Cranberries and their Bioactive Compounds in Human Health

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• What factors can be manipulated to sustain health throughout life?

• How can cranberry consumption be part of an effective strategy for health maintenance?

• How can eating cranberries help reduce risk factors for certain common diseases and afflictions?

• Can cranberries contribute to reducing the over-use of antibiotics?

• How can cranberries be utilized in the diet to add health functionality and a fresh zing to recipes?
Physical and Mental Health

Successful Aging

Early Life
Growth and development

Adult Life
Maintaining highest level of function

Older Age
Maintaining health and independence

Influenced by:
- genes
- diet
- lifestyle

Disability threshold
Range of function

Age
Unsuccessful Aging?

Still the Terminator?

Eddie Van Halen
How to maintain health?

Health Promotion

- Pharmaceuticals
- Dietary Supplements
- Functional Foods
Functional Foods

- Whole food is consumed - benefit from mixture of phytochemicals
- Nutraceutical effects (beyond basic nutrition)
- Less chance of toxic overdose
- Often less expensive
Cranberries
An Original Functional Food

Folklore Uses
- Scurvy
- Wound healing
- Blood poisoning
- Stomach ailments
- Urinary disorders

Meat Preservative
American Blueberry
_Vaccinium corymbosum_

Concord Grape
_Vitis labrusca_

One of only 3 commonly cultivated fruits native to North America

American Cranberry
_Vaccinium macrocarpon_
Often Mistaken for Cranberry

Lingonberry
*Vaccinium vitis-idaea*

European cranberry
*Vaccinium oxycoccus*
U.S. Cranberry Production Areas

Global Cranberry Production (2007)

- US: 73.4%
- Chile: 3.9%
- Canada: 22.7%

Map of U.S. cranberry production areas with circles highlighting major regions.
Winter Production in South America (Chile)
Cranberries in the bog, before harvest
Berries float on the water - “A sea of red color”
Dry Harvest for Fresh Market (>3% of crop)
How eating cranberries benefits our health, especially if we start when we are young
What’s in Cranberries?
Rich in Healthful Bioactives

**Anthocyanins**
- Red fruit pigments
- Protect fruit from UV

**Flavonols**
- Yellow pigments (flower coloration) attract pollinators
- Pest and insect resistance

**Proanthocyanidins**
- Condensed tannins
- Astringency
- Plant defense compounds
Cranberries Have a Broad-Array of Health Benefits

Bacterial Anti-Adhesion
- Urinary Tract
- Oral Cavity
- Stomach

Cardiovascular Health

Anti-Cancer
Cranberries and Their Bioactive Constituents in Human Health, published in the November issue of *Advances in Nutrition*, provides in-depth information about the bioactive compounds in cranberry and the pathways by which they may help protect against urinary tract infection, cardiovascular health and diabetes.

Cranberry Consumption and Pathogenic Bacteria
Urinary Tract Infections (UTIs)

90% are caused by *E. coli*

11 million cases/year in U.S.A.

25% recurrence rate
Cranberry Juice Linked to UTI Prevention in Humans

First reports in medical literature in 1914, 1923

Mechanism thought to be due to the acidic pH inducing bacteriostatic effect in urine

Disproved pH theory - bacteriostatic pH rarely achieved with normal serving sizes of cranberry
Preventing Bacterial Adhesion to Cells

Cranberry metabolites may bind to proteinaceous fimbrial tips and block adhesion to cell receptors.
Proposed Mechanisms of Action for UTI Prevention

Prevention of bacterial adhesion to urinary tract
- Sobota, 1984 (general anti-adhesion)
- Ofek et al., 1991 (specific bacterial activity)
- Ahuja et al., 1998 (anti-adherence mechanism)
- Howell et al., 1998 (anti-adhesion compounds identified)
- Camesano 2005-8 (molecular adhesion forces, conformation)

May act in both the urinary tract and the colon
- Indirect effects, GALT, immune function, gut microflora

Other potential contributing mechanisms
- Anti-inflammation
- Immune modulation
Bladder Cells with *E. coli* gfp+

