1. Introduction:
   - Natural Products
   - Plant Foods/Berries and Human Disease: Obesity, Cancer, Diabetes

2. Berry Research:
   - Terminologies
   - Challenges and Issues

3. Discussion
Plant Medicines

- Plant medicines have been used by ancient cultures for centuries e.g. Traditional Chinese Medicine, Ayurveda, etc.

- The WHO estimates 80% of developing countries currently use plants as basis of medicinal systems

- Used as foods, extracts, teas, tinctures, soups, herbs, spices, etc.
Natural Products from Plants
Colors in Plants

Protects from solar irradiation & oxidative damage.
Dietary Phytochemicals (Phyto = Plant)

- Epidemiological data suggest that phytochemical-rich diet reduces risk of human diseases e.g. certain cancers, heart disease, neurodegenerative diseases, etc.
Berries: ‘Super-Fruit’; rich in phenolics

Phenolics

Flavonoids
- Anthocyanins
- Flavonols
- Flavanols

Simple Phenolics

Tannins: Hydrolyzable Condensed
Examples of Dietary Polyphenols

**Flavonoids**
- Flavones
  - Apigenin
- Flavonols
  - Quercetin
  - Naringenin
- Flavanones
  - Flavanols (Catechins)
    - (+)-Catechin
- Anthocyanins
  - Cyanidin

**Isoflavonoid**
- Isoflavone
  - Daidzein
- Coumestans
  - Coumestrol

**Lignans**
- Secoisolariciresinol

**Stilbenes**
- Resveratrol

**Phenolic acids**
- Cinnamic acid
- Ferulic acid
- Chlorogenic acid
- Procyanidin trimer (flavanol)

**Phenolic polymers**
- Ellagitannins
  - Casuariin
- Proanthocyanidin
Importance of Plant-Based Diets: Ancient Man vs. Modern Man

- In tropical Africa, man wandered over large areas and ate over 800 varieties of foods, providing over 25,000 different phytochemicals.

- Fewer than 20% of all Americans eat five or more servings of fruits and vegetables a day, as recommended by the National Cancer Institute (NCI).
Similar DNA, different diets!
<table>
<thead>
<tr>
<th><strong>Diets Then and Now</strong></th>
<th><strong>Today</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>50,000 Years Ago</strong></td>
<td><strong>Today</strong></td>
</tr>
<tr>
<td>Fruits, nuts, seeds,</td>
<td>Processed foods: refined pasta, cereals white rice &amp; flour</td>
</tr>
<tr>
<td>roots, tubers, flowers,</td>
<td>white rice &amp; flour</td>
</tr>
<tr>
<td>leaves, stalks, beans</td>
<td>Added fat and sugar</td>
</tr>
<tr>
<td>(Hunter/Gatherers)</td>
<td>Tobacco and alcohol</td>
</tr>
<tr>
<td></td>
<td>(Sedentary Lifestyle)</td>
</tr>
</tbody>
</table>
Divergence from Plant-Based Diet
Instead of these colors.....
We eat these colors...
And these colors...
And Sedentary Lifestyles......
“Childhood obesity is at epidemic levels in the United States.”

- David Satcher

US Surgeon General
Obesity Trends* Among U.S. Adults

**BRFSS, 1985**

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” woman*)

Source: Mokdad AH.
Obesity Trends* Among U.S. Adults

BRFSS, 1990

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” woman)

Source: Mokdad AH.
Obesity Trends* Among U.S. Adults

BRFSS, 1995

(*BMI ≥ 30, or ~ 30 lbs overweight for 5’4” woman)

Obesity Trends* Among U.S. Adults

BRFSS, 2000

(*BMI ≥ 30, or ~30 lbs overweight for 5’4” woman)

Diabetes Trends* Among Adults in the U.S.,
(Includes Gestational Diabetes)
BRFSS, 1990, 1995 and 2001

Cancer Incidence Worldwide

Cases of cancer per 100,000 population:
- Under 100
- 100-150
- 151-200
- 201-250
- 251-300
- 301 and above

From Parkin DM, EJC, 37, 2000, 4-66
THE COLOR WHEEL OF FOODS

Adapted from “What Color Is Your Diet?” Harper Collins 2001
Plant Foods (Berries) are Antioxidants
Antioxidant Measures

- ORAC, DPPH, TEAC, FRAP, etc.
- Cellular tests
- Combinations
The ‘Contradictory Science of Antioxidants’

- Conflicting studies from observational studies and randomized controlled trials
In Vitro vs. In Vivo

- *In vitro* (‘test-tube’) studies commonly use high/non-physiologically achievable concentrations

