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Therapeutic properties of green tea against environmental insults

Lixia Chen¹, Huanbiao Mo², Ling Zhao³, Weimin Gao⁴, Shu Wang⁵, Meghan M Cromie⁴, Chuanwen Lu¹, Jia-Sheng Wang⁶, and Chwan-Li Shen^{*,7}

¹1966 Services, Irving, TX, USA

²Department of Nutrition, Byrdine F. Lewis School of Nursing and Health Professions, Georgia State University, Atlanta, GA, USA

³Department of Nutrition, University of Tennessee, Knoxville, TN, USA

⁴Department of Environmental Toxicology, The Institute of Environmental and Human Health, Texas Tech University, Lubbock, TX, USA

⁵Department of Nutritional Sciences, Texas Tech University, Lubbock, TX, USA

⁶Department of Environmental Health Science, University of Georgia, Athens, GA, USA

⁷Department of Pathology, Texas Tech University Health Sciences Center, Lubbock, TX, USA

Abstract

Pesticides, smoke, mycotoxins, polychlorinated biphenyls, and arsenic are the most common environmental toxins and toxicants to humans. These toxins and toxicants may impact on human health at the molecular (DNA, RNA, or protein), organelle (mitochondria, lysosome, or membranes), cellular (growth inhibition or cell death), tissue, organ, and systemic levels. Formation of reactive radicals, lipid peroxidation, inflammation, genotoxicity, hepatotoxicity, embryotoxicity, neurological alterations, apoptosis, and carcinogenic events are some of the mechanisms mediating the toxic effects of the environmental toxins and toxicants. Green tea, the non-oxidized and non-fermented form of tea that contains several polyphenols, including green tea catechins, exhibits protective effects against these environmental toxins and toxicants in preclinical studies and to a much-limited extent, in clinical trials. The protective effects are collectively mediated by antioxidant, anti-inflammatory, anti-mutagenic, hepato- and neuroprotective, and anti-carcinogenic activities. In addition, green tea modulates signaling pathway including NF κ B and ERK pathways, preserves mitochondrial membrane potential, inhibits caspase-3 activity, down-regulates pro-apoptotic proteins, and induces the phase II detoxifying pathway. The bioavailability and metabolism of green tea and its protective effects against environmental insults induced by pesticides, smoke, mycotoxins, polychlorinated biphenyls, and arsenic are reviewed in this paper.

*Address reprint requests and correspondence to C.-L. Shen, 1A096B, 3601 4th street, Department of Pathology, Texas Tech University Health Sciences Center, Lubbock, TX 79430-8115, USA. leslie.shen@ttuhsc.edu.

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Future studies with emphasis on clinical trials should identify biomarkers of green tea intake, examine the mechanisms of action of green tea polyphenols, and investigate potential interactions of green tea with other toxicant-modulating dietary factors.

Keywords

green tea; pesticides; cigarette smoke; PCB; mycotoxin; heavy metal

Introduction

The biological, physical, and chemical environmental toxins/toxicants are introduced into the body via different routes. Food additives, contaminants, water pollutants, and drugs can be orally ingested. Airborne toxicants, particles, and tobacco smoke (active or passive) are inhaled, whereas cosmetic chemicals are absorbed through dermal contact [1]. Adverse health effects of these environmental toxicants on human bodies are determined by dose, route of exposure, toxicokinetic and toxicodynamic balance, and individual susceptibility.

Acute toxic effects can be attributed to exposure to large quantities of a toxicant, whereas chronic adverse health effects can be caused by prolonged exposures to small quantities of a specific toxicant, which can ultimately result in bioaccumulation [2–7]. Exposure to toxicants can promote the formation of reactive radical (oxygen or nitrogen) species, which are inflammatory molecules inflicting oxidative stress upon cells. Depending on the molecular targets, toxicants may impact human health at the molecular (DNA, RNA, or protein), organelle (mitochondria, lysosome, or membranes), cellular (growth inhibition or cell death), tissue, organ, and overall systemic levels [2–7]. Pesticides, smoke, mycotoxins, endocrine-disrupting chemicals (e.g., polychlorinated biphenyl), and heavy metals (e.g. arsenic) have been listed as the most common toxins/toxicants to humans.

Pesticides enter the body through inhalation of aerosols, dusts, and vapor, ingestion of food additives, and direct contact. Pesticides can damage vital organs, with the liver being the most susceptible due to its role in transforming, metabolizing and eliminating chemicals from the body [8]. Studies have found that many pesticides are potential hepatotoxicants. For example, chlorfenviphos, demeton-S-methyl (DSM), methiocarb, permethrin, chlorpyrifos, triazophos, and pirimicarb cause structural and functional changes in mammalian and avian hepatocytes [8]. Moreover, some neurotoxic pesticides have been associated with diseases characterized by neural damage or failure, such as Parkinson's disease (PD) [9].

