Health Benefits of Wine and Grape Juice

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SUMMARY. There has been a nationwide explosion of interest in consumption of red wine following a "60 Minutes" television segment entitled "The French Paradox." The paradox was due to the fact the French consume more fat, smoke more, and exercise less than Americans and still have fewer heart attacks. A study of 12,000 male British doctors showed that moderate drinkers had the lowest death rates and the lowest vascular death rates compared to nondrinkers or heavy drinkers. The consumption of wine has been shown to provide healthful benefits, such as reducing cholesterol and decreasing cardiovascular disease. A comprehensive literature review of the latest scientific information on this subject is presented in this review.

Wine may indeed be the world's oldest medicine. The Bible tells us to take a little wine for our stomach's sake. Hippocrates prescribed wine as a medicinal as have countless physicians down through the centuries. Modern scientists tell us that wine is one of the most complex beverages containing many substances that are important to health. As a dietary liquid, it is second only to that of milk. Ecclesiastes 31 tells us that wine was created from the beginning to make men joyful and not to make them drunk. The Talmud instructs that wine nourishes, refreshes, and cheers....that wherever wine is lacking, medicines become necessary. This overview of the healthful benefits of wine and grape juice is just that, an overview. It is in no way intended to persuade all people to begin drinking even moderately. Predisposition to alcoholism, contraindicated medications, and other special circumstances would make that persuasion irresponsible. Many scientific foundations for the espoused healthful benefits of moderate consumption of wine have only recently been formed. The new scientific information being gathered on this subject is certainly exciting.

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Healthful diets with wine

In the United States, an explosion of interest in drinking wine with meals occurred following a "60 Minutes" television segment on "The French Paradox." The paradox occurs in that the French eat 30% more fat, smoke more, and exercise less than Americans, yet have fewer heart attacks (Holmgren, 1993; Renaud and de Lorgeril, 1992). An American man has three times the chance of dying of a heart attack compared to a French man of the same age. The main reason for this discrepancy, according to "60 Minutes," could well be the French drinking habits. Wine is taken in moderation, a couple of glasses with meals.

Many areas of Europe are accustomed to a Mediterranean diet, a diet being given serious consideration in this country. The Mediterranean diet is considered by some experts as the healthiest of all diets. The origins of the diet go back to ancient times. During the time of the Greek and Roman empires, the diet was based on three leading ingredients: wheat, olive oil, and wine. The Mediterranean diet has developed as a result of a cultural blend of products and habits from different countries such as Egypt, Greece, Italy, Turkey, and other countries of the Middle East. Later, the diet was influenced by the Arabic people who supplied new foods, herbs, and spices and by the introduction of potatoes and tomatoes from America into southern Europe.

Generally speaking, the Mediterranean diet currently is composed of cereals, dried legumes, fresh fruit and vegetables, fish and some meat (goat, lamb, pork, rabbit, and poultry), wine, olive oil, cheeses (from goat's and sheep's milk), yogurt, nuts, olives, and honey. Combinations of these foods represent about 50% carbohydrates, 30% to 35% animal and vegetable fats, and 15% protein from fish or meat. For cooking, olive oil is used instead of fats or margarines from animal origins.

The health of those eating French and Mediterranean diets would seem to indicate that moderate drinkers of wine at meal times live longer, healthier lives. A new set of dietary guidelines was released in Spring 1993 by Harvard University researchers at the International Conference on the Diets of the Mediterranean. The new guidelines were called the Mediterranean Diet Pyramid and marked a growing scientific consensus that moderate wine consumption is associated with reduced risk of coronary heart disease (Holmgren, 1993).

So, how does wine impart a healthier, longer life? Wine acts in many ways to aid health.

Cardiovascular disease

The world's leading epidemiologist, Emeritus Professor of Medicine at Oxford University Sir Richard Doll, and his coworkers (Doll et al., 1994) summed up the longest (13 years) study of a population, 12,000 male British doctors. The study showed that moderate drinkers had the lowest death rates and the lowest vascular death rates. As a matter of fact, this study also showed that moderate drinkers had fewer deaths from all causes—including cancer—than either abstainers or heavy drinkers (Holmgren, 1995). Britain leads the world in heart disease mortality, and yet it was concluded that moderate drinkers were about 40% less likely to suffer heart attack than nondrinkers or those in the upper ranges of ethanol consumption.

