Green Tea and Garlic as Cardiovascular Life Extension Strategies

Introduction

This year we came across the following article in a local newspaper: "A life expectancy of 100 years is likely if scientists succeed in developing a pill they say could eliminate heart attacks and strokes.... Scientists believe they will perfect the treatment within 10 years.... This will have very wide implications and will revolutionise preventative medicine...."

But these "wonder drugs" already exist in our diet! They are simple everyday herbs, both starting with the letter g: garlic and green tea. We hope to demonstrate in the following review that there is credible evidence for the capacity of garlic and green tea to significantly reduce the risk of heart attack or stroke, by favorably influencing the factors known (and possibly unknown) to lead to these events. The likelihood is that the evidence for green tea and garlic as life extension strategies for the prevention of cardiovascular disease will be far more substantial than what can be generated in the near future for any new drugs.

When research on the polypill was announced there was much acclaim in the media and scientific circles. The concept of using a combination of agents acting on different aspects of cardiovascular disease risk to bring about a substantial overall reduction in cardiovascular disease was considered to be novel and innovative. But we propose that nature has already designed such agents in the form of green tea and garlic.

Green Tea

Tea (Camellia sinensis) is manufactured in three forms: green tea (unfermented), oolong tea (semi-fermented) and black tea (fermented). The "fermentation" during tea manufacture is not a microbiological process but an enzymatic reaction. The polyphenols present in the fresh leaf are oxidized by an enzyme also present in the cells of the leaf, and then undergo condensation reactions to produce a series of compounds which impart the characteristic taste and colour of black tea. In green tea manufacture, the enzymatic action is inhibited by rapid drying so green tea retains the polyphenols in their original state. Oolong tea is intermediate in composition between green and black tea, as it undergoes partial oxidation. Green tea is particularly rich in catechins, of which epigallocatechin gallate (EGCG) is the most abundant. Catechins comprise about 30% by weight of the dissolved solids in green tea, and a typical infusion of green tea contains on average about 600 mg/L of polyphenols. Catechins are associated with the bitter and astringent taste of green tea.

In 2002, an estimated dietary intake of total tea catechins, calculated for an average consumption of 3 cups (200 mL cup, 1% weight/volume of tea leaves) was 405.5 mg/day for green tea. However, the estimation of polyphenol and caffeine consumption calculated from the number of cups of tea consumed is considered inaccurate, as large variations may be caused by differences in leaf quality (and manufacture) and tea preparation. In addition to the quality of the leaf, composition of the infusion is influenced by whether the tea is contained in a teabag (and the size, shape and material of the bag), ratio of leaf to water, infusion time and amount of agitation. In China and Japan, green tea is normally prepared by infusing it in hot, but not boiling water. Generally the first infusion is discarded (to avoid bitterness) and it is the second and subsequent infusions that are consumed. It is also reported that the third cup of brewed tea has substantially decreased levels of EGCG compared to the first two cups.

Green tea is regarded in Japan as a source of folic acid. An analytical study conducted in 1983 found that infusion of green tea had higher amounts of total folate than infusions of black tea or oolong tea. However, black tea infusions contained the highest amounts of free folate. On average green tea contained 11.2 µg/g of total folate.

Cardiovascular Risk Reduction

Coronary Artery Disease, Myocardial Infarction, Stroke

A comparative dietary study involving 393 Japanese patients who had received coronary angiography for suspected coronary artery disease (CAD) from 1999 to 2001 found an...
Greentea & Garlic

inverse association between green tea intake and myocardial infarction (MI). A green tea intake of 1 or more cups per day was inversely associated with MI and independent of traditional risk factors and intake of fruit and vegetables. There was no inverse association observed with CAD. This association between green tea intake and reduced MI was further investigated by the same research team by considering platelet glycoprotein Iba gene polymorphism. MI prevalence among CAD patients who had the Met allele (GPM+) was much lower in those drinking one or more cups of green tea daily (29%) than in those not drinking green tea (56%). (CAD and MI tended to be more prevalent in GPM+ patients than in GPM-patients.) Green tea intake was also protective for GPM-patients but to a lesser extent (the odds ratio for MI with green tea intake was much lower in GPM+ patients than in GPM-patients). Green tea intake may be protective against MI, especially in GPM+ patients.