Smoke has long been recognized as a potent environmental toxicant and human health threat because it contains numerous chemical carcinogens and poisonous gases such as carbon monoxide, hydrogen cyanide, nitrogen and sulfur oxides, halogens, and organic acids [10]. The potential pathophysiological consequence associated with exposure to these poisonous gases may include the formation of carboxyhemoglobin, cyanide poisoning (cyanide blood), organic acid/ethanol intoxication [10], and enzymatic and morphologic alterations [11, 12]. Studies have found that inhalation of environmental smoke, including cigarette smoke,

increases the risk of lung cancer, respiratory diseases, liver lesions, and liver cancer [11, 13] as well as the severity of liver damage in hepatitis patients [14].

Aflatoxins, mainly produced by *Aspergillus flavus* and *A. parasiticus*, are a subcategory of mycotoxins that, much like alcohol, often possess hepatotoxic properties [3]. Aflatoxin B₁ (AFB₁) exposure has been shown to cause acute, sub-acute, and chronic liver failure [14]. Furthermore, AFB₁ is recognized as a potent carcinogen and mutagen [15]; the extent of aflatoxin contamination across regions of the United States has been correlated with incidences of hepatocellular carcinoma [15].

Many environmental contaminants act as endocrine disrupting chemicals (EDCs), capable of mimicking or blocking the action of hormones by binding to or interfering with their receptors. A subset of EDCs is known to affect metabolic processes if exposure occurs during early development, leading to obesity, type 2 diabetes mellitus and the metabolic syndrome. These chemicals are called “obesogens”. One class of the common obesogens is polychlorinated biphenyls (PCBs). PCBs are a major class of highly persistent organic pollutants (PCPs), widely used as synthetic chemical mixtures in industrial settings until it was banned in the United States and other developed countries beginning in 1970s. However, due to its resistance to degradation and bioaccumulation nature, the environmental and health impacts of PCBs are still of concerns. Epidemiological evidence now implicates exposure to PCBs in an increased risk of developing diabetes, hypertension, and obesity, all of which are clinically relevant to the onset and progression of cardiovascular disease. It is also suggested that PCBs exert their cardiovascular toxicity via additional mechanisms, including induction of chronic oxidative stress, inflammation, and endocrine disruption [16].

Exposure to inorganic and organic arsenic compounds in the environment remains a major public health problem, affecting hundreds of millions of people worldwide. Arsenic compounds affect almost every organ in the body, with health effects ranging from skin lesions and cancer to diabetes and lung disease [17, 18]. However, substantial knowledge gaps remain, particularly regarding the mechanisms by which arsenic induces such diverse health effects. Reactive oxygen species (ROS) generation is known to play a fundamental role in the arsenic-associated toxicity and carcinogenesis [19, 20].

Due to the inevitable human exposure to the aforementioned common environmental toxicants, there is a need for effective approaches to reduce or even eliminate their harmful impacts. Complementary and alternative approaches, such as dietary antioxidants or functional foods, could provide a safer way of protection or prevention than currently available options.

Tea, the dried leaves of the *Camellia sinensis* species of theaceae family, is a popular beverage with an annual production of three billion kilograms worldwide [21]. Green tea is a non-oxidized and non-fermented product that is made by drying fresh leaves (roasting) at high temperatures to inactivate the oxidizing enzymes. Green tea contains several tea polyphenols – primarily green tea catechins (GTCs) – that accounts for 30–40% of the extractable solids of dried green tea leaves [21]. Tea catechins include (–) epigallocatechingallate (EGCG), (–) epicatechingallate (ECG), (–) epicatechin (EC), and (–)

epigallocatechin (EGC) [21], among which EGCG is the most abundant and bioactive and the most studied. GTCs are known to increase the amount of anti-oxidative enzymes in the blood, and function as antioxidants to scavenge ROS such as superoxide, hydrogen peroxide (H_2O_2), and hydroxyl radicals [22, 23]. In the past decades, GTCs have demonstrated the ability to quench free radicals generated by oxidative environmental toxicants [24] and consequently, reduce toxicant-mediated cytological damage, mutation-mediated DNA damage, cancer, and apoptosis. This review will discuss the potential benefits of GTCs in the attenuation of the side effects and toxicity associated with common environmental toxicants including pesticides, smoke, mycotoxins, PCBs, and arsenic in *in vitro* and *in vivo* studies.

Bioavailability and metabolism of green tea catechins

The bioavailability of oral GTCs is generally less than 0.2% in humans and research animals [25–28]. Blood concentrations of GTCs peak at approximately 0.5 μM two to four hours after oral consumption of two cups of green tea [27]. The absolute oral bioavailability of EGCG is about 0.1% following the intake of 10 mg of green tea extract per kg body weight in humans and research animals [26, 28].

