

In Vino Sanitas: In Wine There Is Health

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Physicians have used wine for its medicinal qualities for millennia. Receipts for wine based medicines in ancient Egyptian papyri and Sumerian tablets date back circa 2200 BC, making wine the world's oldest documented medicine. The Greek physician Hippocrates (circa 400BC), the "Father of Medicine", is recorded as using wine as a disinfectant, antiseptic, an aid to digestion, a diuretic, a vehicle for other drugs and as part of a healthy diet. Ancient Rome's most famous physician, Galen (2nd century AD), wrote extensively about the medical uses of various wines from different regions of Greece and Italy.

Wine continued to play a central role in medicine until the 19th century, probably due to the lack of safe drinking water as other health benefits were unproven. In the late 19th and early 20th century, alcohol's toxic and addictive effects became clear and it fell out of favour with the medical profession. However, interest in the health benefits of regular wine consumption has grown considerably over the past 30 years; is this interest valid?

Recent resurgence of interest followed St Leger et al's publication in the Lancet in 1979 that there was an inverse relationship between wine consumption and deaths from coronary heart disease in developed countries. Public interest was fuelled by the United States (US) news programme 60 Minutes' broadcast in 1991 on the "French Paradox", which featured Serge Renaud's observation that in France there was low mortality from coronary heart disease despite a high intake of saturated fat, whereas in most countries, high intake of saturated fat was positively related to high mortality from coronary heart disease. He explained that this paradox may be attributable to high wine consumption in France. He also proposed that the protective effect was due to alcohol's ability to inhibit platelet aggregation in the blood clotting mechanism.

Following the 60 Minutes broadcast, US sales of red wine rocketed 44% over previous years. Renaud subsequently published his evidence in the Lancet in 1992.

There has been much scientific debate on

whether all alcoholic drinks confer the same health benefit. Various studies including Rimm et al's review of 25 studies in the BMJ in 1996 and Rimm et al's study of 39,007 men in the NEJM in 2003, suggested that daily consumption of something alcoholic provided some protection from heart disease compared with drinking less often or not at all. Renaud et al's prospective study of 36,250 men in Eastern France, aged 40-60, followed for 12-18 years, in Arch Intern Med in 1999, found that moderate intake of both wine and beer was associated with a lower relative risk of cardiovascular disease, but the risk was more significant with wine. However, only daily wine intake (22-32 g of alcohol) was associated with a statistically significant 33% lower risk of all-cause mortality due to a lower incidence of cardiovascular disease, cancer, violent death, and other causes. Klatsky et al's prospective study of 128,934 adults, followed for 20 years, in Am J Epidemiol in 2003, found that moderate wine drinkers had a statistically significantly lower mortality risk than beer or liquor (spirit) drinkers, largely because of a lower risk of coronary heart disease. There was also a substantially increased risk for heavy drinkers and a slightly higher risk for abstainers resulting in a J-shaped alcohol-mortality curve.

The substantial medical risks of heavy alcohol drinking and the probable existence of a less harmful or safe drinking limit have been well documented. Heavy alcohol drinking is associated with many diseases including liver disease (hepatitis and cirrhosis), cancer (oral, oesophageal and stomach), pancreatitis, cardiovascular disease (alcoholic cardiomyopathy, hypertension, heart rhythm disturbances and haemorrhagic stroke), central and peripheral nervous disorders (dementia, depression, anxiety and sexual difficulties), serious accidents and obesity.

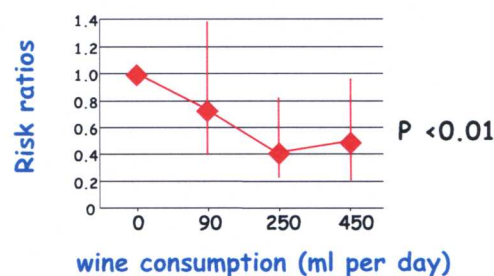
There is a wide variation in recommended safe drinking limits between different countries. Recommended

safe limits of alcohol drinking in the UK are three units per day for men and two units per day for women (pregnant women should abstain). There are one and a half units of alcohol in a small glass (125ml) of an ordinary strength wine (12% alcohol by volume).

Diet and lifestyle are widely accepted to be important modifiable risk factors for good health. The INTERHEART standardised case-controlled study of acute myocardial infarction (heart attack) of 15,152 subjects in 52 countries, published in the Lancet in 2004, demonstrated that abnormal blood cholesterol, smoking, hypertension, diabetes, abdominal obesity and psychosocial factors were negative risk factors, while daily consumption of fruit and vegetables, and regular alcohol consumption and physical activity were positive risk factors for myocardial infarction worldwide in both sexes and at all ages in all regions. Interestingly, a number of other studies showed that wine drinkers had a higher quality diet and consumed more fruit and vegetables and lower levels of carbohydrate and saturated fat, and were less likely to smoke and more likely to exercise.