However, no significant association between green tea intake and CAD was found in another Japanese cross-sectional study involving 512 patients undergoing coronary angiography. A weak, protective association was found in men, which was stronger in the subset of nondiabetic men. Other dietary variables were adjusted for. In this study patients with MI were excluded. A possible weakness is that the study interviewed 167 patients with CAD, compared with 345 control volunteers, and the participants consumed a low average intake of green tea (only 29% of patients drank more than 3 cups/day of green tea compared to about 47% in the general Japanese population). Another study of similar design (but with a better CAD/control ratio) found that green tea consumption was significantly higher in patients without CAD compared to those with CAD (5.9 cups/day versus 3.5 cups/day, p<0.001) and was unrelated to gender. There was no relationship found between plasma lipid concentration and the daily intake of green tea. The study did not investigate the consumption of traditional Japanese foods as a possible variable.

The incidence of stroke and cerebral hemorrhage during a 4-year follow-up of 5910 nondrinking and nonsmoking Japanese women (40 y.o. or older) was two or more times higher in those who drank less than 5 cups/day of green tea compared to those drinking 5 or more cups/day. A study in China involving over 14000 volunteers found that there was a strong inverse correlation between tea drinking and stroke after adjusting for other risk factors. Black tea was more protective than green tea, which was more protective than jasmine tea (a semi-fermented tea).

Blood Pressure

An epidemiological study involving Japanese male self-defense officials (aged 48-56 years) found green tea consumption was unrelated to blood pressure. In an Australian clinical study, ingestion of tea caused larger acute increases in blood pressure than caffeine alone, but the acute effects (up to 60 minutes after drinking) did not translate into significant alterations during regular tea consumption.
(over a week for each beverage). The effect of green tea and black tea was compared to an equivalent amount of caffeine. The acute study was conducted with 20 healthy, normotensive, male volunteers (35-73 y.o.), the second study (involving regular intake over 7 days for each beverage) involved 13 volunteers (25-72 y.o.) with high-normal systolic blood pressure and mild systolic hypertension.\textsuperscript{27}

In contrast, habitual moderate strength green or oolong tea consumption at a volume of at least 120 mL/day for 1 year was associated with significant reduction in the risk of developing hypertension in a Chinese population of Taiwan. A negative linear trend of mean blood pressure was found for increasing tea consumption. Of the 1507 people interviewed, 600 were habitual tea drinkers (at least 120 mL/day for 1 year) with 96.3% drinking green or oolong tea. In this cross-sectional study, volunteers were 20 years or older and did not have a history of hypertension. Several lifestyle and dietary factors confounded the association between tea drinking and hypertension, but the odds ratios did not change much when adjusted for these factors. Habitual tea drinkers were younger, predominantly men, more obese, smoked more, consumed more alcohol, ate fewer vegetables and had more frequent high sodium intake.\textsuperscript{30}

**Endothelial Function**

Green tea reversed endothelial dysfunction in healthy smokers, as measured by a decrease in forearm blood flow during reactive hyperemia (an index of endothelium dependent vasodilatation). In this crossover study, smokers were randomized to receive a single 400-mL serving of green tea or hot water.\textsuperscript{29} Green tea had a beneficial effect on endothelial function in an assessment of Japanese aged 60 years or older. Those drinking at least 5 cups/day in their diet had significantly smaller PWV and higher FMD readings than those drinking less than this amount. (PMV: pulse wave velocity - reflects arterial; FMD: flow mediated dilation of right brachial artery after forearm occlusion for 5 minutes - is a measure of endothelial vasodilator function.). When volunteers increased their intake of green tea to at least 5 cups/day for a period of 4 months, PWV and FMD significantly improved.\textsuperscript{30}

**Overall Mortality**

A follow-up of those involved in the 1986 epidemiological study that surveyed 8552 members of the general population in the Saitama prefecture of Japan was conducted in 1999. The mean age at cancer death among those who consumed over 10 cups/day of green tea was 3.9 or 5.9 years (men/women respectively) later than those consuming below three cups/day (p < 0.05 for trend in both men and women). This effect held for smoking status (assessed in men). Those consuming the largest amounts of green tea consistently showed later ages at cardiovascular death in all age groups. Increased consumption of green tea was also associated with higher age at death from all causes, but was more clearly observed in ages below 79 among both men and women. (Seventy-nine is the average lifespan of Japanese, one of the highest in the world).\textsuperscript{31}

