Phytonutrients and Cardiovascular Disease

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U.S. Department of Defense

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Professor and Assistant Dean for Research and University Scholar at the University of Illinois.

She has published over 190 peer-reviewed scientific publications and 25 chapters in books in the areas of Food Science and Human Nutrition.

The long-range goal of her research program is to enhance the health of individuals by the identification and evaluation of the benefits of bioactive compounds in plant foods.

She is currently working on bioactive phytochemicals, mainly proteins, peptides and flavonoids from legumes, cereals, herbs and fruits and their effect on prevention of chronic diseases.
Learning objectives:

1. Explain the state of the art of the science behind the effect of bioactive compounds in plant foods related to cardiovascular disease.

2. Discuss the potential of fruit and vegetable flavonoids on heart health implications and their capacity to protect against chronic diseases.

3. Identify the sources of bioactive compounds in the diet and educate clients/patients in selecting foods to reduce their risk of cardiovascular disease.
Overview

• Introduction
  • Inflammation and cardiovascular disease
  • Risk factors for heart disease
  • Bioactive compounds related to CVD
    – Phenolic compounds and biological activity
    – Absorption and metabolism of phenolic compounds
    – Anthocyanins and risk of CVD
    – Phytosterols and risk of CVD
    – Proteins and peptides and risk of CVD

• Take-home message
Belief in foods with Health Benefits

Similar to previous years, the majority of Americans continue to agree that certain foods have health benefits beyond basic nutrition.

Now a few questions about food. Each time we use the word “food,” we are referring to everything people eat, including fruits, vegetables, grains, meats, dairy, as well as beverages, herbs, spices and dietary supplements. Do you disagree or agree that certain foods have health benefits that go beyond basic nutrition? (n=1,000)
Awareness of Food Component/Health Pairs

**HEART HEALTH**

Between 85% and 43% of Americans are aware of specific food components and their associated heart health benefits.

- **For reduced risk of heart disease**
  - Omega-3 fatty acids (n=495): 85%
  - Monounsaturated fats (n=505): 76%
  - Folate or Folic acid (n=505): 68%
  - Soy protein/soy (n=495): 64%
  - Plant sterols (n=495): 50%
  - Fiber (n=1,000)†: 43%
  - Whole grains (n=1,000)†: 48%

- **For reduced risk of high BP and stroke**
  - Potassium (n=505): 78%

- **For helping to support blood flow/circulation**
  - Flavanols (n=495)†: 51%

For each of the following food components or nutrients, please tell us whether you are aware that that food component or nutrient is thought to provide each of the following health benefits. (split sample) Fiber and Whole grains pairings asked separately (n=1,000).

†Added in 2011

2011 IFIC Functional Foods/Foods for Health Consumer Trending Survey
Diet and cardiovascular disease

- **Diet** has a significant impact on the development of heart disease
- **Inflammation** is directly involved in the initiation and progression of atherosclerotic lesions
- Several **bioactive compounds** inhibit inflammation (intermediate risk CVD factor).

Risk Factors for Heart Disease

Conditions
- High blood pressure*
- High cholesterol*
- Diabetes*

Behavioral
- Unhealthy diet*
- Physical inactivity
- Obesity*
- Too much alcohol*
- Tobacco use

Family History
- Genetics
- Becoming older
- Ethnicity

SOURCE: Center for Disease Control and Prevention (CDC)
* Diet Related and can be modified by behavioral changes
Inflammation and Atherosclerosis

What are the main components of the Mediterranean Diet?
Key Components of Mediterranean Diet

The Mediterranean diet emphasizes:

• Eating primarily plant-based foods, such as fruits and vegetables, whole grains, legumes and nuts
• Replacing butter with healthy fats such as olive oil and canola oil
• Using herbs and spices instead of salt to flavor foods
• Limiting red meat to no more than a few times a month
• Eating fish and poultry at least twice a week
• Enjoying meals with family and friends
• Drinking red wine in moderation (optional)
• Getting plenty of exercise
The DASH Diet
Dietary Approaches to Stop Hypertension
The DASH diet includes:

- Whole grains (6 to 8 servings a day)
- Vegetables (4 to 5 servings a day)
- Fruits (4 to 5 servings a day)
- Low-fat or fat-free milk and milk products (2 to 3 servings a day)
- Lean meat, poultry, and fish (6 or fewer servings a day)
- Nuts, seeds, and beans (4 to 5 servings a week)
- Healthy fats and oils (2 to 3 servings a day)
- Sweets, preferably low-fat or fat-free (5 or fewer a week)
- Sodium (no more than 2,300 mg a day)
- If you drink alcohol, limit yourself to 2 drinks or less per day for men and 1 drink or less per day for women
- To reduce your blood pressure even more, replace some DASH diet carbohydrates with low-fat protein and unsaturated fats
- For weight loss, reduce your daily calories to 1,600 per day
- Lower your sodium to no more than 1,500 mg per day if you are age 40 or older, are African American, or if you have been diagnosed with high blood pressure
Questions
Bioactive phytochemicals in foods

Chia
(Salvia Hispanica)
Omega-3 fatty acids

Pepper,
(Capsicum)
Capsaicin, carotenoids

Jamaica
(Hibiscus sabdariffa)
Anthocyanins

Nopal
(Opuntia ficus-indica)
Carbohydrates, phenols

Lignans,
Phytoestrogens & phytosterols

Amaranth
(Amaranthus cruentus)
Proteins

Polyphenols
**Herbal Teas**

- *Amaranthus cruentus*
- *Lippia graveolens*
- *Hibiscus sabdariffa*
- *Yerba Mate tea*
- *Mexican oregano*
- *Dried parsley*
- *Celery seeds*

**Bioactive Compounds**

- **Saponins**
- **Isoflavones**
- **Bioactive peptides**
- **Lunasin**
- **Bowman Birk inhibitor**

**Monoanthocyanin**
Putative beneficial biological effects attributed to dietary bioactive compounds

Increased intake of phenolics and dietary flavonoids

Health benefits:
- Decreased incidence of disease
- Decrease cardiovascular disease risk factors
- Improved diabetes tolerance
- Antioxidant Activity: Scavenging free radicals, reducing oxidative stress
- Anti-inflammation: Post-prandial, acute, chronic
- Anti-cancer properties

Burton-Freeman 2010; Del Rio 2010; Miguel 2011; Pan 2010.
Bioactive Compounds in Fruits and Vegetables

Flavonoids
- Apigenin (Flavone)
- Quercetin (Flavonol)
- EGCG (Flavanol)
- Genistein (Isoflavone)

Limonoids
- Limonin

Resveratrol (Stilbenoid)

Curcumin (Curcuminoid)
Chemical diversity of polyphenols

Simple phenols are represented by (a) catechols and (b) stilbenes, and polyphenols in (c) anthocyanins, (d) flavonols, (e) flavanols and (f) isoflavones.
Flavonoid Absorption and Metabolism

Ingestion

Foods containing naringenin

Juice: 15 mg

Absorption

Small and large intestine

$C_{max} = 0.25 \, \mu M$

$C_{max} = 0.048 \, \mu g/L$

Metabolism

- Methylation
- Sulfation
- Glucuronidation
- Acetylation

Excreted in urine, bile or feces

Tissue Absorption

Absorption and Metabolism of Anthocyanins

- Consumption among the highest of all flavonoids due to their wide distribution in foods.

- Estimated daily intake of anthocyanins in the United States is between 180-215 mg, may be as low as 12.5 mg per day.

- Absorption mainly in the small intestine and stomach.
  - Very efficient epithelial tissue uptake.
  - Gut microbiota cleave glycosidic linkages.
  - Reach peak plasma concentrations quickly.
    - 1-120 nM

- Less than 1% recovery in urine.

- Metabolites and degradation products may play a key role in their biological activity.
*Hibiscus sabdariffa* shows scientific support demonstrated in *in vitro*, preclinical and clinical models that its regular consumption may help to control and prevent certain diseases, without health risk.