Bladder Cells

**Without cranberry**

**With cranberry**

**Bladder Cells with *E. coli* gfp+**

**With cranberry**
Adhesion Forces in Urine After Cranberry Juice or Water Consumption
(2 E. coli strains + S. aureus)

Average Adhesion Force (nN)

- 2h Water
- 2h CJC
- 8h Water
- 8h CJC

Bacterial Strains
- BF1023
- CFT073
- S. aureus

Attribution:
T. Camesano
Worcester Polytechnic Institute

Atomic force microscopy
Proanthocyanidins (PACs) Identified as Active Anti-adhesion Compounds

Isolated through bioassay-directed fractionation

- Foo et al., 2000a, *Phytochemistry*
- Foo et al., 2000b, *J. Natural Products*

Have been shown *in vitro* and *ex vivo* in urine to prevent bacterial adhesion
PACs found in some other foods
Unusual double A-type bonds in cranberry

B-linked proanthocyanidin
(grape, chocolate)

A-linked proanthocyanidin
(cranberry)

Anti-adhesion activity
Anti-adhesion Activity of Human Urine After Cranberry Juice and Other PAC-Products
(Single servings)
Urinary Bacterial Anti-adhesion Activity Over Time Following Cranberry Consumption

![Graph showing the change in bacterial anti-adhesion activity over time following cranberry consumption. The x-axis represents hours after ingestion of 300-mL Cranberry Juice 27%, ranging from pre-ingestion to 26-28 hours. The y-axis represents bacterial anti-adhesion activity, ranging from 0 to 2. The graph shows an initial increase, a peak around 6-8 hours, and a decline over subsequent hours.]
Reduction in *E. coli* Gut Colonization: Mechanism of UTI Prevention?

- Uropathogenic *E. coli* (UPEC) in the gut
  Can invade enterocytes and evade macrophage killing

- Rectal P-type UPEC as source of bladder infection

- A-type PACs interfere with mechanisms that may inhibit gut colonization by UPEC
  Development of murine models (Reed & Krueger, Univ. WI)

- Absorption of PACs not needed for proposed mechanism
Cranberry PACs Inhibit Bacterial Invasion of Enterocytes

Cranberry PACs inhibit invasiveness of UPEC

High molecular weight PACs more effective in inhibiting invasiveness

University of Wisconsin (Reed, Krueger)
Is Cranberry Clinically Effective for UTI Prevention? Treatment?

What Product Forms are Active? Dosage?
Selected Positive Clinical Trials

• Avorn et al., 1994 *JAMA*
  Elderly – Cranberry Juice - (~50% red. bacteriurea)
• Walker et al., 1997 *J. Family Practice*
  Women - Cranberry powder (significant red. UTI occurrence)
• Stothers, 2002 *Can J Urol.*
  Women - Cranberry Powder (significant red. UTI occurrence)
• Kontiokari et al., 2000 *British Med. J.*
  University women – Cranberry Juice (20% red. In UTI risk)
• Wing et al., 2008 *J. Urol.*
  Pregnant women – Cranberry Juice (41-57% red. UTI)
  Young girls – Cranberry Juice (~50% red. recurrent UTI)
• Salo et al., 2012 *Clinical Infectious Diseases*
  Children – Cranberry Juice (43% red. UTI occurrences)
• Afshar et al., 2012 *J. Urol.*
  Children – Cranberry Juice (65% red. UTI risk)
• Uberos et al., 2012 *Open Access Journal of Clinical Trials*
  Infants – Cranberry Concentrate Syrup (red UTI recurrence rate)
Overall Clinical Results are Mixed

Suggestions from the Cochrane Review (2013):

- Use product standardized for PAC content (36 mg/dose)
- Use appropriate test for quantifying PACs (DMAC)
- Test for efficacy (Anti-adhesion, *E. coli* invasion)
- Make sure placebo has no efficacy
- Use effective dosage or do dose-response
- Have a good compliance marker for cranberry ingestion
Fluorescence microscopy illustrates stained *E.coli* adhering to uroepithelial cells, cultured in urines collected after consumption of standardized cranberry supplement.

