Wine and Health

- factors involved in data interpretation
- major compounds implicated
- positive health influences
- negative health influences

Its relationship with health is contentious, being associated with:

- **religious bias (alcohol is 'evil')**
- **business bias (spawning disbelief/conspiracy theories)**
- **societal concerns (drunkenness)**
- **personal health & behavior concerns**
- **correlation conundrum(causal vs. incidental)**
- **the "one solution fits all" error**

leading to

- **claims and counter-claims**
  - **based on insufficient and/or conflicting data**
  - **typically focused only on ethanol**

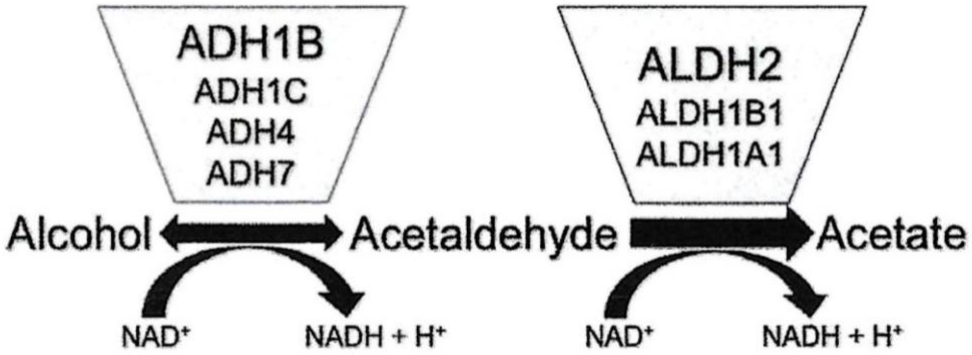
&

- **based on imprecise epidemiological data, explained with results from tissue culture studies using single chemicals**

Dubious Data Interpretation by Ignoring:

- **individual variation in:**
  - **ethanol metabolism**
    - **several enzymes and isoforms of both alcohol (ADH) and aldehyde (ALDH) dehydrogenases**
    - **substrate and tissue specificity**
      - **circadian production/elimination**

Figure 1 Primary alcohol metabolism
From Edenberg & McClintick 2018



  - **gender, BMI, weight**
  - **health**

- psychology

• cultural variation:

- ethnicity

- education

- wealth

- nutrition

• consumption variation

- amount, frequency, alcohol content, matric compounds, context (alone vs group; with food - timing)

• self-reporting is unreliable

• '*paper trail*' – connecting intake, uptake, survival, mechanistic action through to ➛ ➛ ➛ decade-long epidemiological studies

- **ideally double-blind experiments (ethically unacceptable)**
- **ignoring these can result in dogmatic conclusions based on:**
  - **combining data derived under diverse conditions**
  - **focusing only on a single health concern (e.g., cancer)**
  - **focusing on single constituent (e.g., ethanol)**

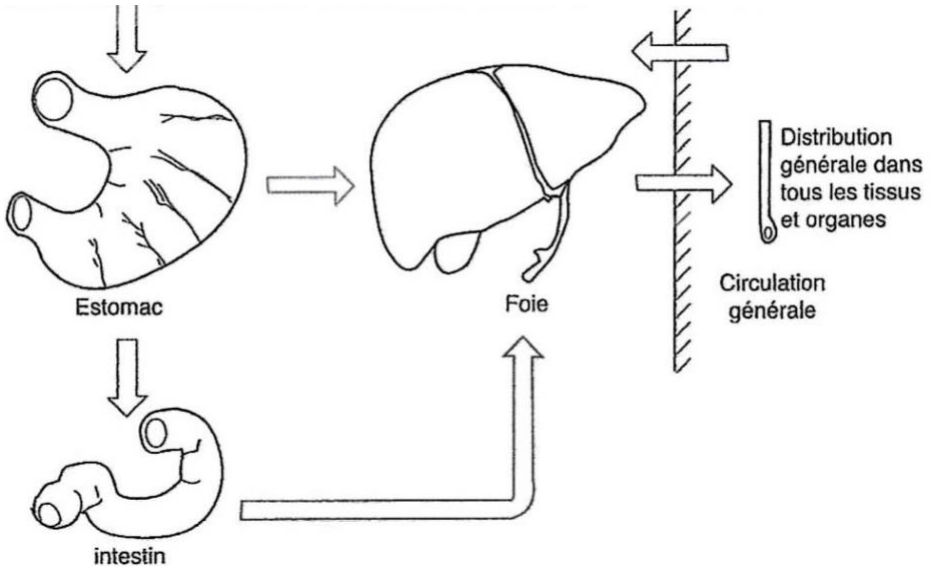
leading to

- **conflicting public statements, spawning distrust of government/science pronouncements**
  (e.g., fat vs. sugar, butter vs. margarine, baby aspirin, vitamin D)
- **are scare tactics, due to alcohol consumption's potential negative effects, justifiable?**

- **least likely to affect the behavior of those for whom it is needed**

Ethanol metabolism

Figure 2 *from Kaltenbach M., et al., 2001.*



- **some stomach metabolism**
- **absorption via the small intestine (duodenum)**
- **passes to the liver, where ~90% of metabolism occurs**

ethanol ➛ acetaldehyde ➛ acetic acid

respired (Krebs Cycle) **or stored as fat (liver)**

- **remainder: metabolized in the liver (via systemic blood rerouting), absorption (by tissue), evaporates (via the lungs), excreted (via the kidneys)**

- **alternative metabolism via CYP450 2E1 (at elevated ethanol contents) → toxic ROS (reactive oxygen) radicals**

