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Review article

GREEN TEA ANTIOXIDANT EFFECTS AND ITS AMELIORATIVE ROLE AGAINST MANY DISEASES

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ABSTRACT: Green tea flavonoids have been found to play important roles in the non-enzymatic protection against oxidative stress, especially in case of cancer. Epidemiological and laboratory studies have reported that green tea presents diverse beneficial health effects including antioxidant , hypocholesterolemic , anti-hyperglycemic, antiparasitic, anti-inflammatory, antimicrobial, hepatoprotective , antinephrotoxcity and anticarcinogenic effects. Green tea ameliorating effects against oxidative stress caused by many pollutants and chemical toxins are also recorded by many studies.

Key words: Green tea, *camellia sinensis*, Antoxidant, antiinflammatory, diseases, natural herb

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INTRODUCTION

Herbal medicines derived from plant extracts are being increasingly utilized to treat a wide variety of clinical disease (Gupta et al., 2004). More attention has been paid to the protective effects of natural antioxidants against drug-induced toxicities especially whenever free radical generation is involved (Frei and Higdon, 2003). Flavonoids have been found to play important roles in the non-enzymatic protection against oxidative stress (Okada et al., 2001; Babich et al., 2005), especially in case of cancer. Flavonoids are group of polyphenolic compounds that occur widely in fruit, vegetables, tea, cocoas, and red wine (Arts et al., 1999; Bearden et al., 2000; Matito et al., 2003). Flavonoids, including flavones, flavanone, flavonols, flavanols and isoflavones, are polyphenolic compounds which are widespread in foods and beverages and possess a wide range of biological activities (Harborne and Williams, 2000), of which antioxidation has been extensively explored (Bors et al., 1994; Terao et al., 1994; Ioku et al., 1995; Croft, 1998; Pietta, 2000; McPhail et al., 2003; Goupy et al., 2003; Vaya et al., 2003).

Green tea (*camellia sinensis*)

Tea is obtained mainly from leaves and the terminal apical buds of the tropical shrub *Camellia sinensis*. The plant was originally discovered in south East Asia 1000 of years ago. It is now the most popular beverage, next to water, consumed by over two-thirds of the world's population. It is grown mainly in the subtropical zones. It is rich in substances with antioxidant properties and contains traces of proteins, carbohydrates, amino acids and lipids, as well as, more significant quantities of some vitamins and minerals (Gupta et al., 2002). Epidemiological and laboratory studies have reported that green tea presents diverse beneficial health effects including antioxidant (Sung et al., 2000; Nakagawa and Yokozawa, 2002), hypocholesterolemic (Lin et al., 1998; Riemersma et al., 2001; Erba et al., 2005 and Lee et al., 2005), anti-hyperglycemic (Tsuneki et al., 2004 and Li et al., 2006), hepatoprotective (Chung et al., 2003; Fujiki et al., 2005; Bun et al., 2006 and Kaviarasan et al., 2007) , anticarcinogenic (Wang et al., 1992 ; Lou et al., 1999; Hayakawa et al., 2001 and Zaveri, 2006).

The three tea types are green, black and oolong teas. Black tea constitute about 80% of the tea manufactured in the world , green tea about 20% and mainly consumed in Asia, oolong tea about 2% (Ahmad et al., 2000 and Katiyar and Mukhtar, 2001).

To produce green tea, freshly harvested leaves are rapidly steamed of pan-fried to inactivate enzymes, thereby, preventing fermentation and producing a dry, stable product. For production of black tea and oolong tea, the fresh leaves are allowed to wither until their moisture content is reduced to about 55% of the original leaf weight, which result in the concentration of polyphenols in the leaves. The withered leaves are then rolled and crushed, initiating fermentation of the polyphenols. During these processes, the catechines are converted to theaflvins and thearubigins. Oolng tea is prepared by firing the leaves shortly after rolling to terminate the oxidation and dry the leaves. Normal oolong tea is considered to be about half as fermented as black tea. The fermentation process results in oxidation of simple polyphenols to more complex condensed polyphenols to give black and oolong tea their characteristic colors and flavors (Mukhtar and Ahmad., 2000). Theaflavins and thearubigens contain benzotroplene rings with dihydroxy or trihydroxy substitution system and exist as catechin dimmers while the other polymeric polyphenols often called thearubigins are even more extensively oxidized and polymerized. Thus the catechins from the green fresh leaves are preserved in the final dry green product , while about 80% of the fresh catechines are biochemically oxidized in the manufacture of black tea . Oolong tea is partially oxidized (Balentine et al., 1997).

The tea leaves are distinguished by their content of methylxanthines, and polyphenols especially flavonols of the catechin type. The major green tea polyphenols are: (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin-3-gallate (ECG), (+)-gallocatechin (GC), (-)-epicatechin (EC), gallocatechin gallate (GCG) and catechin (C) which together may constitute 30% of the dry leaf weight, in addition to caffeine, theobromine, theophylline and phenolic acid, such as gallic acid are also present as minor constituents of green tea (Gupta et al., 2002, Castro et al.,2010, Mazzanti et al.,2015).

The percentages of catechines in green tea extract according to Sartippour et al.(2001) as follow: EGCG 46.8%, ECG 13.54%, GCG 7.24%, EC 8.07%, EGC 2.28%, GC 2.46%, CG 1.28%, C 2.22% and caffeine <0.3%. Tea also contain small amount of flavonols (kaempferol, quercetin and myricitin) in the form of glycosides. The flavonol content is less affected by processing, and flavonols are present in comparable amount in green and black tea (Balentine et al., 1997).

Metabolism of green tea

The bioavailability of tea catechins appears to be relatively low. When healthy volunteers were given a single serving of 4.5 g of green tea solids dissolved in 500 ml of water, peak plasma concentrations of individual catechins (conjugated and unconjugated) were <2 μmol/L (Yang et al., 1998). Average peak plasma catechin concentrations (conjugated and unconjugated) in healthy volunteers given a single dose of 1.5 mmol of pure EGC, ECG or EGCG were 5.0, 3.1 and 1.3 μmol/L, respectively (Van Amelsvoort et al., 2001). These values represent peak plasma levels after high doses of green tea or pure catechins. Average plasma catechin concentrations are likely to be considerably lower.

Gastrointestinal tract plays a very significant role in the metabolism and conjugation of these polyphenols before the liver is reached. In the jejunum and ileum of the small intestine there is efficient glucuronidation of flavanols by the action of UDP-glucuronosyltransferase enzymes and extensive *O*-methylation by the action of catechol-o-methyl-transferase. Unabsorbed flavanols, and those taken up, metabolized in the small intestine and liver and transported back into the intestinal lumen, will reach the large intestine where they are further metabolized by the gut microflora into smaller phenolic acids and valerolactones. The extent to which these phenolic acids are absorbed in the colon is presently unclear. However, they are detected in plasma and are often further conjugated and metabolized in the liver. Remaining compounds derived from flavonoid intake pass out in the feces (Spencer, 2003 and Sang et al., 2011).

