Tea and Health: The Underlying Mechanisms (44378)

JOHN H. WEISBURGER[1]
American Health Foundation, Valhalla, New York 10595

Abstract. **Detailed multidisciplinary research on the effect of tea and the associated tea polyphenols has led to major advances on the underlying mechanisms. In most studies, green and black tea have similar effects, four of which are reviewed in this paper. 1) Tea polyphenols are powerful antioxidants that may play a role in lowering the oxidation of LDL-cholesterol, with a consequent decreased risk of heart disease, and also diminish the formation of oxidized metabolites of DNA, with an associated lower risk of specific types of cancer. 2) Tea and tea polyphenols selectively induce Phase I and Phase II metabolic enzymes that increase the formation and excretion of detoxified metabolites of carcinogens. 3) Tea lowers the rate of cell replication and thus the growth and development of neoplasms. 4) Tea modifies the intestinal microflora, reducing undesirable bacteria and increasing beneficial bacteria. The accumulated knowledge suggests that regular tea intake by humans might provide an approach to decrease the incidence of and mortality from major chronic diseases.** [P.S.E.B.M. 1999, Vol 220]

Diagnosis of and therapy for major diseases are usually high-cost elements in health management. Thus, there has been increasing emphasis on research to develop an understanding of the causes of chronic diseases, as well as the action of modulating factors, as a basis for prevention, the definite means of disease control. The major chronic diseases worldwide are heart diseases, neoplastic diseases, hypertension and stroke, and adult onset diabetes (1, 2). Through multidisciplinary approaches and techniques involving geographic pathology comparing the incidences of and mortality from a given disease in a given geographic area, the main risk factors have been elucidated. For example, postmenopausal breast cancer is a major condition in the Western world, such as the United States, but has a low incidence in Asia, particularly in Japan. The key risk factor, based on such comparisons, is the type and amount of dietary fat consumed, high in the United States and relatively low in Japan. Laboratory experiments in animals and through *in vitro* studies have permitted the exploration of the relevant mechanisms, providing a solid basis for the epidemiologic findings, and, in fact, leading to recommendations for decreasing the total fat intake in the Western world to lower the risk and, thus, the incidence of this major type of cancer.

Such approaches have provided key evidence that major chronic diseases in the Western world, including coronary heart disease, hypertension, and cancer of the breast, prostate, pancreas, ovary, endometrium, and colon are associated with nutritional habits. These diseases account for approximately 60% of premature mortality due to specific inappropriate nutritional traditions. These facts emphasize the importance of nutrition, and in the past, research in this field has evaluated the intake of solid foods, as macronutrients and micronutrients (3, 4).

In the last 15 years, another area of research has elicited interest, namely the intake of liquids as a modulating factor for chronic diseases. Clearly, worldwide, water is the most important beverage consumed. It is important to ensure clean and wholesome water supplies for people. Second to water, green and black teas are major components of fluid intake (Fig. 1). Since the preparation of tea involves the use of boiling, sterile water, there is a great advantage to the use of tea in areas where the water supply may be contaminated by bacteria.

Tea has a long history of human use, over 4000 years

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[1] To whom requests for reprints should be addressed at American Health Foundation, One Dana Road, Valhalla, NY 10595. E-mail: John_Weisburger@nymc.edu

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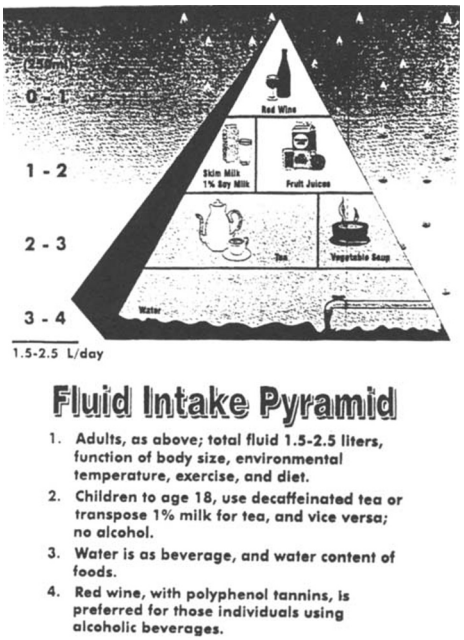

Figure 1. A pyramid showing suggested intakes of beverages that are part of a health-promoting daily fluid intake by adults.

