Green Tea [*Camellia sinensis*]: A Gateway to Health and Longevity

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ABSTRACT

Tea is the most consumed drink in the world after water. Since ancient times, traditional Chinese medicine considers green tea as a healthful beverage. Green tea a 'non-fermented' product contains high level of catechins. Catechins have been found to be strong antioxidants both in vitro and in vivo studies. In addition an adequate presence of minerals and vitamins gives a further philip to the antioxidant potential of green tea. Recent human and animal studies suggest that green tea may contribute to a reduction in the risk of cardiovascular diseases and some forms of cancer, besides contributing towards the promotion of oral health and other physiological functions such as anti-hypertensive effect, body weight control, antibacterial and antiviral activity, solar ultraviolet protection, bone mineral density promotion, anti-fibrotic and neuroprotective effects. Increasing interest in its health benefits has led to the inclusion of green tea in the group of beverages with functional properties. Though research evidence on green tea is very promising, future studies are necessary to fully understand its contributions to human health, so as to make advice for its regular consumption in the diets based on firm grounds.

Keywords: Green Tea, Polyphenols, Catechins, Antioxidant Activity, Human Health, Chronic Diseases

Abbreviations: • EC = [–]-epicatechin • ECG = [–]-epicatechin-3-gallate • EGC = [–]-epigallocatechin • EGCG = [–]-epigallocatechin-3-gallate • GTP = green tea polyphenols • HDL = high density lipoproteins • LDL = low density lipoproteins • GTC= green tea catechins.

INTRODUCTION

"Tea is a miraculous med icine for the maintenance of health. It has an extraordinary power to prolong life". - Eisai *["Father of Tea" in Japan]*

Tea is a popular beverage derived from the plant *Camellia sinensis*, an evergreen shrub of the theaceae family. This plant finds its name in Chinese mythology with Emperor *'Shen Nung'* who discovered it for the first time in 2737 BC *[Mukhtar and Ahmed, 1999]*. The *"Divine Healer"*, as the emperor was called, routinely boiled his drinking water before consuming it, and one day, some leaves from a nearby tree fell into the pot, producing excellent tasting and fragrant beverage. The emperor, upon drinking the concoction, proclaimed the beverage as "heaven sent" and as a result tea was discovered. Tea was introduced in Japan in early 13th century by Buddhist monk, *Eisai*, who acclaimed tea a *"divine remedy and supreme gift of heaven"* for preserving human life.

The various types of teas are prepared from dried leaves of the plant and are generally categorized by their manufacturing process. The three principal varieties of tea include black tea [78%] which is usually consumed in West, green tea [20%] commonly consumed in Asian countries and oolong tea [2%] which is mainly produced in Southern China *[Katiyar and Mukhtar, 1996]*.

The medicinal effect of tea has a long and rich history. The first references to this effect dates back nearly to 5000 years. Regardless of its origin, whether truly divine or not, the ancient Chinese considered tea as a medicine and by 200 B.C., it was purported to have over 200 uses as a cure for various ailments and illnesses. Today it is cultivated in over 300 different countries around the world, with an average per capita intake of 120ml/day. Now its worldwide consumption is second only to water *[Grahm, 1992]*.

Recently it has attracted attention for its health benefits, particularly with respect to its potential for preventing and treating cancer and cardiovascular disease. Increasing scientific and consumer interest in the health benefits of tea has led to the inclusion of tea extracts in oral nutritional supplements and topical preparations *[Higdon and Frei, 2003]*.

PROCESSING, COMPOSITION AND NUTRITIVE VALUE

Green tea is unfermented and is produced when freshly picked leaves are steamed, rolled, dried and fired. Its peculiar green color results from the inactivation of polyphenol oxidase by treating fresh tea leaves with hot steam and air. The other important process is rolling, in which leaves are cut and twisted; it is very similar to the operation as of black tea production. Figure 1 shows the principal difference between green and black tea processing. The firing step at the end of the manufacturing process generates hundreds of volatile compounds which are responsible for the aroma of green tea beverage as shown in Table 1. The final form of green tea depends on the particular variant being produced. Careful manufacturing results in light yellow-green infusion without oxidizing the catechins.

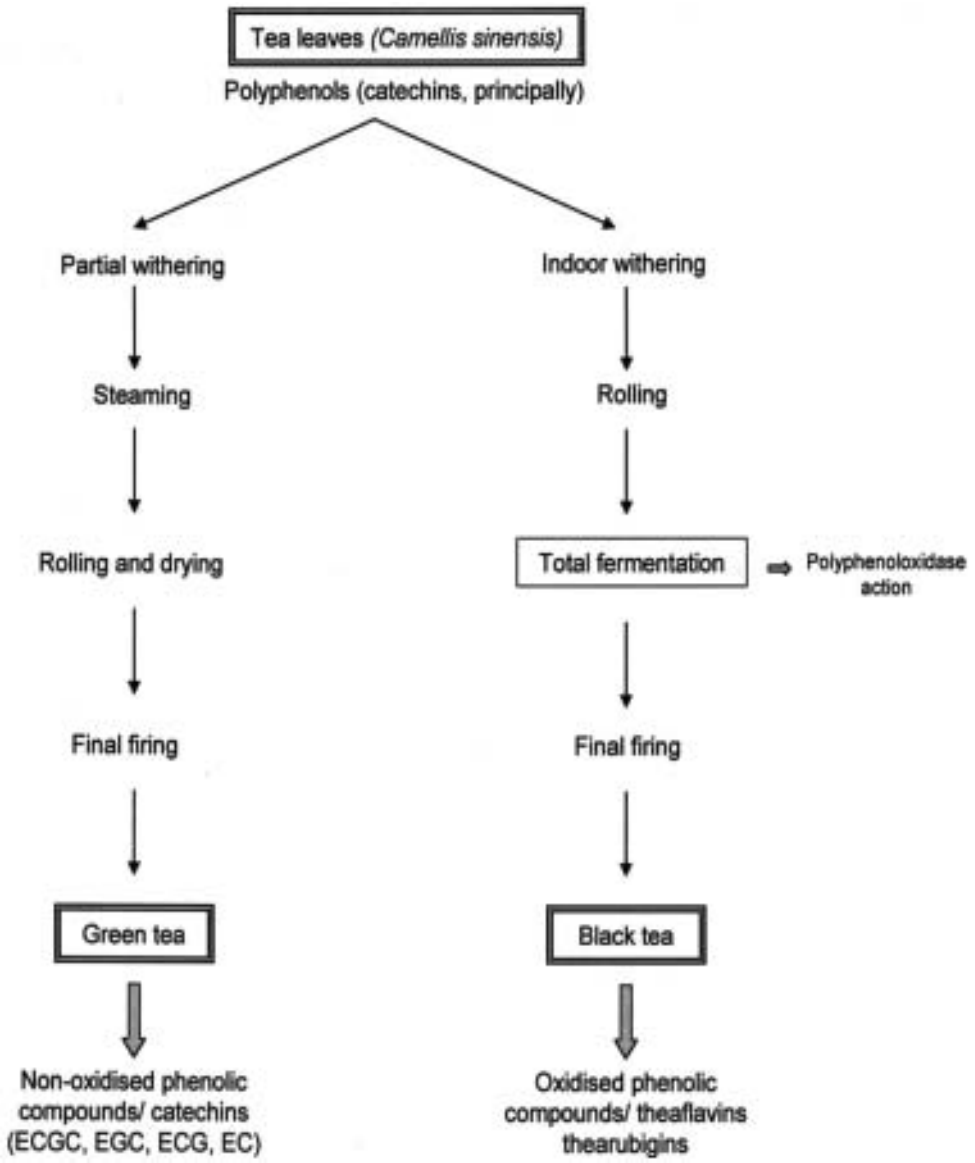


Figure 1: Principal differences between green and black tea processing and its influence on the final polyphenols content.

Table 1: Components of green tea beverage

Components	%
Catechins	30-42
Flavanols	5-10
Other flavanoids	2-4
Theogallin	2-3
Other depsides	1
Ascorbic acid	1-2
Gallic acid	0.5
Quinic acid	2
Other organic acids	4-5
Theanine	4-6
Other amino acids	4-6
Methylxanthines	7-9
Carbohydrates	10-15
Minerals	6-8
Volatiles	0.02

Note: Components measured in wt% of extract solids

Source: Grahm, [1992]

The chemical composition of tea varies slightly with the conditions under which it is grown e.g., climate, season, and local agricultural practices as well as the variety of plant, age of the leaf i.e., the position of the leaf on the harvested shoot and thus, differs very little from that of fresh leaf. It consists of over 2000 different substances of which polyphenols are the most important and include flavanols, flavandiols, flavanoids, phenolic acids. They generally account for up to 30% of the dry weight *[Mukhtar and Ahmed, 2000]*.

Most of the green tea polyphenols are 'Flavon-3-ols' commonly known as *catechins*. They are the pre dominant and most significant group of all the tea components. They account for 6-16% of dry green tea leaves. Catechins are composed of a mixture of [+]-catechin [C] and [+]-gallocatechin [GC] and the corresponding gallate esters of GC [-]-gallocatechin gallate [GCg] as well as their epimers, [-]-epi-catechin [EC] and epi-gallocatechin [EGC] and their corresponding gallate esters [-]-epi-catechin gallate [ECg] and [-]-epi-gallocatechin gallate [EGCg] as shown in Figure 2.