Antioxidant activity of green tea

In order to assess the modifying effect of tea flavonoid on plasma antioxidant status, a variety of methods has been employed , commonly used is the ferric-reducing antioxidant power (FRAP), this the colorimetric assay that measure the ability of plasma to reduce the intense blue ferric tripyridyltriazine complex to its ferrous form, thereby changing its absorbance (Benzie and Strain, 1999).

Leenen et al.(2000) used the FRAP method in their study on 24 volunteers, the treatment consisted of 2 g single dose of green tea or black tea extract in 300ml of hot water, this significantly increased the plasma FRAP. A very strong increase in plasma antioxidant activity in a randomized crossover study with black tea (Langley-Evans, 2000) and was measured with FRAP assay 3hours after the first cup of tea, the antioxidant potential was further increased at 5 hours after the first intake.

Another assay which has been applied in human plasma is the total radical trapping antioxidant parameter (TRAP) (Ghiselli et al., 1995), in this assay the rate of peroxidation induced by 2'-azobis(2-amidinopropane) hydrochloride is monitored through the loss of fluorescence of the protein R-phycoerythrin. In the TRAP assay the lag-phase induced by plasma is compared with that induced by trolox in the same plasma sample. In a study with three groups of five volunteers drinking water, 6 g of black tea or green tea, Serafini et al. (1996) demonstrated a significant and strong increase in TRAP value in the tea groups between 30 and 60 min after a single consumption of 300 ml of either green or black tea. The plasma TRAP value was assessed in a randomized crossover study with green tea, black tea, water or water with caffeine treatments (Hodgson et al., 2000). A small non-significant increase in TRAP was found in both black tea and green tea also no changes occurred with caffeine in water.

The oxygen radical absorbing capacity assay (ORAC) is another commonly applied antioxidant assay based on the ability of a test substance to inhibit the oxidation of B-phycoerythrin by reactive oxygen species relative to trolox (Cao et al., 1995). Cherubini et al. (1999) and Duffy et al. (2001) used this method by giving 3.6 g of black tea extract in 500 ml hot water and measured the ORAC in plasma but there were non-significant results.

The addition of green tea catechins to plasma (Lotito and Fraga, 2000) or LDL (Zhu et al., 1999) resulted in sparing of endogenous α-tocopherol during in vitro oxidation. In hypercholesterolemic rabbits, green and black tea administration increased plasma α-tocopherol concentrations after 8 and 17 weeks of tea administration but not after 21 weeks (Tijburg et al., 1997). The total plasma antioxidant capacity was not affected by green or black tea administration over the 21-weeks study period. In rats, administration of green tea catechins prevented decreases in plasma and erythrocyte α-tocopherol concentrations resulting from a diet high in polyunsaturated fatty acids (Nanjo et al., 1993), but green tea flavonoid administration to marginally vitamin C-deficient Osteogenic Disorder Shionogi (ODS) rats did not increase plasma α-tocopherol concentrations (Kassaoka et al., 2002). Intake of green tea catechins for 4 weeks found to elevate vitamin E level in the mucosa of the rat large intestine (Yamamoto et al., 2006).

Tea administration prevented decreases in tissue glutathione (GSH) concentrations in many animal studies. Consumption of black tea leaves prevented carbon tetrachloride-induced liver depletion of GSH in male rats, but not in female (Sur-Altiner and Yenice, 2000). Similarly, providing green tea extract in the drinking water of male rats prevented decreases in liver GSH concentrations induced by ethanol administration (Skrzydlewska et al., 2002b). In mice infected with *Mycobacterium tuberculosis*, oral administration of green tea extract attenuated decreases in erythrocyte GSH concentrations caused by the infection (Guleria et al., 2002).

On the other hand, green tea does not only exert its antioxidant properties by polyphenols, L-theanine is the primary amino acid in green tea and represents 1%-2% of the leaf dry weight, it is synthetized in the roots of green tea and is concentrated in the leaves. L-theanine chemical structure is similar to glutamic acid, the latest is a precursor of GSH. Studies have shown that L-theanine protects the cell maintaining the levels of GSH in cancer and neurotixicity diseases(Pérez-Vargas et al., 2015).

The intake of green tea can be considered safe when its consumption does not exceed 1-2 cups/d. Nevertheless, hepatotoxicity has been attributed to the intake of green tea when it is used for weight control; furthermore(Mazzanti et al., 2015).

Pérez-Vargas et al (2015) found that L-theanine prevented the increased expression of NF-κB and down-regulated IL-1β and IL-6 and the cytokines TGF-β and CTGF induced by carbon tetrachloride. Moreover, the expression of the corresponding mRNAs decreased accordingly. On the other hand, L-theanine promoted the expression of IL-10 and the fibrolytic enzyme metalloproteinase 13 (MMP13).

In a study performed by Yu et al. (2015) they have shown that EGCG ameliorates liver inflammation, necrosis and fibrosis and suppressed the expression of TNF-α, IL-1β, TGF-β, MMP9, α-SMA, and Col-1α1. Similar results were obtained in HSC cell line LX-2, where EGCG was capable of suppressing TGF-β1, Col-1α1, MMP2, MMP9, TIMP1, and α-SMA.

Administration of tea and tea polyphenols has been reported to prevent or attenuate decreases in antioxidant enzyme activities in a number of animal models of oxidative stress. Providing hairless mice with green tea polyphenols in their drinking water significantly inhibited UVB-induced decreases in epidermal catalase and glutathione reductase activities (Agarwal et al., 1993).

Oral administration of green tea extract to mice infected with *M. tuberculosis* attenuated infection-associated decreases in erythrocyte superoxide dismutase (SOD) activity (Guleria et al., 2002), while oral administration of either black or green tea extract resulted in increased serum SOD activity in mice exposed to the carcinogen, 3-methylcolanthrene (Das et al., 2002). Providing rats with green tea extract in their drinking water attenuated ethanol-associated decreases in serum and liver SOD as well as liver glutathione peroxidase (GPX) and catalase activities (Skrzydlewska et al., 2002b).

Intoxication of rat's liver by tamoxifen (45 mg/kg/day for 7 days) in the study of El-Beshbishy (2005) resulted in significant reduction of antioxidant enzymes activities as GST , GPX , SOD and catalase by 26, 39, 39, 39% respectively also GSH was reduced by 27% compared to normal control , by the effect of green tea extract 1.5% as their sole source of drinking water for 4 days before and along the time of tamoxifen intoxication, the enzyme activities showed significant increment by 25, 24, 48, 60% respectively compared to tamoxifen intoxicated rats and GSH by 18%.

In the study of Erba et al.(2005) the level of lymphocyte glutathione peroxidase activity was significantly decreased in persons who consumed green tea drink, glutathione and glutathione peroxidase were elevated by green tea extract only in the diet and decreased with ethanol intoxication but in case in giving both ethanol and green tea in the diet these were improved significantly in both liver and brain homogenate (Ostrowska et al., 2004).

