Wine and health

G.O. Armstrong[a], M.G. Lambrechts[a,b], E.P.G. Mansvelt[c], D.P. Van Velden[d*] and I.S. Pretorius[a,b,e]

Is it possible that wine may indeed be the world's oldest medicine? Until the 18th century, wine played an integral role in medical practice. Not only was it safer to drink than most available water but its alcohol, antioxidant and acid content inhibited the growth of many spoilage and pathogenic organisms. The paradigm shifted in the second half of the 20th century, when alcohol consumption, including wine drinking, had become the target of health campaigners who, with some success, demanded warning labels on wine bottles. Substantial medical evidence, summarized in this article, was accumulated during the 1990s and indicated that the moderate consumption of especially red wine can reduce the incidence of coronary heart disease. Today it is perceived, and generally accepted, that moderate wine drinking can be socially beneficial, and can also be effective in the management of stress and reducing coronary heart disease. The prudent wine drinkers, however, continue to monitor their drinking habits so as to ensure that the benefits exceed the risks.

As a consequence of aerobic life and energy metabolism, human beings are exposed to a barrage of oxidative damage.[1] While occasionally contributing to this damage, one's diet is also able to provide protection in the form of antioxidant relief. This explains, at least in part, the relationship between diet and chronic diseases such as atherosclerosis and cancer. Coronary heart disease (CHD) has established itself as the leading cause of death in industrialized nations and is increasingly so in the developing world. Through the ages, conventional wisdom and, more recently, epidemiological evidence indicated that the moderate intake of alcoholic beverages is consistent with a healthy life style.

The renewed interest in flavonoids, resveratrol and wine consumption has been spurred on by the dietary anomaly commonly referred to as the 'French paradox'. This phenomenon refers to a remarkable association between a high fat diet and a lower incidence of CHD found in Mediterranean countries, which contrasts with a higher incidence of CHD among most Western cultures.[2] The French eat 30% more fat, smoke more and exercise less than Americans and yet have fewer heart attacks.[3,4] An American male has three times the chance of dying from a heart attack as a Frenchman of the same age.[5] A significant difference in the two cultures is the amount of wine that is drunk. The average annual per capita consumption of wine in France is 58.1 litres, whereas the Americans imbibe a meagre 7.42 litres. The increased benefits that red wine has over white wine arises from the processes used to produce them. During red wine vinification, the grape must is fermented with the grape skin. As the yeast converts the grape sugars to ethanol and carbon dioxide, the fermentation temperature and alcohol content increase. This raises the solubility of the various compounds found in the grape skin, in particular phenolic acids, anthocyanins, tannins and resveratrol. among others, and they are released into the wine. During white wine vinification the grape juice is first separated from the skins in most cases before it is fermented, in order to obtain a clear wine that is low in tannins and other phenolics.

The aim of this review is to provide a compact summary of the vast amount of literature available on the compounds found in wine that are able to provide cardiovascular protection.

Development of cardiovascular disease

Oxidative stress is ubiquitous throughout the body and arises primarily from oxidants produced endo- and exogenously.[6] The superoxide radical (O_2^-), which tends to leak from the mitochondria, is a precursor for the formation of more potent oxidants such as the peroxide ion (O_2^{2-}) and the hydroxyl radical (OH^-). The latter can initiate the peroxidation of lipids and so disrupt biological membranes and render lipoproteins more atherogenic.[7] These processes are accelerated in the presence of free transition metal ions such as Fe^{2+} and Cu^+. Oxidative modification of low-density lipoproteins (LDLs) is recognized as an important factor in the development of atherosclerotic lesions.[8]

Atherosclerosis refers to the progressive accumulation of cholesterol in the blood vessel wall, leading to injury to the blood vessel's endothelial lining, forming an atherosclerotic plaque. Cholesterol in the body exists either in a free form or as a fatty acid ester and is carried in the blood by lipoproteins. The body's cholesterol level is regulated by low-density lipoprotein receptors, which transport cholesterol into the cell. When there is LDL in excess or when the LDL receptor is (genetically) deficient, LDL accumulates in the blood and the ratio of low-density lipoproteins to high-density lipoproteins (HDLs) increases.

