Disclosures

- Scientific Advisory Board/Consultant
  - Public trustee of ILSI NA & advisor to its Flavonoid committee
  - Scientific advisory boards or panels, Conagra Foods, McCormick Inc, DuPont, Bay State Milling, Ocean Spray
  - Speaker: APRE this conference
- Stock: Conagra Foods, McCormick Inc, DuPont, Hershey
- No other relevant affiliations or financial interests
Flavonoids: Case Study

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Food flavonoids

Most common in foods

- >5000 compounds
- 11-26 classes
- 6-7 classes
- 30-40 compounds

[Diagram showing the distribution of flavonoids across different classes and numbers of compounds.]
Is flavonoid science adequate to make consumption recommendations?
Not quite yet, but we can help fill the gaps!
Strengthen science by showing SAFETY in intended uses
Problem: Safety and efficacy of foods and supplements vary in
- Dose
- Content
- Matrices
- Context in which they are used
Foods

many flavonoids and other constituents

Supplements

Fewer constituents, potentially much higher doses
Cocoa products differ

**Food**
- 2 tsp cocoa powder
  - 50 mg cocoa flavanols
  - 10 Calories
- Dark chocolate candy 42 gm bar
  - 170 mg cocoa flavanols
  - 200 Calories

**Supplement**
- 2 tsp stick
  - 250 mg cocoa flavanols
  - 30 Calories
Tea beverages differ from extracts

**Green Tea Beverage**
- Catechins (7)
- Caffeine and other xanthine alkaloids (3)
- Theanine
- Gallic acid
- Other flavonoids (kaempferol, quercetin, myrecetin)
- Theogallin
- Chologenic acid
- As, Se, others

**Green Tea Extract (powder)**
- 80% polyphenols
- 50% catechin ECGC
- Other catechins E, EC, EG
- [5 cups tea = catechins in 1 pill]
Strengthen science by demonstrating Efficacy
Problem: Health benefits vary

- **Cocoa flavonoids** may affect flow mediated dilation, other CVD related outcomes

- **Tea catechins flavan 3-ols** may decrease T2DM, stroke

- **Soy isoflavones** may decrease serum LDL cholesterol

- **Other outcomes**
  - **Cranberry and grape proanthocyanidins on** urinary tract health
  - **Citrus Grapefruit, orange flavonoids** and some cancers
Problem: Which flavonoids have beneficial effects?

- Polyphenols (flavonoids + lignans + others)?
- Total Flavonoids?
- Subclasses of flavonoids?
- Flavonoid acting singly, with other compounds?
- Specific flavonoid compounds?
Many classes have effects in epi studies, varying on outcomes measured.
Problem

Benefits are often based on surrogate biomarkers of effect rather than actual health outcomes (endpoints)
Coronary Heart Disease

Endothelial Dysfunction

↓NO

↑Inflammation

↑Thrombosis

Coronary Risk Factors

Genes

Coronary Heart Disease

Source: Vogel
Flow-mediated vasodilation (FMD)

FMD: Surrogate marker of CVD risk

Impaired endothelium mediated vasodilation

Normal flow conditions

Increased flow conditions

Disease

artery
plaque
endothelium
Surrogate markers of CVD risk (unapproved by US regulators)

- Arterial: Endothelial function (flow mediated dilation)

- Platelet aggregation
Institute of Medicine – National Academy of Sciences reports on biomarkers set the standards
Problem: Biomarkers of risk/effect must reflect disease end points but some don’t

- Ingredient → surrogate biomarker of effect
  - Intervention

- Surrogate biomarker of effect → disease end point
Problem: Why is evidence of flavonoid effects so mixed?

Are there truly no effects? effects may be due to poor diets in general that are also flavonoid poor

Are only specific classes or compounds effective? need further study

Are existing epidemiological and clinical studies insufficient? likely and correctable
Today, is there enough evidence for a Flavonoid Dietary Reference Intake?

- DRIs like EAR and AI are for nutrients

- **Nutrient**: substance essential for growth and maintenance of life
Setting an Estimated Average Requirement (EAR) requires.....

- Plausible common mechanism of action
- Constituent causing effects
- Functional indicator and marker
- Dose -response of some beneficial functional indicator
Since flavonoids are not nutrients, can they have a DRI?

- Fiber has an AI and it is not a nutrient
RISK of Adverse Outcome

INTAKE

EAR  RDA  \textbf{AI??}  UL

\textbf{AI} for a healthy population
Total Flavonoid EAR or AI? NOT YET
Still gaps exist for setting EAR

Plausible common mechanism of action NO (antioxidant theory too simplistic and for other effects mechanisms vary)

Method for setting EAR NO

Intake measures of constituents NO -still crude, and no biomarker of intake

Convincing evidence of consistent effect on functional indicators NO

Unlikely to be top priority for funders
How about an AI for flavan-3-ols?