Antioxidant enzymes in liver homogenate of rats as Cu,Zn-SOD, catalase, GPX, and GSSG-R all of these were improved and elevated significantly by adding green tea extract 7g/L to drinking water. Non-enzymatic antioxidant as GSH, vitamin C, vitamin E, vitamin A and β-carotene were decreased by age, and some of them re-elevated again by green tea extract as GSH, β-carotene, and vitamin E (Augustyniak at al., 2005). In the same study intoxication of ethanol leads to decrease of antioxidant enzymes and most of them were returned to the normal range with green tea extract treatment. The activity of SOD is low in diabetes mellitus. The alloxan-induced diabetic rats when were treated with green tea polyphenols, they showed decrease in lipid peroxidation associated with increased activity of SOD and GSH (Sabu et al., 2002).

A major development over the past two decades has been the realization that free radical mediated peroxidation of membrane lipids and oxidative damage of DNA are associated with a variety of chronic health problems, such as cancer, atherosclerosis, neurodegenerative diseases and aging (Finkel and Holbrook, 2000; Perwez Hussain et al., 2003; Barnham et al., 2004). Therefore, inhibition of oxidative damage by supplementation of antioxidants becomes an attractive therapeutic strategy to reduce the risk of these diseases (Rice-Evans and Diplock, 1993; Brash and Harve, 2002 Vuong et., 2011 and Zhang et al., 2012).

Green tea polyphenols are good antioxidant against free radical initiated lipid peroxidation in solutions (Jia et al., 1998) in micelles (Zhou et al., 2000; 2004 and 2005) in human red blood cells (Ma et al., 2000; Dai et al., 2006 and Rizvi et al., 2006) in human low density lipoprotein (Liu et al., 2000) and in rat liver microsomes (Cai et al., 2002) , and that the antioxidant activities of these polyphenols depend significantly on the structure of the molecules, the initiation conditions and the microenvironment of the reaction medium (Cai et al., 2002). It was found that these green tea polyphenols could interact with α-tocopherol, synergistically to enhance their antioxidant activity (Zhou et al., 2005; Wei et al., 2006a). Dietary green tea catechins inhibit colonic mucosal lipid peroxidation in 1,2-dimethylhydrazine-induced colonic carcinogensis . Intake of green tea catechins in rats fed monounsaturated fatty acids suppressed iron-induced lipid peroxidation of intestinal mucosa homogenate. Age-dependent and ethanol induced lipid peroxidation in the study of Augustyniak et al. (2005) was decreased by 7 g/L green tea in liquid diet. The study of El-Beshbishy (2005) on the effect of tamoxifen on lipid peroxidation of liver homogenate , this showed that, increment of TBRS level significantly in comparing to normal , administration of green tea extract resulted in high improvement in lipid peroxidation . In the study of Coimbra et al.(2006) on 34 portuguese subjects drinking green tea for 4 weeks, the levels of malondialdehyde and malondialdehyde+4-hydrroxy-2(E)-nonenal and the oxidative stress in erythrocyte membrane, namely membrane bound hemoglobin, were reduced significantly.

Epicatechins (antioxidant present in green tea) scavenge a wide range of free radicals including the most active hydroxyl radical, which may initiate lipid peroxidation. It prevents the loss of lipophilic antioxidant α-tocopherol, by repairing tocopheryl radicals and protection of the hydrophilic antioxidant ascorbate (Skrzydlewska et al., 2002a). Therefore, it may decrease the concentration of lipid free radicals and terminate initiation and propagation of lipid peroxidation (Guo et al., 1999). Epicatechins are effective scavengers of physiologically active reactive oxygen and nitrogen species including superoxide (Nakagawa and Yokozawa, 2002; Cui et al., 2005), peroxyl radical (Guo et al., 1999), peroxynitrite (Paquay et al., 2000) and hypochlorous acid (Scott et al., 1993).

It was reported that, epicatechines can react with superoxide radical via one electron transfer mechanism or by a hydrogen abstraction mechanism to form the corresponding semiquinone (Wang et al., 1996). Epicatechins may chelate metal ions, especially iron and copper, which, in turn inhibit generation of hydroxyl radicals and degradation of lipid hydroperoxides which causes reactive aldehyde formation (Azram et al., 2004).

The levels of lipid peroxidation products (lipid hydroperoxide, malondialdehyde and 4-hydroxynonenal) in rats consumed ethanol only in the diet were elevated highly compared to control but by adding green tea extract to the diet all these were improved in the liver homogenate and brain homogenate (Ostrowska et al., 2004). Improvement because the compounds of green tea scavenge a wide range of free radicals , including the most active hydroxyl radical , which may initiate lipid peroxidation, therefore, catechins may decrease the concentration of lipid free radicals and terminate initiation and propagation of lipid peroxidation. Catechins may chelate metal ions, especially iron and copper which, in turn, inhibit the generation of hydroxyl radical and degradation of lipid hydroperoxides, which caused reactive aldehydes formation. Furthermore, the green tea polyphenols have been demonstrated to inhibit iron-induced oxidation of synaposomes by scavenging hydroxyl radicals generated in the lecithin/lipoxidase system. The chelating effect of green tea results in a reduction of the free forms of iron (Guo et al., 1996; Frei and Higdon, 2003). Under in vivo condition GSH acts as an antioxidant and its decrease was reported in diabetes mellitus. The increased GSH content in the liver of alloxan-induced diabetic rats treated with green tea polyphenols may be one of the factors responsible for the inhibition of lipid peroxidation (Sabu et al., 2002).

Oxidative damage to proteins may result in chemical modification of amino acids, aggregation, or cross-linking of proteins or protein fragmentation (Frei and Higdon, 2003). Supplementing the diets of rats with 1% EGCG significantly inhibited increases in muscle protein carbonyl content induced by electrical muscle stimulation (Nagasawa et al., 2000). Protein glycation results from the reactions between primary amino groups of proteins and reducing sugars, such as glucose. Oxidation and structural rearrangement of glycated proteins results in the formation of advanced glycation end products, such as N^{ϵ}-(carboxymethyl) lysine and pentosidine. Old rats (up to 22 month of age) given green tea extract in their drinking water starting at 6 month of age were found to have decreased aortic collagen-linked Maillard-type fluorescence, a marker for advanced glycation endproducts (Song et al., 2002). As mentioned above, oral administration of green tea prevented ethanol-induced increases in 4-HNE adducts to liver proteins (Arteel et al., 2002). The controlled study to examine the effect of tea polyphenol consumption on oxidative damage to proteins in humans compared a low flavonoid diet with the same diet fortified with green tea extract over a 3-weeks period (Young et al., 2002). Levels of oxidatively modified plasma and hemoglobin proteins were not significantly different between the two diets.

Protein oxidation which induced by ethanol or caused by aging detected by carbonyl and bis-tyrosine content in rat's liver homogenate were increased markedly, green tea provided some protection for protein against oxidative modification (Augustyniak et al., 2005).

