National Cancer Institute

Consumption of Fermented Beverages and their Influences on Health and Disease

Sharon Ross, PhD, MPH
rosssha@mail.nih.gov

Nutritional Science Research Group
Division of Cancer Prevention
National Cancer Institute
Bethesda, MD

Disclosures: No Relevant Financial Relationship to disclose.

Disclaimer: The views and opinions expressed in this presentation solely reflect my experience and perception and do not necessarily state or reflect those of the NCI, NIH, DHHS or U.S. Government.

Types of fermented beverages

Fermented beverages include those that utilize grains (beer, rice wine, maize-based beverages), fruit (wine), tea (kombucha), and milk products (fermented mare's milk, kefir).





Nigori, or unfiltered sake

https://en.wikipedia.org/wiki/Sake



Chicha de jora is a corn beer

https://en.wikipedia.org/wiki/Chicha_de_jora

Fermented (alcoholic) beverages from around the world

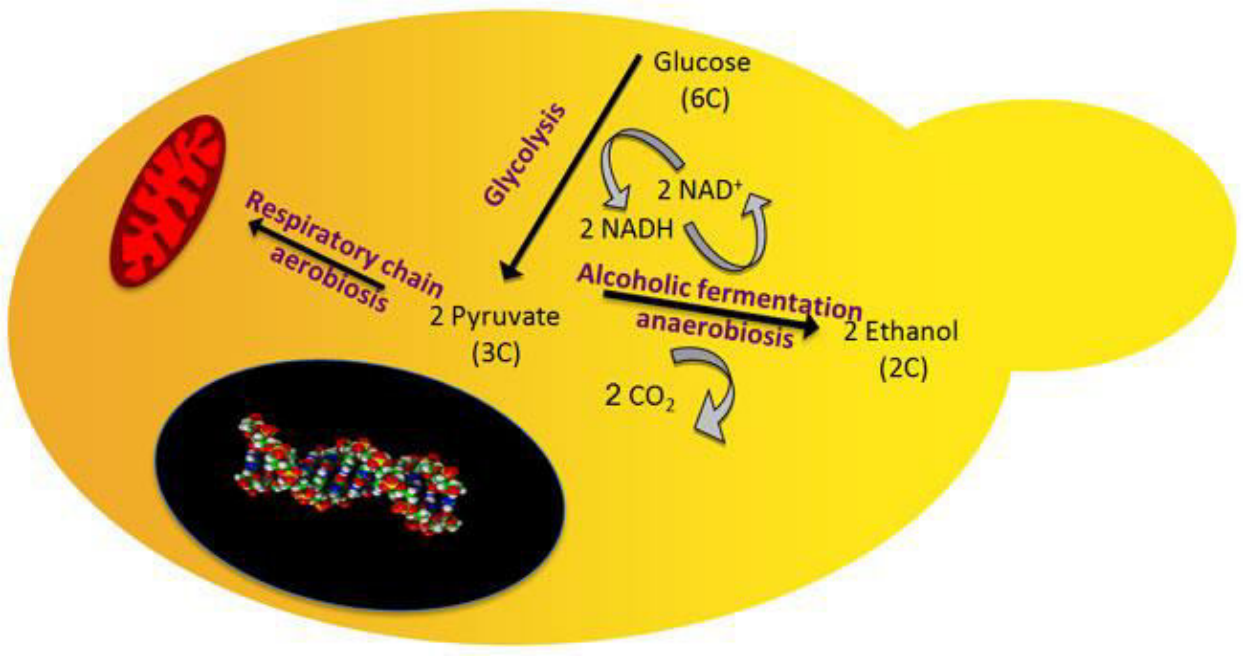
Marshall E & Mejia D. Traditional fermented food and beverages for improved livelihoods. Rural Infrastructure and Agro-Industries Division, Food and Agriculture Organization of the United Nations Rome 2011

Source	Name of fermented beverage	Name of distilled beverage
Barley	beer, ale	Scotch whisky
Rye	rye beer	rye whisky
Corn	corn beer	bourbon whiskey
Wheat	wheat beer	wheat whisky, Korn (Germany)
Rice	sake sonti	shochu (Japan), soja (Korea)
Juice of fruits, other than apples or pears	wine (most commonly thought of from grapes)	brandy, cognac (France), Branntwein (Germany), pisco (Peru/Chile)
Juice of apples	("hard") cider, apfelwein	applejack (or apple brandy), Calvados
Juice of pears	perry, or pear cider	pear brandy
Juice of sugar cane, or molasses	basi, betsa-betsa (regional)	rum, cachaça, aguardiente, guaro
Juice of agave	pulque	tequila, mezcal
Juice of plums	plum wine	slivovitz, tzuica, palinca
Pomace	pomace wine	grappa (Italy), Trester (Germany), marc (France)
Honey	mead	distilled mead ("mead brandy" or "honey brandy")
Potato and/or grain	potato beer	vodka: potato mostly used in Ukraine, otherwise grain
Milk	Kumis	Araka

Source: FAO.2011. Manufacturing fruit wines-a practical guide, by J. De La Cruz Medina & H.S. Garcia, Rome (Unpublished)

Alternative metabolic routes following glycolysis

Yeasts produce ethanol as the main fermentation product, and the main fermentation product of lactic acid bacteria is lactic acid. Fermentation by yeast is primarily an anaerobic process converting sugars, such as glucose, to other compounds like ethanol, while producing energy for the microorganism.



A budding yeast cell is shown with the aerobic and anaerobic metabolic pathways following glycolysis. The nucleus (black) and mitochondrion (red) are also shown.

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Drinking Data Shows U.S. at the Top by Volume, but Europe Dominates Per Capita - US News & World Report

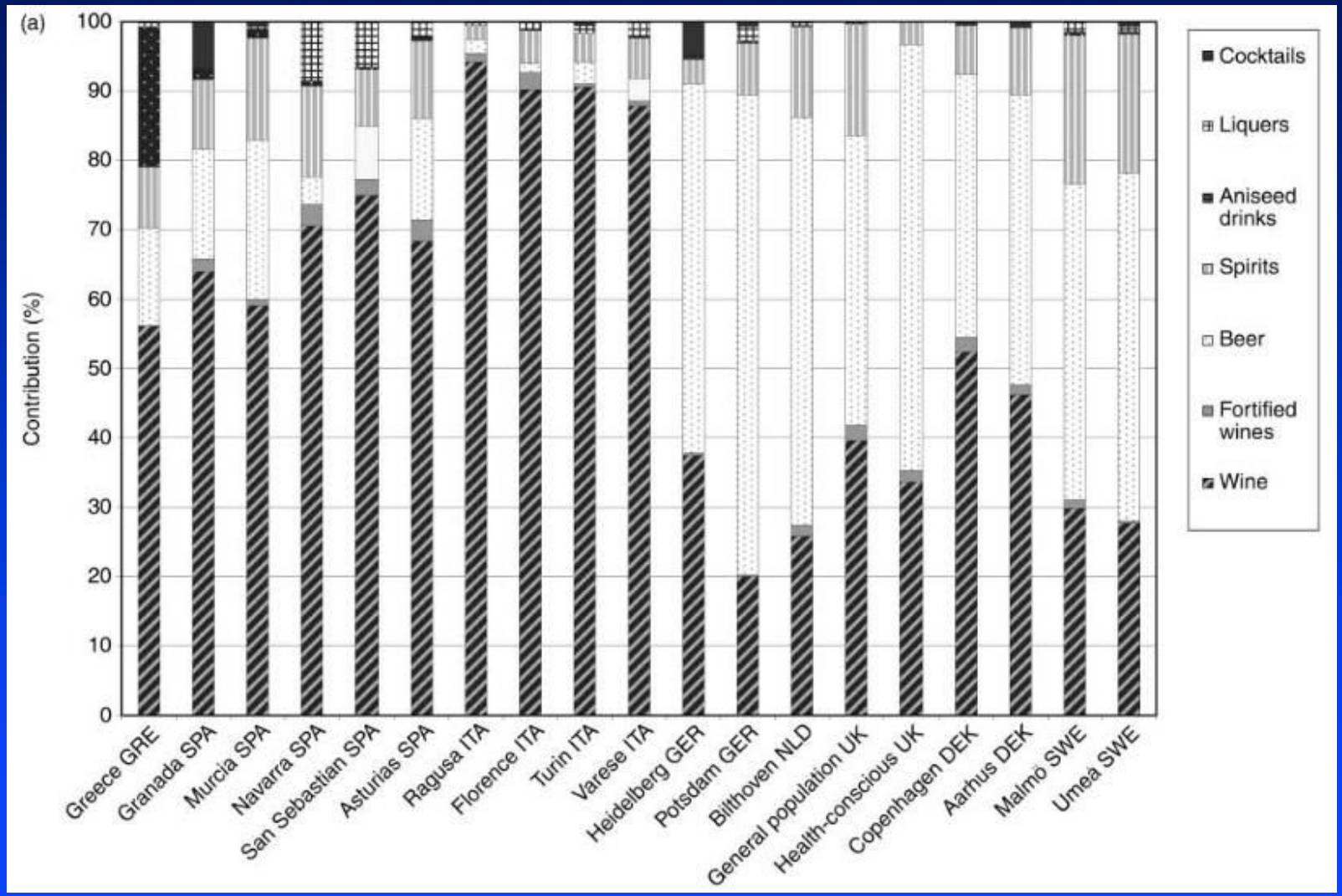
Findings Need Replication



comparecamp Author: Robin Renford Designed by: comparecamp.com Author: Chris Sibbet

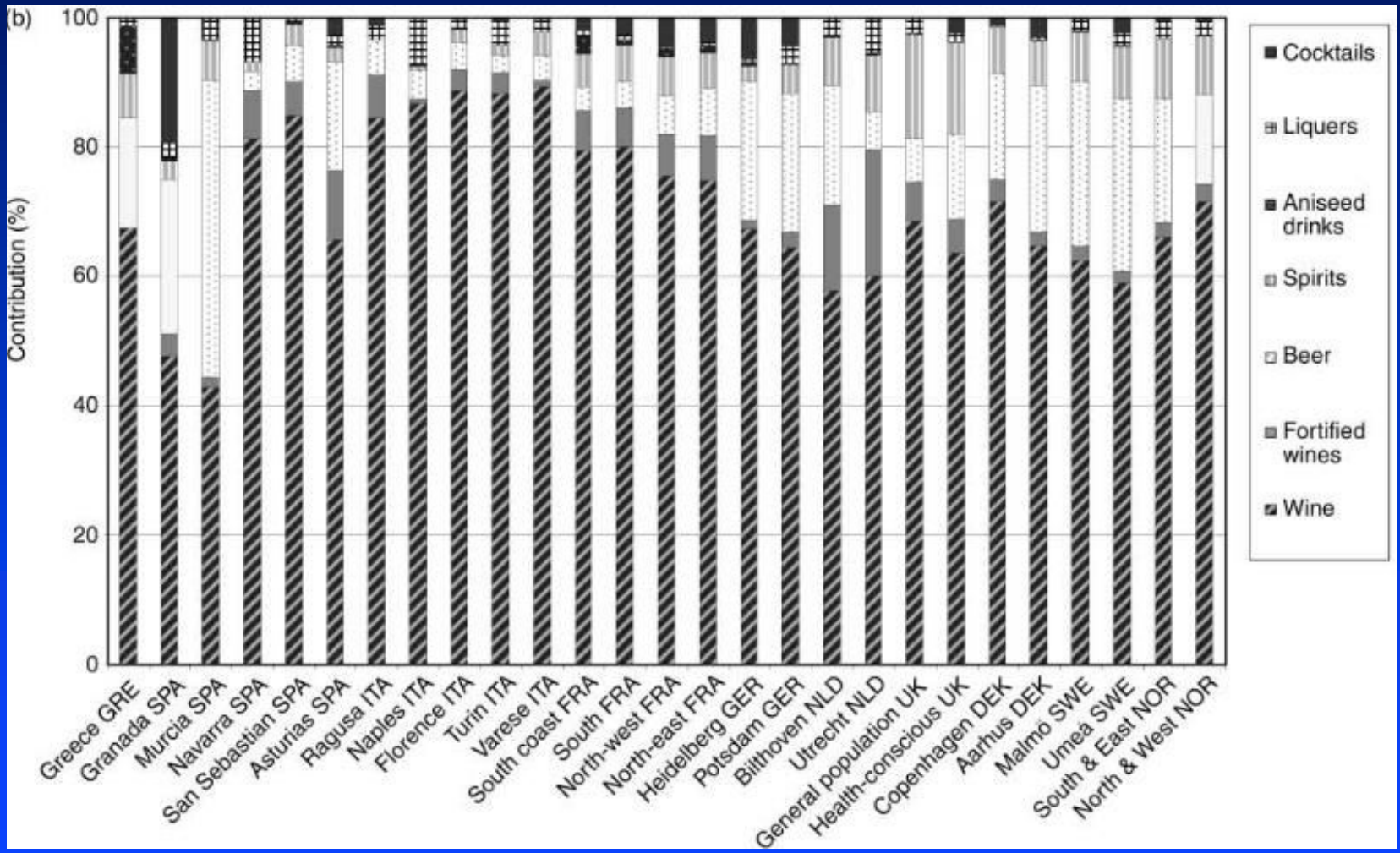
http://www.usnews.com/news/blogs/data-mine/2014/10/02/drinking-data-shows-us-at-the-top-by-volume-but-europe-dominates-per-capita

Main sources of alcohol intake for men by center in the European Prospective Investigation into Cancer and Nutrition (EPIC) project



Sieri S, et al. Public Health Nutr. 2002 Dec;5(6B):1287-96.