Oxidized LDL can be taken up by endothelial cells or ingested by monocytes through their scavenger receptors, leading to the formation of cholesterol ester-loaded foam cells in the arterial walls. These inflammatory events are believed to precede the formation of the atherosclerotic plaque, which eventually leads to the formation of a thrombus.[9]

Atherosclerosis is characterized by the presence of lipid-laden macrophages within the intima of arteries. Macrophages *in vitro* take up and degrade only small amounts of unoxidized human LDL due to down regulation of their LDL receptors and do not accumulate cholesterol. However, the uptake of oxidized LDL is rapid and not subject to down regulation. Oxidized LDL is also chemotactic for macrophages[10] and cytotoxic to the vascular endothelium.[11]

A consequence of atherosclerotic lesions is a natural inflammatory response in the arterial intima which focally promotes adhesion and aggregation of blood platelets at the site of intimal disruption. Platelet activation, adhesion and aggregation are natural responses of platelets at sites of vessel injury. Platelet aggregation is mediated by the enzymatic conversion of arachidonic acid by cyclo-oxygenase, to form thromboxane A_2, a potent pro-aggregatory agent.[12] This forms the basis of thrombosis and compounds the risk of developing severe cardiovasular disease. Such thrombus formation eventually reduces the blood flow to the downstream tissues, a condition known as ischaemia. Finally, complete blockage of the arterial lumen occurs through thrombosis, resulting in the death of these tissues, so-called myocardial infarction or a heart attack.

As a result of these serious health effects as well as their economic impact, research

[a]Institute for Wine Biotechnology, Faculty of Agriculture, University of Stellenbosch.
[b]Department of Viticulture and Oenology, Faculty of Agriculture, University of Stellenbosch.
[c]Department of Haematology, Faculty of Medicine, University of Stellenbosch.
[d]Department of Family Medicine and Primary Care, Faculty of Medicine, University of Stellenbosch.
[e]Department of Microbiology, Faculty of Science, University of Stellenbosch.
*Author for correspondence. Department of Family Medicine and Primary Care, University of Stellenbosch, P.O. Box 19063, Tygerberg, 7505 South Africa.
E-mail: dpvv@maties.sun.ac.za

into the causes, prevention and treatment of atherosclerosis has been intense.

Principal protective compounds found in wine

Phenolic compounds

Flavonoids are a group of natural phenolic compounds, consisting mainly of flavonols, flavanols and anthocyanins.[13] They respond to light and are known to control the level of auxins, which regulate plant growth and differentiation.[14] In food plants flavonoids provide colour, texture and taste.[15] They occur naturally in fruit, vegetables and beverages (tea, wine and fruit juices) and form an integral part of the human diet. This group of polyphenols exhibit a wide range of biological activity as antimicrobials, anti-allergics and vasodilators.[16] Wine polyphenols are able to exhibit anti-inflammatory and antithrombotic activity by respectively inhibiting 12-lipoxygenase and cyclo-oxygenase and hence the production of 12-hydroxyeicosatetranoate and thromboxane A_2.[17] Flavonoids are the main polyphenolic compounds found in wine. Red wine and grape juice are particularly rich in flavonoids, containing more than 1 g l^{-1} in comparison with <60 mg l^{-1} found in white wine.[18] The two main classes of flavonoids are anthocyanins (0.2–0.8 g l^{-1}) and flavanols (1–3 g l^{-1}). Flavanols are present as monomers (catechins) and as oligomers (procyanidins or condensed tannins).[19] Catechin and epicatechin have been shown to exert potent biological effects as antioxidants and as inhibitors of free-radical formation.[20] The biosynthetic polymerization of these free phenols and of their gallic esters generates the procyanidins and condensed tannins, which in themselves have powerful anticoagulation activities.[21] One of their more pronounced effects is their antioxidant ability, to such an extent that it is several times more potent than that of α-tocopherol (vitamin E).[22,23]

Quercetin, a flavonol, is the most frequently studied flavonoid and has been shown to exhibit biological properties that are consistent with its protective effect on the cardiovascular system.[2] Its concentration in red wine ranges from 4–16 mg l^{-1} with white wine containing <1 mg l^{-1}.[2] Of a number of international wines studied, the quercetin content of the South African wines was among the highest for their respective cultivars. Merlot was the highest at 10.3 mg l^{-1}, followed by Shiraz at 9.2 mg l^{-1}; Pinotage, South Africa's exclusive red wine cultivar, contained an average of 4.7 mg l^{-1}.[24]

