Nutraceuticals and their Effect on Cardiovascular Risk

Shaista Malik, MD, PhD, MPH
Medical Director, Preventive Cardiology and Cardiac Rehab Programs
Executive Director, Susan Samueli Integrative Health Institute
Associate Vice Chancellor, Integrative Health
Susan and Henry Samueli College of Health Sciences

October 31st, 2020
Integrative Health Approach
Overview

1. Integrative Cardiology Approach to Therapy
2. Nutraceutical Definition
3. Dyslipidemia and Statin Intolerance
4. Evidence Dietary Supplements
5. Future Research in Adjunctive Role of Nutraceuticals
Cardiovascular Risk Factors

• Non-modifiable
  - Advancing Age
  - Male Gender
  - Family History/Genetics

• Metabolic
  - Hypertension
  - Hyperlipidemia
  - Diabetes mellitus
  - Metabolic Syndrome
  - Overweight/Obesity

• Lifestyle
  - Diet
  - Physical Activity
  - Smoking

• Novel
  - Homocysteine
  - Lipoprotein (a)
  - Small dense LDL-C
  - Inflammatory markers
  - Imaging markers
Integrative Cardiology: Assessment Framework

- Comprehensive History and Physical
- Nutrition and Exercise
- Stress & Relationships
- Advanced Biomarkers
- Cardiovascular Genomics
- Subclinical Disease Imaging
Advanced biomarker testing, Assess residual risk and novel risk factors

Addressing Actionable Genetic variations
- ApoE
- MTHFR
- SLOCO1B1

Subclinical atherosclerosis or Microvascular Disease

Optimal Medical Management, Nutraceuticals

Nutrition and Lifestyle Prescriptions

Mind-Body Interventions
- Mindfulness/Meditation
- Social Connection
Nutraceuticals

• Term introduced in 1989 by the US Foundation for Innovation in Medicine
  • “any substance that is a food or a part of a food and provides medical or health benefits, including the prevention and treatment of disease”

• Dietary Supplements (vitamins, minerals, herbs)

• Functional foods (whole foods, or enriched and fortified foods)
  • Biologically active compounds in addition to micro and macronutrients
### Functional Foods with Cardioprotective Effects

<table>
<thead>
<tr>
<th>Functional foods</th>
<th>Bioactive compounds</th>
<th>Potential mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Nuts</td>
<td>- Tocopherols, omega-3 fatty acids</td>
<td></td>
</tr>
<tr>
<td>- Legumes</td>
<td>- Fiber and polyphenols</td>
<td></td>
</tr>
<tr>
<td>- Fruits and vegetables</td>
<td>- Fiber (pectin)</td>
<td></td>
</tr>
<tr>
<td>- Margarine</td>
<td>- Phytosterols</td>
<td></td>
</tr>
<tr>
<td>- Fish oil</td>
<td>- Omega-3 fatty acids</td>
<td>Lowering blood cholesterol</td>
</tr>
<tr>
<td>- Whole grains</td>
<td>- Fiber and phytochemicals</td>
<td></td>
</tr>
<tr>
<td>- Soy proteins</td>
<td>- Genistein and daidzein</td>
<td></td>
</tr>
<tr>
<td>- Dark chocolate</td>
<td>- Flavonoid</td>
<td></td>
</tr>
<tr>
<td>- Fish</td>
<td>- Omega-3 fatty acids</td>
<td>Inhibition of LDL-C oxidation</td>
</tr>
<tr>
<td>- Green leafy vegetables, fruits</td>
<td>- Carotenoids</td>
<td></td>
</tr>
<tr>
<td>- Citrus fruits and vegetables</td>
<td>- Vitamin C</td>
<td></td>
</tr>
<tr>
<td>- Tomato</td>
<td>- Lycopene</td>
<td></td>
</tr>
<tr>
<td>- Extravirgin olive oil</td>
<td>- Polyphenolics and oleic acid</td>
<td></td>
</tr>
<tr>
<td>- Green tea</td>
<td>- Tea polyphenolics</td>
<td></td>
</tr>
<tr>
<td>- Soy proteins</td>
<td>- Genistein, daidzein, and glycine</td>
<td></td>
</tr>
<tr>
<td>- Dark chocolate</td>
<td>- Flavonoid</td>
<td></td>
</tr>
<tr>
<td>- Pomegranate</td>
<td>- Polyphenols</td>
<td></td>
</tr>
</tbody>
</table>

