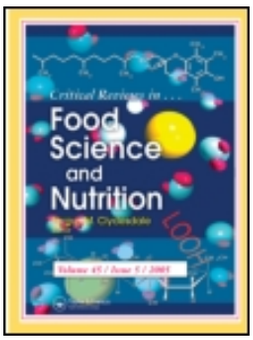

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Tea and Its Consumption: Benefits and Risks

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The recent convention of introducing phytochemicals to support the immune system or combat diseases is a centuries' old tradition. Nutritional support is an emerging advancement in the domain of diet-based therapies; tea and its constituents are one of the significant components of these strategies to maintain the health and reduce the risk of various malignancies. Tea is the most frequently consumed beverage worldwide, besides water. All the three most popular types of tea, green (unfermented), black (fully fermented), and oolong (semifermented), are manufactured from the leaves of the plant Camellia sinensis. Tea possesses significant antioxidative, anti-inflammatory, antimicrobial, anticarcinogenic, antihypertensive, neuroprotective, cholesterol-lowering, and thermogenic properties. Several research investigations, epidemiological studies, and meta-analyses suggest that tea and its bioactive polyphenolic constituents have numerous beneficial effects on health, including the prevention of many diseases, such as cancer, diabetes, arthritis, cardiovascular disease (CVD), stroke, genital warts, and obesity. Controversies regarding beneficialts and risks of tea consumption still exist but the limitless health-promoting benefits of tea outclass its few reported toxic effects. However, with significant rise in the scientific investigation of role of tea in human life, this review is intended to highlight the beneficial effects and risks associated with tea consumption.

Keywords Tea consumption, health effects, risks, cardiovascular health, black tea, green tea

INTRODUCTION

The term functional food was first time introduced in 1980 in Japan. Functional foods are defined as "any substance containing ingredients which in addition to fulfill basic nutrition requirements provides physiological benefits." Functional foods are being derived from plant as well as animal sources. Tea is one of the most important functional foods.

Tea holds second position in consumption among all beverages. Tea has been obtained from leaves of plant *Camellia sinensis* for almost 50 centuries ago. The plant of tea was originated from Southeast Asia and is now being cultivated in more than 30 countries. About three billion kilograms of tea is produced and consumed yearly. Tea has been categorized into three main types on the basis of processing during manufacturing. Of the tea produced worldwide, 78% is black tea, which is usually consumed in the Western countries, 20% is green tea, which is commonly consumed in Asian countries, and 2% is oolong tea which is produced (by partial fermentation) mainly in southern China (Mukhtar and Ahmad, 2000; Cabrera et al., 2006; Khan and Mukhtar, 2007; Butt and Sultan, 2009).

Three main types of tea, i.e., green, black, and oolong tea differ in manufacturing processes. For the production of green tea, freshly harvested leaves are rapidly steamed or pan-fried to inactivate enzyme polyphenol oxidase, thereby preventing fermentation and producing a dry, stable product. To produce black and oolong teas, the fresh leaves are allowed to wither until their moisture content is reduced to <55% of the original leaf weight, which results in the concentration of polyphenols (PPs) in the leaves. The withered leaves are then rolled and crushed, initiating fermentation of the PPs. During these processes the catechins (a group of natural PPs in green tea, accounting for its characteristic color and flavor) are converted to polymeric compounds, theaflavins (TFs) and thearubigins, consequently decreasing the catechin content. Oolong tea is prepared by firing the leaves shortly after rolling to terminate the oxidation and drying the leaves. Normal oolong tea is considered to be nearly half as fermented as black tea. The fermentation process causes oxidation of simple PPs to more complex condensed PPs which give black and oolong teas their characteristic colors and flavors.

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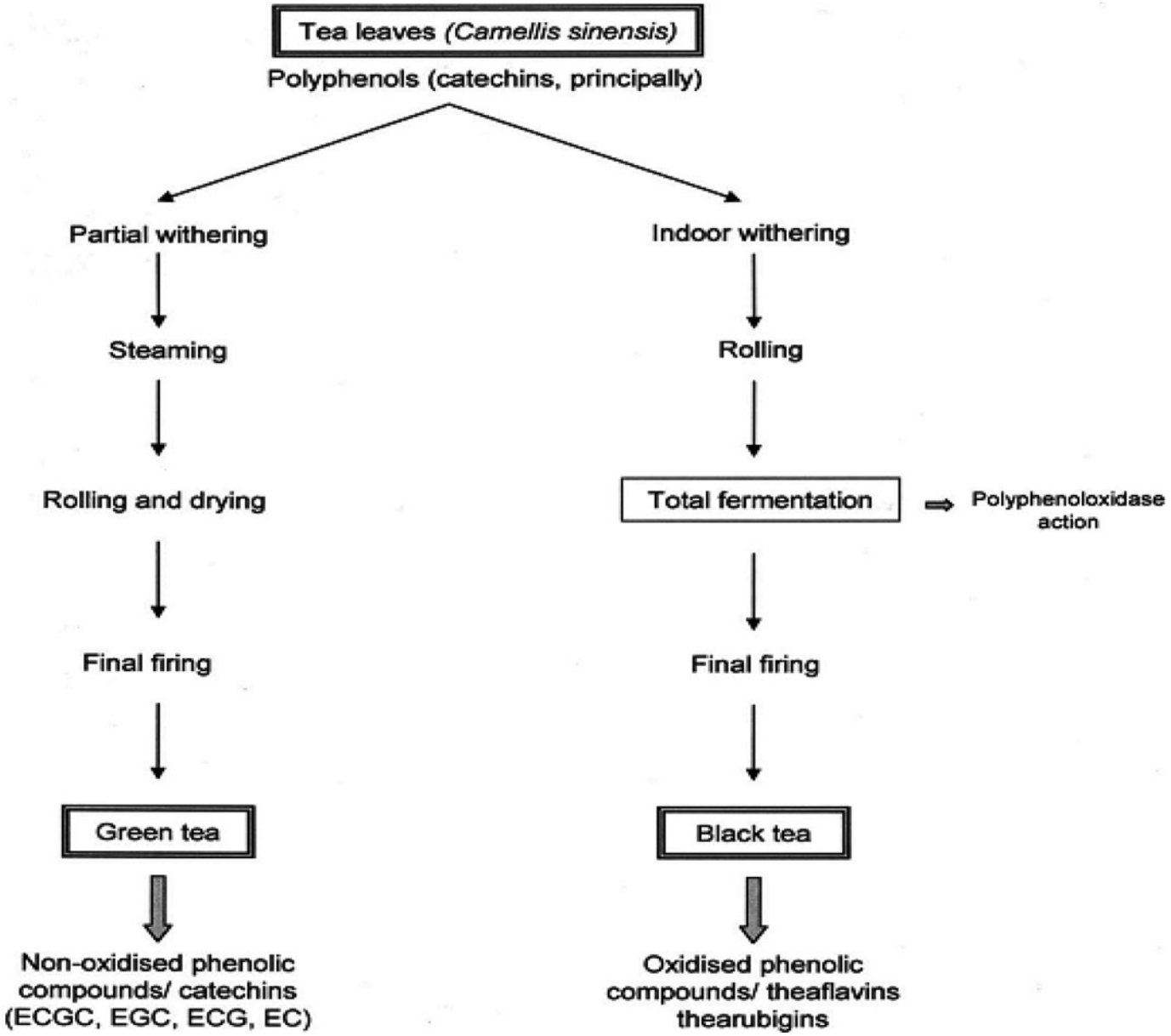

Figure 1 Principal differences between green and black tea processing and its influence on the final polyphenols content (source: Cabrera et al., 2006).

The extended fermentation lowers the PP content and elevates the caffeine content. Black tea has 2–3 times more caffeine as compared to the green tea (Adak and Gabar, 2011). Figure 1 summarizes the principal differences between green and black tea processing.

The tea composition depends on a variety of factors, including horticultural practices, climate, season, the type, and age of the plant. The important constituents of green tea are PPs particularly flavonoids. The main flavonoids present in green tea include catechins (flavan-3-ols), which account for 6–16% of the dry green tea leaves. The four major catechins are (–)-epigallocatechin-3-gallate (EGCG), that represents approximately 59% of the total of catechins; (−)-epigallocatechin (EGC) (19% approximately); (−)-epicatechin-3-gallate (ECG) (13.6% approximately); and (−)-epicatechin (EC) (6.4% approximately). Another group of PP pigments found in both black and oolong teas are TFs. These are formed from polymerization of catechins at the fermentation or semifermentation stage during the manufacture of black or oolong tea, respectively. TFs contribute to the characteristic bright orange-red color of black tea and account for approximately 2 g/100 g of the dried water extract of black tea. The major TFs in both black and oolong tea are theaflavin (TF_1), theaflavin-3-gallate (TF_2A), theaflavin-3′-gallate (TF_2B), and theaflavin-3,3′-digallate (TF_3) (Leung et al., 2001; Cabrera et al., 2006).

The limitless benefits of tea have been evidenced by in vitro animal and in vivo studies in the last few decades. Beneficial health effects have been attributed to the presence of PPs. Many papers have discussed its role against cancer, cardiovascular

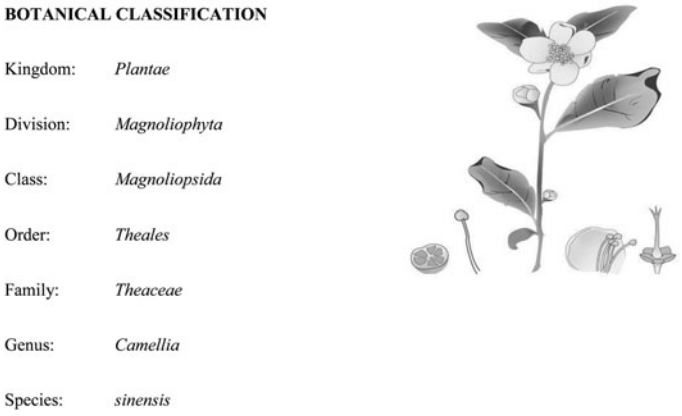

Figure 2 Morphology of *C. sinensis* (source: Ravindranath et al., 2006).

diseases (CVDs), congenital impairments, neurodegenerative diseases, depression, and many other diseases. Because little has been debated about the risk factors associated with tea, the purpose of this review is to focus primarily on the potential of tea for adverse effects along with benefits and to raise awareness of the rare, yet underappreciated risks. Figure 2 shows the botanical classification and morphology of *C. sinensis.*

BENEFITS OF TEA CONSUMPTION

Cardiovascular Health and Tea

CVDs are the leading cause of death all over the world. Several intrinsic and extrinsic factors play an important role in the onset and pathogenesis of CVDs. The American Heart Association (AHA) has categorized high cholesterol, high homocysteine level, atherosclerosis, arterial calcification, and several other factors as a risk for CVDs (Ramaa et al., 2006). There is increasing evidence from human, animal and cell culture models which suggests that green tea catechins, specifically EGCG, have a positive impact on endothelial and overall vascular functions (Moore et al., 2009).

The relationship between tea consumption and CVD risk has been investigated in a number of epidemiological studies. Negishi et al. (2004) concluded that both black and green tea PPs attenuate the development of hypertension (HTN), through their antioxidant properties, in stroke-prone spontaneously hypertensive rats. Because the amounts of PPs used in this experiment correspond approximately to those in 1 L of tea, the regular consumption of black and green tea by humans may also provide some protection against HTN. Similarly, Yang et al. (2004) conducted a cross-sectional study and observed that habitual moderate strength green tea or oolong tea consumption, 120 mL/day or more for one year significantly lowers the risk of developing HTN in the Chinese population.