GTCs are metabolized *in vivo* through various metabolic transformations including methylation, glucuronidation, sulfation, oxidative degradation, and ring-fission metabolism [29–33]. The liver and intestine are generally considered to be the main organs to metabolize GTC. One third of GTCs in mesenteric plasma are in the form of glucuronide conjugates of catechin and 3'-O-methyl catechin (3'OMC), suggesting that glucuronidation and methylation occur in the intestinal tract [34]. The absorbed GTC and associated metabolites are first delivered to the liver where high levels of UDP-glucuronyltransferase [35, 36], sulfotransferase [37, 38], and catechol-O-methyltransferase (COMT) [39], among other enzymes, further metabolize GTC. After exiting the liver, GTCs and their metabolites are released into circulation system and distributed to different organs and tissues. Although GTCs have many metabolites in the human body, the biological activity of those metabolites remains unknown.

Green tea modulates pesticide-related damage or disease

Massive application of pesticides worldwide has conferred immense agricultural advances that in turn have led to improved nutrition and health. Most pesticides work *via* inhibition of pest growth and development or direct toxicity. Though researchers initially believed pesticides were harmless to living organisms, including humans, the advancement of technology has revealed many toxic effects, such as hematologic and immunological abnormalities, genotoxicity, embryo toxicity, neurological alterations, and hepatic dysfunction [40]. The hepatotoxicity of pesticides is related to metabolism through cytochrome P450 (CYP450) enzymes. The nephrotoxic effects include the formation of calculi, renal dysfunction, renal tubular acidosis, crystal uria, and hematuria. Additional adverse effects induced by pesticides, such as scyromazine, include high blood pressure, reduced body weight, and epithelial hyperplasia [40]. Most damage to membranes and tissues caused by pesticides is attributed to oxidative stress mediated by ROS such as hydroxyl radicals and H_2O_2 [40].

Table 1 lists the *in vitro* and *in vivo* studies showing the protective effects of green tea against different pesticides [9, 41–51]. Green tea extracts and polyphenols diminish pesticide-induced inhibition of cellular proliferation [9, 41, 42, 47, 49] and apoptosis [9, 41, 50], modulates intracellular signal transduction pathways [9], and elicits protective effect in a variety of neural cells [9, 45, 46]. For example, pretreatment with 500 μ M L-theanine, a green tea ingredient, in SH-SY5Y neuroblastoma cells for 1 h significantly attenuated rotenone-induced loss of cell viability [9]. In PC12 cells, a commonly used cell line that retains the features of dopaminergic neurons, EGCG at low concentrations (1, 5, and 10 μ M) significantly decreased paraquat-induced cell death, whereas higher concentrations of EGCG (50, 100, 200 μ M) did not show any protective effect against paraquat damage [41]. In transformed RGC-5 retinal ganglion cells, EGCG (10–100 μ M) and EC (10–75 μ M) attenuated the rotenone-induced loss of cell viability [42]. In mouse hepatocytes and normal human epidermal keratinocytes (NHEK), 0.05–50 μ g/mL green tea antioxidant (GTA) prevented the killing of hepatocytes by paraquat (1–10 mM) [47]. Tai *et al.* reported that EGCG protects SH-SY5Y from dichlorodiphenyl-trichloroethane (DDT)-induced cell death in a time-dependent manner [49].

Green tea bioactive compounds (i.e., L-theanine or EGCG) have also demonstrated the ability to inhibit pesticide-induced apoptosis [9, 41, 50]. For instance, L-theanine (500 μ M) inhibited pesticide-induced apoptosis in SH-SY5Y cells as shown by the marked attenuation of caspase-3 activities [9, 41], chromatin condensation, and nuclear fragmentation [9, 41]. EGCG (1, 5, 10 μ M) was found to markedly reduce pesticide-induced DNA fragmentation [41]. The potential mechanisms include the maintenance of the mitochondrial membrane potential, inhibition of caspase-3 activity, and the down-regulation of the expression of the pro-apoptotic protein, Smac, in the cytosol [41]. EGCG and catechins at 10.0 μ M both reduced the effect of paraquat on the cell cycle rate [50].

Furthermore, both L-theanine and EGCG have been shown to protect against pesticide-mediated neuronal damage [9, 45, 46]. Glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) act as potent and specific neurotrophic factors for midbrain dopaminergic neurons [52]. Cho *et al.* reported that L-theanine attenuated rotenone-mediated down-regulation of GDNF and BDNF in dopaminergic neurons [9]. Moldzio *et al.* also reported that EGCG significantly blocked rotenone-mediated increase in propidium iodide uptake, a measure of cell death, and 4-amino-5-methylamino-2'-7'-difluorescein diacetate (DAF-FM) fluorescence intensity in organotypic striatal cultures from mice [45]. EGCG provides some protection for striatal slices by counteracting the rotenone-induced nitric oxide production. Pan *et al.* first reported that green tea polyphenols (GTP) exert a partial inhibitory effect on the uptake of 3 H-dopamine (3 H-DA) and 3 H-1-methyl-4-phenylpyridinium (MPP+) by DA transporters (DAT) and provide partial neuro-protection from MPP+-induced injury in DAergic neurons, probably via their ability to block the DAT-dependent uptake of neurotoxin MPP+ [46].

