Wine and Ocular Health

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Certified Level

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Understanding Wine

- Ocular health benefits
- General health benefits
- Risks of excessive drinking

Wine and Ocular Health

- The French Paradox
- Heavier foods, creams and meats in diet
- Longer life expectancy than in the US
- Develop cataracts later in life (?)

H

Wine and Ocular Health

- 1045 Subjects
- Compared through photofluormetry, the density changes in cataracts
- 22% for moderate wine consumption
- 32% for no wine consumption

H Sasaki, F Jonasson, Y Suwa et al. The Protective Effect of Wine Intake on Five Year's incidence of Cataract – Reykjavik Eye Study. ARVO Wed May 04, 2005 Apstract/Poster# 3840/B198

Wine and Ocular Health

- 3072 adults 45 to 74 years of age with macular changes indicative of AMD
- National Health Administration Eye Health survey & fundoscopy
- The researchers observed a statistically significant negative association between AMD and alcohol consumption ($p<0.01$)
- No benefit to beer or hard liquor – only wine in moderate consumption

Obisesan TO, Hirsch R, Kosoko O et al. Moderate wine consumption is associated with decreased odds of developing age-related macular degeneration in NHANES-1. Journal of the American Geriatric Society. 1998 Jan;36(1):1-7

Wine and Ocular Health: Resveratrol

- Can be consumed as a supplement or in red wine in particular
- Is a phytoestrogen
- Shown to fight inflammation, prevent oxidation of certain cells and prevent apoptosis

Wine and Ocular Health: Cataracts

- An experimental cataract model on lab rats
- It has been shown that a subcutaneous injection of selenite can induce senile cataract development.
- In the study rats were either injected with normal saline, Sodium selenite alone or sodium selenite with 40mg/kg of resveratrol.
- Cataract development was graded 11 days later using photography and the lenses were analyzed for lipid peroxidation, a marker present in cataract development

Doganay S. Boranzan M, Iraz M et al. The effect of resveratrol in experimental cataract model formed by sodium selenite. Current Eye Research. 2006 Feb;31(2):147-53

Wine and Ocular Health: Cataracts

- The results showed that all the control crystalline lenses (Saline injection) were clear as expected, the lenses in group two (selenite injection) had a 100% incidence of cataract and all were graded as grade 3 to 6 (6 being the highest)
- Finally in group 3 in which the rats also received resveratrol, 7 of the 16 animals showed 0% cataract development and of the remaining 9 they were all graded at 3 or less
- This was statistically significant ($p<0.05$)

Doganay S. Boranzan M, Iraz M et al. The effect of resveratrol in experimental cataract model formed by sodium selenite. Current Eye Research. 2006 Feb;31(2):147-53

Wine and Ocular Health: AMD

- Antioxidant and antiproliferative effects of resveratrol were examined in a human RPE cell line
- The results showed that treatment with 50 and 100 micromol/L resveratrol significantly reduced proliferation of RPE cells by 10% and 25% respectively ($P< 0.05$)
- Resveratrol was shown to inhibit intracellular oxidation and protect the RPE cells from cell death

King RE, Kent KD, Bomser JA. Resveratrol reduces oxidation and proliferation of human retinal pigment epithelial cells via extracellular signal-regulated kinase inhibition. Chemistry and Biology Interaction. 2005 Jan 15;151(2):143-9

Wine and Ocular Health: AMD

- The observed reduction in cell proliferation was associated with inhibition of protein kinase
- Protein kinase was shown to be inhibited with resveratrol concentrations as low as 5 micromol/L
- These results suggest that resveratrol can reduce oxidative stress and hyperproliferation of the RPE cells of the retina.