A cohort study found no effect for green tea consumption on all-cause mortality in a rural Japanese population (2855 volunteers) after a follow-up of 9.9 years. A non-significant decreased risk of mortality from apoplexy (cerebrovascular accident) was observed for men in the high green tea consumption category (≥ 4 cups/day). This study had a small sample size.\textsuperscript{32}

**Antioxidant Activity**

The antioxidant activity of green tea may contribute to the prevention of cardiovascular diseases and cancer.\textsuperscript{22,33} Much of the evidence supporting the antioxidant activity of green tea and green tea polyphenols is derived from *in vitro* assays. The majority of human intervention trials demonstrate a modest increase in plasma antioxidant potential after the consumption of green tea, however studies have reported contradictory results for lipid peroxidation. Research involving larger numbers of volunteers should employ sensitive and specific markers of oxidative damage to lipids, proteins and DNA, such as F2-isoprostanes (the most reliable indicator for lipid peroxidation), protein carbonyls and 8-hydroxydeoxyguanosine (8-OHdG). (8-OHdG is the oxidation product of the DNA base guanine.) So far, changes in urinary F2-isoprostanes as a result of ingestion of green tea have not been demonstrated. Significant reduction of DNA damage after consuming green tea has been reported in small population studies.\textsuperscript{34-36} Consumption of green tea has been shown to significantly decrease 8-OHdG in both white blood cells and urine of smokers and non-smokers,\textsuperscript{27} and to decrease urinary 8-OHdG in smokers (decaffeinated green tea (4 cups/day).\textsuperscript{38} But in another study, urinary excretion of 8-OHdG was unaffected by intake of green tea extract (containing 18.6 mg/day of catechins which is a low intake).\textsuperscript{39}
Green Tea & Garlic

Inflammation

Chronic inflammation has been implicated as a potential factor in cardiovascular risk. Ingestion of green tea (600 mL/day) by healthy smokers significantly reduced serum P-selectin after 2 and 4 weeks compared to baseline values. (P-selectin is induced by platelet activation and acts on the adhesion of white blood cells to endothelial cells in the early phase of inflammation. Plasma levels of P-selectin have been found to be higher in smokers than nonsmokers.) C-reactive protein (CRP) and soluble vascular cell adhesion molecule-1 (sVCAM-1) levels were not significantly lowered. Although in another study involving 12 healthy volunteers the concentration of sVCAM-1 decreased significantly after 4 weeks of the same dosage of green tea. (VCAM is involved in mediating the adherence of leukocytes to the vascular endothelium, thus affecting early inflammatory reactions in the progression of atherosclerosis.)

High consumption of green tea (> 10 cups/day) was negatively associated with the risk of chronic atrophic gastritis (a precancerous lesion of the stomach) in a cross-sectional study of 636 Japanese villagers. This association was found even after adjustment for Helicobacter pylori infection and lifestyle factors associated with green tea consumption.

Green tea consumption was also found to be protective against chronic gastritis in a population-based case-controlled study conducted in an area of China with one of the highest rates of alimentary cancer in the world. Green tea drinkers had a 51% lower risk of chronic gastritis than nondrinkers after adjusting for potential confounding factors (such as alcohol intake and cigarette smoking). Another epidemiological study in Japan found green tea consumption was related to decreased risk of severe atrophic gastritis, although not statistically significant. Fruit, vegetables or alcohol intake and cigarette smoking were associated with green tea consumption.

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Cognitive Function

Epidemiological data involving elderly Japanese volunteers found that those with normal cognitive function drank green tea daily and in higher amounts than those with cognitive impairment. A statistically significant positive association between the daily intake of green tea and cognitive function was observed. Volunteers with cognitive impairment showed higher plasma levels of total homocysteine (tHcy). A statistically significant positive relationship was observed between plasma tHcy and platelet amyloid precursor protein levels (a risk factor of Alzheimer’s disease). Green tea reduced tHcy levels and the reduction may be related to the protective effect of green tea against cognitive impairment. A two-year followup found that volunteers with normal cognitive function had a green tea intake corresponding to 0.8 g/day of polyphenols and no change to their Mini Mental State Examination (MMSE) scores, whereas those with probable Alzheimer’s disease consumed less green tea (0.3 g/day of polyphenols) and showed a decline in MMSE scores. A comparison in the percentage of senile dementia in the population of a town famous for green tea production and a control town found a 7 times lower percentage in the former (0.4% vs 2.8%). The available information in English abstracts reporting this data is light on detail and probably covers several studies, with overlap of the information not known. The study or studies may not have been well controlled for confounding factors, and may not have investigated actual intake of green tea – more rigorous studies are warranted to verify this possible association.

