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Review Article

Green tea as a functional food for better health: A brief review

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ABSTRACT

Tea is the most popular drink after water, consumed everyday by millions of people around the world. Tea is generally consumed in the forms of green, oolong, and black tea, all of which originate from the leaves of the plant Camellia sinensis. Tea consumption began about 5000 years ago in southwest China, where it was used medicinally to treat various illnesses. Health benefits are believed to be largely due to the presence of high levels of flavonoids. Recent human studies suggest that green tea may contribute to a reduction in the risk of cardiovascular disease and some forms of cancer, as well as to the promotion of oral health. In addition, green tea possesses significant antioxidant, anti-inflammatory, antimicrobial, antihypertensive, thermogenic properties. Increasing interest in its health benefits has led to the inclusion of green tea in the group of beverages with functional properties. The present review focuses on the beneficial effects of tea consumption on human health.

Keywords: Green tea, catechins, antioxidant, anti-inflammatory, anti-cancer, coronary heart disease, obesity, antioxidant.

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INTRODUCTION

Tea is one of the most widely consumed beverages in the world today, second only to water, well ahead of coffee, beer, wine and carbonated soft drinks [1,2]. The tea plant, Camellia sinensis, is a member of the Theaceae family, and black, oolong, and green tea are produced from its leaf and buds. It is an evergreen shrub or tree that can grow to a height of 30 feet, but is usually clipped to a height of 2.5 feet in cultivation. The tree or shrub is heavily branched with dark-green, hairy, oblong, ovate leaves cultivated and preferentially picked as young shoots. Green tea is produced from steaming fresh leaves at high temperatures, thereby inactivating the oxidizing enzymes and leaving the polyphenol content intact. Tea consumption began about 5000 years ago in southwest China. Western cultures favour black tea, which is prepared through the oxidation, curing process of maceration and exposure to atmospheric oxygen [3-5]. In USA, the 80% of tea consumed is black ice tea [6]. Tea leaves as well as the resulting beverage tea are known to possess high amounts of polyphenols, especially flavanols catechins [7]. Chemical analyses revealed that green tea contains significant amounts of vitamins and minerals such as ascorbic acid, riboflavin, niacin, folic acid, pantothenic acid, magnesium, potassium, manganese, and fluoride [8, 9].

Several epidemiological studies and clinical trials showed that green tea might reduce the risk of many chronic diseases, including cardiovascular disease, reduce the risk of stroke and coronary heart disease [10-12]. Some studies performed in experimental animals suggested that green tea might protect against the development of coronary heart disease by reducing blood glucose levels, and body weight [13, 14]. Furthermore, green tea consumption has also been linked to the prevention of many several types of cancer including lung, colon, esophagus, mouth, stomach, small intestine, kidney, pancreas, and mammary glands [15]. The present review focuses on the beneficial effects of tea consumption on human health.

Chemistry, Composition, and Consumption of tea:

The tea plant C. sinensis is native to Southeast Asia but is currently cultivated in more than 30 countries around the World. Tea is the most consumed beverage in the World next to water, with consumption of about 120 ml/day [16]. Of the total amount consumed in the World, 78% is black, 20% green and 2% oolong tea [5]. Black tea is consumed in the western countries and in some Asian countries, whereas green tea in China, Japan, India and a few countries in North Africa and Middle East [5, 17]. Oolong tea production and consumption are confined to southeastern China and Taiwan [16]. The production of green tea is characterized by an initial heating process, which kills the enzyme polyphenol oxidase, which is responsible for the conversion of the flavanols in the leaf into the dark polyphenolic compounds that colour black tea. The other important process is rolling, in which leaves are cut and twisted. The final form of green tea depends on the particular variant being produced. The rolling stage is very similar to the operation with the same name in black tea production. Green tea production is restricted mainly to China and Japan [18]. To produce green tea, freshly harvested leaves are rapidly steamed or pan-fried to inactivate enzymes, thereby preventing fermentation and

producing a dry, stable product. They also showed that epicatechins are the main compounds in the green tea and accounting for its characteristic color and flavor [19].

For the production of black and oolong teas, the freshly leaves are allowed to weather until their moisture content is reduced to about 55% of the original leaf weight, which result in the concentration of the polyphenols in the leaves. The weathered leaves are then rolled and crushed, initiating fermentation of the polyphenols. During these processes, the catechins are converted to theaflavins and thearubigins [19]. Oolong 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 [20]. The fermentation process results in oxidation of simple polyphenols to more complex condensed polyphenols to give black and oolong teas their characteristic colors and flavors [20]. The greater the fermentation, the lower the polyphenol content and the higher the caffeine content. Black tea has 2-3 times the caffeine content of green tea [21]. Green tea chemical composition is complex: proteins (15-20% dry weight) whose enzymes constitute an important fraction; amino acids (1–4% dry weight) such as teanine or 5-N-ethylglutamine, glutamic acid, tryptophan, glycine, serine, aspartic acid, tyrosine, valine, leucine, threonine, arginine, lysine; carbohydrates (5-7% dry weight) such as cellulose, pectins, glucose, fructose, sucrose; lipids as linoleic and linolenic acids; sterols as stigmasterol; vitamins (B, C, E); bases such as caffeine and theophylline; pigments as chlorophyll and carotenoids; volatile compounds as aldehydes, alcohols, esters, lactones, hydrocarbons, etc.; minerals and trace elements (5% dry weight) such as Ca, Mg, Cr, Mn, Fe,Cu, Zn, Mo, Se, Na, P, Co, Sr, Ni, K, F and Al [22, 23]. The composition of the tea depends on a variety of factors, including climate, season, horticultural practices, the type and age of the plant [19]. Green tea contains two groups of compounds, polyphenol and alkaloids. Alkaloids found in tea include caffeine, theobromine, and theophylline provide the stimulant effects of tea and build prominently in the experience of tea drinking, although they are not thought to be central to tea medicinal effects [24,20]. On the other hand, polyphenols include flavanols, flavanoids and phenolic acids and account for 30% of the dry weight of green tea leaves [19].
The polyphenols found in all tea give its astringent, somewhat bitter flavor. Most of the polyphenols in green tea are flavanols, commonly known as catechins e.g. (-)-epicatechin (EC), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epigallocatechin-3-gallate (EGCG). In black teas, the major polyphenols are theaflavin and thearubigin [19, 25]. Analysis by HPLC of the aqueous tea extracts showed that the total flavanol content of the green variety was much higher than the black varieties [26].

Bioavailability of tea polyphenols:

Fujiki et al. [27] revealed that EGCG had wide distribution in mouse organs such as esophagus, stomach, duodenum, colon, liver, lung, pancreas, skin, breast, bladder, prostate, brain, kidney, uterus and ovary or testes. They also found that EGCG had incorporated into the cytosol as well as the nuclei. Several pharmacokinetic studies showed that catechins were found in human saliva and blood at very minute levels after mouth rinsing and oral administration [28-31]. Topical application of EGCG in hydrophilic ointment to human or mouse

skin resulted in transdermal penetration only in mouse skin; however, EGCG does not enter into the systemic circulation in human [32].