Alissa, 2012, Journal of Nutrition and Metabolism
<table>
<thead>
<tr>
<th>Food Group</th>
<th>Nutrient(s)</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fish</td>
<td>- Omega-3 fatty acids</td>
<td>Lowering blood triglycerides</td>
</tr>
<tr>
<td>- Legumes</td>
<td>- Omega-3 fatty acids</td>
<td></td>
</tr>
<tr>
<td>- Whole grains</td>
<td>- Fiber and phytochemicals</td>
<td></td>
</tr>
<tr>
<td>- Citrus fruits</td>
<td>- Ascorbic acid</td>
<td>Decreasing blood pressure</td>
</tr>
<tr>
<td>- Ginseng</td>
<td>- Ginsenosides</td>
<td></td>
</tr>
<tr>
<td>- Onion and garlic</td>
<td>- Quercetin</td>
<td></td>
</tr>
<tr>
<td>- Green and black teas</td>
<td>- Tea polyphenols</td>
<td></td>
</tr>
<tr>
<td>- Grapes and red wines</td>
<td>- Grape polyphenols</td>
<td></td>
</tr>
<tr>
<td>- Dark chocolate</td>
<td>- Flavonoid</td>
<td></td>
</tr>
<tr>
<td>- Fruits and vegetables</td>
<td>- Folate</td>
<td>Lowering blood homocysteine</td>
</tr>
<tr>
<td>- Whole grains</td>
<td>- Phytochemicals</td>
<td></td>
</tr>
<tr>
<td>- Citrus fruits and vegetables</td>
<td>- Fiber and phytochemicals</td>
<td></td>
</tr>
<tr>
<td>- Nuts, seeds, and oils</td>
<td>- Vitamin C</td>
<td></td>
</tr>
<tr>
<td>- Vitamin E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tomatoes</td>
<td>- Lycopene</td>
<td></td>
</tr>
<tr>
<td>- Green leafy vegetables, fruits</td>
<td>- Carotenoids</td>
<td></td>
</tr>
<tr>
<td>- Vegetable oils</td>
<td>- Tocopherol, tocotrienols</td>
<td></td>
</tr>
<tr>
<td>- Citrus fruits and vegetables</td>
<td>- Vitamin C</td>
<td></td>
</tr>
<tr>
<td>- Soy proteins</td>
<td>- Genistein and daidzein</td>
<td>Antioxidant action</td>
</tr>
<tr>
<td>- Green and black teas</td>
<td>- Tea polyphenols</td>
<td></td>
</tr>
<tr>
<td>- Anthocyanins, catechins, cyanidins,</td>
<td>- Anthocyanins, catechins,</td>
<td></td>
</tr>
<tr>
<td>- Grapes and red wines</td>
<td>- cyanidins, and flavonols,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- myricetin and quercetin</td>
<td></td>
</tr>
</tbody>
</table>

Alissa, 2012, Journal of Nutrition and Metabolism
<table>
<thead>
<tr>
<th>Endothelial dysfunction</th>
<th>Monocyte recruitment/foam cells formation</th>
<th>VSMC migration/proliferation</th>
<th>Plaque stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>Monocyte → Migration → Adhesion</td>
<td>Endothelial cell</td>
<td>Vascular lumen</td>
</tr>
<tr>
<td></td>
<td>Ox-LDL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Foam cell</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytokines, MMPs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**n-3 PUFAs**
- ↓ expression of VCAM-1, ICAM-1
- ↓ monocyte adhesion
- ↓ chemokine (MCP-1, CCL-20) production
- ↑ atherosclerotic plaque stability

**Flavonoids**
- ↓ oxidative stress and NF-κB activation
- ↑ eNOS level
- ↑ expression of SIRT-1
- ↓ proinflammatory cytokine (TNF-α, IL-2, IL-6, and IL-10) production
- ↑ neointima formation
- ↓ VSMC migration, proliferation, and contraction
- ↓ oxLDL-induced calcification in VSMCs