Oxygen species-induced oxidative stress in human microvascular endothelial cells by 10 mM H_2O_2 or by xanthin/xanthin oxidase enzymatic system resulted in significant decrease of cell viability about 30% of control, by pretreatment of tea polyphenols 10µg/ml the viability of cells were markedly elevated , which indicated that green tea could act as a biological antioxidant in a cell culture experimental system and protect the endothelial cells from oxidative stress-induced toxicity, which might inhibit atherosclerosis under similar pathogenic conditions (Rah et al., 2005). It was suggested that this effect of green tea polyphenols related to the intrinsic properties of them, which pass readily through the cell membrane due to their amphipathic properties, moreover, it has been reported that green tea polyphenols showed excellent adsorption to collagen in the extracellular matrix and various receptors on the cell membrane (Hyon and Kim, 2001; Han et al., 2004). Green tea polyphenols have already shown to be significantly effective for protecting rat calvarial otseoblasts from reactive oxygen species (e.g. H_2O_2 and xanthin/xanthin oxidase)-induced oxidative stress (Park et al., 2003).

Anderson et al. (2001) showed that EGCG is the most active antigenotoxic compound of the catechins. The strand break reducing effects were already seen at micromolar concentrations. There is therefore increasing interest in the possible beneficial effects of EGCG on DNA stability and health (Glei et al., 2003).

Glei and Pool-Zobel (2006) have shown that the continuous presence of physiological relevant EGCG amounts can reduce bleomycin-induced DNA damage in primary leucocytes in vitro. Since, bleomycin induces radical mediated damage the findings also point to a radical scavenging mechanism by EGCG in human cells. This is an important hint that regular tea consumption could possible contribute to similar antigenotoxic effects in humans, as was also demonstrated for fruit juices containing green tea catechins (Bub et al., 2003).

Wei et al. (2006b) in their study on pBR322 DNA damage by 2,2'-azobis(2-amidinopropane hydrochloride) (AAPH) they found that the supercoiled DNA was gradually converted to open-circular DNA with the increase of AAPH DNA was gradually converted to linear DNA (from 10 – 80 mM) . Incubation of DNA with 10 mM AAPH for 90 min resulted in the formation of open circular and linear forms of DNA, indicating both single-strand and double-strand DNA breaks, but by addition of trolox and EGCG to DNA resulted in partial or complete inhibition of conversion of supercoiled DNA to open circular and linear forms, indicating that trolox and EGCG are able to protect plasmid DNA against AAPH-initiated oxidative damage.

The inhibition effect produced by green tea polyphenols was measured with the activity as follow: EC = ECG > EGCG > EGC. Induced lymphocyte DNA damage was improved by green tea extract ingestion (Erba et al., 2005). Topical EGCG inhibited the epidermal formation of the oxidized DNA bases, thymidine glycol, 5-hydroxymethyl-2_-deoxyuridine and 8-hydroxy 2_-deoxyguanosine (8-OHdG) in mice treated with phorbol ester-type tumor promoters (Wei and Frenkel, 1993).

The most commonly measured oxidized DNA base in animal studies of tea administration is 8-OHdG. In addition to decreasing lung adenomas, providing green tea or EGCG to mice in their drinking water significantly inhibited increases in lung DNA levels of 8-OHdG induced by the tobacco carcinogen, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (Xu et al., 1992). Providing green tea extract to rats in their drinking water (Inagake et al., 1995) and black tea polyphenols by gavage (Lodovici et al., 2000) significantly inhibited 8-OHdG increases in colon mucosa induced by the colon carcinogen, 1,2-dimethylhydrazine . In hamsters, providing green tea catechins in the drinking water significantly inhibited 8-OHdG increases in the pancreas induced by the pancreatic carcinogen, *N*-nitrobis(2-oxopropyl)amine (Takabayashi et al., 1997). Administering green tea to rats in their drinking water inhibited increases in liver 8-OHdG induced by the hepatic carcinogen, 2-nitropropane (Hasegawa et al., 1995 and Sai et al., 1998). Green tea administration to rats also inhibited increases in liver 8-OHdG resulting from diethylnitrosamine exposure or cirrhosis induced by a choline-deficient diet (Tamura et al., 1997).

Although pentachlorophenol-induced increases in liver 8-OHdG were significantly inhibited by supplementing the diets of mice with vitamin E, supplementation with EGCG did not significantly inhibit liver 8-OHdG formation (Sai-Kato et al., 1995). Thus, with a few exceptions, tea and tea polyphenols have consistently been found to inhibit increases in 8-OHdG, a biomarker of oxidative DNA damage, induced by a number of different chemical carcinogens in different species and different target tissues.

Numerous studies have demonstrated that tea catechins and polyphenols are effective scavengers of physiologically relevant reactive oxygen and nitrogen species in vitro, including superoxide O_2. (Nanjo et al., 1993; Nakagawa et al., 2002), peroxyl radicals, singlet oxygen (Guo et al., 1999), peroxynitrite $ONOO^-$ (Haenen et al., 1997; Paquay et al., 2000), and hypochlorous acid (Scott et al., 1993). Several structures appear to be important for these antioxidant activities of tea polyphenols, including an *ortho*-3′4′-dihydroxyl (catechol) group or 3′4′5′-trihydroxyl (gallate) group in the B ring, a gallate group esterified at the 3 position of the C ring, and hydroxyl groups at the 5 and 7 positions of the A ring (Rice-Evans et al., 1996).

The ability of a compound to act as a free radical scavenger is partly related to its standard one-electron reduction potential ($E°'$), a measure of the reactivity of an antioxidant as hydrogen or electron donor under standardized conditions. A lower $E°'$ indicates that less energy is required for hydrogen or electron donation and is one factor in determining antioxidant activity. Tea catechins and theaflavins have $E°'$ values comparable to that of α-tocopherol (vitamin E), but higher than ascorbate (vitamin C) which is a superior hydrogen donor (antioxidant) to tea polyphenols (Jovanavic et al., 1996; 1997).

The ability of tea polyphenols to chelate metal ions, such as iron and copper, may contribute to their antioxidant activity by preventing redox-active transition metals from catalyzing free radical formation (Rice-Evans et al., 1997). These metal-chelating properties likely explain the ability of tea polyphenols to inhibit copper-mediated LDL oxidation and other transition metal-catalyzed oxidations in vitro (Brown et al., 1998). However, it is not clear whether metal chelation is a physiologically relevant antioxidant activity, because most transition metal ions are bound to proteins in vivo where they cannot participate in metal-catalyzed free radical formation.

Green and black tea, as well as individual catechins and tea polyphenols, can inhibit the activation of the redox-sensitive transcription factors, nuclear factor-κB (NF-κB) and activator protein-1 (AP-1), in cultured cells. Although other antioxidants also can inhibit these redox-sensitive transcription factors, recent research indicates that tea catechins and polyphenols are acting as kinase inhibitors in complex signaling pathways. Interestingly, the kinase inhibiting activities of tea polyphenols may not be directly related to their ability to function as hydrogen donators or antioxidants (Yang et al., 2002).

