

LE Magazine April 2008 *By Julius Goepf, MD***New Research on the Health Benefits of Green Tea****Erskine Cherry**  
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In laboratories around the globe, green tea is sparking tremendous excitement as new health applications keep being discovered.

The most active green tea constituent is called epigallocatechin gallate. This unique flavonoid favorably alters pathways underlying pathological processes such as cancer, (1-4) cardiovascular disease, (5, 6) diabetes, (7) obesity, (8) and Alzheimer's and Parkinson's diseases. (9-11) All of this points to green tea as a broad-spectrum nutrient that may promote long life. (4, 12)

Green tea is consumed routinely in Asian populations, who have greater longevity and lower mortality rates for diseases that are prevalent in Western society.

Given the huge scientific literature supporting the positive role of green tea in preventing neurodegenerative diseases, not to mention its benefits in helping to prevent cancer and other diseases, as well as its lack of toxicity, there is ample reason for consuming green tea poly-phenols on a regular basis.

In this article, we have interviewed international scientists on their current research into the myriad life-extending and life-enhancing benefits of green tea.

**ABUNDANT RESEARCH CONFIRMS GREEN TEA'S VAST BENEFITS**

Population-based studies (13-15) and clinical trials (4, 16-20) have shown that green tea consumption is beneficial to human health, particularly in individuals who drink five or more cups of this beverage a day. (6) Two Japanese studies suggest that those who drink several cups of green tea daily avoid premature cardiovascular death, which may help them live longer than subjects who consume less green tea. (14,21)

Green tea's benefits for cancer protection and heart health have been confirmed by extensive research in cell culture (22) and in animal experiments. (23, 24) Laboratory studies have also shown that green tea may help protect against loss of brain cells, (9, 25) bacterial and viral infections, (18, 26) allergies, (27) arthritis, (28) and decreased bone mineral density, (29) among other health concerns. (30, 31) A clinical trial in human volunteers has also revealed that a green tea preparation helps improve immunity and prevents cold and flu symptoms. (18)

Swen Wolfram, PhD, from Basel, Switzerland, tells Life Extension, "Due to the tremendous interest of the public and the scientific community, the health benefits of green tea were extensively investigated during the past few years. No other traditional beverage has received such widespread scientific attention, and knowledge about its positive effects is exceptional. The various health benefits of regular green tea consumption may finally result in a prolonged life span."



Pon Velayutham Anandh Babu, PhD, a postdoctoral research associate in Human Nutrition, Foods, and Exercise at Virginia Polytechnic Institute and State University in Blacksburg, tells Life Extension. "Recent studies suggest that green tea possesses various health benefits on cardiovascular disease, cancer, diabetes and diabetic complications, and oral health. The antihypertensive effect, antibacterial effect, antiviral effect and neuroprotective effect of green tea [are] also reported."

The diverse benefits of green tea may arise from its unique constituents, which confer powerful antioxidant capacity. Green tea is particularly rich in healthful polyphenols known as catechins, the most abundant of which is epigallocatechin gallate (EGCG). (5) This potent antioxidant effectively traps reactive oxygen species, or free radicals,(1, 4) which are common culprits in aging and chronic degenerative diseases. A Japanese study recently reported that taking a single dose of green tea catechin extract equivalent to drinking five cups of green tea a day improved the plasma antioxidant capacity of healthy adults. (32)

## **EGCG PROTECTS AGAINST CANCER**

Laboratory studies suggest that EGCG works at the cellular level to intervene against various cancers, including cancer of the breast, (33, 34) pancreas, (35) mouth, (36) colon, (37) and prostate. (38, 39)

According to results from several epidemiological studies, individuals who drink green tea regularly may have less frequent or less severe cancer in various areas of the body, including the ovary, (40) prostate, (13, 41) and head and neck. (42) There is some evidence suggesting that regular intake of green tea at a level of more than three cups daily may reduce the risk of lung cancer in smokers. (43) Even more encouraging is a recent intervention study confirming the preventive effects of green tea catechins in prostate cancer. (44) Clinical trials in other types of cancer are ongoing. (1)



“The main evidence suggesting that green tea (and tea in general) is beneficial to human health has generally been studies relating to the ‘Asian paradox’—specifically that Asians exhibit behavior (e.g., smoking) that has been associated with heart disease and cancer for a long time in North America, yet their rates of these diseases are much lower,” Sean Eddy, PhD, a research associate in biochemistry at Boston University School of Medicine, tells Life Extension. “Green tea consumption, with its high levels of antioxidant flavonoids such as EGCG, has been noted as one of the potential reasons for this. Green tea works on multiple levels from protection and prevention to treatment, blocking inflammation and cancer.”