(5, 6). Initially, tea, an extract of the leaves of the plant *Camellia sinensis,* was used in China, with emphasis on green tea, although in the Southern part, a partially oxidized form, oolong tea was favored. Black tea is thought to have been introduced in Northern India. These three main types of tea stem from the production methods of the tea leaf after harvest. The tea leaf contains as a main component (over 30% of the dry weight) a powerful antioxidant, the polyphenol epigallocatechin gallate (EGCG). The leaf also contains the enzyme polyphenol oxidase. Immediate heating of the harvested leaves inactivates the enzyme; the result is green tea, containing mainly EGCG. Biochemical oxidation of the ground leaves mediated by the enzyme for about 30 min, followed by heating and drying, yields oolong tea, and allowing the reaction to proceed for 90–120 min, then heating and drying the product, produces black tea. The chemistry of the enzyme-mediated oxidation of EGCG has been worked out. Black tea contains a series of polyphenols, the simplest of which is theaflavin, and polymeric products such as thearubigens. All of the tea polyphenols have similar, powerful antioxidant properties, based on their polyphenol content. Depending on soil quality and micronutrient content, tea also provides small amounts of fluoride and other micronutrients.

Extensive recent research has explored the probable health benefits of tea through studies in humans, in animal models, and through *in vitro* laboratory research. In most systems, green tea and black tea have yielded quite similar results, and it would appear that the total polyphenol content, irrespective of the specific chemical structure, accounts for these results. An interpretation of currently available data suggests that tea and tea polyphenols can and do operate through at least four mechanisms (Table I).

Table I. Mechanisms of Action of Tea on Parameters Bearing on Health

Action of tea and tea polyphenols	Consequence
1. Display potent antioxidant activity	Lower risk of heart disease; decreased formation of oxidized nucleotides in DNA and possibly inhibition of carcinogenesis
2. Selectively induce Phase I and II metabolic enzymes	Increased formation of detoxified metabolites of carcinogens
3. Inhibit cell proliferation rates	Decreased growth of abnormal cells and neoplasms
4. Selectively modify intestinal bacterial flora	Undesirable components of the flora replaced by beneficial bacteria, with improved metabolic profiles

Tea as an Inhibitor of Adverse Oxidation Processes

Most mammalian systems require oxygen. Without adequate antioxidant supplies, oxygen can generate reactive components such as peroxides, hydrogen peroxide, hydroxy radicals, and similar substances that can damage cells. This fact accounts for the need to provide dietary antioxidants such as extracts of vegetables and fruits, and in the context of beverage intake, of tea. Oxidization of LDL-cholesterol is one of the elements associated with atherosclerosis and coronary heart disease, although there is some conflicting evidence (7–9). Nutritional recommendations have suggested a daily intake of 5–10 servings of fruits and vegetables per day. Research on tea now adds the further desirability of drinking this beverage, typically 5–7 cups per day. Indeed, it has been shown that regular tea drinkers have a lower risk of heart disease than nonusers, when comparing people with similar risk factors (10–12). Tea, consumed at moderate temperatures, is not harmful. Records show that in some populations, individuals consumed 10 or more cups of tea per day, with no adverse effects and, in fact, improved health.

Genotoxic carcinogens have been found traditionally to yield the appropriate DNA adducts stemming from their reaction of the electrophilic reactant derived from the carcinogen by metabolism. However, in recent years, it was discovered that the effect of carcinogens and radiation also yields oxidized changes in DNA. The major modification is the formation of 8-hydroxy-2′-deoxyguanosine(8-OHdG). This oxidative process can be inhibited by antioxidants and specifically by the antioxidants from green or black tea (13–19).

Tea as a Selective Inducer of Enzymes

In the area of nutrition and health, and with emphasis on nutritional modulation of cancer, it was Wattenberg (20)

who introduced the term chemoprophylaxis. Indeed, he discovered that rats fed a semipurified diet had a lower level of specific enzymes, now called Phase 1 enzymes, in the small intestine, than when the rats were fed a diet composed of natural ingredients. The natural diet included foodstuffs stemming from vegetables that could increase the level of enzymes such as benzpyrene hydroxylase. This enzyme belongs to the group of cytochrome P450 enzymes systems performing oxidation reactions. These enzymes are inducible by a variety of chemicals, including the substrates subject to the action of a given enzyme.

It has been found that subchronic intake of tea induces specific enzymes of the cytochrome P450 class, including cytochrome P450 1 A1, 1 A2, and 2B1, but not significantly other Phase I enzymes. Among the Phase II enzymes, tea increases only glucuronyl transferase, but not other Phase II enzymes to any extent (21–23). It would appear that the raised level of glucuronyl transferase accounts for the lower carcinogenicity of a number of carcinogens. Some are metabolized to reactive products, such as N-hydroxy compounds from arylamines or heterocyclic amines, or diol epoxides and phenols from polycyclic aromatic hydrocarbons. Many years ago, Peraino *et al.* (24) reported that administration of phenobarbital to rats sharply decreased the carcinogenicity of 2-acetylaminofluorene. We accounted for this inhibition by demonstrating a higher excretion in urine of detoxified metabolites of 2-acetylaminofluorene, especially the glucuronides (25). Thus, it would appear that the lower rate of cancer induction in animal models with specific classes of carcinogens is accounted for by the formation of detoxified metabolites, generated by higher levels of detoxifying enzymes such as glucuronyl transferase through the action of tea.