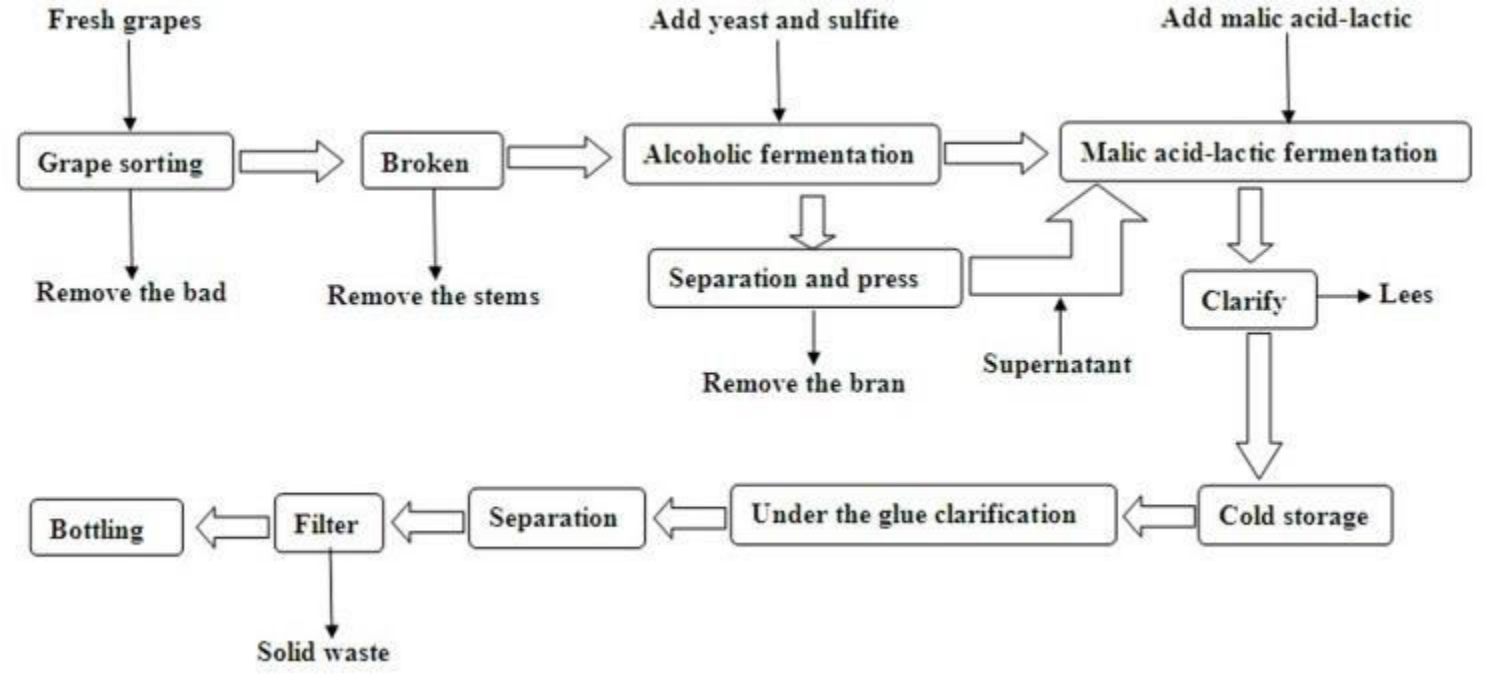
Main sources of alcohol intake for women by center in the European Prospective Investigation into Cancer and Nutrition (EPIC) project



Sieri S, et al. Public Health Nutr. 2002 Dec;5(6B):1287-96.

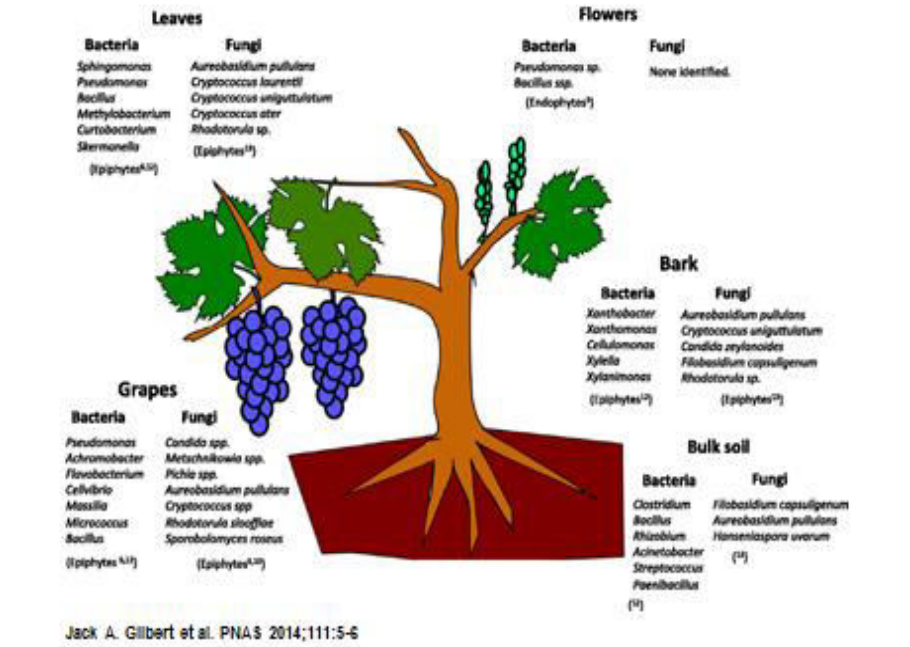
Wine making process schematic.

Saccharomyces cerevisiae



Wang R, et al. PLoS One. 2015; 10(2): e0116690.

Microbial terroir for wine grapes

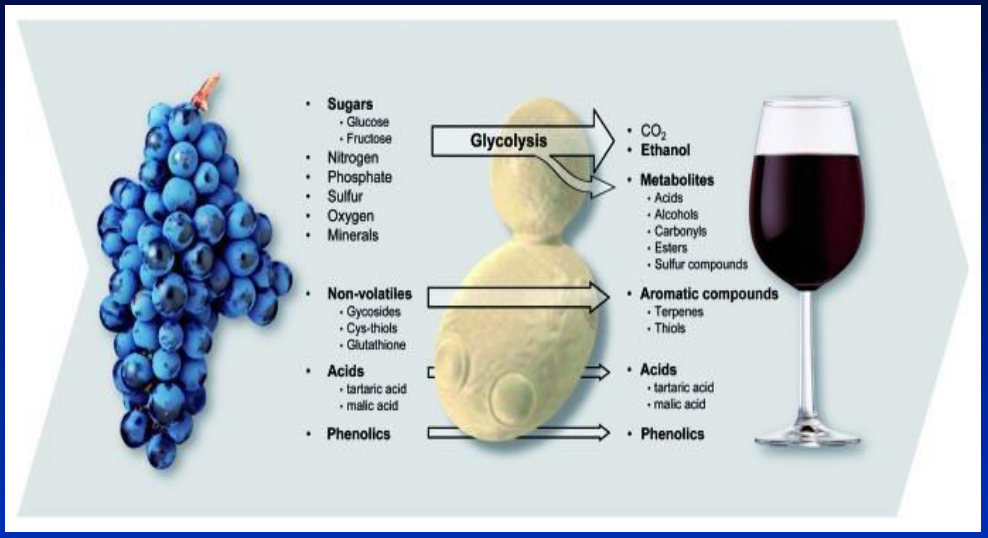


Significance

We demonstrate that grape-associated microbial biogeography is nonrandomly associated with regional, varietal, and climatic factors across multiscale viticultural zones. This poses a paradigm shift in our understanding of food and agricultural systems beyond grape and wine production, wherein patterning of whole microbial communities associated with agricultural products may associate with downstream quality characteristics. Elucidating the relationship between production region, climate, and microbial patterns may enhance biological control within these systems, improving the supply, consumer acceptance, and economic value of important agricultural commodities.

Nicholas A. Bokulich et al. PNAS 2014;111:E139-E148

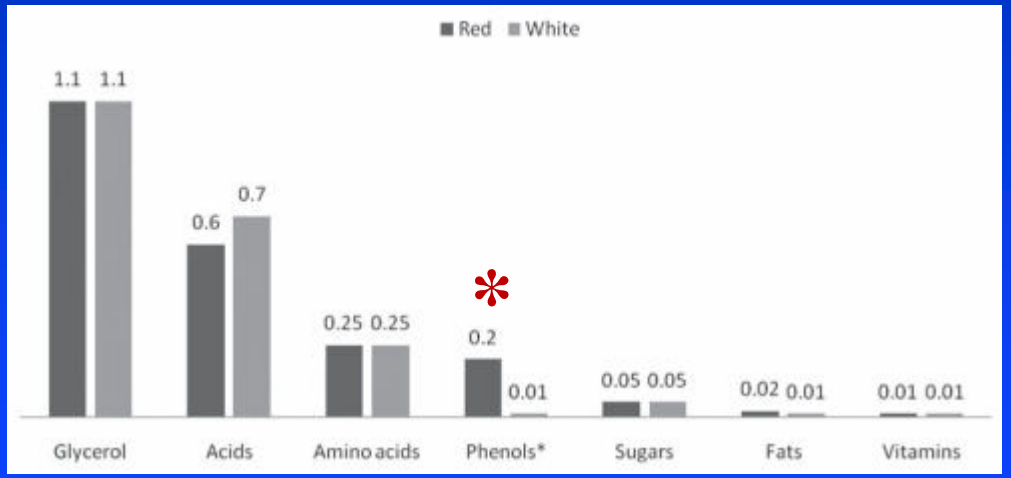
Components of Wine



Pretorius IS, et al. Bioeng Bugs. 2012 May 1; 3(3): 147–156.

Yeast is integral to crafting complex wines from simple, sugar-rich grape juice. Grape juice is converted into wine by the action of wine yeast. **Some wine components are wholly generated by yeast as part of metabolism while others are essentially created by the grapevine.** The large number of compounds synthesized or modified by wine yeast have a major impact on wine quality and style---**possibly also on health and disease**

Estimates of typical gross composition (percentage weight). *Phenols constitute the major compositional difference between red and white table wines. Water and ethanol content is similar for both types of wine (87% and 10%, respectively).



Cordova AC, et al., Int J Angiol. 2009 Autumn; 18(3): 111–117.