Figure 3 *From Pavlic et al 2007*

• **metabolic rate relatively constant** BAC blood alcohol BrAC breath alcohol

• **as noted, marked individual and ethnic variation in isoenzyme and tissue differences**

thus

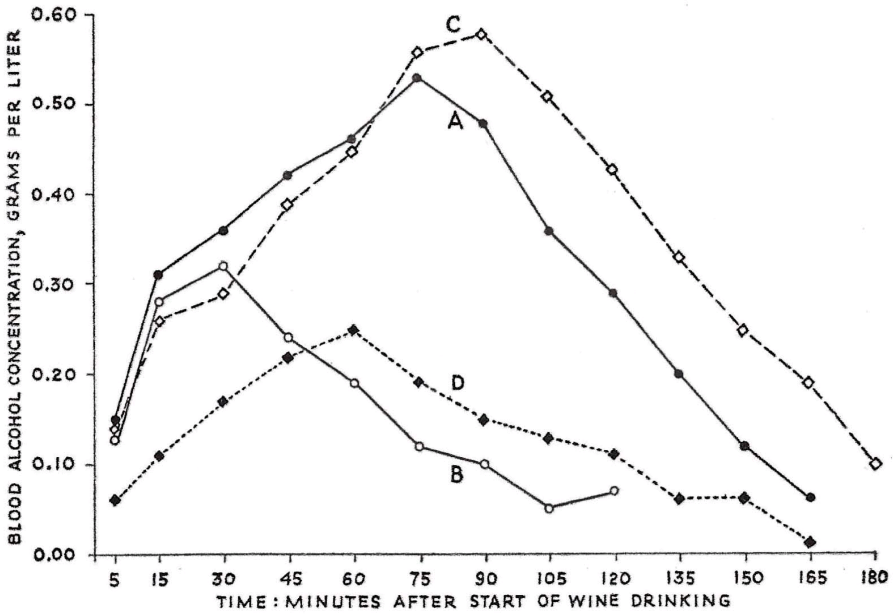
• **significantly affect alcohol and acetaldehyde levels (with the same intake)**

affecting

• **affect health potential and risk**

• **e.g., rapid ADH and slow ALDH reduces alcoholism risk, but increases that of breast, throat and GI tract cancers**

Figures 4 *From Serianni et al 1953*



- **consumption with food delays transfer to intestine**
- **significantly lowers blood alcohol content**

A, C: fasting 3 vs 6 doses; B, D: meal 3vs 6 doses

young men (70–82 kg; 0.5g/kg EtOH; 11% wine (~ 400 ml),
meal of 1898 kcal (beef, spaghetti, potatoes)

- **enhanced metabolism by increased blood flow & mitochondrial oxygen uptake**

- **fructose (in wine) increases NAD^+ required for ethanol metabolism**

Figure 5 *From Kaltenbach et al 2001*

- **ethanol readily diffuses into muscle cells**
- **poorly into fatty tissue**
- **men's higher muscle mass means lower BAC than women**