Other studies examined the anti-oxidative activity of GTA, L-theanine, and EGCG in protection against pesticides. GTA prevents H₂O₂-induced cytotoxicity in cultured mouse hepatocytes (B6C3F1) and NHEK cells in a concentration-dependent manner [47]. Kamalden *et al.* found that green tea attenuates lipid peroxidation and rotenone toxicity in

RGC-5 cells [42]. Heme oxygenase-1, a cellular stress protein expressed in brain and other tissues, responds to oxidative challenge [53]. L-theanine suppressed the production of ROS and the subsequent expression of heme oxygenase-1 induced by PD-related neurotoxins in SH-SY5Y cells [9]. L-theanine treatment also blocked the rotenone-induced oxidative stress and down-regulation of extra-cellular signal-regulated kinase 1/2 (ERK 1/2) phosphorylation [9]. Tanaka *et al.* reported that EGCG and green tea decreased the frequency of sister-chromatid exchanges (SCE) induced by paraquat, a generator of ROS, suggesting that green tea and polyphenol-containing foods may protect against ROS-induced genotoxicity [50].

Apart from *in vitro* testing, animal studies further confirmed the beneficial effects of green tea extracts (GTE, a mixtures of green tea polyphenols) against pesticide-induced toxicities including oxidative stress [40, 43, 46] in the liver [40], lung [43], and the nervous system (Table 1). Administration of the pesticides cyromazine and chlorpyrifos to rats led to significant elevations of transaminases and lactate dehydrogenase in the serum and a decrease in liver function. There were rises in catalase, hepatic SOD, and lipid peroxidation, and a decrease in glutathione (GSH), indicating increased oxidative stress [40]. Histopathological evaluation revealed that green tea supplementation mitigated mild hepatocyte necrosis and liver degeneration. Additionally, green tea normalized catalase, SOD, and liver function in the rats. Kim *et al.* showed that GTE significantly decreased pulmonary fibrosis induced by oxidative stress attributed to paraquat exposure in rats. GTE acted putatively by suppressing oxidative stress and endothelin-1 expression [43].

Lastly, green tea extract has been shown to suppress liver carcinogenesis induced by the pesticide pentachlorophenol (PCP) [48, 51]. In general, green tea extract contains, in descending order of abundance, EGCG, EGC, EC, ECG, and catechin. Umemura *et al.* found that a 2% green tea infusion prevented diethylnitrosamine (DEN)-induced and PCP-promoted hepatocellular tumors, and arrested the progression of cholangiocellular tumors, plausibly by counteracting carcinogen-mediated increases in serum alanine transaminase (ALT) activity and 8-oxodeoxyguanosine (8-oxodG) levels in the liver [51]. In a similar study, Sai *et al.* found that green tea acted as an anti-promoter against PCP-induced mouse hepatocarcinogenesis *via* its ability to prevent down-regulation of gap junction protein 1c (GJIC) [48]. Korany *et al.* [44] also showed that green tea pretreatment significantly reduced histopathological alterations induced by the pesticide fenitrothion. These studies, though limited in number, further elucidate the possible role of green tea in the inhibition of pesticide-induced carcinogenesis.

In summary, preclinical studies showed that the protective effects of green tea against pesticide toxicity are, in part, due to its antioxidant and free radical scavenging activity. Most prominently, green tea extracts and polyphenols have been shown to decrease the toxicity of rotenone [42, 45], DDT [49], and paraquat [41, 47]. Future investigations should further examine these findings in preclinical and hopefully clinical studies since the latter is a noticeable research gap in the current literature. The role of green tea as a prophylactic agent prior to pesticide exposure may also warrant examination.

Green tea modulates smoke related diseases or damage

Smoking has been linked to malignant transformation or abnormal cell proliferation [54], and tobacco smoke is regarded as one of the leading causes of lung cancer [41, 47, 55]. Carcinogenic materials present in smoke produce DNA adducts and a mutagenic and carcinogenic response [56]. Toxins in cigarette smoke might also initiate and exacerbate tissue injury [23]. Another smoking related ailment is Chronic Obstructive Pulmonary Disease (COPD). Oxidative stress caused by a high concentration of free radicals and other oxidants in cigarette smoke can lead to inflammation, direct damage to epithelial cells, inactivation of anti-protease, and lipid peroxidation [57].