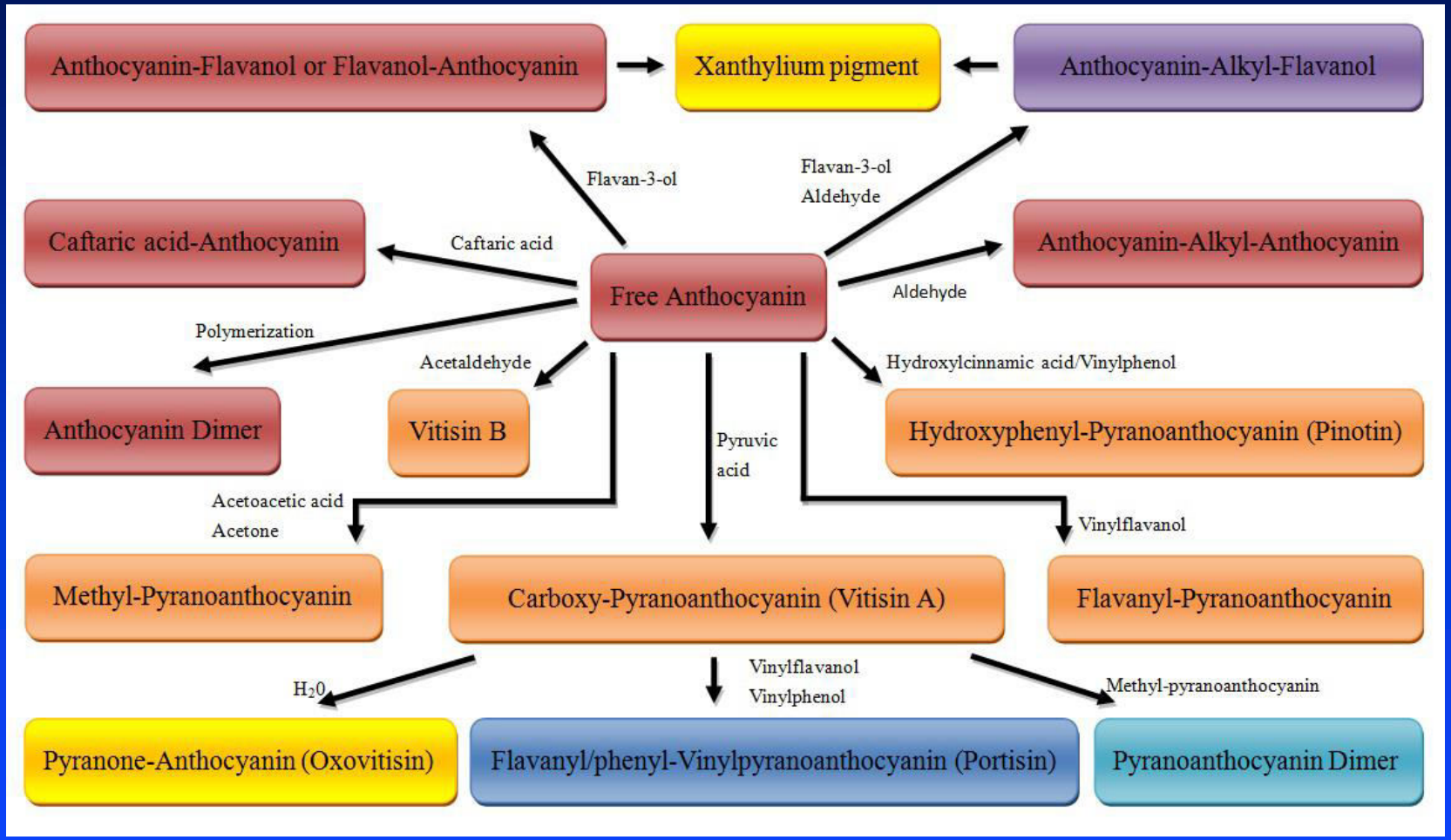
The phenolic content in wine

- Phenolic compounds in wine a large group of several hundred chemical compounds that affect the taste, color and mouthfeel of wine.
- These compounds include phenolic acids, stilbenoids, flavonols, dihydroflavonols, anthocyanins, flavanol monomers (catechins) and flavanol polymers (proanthocyanidins).
- Broadly separated into two categories, flavonoids and non-flavonoids.
- Flavonoids include the anthocyanins and tannins which contribute to the color and mouthfeel of the wine.
- The non-flavonoids include the stilbenoids such as resveratrol and phenolic acids such as benzoic, caffeic and cinnamic acids.

Garrido J & Fernanda Borges F. Food Res Intern. 54:1844-1858, 2013.

https://en.wikipedia.org/wiki/Phenolic_content_in_wine

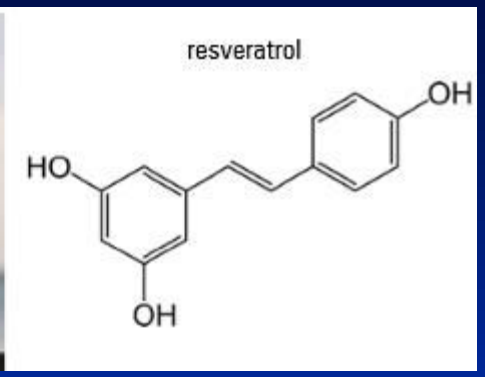
Evolution of anthocyanins in aged red wines



He F, et al. Molecules 2012, 17, 1483-1519;

Bioactive Phenolics in Wine





Rossi T, et al. Pol Arch Med Wewn. 2014;124(12):713-22

Analysis of red wine originating from diverse countries show variation in ranges of resveratrol concentrations of up to 6.8 mg/ L.

Wenzel E & Somoza V. Mol Nutr Food Res. 2005 May;49(5):472-81.

Biological Response to Resveratrol:

The lower end of supplementation tends to be for cardiovascular health, insulin sensitivity, and longevity for individuals who are otherwise unhealthy is 5-10 mg daily. For persons who are otherwise healthy, dosages between the range of 150-445 mg have been used (with no clear indication for what is the optimal dose).

Supplementing for cerebral blood flow requires a dose in the 250-500mg range whereas supplementation for aromatase inhibition requires 500 mg as well.

http://examine.com/supplements/Resveratrol/

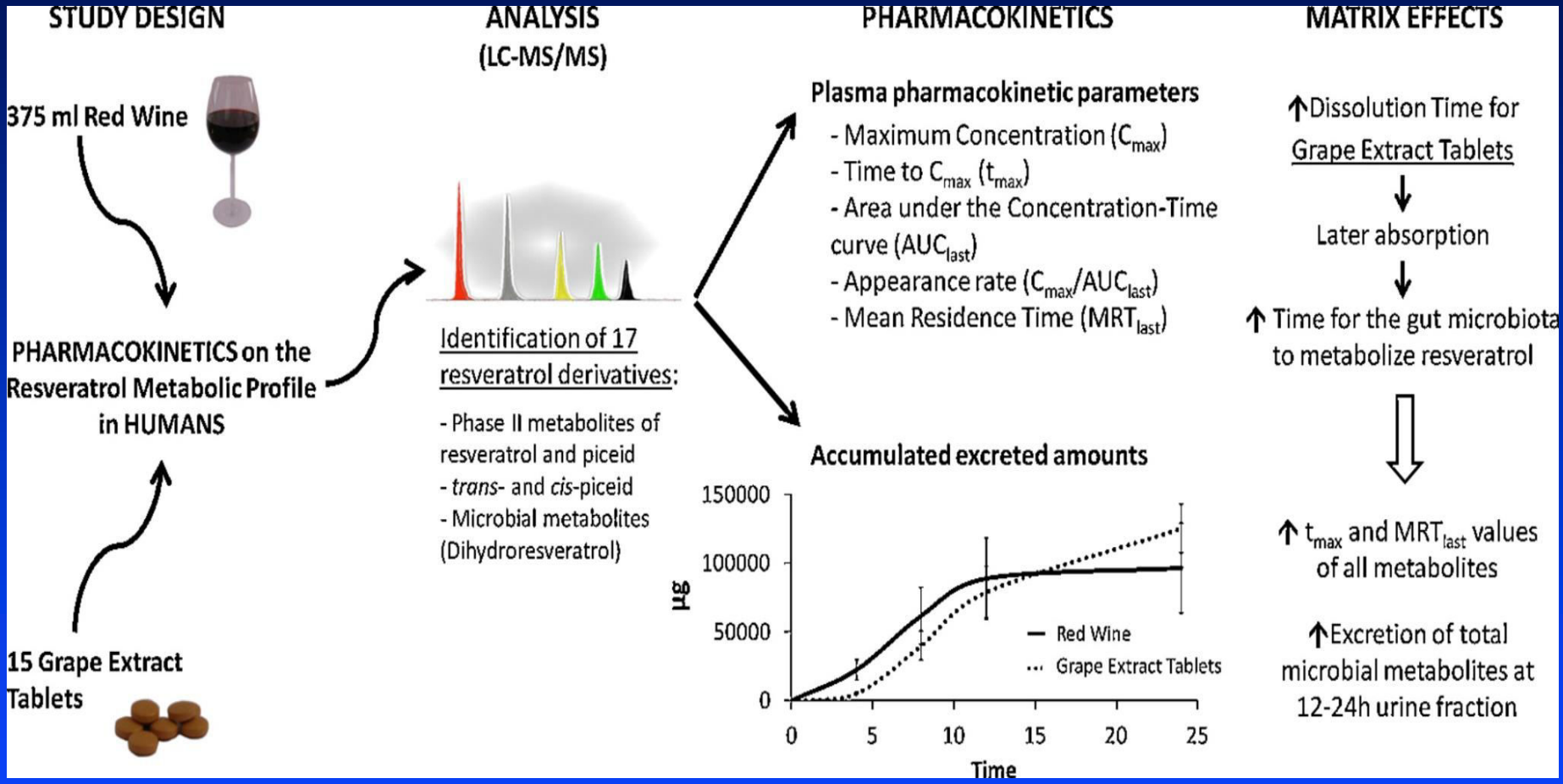
Data from several relevant reviews about levels of polyphenolic metabolites in plasma and urine after wine or beer consumption in adults suggest variability

Table 3. Main polyphenolic metabolites described in literature from wine and beer.

Polyphenol group	Polyphenol metabolite	Source	Dose per day	No. subjects	Urine		Plasma		Ref.
					Urinary excretion	Tmax (h)	Mean Concentration	Tmax (h)	
Flavanols	Catechin	Red wine	35 mg (120 mL)	9		3.1	0.091 µmol/L	1.5	[76]
		Red wine	35 mg (120 mL)	9		3.2	0.077 µmol/L	1.44	[77]
		Red wine	35 mg (120 mL)	9	3%–10% of intake				[78]
	(+)-Catechin	Red wine	120 mL	9				1.6	[76]
	3′-*O*-Methylcatechin	Red wine	120 mL	9				1.2	[76]
Anthocyanins	Total anthocyanins	Red wine	218 mg (300 mL)	6	1.5%–5.1% of intake/12 h	6			[79]
	Malvidin 3-glc	Red wine	68 mg (500 mL)	6	0.016% of intake/6 h	<3	0.0014 µmol/L	0.83	[80]
Hydroxycinnamic acids	Caffeic acid	Red wine	0.9–1.8–2.7 mg (100, 200, 300 mL)	5			0.007–0.027 µmol/L	1	[81]
		Red wine	1.8 mg (200 mL)	10			0.037–0.060 µmol/L	0.5–1	[82]
		Red wine	55 µg/kg bw	12			0.084 µmol/L	2	[83]
		Red wine	5 mL/kg bw	12					[83]
	Ferulic acid	Beer	500 mL	10			0.05–0.07 µmol/L	1	[83]
		Beer	500 mL	10			0.11 µmol/L	1	[83]
	4-Hydroxyphenylacetic acid	Beer	500 mL	10		8	1.4–1.17 µmol/L	0.5–1	[84]
	Vanillic acid	Beer	500 mL	10			0.11 µmol/L	1	[84]
	p-Coumaric acid	Beer	500 mL	10			0.05–0.07 µmol/L	1	[84]
Hydroxybenzoic acids	Gallic acid	Red wine	4 mg (300 mL)	2			0.22 GA + 1.1 4-MeGA + 0.25 3-MeGA µmol/L		[85]
	Methylgallic acid	Red wine	47 µg/kg bw	12			0.18 4-MeGA µmol/L	2	[83]
	4-*O*-Methylgallic acid	Red wine	5 mL/kg bw	12					[83]
Stilbenes	*Cis*-resveratrol 3-sulfate	Red wine	250 mL	5	221.2 nmol/g creatinine	4			[86]
	Trans-resveratrol 3-*O*-glucuronide	Red wine	250 mL	5	179.2 nmol/g creatinine	4			[86]
	Trans-resveratrol 4′-*O*-glucuronide	Red wine	250 mL	5	59.6 nmol/g creatinine	4			[86]
	Cis-resveratrol 4′ sulfate	Red wine	250 mL	5	9294.2 nmol/g creatinine	4			[86]
	Trans-Resveratrol 3-sulfate	Red wine	250 mL	5	74.7 nmol/g creatinine	4			[86]
	Trans-Resveratrol 4′-sulfate	Red wine	250 mL	5	2.4nmol/g creatinine	4			[86]
	Cis-resveratrol 3-*O*-glucuronide	Red wine	250 mL	5	893.5 nmol/g creatinine	4			[86]
	Cis-resveratrol 4′-*O*-glucuronide	Red wine	250 mL	5	355.8 nmol/g creatinine	4			[86]

Arranz S, et al. Nutrients. 2012 Jul;4(7):759-81.