Epidemiological and population-based studies have also shown that young Asian women migrating to the US dramatically increase their lifetime risk of developing breast cancer and of dying from breast cancer, which suggests that environmental rather than genetic factors explain the “Asian paradox.” (45-47)

“Studies in Japan show that drinking three to six cups of green tea a day can have a protective effect against patients in remission treated for early-stage breast cancer,” Dr. Eddy says. “Green tea and/or EGCG has been shown to inhibit every type of cancer cell, at least in [a laboratory] setting. It’s also been shown to act as an anti-inflammatory, antithrombotic, cholesterol-lowering, and potentially antiviral and antibacterial agent, which would explain green tea’s protective effect in heart disease.”

At the molecular level, EGCG directs cell signals that block harmful or dangerous activity that could lead to the uncontrolled growth characteristic of cancer cells. (48)

The cancer-preventive effects of green tea may be at least partly explained by the interaction of EGCG with a recently identified cellular-control mechanism (known as the 67-kDa laminin receptor), according to Dr. Wolfram. (49) Green tea has been shown to suppress tumor growth by blocking angiogenesis, or formation of new blood vessels supplying the tumor. (35, 50)

Studies by Dr. Eddy's group have shown that green tea also inhibits a growth factor receptor called HER2, which is present in excess in about 30% of breast cancers and is associated with poor outcomes. Not only does EGCG inhibit growth of breast cancer cells in mice, but in one study it blocked the growth of breast cancer cells taken from a patient who did not respond to treatment with an antibody against HER2. Known as trastuzumab, this antibody is often used for immunotherapy in patients with HER2-positive tumors. Unlike trastuzumab, EGCG can enter into the brain, making it potentially useful in patients with breast tumors that have spread to the brain. (51)



Through a cascade of intermediate signals, HER2 inhibition ultimately induces a protein that dramatically suppresses tumor growth. Other studies have shown that EGCG and green tea block other signaling cascades involved in the proliferation and spread of cancer. (52)

“All of these cascades are important in cancer, heart disease, diabetes and/or inflammation,” Dr. Eddy says. “If you block their activation, you significantly block disease progression. While drug companies attempt to target one specific cellular target, green tea polyphenols affect a plethora of pathways, which makes it potentially better as a real therapy.”

**EGCG PROTECTS CARDIOVASCULAR HEALTH** Green tea acts in many other ways to promote cardiovascular health. Thanks to potent antioxidant activity, green tea and EGCG scavenge damaging free radicals, or reactive oxygen species that cause cellular injury leading to heart disease. (24, 53, 54)

Heart disease can develop in many ways, such as:

- ! Inflammation of blood vessel walls and proliferation of the muscle cells within blood vessel walls, which contribute to atherosclerosis.
- ! Endothelial dysfunction and constriction of blood vessels, which reduce blood flow to the heart muscle and increase blood pressure.
- ! Abnormal platelet aggregation within blood vessels, which can lead to a deadly heart attack or stroke.

High levels of low-density lipoprotein (LDL), particularly when oxidized, which further aggravate all of these problems.

Amazingly, green tea can help protect against all of these culprits leading to heart disease and stroke. (55-60) In a well-controlled study, human volunteers showed short-term improvements in blood flow with EGCG compared with placebo. (20)

“Green tea has been reported to beneficially impact parameters associated with cardiovascular dysfunction including lipoprotein oxidation, vascular inflammation, proliferation of vascular smooth muscle cells, platelet aggregation, and vascular reactivity,” Dr. Babu says, referring to his own laboratory studies. (61-63) “Catechins, the major polyphenolic compounds in green tea, exert vascular-protective effects through multiple mechanisms including antioxidative, anti-inflammatory, antithrombotic, antiproliferative and lipid-lowering effects. Green tea catechins were also reported to regulate vascular tone.”