A randomized, double-blind, placebo-controlled clinical trial, 65 pre- and mildly hypertensive adults, age 30–70 y, not taking blood pressure (BP)-medications, with either 3 240 mL servings/d of brewed **hibiscus tea** or placebo beverage for 6 wk. A standardized method was used to measure BP at baseline and weekly intervals.

- At 6 wk, hibiscus tea lowered systolic BP (SBP) compared with placebo (-7.2 +/- 11.4 vs. -1.3 +/-10.0 mm Hg; P = 0.030).
- Participants with higher SBP at baseline showed a greater response to hibiscus treatment (r = -0.421 for SBP change; P = 0.010).

The dietary change assessed, regularly incorporating 3 servings/d of hibiscus tea into the diet, effectively reduced BP in pre- and mildly-hypertensive adults.
Anthocyanins in foods as modulators of inflammatory pathways to prevent the development of chronic diseases

Anthocyanins: A colorful array of health promoting properties
Blueberry

(Vaccinium floribundum)

Berry spherical, 5-8 mm diam., blue-black.

Best recognized for high content of flavonoids (anthocyanins) and tannins [condensed tannins (proanthocyanidins)]

Health benefits:

Antioxidant activity, anti inflammatory effects, cardiovascular protection anti-diabetic and anti-obesity properties, inhibition of carcinogenesis

Role of anthocyanins from berry beverages

- Inhibition of α-amylase and α-glucosidase
- Decreased *in vitro* markers of inflammation
- Stimulated insulin secretion & decreased glucose absorption
- Inhibition of dipeptidyl peptidase IV
- Increased antioxidant capacity
- Inhibition of oxidation & ROS scavenging

Anthocyanins from fermented berry beverages.

- Anti-Inflammatory Properties
- Reduced metabolic syndrome complications
- Reduced oxidative stress
Phenolic compounds in fruits and vegetables, specifically flavonoids reduce inflammation

<table>
<thead>
<tr>
<th></th>
<th>LUTEOLIN mg/100 g</th>
<th>APIGENIN mg/100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juniper berries</td>
<td>69</td>
<td>3</td>
</tr>
<tr>
<td>Vinespinach</td>
<td>--</td>
<td>62</td>
</tr>
<tr>
<td>Mexican oregano</td>
<td>1029</td>
<td>18</td>
</tr>
<tr>
<td>Kumquat</td>
<td>--</td>
<td>22</td>
</tr>
<tr>
<td>Celery heart</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>Parsley</td>
<td>1</td>
<td>215</td>
</tr>
<tr>
<td>Pimento peppers</td>
<td>--</td>
<td>10</td>
</tr>
<tr>
<td>Radicchio</td>
<td>48</td>
<td>--</td>
</tr>
</tbody>
</table>
**Summary of results for phenolic compounds and CVD**

<table>
<thead>
<tr>
<th>Phenolic Compound</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESVERATROL</strong></td>
<td>No reports on long-term health or survival in humans</td>
</tr>
<tr>
<td>CATECHOLS (curcumin)</td>
<td>Non-significant effect of curcumin on lipid profile when considering heterogeneous populations</td>
</tr>
<tr>
<td>Beer or Wine POLYPHENOLS</td>
<td>Not strong evidence showing that consumption of beer or wine could help to improve risk of CVD</td>
</tr>
<tr>
<td>ANTHOCYANINS B</td>
<td>Not strong evidence supporting that anthocyanins help to decrease risk of CVD and further studies are required</td>
</tr>
<tr>
<td>CATECHINS B</td>
<td>No robust evidence to suggest a beneficial effect of tea catechins on prevention of CVD</td>
</tr>
<tr>
<td>FLAVANOLS (dark-chocolate) B</td>
<td>Efficacy of cocoa flavanols in BP and heart function improvement, studies needed using flavanol-free controls</td>
</tr>
<tr>
<td>FLAVONOLS (quercetin) B</td>
<td>Effective at reducing BP in hypertensive men, further analysis in greater cohorts are needed.</td>
</tr>
<tr>
<td>ISOFLAVONES B</td>
<td>Greater population sizes. Significant improvement in women with low baseline Flow Mediated Dilation levels</td>
</tr>
<tr>
<td>PROANTHOCYANINS C</td>
<td>Insufficient evidence to determine if extracts containing procyanidins could improve CVD risk</td>
</tr>
</tbody>
</table>