Pharmacokinetics:

Auger et al. [21] and Yang et al. [33] reported that the bioactive constituents of green tea are absorbed following oral administration in a dose dependent manner. The catechins are metabolized by the liver and kidneys, and cleared from the body chiefly by the kidneys. They also reported that the plasma half-life of epigallocatechin gallate is 5.5 hours. P-gp, multidrug resistance (MDR1) gene product, in the apical membranes of intestinal cells may reduce the absorption of EGCG by transporting this catechin back into lumen of the intestine [34].

In physiological conditions, it is very likely that EGCG is oxidatively decomposed, but not (+)-catechin. The decomposition of EGCG and EGC was found in a short time, even at pH 7.4 [35]. Despite having more intensive activity, EGCG appears to be inferior in bioavailability because it is possibly decomposed during intestinal absorption and in blood. The major fractions of orally administered catechins are present as sulfate and glucuronide conjugates in human blood [30]. Less active but more stable (+)-catechin is preferable as a hepatoprotective agent than EGCG. Although green tea catechins have the intensive activity to reduce membrane fluidity, it is presumed that there is no possibility for catechins to show unwanted actions in vivo because of metabolic conjugation in addition to low bioavailability [25].

Catechins metabolites such as 5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone and 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone were detected in plasma, feces, and urine of human volunteers after ingestion of green tea [36]. They were produced by intestinal microorganisms from EGC and EC respectively [36]. Catechins metabolites such as 4-hydroxybenzoic acid, 3,4-dihydroxybenzoic acid, 3-methoxy-4-hydroxy-hippuric acid and vanillic acid have also been detected in urine [37].

Catechins pass through glucuronidation, sulfation and O-methylation in the liver of animals and humans [38, 39]. Conjugates can move from bile to the small intestine where they are deconjugated and cleaved by microorganisms to simple phenolic acids and lactones, which are then absorbed via the intestinal mucosa and excreted in bile and urine [39].

Lu et al. [40] studied the cytosolic catechol-O-methyltransferase (COMT) catalyzed methylation of EGCG and EGC in humans, mice, and rats. EGCG was readily methylated by liver cytosolic COMT to 4′-O-methyl-EGCG and then to 4′,4′-di-O-methyl-EGCG, and EGC was methylated to 4′-O-methyl-EGC. The K_m and V_{max} values for EGC methylation were higher than EGCG. Rat liver cytosol had higher COMT activity than that of humans or mice. The small intestine had lower specific activity than the liver in the methylation of EGCG and EGC. It was reported that EGCG is mainly excreted through the bile, and that EGC and EC are excreted through the bile and urine [32].

Toxicity:

Sano et al. [41] reported that green tea consumption in both human and experimental animals have no any toxicity. Single doses of decaffeinated green tea solids up to 4.5 g/day (45 cups of tea) have been well tolerated by humans [42].

Detoxification activity:

Glucuronidation, the predominant human phase II liver detoxification pathway, has been shown to be enhanced with green tea administration [26, 43]. Glucuronic acid is conjugated with toxins to facilitate their elimination from the body via bile [20]. Green tea administration in rats (as the only drinking fluid) increased glucuronidation by 100 %. Bu-Abbas et al. [26] suggested that the increase in glucuronidation might contribute to the anti-carcinogenic effect of green tea by facilitating the metabolism of the chemical carcinogens into inactive, readily-excrete able products.

HEALTH BENEFITS

Consumption of green tea provides a protection against stroke [44], liver disease [45], bacterial infection [46,47], cancer [48], viral infection [49, 50] and lowers the risk of osteoporosis [51, 52]. Green tea catechin was reported to have a protective effect on mammalian hepatic cells, leading to its therapeutic use for hepatitis [53, 54]. The catechin incorporated in cell membranes was shown to prevent or reduce the morphological and biochemical alterations of hepatocytes induced by hepatotoxicity agents [55, 56]. Tsuchiya [25] suggested that the reduction in membrane fluidity is responsible for the anti-plaque and hepatoprotective effects of green tea catechins.

Green tea catechins inhibit the growth of various bacteria [57, 58]. A comparative study recently revealed that the minimal inhibitory concentration of EGCG was much lower than that of EC. Also reported that EGCG causes more intensive damage of the membranes compared with EC, indicating the importance of a galloyl moiety for the effects of catechins [59]. Catechins and green tea extracts show minimal inhibitory concentrations ranging from 100 to 1000 µ mol / L against various bacteria [57-59]. In an oral pharmacokinetic study, catechins maintain the µ mol /L concentrations in human saliva after oral application of green tea extract [31]. At the corresponding concentration levels, all the eight catechins reduced membrane fluidity [25].

Anti-inflammatory effects of tea:

The polyphenolic fraction from green tea was shown to protect against inflammation caused by certain chemicals, such as 12-O-tetradecanoylphorbol-13-acetate, a principal irritant in croton oil [60,61,16], or by ultraviolet radiation [62]. Green tea has also been shown to be effective against the immunosuppression caused by ultraviolet radiation [60, 16]. In addition, green tea polyphenols have shown protection against cytokines induced by tumors [60]. Green

tea polyphenols are potent anti-inflammatory agents and have been shown to inhibit nitric oxide (NO) production in tumor cell lines [62]. Haqqi et al. [63] suggested that green tea polyphenol (GTP), that is potent antioxidant, might be useful in the prevention of onset and severity of arthritis. Dona et al. [64] provide molecular and cellular insights into the claimed beneficial properties of green tea and indicate that EGCG is a potent anti-inflammatory compound with therapeutic potential.

Anticancer effects of tea:

Worldwide interest in green tea as a cancer preventive agent for humans has increased, because it is non-toxic and it is effective in wide range of organs. Consumption of green tea is a practical and effective cancer preventive both before cancer onset and after cancer treatment [64]. Several researches indicate that polyphenolic antioxidants present in green and black tea can reduce risk in a variety of animal tumor bioassay systems [16, 65, 66]. The consumption of tea and its polyphenolic constituents affords protection against chemical carcinogen or ultraviolet radiation-induced skin cancer in the mouse model. Tea consumption also affords protection against cancers induced by chemical carcinogens that involve the lung, fore stomach, esophagus, duodenum, pancreas, liver, breast, colon, and skin in mice, rats, and hamsters [16]. Recent studies have indicated that green tea and its polyphenolic constituents impart inhibitory effects on the activities of many enzymic, metabolic, and signaling pathways that have relevance to cancer development and progression [67-71].

Cell culture studies have shown that GTP and EGCG inhibit growth of several types of human prostatic cancer cells [72-74, 33]. Gupta et al. [75] reported that 0.1 % green tea polyphenols provided to transgenic adenocarcinomas of the mouse prostate (TRAMP) mice resulted in (i) significant delay in primary tumor incidence and tumor burden, (ii) significant decrease in prostate (64%) and genitourinary (72%) weight, (iii) significant inhibition in serum insulin-like growth factor-I and restoration of insulin-like growth factor binding protein-3 levels, and (iv) marked reduction in protein expression of proliferating cell nuclear antigen (PCNA) in the prostate compared with water-fed TRAMP mice. These results were verified by Sadzuka et al. [76] who showed that green tea treatment increases the concentration of doxorubicin in tumor but not in normal tissue.