King RE, Kent KD, Bomser JA. Resveratrol reduces oxidation and proliferation of human retinal pigment epithelial cells via extracellular signal-regulated kinase inhibition. Chemistry and Biology Interaction. 2005 Jan 15;151(2):143-9

Wine and Ocular Health: AMD

- In one paper, researchers have found that a combination of grape seed proanthocyanidin (tannins in red wine) and resveratrol prevents inducible secular endothelial growth factor (VEGF) expression, a key element supporting angiogenesis
- Anti-VEGF therapy is the basis for all the current wet AMD therapies such as Avastin

Sen CK, Khanna S. Gordillo G et al. Oxygen oxidants and antioxidants in wound healing: an emerging paradigm. Annual NY Academy of Science. 2002 May;957:239-49

Wine and Ocular Health: Cornea

- Research has shown resveratrol's ability to suppress the enzyme MMP
- MMP has been found to be an instrumental in causing recurrent corneal erosion and persistent epithelial defects
- This study also went on to show that resveratrol is able to actually reduce corneal neovascularization in mice eyes

Oak MH, El Bedoui J, Chini-Kerth VB. Antiangiogenic properties of natural polyphenols from red wine and green tea. Journal of Nutritional Biochemistry. 2005 Jan;16(1):108

Treatment for Recalcitrant RCE:

- Muro 128 ung x 2 mo
- FreshKote drops tid x 2 mo
- Lotemax qid x 2 weeks then bid x 6 weeks
- Doxy 50 mg PO BID x 2 mo

Ease of Use: Cryopreserved

3 Steps to a Successful Placement

- Topical anesthetic
- Have patient look down, insert under upper eyelid, then lower eyelid as patient looks up
  - (Insert into lower lid first in small fissures)
- Check for air bubbles or PMMA section on limbus

Ease of Use: Dehydrated

3 Steps to a Successful Placement

- Topical anesthetic
- Membrane placement in the Bandage Contact Lens
- Placement on the affected eye

Ease of Use

3 Steps to a Successful Placement

- Topical anesthetic
- Membrane placement on the cornea while at the slit lamp, smooth out membrane
- Placement of SleepTite lid seal

Neurotrophin-3/Neurotrophin-4	NT-3/NT-4
Basic fiberblast growth factor	bFGF
Beta nerve growth factor	β-NGF
Epidural growth factor/Epidermal growth factor receptor	EGF/EGF-R
Glial cell line-derived neurotrophic factor	GDNF
Heparin binding growth factor	HB-EGF
Hepatocyte growth factor	HGF
Platelet-derived growth factor	PDGF-AA/PDGF-BB
Placenta growth factor	PlGF
Stem cell factor	SCF/SCF-R
Transforming Growth Factor Alpha	TGFa/TGFb1/TGFb3
Vascular endothelial growth factor	VEGF

Protein	Abbreviation
Growth differentiation factor 15	GDF-15
Interleukin 1α	IL-1α
Interleukin 1 Beta	IL-1β
Interleukin 1 receptor antagonist	IL-1ra
Interleukin 12 p40	IL-12p40
Interleukin 17	IL-17
Osteoprotegerin	OPG
Interleukin 8	IL-8
Intercellular adhesion molecule 1	ICAM-1
Tumor necrosis factor	TNF
Interleukin 4	IL-4
Interleukin 5 receptor	IL-6R
Macrophage colony-stimulating factor 1 receptor	MCSF R
B lymphocyte chemoattractant (CXCL 13)	BLC
Eotaxin 2	Eotaxin-2

Interleukin 16	IL-16
Monocyte chemotactic protein 1 (CCL2)	MCP-1
Monokine induced by gamma interferon (CXCL9)	MIG
Macrophage inflammatory protein 1 alpha (CCL3)	MIP-1α
Macrophage inflammatory protein 1 beta (CCL4)	MIP-1β
Macrophage inflammatory protein 1D (MIP-5, CCL 15)	MIP-1d
Regulated on activation, normal T cell expressed and secreted (CCL5)	RANTES
Brain-derived neurotrophic factor	BDNF
Bone morphogenetic proteins	BMP-4/BMP-5/BMP-7
Endocrine gland-derived vascular endothelial growth factor	EG-VEGF
Fibroblast growth factor 4	FGF-4
Keratinocyte growth factor	FGF-7
Growth Hormone	GH
Insulin-like growth factor 1	IGF-1
Insulin-like growth factor binding proteins	IGFBP-1-6
Tissue inhibitor of metalloproteinases	TIMP-1/TIMP-2

