Blueberries – a hyperberry for hypertension.

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Hypertension: the problem

- BP ≥140/90 mm Hg (Canadian Hypertension Education Program; American Heart Association)
- a major risk factor for heart attack, stroke, kidney disease
- worldwide prevalence ~26% of adults, 1 in 8 people
  (Savica et al. 2010); ~29% of US adults (+31% are pre-hypertensive)
- Costs ~$60B in US and $300M in Canada
- a reduction in BP of only 3mmHg may reduce mortality by 5–8% (Padwal et al. 2005)

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- Funding

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Vaccinium angustifolium

- Member of heath family (Ericaceae). Lowbush variety in N.E. North America grow ‘wild’.
- Shoots emerge in the spring, flower, pollinated by bees, and fruit 2–3 months later.
- Contain many polyphenolic compounds, esp flavonoids:
  - >20 different anthocyanins ([Matchett et al. 2005]; structurally similar to tea flavanols [Manach & Donovan 2004])
  - Large proanthocyanidins (condensed tannins [Matchett et al. 2005])
  - Mitigate oxidative stress.
  - Have other bioactivities e.g. anti-inflammatory.

**Table 1: Blood pressure reductions achieved with lifestyle interventions**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Most blood pressure reduction (mmHg, % reduction)</th>
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<tbody>
<tr>
<td>Sodium</td>
<td>4.5±1.6</td>
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<tr>
<td>Dietary</td>
<td>2.6±1.1</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>2.3±1.0</td>
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<tr>
<td>L-arginine</td>
<td>1.9±0.9</td>
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**Figure 1:** The effect of **V. angustifolium** extract on blood pressure. Black squares represent the extract group with a significant decrease in blood pressure compared to the control group (white circles). R² = 0.83. Values are means ± SEM. 

**Vaccinium Polyphenol levels**

- Lowbush Blueberry
- Highbush Blueberry
- Cranberry
- Strawberry

**Modeling human hypertension**

Spontaneously hypertensive stroke prone rats (SHRSP) develop hereditary essential hypertension on high salt diets. 

- Reactive oxygen species (O₂⁻) generated
- Down-regulation of endothelium NO
- Oxidative stress
- Vasoconstriction
- Damage (kidneys, blood vessels)
- Hypertension

**CH**

- Manach & Donovan 2004

**CH**

- Matchett et al. 2005

**CH**

- Matchett et al. 2005
**Are antioxidants beneficial in hypertension?**

- Dietary fruits & vegetables/DASH lower BP ([Savica et al. 2010](#)).
- Pharmacological doses of vitamin C ⇒ vasodilation ⇒ ↓ blood pressure, although results from some studies have been inconclusive or disappointing ([Rodrigo et al. 2007](#)).
- Quercitin, a highly abundant flavonol, ⇒ long-lasting anti-hypertensive effects in several animal models of hypertension, as well as in humans ([Perez-Vizcaino et al. 2009](#)).
- Tea catechins are good vasodilators and ↓ BP and ↑ life span in SHRSP ([Uchida 1995; Negishi et al. 2004](#)).
- Anthocyanins ↑ NO and ↓ BP ([Savica et al. 2010](#)).
- Foods rich in flavonols and procyanidins, such as cocoa, ↓ BP ([Ghosh and Scheepers, 2009; Savica et al., 2010](#)).

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**Methods: SHRSP**

1) **Blood pressure:**
- fed control AIN diet or 3% blueberry or cranberry diet + 2% NaCl
- Week 2, 4, 6, 7, 8: systolic BP measured using tail cuff method
- Monitored for SRS

2) **Renal pathology:**
- fed control AIN diet or 3% blueberry diet + 2% NaCl
- Week 16: urinalysis
- Week 17: euthanasia; one kidney fixed for histology; one kidney flash-frozen for glutathione measurement spectro-photometrically.

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**Effect of Vaccinium berries on BP**

- 8 wk old SHSP rats or WKY controls
- Fed control AIN diet or 3% blueberry or cranberry diet + 2% NaCl
- Week 2, 4, 6, 7, 8:
  - systolic BP measured using tail cuff method
  - Monitored for SRS

**Blueberries lower BP at wk 4–7**

([Shangahanavy et al. 2009](#))
Blueberries had no effect, Cranberries increase survival times.