Some polyphenols used as BC such as flavonols decrease risk factors of CVD. Need to develop better quality long-term, crossover design, double-blinded, long term, placebo/controlled, randomized clinical trials as well as elaborate rigorous meta-analysis.
Phytosterols – A well known example of a bioactive compound

- Plant origin compounds similar to the structure of cholesterol.
- Consumption in the diet ~200 – 400 mg/d.
- Minimally absorbed (<1%).
- Typical plasma levels 0.4 – 0.5 mg/dl.
- Act reducing the intestinal absorption of intestinal cholesterol (dietary and endogenous).
- The intake of 1-3 g/day can reduce total cholesterol ~10% and LDL-cholesterol in ~15%.

Efficacy of phytosterols in enriched foods has been confirmed by a meta-analysis of 84 controlled clinical studies.

Demonty et al., 2009. J. Nutr. 139: 271-84
Blood Cholesterol and Mortality due to Coronary Heart Disease

A 1% decrease in blood cholesterol represents a 3% reduction in the risk of coronary heart disease.

Source: MRFIT Study; adapted from JAMA 256, 1986.
Phystosterols & Serum Cholesterol

Averages for 52 studies: 1953-1980

<table>
<thead>
<tr>
<th>Subject number</th>
<th>17 ± 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>13 ± 1.1 g/d</td>
</tr>
<tr>
<td>Duration</td>
<td>27 ± 4 wks</td>
</tr>
<tr>
<td>Cholesterol response</td>
<td>-20 ± 1.5%</td>
</tr>
</tbody>
</table>


The efficacy of phytosterols-fortified foods has been confirmed in a recent meta-analysis of 84 clinical studies (Demonty et al. 2009, J. Nutr. 139:271)
How Sterols Work in the Body

• Phytosterols are believed to interfere with:
  – cholesterol incorporation into mixed micelles *and/or*
  – cholesterol absorption into cells of small intestine *and/or*
  – cholesterol remaining in cells of small intestine

• Phytosterol consumption results in decreased cholesterol absorption leading to decreased serum cholesterol.
Safety Considerations
“Phytosterol is one of the most studied substances in regard to safety”

- Phytosterols are minimally absorbed (<5%).
- Phytosterolemia is a rare genetic condition (1:5,000,000).
- Not mutagenic, not teratogenic.
- Blood levels of fat soluble vitamins are not affected.
- Decrease in blood carotenoid levels lacks clinical significance and can be compensated by a diet rich in fruit and vegetables.
- No convincing evidence of an association between elevated levels of blood phytosterols and increased CHD risk.

Phytosterols are considered safe.
(U.S. FDA, EU-SCF, EFSA, FSANZ, JECFA (FAO/WHO), HC)
U.S. Model Claim (FDA, 2000)
Plant Sterol/Stanol Esters and Risk of Coronary Heart Disease

Foods containing at least 0.65 g per serving of vegetable oil sterol esters, eaten twice a day with meals for a daily total intake of at least 1.3 g, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease.
In 2016 FDA broadened the food categories for the addition of phytosterols to:

- Margarines & Vegetable Oil Spreads
- Dressing for Salads
- Beverages
- Vegetarian Meat Analogs
- Dairy Analogs
- Fruit/Vegetable Juices
- Cheese and Cream
- Edible Vegetable Oils
- Baked Foods
- Adult Ready-to-Eat Breakfast Cereals
- Mayonnaise
- Pasta and Noodles
- Sauces
- Salty Snacks
- Process Soups
- Puddings
- Yogurt
- Adult Confections
- Snack Bars