Hiroyasu et al. [77] induced renal cell carcinoma in rats by ferric nitrilotriacetate (Fe-NTA), which is an established model of reactive oxygen species (ROS)-associated cancer. They also identified the p16 INK4A tumor suppressor gene as one of the major target genes in this model. They concluded that the intake of green tea or processed grain foods stabilizes p16INK4A in the genome, at least in this model, and might be helpful for the prevention of ROS-associated cancer. This novel method is versatile, and may work as a surrogate end-point biomarker for screening the usefulness of agents for cancer chemoprevention.

Tea polyphenols inhibited growth of human lung cancer cell line, PC-9, dose-dependently, the order of potency being ECG, EGCG and EGC, but EC was not effective [78]. These results suggested that EGCG is the most important of the tea polyphenols, because of its

high content (5-fold that of ECG) and its activity. Although EC is the apparently inactive tea polyphenol, Suganuma et al. [79] discovered that EC showed synergistic effects with EGCG on induction of apoptosis in PC-9 cells, concluding that unfractionated green tea has stronger effects than any single tea polyphenol.

Epicatechin (EC) stimulated the cancer preventive activity of EGCG and other polyphenols mediated through enhancement of their incorporation into the cells, demonstrating that green tea itself is a more effective and practical cancer preventive than EGCG alone [64]. The topical application of EGCG to mouse skin inhibited interaction of tumor promoters, hormones, and various growth factors with their receptors [80]. Subsequently, green tea and EGCG in drinking water were found to inhibit carcinogenesis in a wide range of target organs in animal experiments including esophagus, stomach, duodenum, colon, liver, lung, pancreas, skin, breast, bladder and prostate [81-84, 61,48,].

Mice treated with both diethylnitrosamine (DENA) and green tea displayed a significant decrease in mean number of lung and liver tumors, compared to DENA-only treated animals [85]. Other researchers found similar results in rats [86, 87].

Schut and Yao [88] reported that black and green teas are potential chemopreventive agent in PhIP-induced tumorgenesis in F-344 rat. On the other hand, Kang et al. [89] suggested that epicatechin prevent human cancer by preventing the down-regulation of gap junctional intercellular communication during the cancer promotion phase.

It was found that in the presence of green tea epicatechin (GTE; 100 µg/ml) and one of its polyphenolic components, epigallocatechin (ECG; 100 µM), both cellular non-protein (GSH) and protein-sulfhydryl (PSH) levels were significantly decreased and this was associated with a decrease in cell viability. These results identify SH groups as a novel target of green tea polyphenols cytotoxicity in tumor cells [90].

In the PhIP feeding model, administration of 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine (PhIP) alone for 52 weeks induced adenocarcinomas in 40% of rats, but the incidence was remarkably reduced to 5% by the simultaneous treatment with 0.5% 1-O-hexytrimethylhydroquinone (HTHQ), a strong lipophilic phenolic antioxidant, or to 10% by 0.1% caffeine. Administration of 1% chlorophyllin exerted similar, albeit weaker, effects. α-Tocopherol at a dose of 0.5% only reduced the multiplicity of carcinomas, and 1% green tea catechins reduced only the mean size of mammary tumors [91].

Fujiki et al. [92] reported that various cancer preventive agents commonly inhibit TNF-α release from the cells. Suganuma et al. [93] concluded that TNF-α is the key cytokine for tumor promotion on mouse skin. Thus, inhibition of TNF-α release is clearly a useful method of screening for cancer preventive agents [94].

Fujiki et al. [94] named the phenomenon, inhibition of the interaction of tumor promoters with their receptors, as well as those of hormones, growth factors and cytokines, the

sealing effect of EGCG suggesting that the sealing effect of tea polyphenols is the key to its inhibitory action. They found strong evidence that EGCG inhibits TNF-α gene expression in the cells and TNF-α release from the cells. Therefore, it was concluded that the inhibition of TNF-α expression is one of the most important activities of EGCG and GTP for cancer prevention [94]. Few researchers groups found that green tea catechins (GTCs) do not inhibit, but rather way enhances colon carcinogenesis, while not influencing lung and thyroid carcinogenesis [91, 95].

Effect of green tea on blood pressure:

Hodgson et al. [96] concluded that tea ingestion caused larger acute increases in blood pressure than caffeine alone. However, any acute effects of tea on blood pressure did not translate into significant alterations in ambulatory blood pressure during regular tea consumption.

Effect of green tea on coronary heart disease:

Coronary heart disease is most prevalent in the Western world, probably as a diet high in saturated fats and low physical activity, and the large proportion of the population who smoke cigarettes and have high blood pressure. A variety of epidemiologic studies showed the preventive effect of green tea consumption against atherosclerosis and coronary heart disease [97, 98]. Tea consumption has also been shown to reduce the risk of high blood cholesterol concentration and high blood pressure [99]. In addition, studies in experimental animals showed the preventive effect of green tea against atherosclerosis [100]. Priyadarshi et al. [101] reported that green tea extract appears to block the development of cardiac hypertrophy in experimental renal failure.

Effect of green tea on thyroid glands:

The green tea extract catechins was confirmed to have antithyroid and aromatase inhibition effects [102], that is obvious when 5% polyphenone-60 (P-60), green tea extract catechins, was administered to male rats for 2-8 weeks induced goiters and decreased weights of the body. Endocrinologically, elevating plasma thyroid stimulating hormone (TSH), luteinizing hormone (LH) and testosterone levels and decreasing tri-iodothyronine (T_3) and thyroxine (T_4) levels were induced by this treatment. It was also found that P-60 as a whole and some of its constituents exhibited inhibitory effects on human placental aromatase activity [102].

Sakamoto et al. [103] reported that green tea catechin causes marked hypertrophy and/or hyperplasia of thyroid follicles, some with depletion of colloid and some with rich colloid, and formation of a fibrous capsule. Degree and incidence of thyroid lesions were higher in males than in females. Weight of thyroid was increased, all indicating that catechins have goiterogenic effect.

One of the suggested mechanisms of the antithyroid effects of catechins was their inhibition to thyroid peroxidase (TPO). As TPO catalyzes the thyroid hormone biosynthesis, i.e.,

oxidation of inorganic iodide (I^-) to reactive iodine (I_2) for binding of iodine to the tyrosyl residues in thyroglobulin, TPO inhibition in rodent experiments resulted in a decrease in T_3 and T_4 and subsequent TSH increase [104, 102]. Major components of P-60, other than catechins, include caffeine at 9.2 %. Bartsch et al. [105] indicated that the endocrinological effect of P–60 was unlikely due to caffeine. In comparison with humans, rodents are highly sensitive to goitergenic treatment, because of a shorter plasma T4 half-life (12-24 h) in rats than in humans (5-9 days), which derives from the absence of highly-affinity thyroxine-binding globulin in rats that is present in humans. Moreover, male rats are especially sensitive because of their higher circulating levels of TSH than in female rats [104,106,107].

It has been reported that ip injection of EGCG to rats for 7 days suppressed food intake, which was associated with a reduction of testosterone levels, LH levels, testis weight and prostate weight [108]. However, when the same amount of EGCG was given to rats orally for 7 days, these effects were not observed, while, LH levels were less. Satoh et al. [102] conclude that aromatase inhibition may be one of the mechanisms responsible for the endocrinological changes.

