Bioactive Compounds and CVD
Knowledge Gained From Establishing Their Role in Risk Reduction and Mechanisms of Action

Penny Kris-Etherton, PhD, RD
Pennsylvania State University
Outline

• Evidence in support of lowering LDL cholesterol
• Phytochemicals
  – Major classes defined
  – Food sources
  – Effects on CVD risk factors
• Challenges in studying the clinical effects of phytochemicals
  – Biological diversity
  – External factors that modulate response
• Case Study: Plant-derived Omega-3 Fatty Acids
• Summary
Leading Causes of Death for All Males and Females in the U.S.

A. Total CVD  D. Chronic Lower Respiratory Diseases
B. Cancer      E. (Males) Diabetes Mellitus
C. Accidents   F. (Females) Influenza and Pneumonia

Deaths in thousands

AHA Heart and Stroke Facts, 2003
### Trends in Total Cholesterol Levels in the U.S.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>213 mg/dL</td>
<td>205 mg/dL</td>
<td>203 mg/dL</td>
</tr>
</tbody>
</table>

Adpated from Ford et al., Circulation 107:2185, 2003
<table>
<thead>
<tr>
<th></th>
<th>1972 (NHANES I)</th>
<th>1978 (NHANES II)</th>
<th>1990 (NHANES III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Fat % Kcal</td>
<td>36.4</td>
<td>36.3</td>
<td>34.1</td>
</tr>
<tr>
<td>SFA</td>
<td>13.2</td>
<td>12.8</td>
<td>11.7</td>
</tr>
<tr>
<td>PUFA</td>
<td>4.3</td>
<td>5.7</td>
<td>7.1</td>
</tr>
<tr>
<td>ALA**</td>
<td></td>
<td></td>
<td>0.6-0.7**</td>
</tr>
<tr>
<td>EPA+DHA**</td>
<td></td>
<td></td>
<td>0.1**</td>
</tr>
</tbody>
</table>

Ernst et al, 1997, **Kris-Etherton et al, 2000
“The Lower, the Better”

Relative Risk for CHD (Log Scale)

LDL-C (mg/dL)

Features of Therapeutic Lifestyle Changes

LDL-C Raising Nutrients
- Saturated (and Trans) Fats < 7% Kcal
- Dietary Cholesterol < 200 mg/d

Therapeutic Options for LDL-C Lowering
- Plant stanols/sterols 2 g/d
- Increased viscous(soluble) fiber 10-25 g/d

Total Calories
- Maintain desirable body weight/ prevent weight gain

Physical Activity
- Exercise to expend at least 200 kcal/d
## LDL-C Reduction Achievable by Diet

<table>
<thead>
<tr>
<th>Dietary Component</th>
<th>Dietary Change</th>
<th>Approximate LDL Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated Fat, <em>trans</em> fat</td>
<td>&lt;7% of calories, minimum</td>
<td>8-10%</td>
</tr>
<tr>
<td>Dietary cholesterol</td>
<td>&lt;200 mg/d</td>
<td>3-5%</td>
</tr>
<tr>
<td>Weight Reduction</td>
<td>lose 10 lbs</td>
<td>5-8%</td>
</tr>
<tr>
<td><strong>Other LDL-Lowering Options</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viscous fiber</td>
<td>5-10 g/d</td>
<td>3-5%</td>
</tr>
<tr>
<td>Plant Sterol/Stanol Esters</td>
<td>2 g/d</td>
<td>6-15%</td>
</tr>
<tr>
<td><strong>Cumulative Estimate</strong></td>
<td></td>
<td>20-30%</td>
</tr>
</tbody>
</table>

Adapted from Jenkins et al., 2000
Distribution of Plasma Total Cholesterol Levels in Individuals with and without Coronary Heart Disease

35% of CHD occurs in people with total cholesterol <200 mg/dL (<5.3 mmol/L)

Libby, Am J Med, 2004
Serum Cholesterol and 25-Year CHD Mortality. Seven Countries Study

CHD Mortality Rates, %

Serum Total Cholesterol, mg/dL

adjusted for age, smoking and systolic BP
Source: Verschuren et al. JAMA, 1995
CVD Risk Factors

Established Risk Factors

Heart Attack
Stroke
Angina
Arrhythmias

Emerging Risk Factors

↑ LDL-C
Low HDL-C
Diabetes/Insulin resistance
Hypertension
Obesity
Homocysteine
Inflammatory markers
Triglyceride-rich lipoproteins
Lipid oxidation
Endothelial dysfunction
Lp(a)
Platelet function/Clotting factors