Phase II detoxification enzymes promote the excretion of potentially toxic or carcinogenic chemicals. Most phase II enzymes contain *cis*-acting regulatory elements called antioxidant response elements (ARE). Glutathione S-transferases (GST) are a family of phase II enzymes that catalyze the conjugation of glutathione to electrophiles, thereby reducing their ability to react with and damage nucleic acids and proteins (Parkinson, 1996). Green tea polyphenol extract (Yu et al., 1997) as well as individual green tea catechins (Chen et al., 2000) have been found to increase ARE-mediated reporter gene activity in transfected HepG2 cells. Feeding rats green tea leaves significantly increased liver GST activity (Lin et al., 1998), and providing mice with green tea polyphenols in their drinking water also significantly increased GST activity in the liver and small intestine (Khan et al., 1992).

Many in vitro and in vivo studies have demonstrated that several parameters of erythrocyte functions and integrity are negatively affected by increased oxidative stress. In fact, changes in membrane fluidity and inactivation of membrane-bound receptors and enzymes (Halliwell and Gutteridge, 1986), ionic parameters (Maridonneau et al., 1983), an increase in lipid peroxidation (Rohan et al., 1998), oxidation of glutathione and protein sulphohydryl group (Telci et al., 2000) and activation of proteolysis (Davies and Goldberg, 1987) have all been described following the application of oxidative stress to erythrocytes.

Decreased erythrocytes antioxidative capacity in non-insulin dependent diabetes mellitus has been shown to be correlated with several diabetic complications. Atherosclerosis and microvascular complications in diabetes are reported to be linked with a reduced antioxidant status of diabetic erythrocytes (Saltsburg et al., 1999). Rizvi et al. (2005) reported the concentration-dependant protective effect of tea catechins on tert-butyl hydroperoxide oxidation effect which resulted in increase in malondialdehyde content, reduced glutathione, and membrane sulphydryl group in type 2 diabetic erythrocytes.

In vitro study of Dai et al.(2006) on the oxidative hemolysis of AAPH on human red blood cells , it was found addition of AAPH at $37^{o.c}$ to the suspension of RBC caused fast hemolysis after a short time of inhibition period , and addition of flavonols or their glycosides (myricetin, quercetin, morin, kaempferol, Rutin, quercetin galactopyranoside, quercetin rhamnopyranoside, and kaempferol glucopyranoside) significantly suppressed the hemolysis, the addition of myricetin, quercetin, rutin, quercetin galactopyranoside and qurecetin rhamnopyranoside which bears an orth-dihydroxyl functionality showed much more effective anti-hemolysis activity than other glycosides (morin, kaempferol and kaempferol glucopyranoside) bearing no such functionality.

The erythrocyte membrane is constantly subjected to oxidative stress due to high content of peroxidizable. The aging process affects the erythrocyte membrane properties (Dobrzynska et al., 2005). It is manifested by cell thickness decrease (Kelly et al., 1995), by change in membrane asymmetry (Igbavboa et al., 1996) and by change in composition of its phospholipids and fatty acids present therein. The changes in phospholipids content can influence in a significant way electric properties of membrane and equilibrium between components of cell membrane and its environment (Lopez et al., 1995; Zhang et al., 1996; Youdim et al., 2000). The ingestion of green tea (7g/L for 5 weeks in liquid diet) partially prevented decrease in erythrocyte antioxidant abilities observed during aging process (Dobrzynska et al., 2005).

Ethanol and its metabolites can react with the membrane of erythrocyte and reduce the cell membrane surface hydration and affects the membrane protein-lipid structure. Acetaldehyde and ROS can react with proteins and thus modify their structure and functions. Green tea in liquid diet in the study of Dobrzynska et al. (2005) reduced these abnormalities significantly.

Interleukin-2-deficient mice in the study of Varilek et al. (2001) who were received green tea plyphenols 5g/L in drinking water for 6 weeks appeared when hematocrit was measured at the beginning and the end of the experiment that the hematocrit was improved from 26 to 36%.

Effect of tea polyphenols on total WBCs in alloxan-induced diabetic animals was studied by Sabu et al. (2002), total WBCs was found to be 14650/µl in normal rats and in alloxan-diabetic rats it was 9112/µl on 18^{th} day of the study. Administration of green tea polyphenols (100mg/kg body weight) considerably reversed alloxan-induced cellular damage as seen from the increase number of total WBC when compared with diabetic control group.

The ameliorating and protective effect of Green tea against diseases

Stimulation of inflammatory cells such as macrophages by bacterial endotoxins or inflammatory cytokines results in increased expression of inducible nitric oxide synthase (iNOS) and subsequent production of large amounts of nitric oxide (NO^-). Nitric oxide reacts very rapidly with O_2 to form $ONOO^-$ and other NO derived oxidants capable of damaging DNA and proteins (Surh et al., 2001).

Green tea and black tea (Paquay et al., 2000 ; Sarkar and Bhaduri et al., 2001), as well as individual catechins (Chan et al., 1997 ; Lin and Lin, 1997) and theaflavins (Lin et al., 1999), can inhibit lipopolysaccharide- induced iNOS gene expression and iNOS activity in cultured macrophages. Green tea catechins and black tea theaflavins appear to downregulate iNOS by inhibiting NF-κB activation (Lin and Lin, 1997; Lin et al., 1999).

Green tea has an anti-inflammatory effect among its various biological effects (Cheng, 2003). Sueoka et al.(2001) reported that green tea has anti-inflammatory effect via its inhibition of TNF-alpha gene expression which mediated through inhibition of NF-kB and AP-1 activation . The inhibitory effect of green tea on TNF-alpha is the cause of the preventing effect of it on chronic inflammatory diseases such as rheumatoid arthritis and multiple sclerosis. In the same study of Sueoka et al.(2001) they examined TNF-alpha transgenic mice which over express TNF-alpha only in the lung , they found that expression on TNF-alpha and IL-6 were inhibited in the lung after green tea ingestion in drinking water for 4 months.

Green tea has a treatment effect on reperfusion-induced myocardial damage (Aneja et al., 2004) and preventive effects on chronic inflammatory diseases including neurological disorders (Aktas et al., 2004; Li et al., 2004). Green tea can inhibit lipopolysacharide-induced iNOS gene expression and iNOS activity in cultured macrophage. Green tea catechins appear to regulate to down regulate iNOS by inhibiting NF-kB activation (Lin and Lin, 1997; Lin et al., 1999). Through their peroxidase activity, lipoxygenases and cycloxygenases are capable of co-oxidizing molecules other than their regular substrates, with the potential for increasing oxidative in some tissues (Parkinson, 1996). Green tea polyphenols were found to inhibit COX-2 and 5-,12- and 15-lipoxygenase activities in human colon mucosa cells and human colon cancer cells (Hong et al., 2001).

Feeding green tea polyphenols to mice were found to inhibit ultraviolet light induced increase in epidermal COX activity (Agarwal et al., 1993), whereas topical application of green tea inhibited phorbol ester-induced increases in epidermal COX and lipoxygenase activity (Katiyar et al., 1992). Precancerous lesions for colon mucosa and COX-2 activity were lowered in azoxymethan-treated rats given 2% green tea extract in their drinking water compared with control (Metz et al., 2000).