Effect of green tea on brain:

Hong et al. [109] suggested that the minimizing effect of green tea extract on the eicosanoid accumulation and oxidative damage in addition to the reduction of neuronal cell death could eventually result in protective effect on ischemia/reperfusion-induced brain injury and behavior deficit [110,111].

Effect of green tea on liver:

Chen and Zhang [112] reported that EGCG, in two steps, significantly and effectively inhibited the proliferation of primary and passage HSC. The polyphenolic compound initiated its inhibitory action by rapidly blocking the phosphorylation of tyrosine in platelet-derived growth factor-beta receptor (PDGF-βR) elicited by PDGF in serum. This action was short-lived, persisting for a couple of hours. In addition, this antioxidant inhibited the gene expression of PDGF-βR by blocking the activation of transcription factor AP-1 and NF-kB, which were required for the gene transcription.

Accumulating evidence has demonstrated that EGCG results in a dose-based inhibition not in normal cells [113, 19]. EGCG has been found to have no detectable toxicity in activated hepatic stellate cell (HSC) in vitro at a concentration up to 100 M, based on no detectable lactate dehydrogenase release, and a rapid recovery of HSC proliferation after withdrawal of EGCG [114]. The antioxidant potential of EGCG is far greater than that of vitamin E and/or C [115].

Effect of green tea on oxidative stress:

Polyphenols found in green tea have a greater antioxidant activity than do either vitamins C or E and are believed to be suitable for protection against reactive oxygen species (ROS) and their associated pathologies [116]. Green tea polyphenols (GTPs) and especially the gallic acid moiety are known to scavenge O^{-}_{2}, $HO^{\cdot}$ and $ROO^{\cdot}$ [117,118]. It was reported that GTPs can scavenge ROS in all cellular compartments, in a variety of cells and in different body compartments before they have time to cause damage [119].

Yokozawa et al. [120] reported that green tea polyphenol was administered to rats at a daily dose of 50 or 100 mg/kg body weight for 30 days with a 2% w/w arginine diet. In rats given green tea polyphenol the SOD and catalase activities, which were suppressed by excessive arginine administration, were increased dose-dependently, implying the biological defense system was augmented because of free radical scavenging activity.

Young rats when drunken green tea for five weeks, GSH content of serum increased slightly, whereas the index of the total antioxidant status increased significantly and lipid peroxidation products, particularly malondialdehyde (MDA) was significantly diminished [121]. In the central nervous tissue, the activity of SOD and glutathione peroxidase (GSHpx) decreased, while the activity of glutathione reductase and catalase increased after drinking green tea for five weeks by young rats. Moreover, the level of LOOH, 4-HNE and MDA significantly decreased [121,111].

Skrzydlewska et al. [121] reported that Green tea increased the activity of hepatic glutathione peroxidase (GSHpx), glutathione reductase, and the content of reduced glutathione, while it decreased lipid hydroperoxides (LOOH), 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) of rat's drunken green tea for five weeks. The concentration of vitamin- A increased by about 40%. Tea beverages suppress D-galactosamine induced liver injury in rats [122].

Green tea has been found to provide protection to the liver against a variety of toxic insults, including singlet oxygen [123], t-butyl hydroperoxides and bromotrichloromethane [41], alcohol [124], 1,4-naphthoquinone [125], D-galactosamine [126,122]. Miyagawa et al. [125] reported that the hepatoprotective effect of green tea is not dependent on its direct antioxidant effects alone. Green tea catechins have been shown to maintain intracellular protein thiol levels. Protein thiols help to maintain the intracellular reduction-oxidation (redox) balance. Protein tertiary configuration (shape), and therefore cellular function, is dependent on the maintenance of the redox balance. In rat liver cells exposed to 1, 4-naphthoquinone, green tea extract prevented the exposed cellular to damage. This protective effect was suggested to be due to the maintenance of protein thiol levels by green tea.

The effect of green tea on other detoxifying and antioxidant enzymes is controversial. Some researchers found oral feeding of green tea in drinking water (0.2 %, w/v) to mice for 30 days significantly increased the activities of glutathione peroxidase, catalase, and quinone

reductase in small bowel, liver, and lung, and glutathione S-transferase in small bowl and liver. GTP feeding to mice also resulted in considerable enhancement of glutathione reductase activity in the liver [127]. Other researchers reported no increase in glutathione peroxidase, catalase, or SOD following a much larger exposure of rats to green tea for four weeks [26].

Choi et al. [128] reported that EGCG has protective effects against beta A-induced neuronal apoptosis through scavenging reactive oxygen species, which may be beneficial for the prevention of Alzheimer's disease. Levites et al. [129] reported that neuroprotection was attributed to the potent antioxidant and iron chelating actions of the poly-phenolic constituents of tea extracts preventing nuclear translocation and activation of cell death-promoting NF-kappa B. Brain-penetrating property of polyphenols may make such compounds an important class of drugs for treatment of neurodegenerative diseases. They also suggested that green tea extract attenuated the neurotoxic action of 6-hydroxydopamine (6-OHDA)-induced neuronal death.

Green tea scavenges the reactive nitrogen species:

Lin and Lin [113] assessed the effects of EGCG on nitric oxide production by murine peritoneal macrophages. Their results suggest that EGCG blocked early events of nitric oxide synthase (iNOS) induction by inhibiting the binding of transcription factor kB (kappaB) to inducible nitric oxide synthase promotor, thereby inhibiting the induction of iNOS transcription. Human chondrocytes co-treated with EGCG produced significantly less nitric oxide (NO) compared with chondrocytes stimulated with interleukin-1beta (IL-1beta) alone. The inhibition of NO production correlated with the suppression of induction and expression of NF-kappaB-dependent gene iNOS. EGCG inhibited the activation and translocation of NF-kappaB to the nucleus by suppressing the degradation of its inhibitory protein, I kappaB-alpha, in the cytoplasm. These results led them to suggest that EGCG inhibits the (IL-1beta)-induced production of NO in human chondrocytes by interfering with the activation of NF-kappaB through a novel mechanism. Singh et al. [62] suggested that EGCG may be a therapeutically effective inhibitor of IL-1beta-induced inflammatory effects that are dependent on NF-kappaB activation in human osteoarthritis (OA) chondrocytes. Yokozawa et al. [120] reported that green tea polyphenols exerted a slight reduction of nitrite plus nitrate, indicating that green tea polyphenol reduced the production of uremic toxins and NO.

Paquay et al. [130] found that green tea and black tea are able to suppress the lipopolysaccharides (LPS)-mediated induction of iNOS. Oldreive et al. [131] reported that the ability of green tea polyphenols (GTP) to scavenge reactive nitrogen species derived from acidic nitrite may contribute to the protective effects of tea polyphenols against gastric cancer.

Chronic inflammation has been implicated as the underlying factor in the pathogenesis of many disorders. In the past decade, inflammation-related endogenous production of reactive nitrogen species, similar to oxygen free radicals, has also been suggested as a risk factor for cancer, in addition to the well-studied exogenous nitroso compounds. Epidemiological, in vitro, and animal model studies have implicated green tea to be protective against nitroso

compound-induced and inflammation-related cancer. Chan et al. [132] reported that the effect of epigallocatechin-3-gallate (EGCG) on the production of nitric oxide ($NO^{\cdot}$). They showed that EGCG reduces NO production as measured by nitrite accumulation in the culture medium. EGCG may do so by two mechanisms: reduction of inducible nitric oxide synthase (iNOS) gene expression and inhibition of enzyme activity. Addition of 1-10 µM EGCG to lipopolysaccharides- and interferon-gamma-activated mouse peritoneal cells reduced iNOS mRNA expression concentration dependently. Addition of 50-750 µM EGCG, in a concentration-dependent manner, inhibited the enzyme activity of iNOS and neuronal nitric oxide synthase (nNOS) as measured by citrulline formation. EGCG competitively inhibited binding of arginine and tetrahydrobiopterin, and the gallate structure is important for this action.