Epicatechins differ from catechins in the spatial orientation of the hydroxyl group on the pyran ring. Gallocatechins are characterized by the presence of three hydroxyl groups on b ring and catechin gallates are gallic acid esters of the hydroxyl group on the pyran ring. Other catechins like, catechin digallate and some methylated catechins have also been reported. Chalcan- flavans- a bimolecular combination of catechins attached to a chalcone derivative has also been identified.

Flavanols occur both in free state and as glycosides of glucose, rhamnose and other sugars. Their structures are analogus to those of flavanols but represent a different state of oxidation. Green tea also contains the flavanols viz. kaempferol, quercetin and myricetin glycosides which are present in very low concentrations *[Beecher et al., 1999]*.

Despides of tea are condensation products of two different hydroxyl acids- chlorogenic and p- coumarylquinic acids. Theogallin is derived from gallic and quinic acids. It may be unique to tea.

Free gallic acid is present in tea leaf and enters into oxidation reactions during the manufacture of black tea. Quinnic acid makes its inclusion through despides.

In addition, there is an unusual amino acid, 'theanine' (N-methylated derivative of glutamine) along with the normal complements of amino acids. It constitutes about one half of the total amino acid content. Its presence varies with the beverage quality.

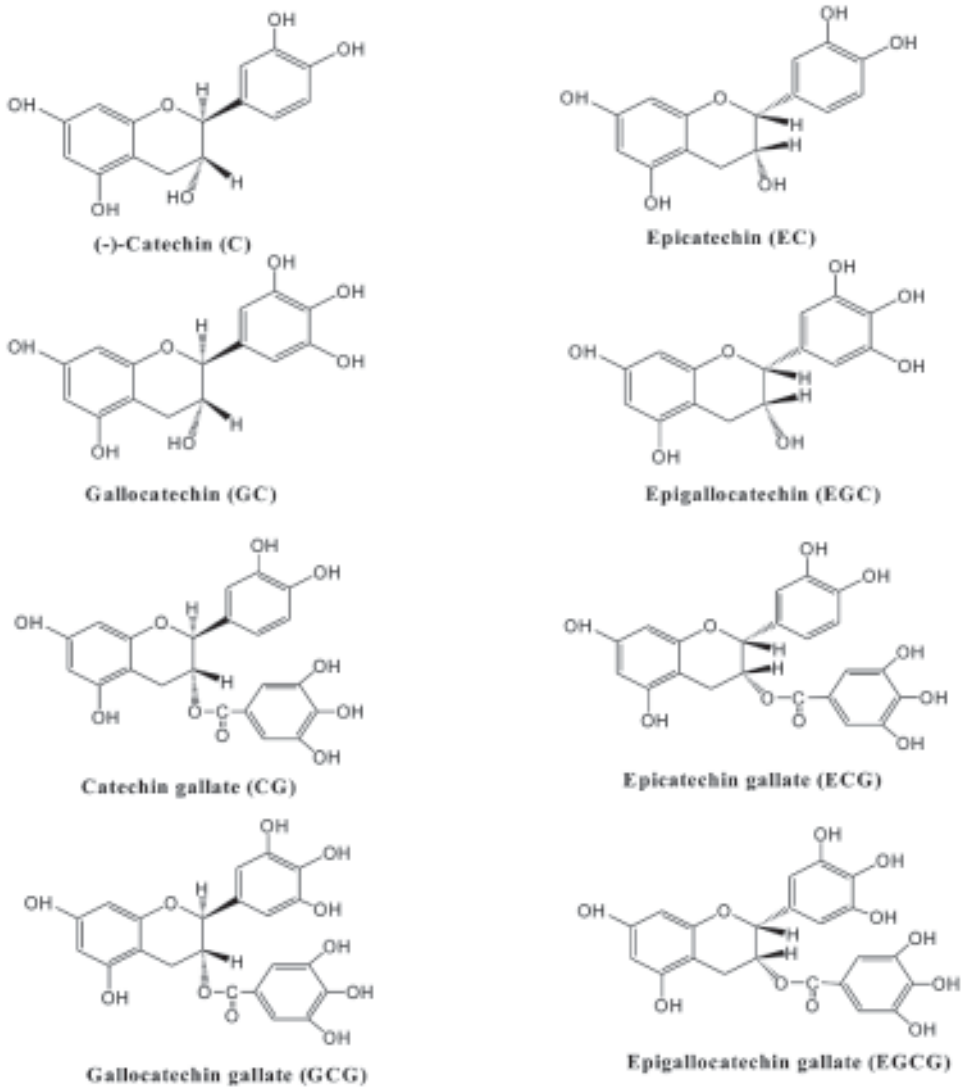


Figure 2: Structures of green tea polyphenols and their epimers

Caffeine is present in moderate amounts (2.5-4.5%) along with small quantities of methyl xanthines, theobromine (0.1%) and theophylline (0.02%).

Trigalloylglucose, a component of green leaf; is a structure that is reminiscent of tannic acid; the latter contains five galloyl groups bonded to the glucose molecule with four or five additional galloyl groups attatched with despide linkages. It is not present in manufactured tea, perhaps because of hydrolysis to the free acid and glucose.

The protein fraction includes various enzymes like, polyphenol oxidase, peroxidase, glucosidases, lipoxidases and methyl xanthine synthesis enzymes. Polyphenol oxidase catalyzes the aerobic oxidation of the catechins. Its activity is greatest in the youngest leaf. Peroxidase has been reported to enter into the pathway of polyphenols oxidation during processing. Glucosidases catalyze the hydrolysis of several aroma precursors, lipoxidases are responsible for the generation of volatile aldehydes.

Carotenoids, like violaxanthine, â-carotene, neoxanthin and lutein are present at low concentration but are important precursors for tea aroma.

The volatile fraction of fresh green tea is extremely small but important in determining the acceptance of the tea beverage. More than 60 volatile components have been identified. These include alcohols, carbonyls, esters, acids and cyclic compounds *[Grahm, 1992]*.

Green tea consumption contributes to the overall daily fluid intake, and if sugar is not added, the calories intake is insignificant; besides, the caffeine intake is lower than in coffee, black tea or cola soft-drinks. In addition, green tea contribution to the dietary intake of antioxidant compounds [catechins and other phytochemical substances] certain vitamins as vitamin C, and minerals as Mn, Cr, Se, Zn, Cu are also present that promotes human health and well being, more than other non-alcoholic beverages that are widely consumed *[Graham, 1992]*. Table 2 summarizes the mean chemical composition of green tea leaves in comparison with black tea leaves and its infusion

Table 2: Mean Composition (%) of green tea and black tea (and its infusion).

Compound	Green tea*	Black tea*	Infusion†
Proteins	15	15	Trace
Aminoacids	4	4	3.5
Fibre	26	26	0
Others carbohydrates	7	7	4
Lipids	7	7	Trace
Pigments	2	2	Trace
Minerals	5	5	4.5
Phenolic compounds‡	30	5	4.5
Oxidised phenolic compounds §	0	25	4.5

** Data refereed to dry weight of tea leaves.*

† Black tea; infusion time: 3 min.

‡ Especially flavonoids.

§ Especially thearubigins and theaflavins.

Source: Belitz and Grosh, [1997].

Tea is considered a rich source of managanese *[Xie et al., 1998; Powell et al., 1998]*. Manganese is a constituent of three metalloenzymes [i.e., arginase, pyruvate carboxylase, and Mn-superoxide dismutase] and it activates a large number of enzymes, such as glycosyl transferases, involved in mucopolysaccharide synthesis. Chromium, selenium and zinc also play an important role in human metabolism, and interest in these elements is increasing since there are reports relating trace element status and oxidative diseases. Chromium is involved in carbohydrate and lipid metabolism; the most frequent sign of Cr deficiency is altered glucose tolerance; this nutrient has been associated with diabetes and cardiovascular diseases *[Mann and Truswell, 1998]*. Selenium functions through selenoproteins, several of which are oxidant defense enzymes; Se acts as enzymatic cofactor of glutathione peroxidase in the elimination of peroxide radicals from the organism. Epidemiological studies have shown the possible effects of Se in the prevention and regression of cancer *[Mann and Truswell, 1998; Shils et al., 1994]*. Zinc enzymes participate in a wide variety of metabolic processes including carbohydrate, lipid, and protein synthesis or degradation. This element is required for deoxyribonucleic and ribonucleic acid synthesis; it may also play a role in stabilizing plasma membranes *[Shils et al., 1994]*. Zinc has been recognized as a cofactor of the superoxide dismutase enzyme, which is involved in protection against oxidative processes *[Mann and Truswell, 1998]*. Copper is required as a cofactor for polyphenol oxidase activity *[Grahm, 1992]*.

Vitamin C content is higher in green tea as compared to black and oolong teas *[Hasegawa et al., 2002]*; the total content of vitamin C in tea leaves decreases during the manufacturing process of fermented teas *[Shimada et al.,1996]*, however bibliographical data on vitamin C content in green tea are scarce. Table 3 shows the mineral content with antioxidant activity in green tea.

Thus green tea can be considered an alternative to other widely consumed drinks, which have a higher content of energy and/or caffeine, and are richer in sugars, alcohol, CO_2, etc. Besides, drinking tea is an optimum way of fighting thirst due to its refreshing properties, its slightly bitter taste, its low binding effect and its fruity and agreeable smell *[Fennema, 2000; Fisher and Scott, 1997]*. Its preparation is easy, uncomplicated and varied [lemon, mint, cinnamon, can be added to it].