Compelling evidence from chronic and acute human intervention studies has established a positive correlation between the consumption of tea and protection against CVD. A more recent meta-analysis demonstrated that individuals consuming $\geq$3 cups of tea (green or black) per day had a 21% lower risk of ischemic stroke than those consuming $<$1 cup per day (Arab et al., 2009). These studies explained that drinking black tea may result in beneficial cardiovascular health effects comparable to those of green tea.

Many cohort and case-control studies demonstrate an inverse association between tea consumption and risk of stroke and coronary heart disease (CHD) but the results are inconsistent owing to the relation of tea consumption with certain other factors that influence the CVD risk. Certain animal and acute human studies signify tea to reduce aggregation of platelets (associated with pro-inflammatory activity) and as beneficial for endothelial functions but the studies involving persistent tea administration show indecisive results.

The effects of chronic tea intake on CVD factors, examined through a randomized, placebo-controlled study, showed favorable outcome regarding platelet activation. In comparison with the placebo beverage, six weeks of tea consumption significantly lowered all the three markers of CHD risk (platelet-monocyte aggregates, platelet-neutrophil aggregates, and total platelet-leukocyte aggregates) with a difference of 9%. Black tea PPs reduce the platelet activation in vitro whereas arachidonic acid induced inhibitory effect of peroxinitrite on platelet aggregation is eradicated by EGCG, another component of black tea. Hence anti-inflammatory effects of black tea are responsible for guarding against CVD development (Steptoe et al., 2007).

Atherosclerosis

The relationship between tea or flavonoid intake and atherosclerosis has been investigated in few human studies. Debette et al. (2008) reported that carotid plaques were less frequent with increasing tea consumption in women. Mursu et al. (2007) showed that decreased carotid atherosclerosis was associated with high intake of flavonoids in middle-aged Finnish men. In contrast there is a significant literature describing studies using animal models to explore the relationship between flavonoid-rich foods or extracts and the development of atherosclerosis. The apolipoprotein E (ApoE) deficient mouse and hamsters have been used to study the effects of flavonoid-rich foods or extracts on the development of atherosclerosis (Hodgson and Croft, 2006). In the ApoE deficient mouse, which develops human-like atherosclerotic plaques, inhibition of atherosclerotic lesion development has been demonstrated with tea and tea-derived flavonoids, red wine-derived PPs, isolated quercetin or catechin, and a pure phenolic acid derivative from honey. More recently, Loke et al. (2010) concluded that isolated quercetin (a flavonol found in both green and black tea) and theaflavin (a dimeric catechin from black tea) can reduce atherosclerotic lesion formation in the ApoE$^{-/-}$ gene-knockout mouse by alleviating inflammation, improving nitric oxide (NO) bioavailability, and inducing heme oxygenase-1. Overall, the results of studies using animal models clearly show that flavonoids present in tea can attenuate the

risk of atherosclerosis development. However, further human studies are needed.

Endothelial Function

The endothelium, the inner lining of all blood vessels, functions as a selectively permeable barrier between blood and tissues. It plays a crucial role in regulating vasomotor tone, platelet activity, leukocyte adhesion, and vascular smooth muscle cell proliferation through release of several factors including NO, which is one of the most important molecules released by the endothelium and an important regulator of arterial wall tone. Endothelial dysfunction develops by the loss of normal endothelium-dependent and NO-mediated vasodilation in the artery. The development of endothelial dysfunction is considered as an early biomarker for the development of CVD and cardiovascular events.

Endothelial function may be estimated in a number of ways. Isolated vessels from animals have been used to assess the effects of potentially vasoactive substances in vitro. The results of several in vitro studies indicate that tea and tea flavonoids cause NO and endothelium-dependent vasorelaxation of rat aortic rings. In humans, ultrasonography has been used to measure flow-mediated dilatation (FMD) of the brachial artery. FMD is a non-invasive technique which measures NO-dependent vasodilation of the artery in response to shear stress induced by increased blood flow.

A number of studies have examined the effects of black or green tea, or tea flavonoids on FMD of the brachial artery. Recent studies have demonstrated a significant improvement in FMD after consumption of black and green tea, and both teas appeared to have similar effects (Hodgson and Croft, 2006). Jochmann et al. (2008) assessed the endothelial function in response to black and green tea in bovine aortic endothelial cells (BAEC) and rat aortic rings. To explain whether these findings are also applicable to humans, FMD, and nitro-mediated dilation (NMD) were quantified by ultrasound in twenty-one healthy women before and 2 h after consumption of both teas (2 h of FMD and NMD), in comparison with control (water). In BAEC, both teas significantly increased endothelial NO synthase (eNOS) activity to the same extent and induced comparable endothelial-dependent vasodilation in rat aortic rings. In human subjects, intake of green and black tea led to significant increases in FMD: from 5.4 to 10.2% and from 5 to 9.1% between baseline and 2 h after consumption of 500 mL green tea and black tea, respectively; no FMD effect was found with hot water. Between any of the groups, NMD did not vary. A recent population study found that FMD-assessed endothelial function increased from 4.4 to 8.1% after 450 ml (6 g of green tea) beverage, with no significant effects shown with the caffeine or water controls (Alexopoulos et al., 2008).

Experimental studies have also reported that isolated flavonoids found in tea can augment NO status. A recent randomized, placebo-controlled, crossover trial in healthy men conducted by Loke et al. (2008) showed that oral administration of dietary flavonoids present in green tea, including quercetin and (−)-epicatechin, could boost NO status-a potent vasodilator and reduce endothelin-1 (ET-1) concentrations-a potent vasoconstrictor. A double blind, placebo-controlled, crossover design study by Widlansky et al. (2007) also demonstrated that acute EGCG supplementation (a single 300 mg dose of EGCG) can improve brachial artery FMD in humans with coronary artery disease (CAD).

Therefore, from consistent randomized controlled trials, there is evidence that consumption of black and green tea, and specific flavonoids present in tea, can significantly improve endothelial function.

Antioxidant Properties of Tea

The antioxidative property of tea PPs in part ascribes to the potential health benefits related with tea consumption. Tea preparations entrap the reactive oxygen species (ROS), such as radicals of superoxide, hydroxyl and peroxyl, singlet oxygen, NO, nitrogen dioxide and peroxynitrite, and thus reduce their damage to lipid membranes, proteins and nucleic acids in cell-free systems. EGCG is the most effective tea catechin which reacts with most ROS. In vitro studies have shown that green and black tea inhibit the oxidation of lipoproteins induced by Cu^{2+} and thus have been proposed to contribute to prevent atherosclerosis and other CVDs. A number of clinical trials have demonstrated that plasma antioxidant capacity of healthy adults is improved within 30–60 min after taking a single dose of tea. Another study verified that biomarkers of oxidative status are decreased by the repeated consumption of tea and encapsulated tea extracts for one to four weeks (Khan and Mukhtar, 2007).

Antioxidant property of green tea is higher than black tea. Erba et al. (2005) described that tea phenols improve antioxidant ability in overall balanced food and also protect against damage ROS. The underlying mechanism is that ROS, such as peroxyl radical, singlet oxygen, hydroxyl radical are trapped by tea phenols and thus provide protection against ROS mediated damage to lipid membranes, protein and DNA in cell free environment. The vicinal dihydroxy or trihydroxy structure can chelate metal ions and prevent the generation of free radical and accounts for the antioxidant activities of catechins. High reactivity to quench free radicals is also enhanced by electron delocalization of this structure. Reactions of EGCG and other catechins with peroxyl radicals lead to the formation of anthocyanin-like compounds as well as seven-membered B ring anhydride dimers and ringfission compounds. The trihydroxyphenyl B ring in EGCG and EGC appears to be the principal site of antioxidant reactions (Kondo et al., 1999).

Absence of Toxicity

Since 2000 years, Pu-erh black tea, a kind of black tea attained by drying and fermenting crude green tea leaves,

has been used as beneficial health beverage in China, Japan, and Taiwan. A study conducted on Sprague-Dawley (SD) rats for evaluating the toxicity of tea extracts did not show any treatment related effect for its dietary administration, suggesting a safety profile for high intake black tea extract (BTE) as dietary supplement for both animals as well as humans (Wang et al., 2011).

Anti-Inflammatory Effect

Tea and its extracts are known to assist health in chemopreventive effects on cancers, CVDs, and inflammation. Various epidemiological studies associated the elevated levels of uric acid (UA) and C-reactive protein (CRP) with cardiovascular risk. According to a study, varying levels of the risk were significantly reduced with tea supplementation that decreased the UA and CRP levels owing to the synergistic effects of tea phenolics. This could be substantial from public health viewpoint as inflammation is involved in every disease progression, including diabetes, arthritis, heart disease, cancer, and obesity (Bahoruna et al., 2010).

Cancer and Tea

The widespread consumption of tea throughout the world has aroused interest in the possibility of its use in chemoprevention of carcinogenesis and its related phenomenon, mutagenesis. Several population-based studies confirm about the cancer protective effects of tea (Vasisht et al., 2003). Cancer is usually caused by oxidative damage resulting from cigarette smoking. Researchers claim that tea PPs are powerful anti-oxidants that induce phase-2 detoxification enzymes which in turn reduce the risk of cancer by reducing damage of DNA in the cell and activation of cancer leading to malignancy (Shim et al., 1995; Beltz et al., 2006; Sharangi, 2009). The anti-carcinogenic and antimutagenic activities of green tea have been reviewed by Butt and Sultan (2009) suggesting that it can reduce the prevalence of cancer and even provide protection. Yang et al. (2000) also supported the fact that tea is not toxic and its consumption is suggested to prevent carcinogenesis. Both green and black teas have significant antimutagenic and anticlastogenic effects. Compared to green tea, reports on black tea are relatively less. Green tea was found to have no mutational toxicity but was able to inhibit mutagenesis, at concentration levels equivalent to daily human consumption. A few reports on thearubigins, which are present in black tea, indicate that it has significant antimutagenic and anticlastogenic effects similar to TFs (Gupta et al., 2002).

Inhibitory effects of BTE and TFs on selenoprotein thioredoxin reductase 1 (TrxR1), high levels of which in cells are associated with enhanced resistance of the cells to anti-cancer drugs that induce oxidative stress, have been demonstrated by Smart et al. (2004). The inhibitory effect of BTE and TFs on TrxR1 means that they could have roles in reducing cancer risk. TFs are major components for black tea to inhibit TrxR1 because TFs account for 3–6% of the water-extractable materials from black tea but TFs are contributed to near 50% inhibitory effects of BTE on TrxR1 (Gardner et al., 2007).

Prostate Cancer Inhibition

Prostate cancer (PCA), the second most important cause of cancer related mortality in United States, is the most recurrently analyzed non-cutaneous cancer (Siddiqui et al., 2005). Studies show that androgen sensitive human prostate carcinoma cells can be inhibited by tea extracts and TFs (Lyn-cook et al., 1999).

Various studies suggest a key role for the oxidative stress induced by ROS in the process of prostate carcinogenesis (Sun, 1990). A strong association exists between androgen hormone and PCA risk but the underlying mechanism of action is unclear. In Wistar rats, antioxidant enzymes level was altered by androgen administration (Siddiqui et al., 2005). Androgen concentration transfers the prostate prooxidant-antioxidant balance towards increased oxidative stress thereby modulating the gene expression and causing prostate tumors (Ripple et al., 1997). In a dose-dependent manner, aqueous tea extracts (ATE) restored eminent amounts of antioxidant enzymes (Siddiqui et al., 2005).

Another study demonstrated an ATE based successful inhibition of oxidative stress induced by testosterone which is a vital cause of PCA development (Siddiqui et al., 2005).

Skin Cancer

Extensive studies have shown the activity of tea and tea PPs on the inhibition of skin tumorigenesis. Growth of well-established skin tumors is inhibited or, in some cases, regressed by the oral administration of green tea, black tea, or EGCG. Papilloma-bearing mice even showed complete regression (Conney et al., 1999). Feeding tumor-bearing mice with black tea significantly decreased the growth of nonmalignant tumors, squamous cell carcinomas, and tumor volume. In addition, DNA synthesis was inhibited and apoptosis was enhanced (Khan and Mukhtar, 2007).