The bioavailability of resveratrol is influenced by several factors, including the food matrix



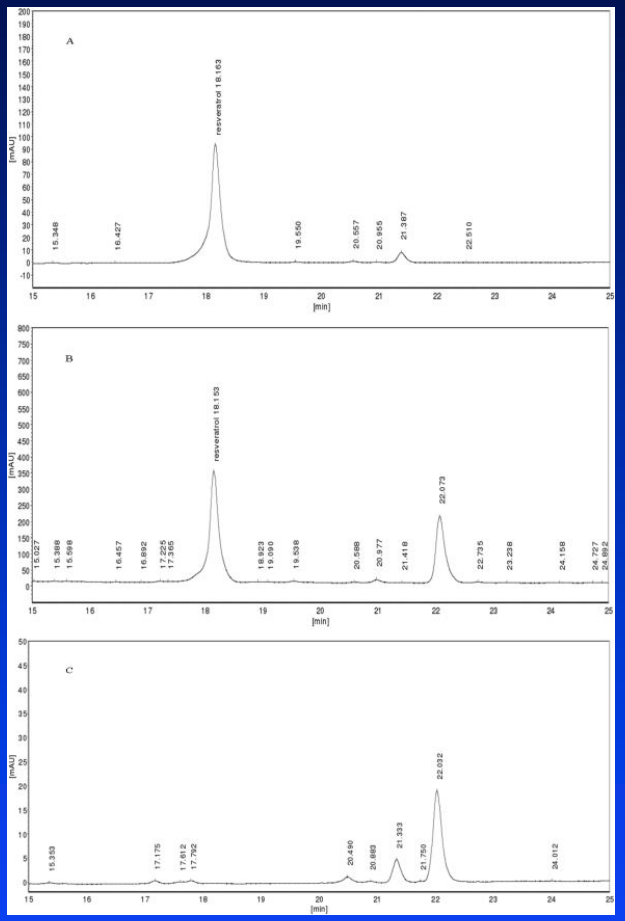
Rotches-Ribalta M, et al. Pharm Res 66:375-382, 2012.

To increase resveratrol production in wines two expression vectors carrying 4-coumarate:coenzyme A ligase gene and resveratrol synthase gene were transformed into strains of *Saccharomyces cerevisiae* EC1118

Chromatogram A represents the authentic standard of trans-resveratrol

Chromatogram B represents extracts from the culture broth of recombinant

Chromatogram C represents extracts from the culture broth of the negative control



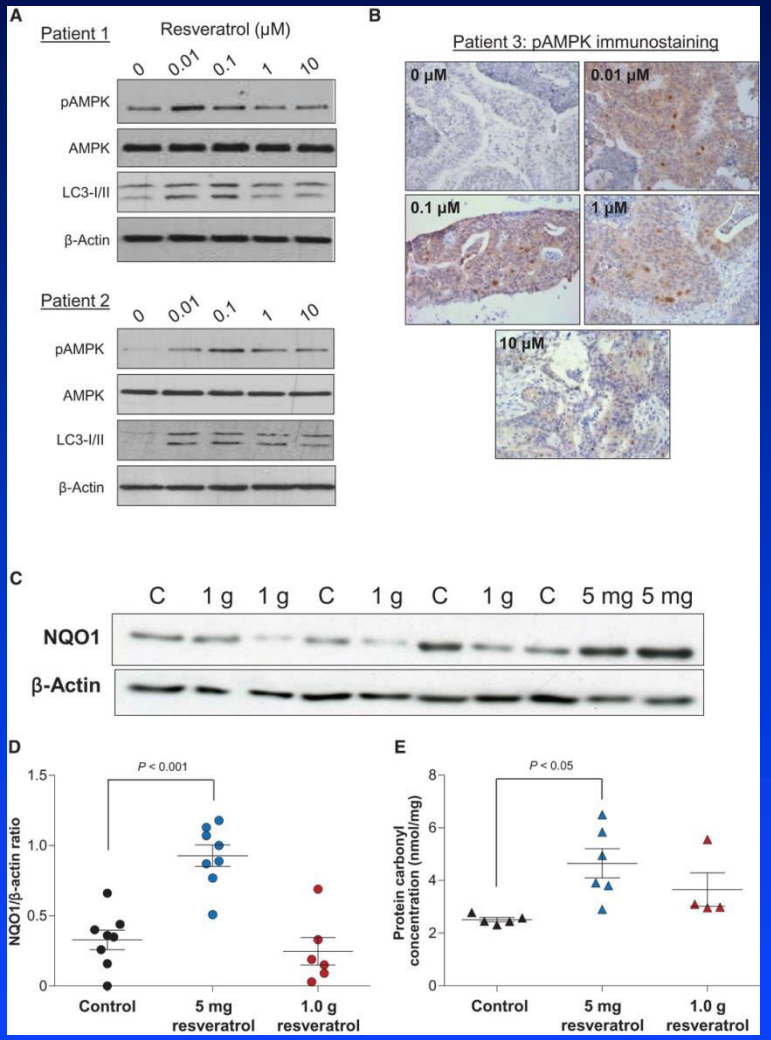
Resveratrol content of the wine fermented with engineered strains was twice higher than that of the control, indicating that engineered strains could increase the production of resveratrol during wine fermentation.

Biotechnology Progress
Volume 31, Issue 3, pages 650-655, 4 MAR 2015 DOI: 10.1002/btpr.2057
http://onlinelibrary.wiley.com/doi/10.1002/btpr.2057/full#btpr2057-fig-0003

Low concentrations of resveratrol activate AMPK and increase markers of oxidative stress in human colorectal tissues.

In Apc^{Min} mice that received a high-fat diet, a low resveratrol dose suppressed intestinal adenoma development more potently than did the higher dose.
Efficacy correlated with activation of adenosine monophosphate–activated protein kinase (AMPK) and increased expression of the senescence marker p21

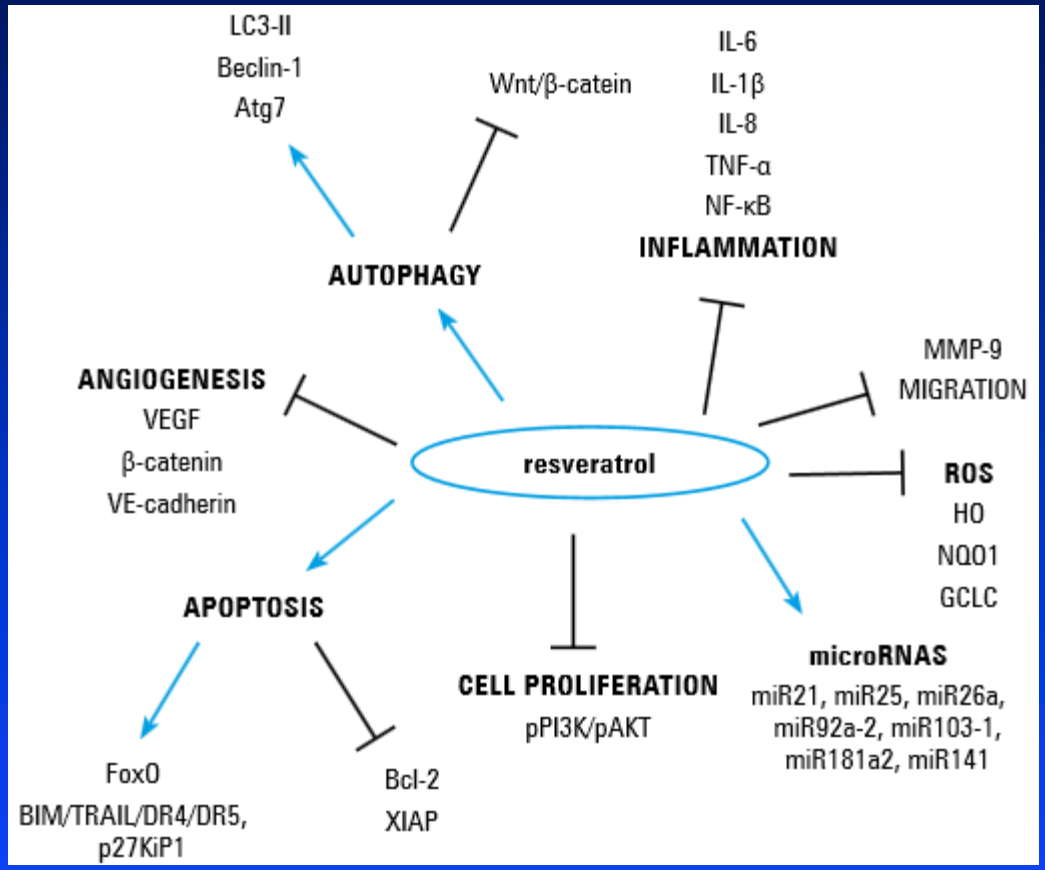
In human colorectal tissues exposed to low dietary concentrations of resveratrol ex vivo, enhanced AMPK phosphorylation and autophagy were observed.
The expression of the cytoprotective NAD(P)H dehydrogenase, quinone 1 (NQO1) enzyme was increased in tissues from cancer patients participating in a [14C]-resveratrol trial.