Morton Gronbaek et al. (1995), of the Danish Epidemiology Science Center in Copenhagen, Denmark, conducted a 12-year heart study. More than 13,000 men and women, aged 30 to 70, were monitored from 1976 to 1988. The results showed those who consumed only wine as an alcohol source had half the risk of dying during these years than those who never drank wine. Significant benefits were shown from one to two glasses per day, but even greater benefits were attributed to three to five glasses per day. Benefits from this much consumption differed from findings in previous research, which has suggested declining benefits from increased consumption. The Danish study also demonstrated the lack of benefit from consuming other types of alcoholic beverages. This finding was also in contrast to some previous studies.

The consumption pattern, that is, with meals as opposed to drinking other alcohol by itself, might be responsible for the difference in benefits. Data from Gronbaek and his coworkers (1995) also showed a 30% decline in coronary heart disease mortality in Denmark since 1980. This decline could be related to a dramatic increase in national wine consumption since 1976, following the opening of the European market.

Arthur Klatsky, chief of the Division of Cardiology of Kaiser Permanente Medical Group, Oakland, Calif., published an 8-year population study that evaluated data from 128,923 adults (Klatsky and Armstrong, 1993). It especially noted the benefits to moderate drinkers over 60. This group, compared to all other age and consumption groups, had the greatest reduction in risk of death from cardiovascular disease, especially coronary heart disease.

Another study, part of the Massachusetts Normative Aging Study (Holmgren, 1993), followed 1823 men for 12 years. The

researchers studied the rates of death from all causes, including heart disease. The rates of overall mortality were lowest for moderate drinkers in each of the age groups of the study. Nondrinkers had mortality rates 30% to 70% higher than moderate drinkers. In this study, heart disease death rates for moderate drinkers were similar to those of nondrinkers except for the oldest men. This older age group had lower rates than either nondrinkers or heavy drinkers. Moderation in this study was defined as up to three 5-ounce glasses of wine per day. In sum, lifetime teetotalers had two to five times the risk for overall and coronary heart disease mortality compared to those who described themselves as occasional, regular, or former drinkers.

According to research published in the *British Medical Journal*, another study reports that women who drink between one and two glasses of wine a day may build more protection against heart disease than women who drink more, less, or do not imbibe at all (Mansson, 1992). The research focused on women aged 25 to 69 who were chosen and tested as part of a gallstone study in the Bristol area. Among the questions they were asked was what their daily alcohol consumption was. Blood samples were taken from the women, then analyzed and matched with their responses to questionnaires. A study reported in 1988 in the *New England Journal of Medicine* collected data from 80,000 female nurses for 4 years (Holmgren, 1993). Data showed that women who were moderate drinkers suffered fewer heart attacks and ischemic strokes.

Apparently it is not the ethanol content alone, that accounts for the healthful benefits of wine. Nonalcoholic ingredients in wine can reduce the risk of heart disease, according to Tom R. Watkins, director of the Kenneth Jordan Heart Foundation & Research Center, Montclair, N.J. (Brennan, 1995). The polyphenol antioxidants in wine help prevent atherosclerosis, keep blood vessels relaxed, and may be responsible for anticoagulant effect of wine. Wine is rich in flavonoid and other polyphenolic antioxidants that could help prevent atherosclerosis by inhibiting oxidation of low-density lipoprotein (LDL), which transports most of the circulating cholesterol. Circulating LDL is susceptible to oxidation by peroxides and other oxidizing agents in blood. When oxidized, LDL is scavenged by white blood cells called macrophages, which remove LDL from the blood stream and deposit it inside the lining of the artery. This leads to a build up of cholesterol in the artery (atherosclerosis), which can cause narrowing of the artery and ultimately clogs the artery. It also contributes to the formation of clots.