Serge Renaud set up the Lyon Diet Heart Study in 1985, a randomised, controlled trial of 605 patients to test the effectiveness of a Mediterranean-type diet, which emphasises fruit, vegetables, bread, cereal, fish and alpha-linolenic acid, on the rate of coronary heart events in patients who have had a first heart attack. After an average follow-up of 46 months, patients following the Mediterranean-style diet had a 50-70% lower risk of recurrent heart disease. The findings from this study imply risk factors beyond lipids and lipoproteins

Lyon Diet Heart Study - after an initial MI wine reduces further vascular events (de Lorgeril M et al., *Circulation* 2002, 106: 1465-9)



Source: Dr Roger Corder

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(cholesterol), the primary focus in secondary prevention. However, when diet was ignored, daily moderate wine consumption was one of the key factors in the secondary prevention of a heart attack, reducing recurrence by half.

The potential beneficial effect of wine on coronary heart disease has been strengthened by various studies showing that wine has a protective effect on blood vessels in other parts of the body such as ischaemic stroke, peripheral artery disease, vascular dementia and age-related macular degeneration. These studies include the Health Professionals Follow-up Study, which showed that daily red wine drinkers had a 40% reduction in the number of ischaemic strokes compared to a small increased risk in regular beer or spirits drinkers. The Framingham Heart Study showed that the incidence of intermittent claudication, leg muscle pain on exertion (typically in the calf), were less common in men and women consuming one to two alcoholic drinks per day. The Nurses' Health Study showed that women drinking at least one alcoholic drink daily performed better in mental ability tests.

Moderate wine consumption has been linked with a variety of other health benefits including a reduced risk of Type II diabetes, complications including heart disease in diabetics, and metabolic syndrome, radioprotective and chemoprotective benefits in cancer treatment patients and better male and female sexual health. However, the strongest health benefits to date have been demonstrated to be in coronary heart disease.

Biological Explanations

The pathological basis of coronary or ischaemic heart disease is the atherosclerotic plaque. This is a collection of intimal macrophages in the coronary arteries uncontrollably ingesting oxidised low density lipoprotein (LDL) cholesterol surrounded by proliferating smooth muscle cells and extracellular matrix. The overlying endothelium (the surface layer of the artery that is in contact with blood) is dysfunctional, reducing its ability to produce vasodilatory, antithrombotic molecules such as nitric oxide and prostacyclin and a rise in the vasoconstrictor endothelin-1. It appears

that this process starts very early on in life and takes decades to become clinically significant (earlier due to diets high in saturated fat or other risk factors); the plaque may grow or rupture exposing the highly thrombogenic plaque causing distal tissue ischaemia (artery blockage by formation of a blood clot causing artery blockage and consequently insufficient blood supply to the tissue or organ) leading to angina or ultimately myocardial infarction.

Scientists have been searching for plausible biological explanations with hundreds of studies published so far. Interest has focused specifically on polyphenols, the main contributors to the colour and taste of red wine. Wine polyphenols can be classified as flavonoids, which comprise flavanols (found in grape seed, green tea and chocolate), anthocyanins (the colour in grape skin, fruit and flowers), flavonols (quercetin), and non-flavonoids, which comprise stilbenes such as resveratrol (found in some red wines) and ellagitannins (found in oaked wines and some fruit and nuts). Grape seed flavanols are present in wine mainly as procyanidins, with a higher amount found in grape varieties with small fruit where there is a higher proportion of grape seed per volume of grape. Procyanidins are the most abundant polyphenol (25-50%) in young red wines and are extracted into the wine as the alcoholic concentration increases during fermentation. Procyanidins are the main source of the astringency in young red wine but react with each other to form longer polymers (condensed tannins) as the wine age until they become insoluble and precipitate at the bottom of the bottle.