Hong Cai et al., Sci Transl Med 2015;7:298ra117

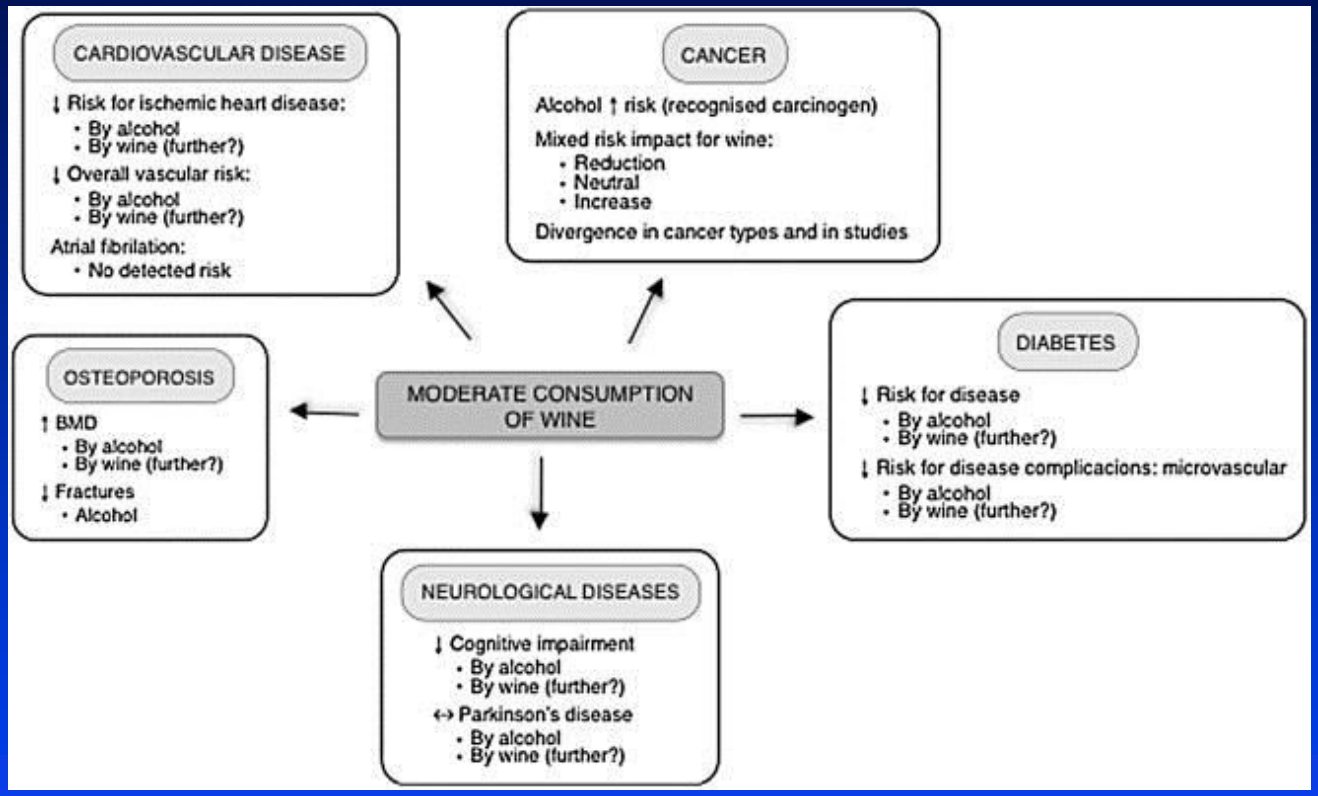
Published by AAAS

Cellular and molecular mechanisms involved in flavonoid associated (resveratrol) chemopreventive and angiopreventive activities



Rossi T, et al. Pol Arch Med Wewn. 2014;124(12):713-22

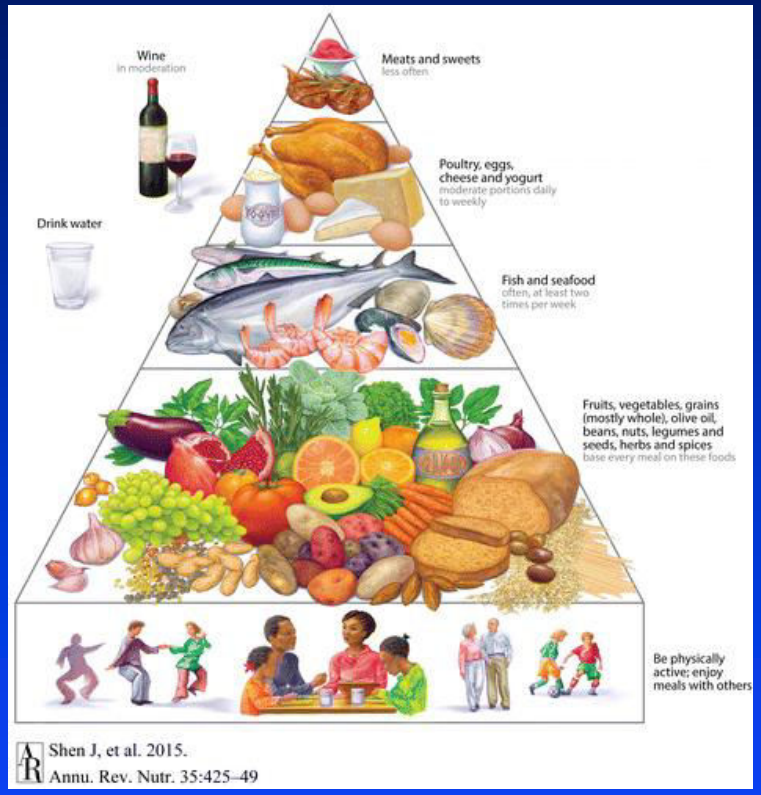
Effects of moderate wine consumption on different diseases, as reported in clinical observational studies.



Several studies cannot differentiate the observed effect of wine from that achieved by alcohol. The putative additive effect of wine has been shown with a question mark in the figure because there are unknowns/inconsistencies.

Ana Artero, Arturo Artero, Juan J. Tarín, Antonio Cano. Maturitas, Volume 80, Issue 1, 2015, 3–13.
http://dx.doi.org/10.1016/j.maturitas.2014.09.007

Moderate alcohol consumption (wine) and adherence to a Mediterranean dietary pattern



Shen J, et al. Annu Rev Nutr. 2015 Jul 17;35:425-49.

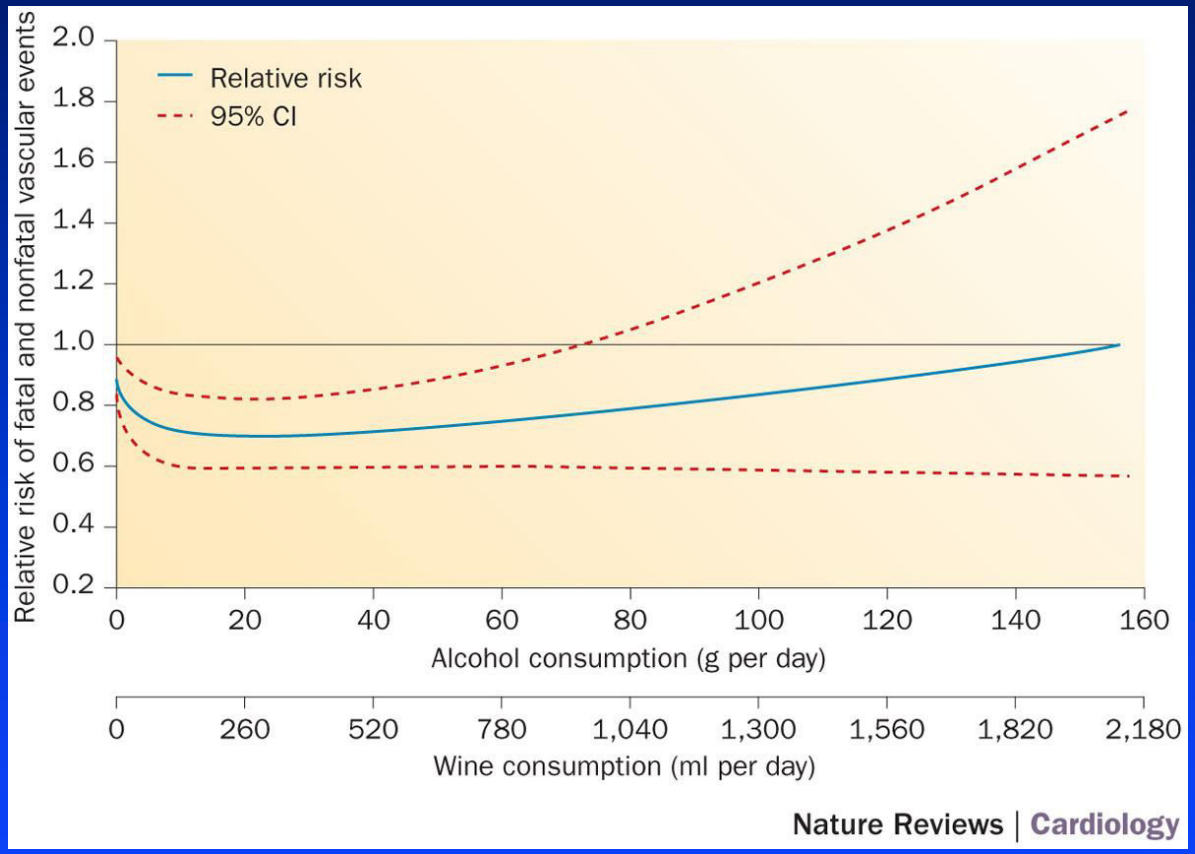
Table 3. Determinants of compliance with Mediterranean diet based on multiple stepwise logistic regression analysis in a study to analyze the variables associated with adherence to the Mediterranean diet in adults[abc]

	β	OR[d] (95% CI)	*P* value
Age: 1			
Age: T2(2)	0.383	1.467 (1.098-1.961)	0.010
Age: T3(3)	0.771	2.162 (1.622-2.882)	0.000
Sex(1)	−0.252	0.777 (0.603-1.001)	0.051
METs[e]/h/wk: T1			
METs/h/wk: T2(2)	0.209	1.233 (0.926-1.640)	0.151
METs/h/wk: T3(3)	0.462	1.588 (1.201-2.100)	0.001
Obesity: C1			
Obesity:C2(2)	−0.231	0.794 (0.610-1.034)	0.087
Obesity:C3(3)	−0.549	0.577 (0.416-0.802)	0.001
Alcohol: C1			
Alcohol:C2(2)	0.294	1.342 (1.045-1.723)	0.021
Alcohol:C3(3)	0.189	1.208 (0.774-1.885)	0.405

Patino-Alonso MC, et al. J Acad Nutr Diet. 2014 Apr;114(4):583-9

Pooled curves of relative risk of fatal and nonfatal vascular events and wine intake, extracted from 17 independent relationships using random models.: J shaped curve versus U-shaped curve

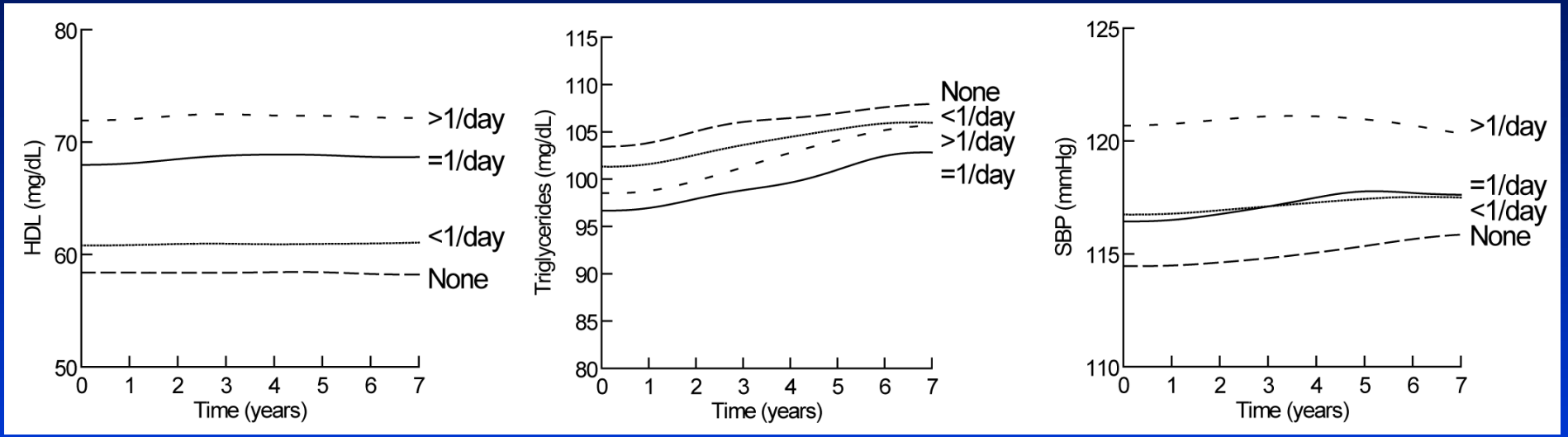
According to a dose–response analysis, the lowest risk of CHD mortality occurs with 0.5–2 drinks per day



Permission obtained from Springer Science+Business Media © Costanzo, S. *et al.* Wine, beer or spirit drinking in relation to fatal and non-fatal cardiovascular events: a meta-analysis. *Eur. J. Epidemiol.* **26**, 833–850 (2011)

Fernández-Solà, J. (2015) Cardiovascular risks and benefits of moderate and heavy alcohol consumption *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2015.91

Components of Metabolic Syndrome by glasses of wine per day.

