Dietary polyphenols in the prevention of cardiovascular diseases: facts, fiction and prospective mechanisms of action

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&
The Microbiome Research Hub

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The Need for Nutrition Education/Innovation Programme (NNEdPro)
Thanks to....
They prevent!!?
Companies are riding the wave.....
Our Super Antioxidants
destroy evil free-radicals.

ALTON BROWN
Polyphenol Pro
TV’s Culinary Genius

The Concord grapes in our Purple 100% Grape Juice are full of amazing antioxidants called polyphenols. Drinking Welch’s helps support a healthy:

WELCH'S
100% Grape Juice

Welch’s. To health.
Life support.
The antioxidant power of pomegranate juice.
But the best comes from Japan!
Unfortunately…
GTC suppression of cellular carcinogenesis.
Blackberry Seed Extracts and Isolated Polyphenolic Compounds Showing Protective Effect on Human Lymphocytes DNA

Dejan Gođevac, Vele Tešević, Vlatka Vajs, Slobodan Milosavljević, and Miroslava Stanković
At low concentrations (< 50 µM), resveratrol appears to activate AMPK without decreasing energy (Dasgupta and Milbrandt, 2007; Suchankova et al., 2009).

Figure 4. Resveratrol Is a PDE Inhibitor
(A) The effect of resveratrol on the activities of recombinant PDEs 1–5.
(B) Velocity of recombinant PDE3 activity as a function of cAMP and resveratrol concentration.
(C) Lineweaver-Burk plot of (B).
(D) Recombinant PDE3 was photoaffinity labeled with the fluorescent cAMP analog 8-azido-[DY-547]-cAMP in the presence of resveratrol or cAMP. 8-azido-[DY-547]-cAMP bound to PDE3 was visualized by fluorescence imaging (left). Quantification of 8-azido-[DY-547]-cAMP binding is shown in the right panel (n = 3).

Work out more physiological models!
Bioavailability of Ellagitannins in Healthy Humans

Time 0 - Ingestion

300 g of strawberries or 160 ml of pomegranate juice allow the administration of approx. 140 µmol of ellagic acid and ellagitannins.

After 1 Hour

Ellagic acid, obtained by basic hydrolysis of ET downline of gastric passage, is detected in plasma at Cmax 0.06 µM, AUC 0.17 µmol*h/L.

After 5 Hours

Ellagic acid disappears from plasma. The amount unabsorbed in the small intestine enters the large intestine where it is bio-transformed by resident colonic microflora.

Large Intestine

The colonic microflora produces four different urolithins by a fixed order: Urolithin D appears first, is modified to Urolithin C, then to A and finally to Urolithin B.

Urolithin D

Urolithin C

Urolithin B

Urolithin A

Urolithins can be glucuronated, sulphated or methylated by Phase I and Phase II enzymes in the liver.

Large Intestine

Urolithin B 3-O-glucuronide

Variability

All reports highlight a great interindividual variability, likely due to different microfloras. Total urinary excretion of ET-metabolites may range from 1 to 63%.
TIME

SMALL INTESTINE

KIDNEY

TISSUE

COLON

LIVER

SMALL INTESTINE

POLYPHENOL
A lot of metabolites

A FEW PLANT POLYPHENOLS
You fancy a coffee?
The dietary proanthocyanidin funnel: A great number of food sources yield a limited pattern of intestinal catabolites.
The phytochemical fan of ellagitannins: A single molecule yields a wide range of intestinal catabolites.
GUT – CV AXI S
In vivo administration of urolithin A and B prevents the occurrence of cardiac dysfunction in streptozotocin-induced diabetic rats

Monia Savi¹,²†, Leonardo Bocchi²†, Pedro Mena¹†, Margherita Dall’Asta¹, Alan Crozier³, Furio Brighenti¹, Donatella Stilli²* and Daniele Del Rio¹*
Vehicle i.p. injection (CTRL, n=10) → STZ i.p. injection (60mg/Kg; D3, n=29) → Glucose blood level measurement → 48 hours → 1. Hemodynamic measurements (CTRL, n=10; D3, n=9; D3_UA, n=8; D3 UB, n=9) → 3 weeks → 2. Cardiomyocytes isolation, cell mechanics and Ca2+ transients (CTRL, n=8; D3, n=8; D3_UA, n=5; D3 UB, n=4) → Cardiomyocytes

**UROLITHIN A** i.p. *daily injection* (2.5mg/kg/gg) (D3_UA, n=10)

**UROLITHIN B** i.p. *daily injection* (2.5mg/kg/gg) (D3 UB, n=10)

**DIABETIC UNTREATED RATS** (D3, n=9)

*Savi et al. Cardiovasc Diabetol (2017) 16:80*
Results: Hemodynamic measurements (Contraction rate)

- Maximum rate of ventricular pressure rise ($+\frac{dP}{dt}$ (mmHg/s))
- Isovolumic contraction time (IVCT) (s)
- Maximum rate of ventricular pressure reduction ($-\frac{dP}{dt}$ (mmHg/s))
- Contraction-Relaxation time (s)

CTRL (n=10)
D3 (n=9)
D3_UA (n=8)
D3_UB (n=9)

* p<0.05 vs CTRL
# p<0.05 vs D3
Cardiomyocytes isolation, cell mechanics
Results: Cell mechanics

Mean diastolic sarcomere length (μm)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTRL</td>
<td>66</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>D3</td>
<td>91</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>D3_UA</td>
<td>100</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>D3_UB</td>
<td>102</td>
<td>1.4 ± 0.2</td>
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</tbody>
</table>

