

Can Moderate Wine Consumption Prevent Genetic Damage?

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All alcoholic beverages have the ability to reduce the risk of all-cause mortality by approximately 20 to 50 percent, when consumed in moderation. This ability has been demonstrated by the extensive epidemiological studies, which have been undertaken in men and women, for different age groups, and for different nationalities or populations (Moore and Pearson 1986, Marmot and Brunner 1991, Rimm et al. 1991, Maclure 1993, Renaud et al. 1993, Doll et al. 1994, Klatsky 1994, Fuchs et al. 1995, Rimm et al. 1996, Rimm et al. 1999). The risk of all-cause mortality increases progressively, however, with immoderate consumption.

Some of these studies have also considered the alcoholic beverage consumed and the reduction in risk of, for example, cardiovascular disease. From these studies it can be concluded that the alcohol component, which is common to all the beverage types, does confer a benefit.

Particular prospective epidemiological studies have indicated that consumers of wine, however, have a greater reduction in the risk of cardiovascular disease and certain cancers than consumers of beer or spirits (Boffetta and Garfinkel 1990, Gronbaek et al. 2000, Klatsky 2003). The reduction in risk of cardiovascular disease was similar to that for consumers of certain fruits, grains and vegetables, where the linkage between wine and these foodstuffs is their concentration of phenolic compounds (Grundy 1986, Block 1992, Block et al. 1992, Ames et al. 1993, Hertog et al. 1993, Kinsella et al. 1993, Willett et al. 1995, Halliwell et al. 1995, Hertog et al. 1995, Renaud 1996). Phenolic compounds, such as flavonols, phenolic acids and their esterified derivatives, are purported to act as antioxidants.

Antioxidants are molecules that inactivate oxidants, and can prevent the oxidation of fats or lipids. Lipoprotein particles, such as low density lipoprotein (LDL), transport fat-soluble antioxidants, including vitamin E, within the blood and to the wall of arteries. Accordingly, they are believed to protect against atherosclerosis and cardiovascular disease by preventing lipids in the artery wall from oxidation. It is postulated that oxidation occurs when the

protective antioxidant compounds present in the LDL particle are depleted (Steinbrecher et al. 1990).

Oxidative free radicals also cause mutation of DNA sequences and breakage of DNA strands, which are the underlying causes of the initiation and progression of cancer (Ames et al. 1995). When the genetic material or DNA of cells is damaged, the characteristics of the cell are altered causing it to malfunction or die. It is the excess occurrence of dead cells and mutant cells in the body that ultimately accelerates cancer and other diseases of old age including Alzheimer's disease (Smith et al. 1996). A number of factors may contribute to this damage, including chemical genotoxins, lifestyle factors (diet, exercise and the environment), and medical therapies including radiotherapy and cytotoxic drugs. Oxidising agents such as hydrogen peroxide and ionising radiation cause chromosome breakage and loss, as well as cell death (Fenech et al. 1999a, Fenech et al. 1999b).

As a diet high in certain fruits, grains and vegetables has also been associated with a reduced risk of cancer, this has prompted researchers to investigate whether any of the wine-derived phenolic compounds might protect cells and DNA from damage leading to cancer. From epidemiological studies, for example, moderate wine consumption has been observed to decrease the risk of Non-Hodgkin's Lymphoma by approximately 20 to 40%, particularly in individuals who began consuming wine as young adults (Briggs et al. 2002), and similar decreases in risk have been observed for aero-digestive tract and lung cancers (Gronbaek et al. 1998, Prescott et al. 1999). The results from numerous *in vitro* (test tube) and animal studies suggest that individual wine-derived phenolic compounds may be protective against DNA damage by inhibiting the oxidising agents (Ames et al. 1995). For example, in 1996, an initial *in vivo* (clinical) study was undertaken by the CSIRO Health Sciences and Nutrition in conjunction with The Australian Wine Research Institute (AWRI) (Fenech et al. 1997) to determine if the acute consumption of 200 mL wine produces a measurable change in the antioxidant capacity of blood plasma, and whether this in turn, reduces oxidative damage to DNA. The results indicated that the consumption of wine, both red and white,