Other Things to Consider in Recalcitrant Cases:

- 1000mg Vitamin C daily
- Consider non-controlled systemic diseases e.g. DM

Wine Descriptor: Black Currant / Cassis

- "Cassis" or black currant flavor of wine
- Black currant is source of malvidin, an anthocyanin found in wine (anthocyanins = purple antioxidant pigment; type of polyphenol)
- Seeds of black currant also deliver **GLA** – unique omega fatty acid found to relieve dry eye in 7 controlled clinical trials

Supplemental GLA for Dry Eye: **7 Controlled Clinical Trials**

- Aqueous-deficient (Barabino S et al. Cornea 22: 97–101, 2003.)
- PRK (Macri A et al. Graefes Arch Clin Exp Ophthalmol 241:561-6, 2003.)
- Sjögren's (Aragona P, et al. Ophthalmol Vis Sci 46:4474-9, 2005.)
- Contact lens (Kokke KH et al. Contact Lens Ant. Eye 31:141-6, 2008.)
- MGD (Pinna et al. Cornea 26:260-264, 2007.)
- Mild-moderate DE (Brignole-Baudouin et al. Acta Ophthalmologica 89:e591-7, 2007.)
- Post-menopausal women (***HydroEye***) (Sheppard JD, Pflugfelder SC, et al. Cornea 32 :1297-1304, 2013.)

Why not just fish oil for dry eye?

- GLA: more compelling array of evidence (vs. Fish oil – with fewer DE studies, often small doses in non-representative populations, e.g. Northern India, Iran)
- GLA has specificity for DE that fish oil omegas lack.
- Combining GLA + modest level EPA from fish oil, other nutrients / cofactors. GLA + EPA has complimentary effect on inflammation

Sheppard JD, Pflugfelder SC, et al. Long-term supplementation with n-6 and n-3 PUFAs improves moderate-to-severe Keratoconjunctivitis Sicca: A randomized double-blind clinical trial. *Cornea* 32:1297-1304, 2013.

Clinical Validation:

Supplement with GLA for Dry Eye Relief


Long-term Supplementation With n-6 and n-3 PUFAs Improves Moderate-to-Severe Keratoconjunctivitis Sicca: A Randomized Double-Blind Clinical Trial

Sheppard JD, Pflugfelder SC, et al. Long-term supplementation with n-6 and n-3 PUFAs improves moderate-to-severe Keratoconjunctivitis Sicca: A randomized double-blind clinical trial. *Cornea* 32:1297-1304, 2013.

SUMMARY OF FINDINGS:

GLA supplement users showed:

- Significant improvement in irritation symptoms & significantly better symptom scores vs. placebo
- Significantly better corneal smoothness vs. placebo
- Significantly lower levels of inflammatory markers vs. placebo.

Sheppard JD, Pflugfelder SC, et al. Long-term supplementation with n-6 and n-3 PUFAs improves moderate-to-severe Keratoconjunctivitis Sicca: A randomized double-blind clinical trial. *Cornea* 32:1297-1304, 2013.

Wine + Omegas

- Cross-sectional study looked alcohol intake and omegas from diet and supplements with coronary heart disease
- Moderate wine consumption (not other alcohols) found to boost blood omega-3 levels from food and supplements
- This may help explain the heart benefits conferred from drinking red wine

De Lorgeril, Michel, et al. "Interactions of wine drinking with omega-3 fatty acids in patients with coronary heart disease: a fish-like effect of moderate wine drinking." *American heart journal* 155.1 (2008): 175-181.