**Kidney redox state**
- Blueberry feeding doubled the GSH/GSSH ratio in SHRSP rats suggesting ↑ redox state.

**Kidney pathology**
- SHRSP rats on control diets had renal damage:
  - Bowman’s capsule thickening
  - Glomerular sclerosis and obsolescence
  - Arcuate artery and renal arteriole myointimal hyperplasia
  - Renal vascular thrombosis
- Blueberry feeding reduced or eliminated all of these pathologies (except renal arteriole myointimal hyperplasia).
Kidney pathology (overall)

- Blueberry fed SHSP rats had less renal damage than control fed rats \( (p = 0.002, N=3) \).

Kidney pathology: individual markers

1. Fibrosis & scarring of the renal glomeruli: early hypertensive changes.


3. Slight proteinuria is normal in urine; excess implies leaking in glomeruli.
**Urinalysis results**

- Urine from blueberry fed SHRSP had slightly less leukocytes and 60% less protein content than SHSP rats on normal diets (N=3).

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<th>Protein</th>
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<td>-</td>
<td>* (10 ± 10)</td>
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<tr>
<td>Control rats, BB diet</td>
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<td>* (10 ± 10)</td>
</tr>
<tr>
<td>SHSP rats, normal diet</td>
<td>+++</td>
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**Renin-angiotensin-aldosterone system**

- ACE: membrane-bound enzyme expressed in many tissues, especially the lungs and vascular endothelium, but a soluble form exists in blood.

**Flavon-3-ols (and food containing them) are ACE inhibitors**

> ACT-464561 (Acta Caroten. A., 2006; 12: 176-181) Flavonoids, a group of compounds, are found in various fruits and vegetables and are known to exhibit anti-aggregatory, anti-inflammatory, and anti-oxidant properties. They have been shown to inhibit ACE activity in vitro and in vivo, leading to a reduction in blood pressure. This effect is due to the inhibition of the renin-angiotensin system, which plays a key role in the regulation of blood pressure. ACE inhibitors are widely used in the treatment of hypertension and other cardiovascular diseases. The study of flavonoids as potential ACE inhibitors is an active area of research, with the potential to develop new and safer therapies for blood pressure control.

**Key points**

- ACE: Angiotensin-converting enzyme
- ACE inhibitors: Drugs that inhibit ACE, leading to a decrease in blood pressure
- Renin-angiotensin system: A hormonal system that regulates blood pressure
- Hypertension: A condition characterized by high blood pressure
- Antihypertensive agents: Medications used to treat hypertension
- Hypertension without other compelling indication: Hypertension not associated with other conditions
- Hypertension with other compelling indications: Hypertension associated with other conditions

**Hypertension in Canada**

- Prevalence of hypertension in Canada is high
- ACE inhibitors are commonly used in the treatment of hypertension
- Combinations of ACE inhibitors with other antihypertensive drugs are often used
- ACE inhibitors are recommended for the treatment of hypertension in patients with diabetes or nephropathy
- The use of ACE inhibitors in pregnant women is restricted
- ACE inhibitors are not recommended for the treatment of hypertension in children under 6 years of age
- The use of ACE inhibitors in patients with a history of angioedema is contraindicated
Flavon-3-ols (and food containing them) are ACE inhibitors (Achta-Goretti et al. 2006, J. Agric. Food Chem. 54: 229–234.)

Our study methods

• male WKY (n=24) and SHRSP (n=24) aged 7 wk acclimated for 1 wk, and then randomly assigned to a diet:
  (1) AIN '93G purified diet + 3% freeze-dried blueberry or
  (2) AIN '93G purified diet lacking BB (control)
• blood taken every 2 weeks
• tissues removed after 6 weeks
• ACE activity determined by colorimetric assay (ALPCO Diagnostics)

ACE activity in lung (Wiseman et al. 2011)

Same trend in other ACE-rich tissues e.g. kidney, testis, blood vessels.

ACE activity in serum (Wiseman et al. 2011)
**Summary**

In spontaneously hypertensive stroke prone rats, feeding blueberries appears to:
- slow the development of hypertension
- reduce the severity of hypertension
- prevent early renal pathologies and increase the redox state of the kidney; inhibit soluble but not tissue ACE: *likely mechanisms for the beneficial effects on hypertension.*
- Cranberries prolong survival in SHRSP