In a study, oral administration of black tea for 11 weeks in female mice, which were allowed to develop tumors by being treated with UVB light, noticeably reduced the number and volume of nonmalignant and malignant tumors (by 54 to 84%). In another study, oral administration of black tea for 11–15 weeks inhibited the growth of established papillomas (by 35–48%) in mice, but inconsistent results were obtained for decaffeinated black tea (Lu et al., 1997). A case-control study conducted in Italy showed protective effect of tea consumption on cutaneous malignant melanoma (Naldi et al., 2004). In a population-based case-control study, a considerable decrease in the SCC development was reported for the subjects consuming hot black tea (Khan and Mukhtar, 2007). Green tea extract (GTE) EGCG like many other applications provides protection against skin carcinogenesis (Katiyar et al., 2007).

Lung Cancer

Studies regarding the effects of green and black tea on lung cancer development in mice can yield promising implications for humans. In mice 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone or nicotine-derived nitrosamine ketone (NNK)-induced pulmonary hyperproliferation and tumorigenesis initiated with NNK can be protected by brewed black tea and TFs, particularly, oral administration of brewed black tea inhibits the development of adenoma to adenocarcinoma in mice with already developed lung adenomas (Yang et al., 1997).

Reports have shown that in mice with benzo[α]pyrene (BαP)-induced lung carcinogenesis, black tea suppresses cell proliferation and induce apoptosis (Banerjee et al., 2005). In mice, the spontaneous formation of lung tumors and rhabdomyosarcomas has been shown to be inhibited by black tea and green tea infusions. Sixty weeks of treatment with black or green tea notably reduced the prevalence of lung cancer from 52 to 27%, multiplicity from 0.72 to 0.33 tumors/mouse and volume from 38.3 to 4.27 mm^3. In addition, the tea-treated groups of mice had significantly lower body weights, particularly the body fat weights, as compared to the control group (Landau et al., 1998).

Examining the effects of black tea and caffeine administration on NNK induced lung tumorigenesis in rats, it was found that total lung tumor (adenomas, adenocarcinomas, and adenosquamous carcinomas) incidence was significantly reduced from 47 to 19% by black tea and from 47 to 10% by caffeine treatment. This implies that caffeine in black tea might actually account for its inhibitory activity (Khan and Mukhtar, 2007).

A case control study conducted in Uruguay demonstrated an association between tea drinking and reduced risk of lung cancer in male cigarette smokers (Khan and Mukhtar, 2007). Regular tea drinking reduces the likelihood of lung cancer among non-smoking women. This fact has been supported by Zhong and his colleagues in 2001 by large population-based case-control study among women inhabitants of Shanghai, China (Zhong et al., 2001).

Liver Cancer

It has been reported that administration of 2% black tea significantly reduced the incidence of NNK-induced liver tumors (from 34 to 12%) in rats. Studies have demonstrated inhibitory effects of individual tea catechins, BTE, and oolong tea extract (0.05 or 0.1%) on the formation of hepatic preneoplastic *glutathione-S transferase* (GST)-positive foci in rats treated with a single dose of *N*-nitrosodiethylamine (NDEA) and then phenobarbital for six weeks in the drinking water (Khan and Mukhtar, 2007).

Breast Cancer

The occurrence of late-onset breast cancer has been mounting in the United States since 1980s. It is estimated that known risk factors, such as genetic modifications, account for approximately 5–10% of breast cancer cases. Moreover, dietary habits may be responsible for the risk as well as prevention of breast cancer. Recently, Wnt signaling in invasive breast cancer cells was found to be suppressed by EGCG (Khan and Mukhtar, 2007). Leong et al. (2008) also studied that black tea has its potential use as a breast cancer chemopreventive agent. Laboratory studies have provided evidence that GTE inhibits breast cancer growth by a direct anti-proliferative effect on the tumor cells, as well as by indirect suppressive effects on the tumor-associated endothelial cells (Sartippour et al., 2006).

Stomach Ulceration

Stomach ulceration induced by nonsteroidal anti-inflammatory drugs (NSAIDs) is a major medical problem, ranking fourth in terms of causing morbidity and mortality (Hawkey, 1990). Several plants and herbs are used in traditional medicine to treat GI disorders. Regular intake of black tea may reduce the risk of stomach ulceration (Adhikary et al., 2011).

Prevention of Pancreatitis

About 80% of pancreatitis cases occur due to alcohol abuse. Although the underlying mechanism is unknown, evidence shows that ethanol (EtOH) not only directly targets the pancreatic acinar cells by its toxic effects but even sensitize them to intracellular zymogen proteolysis stimulated by cholecystokinin (CCK). Combined stimulation by EtOH + CCK results in acute pancreatitis (Das et al., 2006).

BTE provides surplus health benefits through its PPs collectively known as tea flavonoids. The antioxidant properties of tea flavonoids make them a protective dietary component that significantly increases the plasma antioxidant activity and thus reduce various cancer risks. BTE effectively blunted the significantly increased levels of amylase and lipase (biomarkers for pancreatitis) and pancreatic levels of malondialdehyde (MDA) and NO, the biomarkers of oxidative stress in an EtOH + CCK induced pancreatitis rat model. BTE also normalized the suppressed activities of other antioxidative enzymes, blunted the histopathological and inflammatory changes and diminished the increased DNA fragmentation and damage. Thus BTE effectively averted the toxic activity in EtOH+CCK induced pancreatitis rats (Das et al., 2006).

Neurological and Psychological Effects

Various reports indicate that neurologic and psychologic functions can be improved by tea. Recently, in a broad array of cellular and animal models of neurological diseases, it has been reported that tea catechins penetrate the brain barrier and protect neuronal death by its divalent metal chelating, antioxidant and anti-inflammatory activities. In order to evaluate the

effect of acute and chronic administration of green or black tea, mice with experimentally induced convulsions were analyzed. It was found that tea not only accelerates the onset of convulsion, but also increases the duration and mortality. Possibly, tea acts on Ca^{2+} channels and not through gamma-aminobutyric acid (GABA) in brain (Khan and Mukhtar, 2007).

A cross-sectional study in 1058 community-dwelling elderly Japanese individuals aged $\geq$70 has been carried out by Niu et al. (2009). This study showed a positive association between green tea consumption and lower prevalence of depressive symptoms.

In future, the availability of effective brain permeable, iron-chelatable/radical scavenger neuroprotective drugs that would avert the progression of neurodegeneration can be a promising treatment for neurodegenerative diseases and aging (Khan and Mukhtar, 2007).

Role in Neurotrasnsmission

It is believed that green tea induced relaxation is due to the presence of amino acid theanine which is also responsible for its exotic taste. Juneja et al. (1999) experimented that L-theanine accessed rat brain in 30 min without any metabolic change when administered peritonealy. Theanine reduced blood pressure in hypertensive rats and performed the function of a neurotransmitter. After oral administration of L-theanine it reached the brain within 40 min of oral administration and generated α-waves (an index of relaxation) in human volunteers. L-theanine is being produced industrially and supplied under the trade name of Suntheanine™. It is used for designing medical foods targeting relaxation and the reduction of stress.

Reduced Cognitive Impairment

Approximately 30 percent of eukaryotic proteomes remain unfolded and account for many neurodegenerative diseases. For example, tau and amyloid-β (Aβ) in Alzheimer's disease (AD) and α-synuclein (α-syn) in Parkinson's disease (PD) all seem to transition from a highly dynamic, natively unfolded state through heterogeneous molten, oligomers to the generic "cross-β" form of amyloid fibers. EGCG inhibits tau, Aβ, α-syn (by traping Aβ and α-syn in monomeric and oligomeric forms with diminished ability to participate in amyloidogenesis) and polyglutamine fibrillization in vitro and antagonizes polyglutamine aggregation and toxicity in both yeast and fly models of Huntington's disease (Roberts and Shorter, 2008).

Treatment of Diabetes

Population-based studies suggest that green tea consumption is associated with reduced risk of several human malignancies such as cancer and diabetes (Shankar et al., 2007). In a laboratory study published in 2009, scientists discovered that compounds extracted from black tea were more effective at slowing the absorption of blood sugar than those extracted from green tea and oolong tea. Additionally, a 2009 population study of 1,040 elderly adults found that long-term intake of black tea was associated with lower prevalence of diabetes (Panagiotakos et al., 2009).

Heavy consumption (6–10 cups/day) of black tea brew is frequently advised by Sri Lankan physicians for pre-diabetics and mild diabetics owing to the glucose lowering potential and anti-diabetic activity of tea infusion. Sri Lankan Broken Orange Pekoe Fannings (BOPF) grade black tea (a grade containing medium size leaf particles) possesses striking hypoglycaemic, antihyperglycaemic and antidiabetic activities, the former two being dose dependent (Abeywickramaa et al., 2011).

Various components of black tea, including catechins, TFs, anthocyanines, gallic acid, some polysaccharides and PPs, contribute to the impairment of carbohydrate digestion by inhibiting the carbohydrate-hydrolyzing enzymes: alpha-glucosidase and alpha-amylase.

Black tea infusion (BTI) increases the insulin/glucose ratio by its TFs and EGCG, resulting in insulin sensitizing action or enhancement of insulin activity. Black tea PPs possess insulinomimetic activity; suppressing the blood glucose level in *streptozotocin*-induced diabetic rats. The antioxidant activity of BTI assists in reducing the blood glucose level by scavenging ROS which are concerned with the pathogenesis of diabetes mellitus.

Different studies have claimed flavonol and myricetin present in BTI to lower the blood glucose levels by various mechanisms, including high uptake of glucose via cell membranes in adipocytes, enhanced glucose metabolism in cells, high release of insulin upon stimulating action of pancreatic cells and augmented lipogenesis. All these findings are essential as BOPF grade black tea is an everyday natural beverage consumed globally having beneficial effects regarding the regulation of dysglycemia (Abeywickramaa et al., 2011).

Obesity

Reports have shown that feedings of oolong, black, and green tea leaves to rats significantly reduces their body weights and plasma triglyceride, cholesterol and LDL-cholesterol (Murase et al., 2002; Zheng et al., 2004; Kuo et al., 2005; Lin and Lin-Shiau, 2006). In mice supplemented with tea catechins, there was a significant reduction in body weight gain induced by high-fat diet, accumulation of visceral and liver fat, and the development of hyperinsulinemia and hyperleptinemia (Khan and Mukhtar, 2007).

BTE and caffeine are beneficial for the suppression of high-fat diet-induced obesity, and that their effects may be attributed to the inhibition of adipose tissue formation and reduction of adipose tissue mass. Moreover, better results can be achieved by combination of different compounds. BTE and caffeine do

render the most effective anti-obesity action and sufficient supply of BTE and CF may prevent obesity and possibly reduce the risk of associated diseases, such as CHD (Huang et al., 2009).

Anti-Arthritis Effect

Green tea protects against rheumatoid arthritis by modulating arthritis-related immune responses. It suppresses both cytokine IL-17 (an inflammatory substance) and antibodies to Bhsp65 (arthritis inducing protein), and increases cytokine IL-10 (an anti-inflammatory substance) (Kim et al., 2008).

Bone mineral density (BMD) may be influenced by chemical compounds in tea such as caffeine, fluoride and phytoestrogens. Black tea consumption had a moderately positive effect on BMD, particularly in older women. There was a significant increase in BMD with higher levels of tea consumption (four or more cups per day) (Chen et al., 2003). Black tea was also emerged as an independent protective factor for the risk of hip fractures in men in the Mediterranean Osteoporosis Study (Kanis et al., 1999). Johnell et al. (1995); Kanis et al. (1999) and Hegarty et al. (2000) reported that this effect was independent of the addition of milk to tea. In the UK, black tea consumption increased the overall calcium intake of women almost 3% of the Reference Nutrient Intake due to the routine addition of milk (Gardner et al., 2007).

