NUTRI NEWS

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Recent health and nutrition information from Douglas Laboratories *March /April 2003*

Tea and the Heart – An Emerging Story
Including New Data on Cholesterol

Andrew Halpner, Ph.D.

If you were asked what the most consumed beverage in the world is, you might say water. You would be correct. However, if you were asked what the second most consumed beverage in the world is, would you have said tea? Believe it or not, more tea is consumed in the world than soda, beer, or coffee. For more than 50 centuries people in Europe and the Far East have been brewing and drinking some form of tea. In fact, archeological evidence traces the first use of tea as far back as Homo erectus pekinensis over 500,000 years ago. While the health implications of tea may not have been known that long ago, scientific investigations in the last 20 years have been uncovering fascinating links between the consumption of tea and tea-derived products and improvements in health. One of the most compelling areas of tea research that is beginning to emerge is the relationship between tea consumption and reductions in the risk of cardiovascular disease. This link has been reported in a number of different populations around the world and is just now starting to receive significant and extensive scientific investigation. This NutriNews will explore the data that exist on tea and its relationships to heart health in humans and help us to more fully appreciate this simple yet complex plant that we all too often take for granted.

Prior to reviewing the science on tea and cardiovascular health, it is helpful to review the chemistry of tea as well as the manufacturing processes that go into making tea, as this allows one to better understand and interpret the science. The term "tea" actually describes the plant, leaf, or beverage originating from a single species, *Camellia sinensis*, and is generally categorized into three types – green, black and oolong. Although the color and taste characteristics of these three types of tea vary greatly, they all originate from the same basic plant, a fact often misunderstood. The differences in color and taste between these types of tea are determined by the degree of fermentation that the tea leaves are allowed to undergo after harvesting. Tea is an abundant source of polyphenols, especially the complex group of compounds called flavonoids. These compounds are found widely distributed throughout the plant kingdom and help to protect the plant by providing antibacterial and antifungal properties. The degree of fermentation that the tea is subjected to during processing determines the type of flavonoids that will be present in the final product. The

Inside this issue

New – Clinical Protocols and Practice

Douglas Laboratories, in partnership with *Integrative Medicine – a Clinicians Journal*, is proud to bring you Clinical Protocols and Practice. This new bimonthly feature article is exclusive to the Douglas Laboratories website, www.douglaslabs.com. Each peer reviewed clinical protocol and informative practice management article, is provided to help educate clinicians on integrating complementary and alternative medicine into their practices.

The March/April 2003 edition features "Clinical Assessment and Management of 6 Common At-Risk Nutrients in the Older Person". This protocol addresses the recognition and assessment of nutritional needs in older individuals that may contribute to ensuring healthy aging.

Clinical Protocols and Practice is practical, researched and clinically relevant. We hope you find these articles beneficial to your practice and the overall wellness of your patients.

NUTRI NEWS

Volume 5
Number 2

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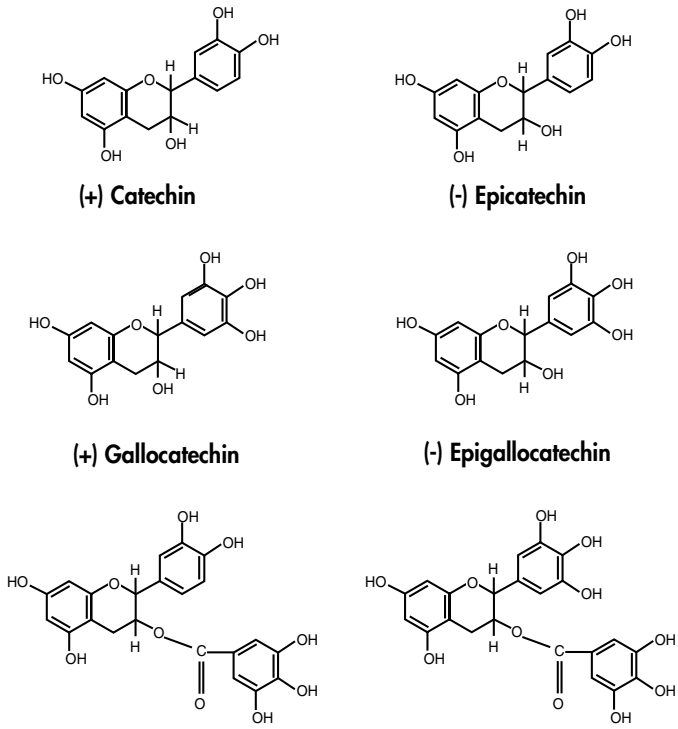
major flavonoids present in green tea include catechins such as catechin (C), epicatechin (EC), epicatechin gallate (ECG), gallocatechin (GC), epigallocatechin (EGC), and epigallocatechin gallate (EGCG) (figure 1). These catechins impart much of what we associate with the flavors and characteristics of green tea, and tend to be colorless, astringent and water-soluble.

