



Review

Pharmacological effects of green tea on the gastrointestinal system

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Abstract

Green tea is rich in polyphenolic compounds, with catechins as its major component. Studies have shown that catechins possess diverse pharmacological properties that include anti-oxidative, anti-inflammatory, anti-carcinogenic, anti-arteriosclerotic and anti-bacterial effects. In the gastrointestinal tract, green tea was found to activate intracellular antioxidants, inhibit procarcinogen formation, suppress angiogenesis and cancer cell proliferation. Studies on the preventive effect of green tea in esophageal cancer have produced inconsistent results; however, inverse relationships of tea consumption with cancers of the stomach and colon have been widely reported. Green tea is effective to prevent dental caries and reduce cholesterol and lipids absorption in the gastrointestinal tract, thus benefits subjects with cardiovascular disorders. As tea catechins are well absorbed in the gastrointestinal tract and they interact synergistically in their disease-modifying actions, thus drinking unfractionated green tea is the most simple and beneficial way to prevent gastrointestinal disorders.

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Keywords: Green tea; Tea polyphenol; Catechin; (–)-Epigallocatechin gallate; Gastrointestinal tract

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1. Introduction

Green tea is prepared from the young shoots of tea plant *Camellia sinensis*. They are rich in flavonoids, and in green tea mostly polyphenolic compounds such as catechins. The

tea leaves are immediately heated with rolling after harvest to inactivate the enzyme, polyphenol oxidase, which is capable of oxidizing the tea catechins to oligomeric and polymeric derivatives, e.g., theaflavins and thearubigins. Green tea is thus less “fermented” and has the highest quantity of tea catechins that are chemically defined as flavan-3-ols. When the enzyme is allowed more time to act, the tea will be fully fermented and most of the tea catechins will be converted into theaflavins and thearubigins that give

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the characteristic aroma and colour of the black tea (Balentine et al., 1997). Semi-fermented tea, e.g., Oolong tea, has limited time of oxidation and is less fermented than the black tea. In general, green tea contains about 30% w/w of catechins in the dry leaves (Graham, 1992). The major catechins, which are found in abundant proportion, are (–)-epigallocatechin gallate, (–)-epigallocatechin, (–)-epicatechin and (–)-epicatechin gallate with (–)-epigallocatechin gallate amounting to over 60% of the total catechins (Yang and Koo, 1997). Other compounds obtainable in green tea are the flavonols (quercetin, kaempferol and rutin), caffeine, phenolic acids, theanine, and flavour compounds (Graham, 1992). Black tea contains less tea catechins (3–10% w/w), while theaflavins and thearubigins account for about 2–6% w/w and 10–20% w/w of the dry weight of the leaves, respectively. Lung Chen tea and Pu-erh tea are typical examples of Chinese green tea and black tea, respectively, while Jasmine tea, Iron Buddha tea, Oolong tea are semi-fermented Chinese teas. The catechin contents in these five Chinese teas are presented in Table 1 and it was found that Lung Chen green tea has the highest quantity of tea catechins when compared with the semi-fermented and black teas (Yang and Koo, 1997).

Green tea is commonly consumed in China, Japan and Eastern Asia, while black tea is mainly brewed in European countries and India. The intake of catechins can be expected to be higher in the Asiatic countries and the health effects of green tea may be more apparent when examined in the Asian communities. The gastrointestinal tract is most likely to be affected by tea drinking, since it has direct contact with the tea solution and its components, usually in high concentrations, irrespective of whether they are absorbed, retained or re-circulated to the gut tissues. In this review, the effects of green tea consumption on the gastrointestinal tract will be explored to find out whether there is any co-relation between green tea consumption and diseases of the gastrointestinal system.

Table 1
Types of Chinese tea with different degrees of fermentation and catechin content

Types of tea	Degree of fermentation	(–)-Epigallocatechin gallate (% w/w)	Total catechins (% w/w)
Pu-erh tea	Full fermentation	4.68±0.11	6.07±0.18
Iron Buddha tea	Semi fermentation	4.68±0.18	7.49±0.22
Oolong tea	Semi fermentation	5.13±0.12	8.05±0.18
Jasmine tea	Semi fermentation	7.48±0.49	12.72±0.70
Lung Chen tea	Less fermentation	9.44±0.76	14.57±1.08

Extracted from Yang and Koo (1997). Values are expressed as mean±S.E.M. of four to five determinations in weight percentage.