Numerous studies of the effect of wine and its polyphenols on cholesterol, an essential element of atherogenesis and platelet aggregation, pivotal in the pathogenesis of acute coronary syndrome, have been inconclusive in developing a mechanism of action. A sub-study of the Lyon Diet Heart Study showed that although there was no correlation between alcohol intake and platelet aggregation in the Mediterranean group, alcohol intake mir-

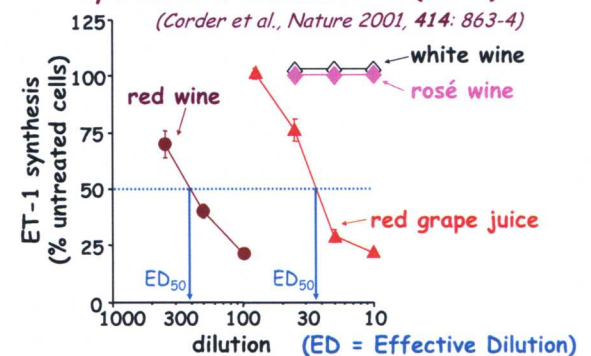
rored improvements in platelet aggregation in the Western group, suggesting that alcohol intake might normalise the impact of saturated fat.

There are numerous in vitro and mouse studies demonstrating the potential antioxidant benefits of resveratrol on cholesterol efflux and platelet aggregation. Resveratrol is produced in grape skin to protect the grape from ultraviolet light and fungal attack. However, the benefits have not been replicated in human studies and the resveratrol concentration required in humans to cause these antioxidant effects are five to ten times the amount typically found in wine, implying that it would not be possible to achieve these effects through wine consumption.

Interestingly, Vauzour et al's randomised, placebo controlled, cross-over interventional study in *Br J Nutr* in 2009 of 15 adults suggested that daily moderate consumption of Champagne may improve vascular performance via the delivery of polyphenols capable of improving nitric oxide bioavailability and reducing matrix metalloproteinase (MMP-9) activity. The authors propose that Champagne in contrast to white wine is relatively rich in polyphenols derived from the two red grapes, Pinot Noir and Pinot Meunier, which are used in its production along with the white grape Chardonnay.

Corder et al's study in *Nature* in 2006 identified procyanidins as the principal vasoactive polyphenols in red wine and showed that they were present at higher concentrations in wine from southwestern France and Sardinia, where traditional production methods ensure that these compounds are efficiently extracted during

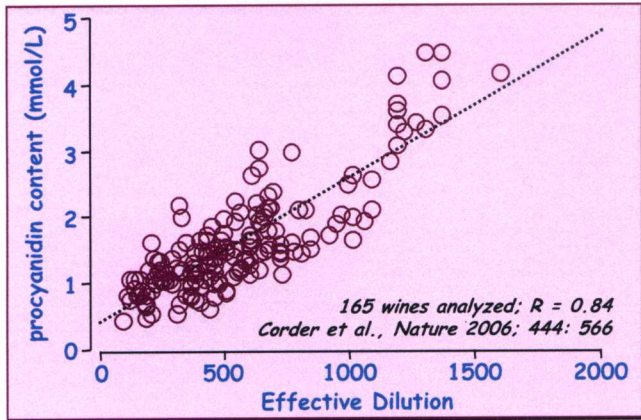
Comparison of wines and red grape juice on synthesis of endothelin-1 (ET-1)



Source: Dr Roger Corder

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Procyanidin levels in wine correlate with the vascular effects



Source: Dr Roger Corder

vinification. These regions also happen to be associated with increased longevity in the population.

High consumption of polyphenols inhibits atherosclerosis in experimental models. Red wine polyphenols induce endothelium dependent vasodilatation of blood vessels and suppress the synthesis of the vasoconstrictor endothelin-1, which may account for their anti-atherosclerotic activity. Corder found that although the total polyphenols concentration of each wine correlated with the suppression of endothelin-1 synthesis, it was the procyanidin levels of the polyphenols that provided the best correlation.

Corder compared wine produced in areas of increased longevity with a broad selection of wines from different countries. Sardinia's Nuoro province has the highest

proportion of centenarians in Europe, while there are relatively more men aged 75 or over in the French department of Gers in southwest France. He found that wine from Nuoro and the Gers area have two to four times more biological activity and procyanidin content than other wine.

The higher procyanidin concentration in wine from southwest France is due to the traditional wine making methods, which ensure that high amounts of procyanidin are extracted and to the flavonoid-rich Tannat grape used to produce local wines in the Gers area but is rarely grown elsewhere.

