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Recent Scientific Studies of a Traditional Chinese Medicine, Tea, on Prevention of Chronic Diseases

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ABSTRACT

Green tea (綠茶 Lǜ Chá), made from the leaves of the plant *Camellia sinensis*, has traditionally been used as a medicine in China for thousands of years. According to the classical work of Li Shizhen (李時珍 Lǐ Shí Zhēn) of the Ming Dynasty, "tea is cold and lowers the fire." Since fire (inflammation) causes many diseases, could tea be effective in the prevention of many diseases? The possible prevention of chronic diseases such as cancer, metabolic syndrome, obesity, diabetes, and cardiovascular diseases has been studied with contemporary scientific methods, and the results are promising. The molecular mechanisms underlining these observations will be discussed in this presentation. One of the reasons for the failure to demonstrate a disease-preventive effect of tea in some epidemiological studies is the lower quantities of tea consumption in humans. Can we increase the quantity of tea consumption to harness its health benefits without causing gastrointestinal irritation? This is a topic for further research.

Key words: Cancer, Cardiovascular diseases, Diabetes, Green tea, Metabolic syndrome, Obesity

INTRODUCTION

Tea, made from the leaves of *Camellia sinensis*, is a popular beverage consumed worldwide. Historically, tea has been used for thousands of years as a medicinal herb and was also used widely as a beverage starting from the Tang and Song Dynasties. In the *Cha Jing* (*Tea Bible*) by Lu Yu of Tang Dynasty[a], the production of tea, the water and utensils used in the preparation of the tea beverage, and the possible health effects were described in detail. Tea was formally considered as a medicine in the *Xin Xiu Ben Cao* of the Tang Dynasty[b]. Tea was described as "… bitter and sweet, slightly cold and with no toxicity. It has the functions of pushing down the perverse rising qi; eliminating thirst, heat and phlegm; diuretic, shortening of sleeping time, and…"[b]. In the classical *Ben Cao Gang Mu* (本草綱目 Běn Cǎo Gāng Mù) by Li Shizhen (李時珍 Lǐ Shí Zhēn) of the Ming Dynasty, "Tea, bitter and cold … is strongly anti-inflammatory. Inflammation is the cause of many diseases."[c]. In modern medicine, it is also now recognized that inflammation is a causative or contributing factor to many diseases. If tea has anti-inflammatory activity, can it help to prevent many diseases?

An important aspect of Traditional Chinese Medicine (TCM) is the concept of preventing diseases before their manifestation; this is similar to modern preventive medicine. However, modern preventive medicine, unlike TCM, does not rely on classical litera-

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ture; it is based on evidence from experiments in animal models and cell lines, human epidemiology studies, and clinical trials. For the past 25 years, tea has been studied for its beneficial health effects. These include the reduction of body weight, alleviation of metabolic syndrome (MetS), and prevention of cardiovascular diseases (CVDs), cancer, and neurodegeneration. Results on its promising beneficial health effects when tea is consumed in sufficient quantities are emerging, and this topic was recently reviewed.[1] Did Li Shizhen, the grandmaster of TCM, have the insight that took 450 years for modern medicine to discern? Or are we interpreting his simple statement more deeply than he intended? What useful information can we obtain from classic TCM literature? These are topics for discussion.

CVDs and cancer are the two most common diseases in modern society. Obesity and diabetes are emerging as major health issues, and the closely related MetS also predisposes individuals to CVDs. If tea could prevent or delay the development of these diseases, the public health implications would be tremendous. Because of this, there is great public interest in this area of research. This article provides a critical review of these topics, discusses the possible common mechanisms involved, and evaluates the human relevance of the published health effects.