2. Diverse actions of tea catechins

Studies have shown that tea possesses diverse pharmacological properties which include anti-oxidative (Ho et al., 1992; Serafini et al., 1996), anti-inflammatory (Mutoh et al., 2000), anti-mutagenic (Kuroda and Hara, 1999; Steele et al., 2000), anti-carcinogenic (Yang and Wang, 1993), anti-angiogenic (Cao and Cao, 1999; Jung and Ellis, 2001), apoptotic (Ahmad et al., 1997), anti-obesity (Dulloo et al., 1999; Han et al., 1999), hypocholesterolemic (Yang and Koo, 1997), anti-arteriosclerotic (Yang and Koo, 2000), anti-diabetic (Zeyuan et al., 1998), anti-bacterial (Hu et al., 2001), anti-viral (Clark et al., 1998; Mukoyama et al., 1991), and anti-aging effects (Esposito et al., 2002). However, these responses cannot always be reflected in human studies. This may be due to the limited bioavailability of tea components and the use of physiologically unattainable tea concentrations in some of the animal and in-vitro experiments. The unreliability of extrapolating and applying results obtained in animal studies to humans should also be contemplated.

In relation to the prevention of diseases by tea consumption, many studies have demonstrated beneficial effects of tea and catechins in the prevention of cancers and cardiovascular disorders (Dufresne and Farnworth, 2000; Hertog et al., 1995; Imai and Nakachi, 1995; Nakachi et al., 2000; NCI, DCPC, 1996). Findings from epidemiological studies involving tea consumption have suggested a chemopreventive effect of green tea on gastrointestinal cancers and disorders when it is consumed regularly in moderate to high quantity (Kuroda and Hara, 1999; World Cancer Research Fund et al., 1997; Zheng et al., 1996). However, some of the studies conducted in the Western countries concerning the effects of tea on gastrointestinal protection have demonstrated no or negative results in cancer prevention, while promising data were obtained mainly in studies performed in Asian countries (Gao et al., 1994; Yang et al., 2001). This has been suggested to be due to the consumption of a much larger quantity of green tea by the Asian people while the Westerners like to drink more black tea. Other factors such as bias in subject selection, diets, alcohol consumption, smoking (Lambert and Yang, 2003), types of tea, total quantity of tea consumption, measurement errors (Imai et al., 1997), temperature of the tea infusion (Wang et al., 1996), and interactions of tea with other dietary factors may influence the outcomes of the studies.

3. Mechanisms of action

The pharmacology and mechanisms of action of tea on its anti-inflammatory and anti-cancer actions have been reviewed in several publications (Bode and Dong, 2002; Surh, 1999). Some suggested mechanisms for its suppressive effects on inflammation and carcinogenesis have been

depicted in Fig. 1. It is well known that green tea is a potent antioxidant with anti-oxidative activity greater than vitamins C and E (Wiseman, 1997). Besides acting as a scavenger for reactive oxygen and nitrogen species, tea also enhances expression of intracellular endogenous antioxidants such as glutathione, glutathione reductase, glutathione peroxidase, glutathione-S-reductase, catalase, and quinone reductase (Khan et al., 1992; Valerio et al., 2001). All of these activities prevent lipid peroxidation and damage to the DNA structure. Green tea and (–)-epigallocatechin gallate also bind to metal ions and further reduce the generation of reactive free radicals (Hider et al., 2001; Morel et al., 1994). In limiting the formation of carcinogens, green tea and its catechins have been shown to promote the elimination of procarcinogens, e.g., polycyclic hydrocarbons and heterocyclic amines, from the body by inducing phase I cytochromes P450 1A1, 1A2, and 2B1 enzymes and phase II detoxification enzymes, e.g., glucuronosyl transferase (Sohn et al., 1994). The procarcinogen activating enzyme cytochrome P450 3A4 is also suppressed (Lin et al., 1999; Muto et al., 2001). Furthermore, the formation of endogenous *N*-nitroso compounds was found to be reduced by tea consumption (Yang and Wang, 1993).

The chemopreventive effect of green tea and its catechins on carcinogenesis have been attributed to their inhibition on cell proliferation (Chen et al., 1998; Lea et al., 1993; Liang et al., 1999; Valcic et al., 1996), cell cycle arrest (Liang et al., 1999), blockade of growth factor receptors (Fujiki et al., 1999; Liang et al., 1977), suppression of mitotic signals (Lin et al., 1999), reduction in cytokines release (Fujiki et al., 1999), inhibition of angiogenesis by interfering with the activities of metalloproteinases, serine proteinases and vascular endothelial growth factor (Jung et al., 2001), prevention of nuclear factor kappa B and activator protein 1 activation (Ahmad et al., 2000; Lin and Lin, 1997), inactivation of topoisomerase I (Berger et al., 2001) and telomerase (Naasani et al., 1988) resulting in apoptosis.