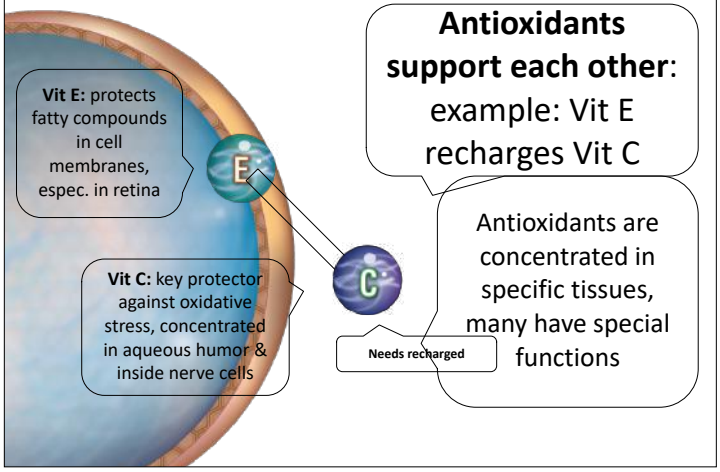
Antioxidants:

Primary health-promoting components in wine (especially reds)

Note: following slides use vit C & E to show how antioxidants work – though C & E not found in wine specifically

How Antioxidants Work

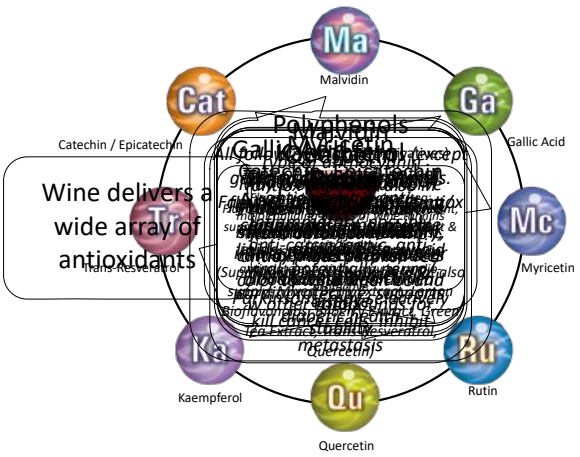
How Antioxidants Work



Antioxidants support each other: example: Vit E recharges Vit C

Antioxidants are concentrated in specific tissues, many have special functions

Wine Antioxidants



Wine delivers a wide array of antioxidants

Wine Antioxidants: Quercetin

- Flavonoid consumption, espec. quercetin, assoc. w lower incidence of heart disease, stroke
- Found to reduce blood pressure in hypertensives
- Study: diabetics on high quercetin diet: less DNA oxidative damage to white blood cells vs low-Q diet.
- In lab studies, shows neuroprotective effects, inhibits retinal/choroidal angiogenesis

1. Lean MEJ, et al. Diabetes 48:176-181, 1999.
2. Hanneken A, et al. Invest Ophthalmol Vis Sci 47:3164-77, 2006.
3. Edwards, Randi L., et al. *The Journal of nutrition* 137.11 (2007): 2405-2411.
4. Kumar, Binit, et al. " *Experimental eye research* 125 (2014): 193-202.
5. Chen, Yi, et al. *Graefe's Archive for Clinical and Experimental Ophthalmology* 246.3 (2008): 373-378.

Wine Antioxidants: Trans-Resveratrol

- Trans-resveratrol: activates protective stress response in cells (via TyrRS enzyme), even at modest doses such as found in 1-2 glasses red wine
- Pre-clinical evidence suggests Trans-resver. supports micro-vessel circulation via antioxidant, anti-inflamm effects, also inhibits neovascularization

1. Sajish M, et al. Nature [Epub ahead of print] Dec 22, 2014.
2. 9. Bola C, et al. Graefes Arch Clin Exp Ophthalmol 252:699-713, 2014.

Whole Grape Extract

- Provides wide range of antioxidants (including myricetin, trans-resveratrol, kaempferol, quercetin, catechin, epicatechin, more)
- Found to reduce oxidative stress and improve lipid profiles in hypertensive, overweight and/or pre-diabetic patients

1. Evans M, et al. J Functional Foods 7:680-91, 2014.

Trans-Resveratrol + Whole Grape Extr.