Figure 1 - Common Catechins Found in Green Tea Leaf



Note: The gallocatechins differ by having one additional hydroxyl group on their ring structure.

The manufacturing process for making green tea is designed to conserve and maintain these catechin components in their native structure. This is typically done by plucking the leaves from the plant, inactivating enzymes naturally present in the leaves that would otherwise oxidize the catechins by steaming or firing the leaves, rolling the leaves (to give a twisted look to the tea), and then either high temperature drying or pan frying to

Table 1 - Principal Catechins Present in Fresh Leaf

(percent dry weight)

(+) Catechin	1-2	(+) Gallocatechin	1-3
(–) Epicatechin	1-3	(–) Epicatechin	3-6
(–) Epicatechin gallate	3-6	(–) Epigallocatechin gallate	7-13

finish the process. This results in a product that is relatively high in catechins. Table 1 shows the typical breakdown of catechins present in young green tea leaf. It is interesting to note that catechins can contribute up to 30% of the dry weight of the leaf, demonstrating how important these compounds are to the plant.

The manufacturing process for black tea is similar to that for green tea, but the focus is on allowing for the oxidation of the catechins present in the leaf. Black tea is made by plucking the leaves and then allowing them to wither. This withering lowers the moisture content and makes the leaves more workable. The leaves are then macerated, which begins the oxidation process by allowing the enzyme polyphenol oxidase to come in contact with the catechins. Oxidation is allowed to continue for a set period of time in the presence of high humidity. The oxidation process is then stopped and the leaves are dried. This oxidation process results in the formation of catechin oxidation products (also known as derived tannins) including but not limited to compounds such as theaflavins and thearubigens. Figures 2 and 3 show an example of this oxidation processes as it relates to the formation of a theaflavin. Thearubigens and theaflavins are complex families of molecules that help to give black tea is unique color and taste characteristics. The third type of tea referred to as oolong tea is less common and more difficult to find. This tea can be described as being at an intermediate state between green and black. The leaves are allowed to oxidize, but for a shorter amount of time compared with black tea. On average, a typical cup of brewed black tea contains approximately 25 mg catechins, 100 mg thearubigens, and 4 mg theaflavins, while an average cup of brewed green tea contains approximately 250 mg catechins and

Figure 2 - Oxidation of Epicatechin and Epigallocatechin to Their Respective Quinones. This is the first step in the formation of theaflavins.

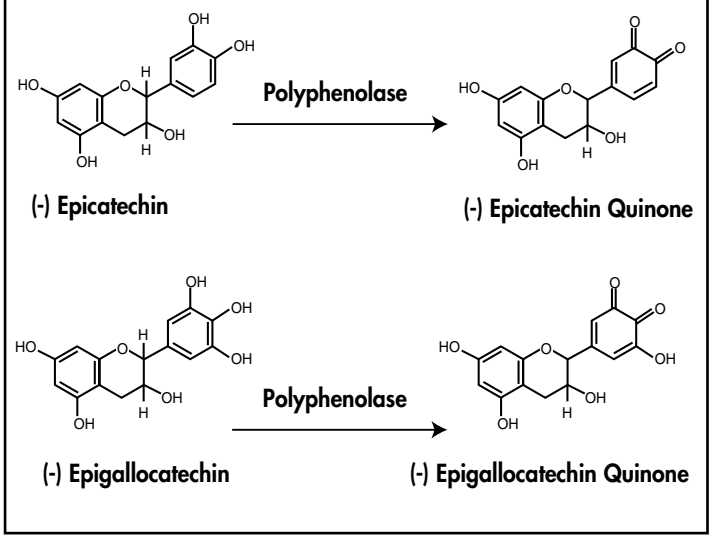
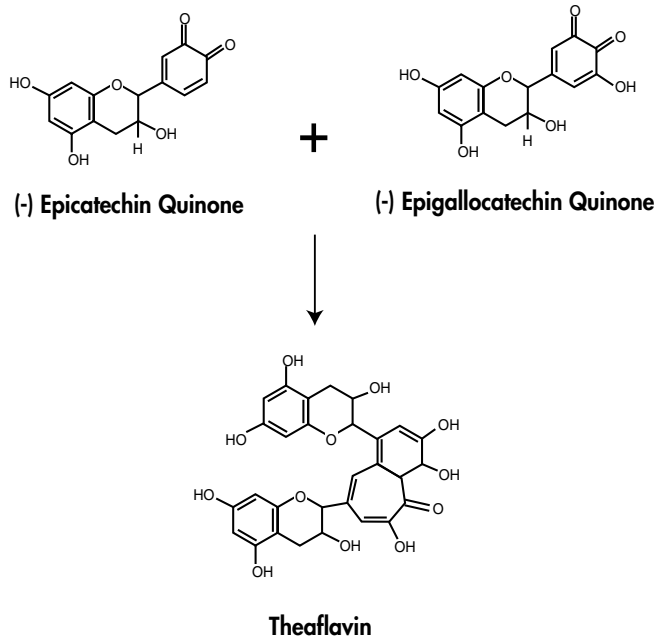