Table 3: Antioxidant minerals content in green tea leaves (data referred to dry weight)

Minerals	Content (mean; range)	Class (origin)	Reference
Cr	238.6 ng/g	Sencha (Japan)	Cabrera et al. [22]
	291.0 ng/g	Jasmine (Japan)	Cabrera et al. [22]
	219.8 ng/g	Kokaicha (Japan)	Cabrera et al. [22]
	111.9 ng/g	Bancha (Japan)	Cabrera et al. [22]
	141.7 ng/g	Paimutan (China)	Cabrera et al. [22]
	118.4 ng/g	Gunpower (China)	Cabrera et al. [22]
Mn	699 µg/g (160–1500)	A set of samples (China)	Xie et al. [21]
	1069.7 µg/g	Sencha (Japan)	Fernández-Cáceres et al. [10]
	1021.5 µg/g	Gunpower (China)	Fernández-Cáceres et al. [10]
	714.9 µg/g	Jasmine (China)	Fernández-Cáceres et al. [10]
	500.7 µg/g	Sencha (Japan)	Cabrera et al. [22]
	354.1 µg/g	Jasmine (Japan)	Cabrera et al. [22]
	651.3 µg/g	Kokaicha (Japan)	Cabrera et al. [22]
	987.6 µg/g	Bancha (Japan)	Cabrera et al. [22]
	236.6 µg/g	Paimutan (China)	Cabrera et al. [22]
	518.9 µg/g	Gunpower (China)	Cabrera et al. [22]
Se	0.18 * µg/g (0.03–7.5)	A set of samples (China)	Xie et al. [21]
	455 ± 184 ng/g	"High Se tea" (China)	Yoshida et al. [179]
	92.9 ng/g	Sencha (Japan)	Cabrera et al. [22]
	89.7 ng/g	Jasmine (Japan)	Cabrera et al. [22]
	48.5 ng/g	Kokaicha (Japan)	Cabrera et al. [22]
	80.1 ng/g	Bancha (Japan)	Cabrera et al. [22]
	75.1 ng/g	Paimutan (China)	Cabrera et al. [22]
	70.2 ng/g	Gunpower (China)	Cabrera et al. [22]
Zn	39.4 * µg/g (20–60)	A set of samples (China)	Xie et al. [21]
	24.6 µg/g	Sencha (Japan)	Fernández-Cáceres et al. [10]
	28.4 µg/g	Gunpower (China)	Fernández-Cáceres et al. [10]
	44.3 µg/g	Jasmine (China)	Fernández-Cáceres et al. [10]
	78.1 ng/g	Sencha (Japan)	Cabrera et al. [22]
	78.6 ng/g	Jasmine (Japan)	Cabrera et al. [22]
	76.1 ng/g	Kokaicha (Japan)	Cabrera et al. [22]
	65.0 ng/g	Bancha (Japan)	Cabrera et al. [22]
	75.1 ng/g	Paimutan (China)	Cabrera et al. [22]
	57.5 ng/g	Gunpower (China)	Cabrera et al. [22]

** Geometric mean*

Source: Cabrera et al. [2006]

BIOACTIVE COMPONENTS

Catechins are colourless, astringent and water soluble compounds and their overall level varies with the age of the leaf, tending to be higher in young leaves *[Dreosti, 1996]*. They are readily oxidized, although oxidation potential varies with the type. This property of catechins is being exploited for their use as antioxidants in food. It has been seen that they retard rancidity in fats caused by aerobic oxidation by quenching free radical peroxide activity *[Grahm, 1992]*.

ABSORPTION AND RELATIVE BIO AVAILABILITY

Despite abundant research, little is known about the bioavailability and absorption of catechins from tea beverage. Though overall catechins are highly water soluble and evidence of physiological response in animals

and humans to tea consumption indicate effective uptake of tea polyphenols from intestines yet the quantitative data on the pharmacokinetics of their absorption and distribution in the body is limited *[Dreosti, 1996]*. Likewise, *Okushio et al., [1996]*, reported that following an oral administration of EC, ECG, EGC and EGCG to rats, the four catechins have been identified in portal vein, indicating that tea catechins are absorbed intestinally. In rats given 0.6% green tea polyphenols [GTP] in their drinking water over a period of 28 days, plasma concentrations of EGCG were much lower than those of EGC or EC, even though the ratio of EGCG to EGC was 5:1 in GTP solution. Plasma catechins levels reached their peak values on day 14 but declined to day 1 levels by day 28. When the same GTP preparation was given to mice, plasma levels of EGCG were much higher than those of EGC and EC, suggesting species differences in the bioavailability of EGCG. Plasma catechins levels in mice peaked on day 4 and then decreased to day 1 levels, indicating an adaptive response of plasma catechins ingestion over time in mice and rats *[Kim et al., 2000]*.

Catechin levels in human plasma reach their peak 2 to 4h after ingestion *[Yang et al., 1998; Van Het Hof et al., 1998; Chow et al., 2001]*. After a single dose of green tea or green tea extract, the highest concentrations of individual catechins measured in human plasma were slightly greater than 1ìM *[Yang et al. 1998]*. A recent study in humans compared the pharmacokinetics of equimolar doses of pure EGC, ECG and EGCG in 10 healthy volunteers: average peak plasma concentrations [conjugated plus unconjugated] after a single dose of 1.5mmol were 5.0ìmol/l for EGC, 3.1 ìmol/l for ECG and 1.3 ìmol/l for EGCG. After 24h, plasma EGC and EGCG returned to baseline, but plasma ECG remained elevated *[Higdon and Frei, 2003]*. In humans, ECG has been found to be more methylated than EGC and EGCG, and the latter is less conjugated than EGC and EC *[Chow et al., 2001]*.

Bioavailability studies indicate that GTP can accumulate in the body at concentrations comparable to those employed *in vitro* by several investigators *[Scalabert and Williamson, 2000]*.Among the different catechins present, the bioavailability varies as *Reitveld and Wiseman [2003]*, stated that epigallocatechin-3- gallate behaves differently from epigallocatechin and epicatechin. The bioavailability of EGCG is lower and is mainly excreted through bile *[Moyers et al., 2004]* as EGCG has not been detected in large quantities in human urine suggesting its utilization along with transformation or excretion through other routes such as bile where as EGC and EC are excreted through urine and bile. Furthermore, 80% of catechins are found as conjugates in plasma and urine. However, these conjugates still contain intact catechol and gallate moieties and have been shown to scavenge superoxide dismutase [SOD] with the same efficacy as their parent compounds.

It has been found that tea taken as black tea or by using milk, delivers equally well as catechins absorption is not antagonized by milk *[Van Het Hof et al., 1998]*.

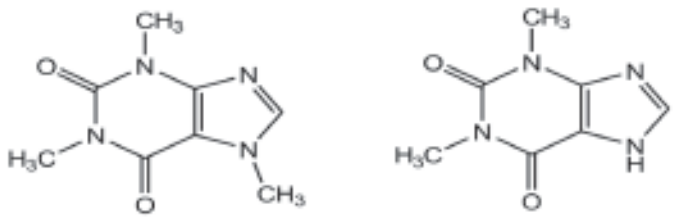
TISSUE DISTRIBUTION

When rats were given 0.6% GTP in their drinking water over a period of 28 days, substantial amounts of EGC and EC were found in the oesophagus, large intestine, kidney bladder, lung and prostate. EGC and EC concentrations were relatively low in liver, spleen, heart and thyroid *[Kim et al., 2000]*. EGCG levels were higher in oesophagus and large intestines, but lower in other organs, likely due to poor systemic absorption of EGCG. Unlike rats, mice given 0.6% GTP in their drinking water for 28 days had higher lung concentrations of EGCG than EGC and comparable liver concentrations of EGCG and EGC, suggesting relatively higher bioavailability of EGCG in mice than rats. Little published data is available on tissue distribution of catechins in humans after tea consumption

GREEN TEA AND HUMAN HEALTH

Green tea has been considered a medicine and a healthful beverage since ancient times. The traditional Chinese medicine has recommended this plant for headaches, body aches and pains, digestion, depression, detoxification, as an energizer and, in general, to prolong life. Green tea leaves contain three main components which act upon human health: xanthic bases [caffeine and theophylline; Figure 3], essential oils and especially, polyphenolic compounds. Caffeine acts mainly upon the central nervous system, stimulating wakefulness, facilitating ideas association and decreasing the sensation of fatigue *[Varnam and Sutherland, 1994]*. Some of the effects caused by caffeine are influenced by theophylline tea content. Theophylline induces psychoactive activity, it also

Figure 3: Chemical Structure of Caffeine and Theophylline



has a slightly inotrope and vasodilator effect, and a much higher diuretic effect than caffeine. However, its most interesting effects can be seen at the bronchopulmonar and respiratory level. Theophylline causes a non-specific relaxation on the bronchial smooth muscle, and respiratory stimulation is also observed. Essential oils are highly volatile and evaporate from the beverage after some time. Among their properties, one of the facilitating digestion must be highlighted *[Wu and Wei, 2002; Bruneton, 2001]*. Green tea has a higher percentage of essential oils *[Varnam and Sutherland, 1994; Bruneton, 2001]*. However, it has received a great deal of attention especially due to its polyphenols content, which is strong antioxidants and have important biological properties. Numerous studies have also demonstrated that the aqueous extract of GTP possesses antimutagenic, antidiabetic, antibacterial, anti-inflammatory, and hypocholesterolemic properties *[Xie et al., 1998; Feng et al.,2001; Amantana et al.,2002; Embola et al., 2002; Kondo et al., 2002; Pan et al., 2003]*. In addition, they also alleviate the toxicity of heavy metal *[Muramatsu et al., 1986]* and regular intake of tea by humans decreases the incidence of mortality from major chronic diseases *[Weisburger, 1999]*. A number of *in vitro* studies suggested that tea flavanoids can modulate a multitude of regulatory pathways that are involved in cell division, proliferation, coagulation, inflammation and immune response. Long back, *Stagg and Millin [1975],* concluded that besides being a pleasant and stimulating beverage it has a therapeutic value in prevention of dental caries, prophylaxis and treatment of vascular and coronary disorders, aids the digestion and body's fluid balance and several beneficial effects on other diseases. In addition, it is an excellent carrier for the medicinal administration of caffeine by eliminating its unpleasant side effects.

