The Effect of Oregon Pinot Noir on Endogenous Lipid Peroxidation

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Degenerative diseases of aging such as cancer, cardiovascular disease, and brain dysfunction are increasingly found to have, in part, an oxidative origin. As a result, dietary antioxidants such as Vitamins C and E and carotenoids play a major role in minimizing this damage and preventing or delaying the pathophysiology. Population groups that generally do not smoke (a significant oxidative insult to the body), do not drink heavily, or do not eat much meat but instead have a diet rich in fruits and vegetables have an overall cancer mortality about half that of the general population and live several years longer. The failure to eat adequate levels of fruits and vegetables may result in significantly greater lipid peroxidation and oxidative damage of DNA and protein (1,2).

There are numerous studies which suggest that moderate consumption of alcoholic beverages confers a beneficial effect on one's well being (3,4). This is due, in part, to the presence of phenolic compounds (such as flavonoids) that possess antioxidant properties in some alcoholic beverages. This is particularly true for red wines where the level of many flavonoids exceeds that found in white wines, beers, and distilled beverages.

The long term goal of our studies is to determine what role phenolics found in Oregon Pinot noir have in the beneficial effects of red wine consumption that were reported in epidemiological studies. We initially determined the level of circulating 8-isoprostanes (5) in untreated rat plasma as an indicator of whole body oxidative stress. We found that the levels of circulating isoprostane in untreated rats were about 110 pg/ml using a commercially available ELISA. As a result, this assay will be valuable to assess lipid peroxidation after different long term treatments.

To begin to examine the mechanism of cellular protection, we are using an in vitro tissue culture model. There are numerous components present in wine. Currently, we are looking at three different phenolics that have been shown to vary in different Oregon Pinot noir wines and comparing it to a flavonoid from green tea, epigallocatechin gallate (EGCG). These phenolics were chosen for investigation since Dr. Barney Watson and his collaborators demonstrated that the levels of these components varied greatly in different samples of Oregon Pinot noir (6). For example, some wines had high levels of quercetin (as well as the quercetin glycosides) with lower catechin levels while others had lower levels of both classes of flavonoids. We will be able to design and perform studies using a mixture of components found in Oregon Pinot noir wines. Our initial studies in vitro use concentrations of the phenolics present in Pinot noir samples. It remains to be determined whether these components concentrate in the body after consumption. From the standpoint of antioxidant capacity, it might be possible to create wines with enhanced ratios of select phenolics. The ability to alter the ratio of phenolics has been and is the subject of continued investigation in Dr. Watson's laboratory and we hope to establish a close collaboration with...
his group as our studies proceed. Very recently, the cancer chemopreventive activity of resveratrol was reported (7). This phenolic was also shown by Dr. Watson to vary significantly in different samples of Pinot noir. Green tea has also long been known to act as an anti-tumor agent and as an antioxidant so we felt it would be of interest to determine whether a major phenolic from this source, epigallocatechin gallate exhibited similar mechanistic features.

One of the beneficial effects of red wine consumption that was reported is a decrease in death due to liver cirrhosis. The mechanism of cirrhosis is thought to involve the function of Kupffer cells, resident macrophages in the liver, as well as lipid peroxidation. As indicated above, wine and green tea phenolics have been reported to be effective antioxidants. We examined this in our laboratory using an *in vitro* lipid peroxidation assay. In these studies, oxygen radical species initiate a chain reaction that generates malondialdehyde. This product is then measured spectrophotometrically. As shown in Fig. 1, the addition of all four components at concentrations equivalent to those found in Pinot noir resulted in significant inhibition of lipid peroxidation. This is consistent with the literature. For example, quercetin, a major flavonol in Pinot noir, inhibited the oxidation of HDL-LDL in an *in vitro* assay in which lipid peroxidation was initiated by artificial agents (8). The mechanism of this inhibition is currently under investigation. Phenolic compounds can also protect against oxidative stress by altering the response of a cell to stress situations. Using a macrophage cell line, we initiated studies to examine the effect of catechin, EGCG, resveratrol, and quercetin on the cell's response to oxidative stress. This is being done by examining factors which alter gene expression by examining direct activation of the factors and by assessing the activation of the genes that are being regulated. Once conditions and responses are established in the cell line, we plan to continue these studies using freshly isolated Kupffer cells and eventually move to whole animal studies.
Figure 1. Effect of phenolics on *in vitro* lipid peroxidation. Hepatic microsomes were incubated with NADPH in the presence of no additional phenolic or in the presence of 600 μM catechin, 50 μM epigallocatechin gallate (EGCG), 20 μM resveratrol or 100 μM quercetin and level of lipid peroxidation was determined and reported as nmol or malondialdehyde (MDA) produced.

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