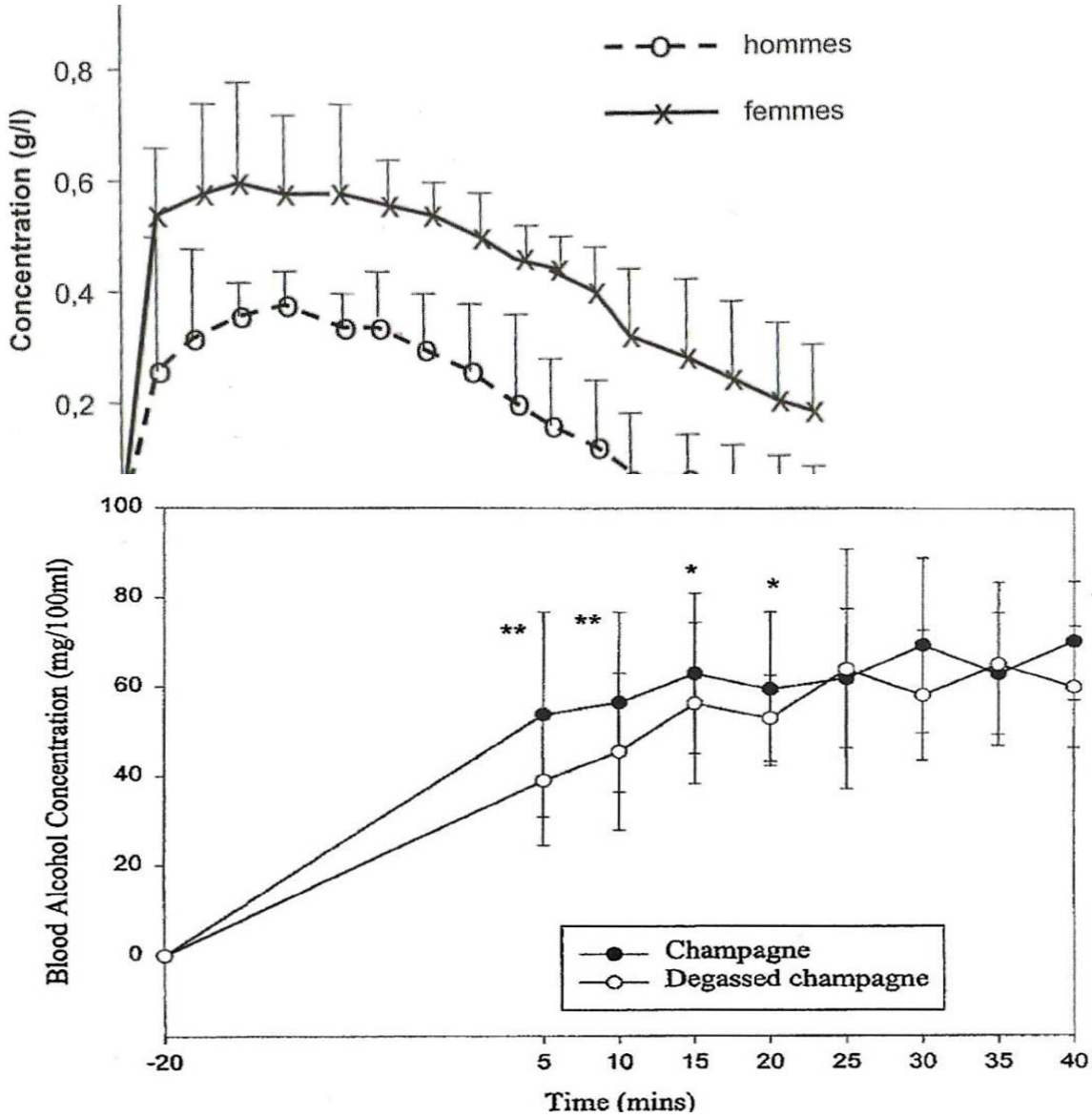


Figure 6 *From Ridout et al 2003*

- **CO_2 marginally speeds emptying of stomach contents into the small intestines**

Various Influences of Ethanol (& Wine)

- **ethanol displaces water, potentially causing cellular dehydration, and thereby disrupting cell function**

- **suppresses vasopressin production (increasing urination)**

- **retards nerve function (e.g., muscle weakness, slower response time, relaxed social inhibitions, drowsiness)**

- **nutrient supply (7.1 kcal/g) vs. carbohydrates (4.1 kcal/g)**

- **moderate source of some B vitamins and some minerals (e.g., K and Fe) and facilitating bioabsorption**

- **promotes saliva and gastric juice production**

Figure 7 *From Klein and Pittman, 1990b*

- **slows stomach emptying**
- **promotes bile release**

and wine

- **suppresses ulceration & adenocarcinoma**

- **favors beneficial gut flora**

- **improves appetite (i.e., the elderly)**

- **has positive social image**

Epidemiological Health Findings

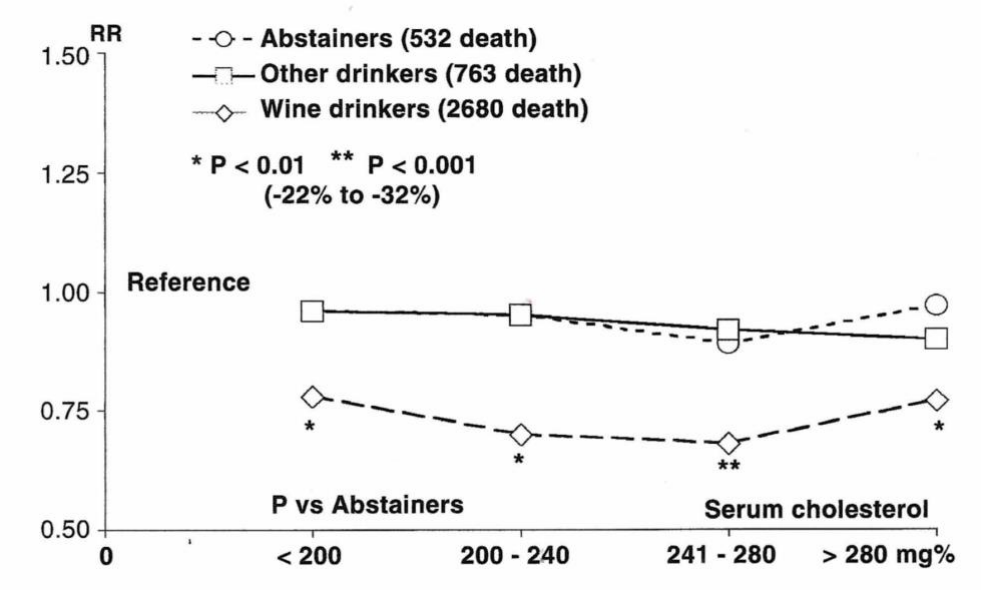


Figure 8 *From Renaud et al., 2004.*
(**J-shaped relative mortality vs. glasses of wine/day**)