ANTI- HYPERTENSIVE EFFECTS

Green tea has long been believed to possess hypotensive effects in popular Chinese medicine. However, conflicting results have been shown among trials and animal studies on the relation between tea consumption and blood pressure. *Abe et al., [1995],* investigated the antihypertensive effect of green tea rich in GABA in young and old Dahl salt-sensitive [S] rats and concluded that GABA rich green tea not only decreased the established high blood pressure but also prevented the the development of hypertension in Dahl S rats fed a high salt diet. *Negishi et al., [2004],* observed that both black and green tea polyphenols attenuate blood pressure increases, through their antioxidant properties, in stroke-prone spontaneously hypertensive rats, but the amounts of polyphenols used in this experiment correspond approx. to those 1L of tea. Recently, some epidemiological studies indicated that green tea consumption slightly reduces blood pressure. *Yang et al., [2004],* concluded that habitual moderate strength green tea or oolong tea consumption, 120 mL/day or more for 1 year significantly reduces the risk of developing hypertension in the Chinese population. *Hodgson et al., [2003],* reported that long-term regular ingestion of green tea may have a favorable effect on blood pressure in older women.

ANTIOXIDATIVE EFFECTS

Green tea is considered a dietary source of antioxidant nutrients; which further enhances its antioxidant potential. The concentration of flavanoids or GTP increases when the tea is brewed for a longer time. The hierarchy of antioxidant potential of GTP is EGCG H" ECG >EGC> GA>ECH" C.

GTP may also function indirectly as antioxidants through [a] inhibition of the redox-sensitive transcription factors; [b] inhibition of 'pro-oxidant' enzymes, such as inducible nitric oxide synthase, lipoxygenases, cyclooxygenases and xanthine oxidase; and [c] induction of antioxidant enzymes, such as glutathione peroxidase [GSHPx], catalase, superoxide dismutases [SOD] and detoxifying enzymes glutathione-S-transferases [GST] and glutathione synthesis thus boost the endogenous antioxidative capacity and indirectly increase the detoxification of ROS.

GTP have been found to be effective *in vitro* conditions by protecting reactive oxygen species-induced degradation of lipids, proteins and 2-deoxyribose *in vitro* condition *[Raza and John, 2007]*, breaking or disrupting propagatory chain reaction and chelating redox-active transition metal ions, like iron and copper to prevent their participation in Fenton and Haber-Weiss reactions *[Mckay and Blumberg, 2002; Kim, 2003; Skrzydlwska et al., 2002 a]*. *Hakim et al. [2003]*, stated that the presence of a catechol group and hydroxyl group at position 3 on â- ring helps in chelating metal ions. This structure allows electron delocalization conferring high reactivity to quench free radicals. The authors further concluded that regular intake of green tea has a protective effect *in vivo* as it protects from the oxidation of biomolecules and prevent lipid peroxidation in phospholipid bilayers, oxidative damage associated with smoking. *Sai et al., [1998]*, demonstrated that green tea intake prevented hepatoxicity, oxidative DNA damage and cell proliferation in the liver of 2-nitropropane treated rats. Incidentally, 2-nitropropane is an active ingredient of tobacco smoke. Likewise, *Klaunig et al., [1999]*, concluded that the consumption of green tea decreased oxidative DNA damage[8-OHdG in WBC and urine] in both groups [smokers and non smokers] and lipid peroxidation [MDA in urine] and free radical generation[2,3-dihydoxy benzoic acid (2,3 DHBA)] in urine in smokers. Furthermore, there was an overall decrease in oxidative stress in non smokers.

Green tea polyphenols (GTP) are absorbed from the gut, thereby increasing the total antioxidant capacity of blood *[Sung et al., 2000; Reitveld and Wiseman, 2003]*. Moreover, they have been found to increase the activity of antioxidant enzymes, thus strengthening antioxidant defense system. Khan et al. [1992] reported that hairless mice given 0.2% green tea polyphenols in their drinking water for 30 days had significant increase in glutathione peroxidase [GSHPx], catalase, glutathione reductase and GST activity in liver and other tissues as compared to controls. In the same vein *Lin et al., [1998]* demonstrated that the rats fed on a diet containing 2.5% green leaves for 63 weeks significantly increased serum SOD and liver catalase and GST activity. *Pilipenko et al., [2008]*, assessed the tolerance of tableted green tea and its effect on the antioxidant status indices. Results revealed that tolerance was good in the treatment group, who showed better dynamics of quality of life indices, especially in scales of body pain and social functioning and a significant decrease was observed in lipid peroxidation index, indicating the safe use of the product.

Diminishing oxidative stress by taking antioxidants may protect against the onset and progression of the ducheme muscular dystrophy [DMD], a lethal muscle wasting condition which is mediated through ill effects of ROS as inferred from studies conducted on experimental mdx mice. *Beutler et al., [2002]*, stated that antioxidants present in green tea extract improve muscle health by reducing or delaying necrosis in mdx mice. *Patil et al., [2010]*, concluded that administration of green tea extract [GTE] can prevent the electrocardiographic abnormalities and pathological changes in biochemical markers induced by doxorubicin [3mg/kg/week].

Thus green tea prevents the generation of free radicals and ROS, the agents provocateurs for DNA damage and chronic diseases like cancer, diabetes, CVD and neurodegenerative disorders.

PREVENTION OF CHRONIC DISEASES

Oxidative damage to biomolecules has been implicated in the pathology of a number of chronic diseases. Chronic or lifestyle-related diseases, including cancer, are also characterized as aging-related diseases, where aging may be the most potent causal factor. Therefore, prevention of lifestyle-related diseases will depend on slowing the aging process and avoiding the clinical appearance of the disease. Dietary components that are capable of retarding cellular aging and inhibiting the growth of cancer cells without affecting the growth of normal cells are receiving considerable attention for the development of novel cancer- preventive approaches *[Chung et al., 2003, Lambert and Yang, 2003, Mittal et al., 2004]*. Tea flavanoids because of their potent antioxidant properties have important applications as adjuncts in the treatment of a myriad of disease processes such as cancer, atherosclerosis and its associated complications, hypercholesterolemia, rheumatoid arthritis,

neurodegenerative diseases and diabetes mellitus. *Sueoka et al., [2001]* concluded that consumption of at least 10 cups of green tea/ day[~2g of green tea extract] have a life prolonging effect and a preventive role in both chronic inflammatory diseases and life style related diseases like cardiovascular diseases [CVD] and cancer. Likewise, *Clement [2009]*, stated that habitual green tea consumption may provide some level of chemoprevention in prostate and breast cancer. It may also attenuate the risk factors associated with the development of atherosclerosis, thus reducing the incidence of cardiovascular events and stroke.

ANTIMUTAGENIC AND ANTICARCINOGENIC EFFECTS

Cancer is often thought to be a single disease; however it is a term that covers a range of malignant conditions that can affect almost any organ or tissue in the body. The multistage process of cancer development is a long process involving initiation, promotion and progression and the advanced metastasized cancers are mostly incurable thus the concept of chemoprevention evolved to control the occurrence of cancer either by slowing, blocking or reversing the development of the disease by administration of naturally occurring or synthetic compounds.

The role of green tea in protection against cancer has been supported by ample evidence from studies in cell culture and animal models *[Chung et al., 2003]*. Animal studies have shown that green tea inhibit carcinogenesis of the skin, lung, oral cavity, esophagus, stomach, liver, kidney, prostate and other organs *[Lambert and Yang, 2003; Inoue et al., 1998; Bianchi et al., 2000; Yamamoto et al., 2003; Laurie, 2005]*. In some studies, the inhibition correlated with an increase in tumor cell apoptosis and a decrease in cell proliferation *[Mittal et al., 2004]*. Today, green tea is accepted as a cancer preventive on the basis of numerous *in vitro, in vivo* and epidemiological studies. The Chemoprevention Branch of the National Cancer Institute has initiated a plan for developing tea compounds as cancer-chemopreventive agents in human trials *[Siddiqui et al., 2004]*.