Antifolate Activity of Green Tea?

An epidemiological study conducted by the US Centers for Disease Control observed a possible association between maternal tea consumption and the risk of anencephaly or spina bifida. The type of tea was not defined (and given the population surveyed was probably black tea), but consumption of other caffeinated beverages was not associated with risk of these birth defects. The data was adjusted for gender, race, period of birth, maternal age, education, alcohol consumption, smoking and periconceptional multivitamins. The authors noted that further studies are required to corroborate these results. The results of this study have been reported as indicating that green tea consumption has been linked to neural tube defects (despite the fact that the type of tea was not defined). In the late 1970s several factors were proposed as etiological factors in neural tube defects including maternal black tea consumption and zinc deficiency, however, these studies were criticized as being of dubious validity and lacking scientific rigour in design. EGCG at concentrations found in the serum and tissues of green tea drinkers has demonstrated inhibition of dihydrofolate reductase (DHFR) in vitro, and this is given as an explanation for both an anticarcinogenic action and the supposed association with neural tube defects. (Inhibition of DHFR results in the disruption of DNA biosynthesis particularly in tumour cells. DHFA inhibitors (such as the drug methotrexate) are known as ‘antifolates.’) This study also incorrectly reports an in vivo antifolate effect of EGCG – the effect was actually demonstrated on isolated cells. Green tea is a source of folic acid, there is no credible epidemiological association of green tea with neural tube defects and EGCG has not yet demonstrated antifolate activity in vivo, let alone at normal human consumption.
Garlic

Heart disease is a major killer in the Western world. Research has shown that there are many risk factors associated with the development of heart disease, such as high cholesterol, high triglycerides, high blood pressure and high levels of fibrinogen in the bloodstream. In a sense, garlic is like an herbal polypill in that it addresses many of these cardiovascular risk factors in the one treatment. In particular, the research has focussed on allicin-releasing garlic products. These contain carefully dried garlic powder which is rich in the sulfur-containing phytochemical allicin and an enzyme known as alliinase. Upon ingestion, the enzyme dissolves in the digestive fluid and becomes active, converting the alliin into allicin. This is exactly what happens when you crush a clove of fresh garlic. In other words, these allicin-releasing garlic products mimic the normal dietary intake of garlic. The best of such preparations are enteric-coated so that they only dissolve in the alkaline small intestine, since gastric acid inhibits the activity of alliinase. This review will focus on the allicin-releasing products, since they have generated the largest amount of data.

Historical Perspective

The first garlic powder products were developed in Germany around 1980. Garlic became one of the top-selling herbal products in Germany as a result of the favorable cardiovascular research on garlic powder products. However, when trials were conducted in other countries on the cholesterol-lowering effects, results were not as favorable. This has led to a negative perception of the value of such products for cardiovascular risk factors. However, the focus on cholesterol lowering may have missed the point. Even in positive trials, effects are modest. The distinct possibility exists that garlic powder products could offer a substantial modification of cardiovascular risk by exerting mild effects over a wide range of risk factors (perhaps some currently not known). What is needed are clinical trials measuring different outcomes (e.g., cardiovascular mortality and morbidity). In this context, studies that have looked at garlic and arterial plaque formation are highly relevant.

Garlic and Plaque Formation

An important trial looked at the effect of garlic powder intake over 4 years on arterial plaque. The trial was a randomized, double-blind, placebo-controlled design involving 152 patients. Plaque volumes in both carotid and femoral arteries were measured by ultrasound. The increase in plaque volume over time was significantly reduced by garlic and in some cases there was a slight regression. The authors were accused of scientific fraud, but subsequently vindicated.

Researchers from Germany report that, in test tubes, garlic prevents formation of "nanoplaques" that can accumulate to cause arteriosclerosis. During a National Institutes of Health workshop on herbs and cardiovascular disease held in Bethesda, Maryland, in August 2002, Dr. Günter Siegel from the Free University of Berlin, described his team's research, which pinpoints exactly how garlic blunts plaque formation. In the presence of calcium, low-density lipoprotein cholesterol binds with molecules secreted from the inner lining of the arteries, forming tiny plaques that can accumulate and harden. High-density lipoprotein cholesterol inhibits this process by absorbing excess plaque-forming molecules. Siegel's team found that garlic extract works exactly the same way, but more potently. "In concentrations relevant to man," he said, "garlic extract was two and a half times more effective" in inhibiting plaque formation than was high-density lipoprotein (HDL) cholesterol. This has led to Siegel describing this form of garlic as phyto-HDL, that is, a herb acting in the same beneficial way as HDL.