CHEMISTRY OF TEA CONSTITUENTS

The classical tea is believed to be mainly green tea (綠茶 Lǜ Chá). In the manufacturing of green tea, the tea leaves are steamed or baked, rolled, and dried. The heating and drying of the tea leaves help to stabilize the tea constituents during storage. Green tea possesses characteristic polyphenolic compounds known as catechins, which include: (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epicatechin (EC). The structures of catechins together with theanine are shown in Figure 1. Catechins account for about 30-42% of the dry weight of brewed green tea, and EGCG is the major form of tea catechins. Tea leaves also contain lower quantities of other polyphenols, such as quercetin, kaempferol, and myricetin, as well as alkaloids such as caffeine and theobromine. A typical brewed green tea beverage (e.g. 2.5 g tea leaves in 250 ml of hot water) usually contains 240-320 mg of catechins, of which 60-65% is EGCG and 20-50 mg is caffeine.[2,3] In the manufacturing of black tea (紅茶 Hóng Chá), the tea leaves are withered and crushed to cause enzyme-mediated oxidation in a process commonly referred to as "fermentation." During this process, most of the catechins are oxidized, oligomerized, and polymerized to form theaflavins and thearubigins, which provide the red-brown color of black tea.[2,3] In brewed black tea, catechins, theaflavins, and thearubigins each account for 3-10%, 2-6%, and greater than 20% of the dry weight, respectively. The caffeine contents in black tea are the same as in green tea. Oolong tea is manufactured by crushing only the rims of the leaves and limiting fermentation to a short period of time to produce the tea's specific flavor and taste. Generally, oolong tea contains catechins, theaflavins, and thearubigins, as well as some characteristic components such as epigallocatechin esters, theasinensins, dimeric catechins, and dimeric proanthocyanidins.[3] The contents of theanine, a characteristic amino acid in tea, vary with conditions of cultivation and manufacturing of tea.

Tea catechins and other tea polyphenols are strong antioxi-

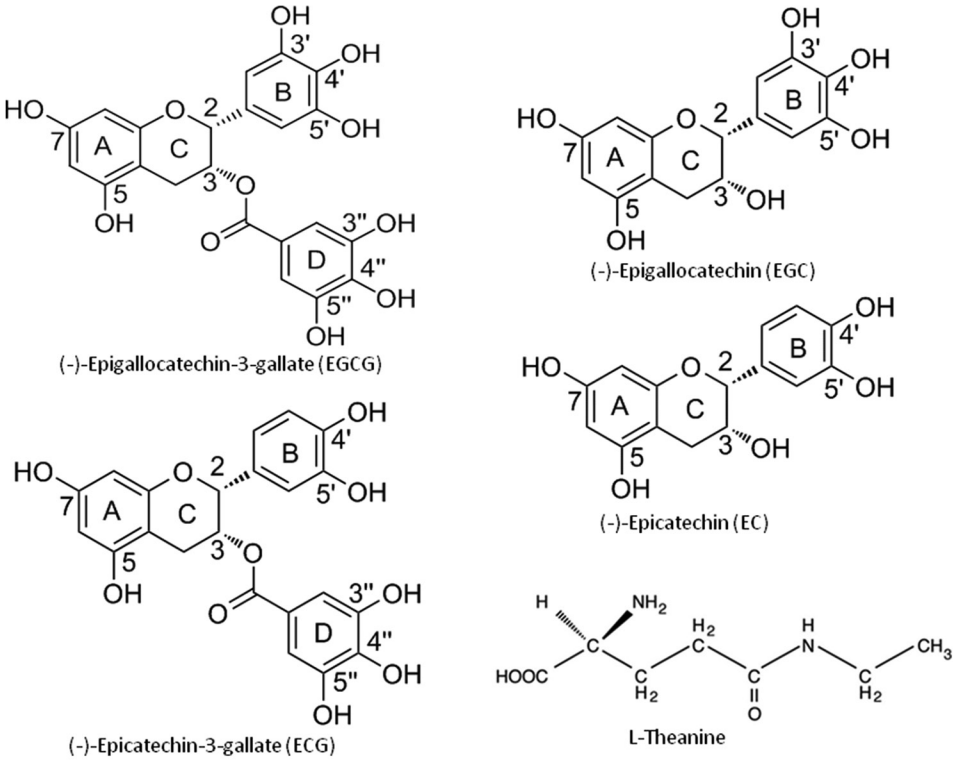

Figure 1. The structures of tea catechins and l-theanine (from [1])

dants, efficiently scavenging free radicals.[3] Tea polyphenols also have a high affinity to bind metals, preventing metal ion–induced formation of reactive oxygen species (ROS).[2,3] The phenolic groups in catechins can be donors for hydrogen bonding. Hydrogen bonding of a catechin molecule to water forms a large hydration shell. This hydrogen bonding capacity also enables tea polyphenols to bind strongly to proteins, lipids, and nucleic acids. For example, EGCG is known to bind to serum proteins such as fibronectin, fibrinogen, and histidine-rich glycoproteins. More recently, EGCG has been shown to bind strongly to 67-kDa laminin receptor, B-cell lymphoma 2 (Bcl-2) proteins, vimentin, and peptidyl prolyl cis/trans isomerase (PIN1), and these proteins have been proposed to be the targets of EGCG for anti-cancer activities. (reviewed in [4,5]) Black tea polyphenols may bind to biomolecules and biomembranes to a greater degree than EGCG.