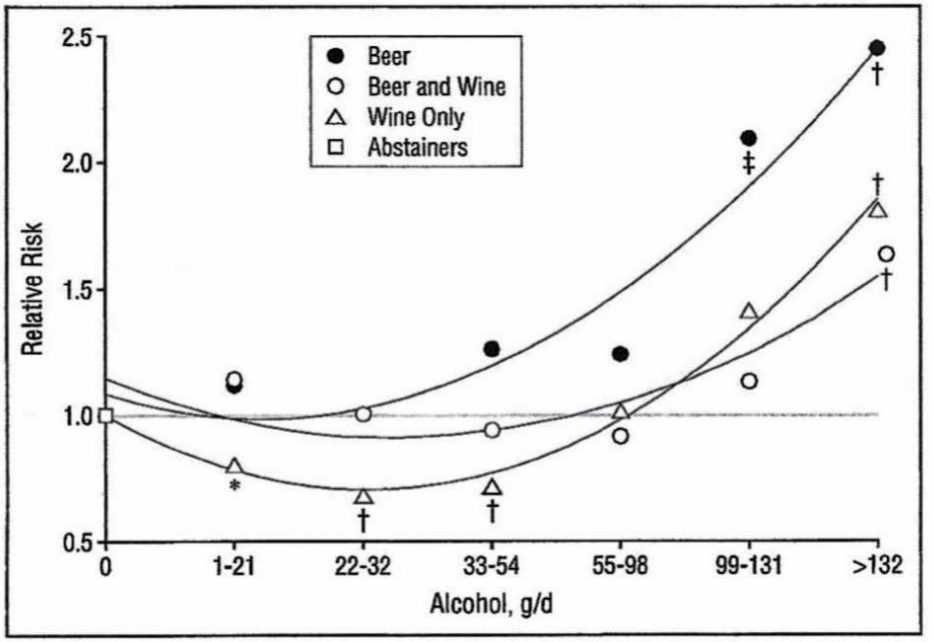


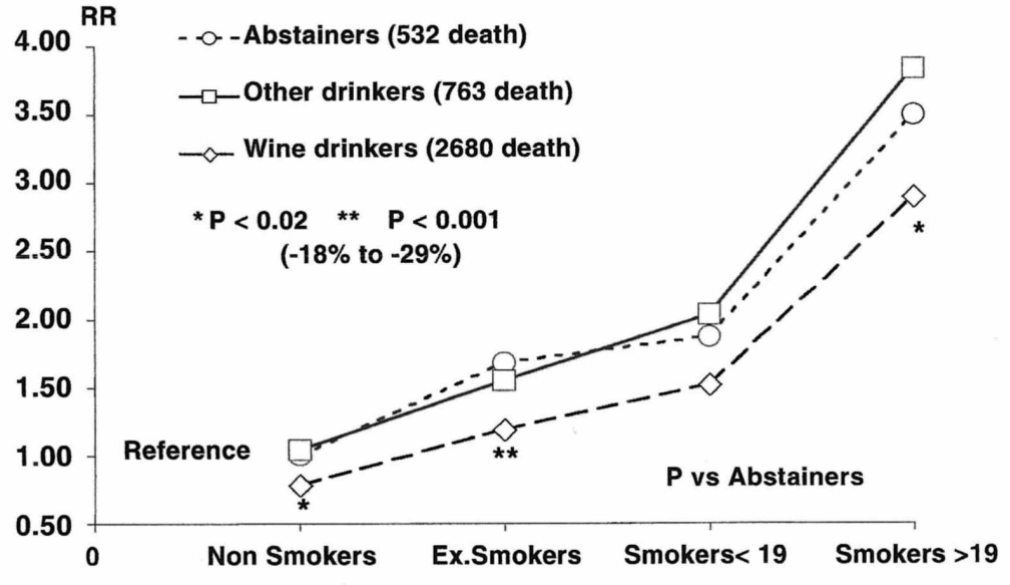
Figure 9 *From Renaud et al 1999.*

(**relative mortality vs alcohol source**)

Figure 10 *From Renaud et al 1999.*

(**relative mortality and cholesterol content**)

Figure 11 *From Renaud et al., 2004.*
(**relative mortality and smoking**)



Phenolics and Bioavailability

• most positive interpretations based on wine's phenolics, *but* which is involved?

e.g. monomeric flavonoids, non-flavonoids, stilbenes, lingans, their polymers (tannins); oxidation, sulfation and degradation products; complexes with cellular constituents

• relative concentration and combination can produce complementary as well as antagonistic influences

• benefits explained in terms of:

antioxidant, anti-inflammatory, anti-mutagenic, and anti-carcinogenic influences

• lesser importance has been placed on antimicrobial effects

Figure 12 *From van Duynhoven, et al., 2011.*

Bioavailability

- ***monomer*** **absorption in the stomach and small intestine**

- ***polymer*** **degradation ➛ absorption in colon**

- **sulfur, methyl, or sugars conjugation increases solubility (reduces biological activity)** ***phase I metabolism***

- ***phase II metabolism*** **further ↑ solubility, facilitates cellular uptake & excretion via the kidneys ➛ low levels in circulation**

- **maintenance of benefits requires frequent replenishment**

Phenolic Effects

- **microbial benefits**
  - **favors desirable gut flora (e.g., *Bifidobacterium*, *Lactobacillus*)**
  - **suppression of pathogenic bacteria (gut and mouth)**
  - **promotes a protective mucus lining**
  - **improves immune function and mental health**

- **activates nerve differentiation, synaptic plasticity and survival**

- **possess anti-inflammatory, anti-cancer, antioxidant, cardioprotective, neuroprotective, and estrogenic effects**

- **e.g., resveratrol suppresses oxidative pathways (e.g., CYP450 that can be mutagenic, carcinogenic, pro-inflammatory)**

Potential Health Benefits of Moderate Wine Consumption

- **reduced incidence of:**
  - **intestinal biome issues**
  - **cardiovascular disease**
  - **neurodegenerative diseases**
  - **macular degeneration**
  - **osteoporosis**
  - **diabetes**
  - **kidney stones**

- **presumed mechanism(s), one or more of**:
  - **antioxidant**
  - **anti-microbial**
  - **anti-inflammatory**
  - **anti-carcinogenic**

• **neuroprotective**

Antioxidant Effects

• **phenolic plasma contents low, *but* trace amounts activate cellular pathways (e.g., limiting LDL peroxidation)**

• **many phenolics actively quench ROS (e.g., H_2O_2, superoxide, and hydroxyl radicals) *and* chelate their metal catalysts**