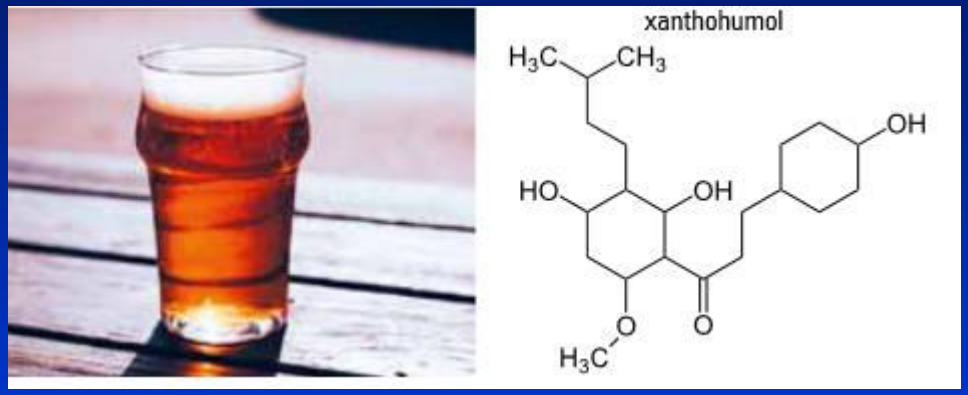


- The strongest association between wine consumption and HDL cholesterol; the higher the wine consumption, the higher the HDL, with all pairwise comparisons being highly significant ($p < 0.001$).
- Triglycerides were significantly lower for moderate wine consumers than abstinent women ($p < 0.001$).
- Blood pressure was higher in women who consumed more than 1 glass of wine per day

Janssen I, et al. J Wine Res. 2011; 22(2): 113–117.

Bioactive Phenolics in Beer

Beer contains hops, which are used to add bitterness and flavor and are also important as a preservative/antimicrobial



Rossi T, et al. Pol Arch Med Wewn. 2014;124(12):713-22

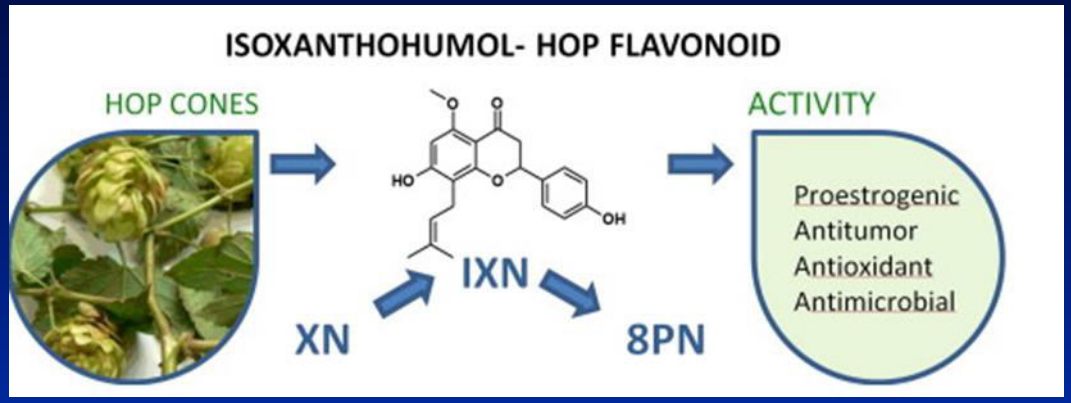
The structural classes of polyphenols in beer include simple phenols, benzoic acid derivatives and cinnamic acid, coumarins, catechins, di- and tri-oligomeric proanthocyanidins, **prenylated chalcones** and α- and iso-α acids derived from hops.

Table 2
Quantities of xanthohumol, isoxanthohumol and other flavonoids in different types of beer [45].

Type of beer	IXN (mg/L)	IXN (%)	XN (%)	Other flavonoids (%)
US major brands				
Lager/pilsner 1	0.50	84.7	5.8	9.5
Lager/pilsner 2	0.68	90.7	1.2	8.1
Lager/pilsner 3	0.40	87.0	3.0	10.0
Northwest/US microbrews				
Am. porter	1.33	45.9	23.8	30.3
Am. hefeweizen	0.30	90.9	1.5	7.6
Strong ale	3.44	86.0	6.0	8.0
India pale ale	0.80	69.0	13.8	17.2
Imported beers				
Imported stout	2.10	78.4	12.7	8.9
Imported lager	0.04	93.0	4.7	2.3
Imported pilsner 1	0.57	83.8	4.1	12.1
Imported pilsner 2	1.06	96.4	1.1	2.5
Other				
Non-alcohol beer	0.11	91.7	2.5	5.8

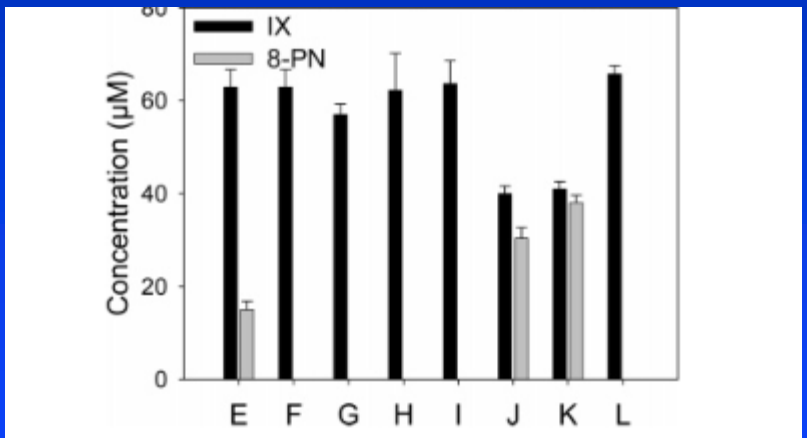
Żołnierczyk AK, et al. Fitoterapia. 2015 Jun;103:71-82.

The value of hops is attributed to their characteristic secondary metabolites; these metabolites are precursors which are transformed during the brewing process



Żołnierczyk AK, et al. Fitoterapia. 2015 Jun;103:71-82

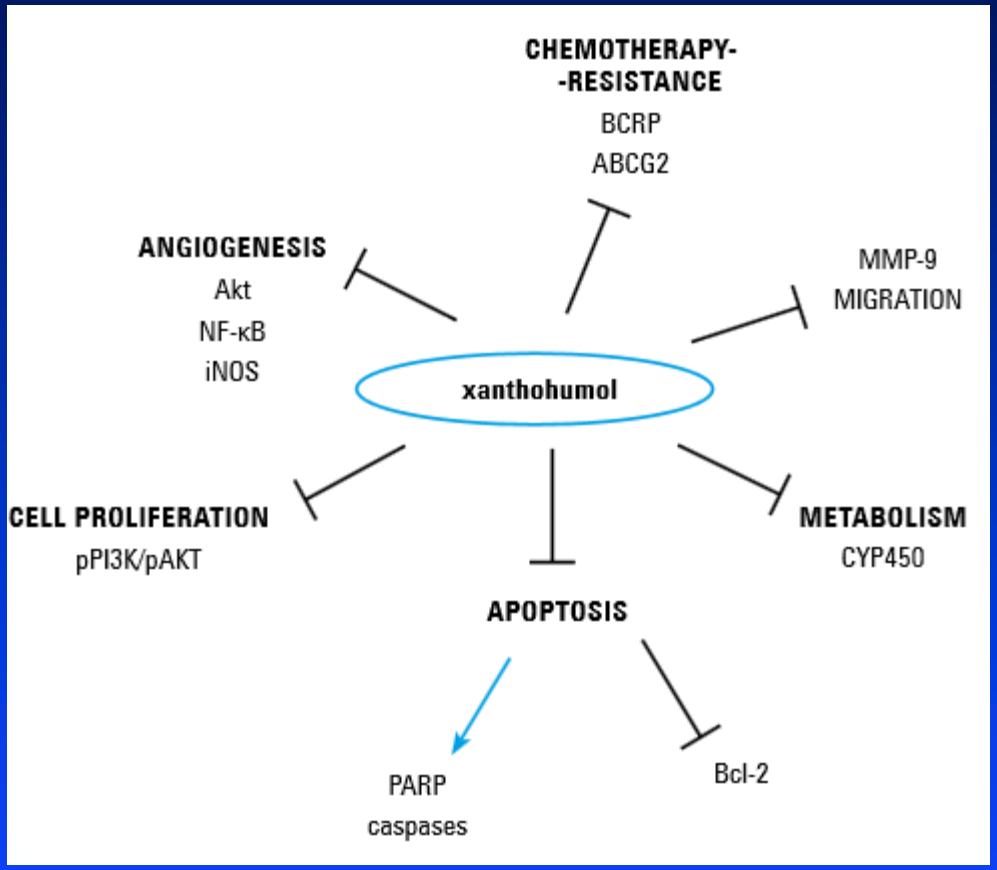
Activation of proestrogens from hops (Humulus lupulus L.) by intestinal microbiota; conversion of isoxanthohumol into 8-prenylnaringenin



igure 2. Transformation of IX by human fecal cultures. Samples E–L ere incubated with 25 mg/L IX for 3 days. Results are presented as verage (+ SD) concentrations of IX and 8-PN recovered ($n = 3$). When o bars are displayed, no 8-PN was detected.

Possemiers S, et al. J Agric Food Chem. 2005 Aug 10;53(16):6281-8.

Cellular and molecular mechanisms involved in xanthohumol associated chemopreventive and angiopreventive activities

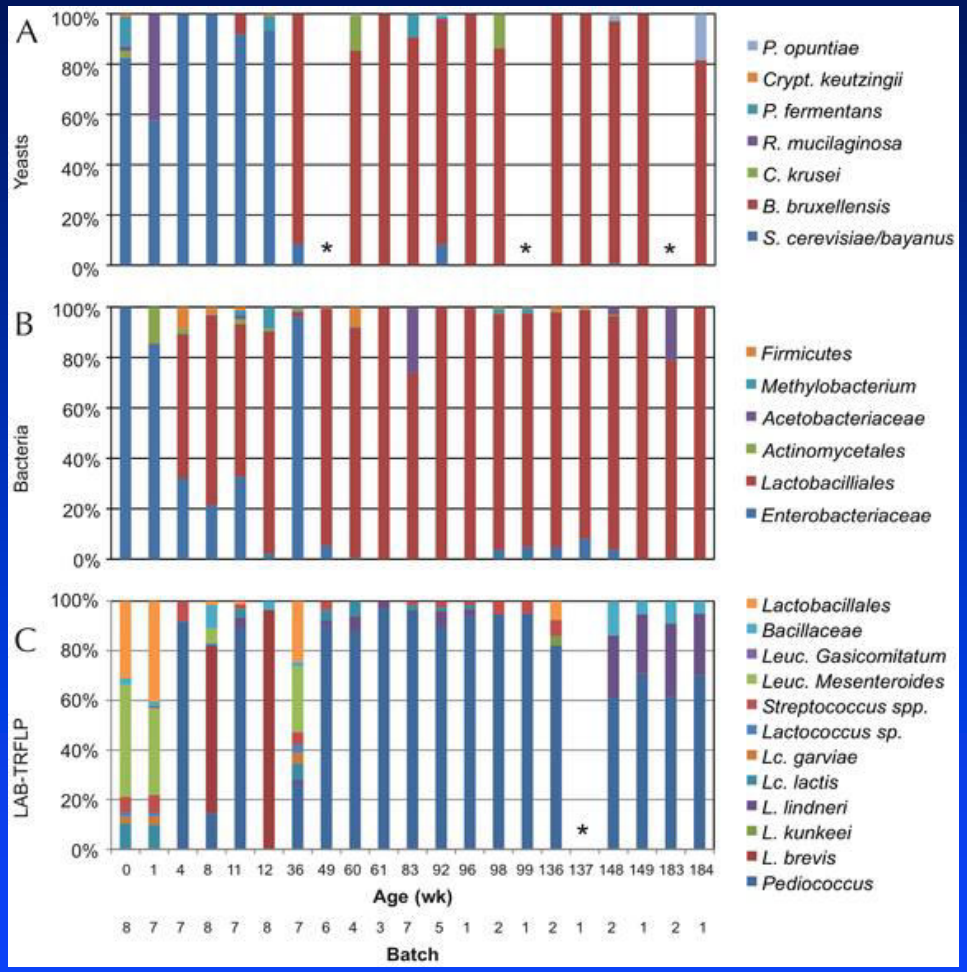


Rossi T, et al. Pol Arch Med Wewn. 2014;124(12):713-22

Brewhouse-Resident Microbiota Are Responsible for Multi-Stage Fermentation of American Coolship Ale

Microbial profile of spontaneous beer fermentations as a target for production control points and quality standards for these beers.