(–)-Epigallocatechin gallate has been found to be a potent inducible nitric oxide synthase and cyclooxygenase-2 inhibitor (Chan et al., 1997; Mutoh et al., 2000; Raso et al., 2001). In suppressing the release of nitric oxide and prostaglandins, which are important mediators for inflammation and tumorigenesis, green tea can limit inflammatory

reactions and promotion of cancer. Recently, (–)-epigallocatechin gallate has been shown to bind to a specific metastasis associated 67-kDa laminin receptor that is expressed on a variety of tumor cells (Tachibana et al., 2004). Green tea may then interfere with the promotion of cancer by preventing metastasis of the tumour. Other factors that are related to metastasis, e.g., urokinase plasminogen activator (Kim et al., 2004), urokinase (Jankun et al., 1997), and matrix metalloproteinases (Sazuka et al., 1997) were also reported to be inhibited by green tea.

It has to be noted that some of the mechanistic studies of tea catechins were performed in the concentration ranges of 10–1000 μM , which is unlikely to be achieved under physiological condition, except with the tissues in the gastrointestinal tract, which comes into direct contact with the tea solution. It has been found that the peak plasma level of (–)-epigallocatechin gallate was only 0.17 μM (77.9 ± 22.2 ng/ml) after 1.6 h of oral consumption of a green tea solution containing 195 mg (–)-epigallocatechin gallate (Lee et al., 2002) and the plasma concentration of (–)-epigallocatechin gallate was usually less than 1 μM (Yang et al., 1998). This could provide a useful reference value for future studies involving the use of cell cultures.

4. Bioavailability of green tea

Tea catechins are well absorbed after oral administration (Nakagawa et al., 1997; Yang et al., 1998) and (–)-epigallocatechin gallate is quite stable in the stomach and small intestine. The content of (–)-epigallocatechin gallate in the intestine was observed to increase sharply within a few hours and was still present in the large intestine after 8 h when a single dose of (–)-epigallocatechin gallate 50 mg was administered to rats (Hara, 1997). Absorbed tea catechins are biotransformed in the liver to conjugated metabolites, i.e., glucuronidated, methylated, sulfated derivatives. While (–)-epigallocatechin and (–)-epicatechin are mainly conjugated, (–)-epigallocatechin gallate is usually present in free form in human plasma (Chow et al., 2001). Some of the catechins delivered to the gut can be glucuronidated by the glucuronosyl transferase in the mucosa of the intestine (Piskula and Terao, 1998). In the

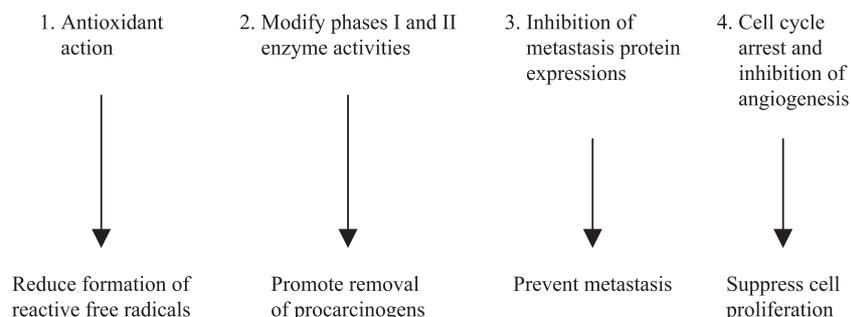


Fig. 1. Postulated anti-inflammatory and anti-cancer actions of green tea and tea catechins.

gut tissue β glucuronidases and microflora could also convert the conjugated products to aglycones (Aura et al., 2002). Some of them will be reabsorbed, while others will be metabolized to form valerolactones, phenylacetic and phenylpropionic acids (Bravo, 1998; Li et al., 2000; Meselhy et al., 1989). Thus tea catechins undergo enterohepatic recirculation quite extensively (Nakagawa and Miyazawa, 1997). After absorption, the catechins are widely distributed in all body tissues with the highest concentration found in the esophagus, intestine and colon (Lambert and Yang, 2003; Yang et al., 2000). High levels of tea polyphenols can be reached in the body when green tea is frequently consumed (Suganuma et al., 1998).