Varilek et al. (2001) in their study on interlukin-2-deficient mice who were received green tea polyphenols 5gm/L in drinking water for 6 weeks demonstrated that green tea polyphenols inhibit inflammatory responses. Explants colon and lamina propria lymphocyte culture supernatants from green tea polyphenol-traeted mice showed decreased spontaneous interferon-γ and tumor necrosis factor-α secretion compared with control , also green tea polyphenol group had less sever colitis and demonstrated by lower histologic score and wet colon weight, this was associated with lower plasma levels of serum amyloid
inhibitory effect on carcinogenesis (Zhu et al., 2006). In the study of Jia et al. (2000) on the A.

One of the beneficial effects of tea is its potentially chemopreventive effects a grade of Zhejiang green tea and tea pigment on Wister rats colorectal carcinogenesis induced by 1,2-dimethylhydrazine , the positive control group developed colorectal tumors about 2.6 tumors per rat and volume 294 mm^3 after 32 weeks , in the groups treated with green tea or green tea pigments the mean number of rats which developed tumors was reduced to about 45% of positive control and the tumor volumes were reduced by 70% of positive control.

Many studies have looked into the possible association between tea consumption and protective or inhibitory effect of gastric (Setiawan et al., 2001; Gao et al., 2002; Hoshijama et al., 2002; Kinjo et al., 2002; Sun et al., 2002 and Mu et al., 2003a,b) , esophageal (Gao et al., 2002; Ke et al., 2000 and Mu et al., 2003), lung (Zhong et al., 2001), breast (Sartippour et al., 2001; Deguchi et al., 2002; Tao et al., 2002 and Yanaga et al., 2002), liver (Zhang et al., 2002; Mu et al., 2003b), prostate (Gupta et al., 2001; Jian et al., 2004) and oral (Hsu et al., 2002) cancers, also skin tumors (Lu et al., 2002 ; Baliga and Katiyar, 2006) and leukemia (Smith and Dou, 2001) .

In the study of Setiawan et al. (2001) which involving 133 stomach cancer cases, 166 chronic gastritis cases and 433 healthy controls, found a protective effect of green tea not only against stomach cancer but also against chronic gastritis. Gao et al., in a case-control study of 141 cases of oesophageal cancer and 223 controls, showed that regular tea consumption reduced the risk of oesophageal cancer. Zhong et al. (2001) conducted a population-based case-control study (649 female cases of primary lung cancer and 675 female controls) and found that among non-smoking women, consumption of green tea was associated with a reduced risk of lung cancer. Sartippour et al. (2001) examined the effect of green tea on breast cancer growth and endothelial cells in vitro and in animal models , and compared the potency of the different catechin components of green tea extract , the results showed that green tea extract and its catechin components were effective in inhibiting breast cancer and endothelial cells proliferation. In mouse experiment, green tea extract suppressed xenograft size and decreased the tumor vessel density.

The effect of powdered green tea in diet on hepatoma-bearing rats was studied by Zhang et al. (2002) and showed that dietary powdered green tea and time-dependently reduced the solid tumor volume and weight. Mu et al. (2003) reported that green tea may have had a significant protective effect on liver cancer among alcohol drinkers and cigarette smokers. Gupta et al. (2001) reported that oral infusion of a polyphenolic fraction isolated from green tea significantly inhibits prostatic cancer development and increase survival in TRAMP mice.

Green tea and its constituents in the study of Hsu et al. (2002) selectively induced apoptosis in oral carcinoma cells while EGCG was able to inhibit the growth and invasion of oral carcinoma cells which suggest that the chemopreventive effects of green tea polyphenols may involve a p57 mediated survival pathway in normal epithelial cells, while carcinoma cells undergo an apoptotic pathway (Hsu et al., 2001). Smith and Dou (2001) reported that the tea polyphenol EGC inhibits DNA replication in three leukemia cancer cell lines, Jurkat T, HL-60 and K562. Among all the tested polyphenols EGC was found to be the most potent in accumulation of S phase cells and inhibition of the S-G_2 progression. In addition, EGC-mediated inhibition of S phase progression results in induction of apoptosis, as determined by sub-G_1 cell population, breakage of endonuclear DNA, cleavage of ply(ADP-ribose) polymerase and loss of cell viability. When used in cells containing low S and high G_1 and G_2/M population, EGC did not induce apoptosis. Furthermore, EGC did not inhibit M-G_1 transition.

In the study of Lu et al.(2002) SKH-1 hairless mice were irradiated with ulteraviolet B twice weekly for 20 weeks after this they were treated with topical application of caffeine or EGCG once a day for 5 days with absence of ulteraviolet radiation. Topical application of caffeine or EGCG decreased the number of non-malignant and malignant skin tumors per mouse, increased apoptosis as measured by the number of caspase 3-positive cells in nonmalignant skin tumors and in squamous cell carcinoma, but there was no effect on apoptosis in nontumor areas of the epidermis.

Bin Dajem *et al*.(2011) used the aqueous extract of green tea in a Schistosoma mansoniinfected mice model to investigate its effect on the oxidative stress, antioxidant system and liver pathology induced by the parasite. They found that green tea extract suppressed the oxidative stress by decreasing the lipid peroxides. However, failed to enhance the antioxidant system and to reverse alterations in the liver such as necrosis.

The cancer chemopreventive properties of green tea have been attributed to its inhibition of tumor cell proliferation and molecular pathways involved in the cell cycle, angiogenesis, invasion, and growth factor-related proliferation (Adhami et al., 2003; Lambert and Yang, 2003 and Zaveri, 2006). EGCG treatment results in G1 growth arrest, inhibition of cyclin-dependent kinases (cdks) and induction of cdk inhibitors p21 and p27 in breast and prostate cancer cells (Park and Dong, 2003 and Gupta et al., 2004). EGCG also inhibits several growth factor signaling cascades, either by direct blockade of growth factor receptors or through downstream effects (Gouni-Berthold and Sachinidis, 2004). EGCG also inhibits transcription factor-mediated gene activation such as that via NF-κB and AP-1 (Ahmad et al., 2000). Inhibition of NF-κB and AP-1-mediated gene activation is the central phenomenon that explains the convergence in the antioxidant activity of the green tea catechins and their effects on specific molecular targets. NF-κB, in response to ROS, activates transcription of many pro-inflammatory and anti-apoptotic/survival genes (Schoonbroodt and Piette, 2000). The ROS-scavenging activity of green tea catechins (Levites et al., 2002) inhibits NF-κB activation, leading to inhibition of expression of these proinflammatory and survival genes. In addition, EGCG has been shown to directly inhibit proteasome activity (Nam et al., 2001), leading to accumulation of the NF-κB inhibitory protein, IκB, and other pro-apoptotic proteins such as Bax. Inhibition of NFκB-mediated gene activation is also the likely mechanism of inhibition of inducible nitric oxide synthase observed with green tea and EGCG, which mediates its anti-inflammatory actions (Singh et al., 2002). Green tea also inhibits angiogenesis and tumor invasion by inhibiting metalloproteinases and the vascular endothelial growth factor receptor expression and signaling in tumor and endothelial cells, respectively (Jung et al., 2001; Masuda et al., 2002; Kojima-Yuasa et al., 2003 and Waleh et al., 2005).