Classification of Dietary Phytochemicals

Phytochemicals

- Carotenoids
  - \(\alpha\)-carotene
  - \(\beta\)-carotene
  - \(\beta\)-cryptoxanthin
  - Lutein
  - Zeaxanthin
  - Astaxanthin
  - Lycopene

- Phenolics
  - See next slide

- Alkaloids

- Nitrogen-containing compounds

- Organosulfur compounds
  - Isothiocyanates
  - Indoles
  - Allylic sulfur compounds

Liu, 2004
Classification of Dietary Phytochemicals

Phytochemicals

- Carotenoids
- Phenolics
- Alkaloids
- Nitrogen-containing compounds
- Organosulfur compounds

Phenolic Acids
- Hydroxybenzoic acid
- Hydroxycinnamic acid

Flavonoids
- Flavanols
- Flavones
- Flavanones
- Anthocyanidins
- Isoflavonoids

- Quercetin
- Apigenin
- Catechin
- Eriodictyol
- Genistein

- Myricetin
- Chrysanthemic acid
- Epicatechin
- Hesperitin
- Cyanidin

- Galangin
- Luteolin
- Epigallocatechin
- Epicatechin gallate
- Naringenin
- Delphinidin

- Fisetin
- Apigenin
- Epicatechin gallate
- Epicatechin
- Daidzein

Liu, 2004
### Food Sources of Bioactive Compounds – Effects on CVD Risk Factors

<table>
<thead>
<tr>
<th>Bioactive Compound</th>
<th>Examples</th>
<th>Food Sources</th>
<th>Effect on CVD Risk Factor</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenolics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flavonoids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flavonols</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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</tr>
<tr>
<td>Flavonols</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flavanols</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quercetin, Kaempferol, Myricetin, Galangin, Fisetin</td>
<td>Onions, apples, tea, berries, olives, red wine, cocoa</td>
<td>↓TC, LDL-C oxid. ↓platelet aggreg. ↑HDL-C ↑Antioxidant effect</td>
<td>Tzeng et al., 1991 Chung et al., 1993 Peterson et al., 1998 Bravo et al., 1998 McAnlis et al., 1999</td>
<td></td>
</tr>
<tr>
<td>Catechin, epicatechin, epigallocatechin gallate, epigallocatechin gallate</td>
<td>Green/black tea, cocoa, plums, apples, berries, pecans</td>
<td>↓LDL oxid. ↓platelet aggreg. ↓BP ↑insulin sensitivity ↑FMD</td>
<td>Grassi et al., 2005 Kondo et al., 1996 Waterhouse et al., 1996 Kondo et al., 1999 Rein et al., 2000 Duffy et al., 2001</td>
<td></td>
</tr>
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<tr>
<td>Organosulfur compounds</td>
<td>Isothiocyanates</td>
<td>Garlic, leeks, onions, cruciferous</td>
<td>↓ TC, LDL-C</td>
<td>Warshafsky et al., 1993</td>
</tr>
<tr>
<td></td>
<td>Indoles</td>
<td>vegetables like broccoli and cauliflower</td>
<td>↓ LDL-C Oxid.</td>
<td>Matsuura, 2001</td>
</tr>
<tr>
<td></td>
<td>Allylic sulfur compounds</td>
<td></td>
<td>↓ TG</td>
<td>Jain et al., 1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ BP</td>
<td>Silagy &amp; Neil, 1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ thrombosis</td>
<td>Borek, 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ platelet aggregation</td>
<td>Steiner &amp; Li, 2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Antioxidant effect</td>
<td></td>
</tr>
</tbody>
</table>