Epigallocatechin gallate also activates endothelial nitric oxide synthase in cells lining blood vessels, or endothelial cells, (58, 64, 65) which Dr. Wolfram says may partially explain the cardiovascular benefits of green tea consumption. Increased release of nitric oxide causes smooth muscle within the blood vessel wall to relax, thereby increasing the diameter of the blood vessel and improving blood flow.

Another important mechanism may be that EGCG reduces the expression of cellular chemicals known as cytokines, which promote inflammation underlying atherosclerosis and heart disease. Epigallocatechin gallate may therefore inhibit inflammation and proliferation of smooth muscle cells within the blood vessel wall, thereby preventing vascular blockage. (59)

“Green tea and EGCG were shown to reduce atherosclerosis and improve arterial compliance and endothelial function,” Dr. Wolfram says. “Regular green tea consumption is associated with reduced risk of cardiovascular disease such as stroke and myo-cardial infarction [heart attack].”

In further research, a clinical trial led by Japanese researcher, Nagao Tomonori, evaluated the effect of a green tea extract rich in catechins on risk factors for cardiovascular disease. (17)

“The continuous ingestion of [green tea extract] reduces body fat, cholesterol levels, and blood pressure in females and males without changing their lifestyles,” Dr. Tomonori tells Life Extension. “We found that increased beta-oxidation (fat burning) in the liver by catechins was associated with the reduction of intra-abdominal body fat, [which] is known to secrete factors causing various chronic diseases. Therefore, its reduction will reduce the risk of lifestyle-related chronic diseases.”

### **WHAT YOU NEED TO KNOW: GREEN TEA**

! Population studies in humans, laboratory studies in animals and in cell culture, and clinical studies in human subjects suggest a wealth of health benefits associated with green tea.

! Green tea is rich in healthful polyphenols, particularly a catechin known as EGCG, which is a potent antioxidant.

! Green tea may help prevent or manage cancer, heart and vascular disease, diabetes, obesity, Alzheimer’s disease and other neurological degenerative diseases, bacterial and viral infections, and other conditions.

! In Japanese populations, green tea consumption has been linked to longer life, especially in subjects drinking five cups or more daily. Western populations consume relatively little green tea.

! Green tea extract supplements may facilitate adequate consumption for maximal health benefits — without requiring lifestyle changes.

! Green tea supplements also avoid potential risks of esophageal cancer associated with drinking hot tea. This risk is thought to be related to the high temperature of traditionally prepared tea, because green tea itself has no known toxicity.

In addition to the mechanisms described above, Dr. Tomonori notes that EGCG also inhibits an enzyme that controls the rate of cholesterol production. He recommends additional research to determine how EGCG ameliorates cardiovascular risk factors and to study the effects of green tea in non-Japanese nationalities.

“The most important treatments for obesity and cardiovascular diseases should be obtained by an appropriate lifestyle such as balanced diet and exercise habits,” Dr. Tomonori says. “Continuous ingestion of a [green tea extract] high in catechins might assist this.”

The largest population-based study to date of the effects of green tea on life span is the Ohsaki study of more than 40,000 Japanese adults followed for up to 11 years.<sup>14</sup> When enrolled in 1994, participants were 40 to 79 years old and had no history of stroke, coronary heart disease, or cancer. The study found that drinking more green tea protected against death from all causes and against death from cardiovascular disease, particularly from stroke, but not against death from cancer.

During follow-up, there were 12% fewer deaths from all causes in men and 23% fewer deaths in women who drank five or more cups of green tea per day, compared with those who drank less than one cup. Even more strikingly, there were 31% fewer cardiovascular deaths in women who drank five or more cups per day, compared with those who drank less than one cup.