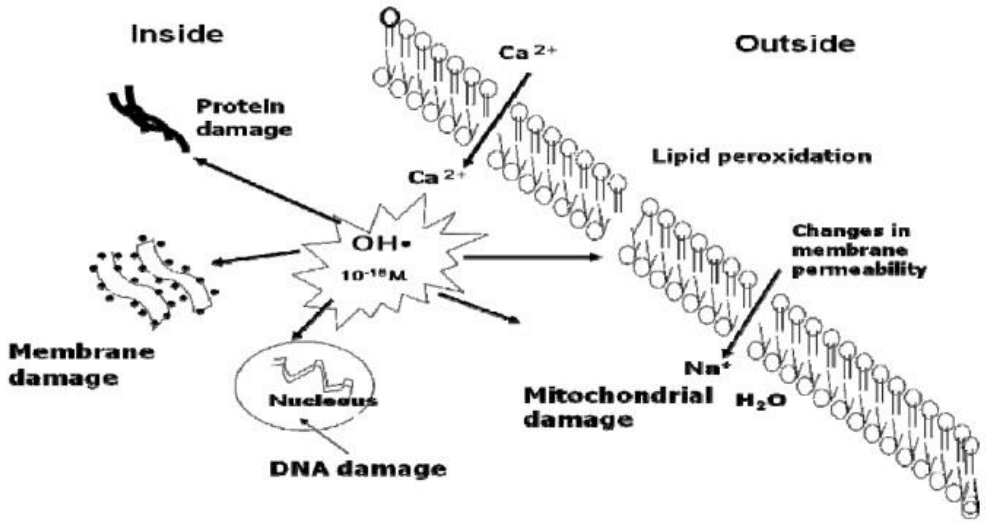


Figure 13 *From Repetto et al 2012*

• **reduces membrane damage and synthesis of pro-inflammatory leukotrines**

• **ethanol favors hydroxyltyrosol synthesis – an antioxidant & anti-inflammatory**

Antimicrobial Effects

- **reduces incidence of intestinal infections**

- **wine's ethanol content is bacteriostatic, *becoming* bactericidal in the stomach (with longer contact time)**

- **wine's phenolic and acidic contents can be bacteriocidal**: e.g.,
  - ***e.g.*, *p*-coumaric suppresses pathogenic *Staphylococcus* & *Streptococcus***
  - **e.g., quercetin suppresses *E. coli*, *Shigella*, *Proteus*, *Vibrio***

- **culture plate studies, confirm these effects under simulated gastrointestinal conditions**

Cardiovascular Diseases

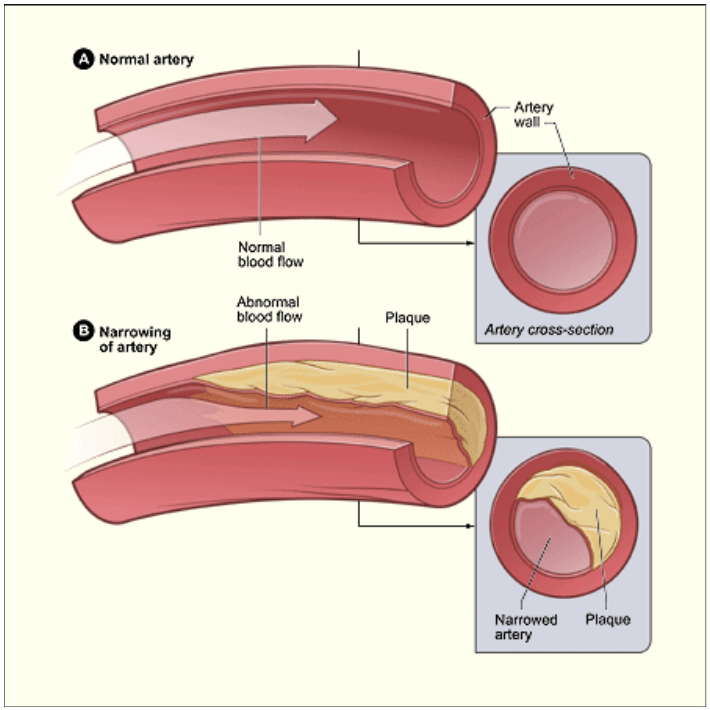


Figure 14 *From National Institute of Health (USA) web site*

• most damage associated with plaque formation

Beneficial actions:

• *ethanol*

- augments "good" (HDL) and reduce "bad" (LDL) cholesterol levels

- removes and limits LDL oxidation and vessel inflammation

- acts as a mild anticoagulant ("blood thinner")

- increases nitric oxide & endothelin production

- activates the anti-inflammatory hormone GIP-1

- ***phenolics***

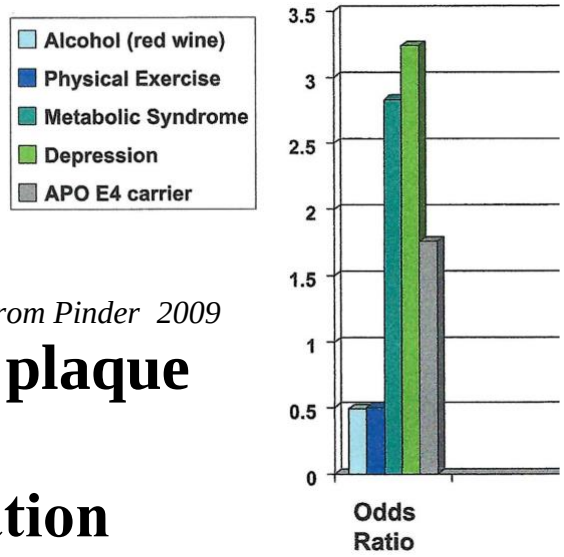
  ↓initiation, progression and rupture of arterial plaque