**SCFAs**
- ↓ expression of VCAM-1
- ↓ activity of HDAC
- ↓ inflammasome activity
- ↓ LDL oxidation
- ↓ proinflammatory cytokine (TNF-α and IL-6) production
- ↑ synthesis of type IV collagen
- ↑ VSMC proliferation and migration
- ↓ atherosclerotic lesion formation
Statin Intolerance or Statin Associated Muscle Symptoms (SAMS)

1. Initiate or intensify therapeutic lifestyle changes (National Cholesterol Education Program Adult Treatment Panel III Guidelines)
2. Decrease statin dose
3. Discontinue statin and rechallenge at a later date
4. Reduce dose of statin and add ezetimibe
5. Use a different statin or statin-like supplement
   a. Fluvastatin
   b. Rosuvastatin at a low dosage
   c. Rosuvastatin once weekly or twice weekly or every other day
   d. Atorvastatin, 10–40 mg, 3 times weekly
   e. Red yeast rice, 1800 mg, twice daily
Red Yeast Rice (RYR)

- RYR Chinese herbal supplement produced by fermenting white rice with a yeast, Monascus purpureus
- Contains Monacolins: inhibit HMGCoA reductase
  - 90% content is Monacolin K (identical to lovastatin)
  - Other active Ingredients: panter sterols, isoflavones, and monounsaturated fatty acids
- RYR dose 2400 mg/day (equivalent to a daily lovastatin dose of 5-7 mg) is as effective as 20 to 40mg of lovastatin in cholesterol lowering effect (Heber, 1999, Am J Clin Nutrition)
Red Yeast Rice (RYR)

• RCT in Statin Intolerance: RYR had 21% decrease with no increase in CPK or muscles symptoms

• Side Effects
  • Similar to statins (SAMS), but lower incidence
  • Rare: Kidney failure, liver failure
    • Citrinin-mycotoxin contaminant
  • Safety assessment of RYR products important

Becker et al, 2009, Annals of Internal medicine
Red Yeast Rice (RYR)

- Multicenter RCT comparing of Xuezhikang (XZK), a partially purified extract of RYR
- Nearly 5,000 Chinese patients with a prior myocardial infarction
  - Red yeast rice extract showed a 45% reduction in coronary events
  - 33% reduction in total mortality compared to placebo

Lu et al, 2008, American Journal of Cardiology
Berberine

- Alkaloid from Barberry, Goldenseal
- Dose 500 mg bid (Berberine HCL)
- Inhibits HMG Co-A reductase, inhibits PCSK9 (benefit in using with Statin)
- Can interact with statin metabolism (CYP2C9)

Figure 3. Main pharmacological effects of berberine on lipid metabolism.

Berberine

- Meta-analysis: reduces A1c 0.72

![Diagram of the main pharmacological effects of berberine on glucose metabolism.](image)

### (3) HbA1c (%)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Mean (SD)</th>
<th>Total</th>
<th>Control Mean (SD)</th>
<th>Total</th>
<th>Weight (95% CI)</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cao 2007 [19]</td>
<td>6.41 (1.92)</td>
<td>30</td>
<td>6.96 (1.19)</td>
<td>30</td>
<td>9.3%</td>
<td>−0.55 [−1.36, 0.26]</td>
</tr>
<tr>
<td>Wang 2008 [14]</td>
<td>6.04 (0.62)</td>
<td>30</td>
<td>6.6 (1.09)</td>
<td>31</td>
<td>31.6%</td>
<td>−0.56 [−1.12, 0]</td>
</tr>
<tr>
<td>Zhang et al 2008 [9]</td>
<td>6.6 (0.7)</td>
<td>58</td>
<td>7.3 (1.1)</td>
<td>52</td>
<td>50.9%</td>
<td>−0.7 [−1.05, −0.35]</td>
</tr>
<tr>
<td>Xiang et al 2011 [21]</td>
<td>6.84 (1.5)</td>
<td>20</td>
<td>8.48 (1.32)</td>
<td>20</td>
<td>8.1%</td>
<td>−1.64 [−2.52, −0.76]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>138 (133)</td>
<td></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>−0.72 [−0.97, −0.47]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 4.92, df = 3 (P = 0.18); I^2 = 39%$

Test for overall effect: $Z = 5.65 (P < 0.00001)$

Dong et al, 2012, Evidence-Based Complementary and Alternative Medicine
Derosa et al, 2012, Expert Opinion on Biological Therapy
Berberine