Lead investigator of this study, Shinichi Kuriyama, MD, PhD, tells Life Extension, “We have confirmed that green tea consumption is associated with reduced mortality due to all causes, cardiovascular disease, but not cancer. Our study provides strong evidence regarding benefits of drinking green tea in humans on cardiovascular disease, but not cancer.”

Dr. Kuriyama, an associate professor of Epidemiology, Public Health, and Forensic Medicine at Tohoku University Graduate School of Medicine in Sendai, Japan, points out that previous studies have suggested green tea may reduce

cardiovascular risk factors such as hypertension and obesity, which may partly explain improved survival linked to green tea consumption. Surprisingly, however, his study showed a protective effect of green tea drinking even in lean subjects and in those with normal blood pressure.

“Therefore, mechanisms other than the effects on traditional cardiovascular disease risk factors might play a role,” Dr. Kuriyama says. “A number of biological mechanisms including radical scavenging and antioxidant properties have been proposed for the beneficial effects of green tea in different models of chronic disease. Green tea polyphenols might directly affect atherosclerosis itself, irrespective of traditional cardiovascular disease risk profiles.”

### **GREEN TEA AND EGCG MAY HELP PREVENT OBESITY, DIABETES**

Because diabetes and cardiovascular disease share some of the same risk factors, particularly obesity, it is not surprising that green tea, by ameliorating these risk factors, (17) can help protect against diabetes as well as against heart disease. (6-8)

“Subjects with long-term consumption of green tea are characterized by a lower percentage of total body fat, smaller waist circumference, and decreased waist-to-hip ratio,” Dr. Wolfram says. “In intervention studies, it was shown that consumption of green tea can reduce body weight and abdominal fat as well as increase fat oxidation and energy expenditure. Furthermore, green tea consumption may reduce the incidence of type 2 diabetes and improve glucose control and insulin sensitivity.”

The exact mechanism of how green tea helps control overweight and high blood sugar is not completely understood, and probably involves several different hormonal and metabolic mechanisms. (8) However, Dr. Wolfram notes that EGCG regulates genes involved in fat oxidation and storage, as well as genes involved in insulin signaling and glucose metabolism. (66-68)

Amazingly, EGCG can even improve survival and function of insulin-secreting pancreatic islet cells grown in the laboratory, and could have future applications in enhancing the success of pancreatic islet cell transplantation. (69) Furthermore, EGCG suppresses glucose production by liver cells. (70) Drinking green tea was shown to improve glucose metabolism in healthy human volunteers, (71) and in a population study, women who drank four or more cups of tea per day had a tendency toward lower diabetes risk, compared with women who drank no tea. (72)

Extensive studies by Dr. Babu’s group of the effects of green tea and its catechins in animal models of type 1 and type 2 diabetes. (53, 61, 62, 73) have shown that green tea helps optimize glucose utilization, thereby reducing blood glucose levels.

“Green tea administration significantly reduced elevated serum glucose level in [drug]-induced diabetic rats and increased glucose tolerance in normal rats,” Dr. Babu says. “Green tea also has been shown to lower blood glucose level both in [chemically induced] diabetic mice and a genetic model of type 2 diabetes.”

By lowering glucose production in liver cells and decreasing the activity of genes that enhance glucose production, “EGCG was reported to mimic insulin,” Dr. Babu explains. “Green tea also reduced accumulation of cholesterol, free fatty acids, and triglycerides in the heart of diabetic rats.”

The chronic, disabling complications of diabetes result from changes to the blood vessels in the limbs, eyes, kidneys, heart, and other organs. In the presence of high blood sugar levels, these complications arise when damaging byproducts of sugar metabolism, called advanced glycation end products (AGEs), interfere with cross-linking of collagen in connective tissue. Abnormal collagen fiber cross-linking contributes to fibrosis, in which the heart muscle and other tissues become increasingly dysfunctional as they stiffen and become rigid, much as pliable metal wires linked together can form an impenetrable coat of armor. Once again, green tea may intervene in this disease process. (53, 74)

“Green tea extract administration reduced the accumulation of collagen, extent of glycation, formation of advanced glycation end products and cross-linking of collagen in [chemically induced] diabetic rats,”

Dr Babu says. "In our study, we proposed that green tea may have a therapeutic effect in the treatment of glycation-induced complications of diabetes."