  ***e.g.*, resveratrol ↓ triglyceride and LCL blood levels**

  ↑nitric oxide production ➛ vasodilation,
  retards platelet aggregation

  e.g., quercetin ↓ blood pressure, antioxidant

Neurodegeneration



- **J-shaped curve relative to dementia (notably Alzheimer's disease)**

Figure 15 (1 = overall risk of dementia) *From Pinder 2009*

- **hydrolyzable tannin reduces β-amyloid plaque formation**
- **resveratrol promotes plaque destabilization**
- **maintains good blood supply**
- **maintains hippocampus function**
- **antibacterial action against *Prophyromonas gingivalis***

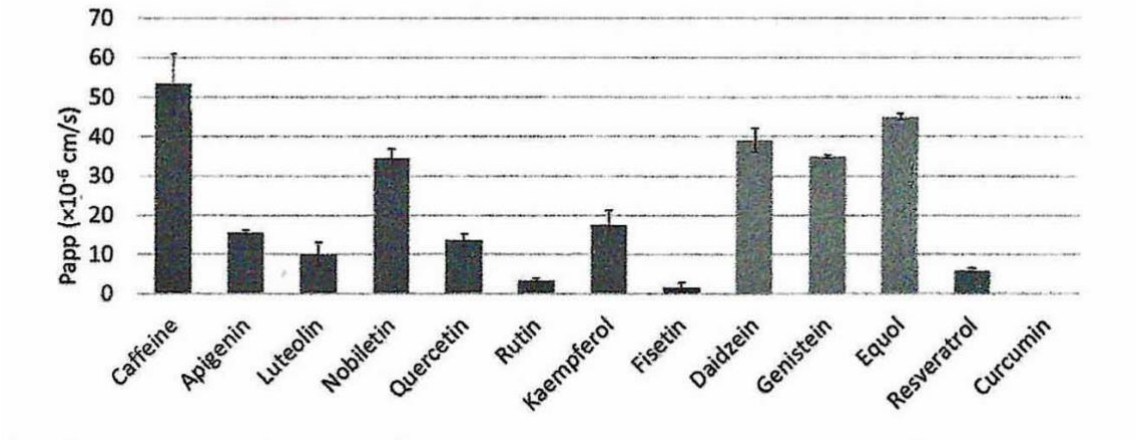


Figure16 (right) *From Shimazu et al 2021* (blood-brain barrier penetration)

Arthritis

- **reduced drug irritation of the stomach**
- **diuretic action reduces joint swelling**
- **muscle relaxation diminishes muscle spasms and stiffness**
- **resveratol limits pro-inflammatory cytokine production**

Diabetes

attenuates Type 2

- **ethanol retards carbohydrate digestion, slows sugar uptake**
- **↓ insulin resistance & blood-glucose levels**
- **↑GIP-1 (glucose-dependent insulinotropic peptide)**

ameliorates Type 1

- **wine's fructose does not activate insulin release**
- **wine's antioxidants slow the progressive kidney failure**

Macular Degeneration

- **frequent J-shaped curve between wine consumption and incidence of macular degeneration**
- **presumably due to reduced retinal atherosclerosis and it reducing O_2 and nutrient access**

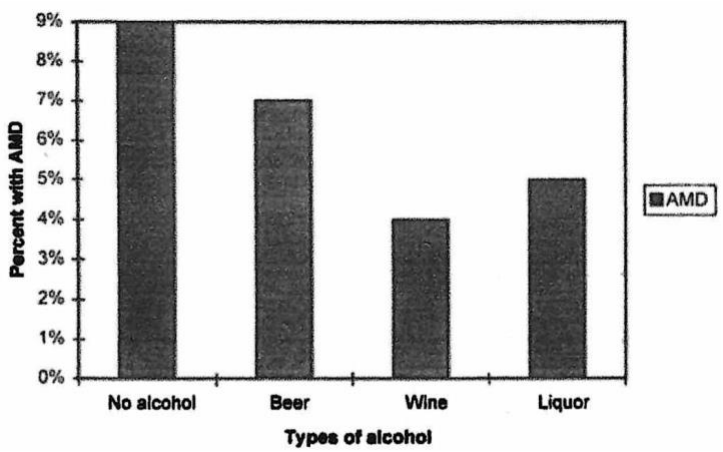


Figure 17 *From Obisesan et al 1998*

Osteoporosis

- **moderate alcohol consumption (notably as wine) is associated with improved calcium retention in bone**
- **may be associated with the phytoestrogen effects of some phenols (e.g., resveratrol and kaempferol)**

Potential Negative Outcomes of Moderate Wine Consumption

- **carcinogenesis**
- **allergic/hypersensitive reactions**
- **headache**
- **dental erosion**
- **contraindications**
- **medication interactions**
- **alcoholism, fetal alcohol syndrome**

Carcinogenesis

- **variable correlations:**
  - **reduced (kidney and lymphoma)**
  - **increased (breast, throat, stomach)**
  - **none (prostrate)**
  - **in alcoholics (liver)**