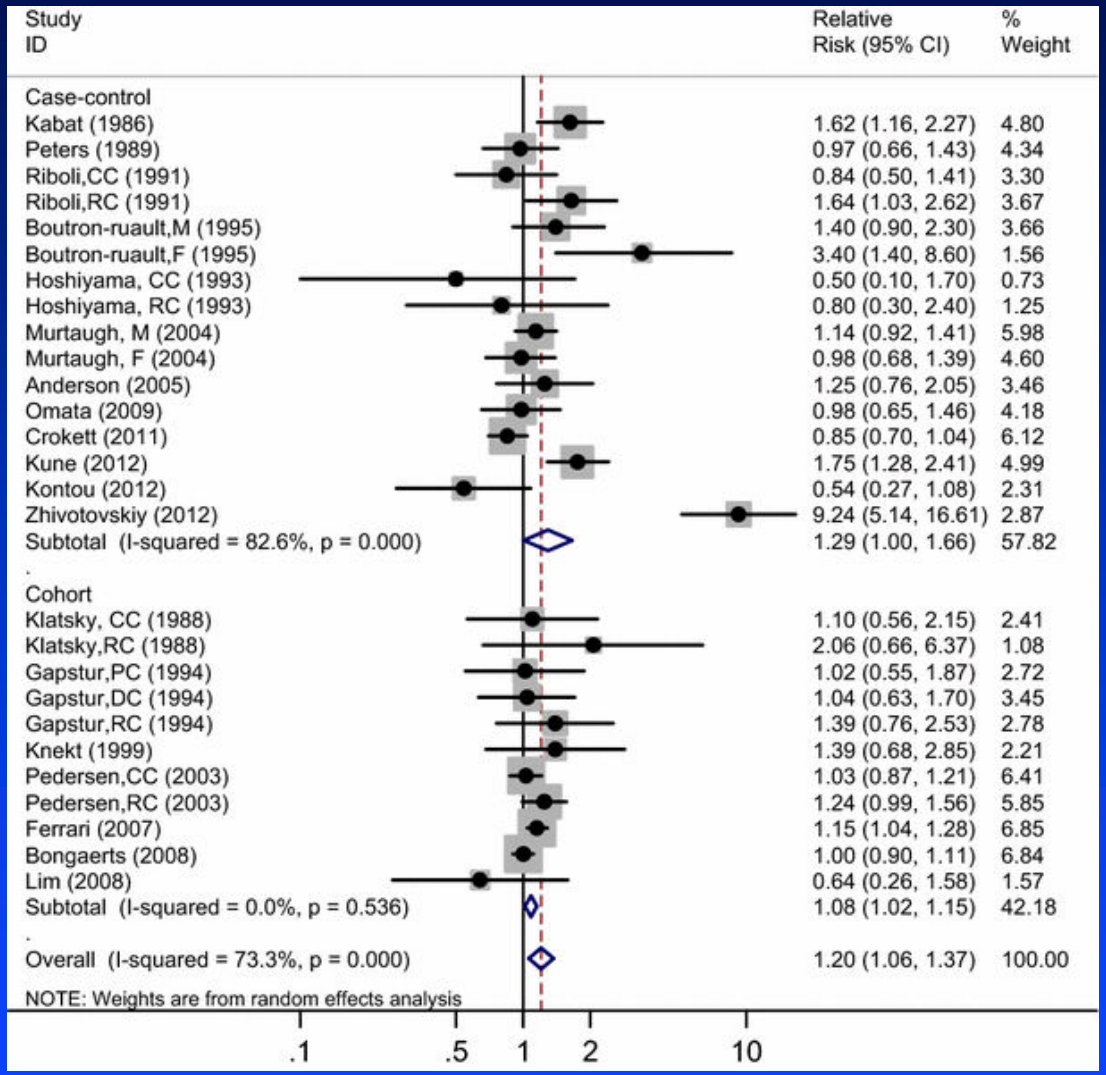
ACA fermentation involves a multiphase, core microbial profile, which is conserved batch-to-batch, supporting the presence of resident brewhouse microbiota responsible for conducting the fermentation.



Bokulich NA, Bamforth CW, Mills DA (2012) Brewhouse-Resident Microbiota Are Responsible for Multi-Stage Fermentation of American Coolship Ale. PLoS ONE 7(4): e35507. doi:10.1371/journal.pone.0035507
http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0035507

PLOS | ONE

Meta-analysis results suggest that ≥2 drinks/day beer drinking may be associated with increased colorectal cancer risk.

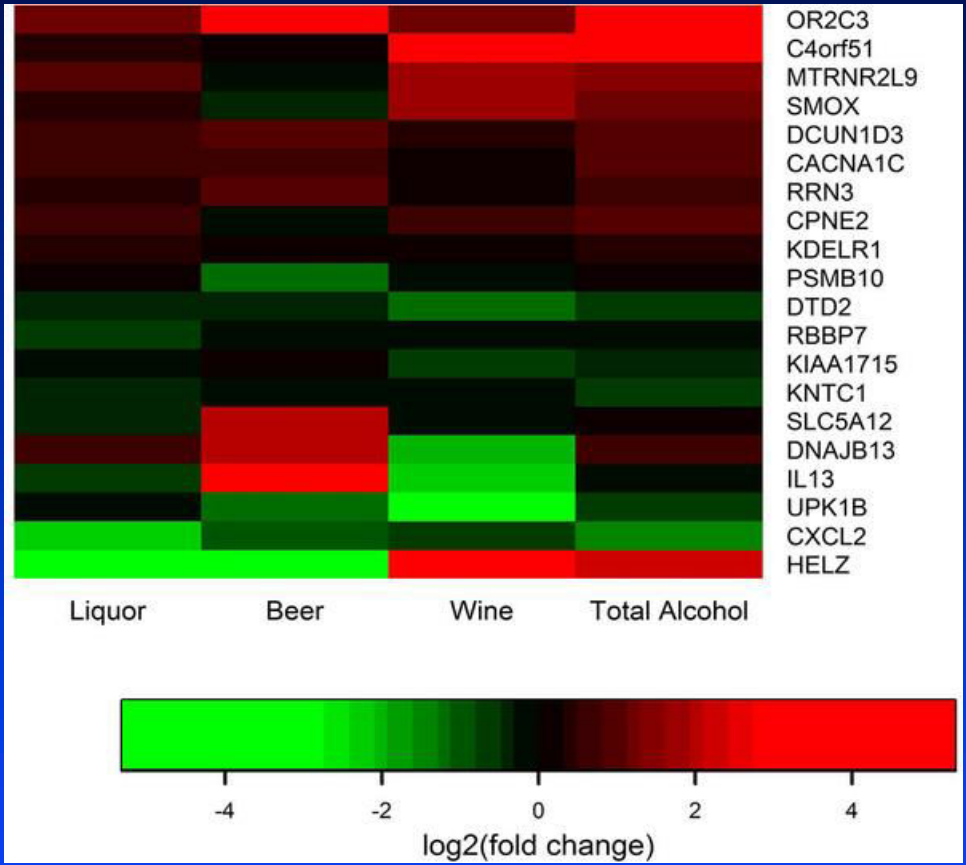


Zhang C & Zhong M. Cancer Causes Control. 2015 Apr;26(4):549-60.

Differentially expressed genes by type of alcohol intake.

RNA-seq data from 144 colon cancer patients who had information on recent cigarette smoking, recent alcohol consumption, diet, and recent aspirin/non-steroidal anti-inflammatory use

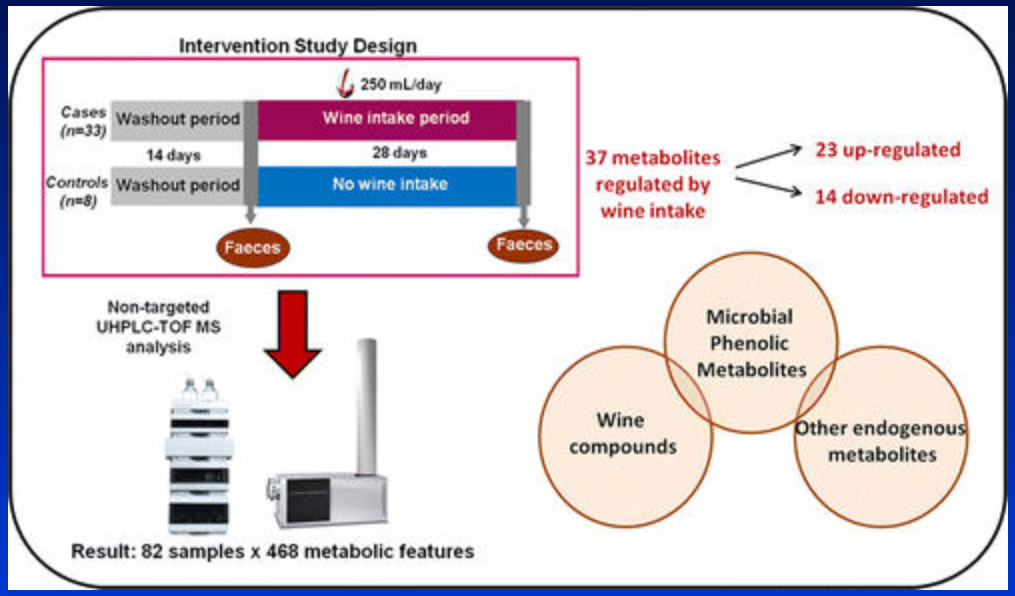
Different differentially expressed genes were associated with type of alcohol intake; five genes were associated with total alcohol, six were associated with beer intake, six were associated with wine intake, and four were associated with liquor consumption.



Slattery ML, Pellatt DF, Mullany LE, Wolff RK (2015) Differential Gene Expression in Colon Tissue Associated With Diet, Lifestyle, and Related Oxidative Stress. PLoS ONE 10(7): e0134406. doi:10.1371/journal.pone.0134406
http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0134406

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Fecal Metabolomic Fingerprint after Moderate Consumption of Red Wine by Healthy Subjects



- 37 metabolites related to wine intake, from which 20 could be tentatively or completely identified, including the following: (A) wine compounds, (B) microbial-derived metabolites of wine polyphenols, and (C) endogenous metabolites and/or others derived from other nutrient pathways.
- After wine consumption, fecal metabolome was fortified in flavan-3-ols metabolites.
- Down regulation of xanthine and bilirubin-derived metabolites such as urobilinogen and stercobilin after moderate wine consumption.