- 1 yr trial in diabetics, hypertensives with coron. artery disease.
  - Findings: synergistic effect: Resv lowered 1 inflammatory cytokine vs placebo, while Resv + whole grape extract combo also lowered 3 additional inflamm compounds
- Another 1 yr trial: those w type 2 diabetes or statin users at risk of heart disease
  - trans-resv + whole grape extr lowered inflamm markers & lowered unhealthy blood clotting better then whole grape extr. alone or placebo

1. Tomé-Carneiro J, et al. Am J Cardiol 110: 356-63, 2012.
2. Tomé J, et al. Pharmacol Res 72: 69-82, 2013

Wine Antioxidants: Myricetin

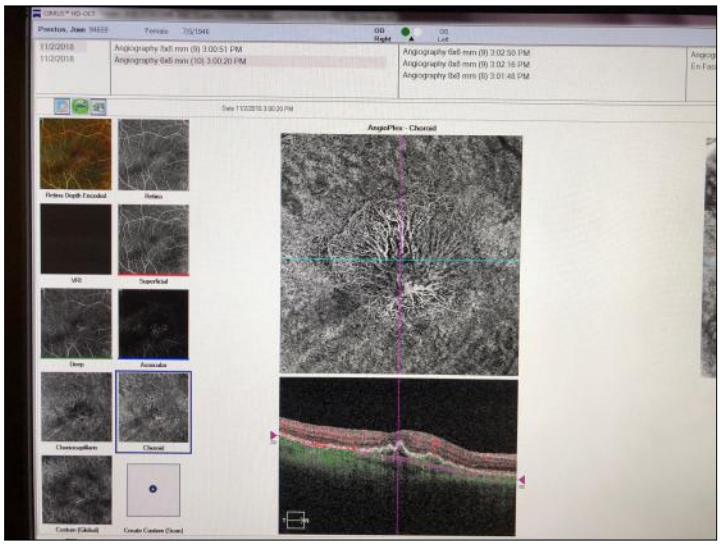
- Lab studies, diabetes:
  - found to improve glucose and glycogen metabolism,
  - Found to lower blood hyperglycemia (in one study by 50%), normalize elevated triglyceride levels, and improve renal function in diabetic rats

1. Ong, Kian C., and Hoon-Eng Khoo. Life sciences 67.14 (2000): 1695-1705.
2. Ong, Kian C., and Hoon-Eng Khoo. Biochemical pharmacology 51.4 (1996): 423-429.
3. Liu, I-Min, et al. Planta Medica 71.07 (2005): 617-621.
4. Liu, I-Min, Shorong-Shii Liou, and Juei-Tang Cheng. J ethnopharmacol 104.1 (2006): 199-206.
5. Ozcan, Filiz, et al. Clinical and experimental medicine 12.4 (2012): 265-272.
6. Kandasamy, Neelamegam, and Natarajan Ashokkumar. Biomed Prev Nutr 2.4 (2012): 246-251.

Quercetin + Myricetin

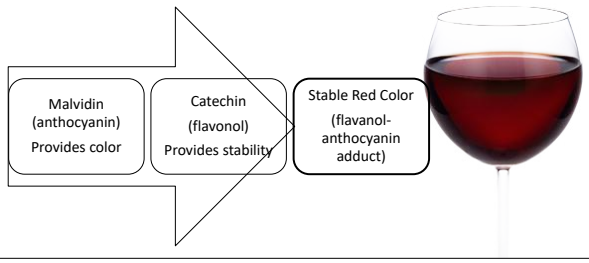
- Human RPE cells, plus in animals:
  - Quercetin + myricetin combo superior vs either alone in reducing ocular inflammation
  - When combined with anthocyanins (purple-red antioxidant pigments found in berries), combo most effective in reducing endoplasmic reticulum stress – key risk factor for diabetic retinopathy

1. 6. Ha JH, et al. J Nutr 144:799-806, 2014.



Wine Antioxidants: Seeing Red

- Wine color comes from its antioxidants!
- Grape color components unstable.
- During aging, complex interactions between antioxidants lead to stable red color. One example:

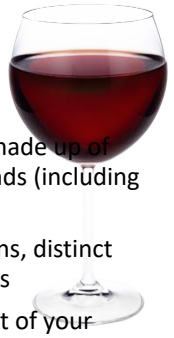


Wine and Health

- One study went one to show that the tannins (polyphenoic antioxidants) in wine are effective in reducing myocardial ischemic reperfusion injury
- Plays a crucial role in cardioprotection
- Where do tannins in wine come from?