To test the antioxidant hypothesis, Edwin N. Frankel, a research chemist at the Univer-

sity of California, Davis, and coworkers removed the alcohol from 20 California wines before in vitro measurement of each wine's ability to prevent oxidation of human LDL (Frankel et al., 1993a, 1993b, 1995). Nonalcoholic red wines inhibited LDL oxidation by 46% to 100%, whereas the white varieties achieved only 3% to 6% inhibition. The antioxidant activity of wine positively correlated with its total phenol content, as well as with the concentration of individual polyphenolics. Antioxidant activity appeared to be distributed widely among the principal phenolic compounds.

The phenolic compounds are well known to enologists for their sensory properties, and for this reason their chemistry has been investigated in wine for decades (Waterhouse, 1995). These substances give wine its bitterness and astringency and are the foundation of long wine aging, since they are effective antioxidants. Wines low in these substances, such as white wines, rarely age gracefully. However, a study published in the *American Journal of Cardiology* (Klatsky and Armstrong, 1993) concluded that "red wine is no better than white wine in fighting death from heart disease." In that study, coinvestigator Arthur Klatsky, explained, "We discovered that white wine actually exhibits a slightly more protective effect on the heart, and that white wine drinkers in general are at less risk of dying from coronary heart disease than beer or liquor drinkers."

RESVERATROL. Cornell plant scientists Evan Siemann and Leroy Creasy were intrigued with a study by French cardiologists who reported that volunteers who drank red wine increased HDL cholesterol (the "good" form of lipoproteins) in their blood (Siemann and Creasy, 1992). White wine had no such net effect. Siemann and Creasy connected this difference with a Japanese study where rats were fed diets supplemented with resveratrol—a naturally occurring fungus fighter in grapes and a key ingredient in several Japanese folk medicines. The result was much less fat in the rats' livers, an indication of low cholesterol levels. Siemann and Creasy thought that the French and Japanese might have been studying the effects of the same chemical. When researchers analyzed wines of the same region as those in the French study, the results confirmed their hunch. The reds contained much more resveratrol than the whites, with one bottle of red containing more than 200 times the amount found in most of the whites.

In 1991, these Cornell University scientists identified resveratrol in samples of grape juice, although none had levels as high as red Bordeaux wines (Snider, 1992). Resveratrol was also found in the skin of grapes used only for grape juice. Table grapes may not contain

this substance because of the special care that is given to protect them against diseases and blemishes. Resveratrol production potentials of berries vary greatly, with high and low potentials for both reds and whites, and specific cultivars must be selected to have high resveratrol levels in wine (Creasy and Coffee, 1988).

THE PLATELET CONNECTION. There are still other avenues through which wine may impact the health of the circulatory system. Overly active platelets, a factor that increases blood's tendency to clot, increase the risk of heart disease and stroke. Watkins ran trials on cardiac patients using red and white wines. These patients consumed six ounces of wine daily for 4 weeks. This addition reduced platelet activity for at least 18 hours. Red and white wines inhibited platelet activity, but the white wine was more effective. In a study using French wines, John D Folts, director of the Coronary Thrombosis & Research Laboratory at the University of Wisconsin, Madison, and his coworkers found that only red wine inhibited platelet activity (Demrow et al., 1995). In this study, anesthetized dogs were subjected to a mechanically induced thrombus-forming paradigm in which the platelet-mediated thrombus led to a cyclic flow reduction (CFR) in coronary blood flow. The CFRs were apparently eliminated or reduced in relatively short time by the intravenous and intragastric administration of diluted red wine and diluted grape juice. Although white wine was used in this study, it did not have any significant effect on the CFRs, due presumably to the low levels of flavonoids. High-performance liquid chromatography (HPLC) analysis of the red wine used in this experiment showed unusually high levels of quercetin. The red wine had 2.7 times the amount of unidentified compounds, presumed to be flavonoids, than the commercial grape juice. HPLC analysis of the grape juice showed 86 mg·L⁻¹ of quercetin and 82 mg·L⁻¹ of rutin, the glycoside of quercetin. However, most commercial grape juices are in fact enriched with high levels of vitamin C. The surprising reduction in CFRs resulting from the infusion of diluted grape juice could possibly reflect the antioxidant action of the added vitamin C. In addition, another study has shown that resveratrol, as well as some flavonoids, inhibit eicosanoid synthesis, a key step in platelet aggregation (Pace-Asciak et al., 1995).