*p<0.01 vs CTRL  # p<0.01 vs D3  § p<0.01 vs D3_UA

Fraction of Shortening (%)

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<th>n</th>
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</tr>
</thead>
<tbody>
<tr>
<td>CTRL</td>
<td>66</td>
<td>7.3 ± 0.5</td>
</tr>
<tr>
<td>D3</td>
<td>91</td>
<td>7.2 ± 0.5</td>
</tr>
<tr>
<td>D3_UA</td>
<td>100</td>
<td>7.1 ± 0.5</td>
</tr>
<tr>
<td>D3_UB</td>
<td>102</td>
<td>7.0 ± 0.5</td>
</tr>
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</table>

*-dL/dt (μm/s) (MAX RATE OF SHORTENING)

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>CTRL</td>
<td>66</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>D3</td>
<td>91</td>
<td>2.4 ± 0.3</td>
</tr>
<tr>
<td>D3_UA</td>
<td>100</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>D3_UB</td>
<td>102</td>
<td>2.2 ± 0.3</td>
</tr>
</tbody>
</table>

# p<0.01 vs D3  § p<0.01 vs D3_UA

+dL/dt (μm/s) (MAX RATE OF RE-LENGTHENING)

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</thead>
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<tr>
<td>CTRL</td>
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<td>2.5 ± 0.3</td>
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<tr>
<td>D3</td>
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<tr>
<td>D3_UA</td>
<td>100</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>D3_UB</td>
<td>102</td>
<td>2.2 ± 0.3</td>
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To sum up:

- Urolithin A and B contribute to a remarkable recovery of heart muscle function after DCM is induced.
- This effect involves calcium transient (as expected)
- ....possibly through actions involving SERCA phosphorilation and PLB
- ....with inflammation potentially involved in the model (Fractalkine).
Trimethylamine-N-oxide (TMAO)-induced impairment of cardiomyocyte function and the protective role of urolithin B-glucuronide

Monia Savi\textsuperscript{1,2,*}, Leonardo Bocchi\textsuperscript{2,*}, Letizia Bresciani\textsuperscript{1}, Angela Falco\textsuperscript{3}, Federico Quaini\textsuperscript{3}, Pedro Mena\textsuperscript{1}, Furio Brighenti\textsuperscript{1}, Alan Crozier\textsuperscript{4}, Donatella Stilli\textsuperscript{2,*}, Daniele Del Rio\textsuperscript{1,*}
“the papers leading to [his] 2016 Lasker prize (with Gregg Semenza and Peter Ratcliffe, for discovering how cells sense oxygen) were published more than a decade ago. Most would be considered quaint, preliminary and barely publishable today. […] Fortunately, an experienced editor intervened, arguing that publication would open the search for the enzyme to other groups; such reprieves seem less common today.”
Mouse saphenous artery

Mouse femoral artery

Mouse aorta
Human interventions...

Effects of Low Habitual Cocoa Intake on Blood Pressure and Bioactive Nitric Oxide
A Randomized Controlled Trial

Dirk Taubert, MD, PhD
Renate Roesen, PhD
Clara Lehmann, MD
Norma Jung, MD
Edgar Schömig, MD

Figure 3. Between-Group Comparisons of Blood Pressure, S-Nitrosoglutathione, and Total 8-Isoprostane Levels After Dark and White Chocolate

Hypertension prevalence declined from 86% to 68%

Error bars indicate 95% confidence intervals of differences in mean change scores. Nominal P values were calculated for pairwise between-group differences in change by 2-tailed t test.
Methylxanthines enhance the effects of cocoa flavanols on cardiovascular function: randomized, double-masked controlled studies

Roberto Sansone, Javier I Ottaviani, Ana Rodriguez-Mateos, Yvonne Heinen, Dorina Noske, Jeremy P Spencer, Alan Crozier, Marc W Merx, Malte Kelm, Hagen Schroeter, and Christian Heiss

Male EPs and non-EPs (n = 14/group) at moderate cardiovascular risk in a double-blind, placebo controlled crossover study to examine the acute effects of soy isoflavones (80-mg aglycone equivalents) on arterial stiffness, blood pressure, endothelial function, and nitric oxide.

In a separate assessment, non-EPs consumed 40 mg S-(–)equol with identical vascular measurements performed 2 h after intake.
In two test phases (dose-1 and dose-2, lasting 3 weeks each) and a 3-week washout period between each phase, 49 participants (BMI > 27 kg/m²) daily consumed one (dose-1, 160 mg phenolics/day) or four (dose-2, 640 mg phenolics/day) PE or placebo capsules. Three (50%) nonproducers (UM-0) became producers following PE consumption.
Subjects 2, 4, 8, 9, & 14 (n=15)

Subjects 3, 5, 11, & 13 (n=12)

Subjects 6 & 15 (n=6)

Trihydroxyphenyl-γ-valerolactone
-glucuronide
-methyl-sulfate

Dihydroxyphenyl-γ-valerolactone
-glucuronide
-disulfate
-sulfate-glucuronide

Monohydroxyphenyl-γ-valerolactone
-glucuronide

Hydroxyphenyl propionic acid
-sulfate
• Plausible mechanisms of actions!
• Critical mass of observational results
• Well designed and well conducted intervention studies!

• Better understanding of the involvement of the gut microbiota &
• Interindividual variability clear in mind!!
Despite the very bad science performed to date....

It could work!
A new Microbiome Research Centre at the University of Parma
Thanks to...my personal microbiota!