The protective activity of green tea and its constituents, including GTE, GTP, EGCG, ECG, EGC, EC, and catechins, on smoke-induced damage has been shown in cell culture, animal, and human studies (Table 2) [22, 51, 57–83]. Cellular studies have shown that EGCG and GTE protect against smoke-induced cellular proliferation [62, 71, 77], DNA damage [66, 80, 83], oxidative stress [22, 62, 71], and tumorigenesis [56, 71] through cell signaling pathways [71, 77]. More specifically, Syed *et al.* reported that EGCG pretreatment (20–80 μ M) of normal human bronchial epithelial cells (NHBE) resulted in significant inhibition of cigarette smoke condensate (CSC)-induced cell proliferation [77]. Pre-, co-, and post-incubation of primary human osteoblasts with sub-toxic concentrations of GTE (0, 50, 100, and 200 μ g/ml) or catechins (0, 50, 100, and 200 μ M) dose-dependently reduced cigarette smoke medium (CSM)-mediated cellular damage and concomitantly increased the viability of human osteoblasts [62].

Aside from inhibiting smoke-induced cellular proliferation in normal cells, green tea polyphenols, such as GTP, EGCG, ECG, EGC, and EC, also reduced smoke-induced DNA damage [66, 71, 80]. Pretreatment with 20–100 μ g/mL GTP for 2 h resulted in a dose-dependent decrease in smoke-mediated DNA damage in A549 cells, and GTP concentration was inversely correlated with the extent of DNA damage observed [66]. In addition, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced single-strand DNA breaks were prevented by EGCG in A549 cells [80]. Rathore *et al.* reported that co-treatment with 10 μ g/mL EC, ECG, EGC, and EGCG for 24 h reduced the NNK- and benzo[a]pyrene (B[a]P)-induced DNA damage in both human MCF10A breast epithelial cells and human MCF7 breast cancer cells [71]. Zhou's study demonstrated the strong anti-clastogenic effect of 0.025–0.075 mg/mL tea extract against extractable-respirable particulate in environmental tobacco smoke (ERP–ETS) in human peripheral blood lymphocytes [83]. The study also found that temperature and extraction soaking time impacted the potency of the tea extract. For example, increased soaking time (from 10, 30 to 60 min) at 100°C reduced the inhibitory activity of tea extract, whereas the same extended extraction period at lower temperatures increased the tea extract activity. Tea extract prepared by soaking at 80°C for 60 min produced the highest anti-clastogenic effect [83]. Further studies could help to confirm the precise mechanisms responsible for the inhibition of DNA damage.

Studies have found that GTE has a protective effect against smoke-induced oxidation [22, 62, 71]. Protein oxidation induced by cigarette smoke in guinea pig lung microsomes was inhibited by 93% upon exposure to the green tea infusion [22]. Holzer *et al.* reported that

osteoblasts pretreated or co-incubated with 0–200 µg/mL GTE or 0–200 µM catechins for 4 h prior to a 15-min exposure to smoke reduced ROS formation dose-dependently [62]. The GTE used for the Hozer's study (Sunphenon® 90LB, Taiyo Kagaku, Japan) was obtained from the leaf of traceable green tea (*Camelliasinensis*) and consisted of >80% polyphenols, of which >80% are catechins, >40% EGCG, and <1% caffeine.

Probable signal transduction pathways involved in EGCG's protective effect against smoke induced injuries include nuclear factor-κB (NF-κB) [77], phosphoinositide 3-kinase (PI3K) signaling [77], extracellular signal-regulated kinase (ERK)1/2 pathway [71], and H2AX pathway [71]. EGCG treatment of NHBE cells suppressed smoke-induced phosphorylation of NF-κB/p65, p38, ERK1/2, and JNK1/2 MAPK in a dose-dependent manner [77]. EGCG not only inhibited DNA-binding of NF-κB, but also resulted in a significant decrease in smoke-induced NF-κB promoter activity [77]. The mechanism of NF-κB inactivation by EGCG involved IKKα phosphorylation and degradation of IκBα [77]. Rathore *et al.* reported that co-treatment with 10 µg/mL EC, ECG, EGC, and EGCG for 24 h reduced the NNK- and B[a]P-induced ERK1/2 and H2AX phosphorylation in both MCF10A cells and MCF7 cells [71].

In vitro studies have also shown that green tea possesses, in addition to altering signal transduction pathways, activity to block smoking-associated tumorigenesis [56, 71]. For instance, EC, EGC, EGCG and with the highest potency, ECG, have been reported to block ROS elevation and ERK pathway activation, and effectively suppress NNK- and B[a]P-induced cellular carcinogenesis [71]. Despite these promising findings, contradictory data exist on whether GTE inhibits mutagenicity [54]. As a potential mechanism for the chemopreventive activity of EGCG in renal epithelial cells, pretreatment with EGCG for 12 h preserved the level of gap junction intercellular communication (GJIC) protein, also known as connexin 43, in Madin-Darby canine kidney epithelial cells (MDCK) exposed to dimethylnitrosamine (DMN) [78].