Figure 3 - Formation of Theaflavin From Catechin Quinone



Note: Various theaflavins can be formed depending on which catechins are undergoing oxidation.

almost no thearubigens or theaflavins. It is important to note that the actual amount of flavonoids that will be present in tea can vary greatly and is influenced by a large number of factors including the variety, age and growing conditions of the plant as well as parameters related to the preparation of the tea, including the strength and type of brewing.

Tea and Cardiovascular Health

Although the field of research that encompasses tea in relation to its impact on cardiovascular health is relatively young, it is a rapidly growing area of investigation. To date, most of the literature supports an inverse relationship in which increased consumption of tea is associated with a reduced risk of cardiovascular disease (myocardial infarction – MI, stroke and coronary heart disease – CHD). The mechanisms by which tea may offer these benefits are only beginning to be understood, but numerous hypotheses have been put forth. One of the major mechanisms by which tea consumption is thought to confer health benefits is via antioxidant protection, as the flavonoids (catechins as well as derived tannins) present in tea have been shown both *in vitro* as well as *in vivo* to have powerful antioxidant properties. For example, consumption of a single dose of green or black tea in humans has been shown to improve plasma antioxidant capacity, and repeated consumption has been shown to decrease markers of oxidative stress including oxidative damage to DNA. Most notably, the catechin components of green tea, especially epigallocatechin gallate (EGCG), as well as components present black tea such a theaflavins have demonstrated significant antioxidant capacity in numerous model systems. However, in addition to having the ability to directly quench free radicals, flavonoids have been shown to chelate metals, inhibit smooth muscle cell proliferation, enhance vasodilation and perfusion, enhance endothelial function, inhibit pro-oxidant enzymes, enhance phase II detoxification and enhance gap junction communication between cells. An interesting example of tea's ability to enhance blood vessel (endothelial cell) function was provided by a study published last year in the journal *Clinical Science*. In this study subjects consumed either 5 cups of black tea/day or a placebo (hot water) for 4 weeks. Endothelial function was assessed by measuring the ability of the brachial artery to dilate after being constricted. Changes in the ability of the artery to dilate were assessed before and after tea consumption. An improvement in the ability of the artery to dilate after being constricted signifies an improvement in blood vessel function. Subjects that ingested the black tea experienced a significant and consistent increase in endothelial function compared to those consuming hot water.

A recent review of the observational data on tea consumption and cardiovascular disease was published in the *American Journal of Epidemiology*. This report reviewed 17 observational studies (10 cohort and 7 case-control) on tea consumption and cardiovascular disease and reported an overall decrease in the risk for cardiovascular disease with increasing consumption of tea. This analysis found that for each 3 cups of tea consumed per day, there was an 11% reduction in the risk for MI and a 26 - 66% reduction in the risk for stroke. When the country in which the study was conducted was accounted for, there was a trend for those studies published in Europe to report a greater inverse effect of tea on cardiovascular disease than studies published

