Learning Objectives

Learners will:

- Gain an understanding of usual fruit & vegetable intake

- Be able to define the term dietary “phytonutrient” or “flavonoid“

- Be able to describe the association between fruit & vegetable intake, and positive health outcomes (reduction of chronic disease risk)

- Be able to describe possible mechanisms for how phytonutrient–rich foods promote health

- Be aware of challenges to implement successful interventions to increase fruit & vegetable intake in a variety of populations

• 10.8% of population eating ≥2 Fruit & ≥3 Vegetable servings
• 23.6% of population eating ≥5 of any Frt/Veg combination
Fruits & Vegetables and Chronic Disease Risk

- **Strong & convincing evidence** of ↑ F/V consumption leading to ↓ risk of the following diseases:
  - Hypertension, Coronary Heart Disease, Stroke

- **Probable evidence**:
  - Cancer, Type 2 diabetes (indirectly through weight control)

- **Possible evidence**:
  - Obesity, Macular degeneration, Dementia, Asthma & COPD

- **Insufficient evidence**:
  - Inflammatory bowel diseases, diabetic retinopathy

Slavin & Lloyd 2012 Adv Nutr 3:506
Boeing et al 2012 Eur J Nutr epub ahead of press
Fruits and Vegetables Decrease Cardiovascular Disease Risk & Clinical Outcomes

Multivariate adjusted* Relative Risk for Frt/Veg consumption ≥ 3 times/day vs. <1 time/day

- **Ischemic heart disease mortality**
  \[ \text{RR} = 0.76 \quad (95\% \text{ CI: } 0.56, 1.03) \]

- **CVD mortality**
  \[ \text{RR} = 0.73 \quad (95\% \text{ CI: } 0.58, 0.92) \]

- **All cause mortality**
  \[ \text{RR} = 0.85 \quad (95\% \text{ CI: } 0.72, 1.00) \]

*adjusted for age, sex, race, energy, physical activity, alcohol consumption, smoking, plus others

Bazzano et al AJCN 2002; 76, 93-99
Cross-sectional studies using biomarker outcomes

- F/V intake is correlated with improved inflammatory status in a community setting
  - N=1000, 18-85 y, food intake assessed & blood samples taken
  - Inverse relationship of inflammatory markers with increasing F/V intake
  - Root et al. *Nutrients* 2012

- F/V consumption is related to makers of inflammation and oxidative stress in adolescents
  - N=285, 13-17 y, food intake assessed & blood samples taken
  - Inverse relationship of inflammatory markers with increasing F/V intake
  - Holt et al. *JADA* 2009
Fruits & Veggies contain...

- **Vitamins** (C, Folate, etc.)
- **Minerals** (Potassium, Magnesium, etc.)
- **Fiber** (mostly soluble)
- **Bioactive compounds**
  - Not traditional nutrients
  - Have biologic activities
    - Examples: Carotenoids (such as lutein, zeaxanthin, lycopene, etc.);
      Phytochemicals (such as various phenolic compounds – ellagic acid, quercetin, anthocyanidins, etc.)
Dietary Phytochemicals

Phytochemicals are a broad and diverse group of phenolic compounds that are produced in and accumulate in plants.

Phytochemical rich foods include: fruits and vegetables, some cocoa products, as well as whole grains and beverages such as tea & wine.

Phytochemicals can alter metabolic & cellular processes.

Most dietary studies indicate that diets rich in phytochemicals are associated with improved health and provide protection against chronic diseases, or alter *in a positive* direction markers for chronic disease.
Phytochemical Nomenclature

Polyphenols

- Phenolic Acids
- Flavonoids
  - C$_6$-C$_3$-C$_6$ skeleton
    - Flavonols
      - Monomers
        - (quercetin: onions, tomatoes)
    - Flavanols
      - Monomers
        - (catechin: tea, cocoa, apples)
    - Isoflavones
      - Soy
        - (genistein, daidzein)
- Others
  - (stilbenes, ligans)
  - Anthocyanins
    - (red pigment in berries and other fruits)
  - Proanthocyanidins
    - Oligomers of Flavanols
      - Catechin/Epicatechin
        - (cocoa, tea, apples, peanuts)
Questions about health promoting effects of food flavonoids

Important issues:

◦ Are the phytochemicals absorbed & do they get to target tissues? How much is absorbed?
◦ What is the best model to study the effects in?
◦ What are the biologic effects on key markers of function or health? (or disease risk)
◦ Is the effect the same in healthy or at risk individuals?
◦ What is/are the specific bioactive component(s)?
◦ How can you monitor intake after consuming the food?
◦ What are the implications for human health? Should there be specific dietary recommendations for intake?
Dietary Flavonoids

