The glass that cheers: Phenolic and polyphenolic constituents and the beneficial effects of moderate red wine consumption

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Abstract: Red wines, moderate consumption of which is associated with beneficial effects on health, including a reduced incidence of cardiovascular disease, contain a rich diversity of simple and complex (poly)phenolic compounds. Subtle changes in the polyphenolic profile occur during maturation of the wine which affects its colour and taste. Although the protective effects of red wine consumption have been linked with resveratrol and procyanidins, the identity of the compounds involved remains unclear.

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The glass that cheers:
Phenolic and polyphenolic constituents and the beneficial effects of moderate red wine consumption

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Red wines, moderate consumption of which is associated with beneficial effects on health, including a reduced incidence of cardiovascular disease, contain a rich diversity of simple and complex (poly)phenolic compounds. Subtle changes in the polyphenolic profile occur during maturation of the wine which impacts on their colour and taste. Although the protective effects of red wine consumption have been linked with resveratrol and procyanidins, the identity of the compounds involved remains unclear.

Wine is basically fermented grape juice with a minimal alcohol level of 8.5% by volume. The wild grapevine originated in the Far East (Mesopotamia) and Egypt and evidence for wine production dates from Neolithic times. Wine was consumed by many ancient civilisations including the Mesopotamians, Egyptians, Greeks and Romans. Once the floods had receded, Noah appears to have over indulged in wine (Genesis, Chapter IX, Verse 21) and St. Paul apparently recommended the consumption of wine on health grounds. Galileo made and drank his own red wines right up to his death at the age of 78 in 1642. More than 350 years later, there is now a widely held view that moderate red wine consumption, preferably with meals, can have beneficial effects on health with reduced incidences of coronary heart disease, some cancers and possibly even a delayed cognitive decline. There are numerous papers on the subject but what brought the topic to a worldwide audience was a 1991 CBS
television programme in the USA, "60 Minutes", in which the epidemiologist Serge Renaud linked moderate consumption of red wine with the relatively low incidence of cardiovascular disease in France despite high consumption of saturated fats - a phenomenon now referred to widely as the "French Paradox". Readers interested in learning more about these events and subsequent research associating the high levels of phenolic and polyphenolic compounds in red wines with their protective effects on health should read Roger Corder's most interesting and informative book "The Wine Diet".¹

Production of wines

A wide variety of processes are used to make red wine. Typically, red grapes of *Vitis vinifera* are pressed and the juice (must), together with the crushed grapes, undergo alcoholic fermentation for 5-10 days at ca. 25°-28°C. The solids are removed and the young wine subjected to a secondary or malo-lactic fermentation, which results in malic acid being converted to lactic acid and carbon dioxide. This softens the acidity of the wine and adds to its complexity and stability. The red wine is then matured in stainless steel vats, or in the case of higher quality vintages in oak barrels, for varying periods before being filtered and bottled. White wines are produced from both red and, more traditionally, white varieties of grapes. The grapes are crushed gently rather than pressed to prevent breaking of skins and seeds. Solid material is removed and the clarified juice fermented, typically between 16° and 20°C for 5 days, before undergoing malo-lactic fermentation, maturation, filtration and bottling.

Red wines are produced from varieties of grapes, including Cabernet Sauvignon, Merlot, Malbec, Pinot Noir, Syrah, Cinsault, Rondinella, Sangiovese, Nebiolo, Grenache, Tannat, Tempranillo, Carignan and Primitivo (Figure 1). The main commercial producers are located in France, Italy, Australia, New Zealand, Spain, Chile, Argentina, California, South Africa, as well as Bulgaria, Romania, southern Brazil, and more recently China and India. Thus, red wines are derived from an assortment of grape cultivars, grown under climatic conditions that can vary substantially, not only in different geographical regions, but also locally on a year-to-year basis. To complicate matters further, grapes at different stages of
maturity are used and vinification and ageing procedures are far from uniform. It is hardly surprising, therefore, that red wines are extremely heterogeneous in terms of their colour, flavour, appearance, taste and chemical composition. Although white wines are also heterogeneous, their production results in either low levels or an absence of skin- and seed-derived (poly)phenolics, so the overall level of these compounds is almost always much lower than that found in red wines.

(Poly)phenolic compounds in red wines

In red wines made with prolonged extraction, the fermented must can contain up to 40-60% of the (poly)phenolics originally present in the grapes. Subtle changes in these grape-derived components occur during the ageing of the wines especially when carried out in oak barrels or, as in recent years, during exposure to chips of oak wood. Consequently, there is much diversity in the (poly)phenolic content of different red wines, with the concentration of flavonols varying by more than 10-fold and the overall level of phenolic constituents by almost 5-fold.