|                           | Antioxidant effect        |                                           | Action                                         |                                              |
|                           |                           |                                           |                                                |                                              |
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<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotenoids</td>
<td>α-Carotene, β-Carotene, Lutein, Zeaxanthin, β-Cryptoxanthin, Lycopene</td>
<td>carrots, sweet potatoes, winter squash, pumpkin, papaya, mango, watermelons, apricots</td>
<td>↓ LDL-C ↓ LDL-C Oxid. ↑ Antioxidant effect</td>
<td>Agarwal et al., 1998 Lowe et al., 1996 Fuhrman et al., 1997</td>
</tr>
</tbody>
</table>
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</thead>
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<tr>
<td>Phytoestrogens</td>
<td></td>
<td>Whole grains, nuts, Flaxseed oil</td>
<td>May ↓ total and LDL-C ↓ postprandial glucose absorption ↓ markers of inflammation ↑ arterial compliance ↑ improved insulin sensitivity ↓ LDL oxidation</td>
<td>Nestel et al., 1999</td>
</tr>
<tr>
<td>Bioactive Compound</td>
<td>Examples</td>
<td>Food Sources</td>
<td>Effect on CVD Risk Factor</td>
<td>Studies</td>
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<tr>
<td>--------------------</td>
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<td>-----------------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Phytoestrogens</td>
<td>Genistein</td>
<td>Clover, peas, soybeans</td>
<td>↑ FMD</td>
<td>Anderson et al., 1995</td>
</tr>
<tr>
<td></td>
<td>Daidzein</td>
<td>Soy protein with genistein</td>
<td>↑ post-occlusion peak flow velocity</td>
<td>Squadrito et al., 2002</td>
</tr>
<tr>
<td></td>
<td>Glycitein</td>
<td>Isolated soy protein (ISP) with</td>
<td>↑ HDL-C</td>
<td>Steinberg et al., 2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>isoflavones</td>
<td>↓ LDL-C in hypercholesrolemic subjects</td>
<td>Anthony et al., 1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ thrombosis</td>
<td>Crouse et al., 1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ LDL-C oxidation</td>
<td>Jenkins et al., 2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tikkanen et al., 1998</td>
</tr>
</tbody>
</table>
Meta-Analysis: Significant Effect of High Isoflavone Intake on LDL-C

Zhuo et al., 2004
No Significant Effect on Plasma LDL-C as a Function of Soy Isoflavone Levels after Dietary Interventions (meta-analysis includes studies with both stringent and general criteria selection)

LDL

mg/day change in isoflavones

Weggemans et al., 2003
Variability of Phytochemical Content of Foods

• Plant variety*
• Ripeness at the time of harvest
• Environmental factors
• Processing
• Storage
• Method of culinary preparation*

* To be discussed

Manach et al., Am J Clin Nutr 79: 727, 2004
Bars with no letters in common are significantly different, p<0.05

Variable Flavonoid Content of 10 Onion Varieties

Bars with no letters in common are significantly different, p<0.05

Bars with no letters in common are significantly different, p<0.05

Variable Carotenoid Content of 11 Wheat Varieties

Lutein (µg/100 g grain)

Zeaxanthin (µg/100 g grain)

β-cryptoxanthin (µg/100 g grain)

a-W7985
b-Jenneh Khetifa
c-Stoa
d-Cham-1
e- Clark’s cream
f- NY6432-18
g- Opata
h- Caledonia
i- Sinton
j- Superior
k- Roane

Various Cooking Methods Affect the Flavonoid Content in Onion

- Microwave cooking without water better retains flavonoids and ascorbic acid
- Frying does not affect flavonoid intake
- The boiling of onion leads to about 30% loss of quercetin glycosides, which transfers to the boiling water

Garlic Products on the Market
Not all garlic preparations may lower cholesterol levels

<table>
<thead>
<tr>
<th>Type of Product</th>
<th>Main Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic Oil</td>
<td>Only 1% oil-soluble sulfur compounds in 99% vegetable oil</td>
</tr>
<tr>
<td></td>
<td>No water-soluble fraction</td>
</tr>
<tr>
<td></td>
<td>No allicin</td>
</tr>
<tr>
<td>Garlic Oil Macerate</td>
<td>Oil-soluble sulfur compounds and alliin</td>
</tr>
<tr>
<td></td>
<td>No allicin</td>
</tr>
<tr>
<td>Garlic powder</td>
<td>Alliin and a small amount of oil-soluble sulfur compounds</td>
</tr>
<tr>
<td></td>
<td>No allicin</td>
</tr>
<tr>
<td>Aged garlic extract</td>
<td>Mainly water soluble compounds</td>
</tr>
<tr>
<td></td>
<td>Small amount of oil-soluble sulfur compounds</td>
</tr>
</tbody>
</table>

Amagase et al., J Nutr, 131: 955S, 2001
Bioavailability of Phytochemicals: Factors to Consider

• Intestinal absorption
  – Influence of chemical structure
  – Food matrix*
  – Excretion back into the intestinal lumen
  – Role of microflora – catabolism of bioactive compounds and production of active metabolites