5. Green tea and the aerodigestive sites

Green tea consumption has been reported to increase the acid resistance of teeth to damage by cariogenic bacteria (Gutman and Ryu, 1996; Hamilton-Miller, 2001). Green tea was shown to inhibit the causative bacteria, which contribute to the formation of dental plaque and caries. It has been demonstrated that tea can inactivate glucosyltransferase and dextran sucrose thus inhibiting the formation of water-insoluble glucan and lactic acid, respectively (Otake et al., 1991). This reduced the adhesion of the causative bacteria most noticeably *Staphylococcus mutans* (Sakanaka et al., 1990), and *Porphyromonas gingivalis* (Sakanaka et al., 1996) to the dental plaque. Its anticariogenic and antimicrobe activities are related to the tea catechins and not due to the action of its fluorine contents (Yu et al., 1995a,b). Tea catechins, in particular (–)-epigallocatechin gallate, inactivate amylase in the saliva, and decrease hydrolysis of starch to maltose thus reducing acid erosion on the teeth enamel (Zhang and Kashket, 1998). Epidemiological studies revealed a reduction in caries formation in tea drinking populations and school kids from tea plantation areas in Japan (Cao et al., 1987; Onisi, 1985, 1993), while subjects given Oolong tea extract was observed to have less dental plaque (Ooshima et al., 1994). Green tea can also clear up bad breath by suppressing the growth of odour producing bacteria (Suzuki, 1983; Ui, 1991).

Green tea has been found to be a potential chemopreventive agent for the treatment of oral leukoplakia, a precursor lesion to oral cancer (Hsu et al., 2002). The concentration of tea catechins in the saliva can reach a higher value than in plasma (Yang et al., 1999). In vitro studies demonstrated that green tea induced G1 cell cycle arrest in oral leukoplakia and promoted apoptosis in oral squamous carcinoma cells. A study involving patients with oral leukoplakias in Beijing found that tea catechins treatment reduced the number of micronuclei and DNA aberrations in the lymphocytes and reduced precancerous mucosa lesions (Li et al., 1999).

The effect of green tea on esophageal cancer is not consistent in that some reported a preventive effect while

others found an increase of incidence in esophageal cancer. However, the worsening effect of tea on esophageal cancer has been attributed to the consumption of high temperature tea solutions rather than to the effect of tea. Inverse relationships between green tea consumption and esophageal cancer were found in epidemiological studies done in China. A study conducted in Jiangsu Province, China demonstrated that the consumption of green tea in an amount of more than 1 g/month reduced the risk of esophageal and stomach cancers independent of the detoxifying enzymes glutathione-S-transferases M1 and glutathione-S-transferases T1 genotype polymorphisms (Gao et al., 1994, 2002). Another large case control study in South America reported that subjects drinking more than 500 ml/day of tea were also less likely to have esophageal cancer (Castellsague et al., 2000). It is possible that the catechins particularly (–)-epigallocatechin gallate inhibit the initiation and promotion phases of cancer development by preventing free radical damage to DNA. Its antiangiogenic effect may account for its suppression of growth of cancerous tissues by limiting their blood supply and inhibition of cancer development (Cao and Cao, 1999). The metastasis of cancer has also been demonstrated to be suppressed by green tea, which reduced the expression of adhesion molecules and metalloproteinases (Garbisa et al., 2001). Finally, green tea induces apoptosis in cancer cells and prevents the promotion of cancer (Ahmad et al., 1997).

6. Green tea and the stomach

Epidemiological studies have shown an inverse relationship of green tea consumption with risk of gastric cancers. The risk of stomach cancer decreases with the quantities of tea consumed (Gao et al., 2002; Inoue et al., 1998; Ji et al., 1996; Kono et al., 1988; Nakachi et al., 2000; Oguni et al., 1992; Setiawan et al., 2001; Yu and Hsieh, 1991; Yu et al., 1995a,b). The mechanisms may involve the inhibition of the growth of *Helicobacter pylori*, the causative microorganism in gastric carcinogenesis and the development of gastric and duodenal ulcers (Graham et al., 1992). Tea catechins, particularly (–)-epigallocatechin gallate, inactivate the urease enzyme (Matsubara et al., 2003; Yee and Koo, 2000) for the conversion of urea into ammonia that buffers the bacteria from digestion by gastric juice, and thereby suppress proliferation of bacteria (Tsujii et al., 1992). This activity of tea can be achieved in the cup of tea concentrations and the minimum inhibitory concentrations (50% to 90%) for Lung Chen Chinese green tea were found to be between 0.125% w/v and 0.25% w/v (Yee and Koo, 2000). An inverse relationship was also found in a study involving the evaluation of patients with gastric disorders with their Chinese tea drinking habit (Yee et al., 2002). It was observed that the incidence of infection with *H. pylori* was lower in subjects who consumed tea regularly. Similar