Weisburger and Chung [2002], reviewed the mechanism of chronic disease causation by nutritional factors and tobacco products and their prevention by tea polyphenols. The authors stated that the chemopreventive effects of tea depends upon [a] its action as antioxidant; [b] the specific induction of detoxifying enzymes; [c] its molecular regulatory functions on cell growth, development and apoptosis; and [d] a selective improvement in the function of the intestinal bacterial flora. The review concluded that tea polyphenols increase the level of antioxidant defenses and thus lower the risk of diseases involving adverse oxidative reactions such as heart diseases and a number of types of cancer and an intake of 6-10 cups of tea/ day assist in lowering the risk of chronic diseases. In an exhaustive review the authors emphasized the role of tea in heart disease prevention *[Hertog et al., 1995; Vinson and Dabbagh, 1998]*, cancer prevention as it can block the formation of mutagens and carcinogens from precursors *[Weisburger et al., 1994]*, and inhibit the biochemical activation of genotoxic carcinogens. Green tea polyphenols increase their detoxification through the induction of higher levels of glucuronosyl transferase *[Embola et al., 2001]*. It was found that glucuronosyl transferase a phase II enzyme was higher in tea drinking animals which may account for the protective effects associated with the intake of tea *[Sohn et al., 1994; Embola et al., 2001]*. *Suganuma et al., [1998]* noted that epigallocatechin gallate acted on cellular membrane and affected tumor necrosis factor formation and gene expression. Furthermore, green tea inhibited promoting elements in prostate cancer *[Gupta et al., 1999; Kurahashi et al., 2008]* which increases the rate of cell cycling and lowers cell to cell communication *[Trosko, 2001]*.

Cancers in lung, oral cavity and oesophagus are associated either with cigarette smoking or tobacco use. Green tea, EGCG and caffeine inhibit lung tumor genesis induced by nicotine derived tobacco carcinogen nitrosamines in strain A mice *[Xu et al., 1992]* and F344 rats *[Chung et al., 1998; 1999]*.

It has also been noted that Japanese smokers who consume a lot of green tea seems to enjoy protection against lung cancer. In fact, the prevalence of smoking among Japanese males is twice that of those in United States but the incidence of lung cancer is only one half *[Chung et al., 2003]*.

Epidemiological studies have established that contamination of food with aflatoxin B_1 [AFB_1] produced by *Aspergillus flavus* is an important risk factor for hepatacellular carcinoma. AFB_1 via cytochrome P_{450} system undergoes metabolic activation to form AFB_1 epoxide which interacts covalently with cellular macromolecules including DNA and thus initiates hepatocarcinogenesis. *Qin et al., [1997; 2000]*, reported that feeding 0.5%

green tea powder in the drinking water resulted in significant inhibition of aflatoxin B_1- induced hepatocarcinogenesis by modulating its metabolism.

Studies indicate that oral administration of green tea or topical application; intraperitoneal injections of green tea polyphenol fraction or EGCG inhibit the progression of pappillomas to carcinomas *[Cooney et al., 1999; Mukhtar and Ahmad, 1999; Katiyaar et al., 2000]. Wang et al., [1992],* reported that oral administration of green tea to DMBA [7, 12- dimethyl benz [a] anthracene] pretreated mice inhibited UVB-induced carcinogenesis. It was found that administration of green tea along with UVB not only decreased the number but also the size of tumors in mice as compared to those treated with UVB alone. Thus treatment of green tea polyphenols to skin has been shown to have a beneficial effect on the biochemical pathways involved in skin inflammation, cell proliferation and chemical tumour promoters.

Leukemia is yet another disease where green tea may prove effective as an adjuvant therapy for treatment. Epigallocatechin gallate [EGCG] was found to inhibit the proliferation of human and mouse leukemic cells *in vitro* and thus is expected to have a new function for leukemia therapy without any side effects *[Otsuka, et al., 1998]*.

It has been seen that EGCG blocks the interaction of tumor promoters to their own receptors on the cell membrane. This is called the *'sealing effect'*. Several studies have shown that the sealing effect is the key determinant to the inhibitory action of green tea polyphenols *[Yoshizawa et al., 1992; Kitano et al., 1997]*. Likewise *Fujiki et al., [1999]* stated that EGCG interacted with the phospholipids bilayer membrane resulting in the formation of aggregates where aromatic groups stack regularly thus confirming the sealing effect of EGCG. Furthermore, green tea polyphenols, due to the presence of galloyl moiety, inhibit tumour necrosis factor- á [TNF-á] gene expression and its release in cells. In addition, high consumption of green tea was also associated with decreased number of auxiliary lymph node metastases among premenopausal stage I and II breast cancer patients and with increased expression of progesterone receptors among postmenopausal ones. *Rosengren [2003],* indicated that the green tea catechins reduce the proliferation of breast cancer cells *in vitro* and decrease breast tumor growth in rodents. Furthermore, *in vitro* studies have demonstrated that the combination of EGCG and tamoxifen is synergistically cytotoxic to breast cancer cells; these results suggest that the catechins have significant potential in the treatment of breast cancer. According to *Wu et al., [2003],* green tea drinkers showed a significantly reduced risk of breast cancer; compared to women who did not drink green tea regularly [i.e., less than once a month], concluding that there was a significant trend of decreasing risk with increasing amount of green tea intake. Two studies in Japanese women diagnosed with breast cancer indicate that green tea consumption is inversely associated with the rate of recurrence, especially in the early stages of breast cancer *[Nakachi et al.,1998, Inoue et al., 2001]. Zhou et al., [2004],* also reported that breast cancer is significantly less prevalent among Asian women, whose diets contain high intake of soy products and green tea. These authors suggested that dietary soy phytochemical concentrate plus green tea may be used as a potential effective dietary regimen for inhibiting progression of estrogen-dependent breast cancer.

It has been shown that EGCG modulate multiple signal transduction pathways in a manner that control, the cell proliferation and thereby imparting strong cancer chemopreventive as well as therapeutic effects *[Khan et al., 2006]*.

HYPOCHOLESTEROLEMIC EFFECTS AND CARDIOVASCULAR DISEASES

Increased levels of plasma total cholesterol, low density lipoprotein- cholesterol [LDL-C] and very low density lipoprotein cholesterol [VLDL-C] are a risk factor contributing to the development of coronary heart diseases. Moreover, oxidative modification of LDL leads to the inception and progression of atherogenic lesions.

Green tea drinking or GTP may exert an antiatherosclerotic action by virtue of its antioxidant properties- by inhibiting formation of free radicals, interrupting the propagation of free radical chain reaction, delay autooxidation and protecting LDL from oxidative modification *[Zhang et al., 1997; Ishikawa et al.,1997; McKay and Blumberg, 2002]* and by lowering serum levels of total cholesterol, LDL-C, apolipoprotein B and higher levels of high density lipoprotein cholesterol [HDL-C] and apolipoprotein A-I, ratio of total cholesterol to HDL-C, thus improving the blood lipid profile *[Coimbra et al., 2006]*.

Muramatsu et al., [1986], long back reported that supplementation of tea catechins at a level of 1% and 2% in diet reduced plasma total cholesterol levels and atherogenic index. Consistent with these results are the data reported by *Hertog et al., [1995]* that demonstrated an inverse correlation between catechin intake and coronary heart disease mortality after a 25-year follow-up of 12763 men from seven different countries. Similarly, another research showed that men and women from the Boston Area Health study who consumed one or more cups per day of green tea in the previous year had a 44% lower risk of myocardial infarction than those who drank no tea *[Sesso et al.,1999]***.** *Peters et al., [2001],* have provided a meta-analysis that suggested a decrease in the rate of cardiovascular disease outcomes with increasing green tea consumption. Through seven studies the incidence rate of myocardial infarction was estimated to decrease by 11% with an increase in green tea consumption of three cups per day. In addition, an inverse association of green tea intake and myocardial infarction and its genetic variation has been found by *Hirano et al., [2002] and Ohmori et al., [2003]*.

The mechanism for the hypocholesterolemic activity of green tea may be due to the inhibition of cholesterol and bile acid absorption resulting into higher fecal excretion of total fatty acids, neutral sterols and acidic sterols *[Chan et al., 1999]*. *Raederstorff et al., [2003],* investigated the dose-response and the mechanism of action of EGCG on these parameters in rats which were fed a diet high in cholesterol and fat; after 4 weeks of treatment, a significant reduction was observed in plasma total cholesterol and LDL-cholesterol levels in the group fed 1% EGCG when compared to the non-treatment group. However, no significant change was observed in plasma triglycerides and HDL-C levels. These authors suggested that one of the underlying mechanisms by which EGCG affects lipid metabolism is by interfering with the micellar solubilization of cholesterol in the digestive tract, which then in turn decreases cholesterol absorption. The catechins may also influence the uptake and intracellular processing of lipids as well as the secretion and assembly of chylomicrons *[Loest et al., 2002]*. *Lee and Kim [2008],* investigated the hypocholesterolemic effect of GTC via upregulation of hepatic cholesterol 7-alpha hydroxylase[CYP7A1] in cholesterol fed rats and concluded that catechins or EGCG diet lowered plasma total cholesterol and LDL-C as well as upregulated CYP7A1 enzyme activity by 4.8- or4.9 fold and CYP7A1 mRNA levels by 2.5- or 2.8 fold suggesting that increase in CYP7A1 gene expression may be a mechanism which can partially account for hypocholesterolemic effect of green tea.

Among the green tea catechins, EGCG is the most potent inhibitor of lipid absorption and lowers the accumulation of other lipophilic organic compounds in tissues. It appears to be more effective in lowering the absorption of lipids of extreme hydrophobicity such as cholesterol and á- tocopherol with little or moderate effect on less hydrophobic lipids such as retinol and fatty acids *[Koo and Noh, 2007]*. Green tea or its catechins may be used as safe and effective lipid lowering therapeutic agents *[Lee et al., 2008]*.