## **GREEN TEA CATECHINS PROTECT BRAIN CELLS**

As with heart disease and other chronic diseases, oxidative damage and inflammation also underlie the ravages of Alzheimer's disease and other neurodegenerative diseases associated with aging. The antioxidant and anti-inflammatory effects of green tea catechins may once again come to the rescue. (10, 11, 75)

"Recently, it has been hypothesized that green tea consumption may reduce the risk of degenerative brain diseases," Bradford L. Frank, MD, MPH, MBA, assistant clinical professor at the University of Buffalo School of Medicine and Biomedical Sciences says. "There is now a large body of scientific evidence, experimental and epidemiological, demonstrating that certain natural compounds, such as catechins from green tea, improve age-related cognitive decline, and are neuroprotective in animal models of Parkinson's disease, Alzheimer's disease, stroke, Huntington's disease, amyotrophic lateral sclerosis (ALS), and other brain diseases."

One such animal model of Alzheimer's disease is a mouse strain that shows accelerated loss of brain cells (atrophy) and memory impairment with aging. The effects of green tea in this model have been studied extensively by Keiko Unno, PhD, an associate professor of Bioorganic Chemistry at the University of Shizuoka in Japan. (76)

"We found that the learning and memory abilities were higher in aged mice that had drunk water containing green tea catechins than those in same-aged mice that had drunk water (control)," Dr. Unno tells Life Extension. "Moreover, brain atrophy was suppressed in aged mice drinking green tea catechins. These results suggest that consumption of green tea is beneficial to prevent cognitive dysfunction."

Similar benefits of green tea polyphenols on behavior, learning, and changes in the brain have been seen in other mouse models of Alzheimer's disease.<sup>77,78</sup> Even young, healthy rats given long-term supplementation with green tea catechins in their drinking water show improved memory and learning compared with control rats, and these psychological benefits have been linked to lower reactive oxygen species in the hippocampus, a brain region involved in memory. (79)

Even more exciting, a population study by Dr. Kuriyama's group<sup>15</sup> showed that in more than 1,000 Japanese adults 70 years of age or older, regularly drinking more green tea is associated with a lower prevalence of cognitive impairment measured on the Mini-Mental Status Examination, a standardized test of memory and cognitive function. Compared with subjects who drank three or fewer cups per week, those who drank one cup per day had a 38% decrease in cognitive impairment. This significant protective effect was not observed with black tea or coffee.

Dr. Unno notes that the concentration of green tea catechins used in his animal experiments was only 0.02%, which is lower than the concentration of 0.05-0.06% found in green tea consumed by humans. He therefore suggests that daily consumption of several cups of green tea or the equivalent may be protective in humans (which would be borne out by Dr. Kuriyama's study). Although the mechanisms by which green tea could benefit cognitive function and neuroprotection are still unclear, Dr. Unno suggests that the very high antioxidant activity of green tea catechins is important.

"Oxidative damage in proteins and DNA was lower in brain and other organs of aged mice that had drunk water containing green tea catechins than [in] control mice," he says. Dr. Frank concurs that oxidative damage caused by reactive oxygen species plays a pivotal role in the age-associated cognitive decline and neuronal loss seen in neurodegenerative diseases, and that green tea has powerful antioxidant effects.

"However, recent studies indicate that the antioxidant property of green tea polyphenols is unlikely to be the sole explanation for their neuroprotective capacity," Dr. Frank says. "In fact, a wide spectrum of cellular-signaling events may well account for their biological actions. There is substantial scientific evidence supporting the beneficial effects of green tea on cognitive function and its use as a natural neuro-protective substance."

Death of nerve cells in Parkinson's, Alzheimer's, or other degenerative brain diseases may result not only from oxidative damage, but from a complex series of toxic reactions also involving inflammation, decline in protective neurochemicals, excess iron, and accumulation of harmful proteins such as amyloid-beta, the biochemical hallmark of Alzheimer's disease.