Wu et al. [123] reported that Chinese tea exerted a relatively strong inhibitory potency for N-Nitroso compounds (NOC) formation both in vitro and in humans. Chen [133] suggested that Chinese tea suppressed the occurrence of esophageal tumors induced by N-nitroso methylbenzylamine in rats. Stich [134] indicated that the simultaneous intake of tea with food products that are being nitrosated within the stomach of human subjects should exert a protective, beneficial effect.

Peroxynitrite ($OONO^{-}$) or its nitrogen dioxide derivatives cause oxidation/nitration leads mutation to DNA, RNA, protein, lipids and sugars [134].The inflammatory mediator peroxynitrite, when generated in excess, may damage cells by oxidizing and nitrating cellular components. Several seleno compounds include s glutathione peroxidase (GPx), selenoprotein P and thioredoxin reductase, ebselen contribute to cellular defense against peroxynitrite [134].

Effect of green tea on lipids:

Concentration of total cholesterol and triglyceride in liver and serum of mice, hamsters and rats administered by green tea or its ingredients were reduced, indicating that fatty accumulation and body weight increase was suppressed by green tea [135-137, 108]. Chan et al. [136] reported that green tea epicatechin (GTE)-supplemented hamsters had higher fecal excretions of total fatty acids, neutral sterols and acidic sterols compared with control group. They also confirmed that the hypolipidemic activity of GTE is not due to inhibition of synthesis of cholesterol or fatty acid but is most likely mediated by its influence on absorption of dietary fat and cholesterol. Chinese green tea lowered plasma cholesterol by increasing fecal bile acids and cholesterol excretion [137].

Sayama et al. [138] reported that the concentration of triglycerides (TG), non-esterfied fatty acids and leptin in serum of mice fed green tea powder for 16 weeks were reduced. Green tea polyphenol may exert an antiatherosclerotic action by virtue of its antioxidant properties and increasing HDL-cholesterol levels [139].

Effect of green tea on obesity:

Bell and Goodrick [140] reported that overweight or obesity is strongly associated with complications such as type-II diabetes mellitus, hypertension, heart disease, gall bladder disease, and sleep apnea. Several nutrients like low-glycemic-index carbohydrates, 5-hydroxytryptophan, green tea extract, and chromium have been identified that may promote weight loss. The first two nutrients decrease appetite, green tea increases the 24-h energy expenditure, and chromium promotes the composition of the weight lost to be fat rather than lean tissue.

MECHANISM OF ACTION

Some mechanisms, regarding the cancer chemopreventive effects of green tea or its polyphenols, largely focused on: (a) protection against mutagenicity and genotoxicity, (b) inhibition of biochemical markers of tumor initiation, (c) inhibition of biochemical markers of tumor promotion, (d) effects on detoxification enzymes, (e) trapping of activated metabolites of carcinogens and (f) antioxidant and free radical scavenging activity [16].

Other observations have raised the possibility that green tea catechins, in addition to their antioxidative properties, also affect the molecular mechanisms involved in angiogenesis, extracellular matrix degradation, regulation of cell death and multidrug resistance [32, 69]. It was also found that green tea inhibits telomerase activity associated with entering crisis and senescence [141], urokinase [68], which is involved in metastasis, and inhibits p38-mitogen-activated protein kinase activation [142]. It was also reported that catechins have inhibitory effects of angiotensin converting enzyme [143], hyaluronidase [144], α-amylase [145], ornithine decarboxylase activity [146], and glucocyltransferase activity [147]. In addition, green tea changes mitochondrial integrity involving cytochrome C release and subsequent activation of caspase-3-like protease [148].

Furthermore, EGCG and tea polyphenols have anti-initiation, antimutagenic, and antimicrobial activities; they inhibit various enzyme activities along with gene expression of inflammatory cytokines related to carcinogensis; and they enhance activities of some biochemical reactions supporting anticarcinogenesis [82]. Liang et al. [149] showed that EGCG could significantly inhibit DNA synthesis in human A431 epidermoid carcinoma cells. In addition, EGCG inhibited the protein tyrosine kinase activities of epidermal growth factor (EGF) receptor, platelet-derived growth factor receptor, and fibroblast growth factor. These findings led the previous authors to suggest that EGCG might inhibit the process of tumor formation by blocking cellular signal transduction pathways.

The activation of mitogen-activated protein kinase by green tea polyphenols was shown to be potential signaling pathway in the regulation of phase II enzyme gene expression mediated by an antioxidant-responsive element [150]. Activation of mitogen-activated protein

kinase leading to induction of gene expression that may protect the cells against toxic insults and enhance cell survival [151].

Apoptotic cell death is a complex, tightly regulated process that involves drastic structural changes in cell morphology, including chromatin condensation, disassembly of the nuclear and cytoplasmic networks, DNA fragmentation and membrane blebbing [152,153]. It was found that EGCG induced apoptosis and cell cycle arrest in human epidermoid carcinoma cells A431, human prostate carcinoma cells DU145, and mouse lymphoma cells LY-R but not in normal human keratinocytes [19,72]. Kennedy et al. [154] reported that epigallocatechin (EGC) caused a decrease in the phosphorylation of the retinoblastoma protein, which was in a cellular thiol-dependent manner, leading to regulation of Ehrlich ascites tumor cells. In addition, it was reported that elevated GSH levels in tumor tissue are associated with resistance to chemotherapy [154]. It was demonstrated that the onset of apoptosis is associated with a fall of intracellular GSH in different cellular systems [155]. Other evidence has demonstrated that GSH levels are elevated in various human cancer tissues as compared with normal tissues in the same region [156]. This cellular thiol-dependent mechanism evoked by EGC may provide a useful insight into additional mechanisms governing cell cycle progression during growth arrest by green tea polyphenols.

It was reported that GTPs, particularly EGCG, interacts with P-gp and inhibits its transport activity [119] P-gp transport inhibition by GTPs is a rapid and reversible process [34]. Thus, GTPs, and especially EGCG, could improve the efficacy of cancer treatment by increasing the accumulation of chemotherapeutic drugs in cancer cells by blocking P-gp function [119].

There is increasing evidence supporting the central role of angiogenesis in tumor growth and metastasis. Angiogenesis, the growth of new vasculature, is an absolute requirement for the maintenance and progression of most solid tumors [119]. EGCG, CG and ECG catechins may also ultimately disturb the assembly of endothelial cells into capillary-like structures by blocking VEGFR-2 activity.

EGCG inhibits activator protein-1 (AP-1) function, which has been associated with the invasive and metastatic characteristics of cancer cells [157]. It was demonstrated that EGCG potently inhibited the chymotrypsin-like activity of the proteasome in vitro [71]. The proteasome plays a critical role in the specific degradation of cellular proteins, allows tumor cell cycle progression as well as protects cells against apoptosis [158], inhibition of proteasome activity EGCG may contribute to the cancer-preventative effect of green tea [119].