Antihistaminic Effect

Antihistaminic effect is exhibited by GTE EGCG. Histamine is released from mast cells in allergic responses, particularly inflammation, dermatis, urticaria, mastocytosis, and asthma, triggered by environment antigens. Tea extract, beside its anti-inflammatory properties, also exhibits an antihistaminic effect on rat peritoneal mast cells and inhibits hyaluronidase activity. Histamine release can be inhibited up to 90% in rat cell culture by EGCG. This inhibitory effect of the histamine release is supposed to be related to the triphenol moiety of the molecule. Quercetin flavonoid produces an anti-inflammatory activity in antigen activated cells and causes a concentration-dependant inhibition of histamine release (Toyoda et al., 1997; Alexis et al., 1999).

Antibacterial, Antiviral, and Probiotic Effects

Screening of methanolic extract of tea leaves for antimicrobial property against 111 bacteria comprising 2 genera of Gram positive and 7 genera of Gram negative bacteria resulted in the inhibition of most of these strains. The protection of Swiss strain of white mice challenged with different dosages of *Salmonella typhimurium* confirmed the antibacterial activity of tea extract in vivo (Bandyopadhyay et al., 2005). Lately, EGCG was found to have an effect on the inhibition of HIV infection and *Staphylococcus aureus* infections (Nance and Shearer, 2003). Drinking tea not only reduces enterobacteria (which produce ammonia and other harmful amines), but also causes a beneficial increase in the level of lactobacilli and bifidobacteria (which produce organic acids) and lower the pH of intestine (Weisburger, 1999). The beneficial effect of tea against viral infection cannot be overlooked. Strong inhibition of rotavirus propagation in monkey cell culture and influenza A virus in animal cell culture was achieved through tea PPs (Khan and Mukhtar, 2007). Several flavonoids including EGCG and ECG have been reported to inhibit the propagation of retrovirus human immunodeficiency virus (HIV) by restraining reverse transcriptase, the enzyme responsible for the establishment of the virus in host cells (Yamamoto et al., 1997), so it can be suggested as a complementary therapy for HIV. But it still needs a lot of work to be done because experiment has been carried out in vitro and in previous studies many substances which proved to be effective against HIV in vitro cannot show the same results in vivo. So it can be used in combination with conventional medicines (Williamson et al., 2006).

Anogenital Wart Suppression

Sinecatechins, a defined GTE, was shown to be effective in the treatment of external genital and perianal warts in a randomized, double-blind, vehicle-controlled trial involving 502 male and female patients aged 18 years and older, with 2–30 anogenital warts ranging from 12 to 600 mm^2 total wart area. Patients applied a topical ointment containing either sinecatechins or vehicle (placebo) to the affected area for up to four months, followed by a three months treatment-free follow-up to assess recurrence. More than half of the patients (57%) in the treatment group experienced a complete resolution of their warts, compared with 34% in the control group. Seventy eight percent of the patients in the treatment group experienced partial improvement (at least 50%) in their warts. It was observed that topical sinecatechins ointments 15 and 10% were effective and well-tolerated in the treatment of anogenital warts, with relatively few side-effects (Tatti et al., 2008).

LACKLUSTER OF TEA CONSUMPTION

No doubt, the benefits associated with the consumption of black and green tea are overwhelming but still need attention in order to explain its detrimental effects on human health. Harmful effects of tea overconsumption (black or green) are primarily due to three main factors: (1) its caffeine content, (2) presence of aluminum, and (3) the effects of tea PPs (TPP) on iron bioavailability. Various compounds present in tea may have deleterious effects at pharmacological concentrations, in certain vulnerable populations, and in certain disease or polypharmaceutical contexts. A day-long consumption of green tea (which contains

less caffeine) improved the psychomotor and cognitive performance of healthy adults in a manner similar to coffee, but it is less likely than coffee to disrupt sleep quality at night. The caffeine content in the same type of tea, but manufactured by different fermentation processes, has been presented by the following order: black tea > oolong tea > green tea > fresh tea leaf. Although green tea caffeine content is low, its consumption is not recommended in cases of special sensitiveness to xanthic bases (Cabrera et al., 2006; Lambert et al., 2007). The reported negative effects produced by caffeine present in many tea products are nervousness, restlessness, tremors, palpitations, sleep disorders, vomiting, diarrhea, headaches, epigastric pain, and tachycardia. However, research on the effects of caffeine in children is limited (Higdon and Frei, 2006). Negative effects of theophylline (member of the xanthine family of stimulants) are similar to those of caffeine, but they only occur with high quantities intake. Thus, green tea should be avoided by the patients suffering from heart conditions or major cardiovascular problems. Pregnant and breast feeding women should drink not more than 1–2 cups/day, since it can augment the heart rhythm. It is also suggested to control the concomitant consumption of green tea and some drugs, due to its diuretic effects (Cabrera et al., 2006).

Tea is "Generally Recognized As Safe" (GRAS) by the US Food and Drug Administration (FDA). Safety studies have looked at the consumption of up to 1200 mg of EGCG (as supplement) in healthy adults over 1–4 week time periods. The adverse effects reported in these studies included excess intestinal gas, nausea, heartburn, stomach ache, abdominal pain, dizziness, and muscle pain (Chow et al., 2003; Chow et al., 2005). Figure 3 summarizes some potentially detrimental effects associated with concentrated GTE.

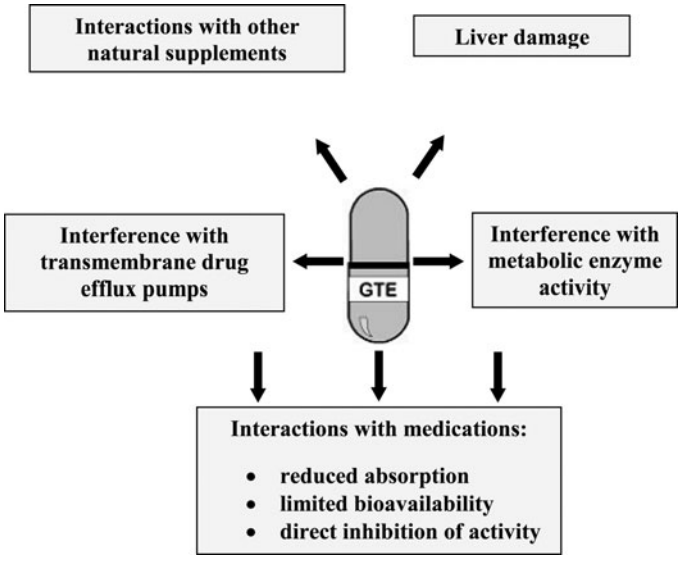

Figure 3 Potentially detrimental effects of concentrated GTE (source: Schönthal, 2011).

Drug Antagonism

Green tea is considered as a significant source of vitamin K, which can antagonize the effect of anticoagulant drugs, such as warfarin. A case report of 44-year-old white man demonstrated that warfarin produces anticoagulation by inhibiting the production of vitamin K-dependent clotting factors (i.e., factors II, VII, IX, X). The exogenous administration of vitamin K limits the effect of warfarin and reduces the patient's degree of anticoagulation (Taylor and Wilt, 1999).

Hepatic and Gastrointestinal Toxicities of Green Tea Polyphenols (GTPP)

Mazzanti et al. (2009) reviewed the current literature on suspected green tea-related hepatic reactions and described 2 new cases reported within the framework of the Italian surveillance system of natural health products. This analysis suggests a causal association between green tea and liver damage. The hepatotoxicity is probably due to EGCG or its metabolites which can induce hepatic oxidative stress. In a few cases, concomitant medications related toxicity could also be involved. Unfortunately, some reports of adverse effects (mainly hepatitis) associated with the consumption of green tea preparations have been published. In April 2003, the manufacturer of *Exolise* (Arkopharma, Carros, France), a GTE containing high EGCG levels and marketed as a weight loss supplement, suspended the sale of this product and withdraw it from the market after 13 reported cases of liver damage due to its consumption. The same product was also removed from the Spanish market due to other hepatotoxicity cases in humans. Since then, much attention has been given to the possible hepatotoxicity from green tea. Despite the removal of *Exolise* from the market, other green tea-based herbal supplements have been marketed; therefore reports of hepatotoxicity from green tea are increasing.

Despite several human studies that reported no toxicity of tea PP preparations and that the major harmful effects associated with consumption of high doses of tea preparations are due to gastrointestinal (GI) irritation, there are a number of recent case reports of hepatotoxicity related to the consumption of high doses (10–29 mg/kg/day, po) of tea-based dietary supplements (Bonkovsky, 2006). In nearly all cases (eight out of nine), patients displayed elevated serum alanine aminotransferase (ALT) and bilirubin levels. In two out of nine cases, periportal and portal inflammation were noticed. All cases resolved after cessation of supplement consumption, suggested by the fact that reinjury was reported following rechallenge with the same preparations.

Laboratory studies in animals (particularly rodents and dogs) have supported the potential toxic effects of high doses of GTEs (Galati et al., 2006; Isbrucker et al., 2006) Oral administration (po) of Teavigo™ (a green tea PP preparation containing 90% EGCG) or Polyphenon E® (a decaffeinated extract of green tea containing 60% EGCG) for 13 or 9 weeks, respectively, to Beagle dogs caused dose-dependent toxicity and death. Vomiting

and diarrhea were noticed throughout both studies. In addition, Teavigo™ (500 mg/kg, po) caused proximal tubule necrosis and elevated serum bilirubin in all treated dogs. Serum aspartate aminotransferase (AST) levels in most male dogs (2/3) were found to be elevated. Female dogs (2/3), but not male dogs, manifested liver necrosis. Oral (po) and intragastric administration (ig) of Teavigo™(2000 mg/kg) to rats caused lethality in 80% of animals treated (Isbrucker et al., 2006).

Experiments performed in rat hepatocytes showed that high concentrations of GTEs and of single tea phenolics are toxic. This cytotoxicity seemed to be related to the gallic acid unit, and the order of cytotoxic effectiveness found was EGCG (the most abundant tea phenolic) > propyl gallate > ECG (also a food additive) > GA, EGC > EC. The major cytotoxic mechanism found with rat hepatocytes was GTEs (particularly EGCG) induced mitochondrial membrane potential collapse or toxicity and ROS formation (prooxidant activity). Hemorrhagic lesions in the stomach and intestine were revealed by histological analysis. Intraperitoneal (ip) administration of EGCG to mice resulted in dose-dependent lethality (associated with increases in serum ALT levels) beginning at 150 mg/kg and thus suggested the involvement of hepatotoxicity. EGCG was also found to be the most cytotoxic to isolated rat hepatocytes and hepatotoxic to mice in vivo (Galati et al., 2006).

These data suggest that high doses of EGCG can produce toxicity in the liver, kidneys, and intestine. Hepatic and renal toxicity appears to be correlated with the bioavailability of EGCG. In the rat (low bioavailability), toxicity is limited to the GI tract following oral administration. In the dog (much higher bioavailability), hepatotoxicity, nephrotoxicity, and intestinal toxicity were reported. Toxicity was much higher in fasted, than in prefed, dogs (Isbrucker et al., 2006). Recent studies in humans have also proved that fasting increases the bioavailability of EGCG. Since there have been no reports of toxicity in human volunteers enrolled in intervention studies, therefore careful monitoring of liver and kidney function is needed until the risk of toxic events associated with tea catechins is established in humans.