The (poly)phenolic compounds in red wines include the hydroxycinnamates coutaric acid, caftaric acid and fertaric acid (Figure 2) which, respectively, are tartaric acid conjugates of coumaric, caffeic and ferulic acids. These compounds are found principally in the flesh of grapes and so occur in both red and white wines. In contrast, skin-derived anthocyanins are feature of red wines and are responsible for their characteristic colour. The main anthocyanin in red wines is malvidin-3-O-glucoside although 12 or more other anthocyanins, including malvidin-3-O-(6‴-O-p-coumaroyl)glucoside, cyanidin-3,5-O-diglucoside (Figure 2), and delphinidin, peonidin and petunidin conjugates also occur in reduced concentrations and as we shall see subtle changes occur in the anthocyanin profile as wines age.

Red wines also contain flavonols, in the form of both free and conjugated quercetin, kaempferol and isorhamnetin, as well as gallic acid and stilbenes (Figure 2). The main stilbenes, albeit in very low concentrations, are trans-resveratrol and trans-resveratrol-3-O-glucoside, and the presence of trans-piceatannol and trans-astrinigin, its 3-O-glucoside, has also been reported. In planta these stilbenes act as phytoalexins and are found in slightly
higher quantities, along with the oxidised dimers \textit{trans-γ-viniferin} and \textit{trans-ε-viniferin}, in vines, growing in colder damp conditions, that have become infected with \textit{Plasmopara viticola} (downy mildew) - circumstances not conducive to the production of grapes that will yield high quality wines\textsuperscript{2}. The flavan-3-ol monomers (+)-catechin and (−)-epicatechin are found in red wines but not in substantial quantities, in contrast to the related seed-derived procyanidin B\textsubscript{1,4} dimers, the C\textsubscript{1} and C\textsubscript{2} trimers and oligomeric and polymeric procyanidins. (Figure 2)

**Changes in constituents of red wines during ageing**

Among the many processes involved in ageing of red wines is the formation of malvidin-3-O-glucoside linked through a vinyl bond to compounds including (−)-epicatechin and the procyanidin dimer B\textsubscript{3}. Other blue coloured compounds, such as malvidin-3-O-(6′′-O-p-coumaroyl)glucoside linked to flavan-3-ols, also form. The production of pyruvate and acetaldehyde by yeast during fermentation of Tempranillo grapes has been associated with the formation of malvidin-3-O-glucoside-pyruvic acid (vitisin A) and malvidin-3-O-glucoside-4-vinyl (vitisin B) which are members of a group of red wine-derived compounds referred to as pyranoanthocyanins\textsuperscript{2}. As wines mature these compounds provide a more stable red colouration than the parent anthocyanins. Maturation of red wines also results in the accumulation of a variety of ethylidene-linked flavan-3-ol and anthocyanin co-pigments\textsuperscript{3}. Some of the structures involved in these processes are illustrated in Figure 3.

When wines are aged in oak barrels or with oak chips, ellagitannins, such as vescalagin, leach from the oak and also form transformation products with anthocyanins. Because of these processes, levels of the red coloured free anthocyanins decline but they are replaced by the more stable co-pigments with the vescalagin-malvidin-3-O-glucoside hybrid imparting a purple rather than a red colour\textsuperscript{4} (Figure 4). The oak-derived ellagitannins also react with flavan-3-ols. Vescalagin and (−)-epicatechin, for instance, yield epiacontissum A (Figure 4) which, along with other ellagitannin-flavan-3-ol transformation products, gives the wine a smooth and velvety astringent taste, even at low concentrations, as opposed to the more bitter astringency imparted by procyanidins\textsuperscript{5}.  

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Red wine and antioxidants

The high concentrations of (poly)phenolic compounds result in most red wines having a high antioxidant capacity and in 1993 Frankel et al. reported that red wine phenolics inhibited the oxidation of human low density lipoprotein in vitro. There is now, however, a realisation that the protective effects of red wine phenolics on cardiovascular disease and other age-related chronic conditions, are unlikely to be a consequence of them functioning as antioxidants in vivo. After ingestion, the concentration of their derived metabolites in the circulatory system is much too low to elicit such effects and current research suggests that they influence disease risk via several complementary and overlapping mechanisms with complex interactions between cell signalling pathways.

What compound(s) impart the protective effects of red wine consumption?

trans-Resveratrol has gained much attention because of its ability to inhibit or retard a wide variety of animal diseases that include cardiovascular disease and cancer. It has also been reported to increase stress resistance and enhance longevity. The protective effects of moderate red wine consumption are regularly attributed to resveratrol in both scientific papers and the popular press. However, this is most improbable as the levels of resveratrol in red wines are so low that for humans to ingest the quantity of resveratrol that affords protective effects in animals they would have to drink in excess of 100 L of red wine per day.