Source: FDA GRAS letter to ADM, GRN No. 000176
Soy Protein

• Soybean possesses biologically active peptides
• *1999 FDA claim*: “25 g of soy protein per day as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease.”
• New studies specifically implicate chronic inflammation as a major contributor to the progression of atherosclerosis
• Necessitates determination of mechanism of action
Physiological Functions of Bioactive Peptides

- Anti-inflammatory
- Anti-cancer
- Hypocholesterolemic
- Immunomodulatory
- Antioxidant
- Antimicrobial
- Anti-obesity
- Opioid
Bioactive Peptides

Lipkin y col., 2005; Torruco-Uco y col., 2008; Silva-Sánchez y col., 2008; Tironi y Añón, 2010
**SUBJECT ELIGIBILITY**
Male (age:18-45). BMI>25, less than 300 lb. Non smoker, non vegetarian, non athletes, free of chronic diseases.

**WASHOUT PERIOD**
(1 week) - Soy free diet

- Low Glycinin Soymilk (LGS) n=19
  12 g protein/day (49.5% β-conglycinin), 1% fat, 200 Kcal
- Conventional Soymilk (S) n=23
  12 g protein/day (26.5% β-conglycinin), 1% fat, 200 Kcal
- Bovine milk (M) n=22
  12 g protein/day (0% β-conglycinin), 1% fat, 200 Kcal

**Soymilk**

IRB # 09454

500 ml /day
3 months

64 subjects scattered
LGS consumption decreased serum oxidized LDL after 3 months.

**Change affected by age (p = 0.03) and initial BMI (p = 0.02)**

All values expressed as means ± SEM

Plasma interleukin-6 decreased after 3 months of LGS and S consumption.
Soymilk increased serum antioxidant capacity after 3 months of consumption.

LGS vs. M (p = 0.001)

S vs. M (p < 0.001)

means ± SEM
Pathogenesis of CVD

- Diet has a significant impact on hypertension, obesity and diabetes, which are major risk factors for the development of CVD, specifically atherosclerosis (Roger et al., 2012).

- Initiation and progression of atherosclerosis is influenced extensively by inflammation (Moore et al., 2011).

- Certain proteins and peptides can regulate atherosclerotic lesions (Antonov et al., 2010; Gauze, 2010).

NIH, https://www.nhlbi.nih.gov/health/health-topics/topics/atherosclerosis
Plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. Over time, plaque hardens and narrows your arteries. This limits the flow of oxygen-rich blood to your organs and other parts of your body.

The build-up of plaque over time causes ___________________________ which can lead to serious problems, including heart attack, stroke, or even death.

What is the main treatment for atherosclerosis?
Questions
Take-home message
2015-2020 Dietary Guidelines

Follow a healthy eating pattern (at appropriate calorie level)

• A variety of vegetables-dark-green, red, and orange; legumes, starchy and other
  – Fruits, especially whole fruits
  – Grains, at least half whole grains
  – Fat-free or low-fat dairy
  – Protein foods, including seafood, lean meats, poultry, eggs, legumes, nuts, seeds and soy products
  – Oils

Limit:

• Saturated fat and trans-fat
• Added sugar
• Sodium

Source: Adapted from ODPHP, HHS/USDA, 2015
American Heart Association Dietary Recommendations

Eat a variety of nutritious foods

• A variety of fruits and vegetables
• Whole grains
• Low fat dairy products
• Skinless poultry and fish
• Nuts and legumes
• Non-tropical vegetable oils

Eat less or avoid

• Saturated fats and trans-fat
• Beverages and foods with added sugar
• High sodium foods and salt
• Alcohol (with moderation)

Source: Adapted from AHA, Oct. 2016
Questions?

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edemejia@illinois.edu
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Evidence-based guidelines for the nutritional management of adult oncology patients

- **Date:** Thursday, May 4, 2017
- **Time:** 11:00 am – 12:00 pm Eastern
- **Location:** [https://learn.extension.org/events/3026](https://learn.extension.org/events/3026)

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