• Transport, metabolism and elimination
  – Circulating metabolites*
  – Cellular uptake
  – Intracellular metabolism
  – Target tissue accumulation

• Physiological factors*

* To be discussed

Manach et al., Am J Clin Nutr 79: 727, 2004
Greater Dose-response Antioxidant Effect of Fruit Mixture vs. Individual Fruits

Liu, 2004
Time course for Plasma Dimer B2, Catechin and Epicatechin Concentrations after Consumption of Cocoa (dose =0.375 g/kg BW, n=5)

Dimer B2 (mmol/L)

Catechin (mmol/L)

Epicatechin (mmol/L)

Holt et al., Am J Clin Nutr: 76, 798, 2002
Positive Correlation between Brachial Artery Flow Levels and Genistein Levels

Squadrito et al., 2002
Positive Correlation between Plasma NO Levels and Genistein Levels

Squadrito et al., 2002
Gender Differences in Response to Soy Intake on Flow Mediated Dilation

Teede et al., J Clin Endocrinol Metab, 86: 3053, 2001
Gene Polymorphisms Affect Diet Responses

• Polymorphisms at Apo A1/C3/A4 gene cluster and the Apo E gene explain inter-individual variability in lipid/lipoprotein responses to diet.

• CYP7A1 A-278C Polymorphism affects plasma lipid response to dietary cholesterol
  – Hofman et al., J Nutr 134: 2200, 2004

• PPARα Leu – 162 Val polymorphism contributes variability in lipid/lipoprotein response to dietary P:S ratio
LDL-Cholesterol Lowering is Less in Overweight vs. Normal Weight Men on a Hi-SFA Diet Compared to NCEP I Diet

<table>
<thead>
<tr>
<th></th>
<th>Cholesterol mmol/L (%)</th>
<th>LDL-C mmol/L (%)</th>
<th>HDL-C mmol/L (%)</th>
<th>TG mmol/L (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI&lt; 25 kg/m² n=26</td>
<td>-0.67 (-16)</td>
<td>-0.55 (-21)</td>
<td>-0.1 (-8)</td>
<td>-0.04 (-5)</td>
</tr>
<tr>
<td>BMI &gt; 25 kg/m² n=15</td>
<td>-0.30 (-7)</td>
<td>-0.24 (-9)</td>
<td>-0.05 (-5)</td>
<td>-0.07 (-5)</td>
</tr>
</tbody>
</table>

Values are means and %; Change is significantly different, p<0.05

Jansen et al., J Nutr, 128:1144, 1998
Eicosanoids from n-6 and n-3 PUFA

Leonard et al., 2004
Balk et al., 2004

Not in mammals

Eicosanoids

Series-1 Prostaglandins: TXA, PGE, PGF1α, PGD1

Series-2 Prostaglandins: TXA2, PGE2, PGF2α, PGD2, PGH2, PGI2

Series-4 Leukotrienes

Series-3 Prostaglandins: PGE3, PGH3, PGI3, TXA3

Series-5 Leukotrienes

18:0 stearic \[\xrightarrow{\Delta9} 18:1n-9\] oleic \[\xrightarrow{\Delta12} \]

18:2 linoleic

18:3 α-linolenic

18:3n-6 γ-linolenic

18:4n-3 stearidonic

20:3n-6 Dihomo-γ-linolenic

20:4n-3 eicosatetraenoic

20:4n-6 arachidonic

20:5n-3 eicosapentaenoic

22:4n-6 adrenic

22:5n-3 α3-docosapentaenoic

24:4n-6 Δ6-tetracosatetraenoic

24:5n-3 Δ3-tetracosapentaenoic

24:5n-6 Δ6-desaturase

24:6n-3 Δ3-tetracosahexaenoic

22:5n-6 β-oxidation

22:6n-3 docosahexaenoic

energy metabolic pathway
Is $\alpha$-linolenic acid a good precursor for EPA and DHA in humans?

$\alpha$-Linolenic acid (18:3n-3) → SDA (18:4n-3) → 20:4n-3 → EPA (20:5n-3) → DPA (22:5n-3) → DHA (22:6n-3)

How well is $\alpha$-linolenic acid converted to EPA?

How well is EPA converted to DHA?

From Bill Harris, 2004
Approaches Used to Study Efficiency of ALA Conversion to Long-Chain n-3 PUFA

• Fatty acid composition of biological samples, primarily plasma and circulating cells.

