Prevention of Coronary Heart Disease and Cancer by Tea, A Review¹

John H. WEISBURGER

Institute for Cancer Prevention, American Health Foundation, 1 Dana Road, Valhalla, NY USA

Abstract

Biomedical research has uncovered the mechanisms whereby tea promotes good health and lowers the risk of major chronic diseases, such as heart disease and many types of cancer. The active components in tea are polyphenols, epigallocatechin gallate in green tea, theaflavins and thearubigins in black tea. Green and black tea and the polyphenols have similar beneficial effects. The mechanisms are categorized into 5 groups. 1) Tea polyphenols are powerful antioxidants. They decrease the oxidation of LDL cholesterol and lower the risk of heart disease, and also inhibit action of reactive oxygen species mediating the oxidation of DNA associated with carcinogenesis 2) Tea polyphenols induce detoxifying enzymes, glucuronosyl transferases, eliminating active forms of carcinogens and other toxicants, accounting for the lower cancer risk. 3) Tea polyphenols lower duplication rates of cancer cells and inhibit the growth of cancer, increase apoptosis and lower angiogenesis. 4) Tea polyphenols alter the intestinal bacterial flora, suppressing undesirable bacteria and favoring growth of beneficial bacteria. 5) Aging phenomena, and diseases associated with the formation of reactive oxygen species (ROS) are inhibited.

Key words: black and green tea, prevention, reactive oxygen species, heart disease, cancer, cell growth inhibition, apoptosis, angiogenesis, bacterial flora, extended aging.

Introduction

Worldwide, tea is a frequently used beverage by people. Tea is an extract of the leaves of the plant *Camellia sinensis* (1). Customarily upon harvest, the best teas are obtained by plucking the top two leaves and the bud of the tea bush. These elements contain the polyphenol, epigallocatechin gallate and an enzyme polyphenol oxidase. When the leaves are dried and steamed, the polyphenol oxidase is inactivated, and result is green tea (2). On the other hand, when the leaves are ground and incubated for about 60 minutes, the polyphenol oxidase converts the polyphenol to other polyphenols, such as theaflavin and thearubigin, typical of black tea. A lesser time of incubation, such as about 25–35 minutes yields an intermediate product, oolong tea that is popular in southern China and in Taiwan (2).

We have described the history of tea and use worldwide (1), including the original discovery of tea in China some 4,000 years ago, in the form of green tea, and at unknown periods, of black tea in Northern India. Currently, green tea is used mainly in China, in Japan and in North Africa (fermented beverages cannot be used

due to religious reasons in north Africa, and the process whereby green tea polyphenols are oxidized biochemically to black tea polyphenols, was called fermentation).

Tea and heart disease prevention

Epidemiological studies in Europe showed that tea drinkers, in this instance, black tea drinkers had a lower incidence of heart disease. The underlying mechanism stems from the inhibition by the tea polyphenols, acting as effective antioxidants that inhibit the oxidation of LDL-cholesterol caused by reactive oxygen species (3–5). This oxidized product has been demonstrated to increase atherogenesis (6). Vinson (7) and Weisburger et al. (8) have demonstrated this process by using a copper catalyzed oxidation of LDL cholesterol, that was inhibited by tea polyphenols. Thus, findings in humans through the techniques of epidemiology are strengthened by appropriate laboratory research as to the relevant mechanism. Other studies display a lower risk of heart disease as a function of tea intake (9–13). In some instances, especially with green tea, a lower risk was observed with a lower serum cholesterol level (14). A meta-analysis of stroke and coronary heart disease “cardiovascular disease” noted most studies involved small groups of people in cohort or case-control approaches and that heart disease decreased 11% by intake of 3 cups of tea per day (about 700 ml) (16). Nakachi et al. (17) noted that the relative risk of cardiovascular disease and cancers were significantly lower with 10 cups of tea per day. Tea beneficially affects platelet aggregation and this appears to decrease the risk of heart attacks

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Reprint requests to: John H. WEISBURGER

American Health Foundation, 1 Dana Road, Valhalla, NY 10595, USA

TEL: +1(914)789-7141, FAX: +1(914)592-6317

E-mail: jweisbur@ifcp.us

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(18–21). Along those lines, Kono et al. (22) noted a significantly lower risk of gastric cancer (relative risk 0.3, compared with the general population) with an intake of 10 cups or more of green tea.

Tea and cancer prevention

Cancer stems from a mutation of the DNA, the genetic material in normal cells, therefore, mutational events can be used as markers for environmental genotoxic products that might act as possible cancer risk, transforming normal cells to neoplastic cells (23). This approach is valuable to evaluate products that might display antimutagenic and thus, likely anticarcinogenic effects.