Garlic and Blood Lipids

"The vast majority of recent, randomized, placebo-controlled studies do not support a role for garlic in lowering blood lipids." The general consensus from several meta-

[Benfotiamin]

Every second of every day, your body's fundamental structural components are being slowly warped by the formation of Advanced Glycation Endproducts (AGE).* AGE form when the body's proteins, lipids, and DNA react with the sugar in your blood, or with ultra-reactive metabolites of the body's glucose metabolism known as triosephosphates. Many supplements are hyped as "AGE-inhibiting" pills. But whatever their other benefits, none of them have been documented to do anything to actually inhibit AGEing ... outside of a test tube.*

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analyses is that garlic’s effect on lowering cholesterol is modest.58 However, some results from negative trials may be explained by the inadequate release of allicin in formulated garlic products.59 This in turn could be due to poor alliinase activity, too slow disintegration of the tablets or lack of enteric-coating, or all of the above. A recent Australian trial using a product validated for allicin release (providing 9.6 mg/day) demonstrated a 6.6% reduction in LDL cholesterol.60 This modest effect is still clinically valuable, but the real benefit of garlic probably lies in the other effects discussed above and below in this review.

Garlic and Other Cardiovascular Risk Factors

A recent double-blind, placebo-controlled study on 23 patients found that garlic powder tablets reduced the atherogenicity of low density lipoprotein (p value not specified).61 This backs up clinically the concept of reduced atherogenicity of low density lipoprotein (p value not specified).61 In a double-blind, placebo-controlled study on 23 patients found that garlic powder tablets reduced the atherogenicity of low density lipoprotein (p value not specified).61 In a double-blind, placebo-controlled study on 23 patients found that garlic powder tablets reduced the atherogenicity of low density lipoprotein (p value not specified).61 This backs up clinically the concept of reduced atherogenicity of low density lipoprotein (p value not specified).61

In a controlled retrospective study on healthy adults (aged 50 to 80 years), 101 individuals who had been taking a garlic powder preparation for two years or more were compared with 101 controls.62 Pulse wave velocity (PWV) and elastic vascular resistance (EVR) were used to measure the elastic properties of the aorta. While blood pressures, heart rate and plasma lipid levels were similar in the two groups, PWV (p<0.001) and EVR (p<0.001) were significantly lower in the garlic group. The authors concluded that chronic garlic powder intake reduced age-related increases in aortic stiffness.

A meta-analysis of eight clinical trials (415 patients) all using the same garlic powder preparation found that garlic caused a modest but significant reduction in both systolic and diastolic blood pressures.63 A platelet-inhibiting effect has been described for garlic.64 In a double-blind, placebo-controlled study on 60 volunteers with elevated cerebrovascular risk factors and increased spontaneous platelet aggregation, it was demonstrated that 800 mg of garlic powder per day over 4 weeks led to a significant reduction in platelet aggregation and circulating platelet aggregates (p<0.01). The confounding issue of the various dosage forms of garlic was highlighted by a study of an oil extract of garlic, which found no significant effect on platelet aggregation,65 and yet a more recent trial on an oil extract observed inhibition of induced platelet aggregation.66 In contrast, consumption of a fresh clove of garlic daily for a period of 16 weeks reduced serum thromboxane by about 80%.67 A review of published studies found that garlic consistently increased fibrinolytic activity after single or multiple doses.68 Garlic oil and garlic powder were both active, sometimes after only a single dose. The average increase in the reviewed studies was 58%. A 1991 controlled study using raw garlic demonstrated a significant increase in clotting time and fibrinolytic activity after two months in normal volunteers.69 In a randomized, placebo-controlled, double-blind, crossover study on ten healthy volunteers, a single dose of 600 mg of garlic powder significantly reduced hematocrit (p<0.001), plasma viscosity (p<0.05) and plasma fibrinogen (p<0.05).70 Fibrinolytic activity was also significantly increased (p<0.01). A similar study design also found that a single 900 mg dose of garlic powder significantly increased capillary skin perfusion by 55% (p<0.01).71 A recent study found that garlic powder (600 mg/day) administered for 7 days increased calf blood flow by approximately 15% (p=0.001).72