BIOAVAILABILITY AND BIOTRANSFORMATION OF TEA CONSTITUENTS

According to Lipinski's rule of five,[6] compounds that have 5 or more hydrogen bond donors, 10 or more hydrogen bond acceptors, a molecular weight greater than 500, and a Log *P* greater than 5 are usually poorly absorbed following oral administration. This is due to their large actual size (high molecular weight), large apparent size (formation of a large hydration shell), and high polarity.[6] The bioavailabilities of tea polyphenols follow this prediction. (reviewed in[7,8]) EGCG and other tea catechins undergo extensive biotransformation. (reviewed in [3]) Because of their catechol structure, EGCG and other catechins are readily methylated by catechol-*O*-methyltransferase. In addition, catechins are also glucuronidated by UDP-glucuronosyltransferases and sulfotransferases. Multiple methylation and conjugation reactions can occur on the same molecule.[3] Active efflux has been shown to limit the bioavailability of many polyphenolic compounds. The multidrug resistance-associated protein 2 (MRP2), located on the apical surface of the intestine and liver, mediates the transport of some polyphenolic compounds to the lumen and bile, respectively.[9] Therefore, EGCG and its conjugates are predominantly effluxed from the enterocytes into the intestinal lumen, or effluxed from the liver to the bile and excreted in the feces, and little to none of these compounds are present in the urine. Tea catechins can be degraded in the intestinal tract by microorganisms to ring fission metabolites with valerolactone structures, which can be found in human urine and plasma samples several hours after the ingestion of tea.[10] These compounds can undergo further degradation to phenylacetic and phenylpropionic acids.[3]

TEA AND CANCER PREVENTION

Cancer is a major disease worldwide and is the most common or second most common cause of death in many countries. The question of whether tea consumption can prevent cancer has drawn great attention of researchers and the general public. Cancer is a disease that involves a series of genetic and epigenetic changes over a relatively long period of time, from 10 to 40 years. In theory, if the constituents of tea can block some of the molecular changes in the process of cancer formation, the onset of this disease can be prevented or delayed. In fact, this has been demonstrated in many animal models during the past 20 years. For example, when experimental mice were injected with cancer-causing substances isolated from cigarettes or cigarette smoke, almost all the mice developed lung tumors in 15-20 weeks. If we put tea extracts in the drinking water, the number of tumors formed would be significantly smaller in the mice drinking it than the number in the mice that drink water without the additional tea extract. In fact, tea and its major constituents have been demonstrated to inhibit tumorigenesis in many animal models for different organ sites, including the lung, oral cavity, esophagus, stomach, small intestine, colon, skin, liver, pancreas, bladder, prostate, and mammary glands.[5] Most of the studies were conducted with green tea (綠茶 Lǜ Chá), green tea polyphenol preparations, or pure EGCG, the major and the most active constituent in tea, administered through drinking water or diet.[5]

In contrast to the strong evidence for the cancer-preventive activities of tea constituents in animal models, results from epidemiological studies have not been consistent in demonstrating the cancer-preventive effect of tea consumption in humans (reviewed in [1]). A recent comprehensive review by Yuan *et al.*,[11] concluded that after adjusting for confounding factors, consumption of green tea was frequently associated with a reduced risk of upper gastrointestinal tract cancers and limited data supported its protective effect against lung and hepatocellular cancer. However, intake of black tea (紅茶 Hóng Chá) was generally not associated with a lower risk of cancer.[11,12]

The disparity in results between animal and human studies, observed not only in cancer prevention but also in the prevention of other diseases, is likely due to the lower quantities of human tea consumption as compared to the doses used in animal studies, as well as the many potential confounding factors involved in epidemiological studies. In humans, many lifestyles, genetic polymorphisms, and other confounding factors may reduce the power of epidemiological studies for detecting a cancer-preventive effect. Smoking appears to be a strong confounding factor. For example, in a case–control study on the effect of green tea consumption on esophageal cancer in Shanghai, a protective effect was only observed in women who were mostly nonsmokers.[13] Similarly, in the Shanghai Men's Health Study, green tea drinking was found to reduce the risk of colorectal cancer among nonsmoking men, but not in men in general.[14] In a recent large-scale, population-based case–control study in urban Shanghai, regular green tea drinking was associated with a 32% reduction of pancreatic cancer risk (compared to those who did not drink tea regularly) in women who were mostly nonsmokers.[15] Such a beneficial effect of tea drinking, however, was not observed in men who were mostly smokers and former smokers; however, among men who never smoked, a trend of decreased risk was observed.[15] Similarly, a recent systematic review of epidemiological studies in Japan on green tea consumption and gastric cancer indicated no overall preventive effect of green tea in cohort studies; however, a small consistent risk reduction was found in women (but not in males because many men were smokers). When the results of all six