- Estimated intake: 0.01-1.0 g/day
- Major Dietary sources:
  - Fruits and vegetables such as apple, grapes, onion: rich in flavonols, (quercetin, anthocyanidin, kaempferol)
  - Citrus fruits: rich in flavanols (hesperidin and naringenin)
  - Soy: rich in isoflavones (Genistein and Daidzein)
Absorption, Distribution, Metabolism, Excretion (ADME) – Factors which impact biologic effects of phytochemicals

- Intake of phytochemical or precursor does not automatically equate with exposure at tissue level
- Inter-individual differences
  - Transport across intestinal wall
  - Biotransformation enzymes (phase I & II) genetic differences & effects of other endogenous or xenobiotic compounds
  - Intestinal Microbiota
  - Gut transit
  - Age, gender, physiologic state
- Diet, food matrix, chemical nature of polyphenol
Metabolism of Flavonoids

- Absorbed mainly in aglycone form, possibly some glycosides
- Peak blood levels occur within 1 to 2.5 hours, or up to 8 hours for some compounds
- Plasma concentration in 1-5 µmol/L range
- Circulate in blood as conjugated metabolites (glucuronides and methylated or sulfated)
- Can be partially metabolized by gut microbes
- Elimination half-life of 23 to 28 hours
- Urinary excretion
- Bioavailability of 20% +/-
Dietary polyphenols have been postulated to modulate the development and progression of several chronic diseases:

- Age related vision loss
- Osteoporosis
- Obesity
- Hypertension
- Cardiovascular disease
- Diabetes
- Cancer
Flavonoid Intake and Risk of CHD Mortality

Age-Adjusted CHD Mortality, %

Mean Flavonoid Intake (mg/day)

Flavonoids, Flavonoid-rich Foods & Chronic Disease Risk

- **AJCN 2008 Hooper et al.** – Meta-Analysis of 133 RCT of various flavonoid food sources on CVD risk
  - Green tea (LDL), cocoa (FMD), soy protein (LDL)
  - Clinically relevant changes observed

- **AJCN 2007 Mink et al.** – Flavonoids and CVD mortality in Iowa Women’s Health Study
  - Found RR for highest vs lowest quintile or any intake vs none for classes of flavonoids between 0.78 and 0.91
  - Individual foods associated w/ risk reduction included bran, apples, pears, red wine, grapefruit, strawberries, chocolate

- **Int J Cancer 2008 Cutler et al.** – Flavonoids and Cancer Risk in Iowa Women’s Health Study
  - Isoflavone intake inversely associated w/ overall cancer incidence
  - Lung cancer incidence inversely associated w/ flavanones & proanthocyanins. Strongest effect in current & past smokers

- **Nutr Rev 2012 Peterson et al.** – Associations between flavonoids and cardiovascular disease incidence and mortality in European and US populations
Comments on Epidemiologic vs Clinical Trials for Investigating Health Effects of Flavonoids

- Observational Epidemiologic studies can confirm or negate theories about importance of flavonoids in the diets of free-living individuals
  - Useful to evaluate human health effects of long-term exposure to physiologic concentrations of flavonoids
  - Cannot prove causality
  - Reliable data on flavonoid contents of foods not available for all classes
  - Correlations between flavonoids & other food components is high, therefore difficult to conclude association truly exist w/ the flavonoid alone

- RCT – human clinical studies
  - Aimed at demonstrating physiologic phenomenon in response to foods or to isolated food flavonoid components
  - Important to consider synergisms of food components & other foods in total diet
  - Help to identify potential mechanistic functions
  - Examine biomarkers, not usually clinical endpoints
Phytochemicals (Flavonoids) - Potential Targets and Mechanisms of Action

- **Cellular & Molecular Targets**
  - Enzyme inhibition or activation
  - Modulation of transcription factors, nuclear receptors & gene expression
  - Modulation of inflammatory response
  - Antioxidant action
  - Cell cycle regulation
  - Competition with endogenous substrates for receptors
  - Modulation
  - Other....
“Let food be thy medicine and medicine be thy food”

Hippocrates
The Father of Medicine
460 BC – 377 BC
The public is embracing the concept of “food as medicine” in response to the evolving health care crisis that is occurring in most developed countries.

The goal of “optimal health” is desired by many, but the promise of the “optimal diet” and “miracle” or “super foods” is often more attractive than the recommendation of a balanced diet rich in fruits, vegetables and plant foods.