CONCLUSIONS

Tea is the most popular drink after water. Green tea has been consumed everyday by millions of people around the world since ancient times in order to maintain and improve health. Nowadays, green tea is considered one of the most promising dietary agents for the prevention and treatment of many diseases. Available data suggests that aqueous extract of the green tea 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. The polyphenols present in tea can also decrease the risk factor of specific type of cancers by inducing phase I and phase II metabolic enzymes that increase the formation and excretion of detoxified metabolites of carcinogens. In addition, 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.

Most modern medicines used to treat cancer have serious side effects, high costs, and other associated risks. Green tea, on the other hand, is safe and widely available as a beverage and a nutritional supplement. 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. Furthermore, growing scientific evidence suggests that green tea is effective in preventing many diseases associated with aging, including prostate and other cancers. It is yet promising area of research for future human studies.

REFERENCES

[1] Costa LM, Gouveia ST, Nobrega JA. Ann Sci 2002; 18: 313-318.
[2] Rietveld A, Wiseman S. J Nutr 2003; 133: 3275-3284.
[3] Graham HN. Preventive Med 1992; 21: 334-350.
[4] Langley-Evans SC. Int J Food Sci Nutr 2002; 51:181-188.
[5] Wu CD, Wei GX. J Nutr 2002; 18:443–444.
[6] Il'yasova D, Martı´n C, Sandler RS. Cancer Causes Control 2003; 14:676-772.
[7] Crespy V, Williamson G. J Nutr 2004; 134 (12): 3431S-40S.
[8] Sato T, Miyata G. J Nutr 2000; 16:315-17.
[9] Higdon JV, Frei B. Crit Rev Food Sci Nutr 2003; 43:89-143.
[10] Hiroshi Y, Hiroshi W. Cardiova Res 2007; 73: 439-440.
[11] Cabrera C, Artacho R, Giménez R. J Am Coll Nutr 2006; 25:79-99.
[12] Yang YC, Lu FH, Wu JS, Wu CH, Chang CJ. Arch Intern Med 2004; 164:1534-40.
[13] Fukino Y, Shimbo M, Aoki N, Okubo T, Iso H. J Nutr Sci Vitaminol (Tokyo) 2005; 51:335-42.
[14] Tsuneki H, Ishizuka M, Terasawa M, Wu JB, Sasaoka T, Kimura I. BMC Pharmaco 2004; 4:18.
[15] Zaveri NT. Life Sci 2006 ; 78:2073-80.
[16] Katiyar SK, Mukhtar H. World Rev Nutr Diet 1996; 79: 154-84.
[17] Zuo Y, Chen H, Deng Y. Talanta 2002; 57:307-316.
[18] Willson KC. New York: CABI Publishing, 1999.
[19] Ahmad N, Cheng H, Mukhtar H. Biochem Biophys Res Commun 2000; 275: 328-334.

[20] Luper S. Altern Med Rev 1999; 4: 178-189.
[21] Auger C, Mullen W, Hara Y, Crozier A. J Nutr 2008; 138(8): 1535S-1542S.
[22] Shu WS, Zhang ZQ, Lan CY, Wong MH. Chemosphere 2003; 52:1475–1482.
[23] Yung KF, Zhang ZQ, Wong JWC, Wong MH. Environ Geochem Health 2003; 25:219-232.
[24] Tyler VE, Brady L, Robberts JE. Pharmacognosy, 9th edition. Lea and Febiger, Philadelphia, PA: 1988; 68-69.
[25] Tsuchiya H. Pharmacology 1999; 59: 34-44.
[26] Bu-Abbas A, Clifford MN, Ioannides C, Walker R. Food Chem Toxicol 1995; 33: 27-30.
[27] Fujiki H, Suganuma M, Okabe S, Sueoka E, Komori A, Suga K, et al. Proc Soc Exp Biol Med 1999; 220: 225-228.
[28] Giles AR, Gumma A. Arzneimittel-Forschung 1973; 23: 98-100.
[29] Balant L, Burki B, Wermeille M, Golden G. Arzneimittel-Forschung 1979; 29: 1758-62.
[30] Lee MJ, Wang ZY, Li H, Chen L, Sun Y, Gobbo S, et al.. Cancer Epidemiol Biomarkers Prevent 1995; 4: 393-399.
[31] Tsuchiya H, Sato M, Kato H, Okubo T, Juneja LR, Kim M. J Chromatogr 1997; 703: 253-258.
[32] Demeule M, Brossard M, Page M, Gingras D, Beliveau R. Biochem Biophys Acta 2000; 1478: 51-60.
[33] Yang CS, Chen L, Lee MJ. Cancer Epidemiol Biomarkers Prevent 1998; 7: 351-354.
[34] Jodoin J, Demeule M. Beliveau R. Biochem Biophys Acta 2002; 1542: 149-159.
[35] Zhu QY, Zhang A, Tsang D, Huang Y Chen ZY. J Agric Food Chem 1997; 45: 4624-4628.
[36] Li C, Lee M, Sheng S, Meng X, Prabhu S, Winnik B, et al. Chem Res Toxicol 2000; 13: 177-184.
[37] Pietta P, Simonetti P, Gardena C, Brusamolino A, Morazzoni P, Bombaredelli E. Biofactors 1998; 8:111-118.
[38] Hollman PC, Tijburg LB, Yang CS. Crit Rev Food Sci Nutr 1997; 37: 719-738.
[39] Bravo L. Nutr Rev 1998; 56: 317-333.
[40] Lu H, Meng X, Yang CS. Drug Metab Dispos 2003; 31: 572-580.
[41] Sano M, Takahashi Y, Yoshino K, Shimoi k, Nakamura Y, Tomita I, et al. Biol Pharma Bull 1995; 18: 1006-1008.
[42] Sai K, Kai S, Umemura T, Hasegawa R, Inoue T, Kurokawa Y. Food Chem Toxicol 1998; 36: 1043-1051.
[43] Sohn OS, Surace A, Fiala ES, Richie JP Jr, Colosimo S, Zang E, et al. Xenobiotica 1994; 24: 119-127.
[44] Weisburger JH. Tea antioxidants and health. In Cadenas E, Packer L, Eds. Handbook of antioxidants. New York: Marcel Dekker, 1996; 469-86.
[45] Jonathan MH. Asia Pac J Clin Nutr 2008; 17(S1): 288-290.
[46] Horiba N, Maekawa Y, Ito M, Matsumoto T, Nakamura H. J Endo 1991; 17: 122-125.
[47] Terada A, Hara H, Nakajyo S. Microbial Ecol Health Dis 1993; 6: 3-9.
[48] Yang CS, Wang ZY. J Natl Cancer Inst 1993; 85: 1038-1049.
[49] Nakayama M, Toda M, Okubo S, Shimamura T. Letter Appl Microbiol 1990; 11: 38-40.
[50] Tao P. Chung Kuo I Hsueh Yuan Hsueh Pao1992; 14: 334-38.
[51] Fujita T. Adv Nutr Res 1994; 9: 89-99.
[52] Kao PC, P'eng FK. Chung Hua I Hsueh Tsa Chih (Taipei) 1995; 55: 209-213.