studies were combined, there was a significant protective effect of tea drinking against stomach cancer in women who did not smoke cigarettes or drink alcohol.[16] These studies demonstrated that the cancer-preventive activities of tea constituents can be manifested in humans. Nevertheless, the effect is mild and cannot be observed in people who smoke. Indeed, cigarette smoke is the dominant factor in causing or influencing the formation of many types of cancer.

Many intervention trials have been conducted with green tea, and some have found a beneficial effect of green tea polyphenols in preventing the development of cancer. For example, in a double-blind Phase II trial in Italy, 30 men with high-grade prostate intraepithelial neoplasia (PIN) were given 600 mg of green tea catechins daily for 12 months.[17] Only 1 patient developed prostate cancer, whereas 9 of the 30 patients with high-grade PIN in the placebo group developed prostate cancer (statistically significant). In a recent study in Japan, in patients who had colorectal adenomas removed by polypectomy, supplementation of green tea extract (1.5 g/day) for 12 months was shown to reduce the development of metachronous colorectal adenomas compared to a group of patients who did not take green tea extract.[18] The results of these studies are promising and would have a large impact if they could be reproduced in trials with larger numbers of subjects. More than 30 human trials with green tea polyphenol preparations are ongoing in the US, China, and Japan [National Institutes of Health (NIH) clinical trials; website http://cancer.gov/clinicaltrials]. Some of these studies may yield clear conclusions concerning the cancer-preventive activities of green tea polyphenols.

The molecular mechanisms for cancer prevention by tea constituents have been extensively studied and reviewed.[4,5] The antioxidant actions of tea catechins could be an important mechanism for cancer prevention. Other well-discussed mechanisms involve the binding of EGCG to target proteins, leading to the inhibition of metabolic or signal transduction pathways.[4,5]

WEIGHT REDUCTION AND ALLEVIATION OF METABOLIC SYNDROME

MetS is a complex of symptoms that include elevated waist circumference and two or more of the following: Elevated serum triglyceride, dysglycemia, elevated blood pressure, and reduced high-density lipoprotein–associated cholesterol.[19] The effects of green tea (綠茶 Lǜ Chá) consumption on body weight and MetS have been studied extensively in animal models, and this topic was reviewed recently.[20] Most of the results showed that consumption of green tea extracts or EGCG significantly reduced weight gain and/or adipose tissue weight, reduced blood glucose or insulin levels, and increased insulin sensitivity or glucose tolerance.[20] In our studies, mice fed a high-fat diet (60% of the total caloric intake) containing EGCG (3.2 g/kg diet) for 16 weeks had significantly reduced body weight gain, percent body fat, hepatic steatosis, and visceral fat weight, as compared to mice without EGCG treatment.[21] These results were also reproduced in a second study using a high-fat/Western style diet (60% of the calories from fat with low levels of calcium, vitamin D, folic acid, choline bitartrate, and fiber).[22] EGCG treatment also attenuated insulin resistance, plasma cholesterol levels, and monocyte chemoattractant protein concentrations in mice on the high-fat diet.[21,22] Tea catechins have also been shown to reduce hepatic steatosis and liver toxicity in rodents treated with ethanol, tamoxifen, endotoxins, and liver ischemia/reperfusion injury (reviewed in[20]).

Overall, these studies in animal models are very impressive. The modulation of the activities of specific enzymes and the expression of specific genes, such as those involved in gluconeogenesis, fatty acid synthesis and degradation, and glucose transport, by tea polyphenols are intriguing.[23-27] Some of the effects were produced by rather high doses of green tea polyphenols. It is not known whether these activities are exerted by tea catechins directly or indirectly through body weight reduction or through energy-sensing proteins such as AMP activated kinases (AMPK).