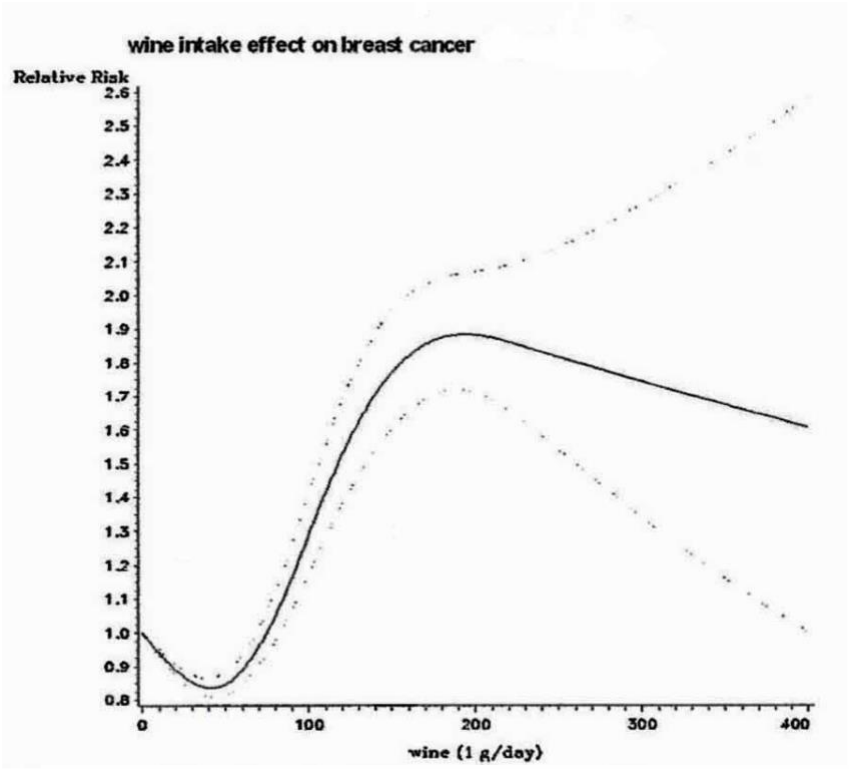


Figure 18 *From Chen et al 2016*

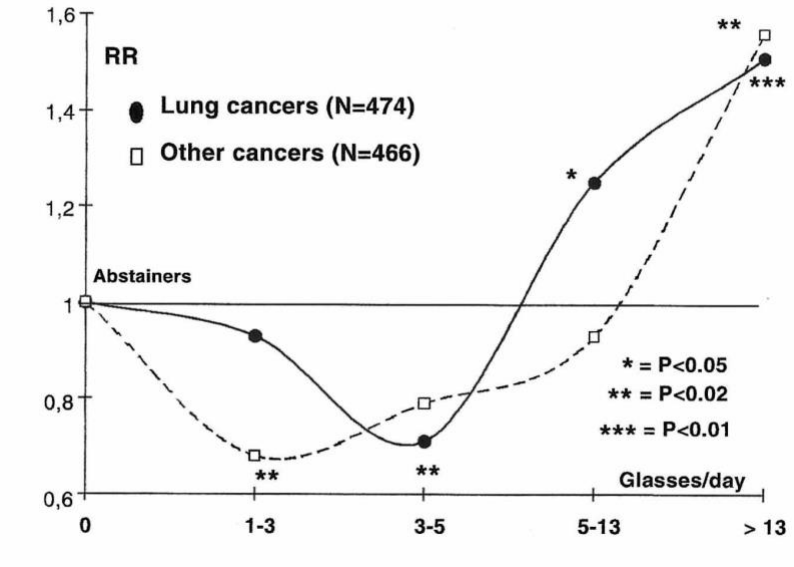


Figure 19 *From Renaud et al 2004*

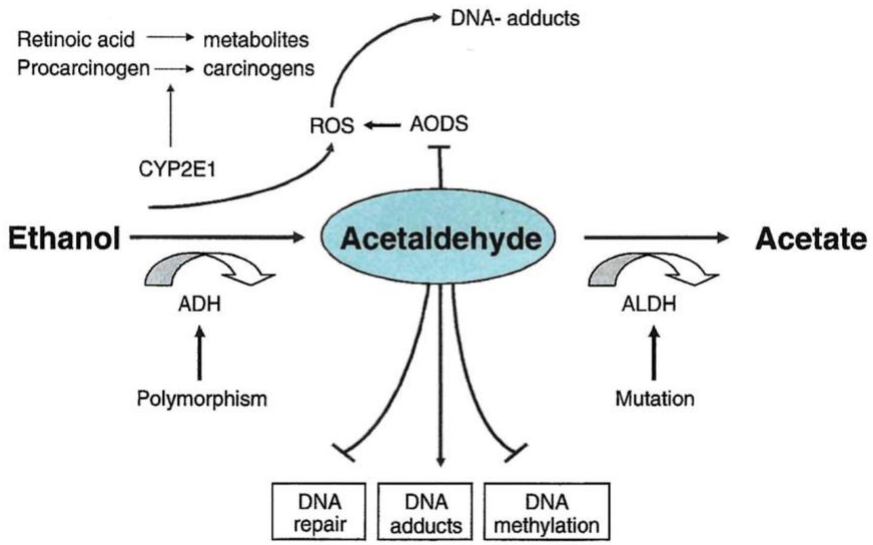
- **studies often J-shaped *and* contradictory**

- **ethanol itself is neither mutagenic or carcinogenic**

• **negative effects likely due to acetaldehyde accumulation— a known carcinogen**

• **individual differences in ADH and ALDH enzyme production, can lead to significant differences in acetaldehyde accumulation**

Figure 20 *From Seitz & Stickel 2010*



***i)acetaldehyde damage*:**

- depletes glutathione

- bonds with proteins & nucleic acid ➛mutagenic & carcinogenic effects

- bond with lipids, disrupting cell and nerve function

***ii) CYP4502E1* ethanol metabolism (*under* high ethanol**

concentrations) ➛ produces reactive oxygen radicals (ROS)

• these cause lipid peroxidation, protein and nucleic acid denaturation, oncogene activation

• *other potential carcinogens*

from grapes

- quercetin (*in vitro* cell culture, *but* anti-cancer *in vivo*)

from diseased grapes

- ochratoxin A

- aflatoxin

- fumonisin B2

- ochratoxin A

- patulin

via fermentation

- ethyl carbamate

Allergies and Hypersensitivities

• potential causes:

a) acetaldehyde –from wine (fino sherries) or inactive ADH & ALDH isozymes) ↑histamine (mast cells) ➛ ➛ flushing, etc.