How to achieve higher fruit & vegetable intakes; what is effective for health outcomes??...
Dietary Patterns --

Examples of diet patterns rich in food phytochemicals…number of F/V servings is ≥ typical USDA dietary guidelines or the American Heart Association recommendations:

- DASH diet
- Mediterranean diet
DASH Diet
Dietary Approaches to Stop Hypertension

Control American Diet

- (37% total fat, 3.6 serv F/V, 2.5 serv meat, 0.4 serv dairy)

Fruit/Vegetable Diet

- (37% total fat, 8.5 serv F/V, 2.5 serv meat, 0.3 serv dairy, 0.6 serv nuts)

DASH Diet

- (27% total fat, 9.6 serv F/V, 1.6 serv meat, 2 serv low fat dairy, 0.7 serv nuts)

Outcomes:

- Change in Blood Pressure: ↓ 5.5 mm Hg systolic, 3.0 mm Hg diastolic on the Dash diet, intermediate results on F/V diet
### Following the DASH Eating Plan

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Daily Servings</th>
<th>Serving Sizes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grains*</td>
<td>6-8</td>
<td>1 slice bread&lt;br&gt;1 oz dry cereal&lt;br&gt;½ cup cooked rice, pasta, or cereal</td>
</tr>
<tr>
<td>Vegetables</td>
<td>4-5</td>
<td>1 cup raw leafy vegetable&lt;br&gt;½ cup cut up raw or cooked vegetable&lt;br&gt;½ cup vegetable juice</td>
</tr>
<tr>
<td>Fruits</td>
<td>4-5</td>
<td>1 medium fruit&lt;br&gt;¼ cup dried fruit&lt;br&gt;½ cup fresh, frozen, or canned fruit&lt;br&gt;½ cup fruit juice</td>
</tr>
<tr>
<td>Fat-free or low-fat milk and milk products</td>
<td>2-3</td>
<td>1 cup milk or yogurt&lt;br&gt;1 1/2 oz cheese</td>
</tr>
<tr>
<td>Lean meats, poultry, and fish</td>
<td>6 or less</td>
<td>1 oz cooked meats, poultry, or fish&lt;br&gt;1 egg*</td>
</tr>
<tr>
<td>Nuts, seeds, and legumes</td>
<td>4-5 per week</td>
<td>½ cup or 1 1/2 oz nuts&lt;br&gt;2 Tbsp peanut butter&lt;br&gt;2 Tbsp or 1 1/2 oz seeds&lt;br&gt;½ cup cooked legumes (dry beans and peas)</td>
</tr>
<tr>
<td>Fats and oils*</td>
<td>2-3</td>
<td>1 tsp soft margarine&lt;br&gt;1 tsp vegetable oil&lt;br&gt;1 Tbsp mayonnaise&lt;br&gt;2 Tbsp salad dressing</td>
</tr>
<tr>
<td>Sweets and added sugars</td>
<td>5 or less per week</td>
<td>1 Tbsp sugar&lt;br&gt;1 Tbsp jelly or jam&lt;br&gt;½ cup sorbet, gelatin&lt;br&gt;1 cup lemonade</td>
</tr>
</tbody>
</table>

* Whole grains are recommended for most grain servings as a good source of fiber and nutrients.
* Serving sizes vary between ½ cup and 1 1/4 cups, depending on cereal type.
* Check the product's Nutrition Facts label.
Examples from PREDIMED Trial

**Prevencion con Dieta Mediterranea**
Large (n=7,447) multicenter European trial of individuals with risk factors but free of CVD. 3 diet arms Med+VOO, Med+nuts, Low fat. Followed multiple years

- **Decreased cellular & circulating inflammatory biomarkers related to cardiovascular risk** (Med diet vs Low fat diet) 2012 *Pharamcol Res*

- **Beneficial changes in apolipoproteins B, A-1 and their ratio** (Med diet vs Low fat diet) 2011 *Atherosclerosis*

- **Reduced diabetes incidence** (up to 52% ↓). After 4 yr follow-up, incidence of T2DM was 10.1% vs 17.9% (Med diet vs Low fat). 2011 *Diabetes Care*
Predictors and Barriers of Fruit & Vegetable Intake

- Predictors
  - Favorable taste preferences
  - F > M
  - ↑ Age
  - ↑ SES
  - ↑ Educational status attained

- Barriers
  - Cost
  - Limited access
  - Time to prepare foods
  - Unfamiliarity with certain foods
Conclusions

- Scientific evidence supports chronic disease risk reduction related to F/V consumption, in some but not all conditions
- Health benefits of F/V appear to be associated with food phytochemicals, such as polyphenolic flavonoids, in addition to traditional nutrients
- Flavonoids are absorbed, metabolized & reach target tissues
- Mechanisms of biologic action for flavonoids are multifactorial & involve cellular events
- Benefits are seen with intake levels for F/V higher than USDA recommendations, and as part of a healthful diet pattern
- Average intake of F/V is low and has not changed much over last 20 years. Significant challenges exist regarding the goal of increasing