In clinical trials, green tea has shown protective effects against various kinds of cancers, including premalignant prostate, esophageal, colon, rectum and pancreatic cancers (Hosseini and Ghorbani, 2015). Nevertheless, in hepatocellular carcinoma, green tea did not have any protective effect (Darvesh et al., 2013).

Green tea consumption has been inversely associated with the development and progression of cardiovascular diseases (Cheng, 2006; Stangl et al., 2006) and associated with a lower incidence of coronary artery disease. The protective effect of green tea in cardiovascular diseases is thought to stem from its antioxidant activity (Higdon and Frei, 2003; Zaveri, 2006). Shen et al. (1998) studied the ability of tea polyphenols to lower serum cholesterol and triglyceride in aged rats and showed that 2% tea polyphenols lowered serum cholesterol with 21.6% and increased the ratio of HDL-C to total cholesterol by 30%.

Lee et al.(2005) studied the long-term effects of green tea consumption on atherosclerotic markers in smokers and concluded that green tea ingestion resulted in decrease of plasma soluble p-selectin and oxidized LDL in plasma . The extract of green tea attenuated blood pressure increase in spontaneously hypertensive rats, an affect attributed to its antioxidant properties (Negishi et al., 2004). It also could lower blood pressure in rats through the inhibition of angiotensin I-converting enzyme activity (Wang and Wang, 1991; Ke et al., 2000; Lin and Omori, 2001; 2002).

Erba et al. (2005) investigated the effect of addition of two cups of green tea containing about 250mg of total catechins to a controlled diet in a group of healthy volunteers against a control group, a part from triacylglycerol level which was significantly higher in the green tea group. However, in both control and experimental group the triglyceride level, total cholesterol and HDL was not modified by green tea consumption.

Oral intake of green tea extract by human volunteers increased resistance of plasma LDL to oxidation in vivo, an effect that may lower the risk of artherogensis (Miura et al., 2000). In apolipoprotein E-deficient mouse model of artherosclerosis, green tea extract in drinking water prevented the development of artherosclerosis without affecting plasma lipids (Miura et al., 2001). Similarly, EGCG at a dose 10 mg/kg given intraperitoneally inhibited the developing atherosclerotic plaque in apolipoprotein E-deficient mice but no effect on established lesions (Chyu et al., 2004).

The study of Maron et al. (2003) reported a double-blind, randomized, placebo-controlled, parallel-group trail in out patient clinics in six urban hospitals in China. A total of 240 men and women 18 years or older on a low-fat diet with mild to moderate hypercholesterolemia were randomly assigned to receive a daily capsules containing theaflavin-enriched green tea extract (375 mg) for 12 weeks. The result showed that green tea extract is effective adjunct to a low-saturated fat diet used to reduce LDL-C in hypercholesterolemic adults.

In the study of Bursill and Roach (2006) When HepG2 cells were incubated with the main green tea constituents, the catechins, epigallocatechin gallate (EGCG) was the only catechin to increase LDL receptor binding activity (3-fold) and protein (2.5-fold) above controls. EGCG increased the conversion of sterol regulatory element binding protein-1 (SREBP-1) to its active form (+56%) and lowered the cellular cholesterol concentration (-28%). At 50μM, EGCG significantly lowered cellular cholesterol synthesis, explaining the reduction in cellular cholesterol. At 200μM EGCG, cholesterol synthesis was significantly increased even though cellular cholesterol was lower, but there was a significant increase seen in medium cholesterol. This indicates that, at 200μM, EGCG increases cellular cholesterol efflux. This study provides mechanisms by which green tea modulates cholesterol metabolism and indicates that EGCG might be its active constituent.

Plants containing flavonoids have been used to treat diabetes in Indian medicine, the green tea flavonoid has been shown to have insulin-like activities (Waltner-Law et al., 2002) as well as insulin-enhancing activity (Anderson and Polansky, 2002). However, epigallocatechin gallate, which is the principal catechin in green tea, differs from insulin in that it affects several insulin-activated kinases with slower kinetics. Furthermore, epigallocatechin regulates genes that encode gluconeogenic enzymes and protein-tyrosine-phosphorylation by modulating the redox state of the cell (Waltner-Law et al., 2002). Thus epigallocatechin gallate may be an antidiabetic agent.

Tsuneki et al. (2004) documented for the first time that a certain serum protein may be involved in the antihyperglycemic effect of green tea. Wu et al. (2004a,b) also demonstrated that green tea increases insulin sensitivity in Sprague–Dawley rats and that the green tea polyphenol is one of the active components. In a fructose-fed rat model, Shimada et al. (2004) found that green tea ameliorates insulin resistance and increases glucose transporter IV content of adipocytes isolated from the epididymal fat pads. In Japan (Shimada et al., 2004) and Taiwan (Hosoda et al., 2003), oolong tea was shown to be an effective adjunct to oral hypoglycemic agents in the treatment of patients with type 2 diabetes. However, if one is a diabetic and likes tea, this is another good reason to keep drinking it. However, one should refrain from using added milk, soy milk, or nondairy creamer, because they may reduce the positive effect of tea on insulin activity (Campbell, 2004).

Administration of green tea polyphenols (500mg/Kg body weight) to normal rats increased glucose tolerance significantly at 60 min. Green tea polyphenols was also found to reduce serum glucose level in alloxan-diabetic rats at a dose level of 100mg/Kg body weight continued daily administration (Sabu et al., 2002). EGCG was found to inhibit intestinal glucose uptake by sodium dependent glucose transporter (SGLT1) indicating its increase in controlling blood sugar (Kobayashi et al., 2000). Streptozotocin-diabetic rats showed increased sensitivity to platelet aggregation and thrombosis and this abnormality was improved by dietary catechins of green tea (Choi et al., 1998; Yang et al., 1999).

Obesity has increased at an alarming rate in recent years and is now a worldwide health problem including China (Cheng, 2004a,b). It has been known for some time that tea helps to control obesity, and this is common knowledge in China.

A Chinese classical pharmaceutical book called the Bencao Shiyi (The Conpendium of Materia Medica) states: ‘‘Drinking tea for a long time will make one live long to stay in good shape without becoming too fat and too heavy’’. The mechanisms of action of tea in obesity are: stimulation of hepatic lipid metabolism (Murase et al., 2002); inhibition of lipases (Chantre and Lairon, 2002); stimulation of thermogenesis (Dulloo et al., 1999; 2000; Chantre and Lairon, 2002); modulation of appetite (Liao, 2001) ; and synergism with caffeine (Kovacs et al., 2004 ; Zheng et al., 2004).