[53] Blum AL, Berthet P, Doelle W, Goebell H, Kortum K, Pelloni S, et al . Lancet 1977; ii: 1153-1155.
[54] Kaul TN, Middleton E Jr., Ogra PL. J Med Virol 1985; 15: 71-79.
[55] Perrissoud D, Maignan MF, Auderset G. Int Cong Symp Ser R Soc Med 1981; 47: 21-25.
[56] Varga M, Buris L. Exp Mol Pathol 1990; 52: 249-257.
[57] Sakanaka S, Okubo T, Akachi S, Mabe K, Matsumoto M. Tables of data on the antimicrobial activities of green tea extracts; in Yamamoto T, Juneja LR, Chu DC, Kim M (Eds): Chemistry and Applications of green tea. New York, CRC Press, 1997; pp 145-149.
[58] Sakanaka S. Green tea polyphenols for prevention of dental caries; in Yamamoto T, Juneja LR, Chu D-C, Kim M (Eds): Chemistry and Applications of green tea. New York, CRC Press, 1997; pp, 87-101.
[59] Ikigai H, Nakae T, Hara Y, Shimamura T. Biochim Biophys Acta1993; 1147: 132-136.
[60] Katiyar SK, Elmets CA, Agarwal R, Mukhtar H. Photochem Photobiol 1995; 62: 855-861.
[61] Katiyar SK, Agarwal R, Ekker S, Wood GS, Mukhtar H. Carcinogenesis1993; 14: 361-365.
[62] Agarwal R, Katiyar SK, Khan SG, Mukhtar H. Photochem Photobiol 1993; 58: 695-700.
[63] Haqqi TM, Anthony D, Gupta S, Ahmad N, Kumar MK, Mukhtar H. Proc Natl Acad Sci 1999; 96: 4524-4529.
[64] Dona M, Dell AI, Calabrese F, Benelli R, Morini M, Albini A, Garbisa S. J Immunol 2003; 170: 4335-4341.
[65] Kohlmeier L, Weterings KGC, Steck S, Kok FJ. Nutr Cancer 1997; 27: 1-13.
[66] Suganuma M, Okbe S, Sueoka N, Sueoka E, Matsuyama S, Imai K, et al. Mutat Res 1999; 428(1-2):339-344.
[67] Liao S, Hiipakka RA. Biochem Biophys Res Comm 1995; 214: 833-838.
[68] Jankun J, Selmon H, Swiercz R, Skrzypczak-Jankun E. Nature 1997; 387: 391.
[69] Cao Y, Cao R. Nature 1999; 398: 381.
[70] Garbisa S, Biggin S, Cavallarin N, Sartor L, Benelli R Albini A. Nat. Med 1999; 5:1216.
[71] Nam S, Smith DM, Duo OP. J Biol Chem 2001; 276: 13322-13330.
[72] Ahmad N, Feyes DK, Nieminen AL, Agrawal R, Mukhtar H. J Natl Cancer Inst 1997; 89: 1881-1886.
[73] Valcic S, Montenegro G, Timmermann BN. J Nat Prod 1998; 61: 771-775.
[74] Paschka AG, Butler R, Young CYF. Cancer Lett 1998; 130: 1-7.
[75] Gupta S, Hastak K, Ahmad N, Jonathan SL, Mukhtar H. Proc Natl Acad Sci 2001; 98: 10350-10355.
[76] Sadzuka M, Imazawa H, Shoji Y, Mita T, Hara Y, Isemura M. Biosci Biotechnol Biochem 1997; 61: 1504-150.
[77] Hiroyasu M, Ozeki M, Miyagawa-hayashino A, Fujiwara Y, Haiai H, Toyokuni S. Redox Rep 2002; 7: 335-342.
[78] Okabe S, Suganuma M, Hayashi M, Sueoka E, Komori A, Fujiki H. Jpn J Cancer Res 1997; 88: 639-643.
[79] Suganuma M, Okbe S, Marino MW, Sakai A, Sueoka E, Fujiki H. Cancer Res 1999; 59: 4516-4518.
[80] Singh R, Ahmad S, Islam N, Goldberg VM, Haqqi TM. Arthritis and Rheumatism 2000; 46: 2079-2086.
[81] Lu Y, Lou YR, Xie JG, Yen P. Huang MT, Conney AH. Carcinogenesis 1997; 18: 2163-2169.

[82] Fujiki H, Suganuma M, Okabe S, Sueoka N, Komori A, Sueoka E, et al. Mutation Res 1998; 18: 307-310.
[83] Landau JM, Wang ZY, Yang GY, Ding W, Yang CS. Carcinogenesis 1998; 19: 501-507.
[84] Weisburger J. Proceedings of the Society. Exp Biol Med vol 220. Blackwell Science, New York 1999.
[85] Cao J, Xu Y, Chen J, Klawaunig JE. Fundam Appl Toxicol 1996, 29: 244-250.
[86] Hirose M, Hasegawa R, Kimura J, et al. Carcinogenesis, 1995; 16: 3049-3055.
[87] Matsumoto N, Kohri T, Okushio K, Hara Y. Jpn J Cancer Res 1996; 87: 1034-1038.
[88] Schut HA, Yao R. Nutr Cancer 2000; 36: 52-59.
[89] Kang KS, Kang BC, Lee BJ, Che JH, Li GX, Trosko JE, Lee YS. Cancer Lett 2000; 152: 97-106.
[90] Kennedy DO, Matsumoto M, Kojima A, Matsui-Yuasa I. Chem Biol Interact 1999; 110: 59-71.
[91] Hirose M, Hoshiya T, Mizoguchi Y, Nakamura A, Akagi k, Shirai T. Cancer lett 2001; 168: 23-31.
[92] Fujiki H, Sueoka E, Komori A, Suganuma M. Carcino Ecotox Revs 1997; C15: 1-40.
[93] Suganuma M, Sueoka E, Sueoko N, Okabe S, Fujiki H. BioFactors 2000; 13: 67-72.
[94] Fujiki H, Suganuma M, Okabe S, Sueoka E, Suga K, Imai K, et al. Cancer detect Prevent 2000, 24: 91-99.
[95] Hirose M, Hoshiya T, Akagi K, Takahashi S, Hara Y, Ito N. Carcinogenesis 1993; 14: 1549-1553.
[96] Hodgson JM, Puddey IB, Burke V, Beilin LJ, Jordan N. J Hypertens 1999; 17: 457-63.
[97] Thelle DS. Curr Opin Lipidol 1995; 6: 25-31.
[98] Weisburger J., Rivenson A, Garr K, Aliaga C. Cancer Lett 1997 114: 323-329.
[99] Stensvold I, Tverdal A, Solvoll K Foss OP. Prev Med 1992; 21: 546-53.
[100] Tijburg L, Wiseman SA, Meijer GW, Weststrate JA. Atherosclerosis 1997; 135: 37-48.
[101] Priyadarshi S, Valentine B, Han C, Fedorova OV, Bagrov AY, Liu J, et al. Kidney Int 2003; 63: 1785-1790.
[102] Satoh K, Sakamoto Y, Ogata A, Nagai F, Mikuriya H, Numazawa M, et al. Food Chem Toxicol 2002; 40: 925-933.
[103] Sakamoto Y, Mikuriya H, Tayama k, Takahashi H, Nagasawa A, Yano N, et al. Arch Toxicol 2001; 75: 591-596.
[104] Capen CC. Toxicol Pathol 1997; 25: 39-48.
[105] Bartsch W, Dasenbrock C, Ernst H, Kamino K, Mohr U. Food and Chem Toxicol 1996; 34: 153-159.
[106] Dohler KD, Wong CC. Von Zur MA. Pharmacol Ther 1979; 5: 305-318.
[107] McClain RM, Levin AA, Posch R, Downing JC. Toxicol Appl Pharmacol 1989; 99: 216-228.
[108] Kao YH, Hiipakka RA, Liao SEndocrinology2000; 141: 980-987.
[109] Hong JT, Ryu SR, Kim HJ, Lee JK, Lee SH, Kim DB, et al. Brain Res Bull 2000; 53: 743-751.
[110] Lee S, Suh S, Kim S. Neurosci 2000, 287: 191-914.
[111] Hong JT, Ryu SR, Kim HJ, Lee JK, Lee SH, Yun YP, et al. Brain Res 2001; 888: 11-18.
[112] Chen A, Zhang L. J Biol Chem 2003; 1-29.
[113] Lin YC, Lin JK. Mol Pharmacol 1997; 52: 465-472.