This approach has been utilized to study the effect of tea polyphenols from black tea and from green tea. It was discovered that both types of polyphenols inhibited in a dose-related fashion the mutagenicity of a variety of different types of carcinogens (24, 25). It has also been found in several animal models for cancer of the colon and the mammary gland that tea decreased the incidence of these neoplasms in rats (26–29). Others have found that cancer of the esophagus, prevalent in parts of China is decreased in animal models by tea (30). This finding parallels a lower risk in other parts of China of cancer of the esophagus in people who customarily drink tea (31). There are currently more cigarette smokers in Japan than in the USA but the incidence of lung cancer in Japan is lower than in the USA. One possible explanation is that there are many more tea drinkers in Japan, providing a protecting effect (32). This has been demonstrated in mice and rats, exposed to the tobacco specific nitrosamines where the incidence of lung tumors was lower when the animals were drinking tea. Chung (32) has examined the associated mechanism and interestingly found that this inhibition by tea stemmed from a lower oxidation of DNA, through the carcinogen associated formation of reactive oxygen species, yielding as marker 8-OH-dG. It would be useful to extend this method to human smokers to determine whether tea would decrease the urinary excretion of 8-OH-dG.

After Sugimura (cf. 33) discovered the formation of powerful mutagens during the cooking, frying or broiling of meat, we have collaborated with the Tokyo group. It has been found that these mutagens are heterocyclic aromatic amines. There are now epidemiological findings (33–36) that regular consumers of well-done cooked meat have a higher risk of cancer of the colon and breast. These are in part, the target organs in rats, where additionally cancer of the prostate and of the pancreas are seen (37–41). The reason meats generate these kinds of compounds was discovered by Jägerstad (42), namely the presence of creatinine, that forms the 2-aminomethylimidazo part of the heterocyclic amines. Jägerstad (42) developed an *in vitro* approach to model cooking, namely to heat glucose, creatinine and an amino acid, such as glycine, or phenylalanine. We have found that the addition of black tea or green tea polyphenols to this *in vitro* system prevents the formation of the appropriate heterocyclic amines (43). In addition, based on that model, it was shown during the realistic cooking of ground meat that addition of green tea or black tea polyphenols prevents the formation of mutagenic heterocyclic amines, that appears to be a practical way without loss of taste of cooked hamburgers (44, 45).

Tea as an enzyme inducer with emphasis on phase II enzymes

Sohn et al. (46) discovered that the administration of 2%

solutions of black tea or green tea as drinking fluid to rats for 6 weeks modified the metabolic enzymes in the liver. Both teas led to higher levels of cytochrome P450 1A1, 1A2 and 2B1, but of no other cytochromes. Importantly, the phase II enzyme UDP-glucuronosyl transferase was significantly increased. This enzyme system serves to detoxify many environmental chemicals. In the context of nutrition, this applies to heterocyclic amines. These chemicals undergo detoxification by C-hydroxylation, but an essential step in the biochemical activation is N-hydroxylation. These hydroxy compounds are subject to reaction with UDP-glucuronosyl transferase which converts the C-hydroxy compounds to glucuronides, but importantly, the proximate carcinogens in the form of N-hydroxy compounds are effectively detoxified by forming the N-hydroxy glucuronides (47). Inasmuch as green and black tea increased the level of the UDP-glucuronosyl transferase, it was established that tea drinking animals form the detoxified metabolites of heterocyclic amines. Previously, we found that decaffeinated tea was less effective than regular tea in carrying out these reactions (43). Thus, caffeine may have a role in the effect of tea, most likely together with the tea polyphenols.

Role of tea in growth control and apoptosis

A number of approaches have repeatedly shown *in vitro* and in animal models that tea and tea polyphenols decrease the rate of growth of tumor cells through molecular and signaling mechanisms involving alterations in gene expression (48–57). Tea even decreased the formation of spontaneous lung tumors in A/J mice that in 1966 was reported to have a stable incidence (58, 59). This suggests that the growth control effect of the polyphenols is marked or significant (60–63). In addition, tea polyphenols increase the rate of apoptosis of tumor cells and lead to the elimination of neoplastic cell systems (64–70). This has been demonstrated and a mechanism explored in early tumor cells. Inhibition of angiogenesis may play a role in growth control and apoptosis. This mechanism may hold even during the developmental phases. A clinical trial with a polyphenon E from green tea is currently under way through the Division of Cancer Prevention at the National Cancer Institute, USA.

Effect of tea intake on the intestinal microflora

Tea polyphenols have displayed an effect on viruses and on bacteria. Specifically, the intestinal tract contains bacteria such as enterobacteriaceae that have mostly unpleasant properties since they generate chemicals of the type of skatol and related indoles. The tea polyphenols appear to suppress the growth of these bacteria but have no adverse effects on beneficial bacteria such as lactobacilli. Therefore, regular tea drinkers have a healthier intestinal bacterial flora. Tea polyphenols display antiviral actions, described in detail in the monograph of Hara (71).