Cardiovascular diseases [CVD] are the diseases of heart and the blood vessels. They are the major causes of deaths in adults worldwide. Several authors have suggested that consumption of green tea is associated with decreased cardiovascular risk and ischemic heart disease *[Geleijnse et al., 1999; 2002]* and a healthier lifestyle *[Menon et al., 2003]* but the mechanisms for these observations have remained uncertain. The oxidation of LDL-cholesterol, associated with a risk for atherosclerosis, heart diseases and other events such as foam cell formation, endothelial cytotoxicity and induction of proinflammatory cytokines [Trevisanato and Kim, 2000; Yokozawa et al. 2002] is inhibited by green tea due to EC and EGCG antioxidant activity. *Gomikawa and Ishikawa [2002],* reported that *in vitro* antioxidant activity of EGCG on LDL oxidation was stronger than that of EC and after ground green tea ingestion, catechins suppressed the susceptibilities of human LDL to oxidation by $CuSO_4$ *in vitro* and plasma oxidation *in vivo*. *Wheeler and Wheeler [2004],* demonstrated that the ability of green tea catechins to enhance the resistance of LDL to oxidation is in the rank order: EGCG = ECG H”EC = C>EGC>GA

Another study conducted by *Miura et al., [2001],* demonstrated that chronic ingestion of green tea extract retard the development of atherosclerosis without changing the plasma lipid levels in apoE- deficient mice probably through antioxidative activity. A similar result was obtained with human trials as seen in a study conducted in Japan that reported that Japanese men who consumed at least 10 cups of tea per day had reduced risk of CHD than those who consumed 3 cups or less per day *[Nakachi et al., 2000]*.

Elevated fibrinogen levels are a well established independent risk factor for coronary, cerebral and peripheral vascular disease. Fibrinogen affects blood coagulation, blood rheology and platelet aggregation and has direct

effect on vascular wall. Green tea catechins particularly EGCG binds with fibrinogen and inhibits its function. *Vinson and Dabbagh [1998],* studied the effect of supplementation of green and black tea on lipids, lipid oxidation and fibrinogen in hamsters and concluded that both green and black tea improves the risk factor for heart disease in both normal and hypercholesterolemic animal by both hypolipidemic and antioxidant mechanism as well as a fibrinolytic effect. Similarly, *Kang et al., [1999],* reported that green tea catechins and EGCG have antithrombotic activities. As a matter of fact, the inner lining of blood vessels known as endothelium play an important role in preventing CVD and helps to maintain vascular homeostasis. It may be adversely affected by a number of risk factors for CVD. Though it has extrinsic and intrinsic ability to resist the affect but if the defense mechanism is unable to compensate, it will develop a pathological phenotype or *'endothelial dysfunction'* which in turn is associated with dysregulation of fibrinolytic and inflammatory system that further promotes the development of lesions thus leads to atherosclerosis. In the same vein, *Vita, [2003],* reviewed the effect of tea consumption on endothelial function and CVD and concluded that consumption of tea improves the vascular endothelium to have a beneficial effect to CVD.

OTHER EFFECTS

A) Body Weight Control

Obesity has increased at an alarming rate in recent years and is now a worldwide health problem. Current interest in the role of functional foods in weight control has focused on plant ingredients capable of interfering with the sympathoadrenal systems *[Dulloo et al., 1999]*. The effects of long-term feeding with tea catechins have been widely studied, and some investigators suggest a potential role of green tea in body weight control. In addition, caffeine and theanine have been found to strengthen polyphenol effects on body weight control and fat accumulation in mice *[Zheng et al., 2004]*. Studies *in vitro* have demonstrated that green tea extracts containing 25% of catechins [in conditions similar to physiological ones] significantly inhibited the gastric lipase and , and to a lower extent pancreatic lipase also. Thus, the lipolysis of long-chain triglycerides is reduced in 37% *[Juhel et al.,2000]*. In addition, green tea extracts have been found to interfere in the fat emulsification process, which occurs before enzymes act, and is indispensable for lipid intestinal absorption *[Juhel et al.,2000; Chantre and Lairon, 2002]* and exhibits a fatty acid synthase inhibitor activity *[Tian et al.,2004]*.

Green tea may have thermogenic properties not only attributable to its caffeine content, but to the joint-effect of caffeine and catechins. EGCG can act upon AMPc levels by increasing the energetic expenditure *[Juhel et al.,2000]. Dulloo et al., [1999]* using a green tea extract rich in catechins and caffeine, concluded that green tea has thermogenic properties and promotes fat oxidation beyond than those explained by its caffeine content per se; the green tea extract may play a role in the control of body composition via sympathetic activation of thermogenesis, fat oxidation, or both. *Dulloo et al., [2000],* indicated that the thermogenic properties of green tea could reside primarily in an interaction between its high content in catechins and the presence of caffeine with sympathetically released noradrenaline; since polyphenols are known to be capable of inhibiting catechol-o-methyl-transferase [the enzyme that degrades noradrenaline], and caffeine of inhibiting trancellular phosphodiesterases [enzymes that break down noradrenaline-induced AMPc]. Such a synergistic interaction between polyphenols and caffeine to increase and prolong sympathetic stimulation of thermogenesis could be of value in assisting the management of obesity. *Kovacs et al., [2004],* reported that weight maintenance after 7.5% of body weight loss in overweight and moderately obese subjects was not affected by green tea treatment and that regular caffeine consumption affected weight maintenance in green tea treatment. According to some authors, green tea extracts [with a 25% of catechins content] may be advisable for overweight treatment in patients whose body mass index ranges between 25 and 29.9 kg/m^2, only if they do not present special sensitiveness to xantic bases *[Kovacs et al., 2004]. Wu et al., [2003a],* indicated that an inverse relationship may exist among regular green tea consumption, body fat percentage, and body fat distribution, especially for subjects who have maintained the habit of tea consumption for more than 10 years. *Weisburger and Chung [2002],* stated that children, who consume less vegetables can be benefited by drinking 3-5 cups of decaffeinated tea rather than from some high sugar beverages associated with obesity.

B) Glucose Tolerance And Insulin Sensitivity

Green tea has been shown to possess anti diabetic activity and is effective in both prevention and treatment of diabetes. Epidemiological observations and laboratory studies have shown that green tea has an effect on glucose tolerance and insulin sensitivity. *Anderson and Polansky [2002]*, reported that green tea increases insulin activity, and that the predominant active compound is EGCG; these same authors indicated that addition of lemon to the tea did not affect the insulin-potentiating activity but the addition of 50 g of milk per cup decreased the insulin-potentiating activity similar to 90%. *Wu et al., [2004]* examined the effect of green tea supplementation on glucose tolerance and insulin sensitivity in rats; rats were divided into two groups: a control group was fed with standard chow and deionized distilled water, while the other was fed with the same chow diet but with green tea instead of water [0.5 g of lyophilized green tea powder dissolved in 100 mL of deionized distilled water]; after 12 weeks of green tea supplementation, this group had lower fasting plasma levels of glucose, insulin, triglycerides, and free fatty acid than the control rats. In addition, GTP significantly increased basal and insulin-stimulated glucose uptake of adipocytes *[McKay and Blumberg 2002]*. Some investigations have also shown that EGCG does not only regulate the glucose level in blood, but also may rehabilitate damaged *beta*-cells, which are responsible for producing insulin *[McKay and Blumberg, 2002, Wu et al., 2003a]*. *Kreydiyyeh et al., [1994]* reported that an active ingredient in tea reduced sodium extrusion from the enterocytes by inhibiting the Na super[+]-K super[+] pump thus, destroying the gradient needed for the mucosal transport of glucose. Reducing the intestinal absorption of glucose and sodium in rats.

C) Oral Health

Oral diseases including dental caries, periodontal disease, and tooth loss may significantly impact a person's overall health. Among these, dental caries is a multifactorial infectious disease in which nutrition, microbiological infection, and host response play important roles. Earlier reports in experimental animals and humans suggested that green tea consumption [without added sugar] reduces dental caries *[Wu and Wei, 2002; Elwin-Lewis et al., 1980; Mitscher et al.,1997]*. Linke and *LeGeros [2003]*, indicated that frequent intake of green tea can significantly decrease caries formation, even in the presence of sugar in the diet. *In vivo* animal studies have shown that specific pathogen-free rats infected with *Streptococcus mutans* and then fed with a cariogenic diet containing GTP have significantly lower caries scores *[Otake et al.,1991]*. Supplementing drinking water of rats with 0.1% GTP along with a cariogenic diet also significantly reduced total fissure caries lesions *[Wu and Wei, 2002]*. Recent findings of *Okamoto et al., [2004]*, suggest that green tea catechins may have the potential to reduce periodontal breakdown resulting from the potent proteinase activity of *Porphyromonas gingivalis*. In addition, green tea decoctions inhibit a-amylase in human saliva, reducing maltose release by 70% and effectively lowering the cariogenic potential of starch-containing food *[McKay and Blumberg, 2002]*. Similarly, *Zhang and Kashket [1998]*, reported that green tea extracts inhibits human salivary amylase and may reduce the cariogenic potential of starch-containing food such as crackers and cakes because it may reduce the tendency of this kind of food to serve as slow-release sources of fermentable carbohydrate. It is likely that the cariogenic challenge in a cariogenic diet may be reduced by the simultaneous presence of green tea in the diet.