A nine-month chronic study was conducted in fasted dogs to take advantage of the reported increased catechin bioavailability with fasting. Kapetanovic et al. (2009) evaluated standardized GTE (i.e., Polyphenon E®; PPE) for exposure and toxicity in Beagle dogs following oral dosing by capsules. Extensive morbidity, mortality, and pathology of many major organs led to early termination of the study at 6.5 months and hindered identification of the toxicity mechanisms. A follow-up 13-week study investigated the exposure to and toxicity of PPE. In general, toxicities were less severe when compared to the chronic study during the same interval. Dosing in a fed state resulted in considerably lower and less variable exposure than observed under fasted conditions. PPE-treated dogs manifested adverse events like diarrhea, emesis, and excessive salivation. In addition, a multitude of PPE-induced toxicities were observed including hematology (decreases in red blood cells, hemoglobin, and hematocrit, increases in white blood cells, neutrophils, monocytes, platelet count), gross pathology (lesions in GI tract, lymph nodes, liver, kidney, lung, heart and tonsils), histopathology (epithelial necrosis in GI tract, liver inflammation including centrilobular necrosis and congestion, renal tubular necrosis, atrophy of reproductive organs, and atrophy and necrosis of hematopoietic tissues) as well as abnormalities in clinical chemistry, coagulation and urinalysis parameters.

Recently, Lambert et al. (2010) investigated the hepatotoxic effects of high doses of the GTPP (particularly EGCG) in male CF-1 mice. A single dose of EGCG (1500 mg/kg, ig) raised plasma ALT levels (marker of liver damage) by 138-fold, reduced survival by 85% and increased hepatotoxic response. Plasma ALT levels were raised 184-fold following two once-daily doses of EGCG (750 mg/kg, ig). Moderate to severe liver necrosis was observed following EGCG treatment. EGCG hepatotoxicity was appeared to be related with oxidative stress including increased hepatic lipid peroxidation (LPO), plasma 8-isoprostane and increased hepatic metallothionein and γ-histone 2AX protein expression. In addition, EGCG also increased plasma interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1).

On the basis of these results, it can be concluded that the suspected hepatic reactions from green tea can likely be attributed to catechins, specifically to EGCG. After oral administration, the bioavailability of catechins is low; however, under fasting and after repeated administration, catechin plasma levels can rise up to toxic levels. Thus, the hepatotoxicity can be ascribed to the capability of EGCG or its metabolites to induce oxidative stress in the liver (Mazzanti et al., 2009).

The experience of Molinari et al. (2006) complemented previous reports of acute liver toxicity observed in individuals consuming supplements containing GTE. After review of the literature and reporting a case of acute liver dysfunction caused by consumption of GTE supplements, it was concluded that many herbal medicines and dietary supplements were associated with severe adverse events, including hepatotoxicity and even fulminant liver failure.

Green Tea-Induced Asthma

Shirai et al. (1994) described green tea dust induced asthma and nasal symptoms in 3 patients working in green tea factories. It was found that all 3 patients displayed an immediate skin and bronchial response to EGCG. Prausnitz-Küstner (immunologic) test with EGCG was also positive. The asthmatic and healthy controls did not show any positive reaction. These results indicated that EGCG is a causative agent of green tea-induced asthma and suggested that an IgE-mediated response may be responsible for causing this type of occupational asthma.

Dietary Flavonoids, Effects on DNA, and Fetal Leukemia Risk

Ross et al. (1994) hypothesized that maternal consumption of dietary topoisomerase inhibitors II (including flavonoids) could

increase the risk of leukemia in offspring. A subsequent epidemiological study suggested the existence of a link between maternal intake of these compounds and acute myeloid leukemia (AML). A statistically significant positive association between AML and increasing the consumption of DNA topoisomerase II inhibitor-containing foods has been reported. No such association was observed between maternal flavonoid consumption and acute lymphocytic leukemia (ALL). Cell line studies with purified flavonoids (including quercetin, luteolin, fisetin, and kaempferol) have suggested that the mechanistic basis for the increased risk of leukemia is inhibition of topoisomerase II activity in the fetus, which causes chromosomal translocation at chromosome 11q23 involving the mixed-lineage leukemia (MLL) gene. Quercetin and fisetin were found to be the most potent DNA topoisomerase II inhibitors (Lambert et al., 2007).

Risk of Pre-Eclampsia

Recently, although promising beneficial effects have been demonstrated by tea in various vascular diseases, yet no uniformity is seen regarding its effects in the human clinical and epidemiological studies. A pregnancy-specific vascular disease, Pre-eclampsia, is concerned with 3 and 10% of all pregnancies worldwide accounting for about 8,370,000 cases annually.

It has been proposed that pregnant mothers consuming tea persistently may be highly associated with any degree of pre-eclampsia risk. Different constituents of tea influence this risk by numerous probable mechanisms like pathways related to oxidative stress or modulation of pre-eclampsia angiogenic factors (Wei et al., 2009).

Polycyclic Aromatic Hydrocarbons (PAHs) Risk

Polycyclic aromatic hydrocarbons (PAHs) are a renowned class of carcinogens, consisting of more than two fused aromatic rings, can be a threat to human health. Due to higher surface area of tea leaves, contact with air can get PAHs to be accumulated. Another way PAHs absorption could occur is while drying the leaves in presence of combustion gases during the production process (Lin et al., 2005).

While studying release of PAHs in tea liquor, black tea is found to contain the highest level of all PAHs. Although the toxic 5–6 rings PAHs fail to be detected in the infusion yet 91.2–97.2% of ΣPAHs are accounted by the milder 2–3 rings PAHs. The rate of PAHs release in tea varies with the infusion time (Lin et al., 2005).

Due to PAHs being less soluble in water, they are not a threat to human health. However solubility of these contaminants increases till 50% (NA) of the actual concentration in tea infusion. The amount of essential oil in tea liquor (which serves as a co-solvent for numerous lipophilic compounds) may account for increasing solubility of the PAHs in water. So consuming liquor formed by tea contaminated with PAHs could pose a health risk. Sanitary Standards are required for tea to check for health risks from PAHs in the tea (Lin et al., 2005).

Fluoride and Metal Risk

As per studies conducted by South and East Asian countries, tea contains certain elements, e.g., arsenic, aluminum, barium, cobalt, cadmium, copper, nickel, manganese, zinc and strontium, which could adversely affect the human health (Gulati et al., 1993; Cao et al., 1996; Wong et al., 1998; Fung et al., 1999; Lung et al., 2003; Nookabkaew et al., 2006).

The risk of dental flourosis due to intake of fluoride from the instant tea bags is not significant. Yet recently an American patient was diagnosed with skeletal flourosis (SF) due to long term use of instant tea bags (Whyte et al., 2005). Environmental risk assessment considers one in million (10–6) as the acceptable risk level for carcinogenic (Kavcar et al., 2006). With respect to Alzheimer's disease, the level of non-carcinogenic risk stayed in control while being exposed to the 10 metals including aluminum. Environmental policies may affect the acceptability levels raising it as much as 10-4 for arsenic concentrations. A study by Sofuoglu and Kavcar (2008) showed the arsenic concentrations to be at levels corresponding to moderately high carcinogenic risk.

Reduced Absorption of Iron

Owing to tannins present in black tea, its consumption with meal reduces the absorption of non-heme iron (Fe). For a meal comprising of hamburger the absorption reduces to 0.12 from 0.32 mg. It was found that on consuming tea the negative balance of iron increased for black and decaffeinated black tea consumption than for consuming no tea (Prystai et al., 1999).

Several studies have demonstrated that black tea appears to inhibit the bioavailability of non-heme iron by 79–94% when both are consumed concomitantly; the impact of this interaction depends on the Fe intake and Fe status of the individual. Similarly, green tea catechins may have an affinity for Fe, and green tea infusions can significantly decrease the Fe bioavailability from the diet. These studies affirmed that tea should not be consumed by patients suffering from anaemia. For example, Fe-deficiency anemia among children in Saudi Arabia and the United Kingdom may be aggravated by the regular consumption of tea with meals. It is proposed that the interaction between tea and Fe can be alleviated by the addition of lemon or consuming tea between meals (Cabrera et al., 2006).

The authors of a systematic review of 35 studies on the effect of black tea drinking on Fe status in the UK concluded that tea drinking reduced the absorption of non-heme Fe from the diet and statistically significant relationships were observed between tea drinking and poor Fe status among preschool children (Nelson and Poulter, 2004).

Gastrointestinal Tract Cancer Risk

Cancers of upper gastrointestinal tracts pose a significant health threat to humans and account for nearly 18% of unexampled cases of cancer worldwide, e.g., oral, hypo- and oropharyngeal, oesophageal, gastric and laryngeal cancers (Parkin et al., 2005).

In an experiment, consuming hot tea in large amounts was found inversely related to the risk of pharyngeal cancer. The hazard ratio (95% confidence limits) found when compared with individuals who did not consume hot tea to ones that consumed 1–6 cups was 0.52 and 0.37 for those that took over one cup a day (Ren et al., 2010). The results showed consistency with the findings of Southern Brazil which reported a 69% decrease of the risk of pharyngeal cancer in hot tea drinkers over the non-drinkers (Pintos et al., 1994). However, a case study conducted in India showed opposite results (Notani and Jayant, 1987). An increase in the risk for pharyngeal cancer was observed for individuals who drank over 3–5 cups per day in contrast to the ones consuming 2 or less cups of hot tea in a day (Vecchia et al., 1992; Mashberg et al., 1993; Tavani et al., 2003; La Ide et al., 2007). Other studies conducted prove that there is no link between consumption of hot tea and pharyngeal, oral cavity tumors or the remaining 5 upper gastrointestinal cancer sites (Ren et al., 2010).

Tea's effect for prevention of cancer has been researched a lot in the past few years (Yang et al., 2008). The tea PPs are believed to affect a number of carcinogenesis areas, e.g., growth of cancer cells, metastasis and apoptosis (Beltz et al., 2006). However, chronic thermal injuries caused due to drinking beverages that are too hot could lead to carcinogenesis in some of the UGI sites (Castellsague et al., 2000; Islami et al., 2009a; 2009b). Furthermore, on processing black tea, carcinogenesis contaminations may be acquired in form of mycotoxins or BαP (Martins et al., 2001; Lin and Zhu, 2004).

Hot tea was found to affect positively for the oesophageal squamous cell carcinoma (ESCC) risk (Ren et al., 2010). In three other case control studies, green tea was found to protect against oesophageal cancer (Gao et al., 1994; Mu et al., 2003; Wang et al., 2007). On the other hand, intake of green tea was found to be linked to oesophageal cancer in men in two studies (Hara et al., 1984; Ishikawa et al., 2006). A recent case control study in Iran revealed existence of no relation of black tea with ESCC (Islami et al., 2009b). While, a case control hospital based study involving 1248 cases of ESCC and 1248 controls, in China reported an inverse association between Chinese black tea, called Congou tea and the ESCC risk (Ke et al., 2002). Furthermore, after an analysis of 13 epidemiological studies, a noticeable inverse relation was found between consumption of green tea and the risk of stomach cancer (Myung et al., 2009). Recently, a case control study in Italy involving 999 gastric cancer patients and 2628 controls reported an implausible association between black tea consumption and the gastric cancer (Ren et al., 2010).

Islami et al. (2009b) investigated the association between tea drinking habits in Golestan province, northern Iran, and risk of oesophageal squamous cell carcinoma in a population based case-control study. In addition, patterns of tea drinking and temperature at which tea was drunk were measured in a cohort study of healthy participants. The results of the case-control study showed that drinking hot or very hot tea was strongly associated with a higher risk of oesophageal cancer, compared to that of drinking luke warm or warm tea. The interval between tea being poured and drunk was inversely associated with risk of oesophageal squamous cell carcinoma. Similarly, compared with drinking tea 4 or more minutes after being poured, drinking tea 2–3 min or less than 2 min after pouring was associated with a significantly increased risk. A previous study reported a significantly higher tea drinking temperature among seven participants with oesophageal disorders (62°C) than among 50 controls (56°C) (Pearson and McCloy, 1989).