- Does not always translate into *in vivo* (living) situation
**In Vitro vs. In Vivo**

- Absorption
- Distribution
- Metabolism
- Excretion

‘the tissue is the issue’
In Vivo Studies

Animals: Rodents

Humans
Challenges

- Analytical challenges in estimation of levels in biological fluids and tissue
- Limited human tissue bioavailability data available: animal = human?
- Lack of correlation with blood/tissue levels and bio-activities relevant to disease states
Berry Polyphenol Metabolism

Oral Ingestion → Small Intestine → Colon Microflora → Feces

Peripheral Tissues

Liver → Bile → Enterichepatic Circulation

Blood Circulation → Kidneys

Small Intestine

Phase I + II metabolism

Phase II Conjugation: Glucuronidation; Sulfation; Methylation
Issues in Evaluating Polyphenol Bioavailability

• Chemical sub-class:
  – Type and extent of food processing
• Food matrix, stability, digestive release and solubility
• Food pairings
• Metabolism: Phase 1 & 2
• Inter-individual variability:
  – Genetic polymorphisms, Gut microflora
Beyond .... Antioxidant

- Anti-Inflammatory
- Anti-neurodegenerative
- Anti-cancer
- Cardiovascular disease
- Effects on enzyme metabolizing pathways, signaling transduction pathways etc.

Inflammation & Disease

THE SECRET KILLER

The surprising link between INFLAMMATION and HEART ATTACKS, CANCER, ALZHEIMER’S and other diseases

What you can do to fight it

TIME FEB. 23, 2004
What is Inflammation?

- Inflammation is an immune response to injury or infection causing pain, redness, heat, and swelling in the affected area.

- Two types:
  - Acute Inflammation
  - Chronic Inflammation

- Causes of Inflammation
  - Trauma
  - Endogenous antigens
  - Chemical agents
  - Microbial pathogens

Cells involved: Macrophages, Mast cells, Neutrophils, Lymphocytes, etc
iNOS Signaling

LBP
LPS

2009 ProteinLounge.com

C SOD Ribonucleotide Reductase Ribonucleotide Reductase

GSH ONOO-

Virus (Herpesvirus, Picornaviruses, Flaviviruses and Coronaviruses)

O2 -O2

NF-κB

IRF1

HMGI/κ

AP-1

Stat1α

NFKB

IRF1

L-Arginine + O2

Destabilization

iNOS mRNA

Viral RNA

NADPH Oxidase

L-Citrulline

Viral Protease

Viral Polyprotein

Virion RNA
Inflammation linked to most diseases

- Pulmonary diseases
- Cardiovascular diseases
- Neurological diseases
- Alzheimer’s disease
- Autoimmune diseases
- Diabetes II
- Arthritis

Inflammation
Inflammation and CaP
Proliferative Inflammatory Atrophy: Possible precursor to CaP

Nuclear Factor Kappa Beta (NF-κB)

Activator

Ubiquitination & Phosphorylation

IκBα Degradation

IκBα

Nuclear import

κB enhancer

Nucleus

Cytoplasm

Garg and Aggarwal, Leukemia, 2002
What activates NF-κB?

- RO inducers (H2O2)
- Cytokines (TNF family, IL-1, IL-17, IL-18, EGF)
- Carcinogens (Urethane, CSC, DMBA, NNK, BP)
- Infection (bacterial/viral; e.g. HIV, EBV-LMP, HTLV1)
- Tumor Promoters (PMA)
- Apoptosis-inducers (Chemotherapeutic agents & γ-irradiation)
- Stress (pH, hypoxia, stress heavy metals)
- Endotoxin (LPS)

Aggarwal BB, Cancer Cell, 2004
Berry Polyphenols Inhibit Pro-Inflammatory Cell Signaling *In Vitro*

Effects of Phosphatidylinositol-3-kinase (PI3K)/ProteinKinase B(AKT)/NFkB pathway on COX-2 expression

Adams, L; Seeram, N; Aggarwal, B; Takada, Y, Sand, D; Heber, D. J. Agric. Food Chem. 2006, 54, 980-985
Research Directions

• Probe for mechanistic insights into anti-inflammatory at cellular levels
  – At the ‘cytokine’ and ‘gene expression’ level, As direct inhibitors of COX-2 and iNOS, etc.
  – Regulatory pathways and sub-cellular signaling
Inflammation and Oxidative Stress are Associated With Chronic Disease

Single Berry Compounds Reduce Inflammation and Oxidative Stress

Combinations of Berry Compounds Reduce Inflammation and Chronic Disease Risk
QUESTIONS?

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