Apart from their polyphenol content, both green and black tea, are a natural source of fluoride and an effective vehicle for fluoride delivery to the oral cavity. According to *Simpson et al., [2001]*, after cleansing the mouth with tea, approximately 34% of the fluoride is retained and shows a strong binding ability to interact with the oral tissues and their surface integuments. This fluoride content may have a beneficial impact on caries and may carry out a wide range of biological activities including prevention of tooth loss and oral cancer *[Okamoto et al., 2004; Lee et al., 2004]*. Nonetheless, the data have suggested that GTP extract may be responsible for the noted effects on oral health and it has been also demonstrated that GTP rather than fluoride contribute to anticariogenic potential *[Wu and Wei, 2002; Otake et al.,1991]* by inhibition of oral bacteria growth such as *Escherichia coli*, *Streptococcus salivarius*, and *Streptococcus mutans*. Several studies have indicated that GTP inhibits growth, acid production, metabolism, and glucosyltransferase enzyme activity of *S. mutans* and dental plaque bacteria *[Wu and Wei, 2002]*. In consequence, green tea has been considered as functional food for oral health and is widely used in toothpaste formulation.

D) Solar Ultraviolet Protection

Epidemiological, clinical and biological studies have shown that solar ultraviolet [UV] light is a complete carcinogen and repeated exposure can lead to the development of various skin disorders including melanoma and non-melanoma skin cancers. The *in vitro* and *in vivo* animal and human studies have suggested that GTP are photoprotective in nature, and can be used as pharmacological agents for the prevention of solar UVB light-induced skin disorders including photoaging, melanoma and non-melanoma skin cancers *[Elmets et al., 2001; McKay and Blumberg, 2002; Wu and Wei, 2002, Lee et al., 2004]*.

Katiyar [2003], indicated that topical treatment or oral consumption of GTP inhibits chemical carcinogen or UV radiation-induced skin carcinogenesis, inflammatory responses, oxidative stress and immunosuppression [local as well as systemic] associated with the inhibition of UVB-induced infiltration of inflammatory leukocytes in different laboratory animal models.

Green tea has been effective in the treatment of psoriasis. The combination therapy of psoralens and ultraviolet A radiation is highly effective but unfortunately leads to substantial increase in the risk for developing squamous cell carcinoma and melanoma. An in vitro study using human and mouse skin demonstrated that pre and post treatment with green tea extract inhibited DNA damage induced by psoralen/ultraviolet A radiation exposure *[Zhao et al., 1999]*.

E) Antimicrobial Activity

Green tea catechins have been reported to have antibacterial and antiviral activity. Green tea effectiveness against any type of diarrhoea and typhoid has been known in Asia since ancient times *[McKay and Blumberg, 2002; Wu et al., 2003; Wu et al., 2003a]*. Nowadays it is also known that it inhibits the reproduction and growth of many bacteria, among which some types of *Salmonella, Clostridium* or *Bacillus* can be named. GTP are found to favour the growth of specific bacterial species *Lactobacilli* and *Bifidobacteria* [that have beneficial odour free metabolites] in the intestinal tract and thus have a favourable metabolic effect in maintaining health. Moreover, it also leads to a reduction in Enterobacteriaceae that produce ammonia, skatole and other amines sources of unpleasant odour of stools. In addition, it also decreases the pH of the intestinal contents through increased formation of organic acids thus inhibiting carcinogenesis *[Goto et al., 1998]*.

Takabayashi et al., [2004], and Yee et al., [2002] reported an inhibitory effect of green tea catechins on *Helicobacter pylori* infection. Moreover, it has been shown that green tea has no effect over intestinal flora, which is a great advantage against other bactericide agents. Regarding its antiviral action, green tea is well known for preventing tobacco crops from being invaded by the *'mosaic virus'* of tobacco. Recent investigations have confirmed that catechins completely inhibit its growth and reproduction *[Wilson, 1999]*. Effects of green tea against the influenza virus, especially in its earliest stage, as well as against the *Herpes simplex* virus have also been demonstrated *[Toda et al., 1989; Mukoyama et al., 1991; Yam et al., 1991]*. Furthermore, *Weber et al., [2003],* observed that adenovirus infection is inhibited *in vitro* by green tea catechins. Epigallocatechin gallate and epicatechin gallate were able to differentially inhibit the enzymes used by HIV virus for replication: reverse transcriptase and various DNA and RNA polymerases *[Nakane and Ono, 1989]*. Studies have shown that EGCG bonds more strongly to CD4 than the HIV virus gp120 thus blocking gp120 and preventing HIV from entering the T4 cell *[Williamson et al., 2006]*. Green tea strengthens the immune system action since green tea protects it against oxidants and radicals. *Bayer et al., [2004],* suggest that oral intake of green tea could act as an adjunctive therapy for prevention of transplant rejection in humans.

Hirasawa and Takada [2004], indicated the antifungal activity of green tea catechins against *Candida albicans*, and the convenience of a combined treatment with catechins and lower doses of antimycotics; This treatment may help to avoid the side effects of antimycotics.

F) Bone Mineral Density

Green tea consumption has also been associated with increased bone mineral density, and it has been identified as an independent factor protecting against the risk of hip fractures; this fact has been considered independent of

smoking status, hormone replacement therapy, coffee drinking and the addition of milk to tea *[Muraki et al., 2003]*. *Park et al., [2003]* observed the positive effects of green tea extracts and GTP on the proliferation and activity of bone cells. However, the mechanism for this effect of tea consumption on bone mineral density is not clear although it has been hypothized that fluoride or flavanoids may play a role. *Wu and Wei [2002],* indicated that bone mineral density may be influenced by several chemical compounds that are contained in tea extracts [i.e., caffeine, phytostrogen, fluoride ...].

A cross- sectional study conducted on British women examined the effect of tea drinking and bone mineral density [BMD] and concluded that women who drank tea had higher BMD than those who did not drink tea. Thus, tea drinking protects against osteoporosis in older women and flavanoids may influence BMD *[Hegarty et al., 2000]*.

Similarly, *Wu et al., [2002],* reported that the longer duration of habitual green tea consumption [more than 10 years] was associated with higher bone mineral density of total body, lumbar spine and hip regions in adults.

Another study conducted by *Adcocks et al., [2002],* investigated the effect of catechins on cartilage extracellular matrix components using *in vitro* model system and concluded that green tea catechins are chondroprotective and its consumption may be prophylactic for arthritis patients by reducing inflammation and slowing cartilage breakdown.

MISCELLANEOUS EFFECTS

Green tea polyphenols are known to have anti-fibrotic properties on the skin and on the arteries. The proliferation of hepatic stellate cells is closely related to the progression of liver fibrosis in chronic liver diseases, and EGCG has a potential inhibitory effect on the proliferation of these cells *[Dorchies et al.,2003; Sakata et al., 2004]*. *Imai and Nakachi, [1995],* stated that increased consumption of green tea especially more than 10 cups a day decreased concentrations of hepatological markers in serum, aspartate aminotransferase, alanine transferase and ferritin. Thus, tea along with its mutifaciers therapeutic effects is also protective against liver disorders.

The neuroprotective power of complex extracts rich in flavonoids like those of *Ginkgo biloba,* green tea or lyophilized red wine have been demonstrated in several studies *[Kakuda, 2004; Dajas et al. 2003]*. There is evidence that iron plays a part in epilepsy. Green tea polyphenols have been found to inhibit or diminish iron-induced epileptic seizures and to inhibit the hyperactivity of dopaminergic neurons *[Kabuto et al., 1992]*. Studies suggest that GTP possibly protect against Parkinson's and Alzheimer's diseases and other neurodegenerative diseases *[Kondo et al., 2002; Weinreb et al., 2004]*. GTP have demonstrated neuroprotectant activity in cell cultures and animal models, such as the prevention of neurotoxin-induced cell injury; the biological effects of GTP may benefit patients with Parkinson's disease, but further in-depth studies are needed to investigate the safety and effectiveness of green tea in humans and to determine the different mechanisms of green tea in neuroprotection *[Kondo et al., 2002]*. In the same way, the neuroprotective effects of the theanine contained in green tea are a focus of considerable attention, and further studies are warranted *[Kakuda, 2004]*. A crossectional study conducted on Japanese individuals aged> 70 years reported that higher green tea consumption was significantly associated with lower prevalence of depressive system in elderly *[Niu et al., 2009]*. Qiong Li et al., [2010] reported that oral administration of green tea catechins [GTC w/v] to 14 months old C57BL/6J mice prevented the increase in SOD and GSHPx activities and reduced TBARS and protein carbonyl contents in the hippocampus. Furthermore, the activation of transcriptional factor- kappa B and lipofuscin formation were reduced in pyramidal cells of hippocampal CA1 region. Moreover long term supplementation with GTC prevented age related reductions of two post- synaptic proteins post-synaptic density 95 and N-methyl-D-aspartate receptor 1 in the hippocampus, indicating GTC prevents oxidative stress related brain aging.

Varilek et al., [2001], stated that green tea and its polyphenols fraction are useful in chronic inflammatory diseases such as inflammatory bowel diseases [IBD]. It has been seen that galloyl and hydroxyl groups at 3' position on EGCG are responsible for its strong anti inflammatory properties. Green tea is also considered to be useful for insect stings mainly due to its antiinflammatory effects and its capacity to stop bleeding *[Sagesaka-Mitane et al., 1997; Dvorakova et al., 1999]*.

