments are needed that provide full documentation for recommendations

- But before getting there, - new research is needed in understanding metabolising of compounds in gastro-intestinal tract and modulation by the bacterial flora, changes in uptake and transport patterns, receptors, thresholds, feedback regulating mechanisms etc.

References 1

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