Animal studies confirmed the anti-oxidative ability of EC, EGC, ECG, and EGCG in a variety of lung injury models. Chan *et al.* [57, 59] treated Sprague-Dawley rats with 2% Lung Chen Tea, a Chinese green tea, in the presence and absence of smoke for 56 days. Lung Chen Tea (2%) with the largest amount of EGCG was found to alter oxidative stress in the serum and lungs in the smoke-exposed group and protect against smoke-induced lung damage as determined by histological and morphometric analyses [57]. Concomitantly, 2% Lung Chen Tea may also help to prevent the smoke-induced up-regulation of matrix metalloproteinase-12 (MMP12) activity, leading to a reduction in ROS [59]. Yang *et al.* reported that catechins reduced oxidative stress by reducing the Bax/Bcl-2 ratio and preserving HSP70 chaperone protein expression in the lung of study animals [57].

Most animal studies – with a few exceptions [60, 81] – further confirmed the beneficial effects of EGCG or GTE on smoke related disease or damage. Administration of GTE, GTP, or EGCG during initiation, promotion, or progression inhibited NNK-induced lung tumorigenesis in rats, mice, and hamsters [84]. Lu's study showed that the administration of tea polyphenols inhibited the progression of existing lung adenoma to adenocarcinoma [68]. In addition, GTP been shown to have protective effects against bladder tumors [69, 73, 75],

hepatocellular tumors [51, 76], and esophageal tumors [70]. These studies provided additional evidence that GTP can possibly be used in conjunction with other therapeutics.

Several clinical studies examined the effects of green tea on smoke-related DNA damage and gene mutations (Table 2) [61, 67, 79]. Lee *et al.* found that drinking green tea inhibited DNA mutations in blood samples from smokers and non-smokers [67]. Another study with 30 male and 90 female smokers found that consuming 4 cups or 960 mL of tea was associated with a significant decrease in urinary 8-hydroxydeoxyguanosine (8-OHdG), an indicator of DNA damage, as determined by ELISA [61]. In addition, green tea has also been shown to reduce the formation of the endogenous carcinogen, N-nitrosodimethylamine (NDMA) [79]. Despite the promising results of these clinical studies, additional data are necessary to not only understand the specific mechanisms involved, but also to fully explore the therapeutic potential of GTC.

In summary, polyphenol-containing green tea may counteract environmental toxins by preventing extensive damage to DNA, proteins, and cells. GTP may reduce smoke-induced cancer risk. However, it is unclear if the action of GTP is specific for smoke-induced carcinogenesis. Besides cigarette smoke, other sources of inhaled pollution, for example, air pollutant, house dust, airborne fungi, allergic irritants and toxins, are also warranted more attention in future studies on how green tea may mitigate the potential risk of health. In addition, future studies may need to address the differential responses to green tea by individuals, and to compare the effects of various types of teas due to their diverse ingredients.

Green tea and mycotoxin-related disease or damage

Aflatoxin and fumonisins, low-molecular-weight secondary metabolites produced by filamentous fungi [85], are the most relevant mycotoxins associated with human diseases [86]. Aflatoxins, comprised of more than 20 fungal metabolites, were first isolated in dead turkey with turkey X disease, which was later reported to be associated with mold-contaminated peanuts [87]. The major naturally produced aflatoxins include B1, B2, G1 and G2 [88]. The letters B and G denote the blue and green fluorescence emitted upon exposure to UV light. The most toxic aflatoxin B1 (AFB₁) is also a potent liver carcinogen widely used in carcinogenesis studies. Acute exposure to aflatoxins leads to acute aflatoxicosis characterized by acute hepatic injury, tissue edema, hemorrhage, and eventual death, whereas chronic exposure to aflatoxins gives rise to the development of malignancies [89]. A high level of aflatoxin exposure can promote hepatic cell necrosis. Fumonisins, first described in 1988, are produced by *Fusarium verticillioides* and *F. proliferatum*. Fumonisin B1 is the most abundant member in this family and has been associated with esophageal cancer [90], most prominently in areas with high incidence of esophageal cancer such as Transkei (South Africa), China, and northeast Italy [91].

The protective effects of green tea polyphenols, i.e. GTE and EGCG, against mycotoxin toxicity such as mutagenicity and DNA damage are summarized in Table 3 [92–107]. *Salmonella typhimurium* strains such as TA100, TA98, and TA97 have been used to test the effect of green tea on AFB₁-induced mutagenicity [92, 103, 107]. Wang reported that GTE,