Researchers at the University of Wisconsin, Madison, Medical School found that two glasses of red wine a day can significantly reduce the stickiness of blood platelets, thus lowering the risk of dangerous blood clots that can cause a heart attack or a stroke (Renaud and de Lorgeril, 1992; Wilcoxon, 1994). Wine is an excellent source of salicylic acid, the active ingredient in aspirin. Doctors frequently prescribe daily aspirin to decrease the risk of a

second heart attack in some patients.

SMOOTH MUSCLE RELAXATION. Wine can also counter constriction of arteries, according to David Fitzpatrick, a professor of pharmacology at the University of South Florida, Tampa, and coworkers (Fitzpatrick et al., 1995). Wine promotes the synthesis of nitric oxide (NO) radicals in the endothelial cell layer that lines the artery. One of the functions in vivo of NO is to relax the smooth-muscle cells of the blood vessel walls. Fitzpatrick's group has studied the relaxation effect of various wines and grape products in vitro on rat aortas contracted with phenylephrine. They achieved virtually 100% relaxation with either red or white grape skin extract and 97% with Concord grape juice, whereas extract of grape pulp showed no activity, and neither did ethanol. Wines varied greatly in relaxation ability, Fitzpatrick pointed out, with Cabernet Sauvignon consistently the most potent vasodilator. The Tampa team also tested the vasodilation effect of several individual polyphenolics in wine. Although the catechin and epicatechin flavonoids proved to be good vasodilators, they were not as potent as the red wine or grape skin extracts.

Fruit and vegetables must be eaten when fresh to provide benefits from the antioxidant properties of their flavonoids, said Frankel, whereas the process of making wine concentrates flavonoids and protects them from being oxidized. "Wine is a horrendous mixture of compounds," he said, "and they seem to work better together than individually."

Other avenues of possible health benefits

ETHANOL AND CANCER. In addition to the cardiovascular system, wine may beneficially affect other body systems. Ethanol consumption and cancer risk studies have generally focused on the overall effects of ethanol on cancer and mortality (Ebeler and Weber, 1996). However, the question of the type of alcoholic drink has been addressed rather superficially. When all causes of mortality are compared, wine consumption clearly is associated with decreased risk. Although not statistically significant, wine consumption is also associated with a decreased risk of death other than cardiovascular and cerebrovascular disease.

In a recent study evaluating the effects of beverage type on cancer incidence, Longnecker et al. (1995) showed that consumption of beer and liquor, *but not wine*, was related to breast cancer risk. Freudenheim et al. (1995), in a case-control study of breast cancer in western New York, also found an indication of a decrease in risk associated with wine intake but a slightly elevated risk associated with increased beer intake (more than one drink a day). Macfarlane et al. (1995) showed a lowered

risk of oral cancer in wine drinkers compared to beer or spirits drinkers in selected populations in United States, Italy, and China.

These recent studies provide increasing evidence that wine may contain nonalcoholic constituents that impart a health protective effect. The actual compounds responsible are not clear. Plant polyphenolics and flavonoids have been shown to have a number of biological effects and to mediate the effects of various degenerative diseases including coronary heart disease and cancer.

INSULIN. In 1988, British researchers (Holmgren, 1992) suggested for the first time that moderate consumption of wine may lower levels of insulin in the blood. Because insulin triggers cholesterol production, this new finding may help explain how ethanol exerts its beneficial effect on total serum cholesterol levels.