Colorectal Cancer Risk

The association of black tea to colorectal cancer when studied for men and women brought forward certain facts. In women black tea showed a protecting effect on colorectal cancer while mild risk enhancement was noted for men. A few studies and reports have established an association of colorectal carcinogenesis protection with the sex hormones (Sun et al., 2006). A population-based case-control study in Moscow showed an inverse association of tea consumption with rectal cancer in women. In men, no such association was evident due to high levels of alcohol consumption which not only is a risk for the disease but also reduces the protective effect of tea (Il'yasova et al., 2003).

Although the nonhuman in vivo and in vitro studies support the chemo-preventive effect of black and green tea on colorectal carcinogenesis, yet the information from epidemiologic studies is not sufficient to prove the preventive effect of tea on human colorectal cancer (Sun et al., 2006).

Osteomalacia and Alzheimer's Disease Risk

Some studies have revealed the high capacity of tea plant to accumulate aluminum (Al), a neurotoxic element. This aspect is important for the individuals with renal failure because accumulation of Al by the body can result in neurological diseases**;** therefore it is necessary to control the intake of food with high amounts of this metal. Studies have found concentrations of Al (which is naturally taken up from soil) in green and black teas (as infusions) that range from 14–27 μg/L to 431–2239 μg/L. One study reported that black tea contains approximately six-fold more Al than green tea, and the extraction of Al in black teas was higher than in the green teas; the Al concentrations in the tea infusions remained constant after 5 min of extraction. The variations in Al content may be due to different soil

conditions, different harvesting periods, and the influence of the water quality. The possible connection between elevated tissue Al content and problems such as osteomalacia and neurodegenerative disorders (i.e., Alzheimer's disease) has enlightened interest in Al intake via diet. Several studies reported that in order to avoid potentially toxic levels Al dietary intake must not exceed 6 mg/day. Several authors consider that Al is poorly absorbed by the body, so future studies are necessary to accurately assess the presence and bioavailability of Al in green tea leaves (Cabrera et al., 2006).

Parkinson's Disease Risk

PD may be attributed to the complex interactions of both genetic and environmental factors. Studies regarding the association of caffeine-containing beverage such as tea and PD risk show conflicting results. Tea consumption was shown to be a risk factor for PD in a case-control study in France. Contrastingly, a cohort study in Singapore Chinese Health study showed an inverse relation of black tea with PD risk but this association was independent of caffeine intake; other components of black tea accounted for this protective effect. Green tea, however, didn't show any effect (Tanaka et al., 2011).

CONCLUSION AND FUTURE DIRECTIONS

According to the recent research in last 30 years, tea has been identified as a Nature's reward for promoting human health. There is a continuous increase in the amount of experimental evidence filing the properties of tea and its constituents. Subsequently, both endogenous and exogenous factors that influence the incidence and development of many chronic diseases are being defined and understood in a better way. Evidence shows that the tea is a source of a large variety of phytochemicals that are digested, absorbed, and metabolized by the body, and that the effects of tea constituents are exerted at the cellular level. Status of tea as a functional food provides credibility to the beliefs of tea drinkers for centuries.

Debate still persists to conclude that whether tea is beneficial or somewhat troublesome for human health. Because of its widespread and long use, it is considered to be safe and effective against various cancers, CVDs as well as diabetes mellitus. Nevertheless, several cases of hepatotoxicity, neurodegenerative disorders, and other adverse effects following the consumption of large amounts or concentrated preparations of *C. sinensis* have been reported.

Future research needs to outline the actual extent of health benefits, ascertain the secure range of tea consumption associated with these benefits and clarify probable mechanisms of action. New experimental systems must be developed in order to further evaluate the effects of tea on humans. Development of methods that are more specific and sensitive with more models of representation together with the development of good predictive biomarkers will enable a better understanding of the interaction of tea with endogenous systems and other exogenous factors. Being one of the most popular beverages worldwide, further studies on tea regarding the assessment of its consumption and PP status should be directed to enumerate its role in the primary and secondary prevention of chronic diseases.

REFERENCES

Abeywickramaa, K., Ratnasooriya, W. and Amarakoon, A. (2011). Oral hypoglycaemic, antihyperglycaemic and antidiabetic activities of Sri Lankan Broken Orange Pekoe Fannings (BOPF) grade black tea (*Camellia sinensis* L.) in rats. *J. Ethnopharmacol.* **135**:278–286.

Adak, M. and Gabar, M. (2011). Green tea as a functional food for better health: A brief review. *Res. J. Pharmaceut., Biol. Chem. Sci.* **2**:645–664.

Adhikary, B., Yadav, S., Roy, K., Bandyopadhyay, S. and Chattopadhyay, S. (2011). Black tea and theaflavins assist healing of indomethacin-induced gastric ulceration in mice by antioxidative action. *Evid. Based Complemen. Alternat. Med.* **2011**:11.

Alexis, A., Jones, V. and Stiller, M. (1999). Potential therapeutic applications of tea in dermatology. *Int. J. Dermatol.* **38**:735–743.

Alexopoulos, N., Vlachopoulos, C., Aznaouridis, K., Baou, K., Vasiliadou, C., Pietri, P., Xaplanteris, P., Stefanadi, E. and Stefanadis, C. (2008). The acute effect of green tea consumption on endothelial function in healthy individuals. *J. Cardiovascul. Risk.* **15**:300–305.

Arab, L., Liu, W. and Elashoff, D. (2009). Green and black tea consumption and risk of stroke: A meta-analysis. *Stroke.* **40**:1786–1792.

Bahoruna, T., Luximon-Ramma, A., Gunness, T., Sookar, D., Bhoyroo, S., Jugessur, R., Reebye, D., Googoolye, K., Crozier, A. and Aruoma, O. (2010). Black tea reduces uric acid and C-reactive protein levels in humans susceptible to cardiovascular diseases. *Toxicology.* **278**:68–74.

Bandyopadhyay, D., Chatterjee, T., Dasgupta, A., Lourduraja, J. and Dastidar, S. (2005). In vitro and in vivo antimicrobial action of tea: The commonest beverage of Asia. *Biol. Pharm. Bull.* **28**:2125–2127.

Banerjee, S., Manna, S., Saha, P., Panda, C. and Das, S. (2005). Black tea polyphenols suppress cell proliferation and induce apoptosis during benzo(a)pyrene-induced lung carcinogenesis. *Eur. J. Cancer Prev.* **14**:215–221.

Beltz, L., Bayer, D., Moss, A. and Simet, I. (2006). Mechanisms of cancer prevention by green and black tea polyphenols. *Anticancer Agents Med. Chem.* **6**:389–406.

Bonkovsky, H. (2006). Hepatotoxicity associated with supplements containing Chinese green tea (*Camellia sinensis*). *Ann. Intern. Med.* **144**:68–71.

Butt, S. and Sultan, M. (2009). Green tea: Nature's defense against malignancies. *Cri. Rev. Food Sci. Nutr.* **49**:463–473.

Cabrera, C., Artacho, R. and Giménez, R. (2006). Beneficial effects of green tea - A review. *J. Am. College Nutr.* **25**:79–99.

Cao, J., Bai, X., Zhao, Y., Liu, J., Zhou, D., Fang, S., Jia, M. and Wu, J. (1996). The relationship of fluorosis and brick tea drinking in Chinese Tibetans. *Environ. Health Persp.* **104**:1340–1343.

Castellsague, X., Munoz, N., De Stefani, E., Victora, C., Castelletto, R. and Rolón, P. (2000). Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. *Int. J. Cancer.* **88**:658–664.

Chen, Z., Petinger, M., Ritenbaugh, C., LaCroix, A., Robbins, J. and Caan, B. (2003). Habitual tea consumption and risk of osteoporosis: A prospective study in the Women's Health Initiative Observational Cohort. *Am. J. Epidemiol.* **158**:772–781.

Chow, H., Cai, Y., Hakim, I., Crowell, J., Shahi, F., Brooks, C., Dorr, R., Hara, Y. and Alberts, D. (2003). Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clin. Cancer Res.* **9**:3312–3319.

Chow, H., Hakim, I., Vining, D., Crowell, J., Ranger-Moore, J., Chew, W., Celaya, C., Rodney, S., Hara, Y. and Alberts, D. (2005). Effects of dosing

condition on the oral bioavailability of green tea catechins after single-dose administration of polyphenon E in healthy individuals. *Clin. Cancer Res.* **11**:4627–4633.

Conney, A., Lu, Y., Lou, Y., Xie, J. and Huang, M. (1999). Inhibitory effect of green and black tea on tumor growth. *Proc. Soc. Exp. Biol. Med.* **220**:229–233.

Das, D., Mukherjee, S., Das, A., Mukherjee, M. and Mitra, C. (2006). Aqueous extract of black tea (*Camellia sinensis*) prevents ethanol + cholecystokinin-induced pancreatitis in a rat model. *Life Sci.* **78**:2194–2203.

Debette, S., Courbon, D., Leone, N., Gariepy, J., Tzourio, C., Dartigues, J., Barberger-Gateau, P., Ritchie, K., Alperovitch, A., Amouyel, P., Ducimetiere, P. and Zureik, M. (2008). Tea consumption is inversely associated with carotid plaques in women. *Arteriosclerosis, Thromb. Vas. Biol.* **28**:353–359.

Erba, D., Riso, P., Bordoni, A., Foti, P., Biagi, P. and Testolin, G. (2005). Effectiveness of moderate green tea consumption on antioxidative status and plasma lipid profile in humans. *J. Nutr. Biochem.* **16**:144–149.

Fung, K., Zhang, Z., Wong, J. and Wong, M. (1999). Fluoride contents in tea and soil from tea plantations and the release of fluoride into tea liquor during infusion. *Environ. Pollut.* **104**:197–205.

Galati, G., Lin, A., Sultan, A. and O'Brien, P. (2006). Cellular and in vivo hepatotoxicity caused by green tea phenolic acids and catechins. *Free Radical Biol. Med.* **40**:570–580.

Gao, Y., McLaughlin, J., Blot, W., Ji, B., Dai, Q. and Fraumeni, J. (1994). Reduced risk of esophageal cancer associated with green tea consumption. *J. Nat. Cancer Inst.* **86**:855–858.

Gardner, E., Ruxton, C. and Leeds, A. (2007). Black tea - helpful or harmful? A review of the evidence. *Eur. J. Clin. Nutr.* **61**:3–18.

Gulati, P., Singh, V., Gupta, M., Vaidya, V., Dass, S. and Prakash, S. (1993). Studies on the leaching of fluoride in tea infusions. *Sci. Total Environ.* **138**:213–222.

Gupta, S., Saha, B. and Giri, A. (2002). Comparative antimutagenic and anticlastogenic effects of green tea and black tea: A review. *Mutat. Res.* **512**:97–65.

Hara, N., Sakata, K., Nagai, M., Fujita, Y., Hashimoto, T. and Yanagawa, H. (1984). Statistical analyses on the pattern of food consumption and digestive-tract cancers in Japan. *Nutr. Cancer.* **6**:220–228.

Hawkey, C. (1990). Non-steroidal anti-inflammatory drugs and peptic ulcers. Facts and figures multiply, but do they add up? *Brit. Med. J.* **300**:278–284.

Hegarty, V., May, H. and Khaw, K. (2000). Tea drinking and bone mineral density in older women. *Am. J. Clin. Nutr.* **71**:1003–1007.

Higdon, J. and Frei, B. (2006). Coffee and health: A review of recent human research. *Cri. Rev. Food Sci. Nutr.* **46**:101–123.

Hodgson, J. and Croft, K. (2006). Dietary flavonoids: Effects on endothelial function and blood pressure. *J. Sci. Food Agr.* **86**:2492–2498.