1Howell et al, *BMC Infectious Diseases* 2010:94
Current Management of UTIs

Low-dose antibiotic use for prevention of recurrent infections leading to yearly increases in antibiotic resistance

In the U.S., nearly 2 million patients/year are infected with a resistant infection

- 23,000 deaths associated with these infections in US
  10 million deaths worldwide

- Healthcare costs to the U.S. economy for antibiotic-resistant infections are nearly $20 billion

Novel alternatives for disease prevention are needed
Antibiotic Resistance and UTIs

First line – trimethoprim-sulfamethoxazole
- 25-30% resistance in USA
- Higher in other countries

Second line – Ciprofloxacin
- 60% resistance in China
Resistance Rates of *Escherichia coli* to Selected Antibiotics (1994-2005) in Hospital

Address geocoding of urinary *E. coli* cases (resistant and susceptible to Ciprofloxacin) in São Paulo, Brazil, 2002.
Antibiotic Resistance Rates Increase in the Elderly

<table>
<thead>
<tr>
<th>Age Group</th>
<th>N</th>
<th>Ampicillin</th>
<th>Ciprofloxacin</th>
<th>Nitrofurantoin</th>
<th>Norfloxacin</th>
<th>Trimeth-sulfa</th>
<th>Tetracycline</th>
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<td>&lt; 4</td>
<td>969</td>
<td>60.8</td>
<td>0.9</td>
<td>1.9</td>
<td>1</td>
<td>49.6</td>
<td>33.7</td>
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<td>≥ 4 and &lt; 13</td>
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<td>57.4</td>
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<td>1</td>
<td>2.1</td>
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<tr>
<td>≥ 13 and &lt; 60</td>
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<tr>
<td>≥ 60</td>
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<td>46.1</td>
<td>24.3</td>
<td>5.9</td>
<td>24.4</td>
<td>37.0</td>
<td>37.3</td>
</tr>
</tbody>
</table>
Consuming Cranberry Prevented Adhesion of Antibiotic Resistant *E. coli* in urine by 80%

Preventing infections with cranberry could:

- Reduce the subsequent need for antibiotics
- Thereby slowing pace of resistance development

Howell and Foxman, 2002, *JAMA*
3 Recent Pediatric Trials with Cranberry: Reduced UTI Incidence And Less Antibiotics Use

40 children, cranberry juice vs placebo: 65% reduction in UTI incidence  
Afshar et al., J Urol. 2012 188(4 Suppl):1584-7

84 girls, 50 ml cranberry juice or controls for 6 mo: lower UTI incidence (18.5%) compared to placebo (48.1%)  

263 children, cranberry juice or placebo for 6 mo: Lower incidence density (27 vs 47), decreased number of days on antibiotics (12 vs 18)  
Cranberry Juice for the Prevention of Recurrences of Urinary Tract Infections in Children: A Randomized Placebo-Controlled Trial

Salo et al., Clinical Infectious Diseases, 2012

263 children monitored for 1 year, recurrent UTIs recorded. Performed in 7 hospitals in Finland.

Dosage: up to 300 mL Cranberry Cocktail/day (5 mL/kg body weight), 1 or 2 doses/day for 6 months with follow-up monitoring

Cranberry reduced UTI recurrences by 43%: 27 episodes of UTI in the cranberry group and 47 in placebo group

No reduction in number of children experiencing at least 1 UTI after initial infection, due to lower than expected recurrence rate of 22% (expected 30%)

*Children in the cranberry group had significantly fewer days on antimicrobials* (26 days per patient-year; 95% CI, P < .001)
Cranberries vs Antibiotics to Prevent Urinary Tract Infections. A Randomized Double-blind Non-inferiority Trial in Premenopausal Women

Beerepoot et al., *Archives of Internal Medicine*, 2011

12-months’ prophylaxis with either low-dose antibiotic trimethoprim/sulfamethoxazole (480 mg) or cranberry capsules

High resistance rates after just 1 month of TMP/SMX prophylaxis. Resistance to TMP/SMX, trimethoprim and amoxicillin increased from 21-28% to 73-91% in both feces and urine

Ciprofloxacin and norfloxacin in urinary *E. coli* isolates increased from 8% at baseline to 23% after 12 months of TMP/SMX