Gerald Reaven (1988 and 1993) and collaborators at Stanford Medical School made a very significant observation about the underlying cause of some common diseases that shed light on a possible method by which ethanol may protect health. There seems to be a close relationship between appearance of disease and a phenomenon called insulin resistance. Insulin, of course, regulates glucose in the body. When persons become insulin resistant, their cells no longer respond properly to insulin, and levels of glucose in the bloodstream become elevated. The resultant misuse of glucose affects the use of other energy sources. Reaven coined the name "Syndrome X" for this condition (Reaven, 1988 and 1993). Fat metabolism is under the control of the central nervous system, and ethanol is used for energy in preference to existing fat stores. Ethanol's role as a metabolic fuel may, therefore, be important in preventing the development of "Syndrome X," thereby decreasing the risk of development of coronary heart disease (Bisson et al., 1995; Ferrannini, 1993).

GASTRIC PATHOGENS. *Helicobacter pylori*, a gastric pathogen, was first isolated and identified in 1983 (Warren and Marshall, 1983). Since then, a profusion of research and epidemiologic studies have confirmed its role in the etiology of numerous gastric disorders, malabsorption syndromes, and stomach cancers. There also seems to be a relationship between *H. pylori* infection and cardiovascular risk factors and disease. Statistically, the incidence of the associated diseases are higher in countries that traditionally are wine abstaining countries than in countries that traditionally drink wine. It becomes quite reasonable that wine consumption might offer a degree of natural protection against *H. pylori* (Fugelsang and Muller, 1996).

Ethanol alone is not very effective in controlling *H. pylori*. However, red wines showed

bactericidal activity within 15 minutes after inoculation. This showed that red wine exerts bactericidal action on *H. pylori* within a reasonable time frame relative to a meal. Wiesse et al. (1995) had very similar results in their work with the bactericidal activity of wine on enteric pathogens.

EFFECTS ON HUMAN FETUSES. Fetal alcohol syndrome, or FAS, is a debilitating condition in newborns that is irreversible and is caused by heavy alcohol consumption during pregnancy (Matthews, 1994). The most authoritative estimate of the incidence of FAS comes from Ernest Abel and Robert Sokol (1991). In a 1991 study reviewing the available evidence, they concluded: "We now estimate the incidence of FAS in the Western world at 0.33 cases per 1000," or 1176 FAS babies in the United States per year out of a total of about 3.9 million live births. This is a revision of a 1987 estimate by the same authors, which put the incidence at 1.9 cases per 1000 births—almost 6 times higher. In a recent interview, Sokol stood by the later, lower estimate. Who are these 1176 mothers? Without exception, as far as the literature reveals, they are chronic alcohol abusers. They drink heavily throughout pregnancy, with an average alcohol consumption of at least six drinks per day and generally much more. When 245 cases of FAS were reviewed, 75% of the mothers were dead or missing from alcohol-related problems within 5 years of the births of their babies. Even though only alcohol-abusing mothers give birth to FAS babies, not every pregnant alcoholic does; estimates of births classified as FAS babies range from around 30% to as low as 2.5%.

A research project reported in the *British Medical Journal* in 1991 (Forrest et al., 1991) attempted to correlate maternal alcohol consumption before, during, and after pregnancy and infant mental and motor development at 18 months. These investigators did not detect any fetal effects from moderate consumption of alcohol up to 12 drinks per week. Surprisingly, the study also found that the mental and motor development of the children of mothers drinking up to five glasses of alcoholic beverages a week appeared greater than that of abstainers. Sokol reports finding none of the so-called FAS traits in offspring of women who drank up to 1.6 ounces (three drinks) of ethanol a day (Holmgren, 1991). Similarly in a scientific review, Knupfer (1991) concluded that there is no evidence today that light drinking is harmful to the fetus.

Scientists today may be finding evidence of what the Bible and the Talmud purported so long ago—that wine is good for us. It must be repeated that this overview of the research on the healthful benefits of wine has no intention to persuade all people to begin drinking even in moderation. For many individuals that persua-

sion would be irresponsible. The literature covering the new scientific foundations for the long-standing espoused healthful benefits of moderate consumption of wine are exciting and thought provoking. However, even in these limited number of studies, some of the results conflict with each other. Our review of the research does not suggest that wine is a medical panacea, but that health benefits may be derived from wine and grape juice consumption, especially with other foods.

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