The effects of tea on body weight in humans have been studied in many small, randomized controlled trials (RCTs) and the results have been reviewed.[28,29] Most of these studies observed a decrease of body weight or body fat due to daily consumption of four or more cups of green tea or 600-900 mg of tea polyphenols.[28-30] The role of caffeine in these studies was inconsistent among the different studies.[31] Several human studies have also provided evidence that tea drinking could ameliorate features of MetS and the subsequent risk for type 2 diabetes.[32] A cross-sectional study of US adults showed that hot (brewed) tea, but not iced tea, intake was inversely associated with obesity and decreased biomarkers of MetS and CVDs.[33] A study of elderly male Taiwan residents in a rural community also indicated that tea drinking, especially by individuals who had drank 240 ml or more of tea daily, was inversely associated with MetS.[34] There is evidence from some, but not all, human studies that tea consumption (3-6 cups per day) is associated with a reduced risk of type 2 diabetes.[28,35,36]

TEA AND CARDIOVASCULAR DISEASES PREVENTION

There have been many human studies about tea and CVDs, and this topic has been reviewed recently.[37,38] The strongest evidence for the reduction of CVD risk by the consumption of green tea (綠茶 Lǜ Chá) is provided by large cohort studies in Japan. In the first study, daily consumption of 1-2 to >5 cups of tea was found to reduce death due to CVDs,[39] but in another study, consumption of >6 cups of tea daily seemed to result in a reduced CVD mortality rate.[40] This discrepancy reflects the lack of preciseness of epidemiological studies. A case–control study in China also showed a correlation between consumption of green or oolong tea and a decreased risk of ischemic stroke.[41] Many, but not all, studies in the US and Europe demonstrated an inverse association between black tea (紅茶 Hóng Chá) consumption and CVD risk.[37] Apparently, lifestyle and socioeconomic status may have confounded the results of many studies.[37] The quantity and types of tea consumed are also key factors for prevention of CVDs. In a recent meta-analysis of 13 articles on the effects of green tea and black tea on the risk of coronary artery diseases, consumption of green tea, but not black tea, was found to be beneficial.[42]

NEUROPROTECTIVE EFFECTS OF TEA

The loss of cognitive function due to the loss of structure and function of neuronal cells is a common process in neurodegenerative diseases including Alzheimer disease (AD), Parkinson's disease (PD), and Huntington's disease.[43] Many epidemiological studies have suggested that tea drinking is associated with the improvement of cognitive function. Several studies have described a moderate risk reduction of PD in tea drinkers. A meta-analysis covering 11 case–control and 1 cohort study concluded that tea consumption could protect against PD, especially in Chinese populations.[2] A recent meta-analysis also supported the conclusion that tea drinking can lower the risk of PD.[44] Tea drinking was also associated with lowering the risks of depressive symptoms[45] and psychological distress.[46]

The characteristic amino acid theanine, which can cross the blood–brain barrier, is considered to be an important compound for the neuroprotective actions of tea. Theanine has been investigated for the treatment of anxiety, depression, stress, insomnia, sleep disturbance, and some schizophrenic symptoms. Several studies indicated that theanine relieved anxiety symptoms in patients with schizophrenic and schizoaffective disorders,[29] and a combination of green tea (綠茶 Lǜ Chá) extract and theanine improved memory and attention in subjects with mild cognitive impairments.[10,40] Theanine was also effective in improving sleep quality in boys diagnosed with attention deficit hyperactivity disorder.[10]

MECHANISTIC CONSIDERATIONS

The possible common mechanisms for the prevention of many diseases as discussed above are summarized in Figure 2. The antioxidant actions of tea polyphenols are likely to be important in the prevention of cancer and CVDs and in the alleviation of the inflammation in obesity and MetS. Decreased absorption of lipids and proteins appears to be a major mechanism for body weight reduction,[21,47] which also proves beneficial against MetS, diabetes, and CVDs. The effects of catechins (such as EGCG) on specific enzymes, transporters, receptors, and signaling molecules[5,23-27] are interesting topics for further investigation. How a molecule such as EGCG could specifically affect the expression of different genes is intriguing and also requires further investigation.