[114] Chen A, Zhang, Xu J, Tang J. Biochem J 2002; 368(3): 695-704.
[115] Rice-Evans C. Proc Soc Exp Biol Med 1999, 220: 262-267.
[116] Mitscher LA, Jung M, Shankel D, Dou JH, Steele L, Pillai SP. Med Res Rev 1997; 17: 327-365.
[117] Guo Q, Zhao B, Shen S, Hou J, Hu J, Xin W. Biochem Biophys Acta 1999; 1427: 13-23.
[118] Lin JK, Chen PC, Ho CT, Lin-Shiau SY. J Agric Food Chem 2000; 48: 2736-2743.
[119] Demeule M, Michaud-Levesque J, Annabi B, Gingras D, Boivin D, Jodoin J, Lamy S, Bertrand Y, and Beliveau R. Curr Med Chem 2002, 2: 441-463.
[120] Yokozawa T, Cho EJ, Nakagawa T. J Agric Food Chem2003; 51: 2421-2425.
[121] Skrzyddlewska E, Ostrowska J, Farbiszeski R, Michalak K. Phytomedicines 2002; 9: 232-239.
[122] Sugiyama K, He P, Wada S Saeki S. J Nutr 1999; 129: 1361-1367.
[123] Wu Y. Chung Kuo I Hsueh Yuan Hsueh Pao 1993; 15: 354-359.
[124] Kushnerova NF, Fomenko SE, Polozhentseva MI, Bulanov AE. Vopr Med Khim 1995; 41: 20-23.
[125] Miyagawa C, Wu C, Kennedy DO, Nakatani T, Ohtani K, Sakanaka S, et al. Biosci Biotechnol Biochem 1997 61:1901-1905.
[126] Sugiyama K, He P, Wada S. and Saeki S. Biotechnol Biochem 1998; 62: 609-611.
[127] Khan SG, Katiyar SK, Agarwal R, Mukhtar H. Cancer Res 1992; 52: 4050-4052.
[128] Choi YT, Jung C., Lee SR, Bae JH, Baek WK, Suh MH, et al. Life Sci 2001; 70: 603-614.
[129] Levits Y, Youdim MB, Maor G, Mandel S. Biochem Pharmacol 2002; 63: 21-29.
[130] Paquay JB, Haenen GR, Stender G, Wiseman SA, Tijburg LB, Bast A. Protection against nitric oxide toxicity by tea. J Agric Food Chem 2000, 48: 5768-5772.
[131] Oldreive C, Zhao K, Paganga G, Halliwell B, Rice-Evans C. Chem Res Toxicol 1998; 11: 1574-1582.
[132] Chan MM, Fong D, Ho CT, Huang HI. Biochem Pharmacol 1997; 54: 1281-1286.
[133] Chen J. Prev Med 1992; 3: 385-391.
[134] Stich HF. Prev Med 1992; 21: 377-384.
[135] Yang TT, Koo MW. Pharmacol Res 1997; 35: 505-512.
[136] Chan PT, Fong WP, Cheung YL, Huang Y, Ho WK, Chen ZY. J Nutr 1999; 129: 1094-1101.
[137] Yang TT, Koo MW. Life Sci 2000; 66: 411-423.
[138] Sayama K, Lin S, Zheng G, Oguni I. In Vivo 2000; 14: 481-484.
[139] Yokozawa T, Nakagawa T, Kitani K. J Agric Food Chem 2000; 50: 3549-3552.
[140] Bell SJ, Goodrick GKA. Crit Rev Food Sci Nutr 2002; 42: 163-178.
[141] Naasani I, Seimiya H, Tsuruo T. Biochem Biophys Res Comm 1998; 249: 391-396.
[142] Chen W, Dong Z, Valcic S, Timmermann BN, Bowden GT. Mol Carcinogen 1999; 24: 79-84.
[143] Hara Y, Matsuzaki T, Suzuki T. Nippon Nogeikagaku Kaishi 1987; 61: 803-808.
[144] Maeda Y, Yamamoto M, Masui T, Sugiyama K, Yokota M, Nakagomi K, et al. J Food Hygienic Soc Jpn 1990; 31: 233-237.
[145] Hara Y Honda M. Agr Biol Chem 1990; 54: 1939-1945.
[146] Kennedy D, Nishimura T, Hasuma T, Yano Y, Otani S, Matsui-Yuasa I. Chem Biol Interact 1998; 110: 159-172.

[147] Hattori M, Kusumoto IT, Namba T, Ishigami T, Hara Y. Chem Pharnaceut Bull 1990; 38: 717-720.
[148] Kennedy D, Kojima A, Hasuma T, Yano Y, Otani S, Matsui-Yuasa I. Chem Biol Interact 2001; 134: 113-133.
[149] Liang YC, Lin-shiau SY, Chen CF, Lin JK. J Cell Biochem 1997; 67: 55-65.
[150] Yu R, Jiao JJ, Duh JL. Gudehithlu K, Tan T. Carcinogenesis 1997; 18; 451-456.
[151] Kong AN, Yu R, Lei W, Mandlekar S, Tan TH, Ucker DS. Restor Neurol Neurosci 1998; 12: 63-70.
[152] Kerr J, Wyllie A, Currie A. Br J Cancer 1972; 26: 239-257.
[153] Wyllie AH, Kerr JF, Currie AR. Int Rev Cytol 1980; 68: 251-306.
[154] Kennedy DO, Kojima A, Moffatt J, Yamagiwa H, Yano Y, Hasuma T, et al. Cancer Lett 2002; 179: 25-32.
[155] Kannan K, Jain SK. Pathophysiology 2000; 7: 153-163.
[156] Schelldorfer T, Gansuge S, Gansuge F, Schlosser S, Beger HG, Nussler AK. Cancer 2000; 89: 1440-1447.
[157] Crawford HC, Matrisian LM. Enzyme Protein 1996; 49: 20-37.
[158] Hochstrasser M. Curr Opin Cell Biol1995; 7: 215-223.