Sickle cell characterized anemia as "dense cells" may trigger vaso-occlusion and painful sickle cell "crisis". *Ohishi et al., [2000];* demonstrated that 0.13mg/ml green tea extract was capable of inhibiting dense cell formation by 50 percent.

Some studies have suggested an inverse association between green tea consumption and the risk of kidney stone formation *[Mckay and Blumberg, 2002; Ishizuk et al., 2003]*. Supplementation of decaffeinated green tea extract [catechins] have been found to be effective in reducing haemodialysis- induced ROS and palliating the subsequent adverse events-atherosclerosis and proinflamation *[Hsu et al., 2007]*. *Ashraf et al., [2009],* investigated the effect of green tea fortified bread against renal failure induced by excessive dietary arginine [20g/kg diet] in albino rats and concluded that kidney functions improved along with liver functions and lipid parameters with the consumption of green tea fortified bread with 2% and 4% level of incorporation; however, the results were more promising in the latter.

In addition, green and black tea extracts led to a retardation of the progression of lens opacity in rats with cataracts induced by selenite *[Thiagarajan et al., 2001]*. *Gupta et al., [2002],* reported that green tea acts by preserving the antioxidant defense system of the lens. *Skrzydlewska et al., [2002b]*, indicated a beneficial effect of green tea in alcohol intoxication.

Besides all the above mentioned properties, which have helped to the recognition of green tea as functional food by some authors *[Ferrari and Torres, 2003],* One must not forget its current use in the preparation of pharmaceutical preparations, dentifrices, cosmetics and a variety of food, *[Arburjai and Natshah, 2003]*. This additional use is mainly due to its antioxidant activity, which makes it a natural, efficient and safe preservative.

A study demonstrated that *yogurt* enriched with green tea powder (0.5%) was more acceptable as compared to the one prepared with 1%.green tea powder. Moreover, the purchase intent increased up to 21% after consumers learned about green tea's health benefits and were ready to compromise their liking of a product for health benefits offered by adding green tea to yogurt (http://www.thefreelibrary.com). *Wang et al., [2007]* stated that green tea extract at only the level of 5g/kg flour significantly reduced the sweetness and increased the astringency, hardness and stickiness of the green tea fortified bread as compared with control. Likewise, *Ashraf et al., [2009]* stated that the best level of fortification for bread with green tea was 2% followed by 4%.

Dang [2009], studied the effect of application of green tea extract to biscuit cream and concluded that it provides stability and inhibit oxidation of lipids present in cream. In addition, the green tea extract fortified biscuit could be a functional food product with additional health benefits.

HARMFUL EFFECTS AND TOXICITY EVALUATION

Harmful effects of tea over consumption [black or green] are due to three main factors: [a] its caffeine content, [b] aluminum presence, and [c] the effects of tea polyphenols on iron bioavailability. A day-long consumption of green tea improved the cognitive and psychomotor performance of healthy adults in a manner similar to coffee, but green tea [which contains less caffeine] is less likely than coffee to disrupt sleep quality at night *[McKay and Blumberg, 2002]*. *Lin et al., [2003],* compared the caffeine content in the same type of tea but manufactured by different fermentation processes, and concluded that the caffeine level presented the following order: black tea > oolong tea > green tea > fresh tea leaf. *Cabrera et al., [2003]* determined the caffeine content in a total of 45 tea samples, including 'fermented' teas [red and black teas], oolong tea and green tea samples; the results showed that caffeine presence is higher in the case of black teas [41.5–67.4 mg/g], whereas green and oolong teas show a mean caffeine content of 32.5 and 29.2 mg/g, respectively. Likewise, *Fernandez et al., [2002],* also reported that caffeine content is higher in the case of 'fermented' teas, showing values between 2.4 and 4.8%, whereas 'non-fermented' teas show caffeine levels ranging between 1.47 and 3.86%. Table 4 depicts the caffeine content of various beverages widely consumed. The caffeine content in green tea may vary according to the type of tea and the form of preparation [i.e., brewing time]; generally, bagged tea produces a higher percentage of caffeine than tea leaves *[Wilson, 1999]*. The negative effects produced by caffeine are nervousness, sleep disorders, vomits, headaches, epigastric pain, tachycardia *[Varnam and Sutheland, 1994, Bruneton, 2001]*. Gastrointestinal disturbances and central nervous system stimulation associated with high doses of green tea extract have been attributed to their caffeine content *[Pisters et al., 2001]*.

Table 4: Caffeine Content in Food and Beverages

Product	Caffeine content*
Normal coffee	80–115 mg/150 mL
Espresso coffee	108–180 mg/150 mL
Instant coffee	65 mg/150 mL
Decaffeinated coffee	1–3 mg/150 mL
Green tea (3 min brewing time)	15–25 mg/150 mL
Black tea (3 min brewing time)	40–70 mg/150 mL
Oolong tea	18–33 mg/150 mL
Decaffeinated tea	0.6–3 mg/150 mL
Iced tea	70 mg/360 mL
Cocoa milk shake	5 mg/240 mL
Hot chocolate	4 mg/150 mL
Plain chocolate (bar)	15 mg/20g
Milk chocolate (bar)	5 mg/20 g
Cola soft drink	38–46 mg/360 mL

** A consumption higher than 200 mg/day is not advisable.*

Quantities vary according to the beverage preparation.

Source: Cabrera et al. [2006]

Regarding aluminum presence in black and green tea, some studies revealed the high capacity of this plant to accumulate aluminium. This aspect is important for patients with renal failures because aluminium can be accumulated by the body, resulting in neurological diseases. *Costa et al., [2002]* observed that black tea contains nearly six-fold more aluminium than green tea, and the extraction of aluminium in black teas was higher than the one observed in green teas; the aluminium concentrations in the tea infusions were constant after 5 min of extraction. These authors also indicated that the variations between different samples may be due to different soil conditions as well as different harvesting periods, and the influence of the water quality.

Several studies have demonstrated that black tea appears to inhibit the bioavailability of non-heme iron by 79% to 94% when both are consumed concomitantly; the impact of this interaction depends on the iron intake and iron status of the individual *[Tuntawiroon, 1991; Hurell 1992]*. Likewise, green tea catechins may have an affinity for iron, and green tea infusions can cause a significant decrease of the iron bioavailability from the diet *[Hamdaoui et al.,2003]*. On the one hand, some authors affirm that tea should not be consumed by patients suffering from anaemia. On the other hand, this effect may be of benefit to patients with genetic hemochromatosis *[McKay and Blumberg, 2002]*. It is worth noting that the interaction between tea and iron can be mitigated by the addition of lemon or consuming tea between meals.

Tea consumed at moderate temperature has not displayed any acute or chronic toxic effects and, in fact, it promotes health. Moreover, increased consumption of green tea polyphenols is not toxic. This has been supported by *Isbrucker et al., [2006]*, in a study which demonstrated that the dietary administration of EGCG [up to 500mg/kg] to rats and dogs for several weeks was not found to be toxic. Adverse or toxic effects of isolated green tea catechins or polyphenols have not been reported in humans.

Tea may go a long way in saving the human kind from physical and economic fallouts of the expensive and side effects causing drug therapy if used as a preventive and therapeutic agent.

CONCLUSION

Green tea has been consumed in China and other Asian countries since ancient times in order to maintain and improve health. Its antioxidant power is also strengthened by the presence of other phenolic compounds, vitamin C and minerals such as Cr, Mn, Se, and Zn, although specific data regarding this fact are still scarce. It is also important to consider the type of tea or its preparation [e.g., short time *vs.* long brewing time and hot tea *vs.* iced tea] due to the marked impact of these factors on polyphenol content and concentration. It is also important

to draw attention on the need of further-in-depth studies on the nature and mechanisms of the active green tea compounds, on the bioavailability of the different catechins in humans, and appropriate dose levels to act as functional food.

Nowadays, green tea is considered one of the most promising dietary agents for the prevention and treatment of many diseases and consequently, it is being studied extensively worldwide. Numerous studies in a variety of experimental animal models have demonstrated that aqueous extract of GTP designed as catechins [EGCG, EGC, ECG and EC] possess antioxidant, antimutagenic, antidiabetic, anti-inflammatory, antibacterial and antiviral, and above all, cancer-preventive properties. Epidemiological studies suggest that consumption of green tea may have a protective effect against the development of several cancers. Pre-clinical studies of green tea and its polyphenolic components have demonstrated antimutagenic and anticarcinogenic activity, and inhibition of growth of tumor cell lines in animal tumor models. Several epidemiological studies with humans have demonstrated that regular green tea consumption has beneficial effects and it shows a significant rate of protection against the development of some oral diseases and against solar radiations. It also contributes to body weight control and to the rise of bone density as well as being able to stimulate the immune system. Furthermore, green tea consumption has been recently reported to act positively against neurodegenerative diseases such as Parkinson and Alzheimer disease.

Since green tea beneficial health effects are being increasingly proved, it could be advisable to encourage the regular consumption of this widely available, tasty and inexpensive beverage as an interesting alternative to other drinks, which do not only show the beneficial effects of green tea, but are also more energetic, contain more caffeine [green tea contains less caffeine than black tea, coffee or cola soft-drinks], are rich in additives and/or CO_2. While no single food item can be expected to provide a significant effect on public health, it is important to note that a modest effect between a dietary component and a disease having a major impact on the most prevalent causes of morbidity and mortality, i.e., cancer and heart disease, should merit substantial attention. Taking all this into account, it would be advisable to consider the regular consumption of green tea in the diets.

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