results were reported in animal studies confirming an anti-*H. pylori* effect of tea and the active principles were demonstrated to be the tea catechins (Matsubara et al., 2003). Green tea also prevents chronic active gastritis and lowers stomach cancer risk (Kuwahara et al., 2000; Setiawan et al., 2001; Shibata et al., 2000).

Another important factor contributing to gastric carcinogenesis is the challenge of nitrogenous mutagens and heterocyclic amines in the stomach. Endogenously formed *N*-nitroso compounds can increase the risk of gastric and esophageal cancers (Mirvish, 1995). Nitrosation occurs in the stomach and other part of the gut between amine and amide precursors and nitrite generated from nitrate (Leach et al., 1987). Tea catechins reduce *N*-nitroso compound formation by reacting with the nitrosating species and self oxidized to quinone (Bartsch et al., 1988). This reduces the gastric levels of nitrosating substances and inhibits the nitrosation of susceptible secondary amines and amides to carcinogenic nitrosamines and nitrosamides (Tanaka et al., 1998). Results obtained from human studies have demonstrated the inhibition of formation of a non-carcinogenic test compound *N*-nitrosoproline from nitrosation of proline by daily intake of 3 to 5 g of green tea (Stich, 1992; Wu et al., 1993; Xu et al., 1993). Heterocyclic amines present in cooked meats are known carcinogens and green tea inhibits the formation of heterocyclic amines (Weisburger et al., 1994). Tea promotes the biotransformation of these compounds to excretable products through enhanced expression of conjugating enzyme, glucuronyl transferase, which is involved in the glucuronidation of heterocyclic amines (Dashwood et al., 1999). Indeed, results from animal study demonstrated the inhibition of chemically induced forestomach cancer in mice treated with tea (Yang and Wang, 1993). Table 2 summarized some of the possible mechanisms of action of green tea in the prevention of gastrointestinal cancers.

Table 2
Possible mechanisms of action for green tea to prevent gastrointestinal cancers

Mechanisms of action	References
(A) Growth inhibition of <i>Helicobacter pylori</i>	Matsubara et al. (2003) Yee and Koo (2000) Yee et al. (2002)
(B) Prevention of chronic gastritis	Setiawan et al. (2001) Shibata et al. (2000)
(C) Reduction of <i>N</i> -nitroso compounds	Bartsch et al. (1988) Tanaka et al. (1998) Wu et al. (1993) Xue et al. (1993)
(D) Decrease conversion of mutagens to carcinogens	Sohn et al. (1994) Yang and Wang (1993)
(E) Suppression of cyclooxygenases and inducible nitric oxide synthase activities	Fujiki et al. (2003) Hong et al. (2001) Ohishi et al. (2002) Suganuma et al. (1999)
(F) Modification of microflora in the intestine	Weisburger (1999) Yamamoto et al. (1997)

7. Green tea and the intestine

Antimicrobial activities of tea have been well demonstrated (Diker et al., 1991; Sugita et al., 1999; Toda et al., 1991), and tea has been shown to inhibit the growth of *Vibrio cholerae*, *Salmonella typhi*, *Campylobacter jejuni*, *Campylobacter coli*, *H. pylori*, *Shigella*, *Salmonella*, *Clostridium pseudomonas*, *Candida*, *Mycoplasma* and *Cryptococcus*. Thus, tea may modify the intestinal microflora. There are studies supporting a role of green tea in modulating microflora in the intestine by selectively increasing the growth of bifidobacteria and lactobacilli (acidophytes) in the gut wall (Weisburger, 1999; Yamamoto et al., 1997). This reduces the formation of ammonia, skatole, harmful amines procarcinogens in the large intestine and the carcinogenic load on the intestine. The production of acids is also lowered leading to a decrease in the pH value of the feces (Yamamoto et al., 1997). Therefore, bacteria profile in the intestine can be modulated by tea drinking and tea may affect the carcinogenic process in the intestine.