b) fining agents and PR proteins ➛➛ hives, welts

c) SO_2 ➛➛ bronchial constriction

• variable responses caused by

- cyclical changes in sulfite oxidase & glutathione *S*-transferase

- oddly more associated with red wines (those lowest in SO_2)

Figure 21 *From Peterson et al 2000*

Gout

- **caused by uric acid accumulation in the joints**

- **historically associated with port consumption (etc.)**
  - **former's storage in lead crystal decanters (up to 25% lead); served in pewter vessels(up to 30% lead); use of lead-glazed dinner ware**
  - **wine acidity effectively dissolves lead**

- **recurrent gout can be correlated with alcohol intake (and much else, such as red meat, fructose, etc.)**

- **former use of tin-lead bottle caps not implicated**

Headache

• common deterrent to wine consumption (notably red wines)

• migraine — *potential* causes:

ethanol - disruption of cerebral glucose metabolism
- cerebral acetaldehyde and ROS generation
- increases GI tract permeability to histamine

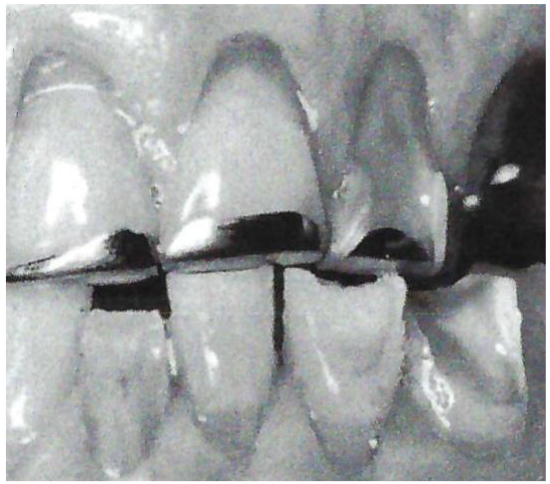
phenols - suppress platelet PST ➛ increases brain uptake & induces prostaglandin production
- restrict access to μ-opinoid receptors
- quercetin inhibits ALDH ↑acetaldehyde

• causes of other headache phenomenon (cluster, red head, red wine headaches) unknown

• hangover- dehydration, electrolyte imbalance, cerebral inflammation (ethanol, acetaldehyde, ROS)

Dental Erosion

Figure 23 ***From Mulic et al 2011***



- **wine-taster - occupational hazard**

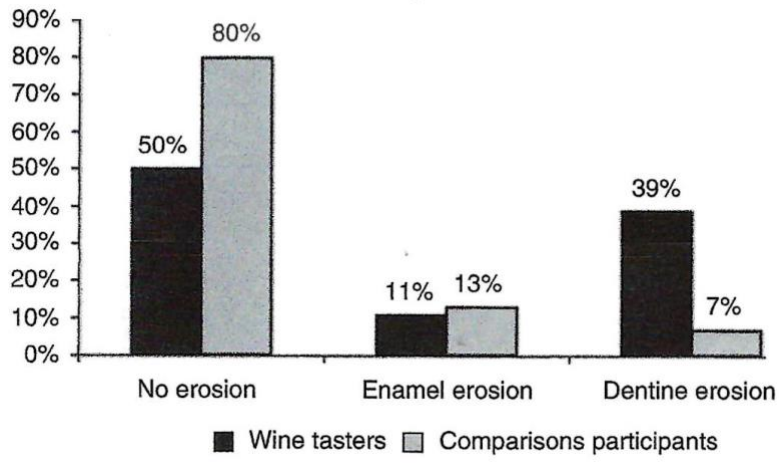
- **exposure to acids dissolves Ca in tooth enamel ➛ softening and loss ➛ exposure of the underlying dentine**

- **accentuates receding of the gums**

Figure 24 Mok et al 2001

- **avoided by delaying tooth cleaning (a hour after tasting)**

- **consumers avoid when consumed with food**



Interaction with Medications

- **ethanol can disrupt action of some medications: *e.g.***
  - **loss of muscle control with tricyclic antidepressants**
  - **disrupt action of MAO hypertension medications**
  - **increases prolonged Tylenol-induced kidney damage**
  - **complicates use of blood-thinners (e.g., Coumadin)**
  - **induction of ALDH enzymes ➛oxidation of some drugs**

- **phenolics can bind to➛ disrupt medication action**

- **similar influences as some foods**

e.g., grapefruit blocks intestinal CYP3A4 *(a Phase II metabolic enzyme degrading xenobiotics (e.g., medicines)*,

leading to

more uptake by the blood than anticipated

Contraindications

- **ethanol's anticoagulant action pre- and post-operation**
- **wine's acidity aggravates oral & stomach ulcers**
- **wine can aggravate acid reflux**
- **wine burdens diseased kidneys and livers with additional stress**
- **wine causes antabuse reactions when consumed with:**
  - **Inky cap (*Coprinus atramentarius*)**
  - **Lurid bolete (*Suillellus luridus*)**
- **family history of alcoholism or other addictions**

CONCLUSION

• moderate wine consumption can have both positive and negative health consequences individually, but their combined influences may be neutral population-wide, *but* is more sensorially enjoyable than teetotaling (to wine lovers)

• regrettably, it is easier to point blame for problems than confirm health benefits

• I leave you with the wisdom, and wit, of Mark Twain.

"The only way to keep your health is to eat what you don't want, drink what you don't like, and do what you'd druther not."

Figure citations

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Fig 14 National Institute of Health (USA) web site.

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