Effect of tea polyphenols on reactive oxygen species

Tea and the associated polyphenols suppress the reactive oxygen species formed during metabolism of cell systems. It was noted above that the oxidation of LDL-cholesterol and of DNA may stem from the reactive oxygen. It turns out that premature aging is also a result of cellular reactive oxygen species (4, 72–78). It can be concluded that regular intake of 5 or more cups of

tea per day facilitates healthy aging, which has been demonstrated on cellular systems, in animal models, and also, through studies of humans where regular tea intake is part of a health promoting lifestyle, as in Japan and parts of the Orient. In that part of the world, one does find populations at advanced ages in good health.

Conclusions

In most research with tea, it was discovered that black and green tea have similar effects. There are some studies that reported green tea but not black tea has an effect on body metabolism, a lower efficiency of utilizing food calories occurred upon intake of green tea so that this beverage assisted in minimizing weight gain. In general, however, both types of tea have similar effects in metabolism in vitro and in vivo. Another form of tea is white tea, studied recently. It is from the bloom and bud of the very top leaves of young tea plants. White tea has been similar to its close relative, green tea, as regards antimutagenicity, action on metabolic enzymes and effects on heterocyclic amine metabolism (79–81). Whereas there appears to be an effect of caffeine together with the tea polyphenols, the latter compounds have biochemical effects by themselves. Thus, it was observed that the mutagenicity of many types of genotoxic carcinogens was inhibited by the tea polyphenols (24, 25). In animal models, tea exerted an anticarcinogenic effect. There appears to be some evidence that intake of appreciable amounts of tea, particularly of green tea, as in Japan, lowers the risk of lung cancer in smokers in that country. This effect has also been validated in rats and mice and it appears to stem from an antioxidant effect. The same mechanism may operate in lowering the risk of heart disease stemming from the oxidation of LDL cholesterol, occurring in vivo, and demonstrated through the copper ion mediated oxidation of LDL cholesterol, inhibited by tea and tea polyphenols. Therefore, an important function of tea and of the polyphenols is to act as antioxidants, beneficial both in lowering the risk of heart disease and of several types of cancer, through control of reactive oxygen species.

In addition, tea has been documented to modify host biochemistry with emphasis on generating higher levels of UDP-glucuronosyl transferase, active in detoxifying many types of harmful chemicals, and especially of the reactive forms of genotoxic chemical carcinogens.

In addition, the modulation of carcinogenesis involves the

property of tea to increase apoptosis, leading to the elimination of transformed neoplastic cells. This has been demonstrated in animal models, but possible extension to therapy of neoplasia maybe warranted.

The modification of the intestinal bacterial flora and an antiviral action by regular intake of tea deserves note. It turns out the beneficial bacteria in the gut thrive in the presence of tea, but the less desirable bacterial species do not appear to survive well. Thus, regular intake of tea improves the metabolic function of the bacteria in the intestinal tract, an important contributor to overall metabolism and health promotion.

Previous studies reported the advantage of drinking as little as 1–2 cups of tea per day to obtain certain health benefits. We suggest that it may be of considerable value to drink 5–7 or more cups per day. This is a healthy and inexpensive way of filling the daily needs of about 2 liters of fluid intake a day for adults. Inasmuch as decaffeinated tea contains virtually all the polyphenols found in regular tea, it may be indicated to have children from ages 6–12 drink 4–5 cups per day of decaffeinated tea per day. This beverage offers advantages often associated with the intake of vegetables and it may be easier to offer children decaffeinated tea since they are notoriously reluctant to eat vegetables.

One point we have not discussed is the use of milk in tea. With the assistance of our colleague Dr. Zeno Apostolides, University of Pretoria, we performed a series of experiments, adding 1.8 percent whole milk to black tea as recommend by the ISO (International Standard Organization), and compared the effects of this modified beverage to the action of regular tea in models of breast and colon cancer (27). The addition of this amount of milk did not reduce the inhibiting effect of tea itself in these models. Yet, we gather that in Great Britain and in India, addition of appreciable amounts of milk to tea is customary. It is not known whether a larger amount of milk than that suggested by the ISO might affect the preventive actions of tea on heart disease and on cancer. Milk did not affect the absorption of the tea polyphenols (82, 83). Certainly, this problem does not arise in the Orient where green tea is consumed neat, without any additions. The use of tea worldwide was featured on the Cover of Cancer Research in 1998 (84). Disease prevention, an effective approach to control the high cost of medical care (85), could be facilitated by an increased consumption of tea.

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