Huang, Y., Liu, Y., Dushenkov, S., Ho, C. and Huang, M. (2009). Anti-obesity effects of epigallocatechin-3-gallate, orange peel extract, black tea extract, caffeine and their combinations in a mouse model. *J. Funct. Foods.* **1**:304–310.

Ide, R., Fujino, Y., Hoshiyama, Y., Mizoue, T., Kubo, T., Pham, T., Shirane, K., Tokui, N., Sakata, K., Tamakoshi, A. and Yoshimura, T. (2007). A prospective study of green tea consumption and oral cancer incidence in Japan. *Ann. Epidemiol.* **17**:821–826.

Il'yasova, D., Arab, L., Martinchik, A., Sdvizhkov, A., Banovich, L. and Weisgerber, U. (2003). Black tea consumption and risk of rectal cancer in Moscow population. *Ann. Epidemiol.* **13**:405–411.

Isbrucker, R., Edwards, J., Wolz, E., Davidovich, A. and Bausch, J. (2006). Safety studies on epigallocatechin gallate (EGCG) preparations. Part 2: Dermal, acute and short-term toxicity studies. *Food Chem. Toxicol.* **44**:636–650.

Ishikawa, A., Kuriyama, S., Tsubono, Y., Fukao, A., Takahashi, H., Tachiya, H. and Tsuji, I. (2006). Smoking, alcohol drinking, green tea consumption and the risk of esophageal cancer in Japanese men. *J. Epidemiol.* **16**:185–192.

Islami, F., Boffetta, P., Ren, J., Pedoeim, L., Khatib, D. and Kamangar, F. (2009a). High-temperature beverages and foods and esophageal cancer risk-A systematic review. *Int. J. Cancer.* **125**:491–524.

Islami, F., Pourshams, A., Nasrollahzadeh, D., Kamangar, F., Fahimi, S., Shakeri, R., Abedi-Ardekani, B., Merat, S., Vahedi, H., Semnani, S., Abnet, C., Brennan, P., Møller, H., Saidi, F., Dawsey, S., Malekzadeh, R. and Boffetta, P. (2009b). Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: Population based case-control study. *Brit. Med. J.* **338**:929.

Jochmann, N., Lorenz, M., Krosigk, A., Martus, P., Böhm, V., Baumann, G., Stangl, K. and Stangl, V. (2008). The efficacy of black tea in ameliorating endothelial function is equivalent to that of green tea. *Brit. J. Nutr.* **99**:863–868.

Johnell, O., Gullberg, B., Kanis, J., Allander, E., Elffors, L., Dequeker, J., Dilsen, G., Gennari, C., Vaz, L., Lyritis, G., Mazzuoli, G., Miravet, L., Passeri, M., Cano, P., Rapado, A. and Ribot, C. (1995). Risk factors for hip fracture in European women: The MEDOS study. *J. Bone Mineral Res.* **10**:1802–1815.

Juneja, L., Chu, D., Okubo, T., Nagato, Y. and Yokogoshi, H. (1999). L-theanine—A unique amino acid of green tea and its relaxation effect in humans. *Trend. Food Sci. Technol.* **10**:199–204.

Kanis, J., Johnell, O., Gullberg, B., Allander, E., Elffors, L., Ranstam, J., Dequeker, J., Dilsen, G., Gennari, C., Vaz, A., Lyritis, G., Mazzuoli, G., Miravet, L., Passeri, M., Cano, R., Rapado, A. and Ribot, C. (1999). Risk factors for hip fracture in men from Southern Europe: The MEDOS study. Mediterranean Osteoporosis Study. *Osteoporosis Int.* **9**:45–54.

Kapetanovic, I., Crowell, J., Krishnaraj, R., Zakharov, A., Lindeblad, M. and Lyubimov, A. (2009). Exposure and toxicity of green tea polyphenols in fasted and non-fasted dogs. *Toxicology.* **260**:28–36.

Katiyar, S., Elmets, C. and Katiyar, S. (2007). Green tea and skin cancer: Photoimmunology, angiogenesis and DNA repair. *J. Nutr. Biochem.* **18**:287–296.

Kavcar, P., Odabasi, M., Kitis, M., Inal, F. and Sofuoglu, S. (2006). Occurrence, oral exposure and risk assessment of volatile organic compounds in drinking water for Izmir. *Water Res.* **40**:3219–3230.

Ke, L., Yu, P., Zhang, Z., Huang, S., Huang, G. and Ma, X. (2002). Congou tea drinking and oesophageal cancer in South China. *Brit. J. Cancer.* **86**:346–347.

Khan, N. and Mukhtar, H. (2007). Tea polyphenols for health promotion. *Life Sci.* **81**:519–533.

Kim, H., Rajaiah, R., Wu, Q., Satpute, S., Tan, M., Simon, J., Berman, B. and Moudgil, K. (2008). Green tea protects rats against autoimmune arthritis by modulating disease-related immune events. *J. Nutr.* **138**:2111–2116.

Kondo, K., Kurihara, M., Miyata, N., Suzuki, T. and Toyoda, M. (1999). Scavenging mechanisms of (−)-epigallocatechin gallate and (−)-epicatechin gallate on peroxyl radicals and formation of superoxide during the inhibitory action. *Free Radical Biol. Med.* **27**:855–863.

Kuo, K., Weng, M., Chiang, C., Tsai, Y., Lin-Shiau, S. and Lin, J. (2005). Comparative studies on the hypolipidemic and growth suppressive effects of oolong, black, pu-erh, and green Tea leaves in rats. *J. Agr. Food Chem.* **53**:480–489.

Lambert, J., Kennett, M., Sang, S., Reuhl, K., Ju, J. and Yang, C. (2010). Hepatotoxicity of high oral dose (–)-epigallocatechin-3-gallate in mice. *Food Chem. Toxicol.* **48**:409–416.

Lambert, J., Sang, S. and Yang, C. (2007). Possible controversy over dietary polyphenols: Benefits vs risks. *Chem. Res. Toxicol.* **20**:583–585.

Landau, J., Wang, Z., Yang, G., Ding, W. and Yang, C. (1998). Inhibition of spontaneous formation of lung tumors and rhabdomyosarcomas in A/J mice by black and green tea. *Carcinogenesis.* **19**:501–507.

La Vecchia, C., Negri, E., Franceschi, S., D'Avanzo, B. and Boyle, P. (1992). Tea consumption and cancer risk. *Nutr. Cancer.* **17**:27–31.

Leong, H., Mathur, P. and Greene, G. (2008). Inhibition of mammary tumorigenesis in the C3 (1)/SV40 mouse model by green tea. *Breast Cancer Res. Treatment.* **107**:359–369.

Leung, L., Su, Y., Chen, R., Zhang, Z., Huang, Y. and Chen, Z.-Y. (2001). Theaflavins in black tea and catechins in green tea are equally effective antioxidants. *J. Nutr.,* **131**:2248–2251.

Lin, J. and Lin-Shiau, S. (2006). Mechanisms of hypolipidemic and anti-obesity effects of tea and tea polyphenols. *Mol. Nutr. Food Res.* **50**:211–217.

Lin, D., Tu, Y. and Zhu, L. (2005). Concentrations and health risk of polycyclic aromatic hydrocarbons in tea. *Food Chem. Toxicol.* **43**:41–48.

Lin, D. and Zhu, L. (2004). Polycyclic aromatic hydrocarbons: Pollution and source analysis of a black tea. *J. Agr. Food Chem.* **52**:8268–8271.

Loke, W., Hodgson, J., Proudfoot, J., McKinley, A., Puddey, I. and Croft, K. (2008). Pure dietary flavonoids quercetin and (–)-epicatechin augment nitric

oxide products and reduce endothelin-1 acutely in healthy men. *Am. J. Clin. Nutr.* **88**:1018–1025.

Loke, W., Proudfoot, J., Hodgson, J., McKinley, A., Hime, N., Magat, M., Stocker, R. and Croft, K. (2010). Specific dietary polyphones attenuate atherosclerosis in Apolipoprotein E knockout mice by alleviating inflammation and endothelial dysfunction. *Arteriosclerosis, Thromb. Vasc. Biol.* **30**:749–757.

Lu, Y., Lou, Y., Xie, J., Yen, P., Huang, M. and Conney, A. (1997). Inhibitory effect of black tea on the growth of established skin tumors in mice: Effects on tumor size, apoptosis, mitosis and bromodeoxyuridine incorporation into DNA. *Carcinogenesis.* **18**:2163–2169.

Lung, S., Hsiao, P. and Chiang, K. (2003). Fluoride concentrations in three types of commercially packed tea drinks in Taiwan. *J. Exposure Anal. Environ. Epidemiol.* **13**:66–73.

Lyn-cook, B., Rogers, T., Yan, Y., Blann, E., Kadlubar, F. and Hammons, G. (1999). Chemopreventive effects of tea extracts and various components on human pancreatic and prostate tumor cells in vitro. *Nutr. Cancer.* **35**:80–86.

Martins, M., Martins, H. and Bernardo, F. (2001). Fumonisins B1 and B2 in black tea and medicinal plants. *J. Food Prot.* **64**:1268–1270.

Mashberg, A., Boffetta, P., Winkelman, R. and Garfinkel, L. (1993). Tobacco smoking, alcohol drinking, and cancer of the oral cavity and oropharynx among US veterans. *Cancer.* **72**:1369–1375.

Mazzanti, G., Menniti-Ippolito, F., Moro, P., Cassetti, F., Raschetti, R., Santuccio, C. and Mastrangelo, S. (2009). Hepatotoxicity from green tea: A review of the literature and two unpublished cases. *Eur. J. Clin. Pharmacol.* **65**:331–341.

Molinari, M., Watt, K., Kruszyna, T., Nelson, R., Walsh, M., Huang, W., Nashan, B. and Peltekian, K. (2006). Acute liver failure induced by green tea extracts: Case report and review of the literature. *Liver Transplant.* **12**:1892–1895.

Moore, R., Jackson, K. and Minihane, A. (2009). Green tea (*Camellia sinensis*) catechins and vascular function. *Brit. J. Nutr.* **102**:1790–1802.

Mukhtar, H. and Ahmad, N. (2000). Tea polyphenols: Prevention of cancer and optimizing health. *Am. J. Clin. Nutr.* **71**:1698S–1702S.

Murase, T., Nagasawa, A., Suzuki, J., Hase, T. and Tokimitsu, I. (2002). Beneficial effects of tea catechins on diet-induced obesity: Stimulation of lipid catabolism in the liver. *Int. J. Obes. Relat. Metab. Disord.* **26**:1459–1464.

Mursu, J., Nurmi, T., Tuomainen, T., Ruusunen, A., Salonen, J. and Voutilainen, S. (2007). The intake of flavonoids and carotid atherosclerosis: The Kuopio ischaemic heart disease risk factor study. *Brit. J. Nutr.* **98**:814–818.

Mu, L., Zhou, X., Ding, B., Wang, R., Zhang, Z., Chen, C., Wei, G., Zhou, X., Jiang, Q. and Yu, S. (2003). A case-control study on drinking green tea and decreasing risk of cancers in the alimentary canal among cigarette smokers and alcohol drinkers. *Zhonghua Liu Xing Bing Xue Za Zhi.* **24**:192–195.

Myung, S., Bae, W., Oh, S., Kim, Y., Ju, W., Sung, J., Lee, Y., Ko, J., Song, J. and Choi, H. (2009). Green tea consumption and risk of stomach cancer: A meta-analysis of epidemiologic studies. *Int. J. Cancer.* **124**:670–677.

Naldi, L., Gallus, S., Tavani, A., Imberti, G. and La Vecchia, C. (2004). Risk of melanoma and vitamin A, coffee and alcohol: A case-control study from Italy. *Eur. J. Cancer Prev.* **13**:503–508.