*Cranberry not quite as effective as low-dose antibiotics, but preferred due to absence of substantial antibiotic resistance issues*
Anti-adhesion Mechanism Interfering with Initial Step in the Infection Process

*Not Killing the Bacteria, as an antibiotic would*

- Greatly reducing selection pressure for proliferation of antibiotic resistant bacterial strains
- Possibly increasing selection for non-adherent uropathogenic rectal strains
- May encourage growth of probiotics
No Interaction of Cranberry with Beta-lactam Antibiotics

Effects of Cranberry Juice on Pharmacokinetics of Beta-lactam Antibiotics Following Oral Administration

Meng et al., *Antimicrob Agents Chemother.* 2009

Results suggest that the use of cranberry juice at usual quantities is not likely to alter the pharmacokinetics of amoxicillin and cefaclor in UTI prophylaxis.
Cranberry Prevents Bacterial Adhesion in Other Parts of the Body
To the bladder and beyond!
Cranberry Prevents Bacterial Adhesion of \textit{Helicobacter pylori} to Stomach Cells

\textit{H. pylori} infection can lead to progression of gastric ulcer.
Worldwide *H. pylori* Infection
Ulcer Treatment Can Compromise Patients

6-8 weeks of treatment with antibiotics and proton-pump inhibitors

H. pylori are becoming RESISTANT to these antibiotics
Cranberry and Stomach Health

- PACs prevent *H. pylori* adhesion to both mucus and gastric cells, and inhibit bacterial growth

- **Clinical in China**  *(Zhang, Helicobacter, 2005)*
  Cranberry Juice Cocktail (500 mL/day) for 3 months, suppressed over 15% of *H. pylori* infections

- **Clinical (on children) in Chile**  *(Gotteland, Nutrition, 2008)*
  Cranberry juice (200 mL/day) for 3 weeks, eradicated nearly 17% of *H. pylori* infections

- **Clinical in Israel**  *(Shmuely, Mol. Nutr. Food Res., 2007)*
  Cranberry Juice Cocktail (250 mL/day) combined with triple antibiotic therapy improved eradication rate
Cranberry PACs and Dental Health

Cranberry PACs

- Reduce biofilm (plaque) formation
- Inhibit coaggregation of oral *streptococci*
# Potential Benefits of Cranberry PACs for Periodontal Health

**Daniel Grenier – Laval Université**

## Periodontopathogen colonization
- Inhibition of biofilm formation by *P. gingivalis*
- Inhibition of adherence properties of *P. gingivalis*

## Cranberry PACs

## Host immunoinflammatory response
- Inhibition of cytokine production

## Connective tissue and bone destruction
- Inhibition of *P. gingivalis* collagenase activity
- Inhibition of MMP production and activity
- Inhibition of osteoclast formation and activity

## Signs of Periodontitis
- Potential periodontal health benefits
Oral Health Product

Product development with cranberry PAC - Not whole cranberry

Need adequate “contact time” on teeth and gums
Other Health Benefits of Cranberry

• Reduce Risk Factors for Heart Disease and Cancer
• Antioxidant
• Anti-inflammatory
Oxidative Stress

Lifestyle Factors

Cigarette Smoking

$\sim 10^{15}$ free radicals per puff

G.G. Duthie
Antioxidant Food Supplements in Human Health
Stress → Illness/Disease

Sun Exposure

Pollution

"STRESS"
Poor Diet
High in “bad” fats and sugar
Fats in meat exposed to high cooking/grilling temperatures

“Excessive” alcohol consumption

Too much Exercise
Oxidation Inflammation

- Pulmonary diseases
- Neurological diseases
- Autoimmune diseases
- Cancer
- Cardiovascular diseases
- Alzheimer's
- Diabetes
- Arthritis

Obesity is an Oxidative, Pro-Inflammatory State
Metabolic Syndrome

If you have any 3 of these conditions:

✓ Abdominal obesity (pot belly)
✓ High cholesterol/Triglycerides
✓ High blood pressure
✓ High blood sugar/Insulin resistance
✓ Inflammation (High CRP)

You are at increased risk for:

Diabetes (5X), Heart Disease, Reduced Cognitive Functioning
Metabolic Syndrome

25% of people in USA have it!