Oolong tea has been shown to be effective in the treatment of obesity by increasing plasma adiponectin levels (Shimada et al., 2004), enhancing the effect of caffeine in oolong tea on noradrenaline-induced lipolysis in adipose tissue, and inhibiting pancreatic lipase activity (Han et al., 1999). Simple tea drinking may have easier acceptance by the patients than prescription drugs, exercise, and bariatric surgery. There are 5 main attractions of this approach: (1) more natural; (2) safer; (3) no need for professional supervision; (4) readily accessible and affordable; and (5) attractive alternatives to failed attempts at weight reduction by other more conventional approaches (Heber, 2003).

In the study of Ostrowska et al. (2004), by electron microscope investigation of rat’s liver intoxicated with ethanol with or without treatment with green tea in diet, in case of ethanol only, impairment of the biologic membranes were found, these changes extended to subcellular structures (lesion of internal structure and, occasionally, blurring of membranes surrounding cellular organelles) as well as plasmolema.

Liver showed also pronounced changes in the cell membrane on the hepatocyte surface directed to Disse's space, where irregular decomposition or total atrophy of microvilluses was observed. In addition, markedly widened perisinusoid space was seen to fill with varied contents. Feeding of green tea with ethanol resulted in more orderly arrangement of subcellular structures of hepatocytes and pathologic changes of cell membrane were slight, the vascular surface of liver cells was covered by regularly distributed microvilluses found in Disse's space, which are separated from the sinusoid by endothelial cells. Ethanol intoxication in the study of Augustyniak et al. (2005) leads to increase in liver enzymes ALT, AST, by treating with green tea extract 7g/L in drinking water these parameters were significantly improved.

The study of Hosnuter et al (2015) demonstrate that EGCG treatment, prevented multiorgan damage in thermal trauma by inhibiting proinflammatory and oxidative pathways, which causes a concomitant decrease in lipid peroxidation and an increase in tissue antioxidant defense. Thus, EGCG treatment merits consideration as a potential therapeutic agent for organ damage following thermal injury.

For detection green tea hepatoxicity 2500mg/Kg/day of green tea extract were given to rats for 6 weeks , liver enzymes were analyzed (ALT, AST, ALP, GGT) in the study of Bun et al. (2006), there were no any significant changes were observed . This means that green tea has no any hepatotoxic effect.

Many studies proved the hepatoprotective role of green tea extract (Hamden et al., 2009 and Gad et al., 2013) The great beneficial influence of GTE was attributed to the high content of catechins. Epicatechin, epicatechin gallate (ECG), epigallocatechin (EGC), and epigallocatechin

gallate (EGCG) are the major catechins present in green tea extract (Matsumoto et al.,2012).

Induced liver injury by lipopolysaccharide and D-glactosamine in rats was suppressed by adding green tea extract 30g/Kg to the diet, this hepatoprotective effect of green tea through the inhibition of TNF-α-induced apoptosis of hepatocyte, rather than through the suppression of TNF-α production, although the suppressed production of TNF-α may be associated with the hepatoprotective effect of caffeine (He et al., 2001). Singal et al. (2006) also demonstrated that green tea extract significantly attenuated lipopolysaccharide-induced sickness behavior as well as hepatic damage either by its antioxidant activity or by inhibiting induced cytokine production in rats. Induced hepatotoxicity with alloxan 120mg/Kg body weight i.p in a single dose leads to increase in hepatic enzymes as ALT, AST and ALP, all these were returned to normal range with green tea polyphenols administration (Sabu et al., 2002). Tamoxifen intoxication in rats with 45mg/Kg/day for 7 days i.p resulted in elevation in serum liver enzymes ALT and AST. The oral administration of green tea extract 1.5% 4 days before and 14 day after tamoxifen intoxication as a sole source of drinking water decrease the liver transaminases levels , which speculated that 1.5% green tea extract has the capacity to scavenge free radicals can protect liver from tamoxifen hepatoxicity (El-Beshbishy et al., 2005).

In a study performed by Halegoua-De Marzio *et al* (2012) they have shown, after a single oral dose of green tea (400 mg), in patients with cirrhosis induced by HCV, that it is safe and well tolerable by all patients, therefore suggesting the use of green tea in the treatment of cirrhosis in the future.

The study of Ibrahim et al. (2015) concluded that excessive accumulation of copper nanoparticles in the liver caused several adverse effects including changes in liver enzyme activities, generation of ROS, marked pathological changes, DNA damage, and apoptosis. on the other hand green tea extract could provide a cushion for prolonged protective benefit against copper nanoparticles -induced hepatotoxicity without harmful side effects through its potent antioxidant and antiapoptotic properties.

Induced nephrotoxicity with cyclosporine A (20mg/day for 21 days ip) leads to harmful effects on kidney functions as elevation of serum creatinine, blood urea, serum uric acid and urinary glucose, also lowering in creatinine clearance. By giving green tea extract (1.5%) in drinking water before cyclosporine intoxication with one week and along the time of the experiment all these defects were ameliorated (Mohamadin et al., 2005). All these defects as a result of the oxidative stress which induced by cyclosporine which also detected in the same study by measurement of GSH, catalase, SOD, GSH peroxidase, GSH reductase and GST in kidney homogenate, all these parameters were affected by lowering their activities and concentrations significantly compared to control animals and ameliorated by green tea extract drinking, also the same occurred by measuring lipid peroxidation in kidneys, this might indicate the usefulness of green tea as an excellent source of antioxidant in modulating the oxidation stress kidney diseases.

Lysosomal enzymes as N-acetyl-β-glucosaminidase , β-glucuronidase and acid phosphatase are known to be involved in the cell and tissue damage and were elevated by induced nephrotoxicity (Whiting et al., 1986 ; Schmid et al., 1993) , these elevations were reduced by green tea extract in drinking water (Mohamadin et al., 2005). Induced alloxan renal dysfunction with 120 mg/Kg body weight interaperitoneally in a single dose was improved with green tea polyphenols administration (Sabu et al., 2002).

Yokozawa et al. (1996) has showen that green tea tannin suppressed the progression of renal failure in nephroectomized rats. There were increases in blood urea nitrogen, serum creatinine, urinary protein, and decrease in creatinine clearance in the nephroectomized rats, whereas better results for these parameters were obtained in rats given green tea tannin after nephroectomy.

The protective effect of green tea extract and its constituent polyphenols on the nephrotoxicity induced by immuno-suppressant FK506 in a porcine renal proximal tubular cell line, LLC-PK1 cells, was evaluated in the study of Hisamura et al. (2006), FK506 caused a significant increase in apoptotic cells but the addition of green tea extract, and particularly its major polyphenolic components EGC and EGCG, suppressed the cell death. Yokozawa et al. (2003) examined the effect of green tea polyphenols in arginine-fed rats, a useful experimental model of renal failure resulting from uraemic toxins and nitric oxide synthase caused by excessive dietary arginine and suggested that green tea polyphenols would ameliorate renal failure induced by excessive dietary arginine be decreasing uraemic toxin and nitric oxide production and increasing radical-scavenging enzyme activity.

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