Tea as a Moderator of Cell Duplication Rates

Cell duplication rates play an important role in cancer causation and development (26–29). Reactive carcinogens induce mutational events that modify DNA. The altered DNA can be repaired by a series of specific enzymes systems. This is important since the mutated DNA acts as a template for reproduction of copies of the altered DNA, and cells containing such DNA are the progenitors of neoplasia. Therefore, the rate of cell division is important, since a high rate may decrease the operation of the repair enzyme system. A striking example of these facts is the higher incidence of breast cancer in those Japanese women in the 10–15-year-old age group exposed to radiation at the time of the Hiroshima explosion, compared to the older age groups exposed to the same radiation (1). The explanation for this higher sensitivity of the 10–15-year-old age group rests on the fact that the mammary tissue was in a high rate of DNA synthesis and cell duplication. The same observation stems from the results of Huggins (30) who demonstrated that the carcinogen 7,12-dimethylbenz[a]anthracene induced breast cancer optimally in female Sprague-Dawley rats at age 50 days, when the mammary tissue was in maximal DNA synthesis and mitosis.

Our group has recently demonstrated that the colon of rats given the chemical carcinogen danthron (chrysazin, formerly used as a cathartic and laxative) displayed a high rate of DNA synthesis in that tissue, recorded as PCNA (Moucha-Hantar, Weisburger, Fiala *et al.*, unpublished data). Rats given tea together with the chemical had a sharply decreased number of cells expressing PCNA in the colon. In fact, animals given tea alone had a significantly lower number of cells expressing PCNA than control animals that drank water. The exact mechanisms whereby tea displays an inhibiting effect on cell duplication rates is under investigation. Clearly, however, a lower rate of cell duplication may reflect a lower risk of cancer development and growth. The Conney (31) laboratory found that the growth of UV- or DMBA-induced skin tumors in mice was inhibited by tea. Tea was also an inhibitor of tumor growth in other models (32–40).

Green tea and black tea have similar physiological and biochemical effects, mediated mainly through their content of antioxidant polyphenols. While comparing the effect of regular tea with that of decaffeinated tea in a model of mutagenicity induced by the heterocyclic amine 2-amino-1-methyl-6-phenyl[4,5-*b*]pyridine{PhIP}, we discovered that the regular tea was somewhat more active as an inhibitor of mutagenicity. This led to a test of caffeine, and this chemical was antimutagenic in this system, as were other antioxidants (41).

Tea as a Modifier of Metabolism by Intestinal Bacteria

Although not frequently considered, the intestinal microflora play an important role in the metabolism of endogenous and exogenous compounds. Such chemicals are present at that site either by direct migration of food or food components after oral intake, or by secretion in the bile of metabolites derived from the liver. The intestinal flora provides batteries of enzymes with numerous functions, including hydrolytic and reductive functions. Less frequent are enzymes with oxidation potential, mainly because the contents of the intestinal tract are usually reductive. The intake of tea and tea polyphenols over a period of weeks or, indeed continuously, leads to a reduction in Enterobacteriaceae that produce ammonia, skatole, and other amines that are the source of the unpleasant odor of stools, and sharply increases the level of Lactobacilli and Bifidobacteria that have beneficial metabolites (42). As a result of the increased formation of organic acids, there is also a decrease in the pH of the intestinal contents. Thus, the regular intake of tea, together with soluble and insoluble fibers, appears to be beneficial in avoiding a number of events that can adversely affect health (1).

Conclusions

The results presented show that tea and tea polyphenols, some of which are available as purified commercial

chemicals, displayed multiple effects: 1) a decrease in certain oxidation reactions, with adverse effects in relation to heart disease, and some types of cancer; 2) a selective induction of specific enzymes involved in the detoxification of carcinogens; 3) a decreased rate of cell duplication; and 4) an improved composition of the intestinal bacterial flora with beneficial metabolic actions. Some of the results achieved under controlled laboratory conditions have also been seen in epidemiological approaches in humans, albeit more extensive research is needed to extend knowledge of the effects of tea in humans. Except when consumed as a very hot beverage causing cancer of the esophagus, tea has not had any adverse effects when consumed at moderate temperatures or, in fact, as a cold beverage. The determining element is the amount of tea or tea polyphenol consumed per day. On the other hand, as reviewed in this paper, tea has many beneficial effects in disease prevention or disease control, and the underlying mechanisms have been clarified in many instances. Thus, tea is a valuable addition to the field of health promotion worldwide.

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