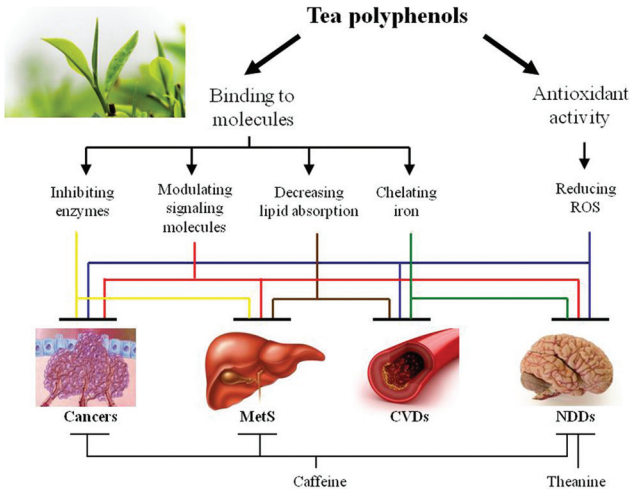

Figure 2. The proposed mechanisms by which tea constituents (polyphenols, caffeine, and theanine) prevent chronic diseases. ROS: Reactive oxygen species; MetS: Metabolic syndrome; CVDs: Cardiovascular disease; NDDs: Neurodegenerative diseases (from [1])

Bioavailability is an important issue in determining the biological effects of tea polyphenols in internal organs. This factor could explain some of the results that many of the beneficial effects were observed with green tea (綠茶 Lǜ Chá) but not with black tea (紅茶 Hóng Chá), because the black tea polyphenols, theaflavins and thearubigins, are practically not bioavailable. Tea polyphenols such as EGCG, theaflavins, and thearubigins, which are not absorbed into the blood, may exert their effects in the gastrointestinal tract by decreasing lipid and protein absorption or affecting intestinal receptors. This is probably why black tea is also effective in lowering body weight, body fat, and blood cholesterol levels. The intestinal microbiota is known to degrade green tea polyphenols.[10] Some of the metabolites may have interesting biological activities. The degradation of theaflavins (from black tea) by gut microbes has been reported,[48] and more research on the microbial metabolism of tea constituents is needed. Tea consumption has been shown to affect intestinal microorganisms, in general, in favor of the growth of microbes that are beneficial to human health.[49,50] Additional research on the effects of tea consumption on gut microbiota may provide more information relating to body weight reduction and diabetes.

CONCLUDING REMARKS

As discussed above, the possible beneficial health effects of tea consumption in the prevention of chronic diseases have been suggested by many laboratory studies and epidemiological studies. Lack of beneficial effects of green tea (綠茶 Lǜ Chá) consumption observed in some human studies could be due to the lower quantities of tea consumed. Shall we increase our tea consumption to harness the possible beneficial health effects? Caution should be applied in the use of high quantities of tea for disease prevention. Gastrointestinal irritation caused by the ingestion of tea, especially with an empty stomach, has been experienced by many people. Some experts on TCM indicated that ginger may alleviate such a problem[e]. Is this true? What is the physiological basis of such an interaction? In *Ben Cao Gang Mu* (本草綱目 Běn Cǎo Gāng Mù), Li Shizhen (李時珍 Lǐ Shí Zhēn) gives a very detailed description about the symptoms: "Long term consumption of tea by individuals with weak body and blood will cause severe irritation of the stomach and spleen…"[c]. This is a topic that warrants further studies. Hepatotoxicity in individuals consuming high doses of green tea extracts in dietary supplements for the purpose of weight reduction has been well documented.[1]

The possible health benefits of tea consumption as discussed in this review are important public health issues. The protection against some chronic diseases has been reported in individuals with daily consumption of four, five, or more cups of tea. The effects of lower levels of tea consumption (1-3 cups per day) may be subtle, but could be additive to other plant-based food or beverages. In

comparison to other beverages, such as sugary or non-sugary soft drinks or ready-made tea drinks, freshly brewed green or black tea (紅茶 Hóng Chá), consumed without added sugar, appears to be a healthier beverage.

FOOTNOTES

a 唐代陸羽《茶經》

b 唐代的《新修本草》，該書將茶列於木部中品, 言其味甘,苦, 性微寒, 無毒, 其功效有下氣, 去痰, 熱, 渴, 令人少睡, 消宿食, 利小便, 治瘺瘡等。

c 李時珍《本草綱目》：“茶苦而寒，陰中之陰，沉也，降也，最為降火。火為百病…”

d 如虛寒及血弱之人，飲之既久, 則脾胃惡寒, 元氣暗損,土不制水, 精血潛虛, 成痰飲, 成痞脹, 成痿痺，成黃瘦，成嘔逆，成洞瀉，成腹痛，成疝瘕，種種內傷，此茶之害也。民生日用, 蹈其弊者, 往往皆是, 而婦嫗受害更多, 習俗移人，自不覺爾。

e Personal communications from Professor Lee-Yan Sheen, National Taiwan University.

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