- Meta-analysis from 16 RCT, 2147 participants: Decrease in LDL, in TG, neutral HDL

![Fig. 4. Forest plot of outcome measure LDL-C.](image)

![Fig. 5. Forest plot of outcome measure TG.](image)
Citrus Bergamot

- High in Flavonoids
- Inhibits HMG-CoA reductase, reduction of ApoB production, increase cholesterol bile acid secretion
- Decreased oxidation/lipid peroxidation: reduction of LOX-1 and phosphorylation of PKB
- Dose 600-675 mg bid: 20% decrease in LDL, 8-10% increase in HDL; increases HDL and LDL size

Gliozzi, Int J Card, 2013
Toth, Front Pharmcotherapy 2016
Di Donna, J Natur Prod 2009
Citrus Bergamot

Gliozzi, Int J Card, 2013
Toth, Front Pharmcotherapy 2016
Di Donna, J Natur Prod 2009
Garlic

- Functional component: Allicin
  - Allicin is a thiosulfinate, produced after damage of the plant tissue by an enzymatic reaction

- Aged garlic extract in cell culture
  - prevented endothelial cell dysfunction
  - increased cellular concentrations of thiol antioxidants, such as cysteine and glutathione

- In folate-depleted animal model
  - decreased plasma Homocysteine concentrations by 30%

- RCT
  - Reduced LDL 9 mg/dl, decreases oxLDL, HDL increase 1.5 mg/dl
  - Reduced CAC Progression (7.5 vs. 22) over one year
  - Improved Pulse wave velocity

- Dose: Aged Garlic (600 mg bid)

Budoff et al, 2004, Preventive Medicine
Yeh et al, 2006, J of Nutrition
Annals of Int Med, 2000
J Card D Res, 2012
Curcumin

• Meta-analysis on effect on Dyslipidemia

Qin et al, 2017, Nutrition Journal
Cocoa Flavanols
• Flavanol, epicatechin: ROS and Nitric Oxide

Ludovici, 2017, Frontiers in Nutrition
Cocoa Flavanols

MITOCHONDRIAL TARGETS OF FLAVONOIDS

Antioxidant response

Mitophagy

Mitochondrial biogenesis

Apoptosis

MOMP

ROS

MPTP

Ca^{2+}

GST, HO-1, NQO1

FKT1

H_{2}O_{2}

H_{2}O

H_{2}O_{2}

O_{2}^{\cdot-}

O_{2}^{\cdot-}

OH^{\cdot-}

Ca^{2+}

m\Delta\Psi^{\cdot}

PGC-1\alpha

NRF2

NRF1

Smac/DIABLO

SMAC/DIABLO

1020, Circulation Research
Cocoa Flavanols

- Double-blind RCT, 15 g of cocoa and 75 mg of epicatechin daily, improved 6 minute walk distance
- In calf muscle biopsies, cocoa improved mitochondrial COX (cytochrome c oxidase) activity ($P=0.013$), increased capillary density ($P=0.014$), improved calf muscle perfusion ($P=0.098$), and reduced central nuclei ($P=0.033$), compared with placebo

| Table 3. Adjusted Effects of Cocoa on Change in 6-min Walk Distance at 6-mo Follow-Up* |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Intention-to-treat results      |                 |                 |                 |                 |                 |                 |
| 6-mo change in 6-min walk distance at 2.5 h after the study beverage, m |                 |                 |                 |                 |                 |                 |
| Cocoa                          | 17              | 348.6 (74.2)    | 356.6 (64.0)    | +18.4 (+0.34 to +36.5) | +42.6 (+22.2 to +x) | 0.005          |
| Placebo                        | 20†             | 337.3 (85.2)    | 322.0 (96.4)    | −24.2 (−40.7 to −7.8) | ...             | ...             |

McDermott, 2020, Circulation Research
Conclusions

• Nutraceuticals have a significant effect on cardiovascular risk and include dietary supplements as well as functional foods
• Role as stand alone therapies as well as adjunctive therapies
• Mechanism of action can target many pathways
• Meta-analysis of several nutraceutical supplements have shown efficacy
• More rigorous research showing mechanisms as well as changes in cardiovascular risk or event reduction needed