GTP, and EGCG inhibited the mutagenicity of each promutagen in a dose-dependent manner. At the highest dose of GTP (500 µg/plate), the mutagenicity was inhibited by more than 95% [107]. Hour *et al.* determined that oolong tea, black tea, and green tea had anti-mutagenic properties and prevented cancer development, while GTE (0.1–100 µg/plate) showed the greatest inhibitory effect in strain TA100. In Snijman's study, 0.8µM EGCG was also shown to prevent AFB₁-induced mutagenicity [103]. Additionally, the anti-mutagenic properties of flavonoids were related to their lipophilicity or hydrophilicity, which ultimately influences methylation, hydroxylation and glycosylation. Wang *et al.* reported that green tea reduced DNA damage caused by AFB₁ [107] and in a dose-dependent manner, the frequency of SCE, chromosomal aberrations, and 6-thioguanine (6-TG)-resistance in Chinese hamster lung fibroblasts (V79); 100 µg/mL GTP induced 75% inhibition of SCE [107]. In addition, Mo's group reported that the tea extracts inhibit aflatoxin synthesis through the down-regulation of the transcription of aflR and aflS, two genes involved in the regulation of aflatoxin biosynthesis [100]. Green tea also inhibits gene forward mutation and reduces the frequencies of SCE and chromosomal aberrations. Animal studies confirmed the effect of green tea on AFB₁-induced carcinogenesis [98, 102, 108, 109]. Marnewick *et al.* [98] found that green tea enhanced hepatic microsomal fractions and protected from AFB₁-induced mutogenesis in Male Fischer rats.

Consumption of green tea during initiation or promotion phases of AFB₁-induced carcinogenesis inhibited the glutathione S-transferase positive hepatic foci in male Fischer rats [102]. Li's team [109] demonstrated that green tea was effective in inhibiting the hepatocarcinogenic effects of pre-inoculated diethylnitrosamine in rats. Boer *et al.* found that green tea markedly reduced the mutagenic potency of AFB₁ and other carcinogens in a transgenic rodent model [108], while Tulayakul *et al.* showed that the GTE increased AFB₁ detoxification *via* conjugation of AFB₁ to GSH in the intestinal tissues, but not the liver.

Dietary AFB₁ has been identified as one of the major etiologic factors for primary liver cancer (mainly hepatocellular carcinoma) in the developing world, such as Southwest Asia and sub-Saharan Africa [106]. GTP has been shown as safe and effective chemopreventive agents in various AFB₁-induced liver tumors. In a randomized, double-blinded, and placebo-controlled phase II chemoprevention trial in China, Wang's team evaluated the efficacy of GTP intervention on urinary 8-OHdG in 124 high-risk individuals with aflatoxin exposure [106]. All participants tested positive for aflatoxin-albumin adducts and took either a placebo or a capsule containing 500 mg or 1,000 mg GTP daily for 3 months. Prior to the intervention and at the first and third months of the study, 24-hour urine samples were collected. The purity of GTP capsules was > 98.5% and the GTP consisted of a mixture of EGCG, EGC, ECG, EC, and catechin. Wang's study demonstrated that (i) in GTP-treated groups, urinary EGC and EC levels displayed significant and dose-dependent increases, and (ii) at the end of 3-month intervention, urinary 8-OHdG concentrations decreased significantly in both GTP-treated groups [106], suggesting GTP is effective in diminishing oxidative DNA damage. A meta-analysis by Guyton *et al.* supported the preventive activity of green tea in liver cancer mediated by hepatotoxic contaminants including aflatoxins [110], but further studies are necessary to better understand the clinical applications of GTP upon mycotoxin exposure.

AFB₁ metabolism and specific AFB₁ biomarkers were studied to evaluate the efficacy of chemopreventive agents such as GTP, in order to determine if they could provide mechanistic information for human intervention trials. From the same clinical study by Wang's research team, Tang *et al.* further elucidated that daily administration of GTP (500 mg) significantly (15%) reduced levels of AFB₁-albumin adducts (AFB-AA) after 3 months, compared with levels of the placebo and baseline groups. Similar results were also observed in the 1000 mg GTP group at 1 and 3 months after the intervention. In addition to AFB-AA, urinary aflatoxin M₁ (AFM₁) is another biomarker for AFB₁ exposure that correlates well with dietary intake of AFB₁ and the risk of human hepatocellular carcinoma (HCC). A reduction in urinary levels of AFM₁ at 3 months of intervention was also observed in Tang's study [104]. Intervention with 500 and 1000 mg GTP significantly elevated urinary levels of AFB₁-mercapturic acid (AFB-NAC), the major detoxifying metabolic product of AFB₁-8,9-epoxide. The increase in the AFB₁-NAC:AFM₁ ratio in GTP-treated groups further demonstrated the GTP-mediated induction of the phase II detoxifying pathway in AFB₁ metabolism. Future studies should identify the optimal doses of green tea for the prevention of aflatoxin damage, taking into account variation in individual aflatoxin levels as a confounding factor that is largely attributed to differences in food products and most important in regions with high aflatoxin exposure.