produced significant, changes in the plasma which protected DNA from damage induced by hydrogen peroxide, but only red wine consumption, however, reduced spontaneous chromosome damage. This was the first evidence that moderate wine consumption could minimise the DNA-damaging effects of oxidizing agents and subsequent studies have supported these results (DeFlora et al. 1997, Andreassi et al. 2000, Izzotti et al. 2001). An observation that the duration of this protective effect was diminished by eight hours post-dose, implies that the regular consumption of wine is important to maintain a protective effect. Leighton et al. (1999) has also recently shown that the short-term consumption of red or white wine, in particular in combination with a Mediterranean diet, could significantly reduce DNA damage in both elderly men and women. Interestingly, the women consumed half the amount of wine consumed by the men but showed a similar reduction in extent of DNA damage. No cellular mechanism of action has, however, been determined.

The diseases of old age such as cardiovascular disease, cancer and Alzheimer's Disease are expected to increase significantly over the next few decades as people increasingly survive beyond the age of 80 years. Consequently there is interest in identifying lifestyle factors and molecular mechanisms that can minimise the risk of these debilitating conditions. Accordingly, a recently completed GWRDC-funded project by the CSIRO Health Sciences and Nutrition was undertaken in two phases:

Two studies were undertaken in Phase I. The first study was an *in vitro* study which tested human plasma or whole blood from four healthy male subjects ages 20-25 years that was spiked with different wine components for protection against hydrogen peroxide and ionizing radiation induced DNA damage. The components examined were ethanol, glycerol, tartaric acid, and

caffeic (a hydroxycinnamic acid phenolic compound)/catechin (a flavanol phenolic compound) mixture and compared to a Riesling wine stripped of phenolic compounds and a control salt solution, which was a diluent for the wine components. The components were added at 2.5% and 10% of the concentration observed in wine, where 2.5% corresponds to the concentration observed in the body fluids of a 60 kg volunteer after consuming 300 mL (approximately three glasses) of white wine. The cells were then analysed via the cytokinesis block micronucleus assay, which enables chromosome or DNA damage to be scored (Fenech 1993).

It was observed that the phenolic compounds, such as catechin and caffeic acid, and the mixture including these components, significantly decreased baseline DNA damage and DNA damage caused by ionising radiation. It was observed that the ethanol component significantly increased base-line DNA damage, but the mixture that included both ethanol and the phenolic compounds, completely countered the DNA damaging effects of ethanol. These effects were observed for both the 2.5% and 10% concentration of the components, although the protective effect of the phenolic compounds was most significant for the 10% concentration. Ethanol, as

well as the component mixtures, produced the strongest protective effects against DNA damage by hydrogen peroxide. The protective effect of the mixture did not account for the expected additive protective effects of the individual components, which suggests that the components may be exerting their effects through similar mechanisms, which are saturated at the concentration tested.

In conclusion, these observations suggest that the primary phenolic and ethanol components of wine can reduce the DNA damaging effects of two important oxidants, hydrogen peroxide and ionising radiation, in a

physiologically relevant in vitro system. This has important clinical indications, such as in radiotherapy for the treatment of cancerous cells and the protection of normal tissue.

The second study was an ex vivo study in which blood from six healthy male subjects was tested for its resistance to DNA damage induced by hydrogen peroxide or ionising radiation, following the consumption of 300 mL red wine, dealcoholised red wine or a model wine (12% alcohol solution). The subjects were placed on a plant phenolic compound free diet for 48 hours prior to each study day. The results of this study showed a clear

protective effect of the dealcoholised wine, an aggravating or negative effect of alcohol and an intermediate but protective effect of whole wine. The most significant protective effects were observed at two hours post consumption. These results were important in verifying that it is the non-alcoholic phenolic fraction of wine, which has DNA-protective properties in blood and body tissues in vivo.

Other researchers have examined the effect of specific wine-derived phenolic compounds on cancer, such as resveratrol (stilbene), quercetin (flavonol), catechin (flavanols) and gallic acid (hydroxybenzoic acid). These

wine-derived phenolic compounds appear capable of inhibiting each of the three steps involved in the development of cancer. In particular, in vitro, animal and limited in vivo studies suggest that resveratrol inhibits the cellular events associated with cancer initiation by acting, for example, as an antioxidant and antimutagen, mediates anti-inflammatory and other effects associated with cancer promotion, and induces cell differentiation associated with cancer progression (Jang et al. 1997).

Creina Stockley is a member of the AIM Council.

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