Nance, C. and Shearer, W. (2003). Is green tea good for HIV-1 infection? *J. Allergy Clin. Immunol.* **112**:851–853.

Negishi, H., Xu, J., Ikeda, K., Njelekela, M., Nara, Y. and Yamory, Y. (2004). Black and green tea polyphenols attenuate blood pressure increases in stroke-prone spontaneously hypertensive rats. *J. Nutr.* **134**:38–42.

Nelson, M. and Poulter, J. (2004). Impact of tea drinking on iron status in the UK: A review. *J. Human Nutr. Diet.* **17**:43–54.

Niu, K., Hozawa, A., Kuriyama, S., Ebihara, S., Guo, H., Nakaya, N., Ohmori-Matsuda, K., Takahashi, H., Masamune, Y., Asada, M., Sasaki, S., Arai, H., Awata, S., Nagatomi, R. and Tsuji, I. (2009). Green tea consumption is associated with depressive symptoms in the elderly. *Am. J. Clin. Nutr.* **90**:1615–1622.

Nookabkaew, S., Rangkadilok, N. and Satayavidad, J. (2006). Determination of trace elements in herbal tea products and their infusions consumed in Thailand. *J. Agr. Food Chem.* **54**:6939–6944.

Notani, P. and Jayant, K. (1987). Role of diet in upper aerodigestive tract cancers. *Nutr. Cancer.* **10**:103–113.

Panagiotakos, D., Lionis, C., Zeimbekis, A., Gelastopoulou, K., Papairakleous, N., Das, U. and Polychronopoulos, E. (2009). Long-term tea intake is associated with reduced prevalence of (type 2) diabetes mellitus among elderly people from Mediterranean islands: MEDIS epidemiological study. *Yonsei Med. J.* **50**:31–38.

Parkin, D., Bray, F., Ferlay, J. and Pisani, P. (2005). Global cancer statistics, 2002. *CA-A Cancer J. Clin.* **55**:74–108.

Pearson, R. and McCloy, R. (1989). Preference for hot drinks is associated with peptic disease. *Gut.* **30**:1201–1205.

Pintos, J., Franco, E., Oliveira, B., Kowalski, L., Curado, M. and Dewar, R. (1994). Mate, coffee, and tea consumption and risk of cancers of the upper aerodigestive tract in southern Brazil. *Epidemiology.* **5**:583–590.

Prystai, E., Kies, C. and Driskell, J. (1999). Calcium, copper, iron, magnesium and zinc utilization of humans as affected by consumption of black, decaffeinated black and green teas. *Nutr. Res.* **19**:167–177.

Ramaa, C., Shirode, A., Mundada, A. and Kadam, V. (2006). Nutraceuticals an emerging era in the treatment and prevention of cardiovascular diseases. *Curr. Pharm. Biotechnol.* **7**:15–23.

Ravindranath, M., Saravanan, T., Monteclaro, C., Presser, N., Ye, X., Selvan, S. and Brosman, S. (2006). Epicatechins purified from green tea (*Camellia sinensis*) differentially suppress growth of gender-dependent human cancer cell lines. *Evid. Based Complement. Altern. Med.* **3**:237–247.

Ren, J., Freedman, N., Kamangar, F., Dawsey, S., Hollenbeck, A., Schatzkin, A. and Abnet, C. (2010). Tea, coffee, carbonated soft drinks and upper gastrointestinal tract cancer risk in a large United States prospective cohort study. *Eur. J. Cancer.* **46**:1873–1881.

Ripple, M., Henry, W., Rago, R. and Wilding, G. (1997) Prooxidant–antioxidant shift induced by androgen treatment of human prostate carcinoma cells. *J. Natl. Cancer Inst.* **89**:40–48.

Roberts, B. and Shorter, J. (2008). Escaping amyloid fate. *Nat. Struct. Molecular Biol.* **15**:544–546.

Ross, J., Potter, J. and Robison, L. (1994). Infant leukemia, topoisomerase II inhibitors, and the MLL gene. *J. Natl Cancer Inst.* **86**:1678–1680.

Sartippour, M., Pietras, R., Marquez-Garban, D., Chen, H., Heber, D., Henning, S., Sartippour, G., Zhang, L., Lu, M., Weinberg, O., Rao, J. and Brooks, M.N. (2006). The combination of green tea and tamoxifen is effective against breast cancer. *Carcinogenesis.* **27**:2424–2433.

Schönthal, A. (2011). Adverse effects of concentrated green tea extracts. *Mol. Nutr. Food Res.* **55**:874–885.

Shankar, S., Ganapathy, S. and Srivastava, R. (2007). Green tea polyphenols, biology and therapeutic implications in cancer. *Front Bioscience.* **1**:4881–4899.

Sharangi, A. (2009). Medicinal and therapeutic potentialities of tea (*Camellia sinensis* L.). *Food Res. Int.* **42**:529–535.

Shim, J., Kang, M., Kim, Y., Roberts, C. and Lee, I. (1995). Chemopreventive effect of green tea (*Camellia sinensis*) among cigarette smoke. *Epidemiol. Biomarkers Prev.* **4**:387–391.

Shirai, T., Sato, A. and Hara, Y. (1994). Epigallocatechin gallate. The major causative agent of green tea-induced asthma. *Chest.* **106**:1801–1805.

Siddiqui, I., Raisuddin, S. and Shukla, Y. (2005). Protective effects of black tea extract on testosterone induced oxidative damage in prostate. *Cancer Lett.* **227**:125–132.

Smart, D., Ortiz, K., Mattson, D., Bradbury, C., Bisht, K., Sieck, L., Brechbiel, M. and Gius, D. (2004). Thioredoxin reductase as a potential molecular target for anticancer agents that induce oxidative stress. *Cancer Res.* **64**:6716–6724.

Sofuoglu, S. and Kavcar, P. (2008). An exposure and risk assessment for fluoride and trace metals in black tea. *J. Hazard. Mater.* **158**:392–400.

Steptoe, A., Gibson, E., Vuononvirta, R., Hamer, M., Wardle, J., Rycroft, J., Martin, J. and Erusalimsky, J. (2007). The effects of chronic tea intake on platelet activation and inflammation: A double-blind placebo controlled trial. *Atherosclerosis.* **193**:277–282.

Sun, Y. (1990). Free radicals, antioxidant enzymes and carcinogenesis. *Free Radical Biol. Med.* **8**:583–599.

Sun, C., Yuan, J., Koh, W. and Yu, M. (2006). Green tea, black tea and colorectal cancer risk: A meta-analysis of epidemiologic studies. *Carcinogenesis.* **27**:1301–1309.

Tanaka, K., Miyake, Y., Fukushima, W., Sasaki, S., Kiyohara, C., Tsuboi, Y., Yamada, T., Oeda, T., Miki, T., Kawamura, N., Sakae, N., Fukuyama, H., Hirota, Y., Nagai, M. and Group, F. K. P. s. D. S. (2011). Intake of Japanese and Chinese teas reduces risk of Parkinson's disease. *Parkinsonism Related Disorders.* **17**:446–450.

Tatti, S., Swinehart, J., Thielert, C., Tawfik, H., Mescheder, A. and Beutner, K. (2008). Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: A randomized controlled trial. *Obstet. Gynecol.* **111**:1371–1379.

Tavani, A., Bertuzzi, M., Talamini, R., Gallus, S., Parpinel, M., Franceschi, S., Levi, F. and La Vecchia, C. (2003). Coffee and tea intake and risk of oral, pharyngeal and esophageal cancer. *Oral Oncol.* **39**:695–700.

Taylor, J. and Wilt, V. (1999). Probable antagonism of warfarin by green tea. *Ann. Pharm.* **33**:426–428.

Toyoda, M., Tanaka, K., Hoshino, K., Akiyama, H., Tanimura, A. and Saito, Y. (1997). Profiles of potentially antiallergic flavonoids in 27 kinds of health tea and green tea infusions. *J. Agr. Food Chem.* **45**:2561–2564.

Vasisht, K., Sharma, P., Karan, M., Rakesh, D., Vyas, S., Sethi, S. and Manktala, R. (2003). Study to Promote the Industrial Exploitation of Green Tea Polyphenols in India. International Centre for Science and High Technology—United Nations Industrial Development Organization, Italy.

Wang, J., Xu, B., Rao, J., Shen, H., Xue, H. and Jiang, Q. (2007). Diet habits, alcohol drinking, tobacco smoking, green tea drinking, and the risk of esophageal squamous cell carcinoma in the Chinese population. *Eur. J. Gastroen. Hepatol.* **19**:171–176.

Wang, D., Xu, K., Zhong, Y., Luo, X., Xiao, R., Hou, Y., Bao, W., Yang, W., Yan, H., Yao, P. and Liu, L. (2011). Acute and subchronic oral toxicities of Pu-erh black tea extract in Sprague-Dawley rats. *J. Ethnopharmacol.* **134**:156–164.

Weisburger, J. (1999). Tea and health: The underlying mechanisms. *Proc. Soc. Exp. Biol. Med.* **220**:271–275.

Wei, S., Xu, H., Xiong, X., Luo, Z., Audibert, F. and Fraser, W. (2009). Tea consumption during pregnancy and the risk of pre-eclampsia. *Int. J. Gynecol.Obst.* **105**:123–126.

Whyte, M., Essmyer, K., Gannon, F. and Reinus, W. (2005). Skeletal fluorosis and instant tea. *Am. J. Med.* **118**:78–82.

Widlansky, M., Hamburg, N., Anter, E., Holbrook, M., Kahn, D., Elliott, J., Keaney, J. and Vita, J. (2007). Acute EGCG supplementation reverses endothelial dysfunction in patients with coronary artery disease. *J. Am. College Nutr.* **26**:95–102.

Williamson, M., McCormick, T., Nance, C. and Shearer, W. (2006). Epigallocatechin gallate, the main polyphenol in green tea, binds to the T-cell receptor, CD4: Potential for HIV-1 therapy. *J. Allergy Clin. Immunol.* **118**:1369–1374.

Wong, M., Zhang, Z., Wong, J. and Lan, C. (1998). Trace metal contents (Al, Cu and Zn) of tea: Tea and soil from two plantations, and tea products from different provinces of China. *Environm. Geochem. Health.* **20**:87–94.

Yamamoto, T., Juneja, L., Chu, D. and Kim, M. (1997). Chemistry and Applications of Green Tea. CRC Press, LLC, Boca Raton, USA.

Yang, C., Chung, J., Yang, G., Chhabra, S. and Lee, M. (2000). Tea and tea polyphenols in cancer prevention. *J. Nutr.* **130**:472S–478S.

Yang, C., Ju, J., Lu, G., Xiao, H., Hao, X., Sang, S. and Lambert, J. (2008). Cancer prevention by tea and tea polyphenols. *Asia Pac. J. Clin. Nutr.* **17**:245–248.

Yang, Y., Lu, F., Wu, J., Wu, C. and Chang, C. (2004). The protective effect of habitual tea consumption on hypertension. *Arch. Internal Med.* **164**:1534–1540.

Yang, G., Wang, Z., Kim, S., Liao, J., Seril, D., Chen, X., Smith, T. and Yang, C. (1997). Characterization of early pulmonary hyperproliferation, tumor progression and their inhibition by black tea in a 4-(methylnitrosamino)-1-(3-pyridyl)-1 butanone (NNK)-induced lung tumorigenesis model with A/J mice. *Cancer Res.* **57**:1889–1894.

Zheng, G., Sayama, K., Okubo, T., Juneja, L. and Oguni, I. (2004). Anti-obesity effects of three major components of green tea, catechins, caffeine and theanine in mice. *In Vivo.* **18**:55–62.

Zhong, L., Goldberg, M., Gao, Y., Hanley, J., Parent, M. and Jin, F. (2001). A population-based case-control study of lung cancer and green tea consumption among women living in Shanghai, China. *Epidemeology.* **12**:695–700.