Increases with age

Ages 18-39: 10% have it
Ages 60-79: 40% have it!
How can we reduce oxidants and be healthier?
Our bodies have natural defenses against OXIDANTS.

We produce ANTIOXIDANTS to stop damage.

As we age, our bodies produce fewer natural antioxidants.

We can get extra antioxidants from eating fruits and vegetables.

Cranberries are very high in Unique ANTIOXIDANTS.
Antioxidant Capacity Varies Among Fruits and Vegetables

Antioxidant capacity (as the FRAP value); μmol 100 g⁻¹ fresh weight wet
Cranberries and Cancer

Inhibit cancer cell growth
- breast, colon, esophageal

Induce apoptosis (programmed cell death)
- reduces tumor formation in culture

Increase effectiveness of chemotherapy agents used to treat ovarian cancer
Cardiovascular Benefits

Heart Disease...

It’s all about

Improving Blood Flow

Cranberries

Inflexibility of arteries

LDL cholesterol oxidation

Inflammation (similar to aspirin - inhibit COX-2 expression, decreases proinflammatory prostaglandin synthesis)
Future Cardiovascular Events

Risk factor

- Lipoprotein(a)
- Homocysteine
- IL-6
- Total Cholesterol
- LDL C
- sICAM-1
- SAA
- Apo B
- TC: HDLC

CRP (Inflammation)

CRP + Total Cholesterol

Relative Risk

0  1.0  2.0  4.0  6.0

increasing risk

Cranberry increases plasma HDL-cholesterol concentrations in men

Changes in plasma HDL-cholesterol (mmol/l)

- Abdominally obese men
- Increasing doses, 4 wks each
- 250mL Light CJC/day
- 8.6% increase in HDL
- Drugs ~ 10% increase
How much cranberry each day for health benefits?

Research continues on dose-response, etc.
- Cranberry juice cocktail (27%)*  8-10 oz.
- 100% Cranberry juice**  2 oz.
- Fresh cranberries  1/4 cup
- Dried cranberries  1/3 cup
- Cranberry sauces  1/4 cup
- Cranberry powders (pills)  250-1000 mg
- PACs (in products)  36-72 mg

*Cranberry juice cocktail is 27% juice with a sweetener added due to its tartness. Most of the health science research is based on cranberry juice cocktail.

**100% juice is available but usually diluted with water or other juices for palatability.
Cranberry Dilemma:
Powerful and Unique Health Benefits...
But with Low, Naturally Occurring Sugar

* CJC cranberry juice cocktail (27% cranberry)
The amount of sugar in dried cranberries is equal to that of other dried fruits, like raisins and dried cherries.

- Dried cranberries are also a good source of fiber - 10% of the Daily Value - with 2.3 grams per serving (40 grams).

- 1/2 cup of dried cranberries is equal to one serving of fruit (one cup) according to MyPlate recommendations.
Practical Tips for Clients to Eat more Cranberries

A few ways RDs can help clients add the exceptional cranberry to their diet!
Cranberry Sauce

Sandwich or Wrap

Baked Brie for Parties

Crackers
Dried Cranberries

Oatmeal

“Red Ants on a Log”

Rice or Couscous

Salads

Cookies
Fresh or Frozen

Relish or Chutney

Fruit Smoothie

Whole Grain Baked Goods
Incentives to Utilize Cranberry for UTI Prevention

• Inexpensive, convenient functional food product

• Effective at reasonable dosages

• No bacterial resistance issues

• May help slow pace of antibiotic resistance if used instead of low-dose antibiotics for prevention

• Additional health benefits possible
  - Anti-adhesion in other sites in the body
  - Antioxidant/anti-inflammatory/heart health
What’s Next?

• There is a growing consensus among researchers and health experts that bioactives in berry fruit (including cranberries) are a rich source of polyphenolics and flavonoids associated with health-promotion and reducing the risk of chronic disease.

• Dietary guidance for consumers to select a broad array of berries and other fruits should help increase intake of these bioactive compounds.
For Recipes and Additional Information

Visit: uscranberries.com

Link to Cranberry Bioactives Review Article:

http://advances.nutrition.org/content/4/6/618.full
Any Questions??