Green tea has been found to inhibit the expression of cyclooxygenases and inducible nitric oxide synthase in colonic tissues, which are constantly found to be elevated in subjects with ulcerative colitis (Hendel and Nielsen, 1997) and colorectal cancers (Kutcher et al., 1996; Sano et al., 1995). The suppression of cyclooxygenase-2 by non-steroidal anti-inflammatory drugs, e.g., sulindac, has been found to reduce cancer development in patients with large bowel adenoma (Giovannucci et al., 1995; Greenberg et al., 1993; Nugent et al., 1993). Green tea polyphenols consistently inhibit cyclooxygenase-2 activity in human colon tumour tissues (Hong et al., 2001) and tea co-administration produces an enhancing effect with the cyclooxygenase inhibitors (Ohishi et al., 2002; Suganuma et al., 1999). Similar synergistic effect of (–)-epigallocatechin gallate with sulindac co-administration was observed in multiple intestinal neoplasia (Min) mice which has a germline mutation of the murine adenomatous polyposis coli gene and develops intestinal tumors similar to the familiar adenomatous polyposis patients (Fujiki et al., 2003).

An inverse relationship to colorectal cancer risk was observed with green tea consumption (Kato et al., 1990). A protective effect on rectal cancer incident was also observed in Chinese females from Hebei who drink tea regularly (Zheng et al., 2002). A population study in Japan found that there was a delay in cancer occurrence in subjects consuming green tea (Imai et al., 1997). The incidence of colorectal cancer was found to be lower in patients who had consumed over 10 cups of green tea per day (Nakachi et al., 2000). A threshold quantity for the protective effect of tea may exist, since no significant difference was observed in subject drinking less than 10 cups a day. This dose–response relationship was also reported in a case control study on black tea consumption

and risk of rectal cancer in Moscow (Il'yasova et al., 2003). It has been proposed that (–)-epigallocatechin gallate at physiological concentrations arrests cell growth at Go/G1 phase by inhibiting topoisomerase I activity and induces apoptosis in several human colon carcinoma cell lines. These findings suggest that it could be combined with other anticancer drugs in the treatment of colon cancer (Berger et al., 2001).

Green tea may exert a protective effect on the gastrointestinal mucosa. In a study involving the induction of mucosal damage by fasting in rats, the administration of 0.6% w/w green tea was shown to prevent atrophy of the intestinal mucosa and promote healing of mucosal damage. It is suggested to be mediated by the antioxidant activity of tea catechins thus may prevent bacterial and toxin translocation in critically ill or nutritionally depleted patients (Safar et al., 2003).

The absorption of fat and sugar was found to be reduced by tea consumption. Tea has been shown to inhibit digestive lipases (Han et al., 1999; Juhel et al., 2000) and interfere with lipid-micelle formation in the intestine (Ikeda et al., 1992) leading to a decrease in fat absorption. These effects coupled with its upregulation on low density lipoprotein receptor through inhibition on proteasome activity (Bursill et al., 2001; Kuhn et al., 2004) contribute to its lipid lowering effect. Studies have also shown that tea lowered the uptake of sugar and reduced blood sugar level through suppression on glucose transporter activity in the intestinal epithelium (Shimizu, 1999). This may be beneficial to diabetes subjects in lowering their blood sugar levels.

A trial on the effect of tea catechins in bowel movements in healthy volunteers has demonstrated an improvement of the bowel activity after taking 500 mg (–)-epigallocatechin gallate tablets for 3 months. The bowel movements became more regular and this may be attributed to the inhibition of α -amylase and the modulating effects of tea catechins on the fecal flora (Hara, 1997).

8. Overall perspectives

Tea is widely consumed worldwide and it is without observable side effects even when taken chronically (Graham, 1992). Epidemiologic studies have suggested an inverse relationship of green tea consumption with gastric and colorectal cancers. In Japan, green tea has already been promulgated as a chemopreventive beverage. Further investigations relating to the health effects of tea drinking are now being conducted, and this may help to clarify the usefulness of green tea in disease prevention. Tea catechins were shown to act synergistically with each other and with caffeine in their disease-modifying actions. Thus, unfractionated green tea solution is more beneficial than individual tea catechin component if one has to harvest the potential health promoting effects of green tea in the

prevention of gastrointestinal diseases (Fujiki, 1999; Suganuma et al., 1999).

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