- Plausible common mechanism of action? YES
- Intake available? YES
- Constituents causing effects known? POSSIBLY
- Functional indicator? NOT YET
AI for flavan-3-ols?

- Dose-response of constituents vs functional indicator available? **NOT YET**

- Data on blood pressure, cholesterol, morbidity, mortality mixed or unavailable

- Other surrogate effect biomarkers (endothelial function-flow mediated dilation) available but US regulatory authorities do not recognize them as valid
Cocoa flavanol AI?
AI for Cocoa Flavanols?

- **Plausible common mechanism of action** YES
  - Alters blood pressure and ultimately CVD?

- **Constituent causing effects?** YES
  - **YES**: Flavan-3-ols but **NO** intake biomarker

- **Functional indicator and marker** YES
  - Flow mediated dilation

- **Dose component vs. response of some beneficial functional indicator?** YES but not for approved biomarkers in US
AI for tea flavan 3 ols?
What tea constituents cause beneficial health effects on CVD?

- Specific catechins?
  - EGCG?
- Combinations of flavonoids and other compounds?
- Total flavonoids?
- Total polyphenols?
- Other constituents?
Many catechins to choose from!
Figure 3. Tea bioactive compounds

- **Caffeine**
- **Theanine**
- **Theobromine**
- **Quercetin**
AI for Tea Flavonoids?

- **Plausible common mechanism of action?** YES
  - antioxidant theory too simplistic; possibly blood pressure and flow mediated dilation)

- ** Constituent causing effects?** POSSIBLY
  - catechin (ECGC) effects on intermediate biomarkers?
  - intake biomarker: NO

- **Functional indicator and marker?** NOT YET
  - CVD (or proxies BP and flow mediated dilation)

- **Dose-component vs. dose-response of some beneficial functional indicator?** NOT YET
  - Few studies, mostly observational so far
Total flavonoid structure–function claim?

- **Food or constituent in food and beneficial effect?** NOT YET
  - Strength, consistency, specificity of evidence
  - Temporal occurrence, dose-response
  - Biological plausibility

- **Reasonable quantity of food and pattern of consumption required to get claimed effect as part of balanced diet** YES

- **Specific groups show relation and can be associated with larger target population** POSSIBLY

- **Avoids consumer confusion and protects public’s health** YES
Strengthen science to prove flavonoid benefits justify recommendations for consumption
What about biomarkers of healthy function?

- Mechanisms keeping people healthy that are at an earlier stage on continuum than those causing disease

- EU concept
The endothelium maintains vascular health

- Dilatation
- Growth inhibition
- Antithrombotic
- Anti-inflammatory
- Antioxidant

- Constriction
- Growth promotion
- Prothrombotic
- Proinflammatory
- Pro-oxidant
Flow-mediated vasodilation (FMD)

Healthy endothelium mediated vasodilation

Normal flow conditions

creased flow conditions

Health

Marker of vascular health
EU guidance for beneficial effects on heart health of food components (Article 13)

- Beneficial physiological effects (article 13 like stronger US structure-function claim)
  - endothelial function (endothelium-dependent vasodilation) improvement over 4 wk
  - reduced platelet aggregation

- Not risk reduction (article 14 which is like US health claims)
  - Source: EFSA Journal 2011 9(12): 2474
Some beneficial physiological effects related to heart health are allowed in EU

- **Walnuts**: endothelial function-flow mediated dilation
- **Tomato extract**: endothelial function-flow mediated dilation
- **Cocoa flavanols** (provisional; sent to EU parliament)
Problem: Permissible “Public Speech” in USA is different

- These are statements falling between content claims, structure function claims and general health advice

- Not allowed in US if based on surrogate health outcomes (effect biomarkers) not yet approved by FDA
Problem:
Biomarkers of health do not yet meet US standards or law
Build evidence for biomarkers of health

- Ability to maintain flexibility in reacting to the environment

- Examples for CVD
  - Endothelial function (Flow mediated dilation and other measures)
  - Platelet function
How to strengthen the science

- Harmonize research to fill gaps
- Improve research study reporting
How to strengthen the science

- Hypothesis driven research
- Characterize active ingredient/s and relate them to claimed effects
How to strengthen the science

- Mount stronger cohort studies
- Conduct intervention studies using accepted as well as new effect biomarkers
How to strengthen the science

- Use new techniques to better summarize existing data
- Model size of potential effects
Better systematic reviews
Show flavonoid benefits justify intake recommendations by crafting messages that reflect the science.
Dietary Guidance-type statements on flavonoids?

- Eat more and more fruits and vegetables
  - Fits in with MyPlate, existing dietary guidance on more vegetables, fruits, plant foods

- BUT not very specific, not very helpful and not true— not all of these foods are high in flavonoids
- Needs more specificity
Eat 5-9 servings fruits and vegetables including those rich in flavonoids such as cocoa, tea, soy, berries and citrus??
Show flavonoid benefits justify consumption recommendations:

- Strengthen the science
- Craft messages reflecting it
Thank you!

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