Das Dk, Sato M, Ray PS et al. Cardioprotection of red wine : role of polyphenolic antioxidants. Drugs Experimental and Clinical Resources. 1999;25(2-3):115-20

The taste of antioxidants - Tannins



- Tannins (and pseudo tannins) are polymers made up of antioxidant phenol and polyphenol compounds (including gallic acid, catechin, epicatechin).
- Oak barrels are an important source of tannins, distinct from those provided by grape skins and seeds
- Tannins impart a parched dryness at the front of your mouth, and can taste bitter near the middle of the tongue

Wine and Health: Fountain of Youth

- A study in mice found that resveratrol possessed pro-inflammatory properties and prevented the formation of blood clots
- Mice who consumed large quantities of the resveratrol compound, lived about 33% longer

Resveratrol improves health and survival of mice on a high-calorie diet. Nature. 2006 Nov 16;444(7117):337-42. Epub 2006 Nov 1.

Wine and Health: Excess Wine

- Been linked to an increase accidents and death
- 5-year Study of 14 western European countries, age and gender adjusted. Accidents were measured on a per consumption basis. Data confirmed that accident mortality rates were affected by per capita consumption[i].

- [i] Skog, OJ. Alcohol consuptmion and overall accident mortality in 14 European countries. Addiction. 2001 Feb;96 Suppl 1:S35-47

Wine and Health: Excess Wine

- Been linked to an increase in heart disease
- Research has shown that when looking specifically at Ischemic Heart Disease (IHD)
- Mortality rates were directly affected by consumption levels
- Ranged from protective effects with moderate alcohol consumption to harmful heart effects with heavy drinking

- Kerr WC, Ye Y. Population-level relationships between alcohol consumption measures and Ischemic Heart Disease mortnality in U.S. time-series. Alcohol Clinical and Exerimental Resource. 2007 Nov;31(11):1913-9

Wine and Health: Excess Wine

- Liver damage and excessive drinking
- More recent research has found that the main mechanism in liver cirrhosis is the activation of hepatic stellate cells, which acquire a myofibroblast-like phonotype.[i]
- Phenolic compounds contained in red wine have been shown to have antifibrotic properties, alcholol in excess can cause fibrosis to activated hepatic stellate cells resulting in cirrhosis

- Svegliati-Baroni G, Jezequel AM, Orlandi F. Wine: risk factors for liever disease and antibirotic coupounds. Drugs Experiemntal and Clinical Resource. 1999;25(2-3):143-5

Wine and Health: Excess Wine

- Epideliological data have identified chronic, excessive alcohol consumption as a risk factor to cancers including those of the respiratory tract, upper gastrointestinal, liver, breast and colorectal.
- The pathophysiological mechanisms include acetaladehyde (AA), free-radical damage and loss of nutritional factors.

- Seitz HK, Maurer B, Stickel F. Alcohol consumption and cancer of the gastrointestinal tract. Digestive Diseases. 2005;23(3-4):297-303.
- Seitz HK, Meier P. The role of acetaldehyde in upper digestive tract cancer in alcoholics. Transl Resources. 2007 Jun;149(6):293-7

Wine and Health: Excess Wine

- Important for clinicians to assess the level of alcohol intake during a patient history
- The differences between daily intake of small to moderate alcohol versus large quantities may be the difference between preventing and causing disease
- 1-2 glasses per day, likely beneficial
- 1-2 bottles per day, likely NOT so good

Understanding and Health

- Resveratrol is also present in berries, grapes, nuts and grape juice
- Ounce for ounce, red wine packs two times more flavonoids
- The fermentation process allows resveratrol to be absorbed by the body more readily

Wine and Ocular Health

- Ocular health benefits
  - Retinal disease - AMD
  - Cataracts?
  - Corneal disease – RCE?
  - Other diseases that involve anti-VEGF?
- General health benefits -French Paradox
- Risks of excessive alcohol and optometry's role

Thank You

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