Qualitative and quantitative changes in polyphenols can occur during the processing and ageing of wine. This can affect the bioavailabilty and antioxidant potential of these compounds. A number of interesting issues have been raised: (i) the effect of flavonoid conjugation with other substances on the rate of intestinal absorption; (ii) the modulation of the bioavailability of flavonoids by other food matrix molecules, such as proteins, lipids and fibres; (iii) the role of intestinal microflora, especially on polymeric polyphenols; (iv) the quantitative and qualitative regulation by liver metabolism and resecretion in bile; and (v) the biological consequences of chelation of metal ions by polyphenols.[19] There is, however, a limited amount of information available that may be able to clarify some of the above points. Reports have indicated that quercetin glycosides are more efficiently absorbed by the small intestine than free quercetin.[25] Human serum albumin is the primary protein that binds quercetin.[26] After crossing the intestinal mucosa, it is bound to albumin and transported via the portal vein to the liver.[2] Here it is subjected to various reactions, including methylation, sulphation and glucuronidation, leading to various conjugated forms.[27] Fortunately, quercetin, in its conjugated form, is able to maintain its antioxidant activity.[28] Quercetin as a glucoside is a cancer-producing substance, but if the sugar moiety is split from the molecule, during digestion in the gastrointestinal tract, it becomes an anti-cancer molecule. Studies involving animals have shown that the absorption of catechin is approximately five times higher than quercetin.[29] It has, however, been reported that flavonoids are poorly absorbed in the stomach and are subject to intestinal degradation by intestinal microorganisms.[2] Data on the pharmokinetics of absorbed polyphenols are relatively scarce and inconclusive.

Resveratrol

The biosynthesis and accumulation of the stilbene resveratrol is one of the key components in the grape's disease defence mechanism. These low molecular weight, antimicrobial stress metabolites are produced *de novo* in the grape skin.[30] It is here that they form the primary defence against attack from fungi, the majority of which is made up of *Botrytis cinerea*.[31] The resveratrol concentration ranges between 5 and 7 μg g^{-1} fresh weight in the skin cells, whereas only traces can be detected in the fruit flesh (<0.1 μg g^{-1} fresh weight).[32] The actual amount of resveratrol found in wine varies considerably and is dependent on a number of factors including climate,[33] cultivar,[34] *Botrytis* pressure in the vineyard[35] and influence of enological procedures.[36] Resveratrol may also be found in the form of a glucoside, known as a piceid molecule. This chemical still retains its antioxidant activity identical to that of free resveratrol.[37] During malolactic fermentation, however, malolactic bacteria, containing β-glucosidase activity, are able to cleave off the glucose molecule, thereby increasing the amount of free resveratrol.[38] Resveratrol has also been shown to exhibit anti-inflammatory activity in a similar fashion to that of the polyphenols.[17] The total resveratrol concentration in red wine varies between 0.1 and 12 mg l^{-1}.[39] Although this is considerably less than the amount of flavonoids found in red wine, resveratrol has still enjoyed the strongest association with the 'French paradox'. This may be because resveratrol has been reported in very few components of the human diet, with red wine being the only significant source, thereby distinguishing it from other alcoholic beverages.[40]

Resveratrol as a phytoestrogen

Oestrogen replacement therapy (ERT) has an anti-atherogenic effect as it reduces the risk of cardiovascular disease. Oestrogen also prevents osteoporosis in postmenopausal women.[41] Oestrogen users show a reduced risk of stroke and consequent mortality, as well as a reduced risk of Alzheimer's disease.[42,43] The data and knowledge currently available strongly indicate that women's overall quality of life is enhanced with oestrogen use.[44]

On the basis of the structural similarity of resveratrol and the synthetic oestrogen diethylstilbesterol, some researchers have postulated that resveratrol could be a phytoestrogen.[45,46] The oestrogenic actions of resveratrol broaden the spectrum of its biological actions and may be relevant to the cardiovascular benefits of drinking wine. The clinical significance of the oestrogenic effect of resveratrol needs to be investigated in more depth before it can be recommended for clinical use such as in the prevention of osteoporosis.

Salicylic acid

Various compounds are produced by plants as constitutive and as inductive defence chemicals. Salicylic acid is one of these and is part of the plant's systemic

acquired resistance.[47] It actually performs so many functions in plants that it has previously been postulated to be a plant hormone.[48] Salicylic acid levels in 12 South African wines studied ranged from 126–383 $\mu g\ l^{-1}$.[12] Once again the content is dependent on variety, vine health and processing practices, among other factors.[47] The pharmacological activities of this ubiquitous compound include antipyretic, anti-inflammatory and analgesic properties.[47]

Fibrin formation following adhesion and aggregation of platelets is an important consequence of low-density lipoprotein oxidation in the aetiology of atherosclerotic plaque formation.[49] Salicylic acid and its metabolites, 2,3 dihydrobenzoic acid and 2,5 dihydrobenzoic acid, all have vasodilator and anti-inflammatory activities.[12] As it happens, salicylic acid is also an outstanding antioxidant and in this regard it may be able to exhibit anti-atherogenic properties by limiting LDL oxidation.[50] This still needs to be established *in vivo.*