elsewhere. One particularly impressive prospective study published last year in the *American Journal of Clinical Nutrition* investigated the association of tea and flavonoid intake with the incidence of MI in almost 5,000 men and women in the Netherlands. This study, known as the Rotterdam Study, reported that during a 5.6 year follow up, those that consumed > 375 mL/day of tea had a 43% reduction in the risk of MI and a 70% reduction in the risk for a fatal MI. These reductions in risk remained significant after adjustment for numerous variables including age, sex, body mass index (BMI), smoking status, education level, alcohol, coffee and fat consumption. When the data were divided by sex, a stronger inverse relationship was observed in women compared with men. This finding is intriguing as tea contains natural phytoestrogens, and these compounds may have a more pronounced affect in women compared with men. In addition to tea consumption, the total daily intake of flavonoids in the Rotterdam Study was also inversely correlated with the risk of MI. In support of these findings is another study that was published in January of this year examining tea consumption in men and women in the Middle East. Over 3,000 men and women aged 30 - 70 were followed to investigate the link between tea drinking and cardiovascular disease. A dose response relationship was observed between the consumption of tea and a reduction in risk of coronary heart disease. The data revealed that those subjects who consumed > 480 mL tea/day had a significantly lower prevalence of coronary heart disease compared with non-tea drinkers. After adjustment for other variables associated with heart disease, those that consumed > 6 cups/day were shown to have almost a 50% reduction in the risk of coronary heart disease. These data are compelling and support a real potential for a protective effect of tea in cardiovascular disease. It is important to note that in the Middle Eastern study as well as in the Rotterdam study the type of tea consumed was black, as that is the form most commonly consumed in those regions. However, similar data also exist linking the consumption of green tea to a reduction in the risk of coronary artery disease (CAD) and MI. Data published last year in *The American Journal of Cardiology* followed a group of subjects in Japan over a two-year period who had received coronary angiography for suspected heart disease. The participants in the study were divided into 3 groups based on green tea consumption (<1 cup/d, 1 - 3 cups/d, >3 cups/d). While tea consumption did not significantly affect the prevalence of CAD, it was significantly and inversely correlated to MI. Those that consumed > 1 cup/d of green tea had a 42% reduction in the risk for MI compared with non-tea drinkers after adjustment for traditional risk factors as well as for the intake of fruits and coffee.

Interpretation of data with respect to tea and cardiovascular disease can often be challenging and there are a number of factors that must be kept in mind. First, it should be noted that these studies are observational or case-control in design and it is impossible to control for all potential confounding variables. A very limited number of studies have reported that tea consumption was associated with an increased risk for heart disease or stroke. For example, the Caerphilly Study, conducted in South Wales reported an increase in the risk for ischemic heart disease with increasing consumption of tea, with those consuming > 1.2 L/day having the greatest increase in risk. While this does not fit with our biological understanding of how tea may affect health, an

understanding of the significant cultural differences in the manner in which tea is prepared and consumed as well as the socioeconomic differences among countries with respect to tea consumption may help to explain these findings. In many countries tea consumption increases together with increasing affluence. However in South Wales, where the Caerphilly Study was conducted, tea consumption is associated with lower social classes. Consequently, as the authors of this study pointed out, the increase in cardiovascular disease observed in those consuming larger amounts of tea was most likely due to a less healthy lifestyle and an overall increase in all-cause mortality associated with a lower social class and not directly related to tea intake. Although the study made statistical adjustments for social class that diminished the strength of the association, it remained significant due to residual confounding that could not be accounted for in the analyses. In addition to socioeconomic factors, there are a number of other items to keep in mind when reviewing data on tea and disease. For example, in the US, tea is typically prepared half as strong as it is in Europe, and the percentage of people that consume tea in Europe is significantly greater than in the US. Consequently, comparing studies in which subjects consumed the same volume of tea might yield different results due to differences in preparation and ultimately differences in flavonoid intake. Also, in the United Kingdom and in a number of other countries, tea is generally consumed with the addition of milk. The health effects of adding milk to tea are not completely clear, but depending on its fat content, milk has been shown to affect the antioxidant potential of tea. Nonetheless, most studies have demonstrated that milk does not interfere with catechin absorption from tea. To further complicate matters, many studies do not even report the type of tea that was consumed, its method of preparation, or the quantity consumed. Given the significant variations in flavonoid composition between green and black tea, as well as the effect that brewing time and strength can have on the finished product, future studies should make every effort to report exactly the type of tea that was used and how it was prepared. Finally, every culture has a slightly different interpretation of "1 cup." While the definition of one cup from a scientific perspective is about 240 mL, cultural differences dictate what societies view as "a cup" of tea. For example, in Japan many small portions (much less than 240 mL) are consumed during the course of the day. One must not assume when reading the literature that "1 cup" is equivalent to 240 mL.