Recent research has linked procyanidins to the reduced incidence of cardiovascular disease associated with moderate red wine consumption. Healthy blood vessels produce small amount of a peptide, endothelin-1, which maintains the integrity of the vessel wall. Excess endothelin-1 production, however, causes vasoconstriction, hardening of the artery wall and eventually atherosclerosis. Red wine polyphenols suppress the synthesis of endothelin-1 and induce dilatation of blood vessels, an effect that could explain their anti-atherosclerotic activity. When the ability of more than 150 red wines to inhibit the synthesis of endothelin-1 by cultured endothelial cells was tested there was a highly significant correlation between bioactivity and the procyanidin content of the wines. Parallel tests with individual compounds revealed that procyanidin hexamers and heptamers inhibited endothelin-1...
production at low mM concentrations and were much more active in this regard that flavan-3-ol monomers and dimers and other red wine constituents. These findings become especially fascinating when considered along with information gleaned from the French census of 1999 which identified usual patterns of regional ageing with 30% more men over the age of 75 years in the département of Gers in the Midi-Pyrenees. Wines produced in this region, principally from Tannat grapes, have an extremely high procyanidin content. As until very recently, consumption of these Tannat wines was almost exclusively local, this provides a most interesting association between male longevity and procyanidin intake\textsuperscript{9}. Other quite separate research with the Kuna Indians living on the San Blas Islands off the coast of Panama has linked the consumption of cocoa, which also contains sizable amounts of procyanidins, with improved vascular health\textsuperscript{10}.

It is, as yet, unclear as to whether the protective effects of red wines are due to procyanidins acting within the circulatory system or whether they are attributable to compounds formed from procyanidins in the body following ingestion. To date, there is only limited evidence of trace quantities of dietary procyanidin dimers being absorbed into the circulatory system. In the circumstances, the protective effects may be due to the procyanidins passing from the small to the large intestine where they are degraded by the colonic microbiotica producing simpler phenolic acids, including valerolactones, and phenylacetic, phenylpropionic and benzoic acids (Figure 5), which are absorbed into the portal vein and subsequently excreted in urine in some quantity. It is possible that compounds produced from procyanidins in this manner may play a key role in the protective effects, of not just red wine, but fruit and vegetable-rich diets, as recent evidence has shown that colonic catabolites, including 3,4-dihydroxyphenylacetic acid, have \textit{in vitro} and \textit{in vivo} anti-inflammatory effects\textsuperscript{13}.

**References**


Figure Legends

Figure 1. Primitivo grapes growing in a vineyard in Ravello on the Amalfi coast in Italy

Figure 2. (Poly)phenolic compounds found in red wines

Figure 3. Malvidin-3-O-glucoside and flavan-3-ol-related compounds that are formed during the maturation of red wines and which impact on the colour of the wine.

Figure 4. (−)-Vescalagin is among the ellagitannins that are leached from oak during maturation of red wines and among the reactions that take place are interactions with (−)-epicatechin and malvidin-3-O-glucoside forming compounds which can effect the colour (1-desoxyvescalagin-(1β–8)-malvidin-3-O-glucoside) and flavour (epiaactissimin A) of the wine.

Figure 5. Potential pathways for the degradation of the upper and lower (−)-epicatechin units of procyanidin B₁ by human colonic microbiota. The resultant products are absorbed into the portal vein and during circulation through the body some may undergo phase II metabolism in the liver prior to urinary excretion. Based on data obtained by Appeldoom et al.¹¹ and Roowi et al.¹².
Biographical Details

Alan Crozier is a Senior Research Fellow in the School of Medicine, College of Medical, Veterinary and Life Sciences, at the University of Glasgow. His research is focussed on dietary flavonoids and phenolic compounds in fruits, vegetables and beverages, including, wines, fruit juices, teas and coffee, and their fate within the body following ingestion in relation to their potentially beneficial effects on health.

Gina Borges is a Venezuelan biochemist who obtained her PhD at the University of Glasgow in 2006. She currently works as a Research Fellow in the School of Medicine at the University of Glasgow where her recent research has centred on the bioavailability of flavonoids in fruit juices and berries, and the use of anthocyanin and ellagitannin fingerprinting to access the authenticity of wines, pomegranate juices and related products.

Danielle Ryan is a Senior Lecturer in Chemistry at Charles Sturt University. Her research is focussed on the application of analytical chemistry and separation science to complex natural metabolomes (e.g. olive, wine, urine) for the understanding of natural product quality and potential health benefits of bioactive compounds.