Because EGCG may help interrupt this chain reaction, it may potentially have preventive or therapeutic value in Alzheimer's disease<sup>9</sup> and in Parkinson's disease. (25)

"Green tea flavonoids (catechins) have been reported to possess metal chelating (binding and removing excess iron, for example), antioxidant, and anti-inflammatory activities, to penetrate the brain barrier, and to protect [against] neuronal death in a wide array of cellular and animal models of neurological diseases," Dr. Frank says. "Evidence is increasing that green tea flavonoids can protect cells from [amyloid-beta]-mediated neurotoxicity. The main polyphenol in green tea, EGCG, exerts a beneficial role in reducing [amyloid-beta] levels by a variety of cellular mechanisms."

In Alzheimer's disease and in other forms of memory impairment, brain levels of acetylcholine, a chemical used by certain nerve cells to communicate with each other, decrease. In an animal model of Alzheimer's disease, 80 mice that regularly consumed tea polyphenols had higher brain levels of acetylcholine and significant reversals of memory and learning deficits. "This finding suggests that tea polyphenol might be useful in the treatment of Alzheimer's disease," the researchers write. (80)

In Parkinson's disease, oxidative stress is thought to play an important role in nerve cell death. Green tea polyphenols may protect dopaminergic nerve cells against such oxidative stress, offering important neuroprotective effects against Parkinson's disease. (25)

"It would be interesting to substantiate the neuroprotective effects identified in cell culture and in [live animal] studies in well-designed intervention studies in human subjects," Dr. Wolfram says. "This could potentially have implications for the age-related decline in memory and alertness and be beneficial for subjects with Alzheimer's or Parkinson's diseases."

## **PRACTICAL SUGGESTIONS FOR GOOD HEALTH WITH GREEN TEA**

The experts interviewed by Life Extension agreed that research to date strongly supports the health benefits of green tea.

Dr. Wolfram believes that, "The most prominent health benefits are observed in subjects consuming five or more cups of green tea per day. Therefore, it is advisable that the general population increase green tea consumption to approximately this level." Indeed, many of the human clinical trials highlighted in this report have used EGCG doses of up to 500 mg/day (equivalent to drinking up to five or six cups of green tea a day), in yielding optimum benefits for cardiovascular health and for protecting against cancer, diabetes, and neurodegenerative diseases. (13, 15, 16, 17, 20, 43, 72, 81)

However, Dr. Wolfram continues, "Unlike Asians, Europeans and Americans do not consume green tea several times per day throughout the whole year." Use of purified green tea extracts may therefore be a viable alternative that does not involve lifestyle changes, especially because some Western consumers find the characteristic taste of traditional green tea unpalatable. Dr. Wolfram also advises the consumer to buy only green tea or extracts from well-controlled plantations.

"The food industry has recognized the health benefits of green tea catechins and is actively doing research to be able to offer standardized products which can help to support well-being and health of the consumer,"

Dr. Wolfram adds. "More results from well-designed, long-term, multicenter studies with standardized green tea products could potentially transform a beverage traditionally associated with a number of health benefits into an evidence-based functional food."

"Every little bit helps, but more [green tea] is probably better," Dr. Eddy recommends. "This is also the case with fruits/vegetables and other non-processed foods with high antioxidant qualities, like blueberries and pomegranates."

Another reason that green tea supplements may be better than drinking green tea is that the consumption of this traditionally prepared hot beverage has been linked with an increased risk of esophageal cancer. (82, 83) Scientists believe that large quantities of hot green tea may inflict local damage that makes the esophageal tissues more susceptible to cancer. Although total cancer mortality is not significantly different in Japan than in the US, the Japanese age-adjusted rate of death from cardiovascular disease is about 30% lower.

“Through a relatively low rate of cardiovascular disease mortality, the Japanese now have the longest life expectancy in the world,” Dr. Kuriyama concludes. “Although factors other than diet may also be contributory, green tea, a harmless drink with no caloric value, might provide a clue to clarifying the reason for Japanese longevity among dietary factors. In contrast, drinking green tea at high temperature may be associated with increased risk of esophageal cancer incidence and mortality; therefore, we recommend that green tea should be consumed at moderate or low temperature.”

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

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