Tea and Cholesterol

Recent data are revealing that in addition to functioning solely as antioxidants, components in tea may be able to alter lipid levels. This reduction in cholesterol may be another key pathway by which tea is able to modify the risk of cardiovascular disease. A study published last year in *The Annals of Epidemiology* evaluated the effect of green tea consumption on serum lipids in a healthy Japanese population. More than 13,000 men and women aged 40 - 69 completed food frequency questionnaires and serum lipid panels over the course of 1 year. After controlling for confounding variables, the consumption of 1 cup of green tea was shown to be significantly and inversely correlated with a reduction in total serum cholesterol. This relationship appeared to be present in those consuming up to 10 cups/day, after which the relationship leveled off. Unfortunately, other studies in the US and Israel have

failed to find such an association with tea consumption. The lack of findings from other studies may be a reflection of both the type and quantity of tea consumed as well as poor reporting of the exact method of preparation of the tea. Data presented at the Experimental Biology meeting held in 2002 in New Orleans, reported that the consumption of 5 cups/d of black tea for 3 weeks resulted in a 10% reduction in serum LDL-C compared with a placebo tea beverage. While the mechanisms that may be responsible for tea's ability to lower cholesterol are just beginning to be investigated, flavonoids have been shown to inhibit both HMG CoA reductase as well as acyl CoA:cholesterol acyltransferase activities (ACAT). HMG CoA reductase regulates endogenous cholesterol synthesis while ACAT catalyzes the esterification of cholesterol for the creation of lipoproteins. Inhibition of these enzymes could ultimately result in a reduction in circulating cholesterol levels. In addition to inhibiting these two enzymes, catechins present in tea have been shown to alter the secretion of apolipoprotein B (ApoB) in a cell culture model. Reductions in this lipoprotein component could alter the manner in which lipoprotein particles are secreted from the liver into circulation. Animal studies have also shown that tea catechins can reduce intestinal absorption of cholesterol as well as increase fecal excretion of fat and cholesterol.

The most compelling data on the ability of tea flavonoids to alter cholesterol levels comes not from the intake of a tea beverage, but from the study of a unique tea extract. Data from this recent study were presented at the American College of Cardiology meeting in March of 2003. In this double-blind, placebo-controlled trial, 240 men and women with mildly elevated cholesterol levels

About Cholesterol

Cholesterol is a molecule that is vitally important for many processes, including the stability and function of cellular membranes. Without cholesterol, our bodies could not be capable of synthesizing molecules such as CoQ10 or steroid hormones. However, data continue to mount demonstrating the deleterious effects of elevated cholesterol, especially elevated levels of LDL-cholesterol. In fact, data are now clearly showing that reducing elevated LDL-cholesterol can significantly reduce the risk for coronary heart disease. It is estimated that for every 1% reduction in LDL-cholesterol, there will be a 1.0 - 1.5 % reduction in the risk of major cardiovascular events. The third report of the National Cholesterol Education Program (NCEP), Adult Treatment Panel III, recommends that LDL-cholesterol reduction should be a target of lipid lowering therapy. Below is the NCEP Adult Treatment Panel III classification of cholesterol levels.

Cholesterol Classification Based on Recommendations from NCEP Adult Treatment Panel III

	Classification
LDL Cholesterol (mg/dL)	
<100	Optimal
100-129	Near/above optimal
130-159	Borderline high
160-189	High
>190	Very high
Total Cholesterol (mg/dL)	
<200	Desirable
200-239	Borderline high
>240	High
HDL Cholesterol (mg/dL)	
<40	Low
>60	High

were given either 375 mg of a novel theaflavin-enriched green tea extract containing 20% theaflavins and 40% catechins (made via a unique controlled fermentation process of the tea leaves in which some of the catechins present in the green tea are converted to theaflavins) or a placebo for 12 weeks. Subjects in the group receiving the green tea extract experienced statistically significant 11.3 and 16.4% reductions in total cholesterol and LDL-C, respectively. Triglycerides were unchanged and HDL-C rose slightly in the supplemented group but was not statistically different from placebo. There were no findings of adverse effects or changes in routine blood chemistries. This report is among the first documentation of a tea-derived product having the ability to lower LDL-cholesterol in humans in a placebo-controlled trial. These clinical findings support the observational data on tea that has been previously reported.

For thousands of years drinking tea has played a significant role in many cultures, but only recently have researchers realized that tea may hold many more health benefits than previously thought. While the complex nature of tea makes it difficult to study, recent insights gained from both observational as well as controlled trials hint at the fact that we are only beginning to tap the full potential of this plant.

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Correction:
In our last "Special Edition" of NutriNews entitled "Raising the Standard, Continuing a Tradition of Quality", it was incorrectly stated that omega-3 fatty acids do not have an official compendial monograph. While there is no monograph for omega-3 acids in the United States Pharmacopeia (USP), there is a European monograph for fish oil. The Council for Responsible Nutrition has recently proposed a monograph for omega-3 fatty acids that may be submitted to the USP for consideration. However, currently there are no USP specifications for omega-3 fatty acids.