Aspirin (acetyl salicylic acid) is rapidly deacetylated in the body in the portal blood circulation to yield salicylic acid.[51] Thus, in the systemic blood circulation only salicylic acid and its metabolites remain, not aspirin, and many of the medical benefits commonly attributed to aspirin might in fact be due to salicylic acid.[47] It has been shown that salicylic acid and aspirin are equipotent in inhibiting the chemotactic generation of 12-HETE from 12-HPETE in the lipoxygenase pathway of arachidonic acid metabolism by leukocytes, a key reaction in the prevention of inflammation.[52]

Alcohol

The effects of alcohol consumption on cardiovascular disease are complex and remain under close scrutiny. While heavy alcohol intake increases overall mortality[53] and death due to cardiovascular complications,[54] the moderate intake of alcohol appears to exhibit a protective effect against CHD compared to drinking no alcohol at all.[55] The U- and J-shaped curves showing the relationship between alcohol consumption and CHD have been well documented.[56–58] The high points for mortality are abstainers and excessive drinkers. The group at lowest risk are the moderate drinkers. The mechanisms by which alcohol exerts its protective effect are not completely understood. One of the best-established physiological risk factors for vascular disease, that is, decreased serum levels of high-density lipoprotein, has been shown to increase as a direct result of moderate alcohol consumption.[57] HDLs are particles that are able to scavenge cholesterol from membranes and tissues where it is in excess and transport it to the liver for excretion. Alcohol is able to increase, in a dose-dependent manner, the hepatic secretion of apolipoprotein A-I and apolipoprotein A-II, both of which are the primary lipoproteins found in the HDLs.[58,59] Alcohol is also able to block the stimulation of phospholipase A_2, thereby preventing the mobilization of arachidonate, which is essential for the generation of thromboxin A_2, an important platelet aggregant. The amount of alcohol, however, required for this mechanism of protection far exceeds what can be described as moderate consumption.[60]

Conclusion

The accumulating evidence strongly suggests that the moderate consumption of alcoholic beverages, in particular red wine, carries numerous health benefits. There is abundant experimental evidence to indicate that wine-derived compounds improve vascular function and interfere with haemostatic and oxidative mechanisms involved in the initiation and progression of vascular damage. While alcohol has its benefits, the mechanisms through which wine might exert its anti-atherogenic and antithrombotic effects appear to be distinct from those of alcohol.[56] This is attributable to the biological properties of red wine's polyphenolic constituents, and most notably its antioxidant and radical scavenging ability. This notion has received strong support from both epidemiological[61] and experimental studies in man[62] and laboratory animals.[63] Observations that phenolic acids are absorbed from the gastrointestinal tract and are measurable in plasma and urine offer further support.[64] It would be unwise to isolate any single compound, or group of compounds, as the only health-providing substance in red wine, but rather emphasize the synergistic action of a variety of the compounds known to be present. A preliminary study in South Africa shows a definite trend towards the increase in *in vivo* antioxidant activity with the consumption of red wine.[66] Any possible lack of antioxidant activity, however, is unlikely to deter the discerning wine connoisseur from enjoying a good bottle of red wine.

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In Brief...

New status and role for magnetic observatory

The minister of arts, culture, science and technology, Ben Ngubane, has declared the Hermanus Magnetic Observatory a national research facility, which in future will operate under the National Research Foundation.

South Africa's first magnetic observatory was established in Cape Town in 1932, and moved along the coast to Hermanus, a 'magnetically clean' site, in 1941 to avoid electrical disturbances from the city. It was subsequently taken over by the CSIR.

The observatory will continue to carry out fundamental and applied research in the fields of geomagnetism, magnetospheric physics and ionospheric physics, as well as geomagnetic field modelling and data recording. The HMO's new status will lead to an expanded research programme and much greater involvement in the training of postgraduate students. The facility will resume its participation in South African Antarctic research and plans to collaborate in South Africa's satellite programme.

Ocean data network for Africa

The Intergovernmental Oceanographic Commission of UNESCO, based in Paris, has launched a web site linking marine research centres throughout Africa (http://odinafrica.org). Called the ODINAFRICA (for 'Ocean data and information network for Africa') web site, the initiative currently involves 20 African coastal states. All ODINAFRICA products and services are free: they include databases, a bibliographic search service, a directory of African marine scientists, a calendar of oceanographic events, and a database of publications on oceanography. A free monthly electronic newsletter is also available to provide information on what is new in Africa related to the oceans; this can be used by interested parties to publish information and advertise activities online for the benefit of their professional colleagues.

In the months to come, the site will provide additional information on the continent's marine research institutions and their data holdings.