• Stable isotope studies to trace ALA metabolism
Erythrocyte Phospholipid Fatty Acid Profiles after 12 Week Supplementation of Flaxseed Oil Compared to Fish Oil

* Diff. from baseline, p<0.05

Diff. between diets, p<0.05
Summary: \(\alpha\)-Linolenic acid

- Dietary ALA can increase plasma, platelet, red cell and white cell EPA and DPA status (ALA dose important)

- Dietary ALA does NOT increase plasma, platelet, red cell or white cell DHA status

From Bill Harris, 2004
<table>
<thead>
<tr>
<th>Diet</th>
<th>DGLA</th>
<th>AA</th>
<th>EPA</th>
<th>DPA</th>
<th>DHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flax Oil (n = 6)</td>
<td>0.20</td>
<td>0.12</td>
<td>0.29</td>
<td>0.05</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Sun Oil (n = 5)</td>
<td>0.29</td>
<td>0.26</td>
<td>0.19</td>
<td>0.02</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Both Diets (n = 11)</td>
<td>0.23</td>
<td>0.18</td>
<td>0.26</td>
<td>0.04</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Overall conversion is maximum plasma $^{13}$C content as a % of dose of either $^{13}$C-LA or $^{13}$C-ALA.

Summary: Stable Isotope Studies

• More than 75% of dietary ALA is oxidized

• Conversion of ALA to long-chain n-3 PUFA is limited
# Influence of Species and Diet on PUFA Variability in Salmon (3 oz. cooked)

<table>
<thead>
<tr>
<th>Fish</th>
<th>Kcal</th>
<th>Fat (g)</th>
<th>Total PUFA (g)</th>
<th>18:2 n-6 linoleic</th>
<th>18:3 n-3 ALA</th>
<th>20:5 n-3 EPA</th>
<th>22:5 n-3 DPA</th>
<th>22:6 n-3 DHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlantic-wild</td>
<td>155</td>
<td>6.91</td>
<td>2.78</td>
<td>0.19</td>
<td>0.32</td>
<td>0.35</td>
<td><strong>0.31</strong></td>
<td>1.22</td>
</tr>
<tr>
<td>Atlantic-farmed</td>
<td>175</td>
<td>10.5</td>
<td>3.76</td>
<td>0.58</td>
<td>0.10</td>
<td>0.59</td>
<td><strong>---------</strong></td>
<td>1.24</td>
</tr>
<tr>
<td>Coho-wild</td>
<td>118</td>
<td>3.65</td>
<td>1.08</td>
<td>0.05</td>
<td>0.05</td>
<td>0.34</td>
<td><strong>---------</strong></td>
<td>0.56</td>
</tr>
<tr>
<td>Coho-farmed</td>
<td>151</td>
<td>7.0</td>
<td>1.67</td>
<td>0.32</td>
<td>0.07</td>
<td>0.35</td>
<td><strong>---------</strong></td>
<td>0.74</td>
</tr>
</tbody>
</table>

*USDA Nutrient Database*
EPA vs. DHA: What are the Relative Potencies?

- **Differential Effects on Lipoproteins**
  
  *Leigh-Firbank et al., 2002*
  - DHA: ↑ LDL-C
  - EPA: ↓ plasma TG

  *Mori et al., 2000*
  - 4 g/d EPA: ↓ HDL3 (7%)
  - 4 g/d DHA: ↑ HDL2 (29%)
  - DHA: ↑ LDL-C (8%), ↑ LDL size

- **Similar Effects on TGs**
  
  *Woodman et al., 2002, Grimsgaard et al., 1997*
  - 4 g/d EPA or DHA: ↓ plasma TG (19%)
  - 3.8 g/d EPA or 3.6 g/d DHA: ↓ plasma TG (26 & 21%)

- **EPA: primarily responsible for ↓TG**
  
  *Rambjor et al., 1996*
EPA vs. DHA : What are the Relative Potencies?

- EPA, but not DHA, decreases mean platelet volume (early step in platelet aggregation)
  - Park et al., 2002

- DHA, but not EPA, lowers ambulatory blood pressure and heart rate in humans
  - Mori et al., 1999
Summary

- There are numerous bioactive compounds that have the potential to decrease CVD risk
- There’s much to be learned and the physiology of bioactive compounds is complex
- The focus of current and future work should lead to population – based dietary recommendations