Procyanidin-Rich Wine

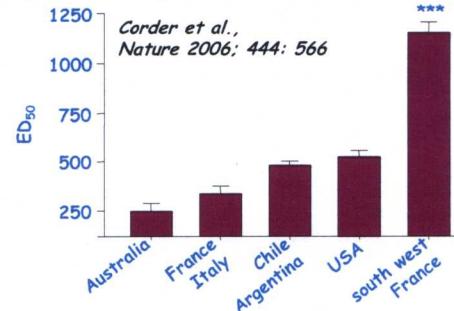
The concentration of procyanidins in wine is affected by vineyard, grape variety, winemaking process and wine age. In the vineyard, wine from infertile land, cooler climates promoting slow ripening, higher altitudes with more but not excessive ultraviolet light, well established vines, increased but not excessive exposure of grapes to direct sunlight, low yields and old vines have been found to contain more procyanidins. Grape varieties known to contain high levels of

procyanidins include Tannat (the highest), Cabernet Sauvignon, Malbec, Nebbiolo, Sangiovese and Aglianico. However, not all grape varieties in all wine producing regions have been tested for procyanidin levels.

The most important aspect of the wine making process is the

length of time the wine spends in contact with the grape seeds and skins during the maceration process to extract colour, flavour and tannins from the grapes. Wine with maceration times of more than three weeks will have the highest procyanidin levels, 10-14 days will have decent levels, but less than seven days will have low levels. Therefore, white wine and modern style red fruity easy drinking (low in tannin and astringency) wine will be low in procyanidins. Fining and filtering of wine to clarify and stabilise wine can remove a variety of polyphenols including procyanidins, the amount removed depending on the agent used; the worst fining agent being polyvinylpolypyrrolidone (PVPP). Older wine will contain less procyanidins because these molecules react with each other over time to form longer polymers, condensed tannins, which eventually be-

Relative inhibition of endothelin-1 synthesis by wines of different origin



Source: Dr Roger Corder

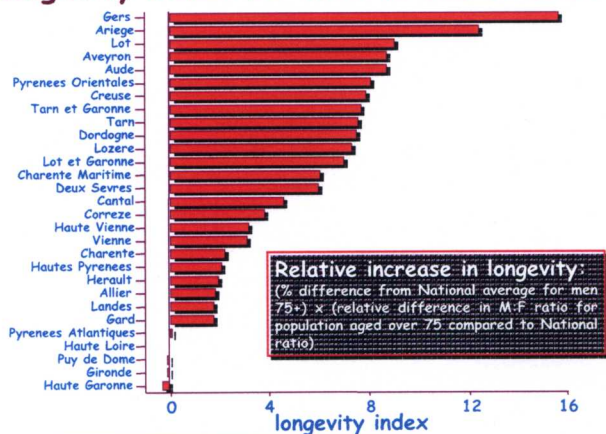
come insoluble and form sediment. However, the effect of age depends on the structure of the wine, cellaring conditions and the length of time.

Corder measured the amount of procyanidins in a number of wines from various wine producing regions, which are published in his book *The Wine Diet*. Fortunately, I have experienced the pleasure of tasting three wines from southwest France with the highest measured content of polyphenols and procyanidins:

- Georges Vigoroux's Château Haute Serre, Cuvée Géron Dadine, Cahors, 2005, 100% Malbec. The wine was very intense, deep inky ruby with an aroma of black fruit, spices, vanilla and slightly toasted; dry and crisp with very high tannins, full bodied, but well balanced and structured with a long finish; quite delicious.

- Domaine de Saint Guilhem, Renaissance,

Longevity index for men in SW France



Source: Dr Roger Corder

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Fronton Rouge, 2006, a blend of Cabernet Sauvignon, Negrette and Syrah. The wine was deep inky ruby with an aroma of blackcurrants, black fruit and farmyard; off-dry and crisp with very high tannins, full bodied, but well structured with a long finish.

• Producteurs Plaimont, Château de Sabazan, VDQS Saint-Mont, 2005, a blend of 70% Tannat, 15% Pinenc and 15% Cabernet Sauvignon. The wine was deep inky ruby with an aroma of black fruit and bubble gum; dry and crisp with high tannins, full bodied, but well structured with a long finish.

All three wines were young but would accompany roasted, stewed and grilled red meat and cheese dishes.

Conclusion

There is compelling evidence that daily light to moderate wine consumption is associated with reduced coronary heart disease morbidity and mortality. Studies suggest that the polyphenols, particularly procyanidins, in red wine may be responsible for inhibiting atherosclerosis and improving vascular health.

Although the absorption of polyphenols and procyanidins and their blood levels have been demonstrated in vivo, little is known about their bioavailability and metabolism. Further investigation of polyphenol and procyanidin-rich wine and food is warranted to understand how vascular function might be optimally maintained; in particular, more in vivo, randomised, placebo controlled, interventional studies in healthy subjects and patients with different diseases.

In addition, structured and independent testing of a much larger range and volume of wine from different wine producing regions and from different vintages would provide much needed insight into the potential health benefits of different types of wine. ♣



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