Wine anthocyanins: gut metabolism key to anti-cancer effects?

Andrew Waterhouse
Viticulture and Enology
Hilo, April 28, 2011
St. Leger et al.
- Factors associated with cardiac mortality in developed countries with particular reference to the consumption of wine

Serge Renaud, French Paradox

Kinsella antioxidant hypothesis

Absorption metabolism issue
Wine, alcohol, platelets, and the French paradox for coronary heart disease

- International Phenomenon
  - Television
- Stimulated public and research interest
- Inadequate explanation (paradox)

Davis Antioxidant Hypothesis
-French Paradox Explanation

“*If potent antioxidant phenolic components are routinely ingested by the regular consumption of red wine they may collectively reduce oxidation of lipoproteins and reduce thrombotic phenomena and thereby contribute to the amelioration of atherosclerosis and morbidity and mortality from coronary artery disease.*”

Wine Contains Antioxidants

- LDL oxidation inhibited by wine phenolics

- Frankel, Kanner, German, Parks, Kinsella, the Lancet, 1993; 341: 454

Fig 2—Inhibition of LDL oxidation by phenolic compounds extracted from wine and by α-tocopherol, measured by conjugated diene absorption.
Antioxidants become Trendy

- Antioxidants "mop up" or "scavenge" free radicals
- Red wine is believed to be "healthier" because it contains antioxidants called polyphenols. These mop up damaging free radicals, and that could prevent fat deposits building up in arteries.
  - [BBC News](http://www.bbc.com)
- Why are antioxidants so important? Because they have a proven track record of fighting free radicals. Your body is being constantly attacked by very harmful substances known as free radicals or oxygen radicals.
  - [Saratoga Supplements Advertising](http://www.saratogasupplements.com)
Antioxidant Papers, 850% Growth

ISI Web of Science

![Graph showing growth in antioxidant papers over years from 1992 to 2010. The y-axis represents the number of papers, and the x-axis represents the years. The graph shows a significant increase in the number of papers, particularly from 2007 onwards.]
Antioxidants in Red Wine

Catechin Metabolism Studies

- Flavonoids converted to metabolites
- Amount of conversion
- Types of metabolites
- GC Analysis
  - Pierre-Louis Teissedre
  - Dave Luthria
  - Jennifer L. Donovan
Absorption of Phenolics into Plasma
Red Wine Catechin

Tissue Levels of Polyphenolics

- **Weak absorption**
  - 1-4% typical

- **Rapid metabolism**
  - Methylation, glucuronidation, sulfation
  - Loss of redox active catechol group!

- **Rapid clearance**
  - Maximum levels at 1-2 hours, minimal levels after 6 hours, some longer

- **Net result is [nM], for a short period**
Endogenous Plasma Antioxidants Overwhelm Polyphenolics

- Ascorbate 30 uM
- Urate 300 uM
- Tocopherols 10 uM
- Glutathione 500 uM
- Tightly regulated

- Carotene
Conclusions

- Direct chemical antioxidant effects of polyphenolics cannot explain observed effects.

- What are the mechanisms that could explain the apparent health benefits of consuming phenolic antioxidants?
Microbial Metabolism of Anthocyanins

- Reduced colon cancer in wine drinkers
- Low absorption rate of flavonoids
- Associations between anthocyanins and reduced cancers
- What forms are present in gut?
Grape Anthocyanins

1

2

3

4
Design

- Isolate anthocyanin mix from grapes
- Add to model large intestine: pig intestinal contents
  - Animal Science Department at UCD
- Observe loss of anthocyanins
- Observe formation of novel compounds-UV active
Observed Metabolites

- MeGal was prepared by synthesis from methyl gallate
Anthocyanin Gut Metabolism

Anticancer Effects of Metabolites

- Metabolites reduce cancer cell growth and induce apoptosis
- Mechanism of these actions under study

Forester et al, JAFC 58: 5320 (2010)
Increased Vascular Dilation

- Helmut Sies
- Methylated epicatechin inhibits superoxide production
- Vascular NO levels higher in presence of epicatechin in HUVEC’s
- No direct superoxide (ROS) scavenging
Proanthocyanidins Inhibit NFκB Activity

- Not caused by ROS capture
- Specific binding to NFκB protein, blocking DNA binding site
- Results in lower inflammatory response
Wine/Alcohol Limit NFκB Activation

- 5 Days, high fat diet, X-over
- NFκB is a key inflammatory control factor
- Blanco-Colio, Atherosclerosis 2007;192:335
Effects of Anthocyanin Metabolites?

- Mechanisms related to
  - Cell Proliferation
  - Apoptosis
Effect on Cell Proliferation Related Protein

- Inhibition of Antiapoptotic c-IAP2
Effect on Cell Cancer Proliferation and Survival

- Inhibition of NF-κB

![Graph showing band intensity for Control, Megal, Gal, and THBA]
Conclusions

- Wine phenolics are not direct antioxidants
- Activity arises from direct interaction with control pathways
- Impact on inflammatory pathways likely to explain effects
Recent Reports on Wine and Health

- Wine vs. other alcohol
- Effect of consumption pattern
- Risk of abuse

- International Scientific Forum on Alcohol Research
  - Ongoing review of published work
  - http://www.bu.edu/alcohol-forum/
All Cause Mortality vs. Wine/Other

- No wine •
- Wine ▲

Morten Grønbæk, Ann Intern Med. 2000; 133: 411
Consumption Patterns


**Figure 2** Wine consumption according to the day of the week for France and Northern Ireland. Results obtained from the subjects consuming at least one unit per week, and expressed in milliliters of ethanol per day.

**Figure 3** Beer consumption according to the day of the week for France and Northern Ireland. Results obtained from the subjects consuming at least one unit per week, and expressed in milliliters of ethanol per day.
Figure 2  Meta-regression of dose–response relation between weekly alcohol intake and relative risk (and the corresponding 95% confidence bands) of coronary heart disease in regular and irregular drinkers.

Bagnardi V et al, J Epidemiol Community Health 2008;62:615
Hazard Ratio for Alcohol Abuse

Men


Figure 2. Risk of alcohol-use disorder for men according to percentage of wine in total alcohol intake and according to total alcohol intake. Hazard ratios (HRs) are set to 1.0 among nondrinkers and are adjusted for smoking, cohabiting status, income, and education.
Marketing Healthy Living?

PEARLS BEFORE SWINE

WELL, RAT, I'M AFRAID YOU HAVE HIGH BLOOD PRESSURE AND HIGH CHOLESTEROL.

SO WHAT DOES THAT MEAN?

IT MEANS YOU NEED TO CUT OUT THE JUNK FOOD, THE SMOKING AND THE DRINKING... AND NO MORE BEING A COUCH POTATO.

BY STEPHAN PASTIS

... FROM NOW ON, YOU'LL NEED TO EAT A LOT OF GREEN VEGETABLES, LIKE BROCCOLI, AND YOU'VE GOT TO GET OUT AND RUN AT LEAST FOUR TIMES A WEEK.

AND IF I DO ALL THAT, WHAT'LL HAPPEN?

YOU'LL LIVE MANY MORE YEARS.

DURING WHICH I CAN EAT MORE BROCCOLI AND RUN EVEN MORE?

YOU BET.

... WELL THAT WAS A NO-BRainer.

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