Jiménez-Girón A, at al. J Proteome Res. 2015 Feb 6;14(2):897-905

Alcohol as a risk factor for cancer

Table 1. WCRF/AICR and IARC evaluation of evidence for a adverse effects of alcohol and cancer sub-sites compared [1,2,8]

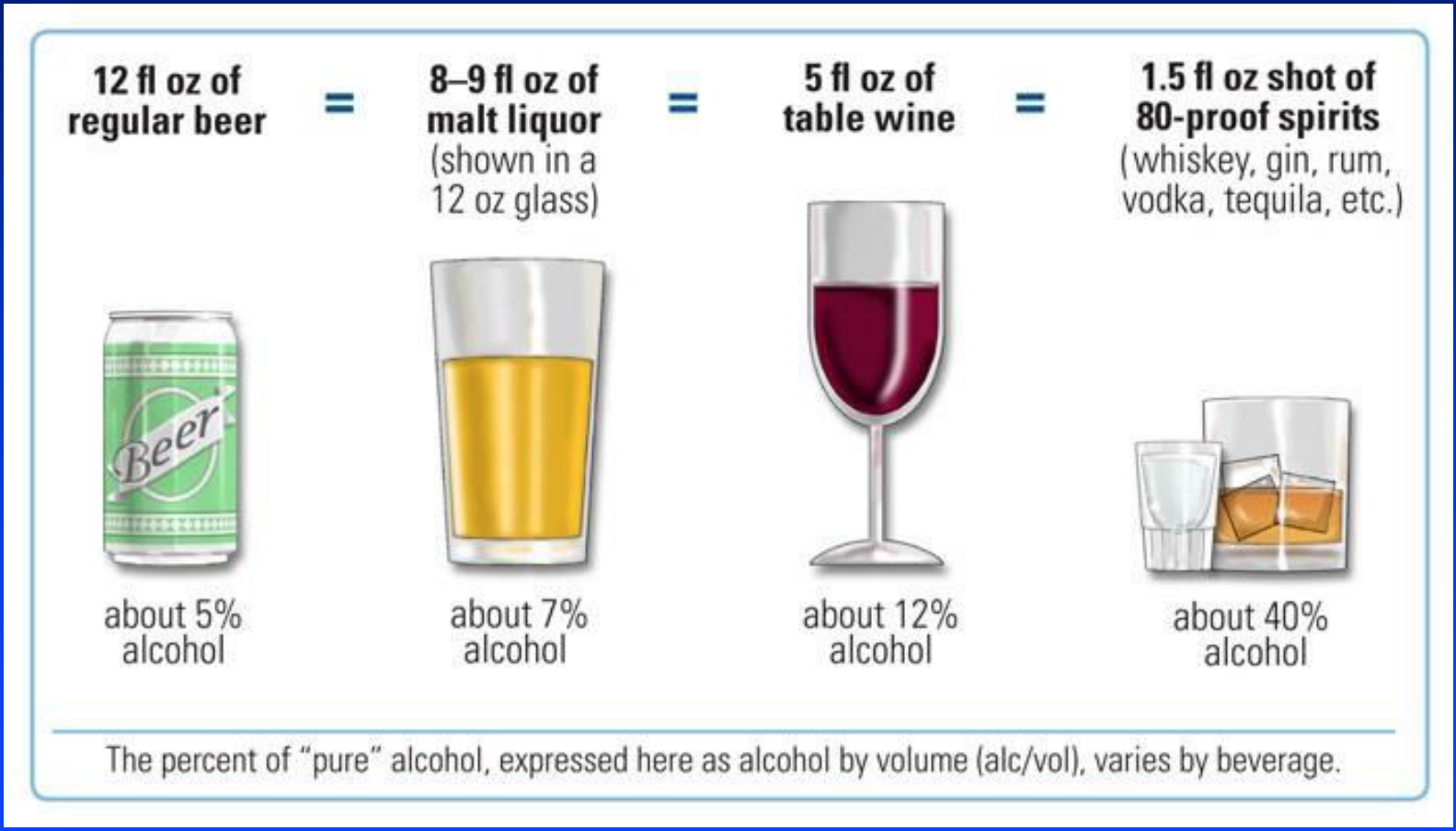
	Exposure	Cancer site	
		WCRF/AICR	IARC
Convincing	Alcoholic drinks	Mouth, pharynx, and larynx Oesophageus Colorectum (men) Breast (premenopausal and postmenopausal)	Oral cavity Pharynx Larynx Oesophageus Colorectum Breast Liver
Probable		Liver Colorectum (women)[1]	-
Limited - suggestive		-	-

WCRF, World Cancer Research Fund; AICR, American Institute for Cancer Research; IARC, International Agency for Cancer Research.
[1]The WCRF/AICR remarks that the difference in grading of evidence in men and women is due to the lower number of studies in women, but also that alcohol seems to assert a stronger effect on colon and colorectal cancer in men compared to women.

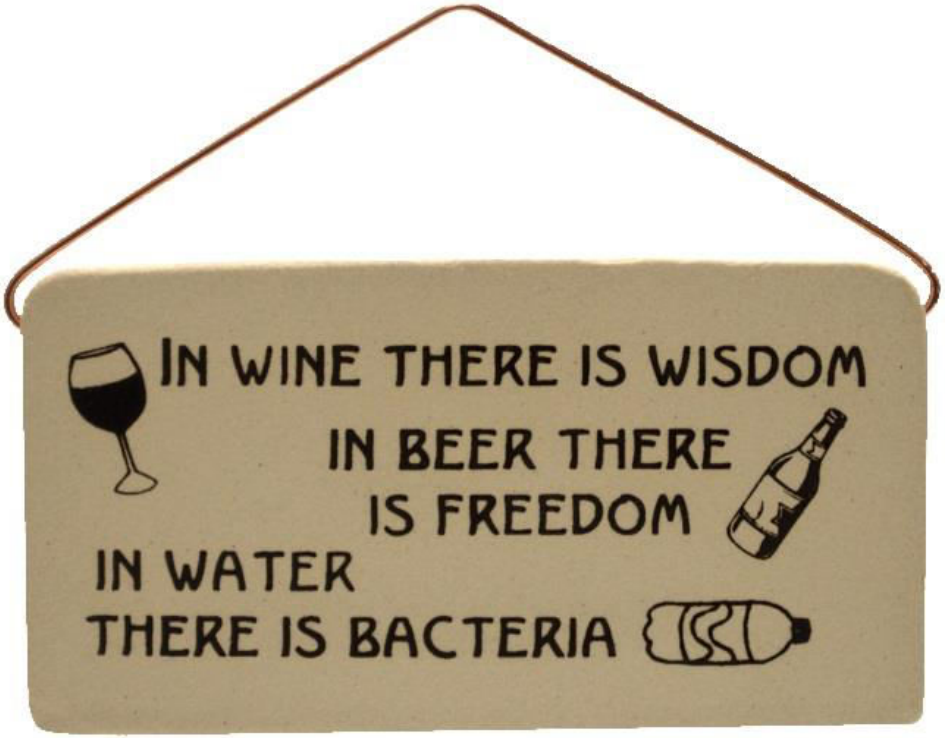
Roswall N & Weiderpass E. J Prev Med Public Health. 2015 Jan;48(1):1-9.

If alcohol is consumed, it should be consumed in moderation—up to one drink per day for women and two drinks per day for men—and only by adults of legal drinking age.

http://health.gov/dietaryguidelines/dga2010/DietaryGuidelines2010.pdf



http://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink



Benjamin Franklin? Olde German saying?

http://www.spiritedrepublic.org

Conclusions

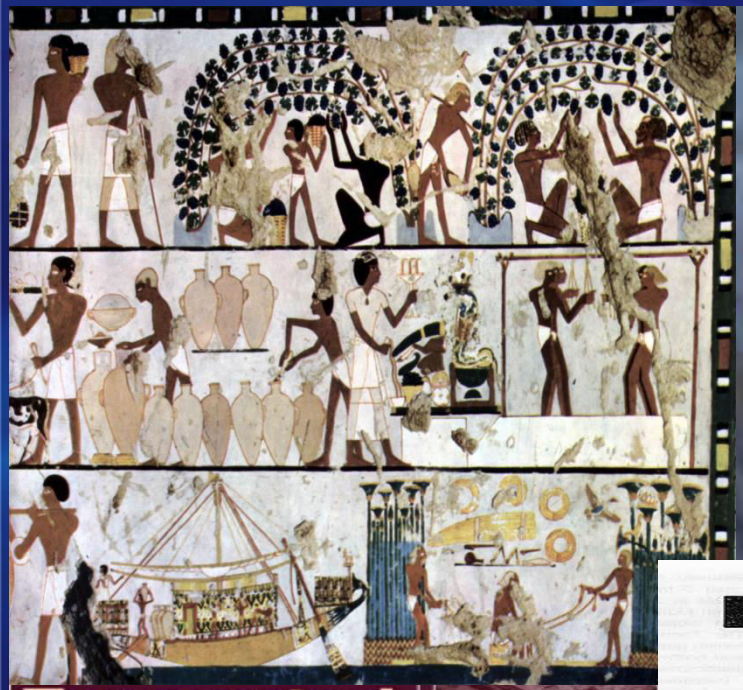




R. Paul Robertson Diabetes 2014;63:31-38

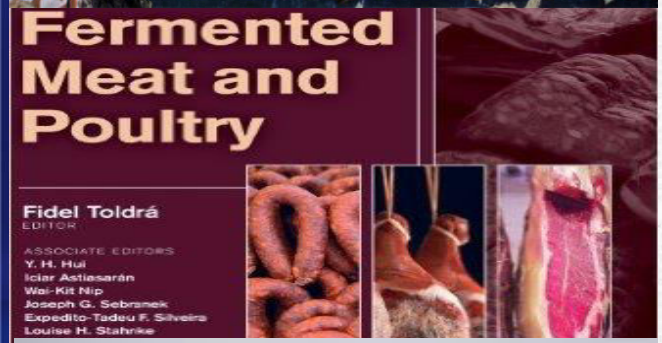
©2014 by American Diabetes Association

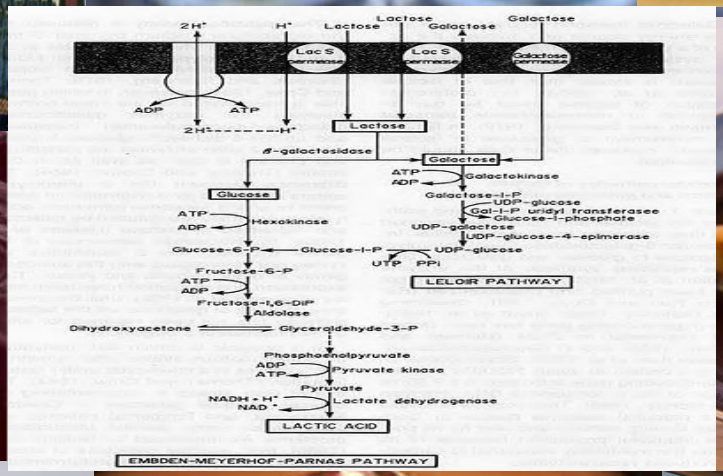
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Pyruvate
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NAD+
Lactate dehydrogenase
LACTIC ACID
EMBDEN-MEYERHOF-PARNAS PATHWAY




THE WHOLE9 MANIFESTO SERIES





What fermented foods do we eat?

legumes ▪ grains ▪ vegetables ▪ fruit ▪ milk ▪ fish ▪ meat



Courtesy Johanna W. Lampe, PhD, RD, Fred Hutchinson Cancer Research Center Seattle, WA.

Steinkraus, KH (ed*), Handbook of Indigenous Fermented Foods*, 1983.

Table 1. Summarized history of medicine.

2000 BC	Polytheistic religions era	Take this herb and eat, it's good for you
1000 AD	Monotheistic religions era	That herb is bad, you'd better say this pray
1500 AD	Renaissance development era	That pray is a superstition, you'd better drink this elixir
1800 AD	Industrial revolution era	What's the use of that elixir, you'd better take this pill
1950 AD	Pharmaceutical revolution era	That pill is ineffective, you'd better take this antibiotic
2000 AD	Electronic media era	That antibiotic is chemical, you'd better eat this herb
2010 AD	Evidence-based medicine era	No study on that herb, you'd better take this probiotic

Ozen M & Dinleyici EC. Benef Microbes. 2015 Jan 1;6(2):159-65