GTP has been considered as one of the major resources of chemopreventive agents against many types of cancers. Huang *et al.* reported that GTP have been shown to be relatively safe at target organs such as the liver [93]. In the same clinical trial, Wang and Luo reported that major GTP, especially EGCG, were detectable in plasma after 1- and 3-month GTP interventions; plasma ECG and EGCG and urinary EC and EGC may be used as reliable biomarkers to reflect the consumption of green tea or GTP supplementation at the population level [96, 106].

Green tea modulates toxicities associated with PCBs

Some coplanar PCBs, e.g., PCB 126, exert their vascular toxicity primarily via stimulation of the aryl hydrocarbon receptor (AhR) and subsequent uncoupling of cytochrome P450 1A1 (CYP1A1), leading to oxidative stress and inflammation [111].

ROS induce the activity of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, glutathione reductase (GSR), glutathione transferases (GST), thioredoxins (Trx) and thioredoxin reductases (TrxR) [111]. The antioxidant enzymes work together either to quench ROS or to reactivate enzymes through a crosstalk of multiple regulatory pathways including the aryl hydrocarbon receptor (AhR) and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcription factors [111]. Petriello *et al.* recently have demonstrated both AhR and Nrf2 signaling pathways are activated by PCBs [111].

Table 4 summarizes the protective effects of green tea against the toxicity of PCBs [112–116]. Anti-inflammatory food components, such as green tea EGCG, can work through both AhR- and Nrf2-mediated mechanisms to prevent PCB-induced inflammation. For example, EGCG can protect against the activation of vascular endothelial cells by coplanar PCBs [112, 115]. EGCG can suppress the expression of AhR-regulated CYP1A1 and induce Nrf2-

regulated antioxidant enzymes, such as GST and NQO1, thus providing protection against PCB-induced inflammatory responses in cultured endothelial cells [112]. In addition, GTE has been shown to decrease oxidative stress in livers of mice exposed to PCB 126 via the induction of SOD1, GSR, NQO1 and GST [114].

In summary, epidemiological studies have linked exposure to POPs, such as PCBs, with an increased risk of developing diabetes, hypertension, and obesity, all of which lead to onset and progression of CVD [16]. Emerging evidence now suggests that green tea with its anti-inflammatory and anti-oxidative properties can decrease vascular toxicity and provide protection against PCBs-induced vascular toxicities.

Green tea modulates arsenic-associated toxicities and cancer

The beneficial effects of green tea on arsenic-associated toxicities were summarized in Table 5 [117–130]. Green tea and its principal polyphenol, (–)-EGCG, efficiently counteracted the cytotoxic effects of arsenic compounds in Chinese hamster lung fibroblast V69 cells [128]. This *in vitro* study is supported by subsequent *in vivo* studies [124]. Arsenic administration (3 mg/kg/day) for 14 days in rabbits resulted in significant oxidative stress, as revealed by reduction of whole blood GSH and elevation of thiobarbituric acid reactive substances (TBARS) and the index of nitrite/nitrate (NOx) levels. GTE administered to arsenic-treated rabbits for 14 days caused a significant elevation of the depleted GSH levels, which is likely attributed to the high polyphenol content of GTE [124]. Similarly, GT ameliorated arsenite (As III)-induced oxidative stress in Swiss albino mice by reducing the levels of lipid peroxides and protein carbonyl [130]. Co-administration of green tea extract also reduced arsenic (NaAsO₂)-induced toxicity in liver, kidney and testicular and lipid peroxidation in experimental rats [122]. Interestingly, it has been reported that GTE significantly altered transport and uptake of As (III) across the Caco-2 cell model system, providing additional means of protection against arsenic exposure [119].

Arsenic exposure is associated with DNA damage, changes in ploidy of cells, and nonrandom chromosome aberrations, leading to development of cancer. Both green tea and its polyphenols ameliorated arsenic-induced genotoxicity in the Chinese hamster lung fibroblast cells (V79) as determined by micronucleus assay [128]. In addition, tea extracts are effective in counteracting the sodium arsenite-induced clastogenicity (chromatid breaks, in particular) and inducing phase II detoxification enzymes, such as SOD and catalase, in the same V79 cells, suggesting that the antioxidant function of tea in reducing clastogenicity may be partly due to the induction of these enzymes [129]. Moreover, tea extracts reduced As III-induced DNA damage in human lymphocytes, as determined by comet assays. Tea also quenched excessive ROS production, reduced the elevated levels of lipid peroxidation, and increased the activities of catalase, SOD, and glutathione peroxidase. Furthermore, tea enhanced recovery from DNA damage, as confirmed by unscheduled DNA synthesis and pronounced expression of DNA repair enzyme poly (ADP-ribose) polymerase [126].

Tea extracts have been shown to reduce oxidative stress and induce DNA repair, all of which led to protection of arsenic-induced cancer. GTE reduced arsenic-induced formation of 8OHdG and induced arsenic-suppressed DNA repair enzymes, such as PARP1, DNA β-

polymerase, XRCC1, DNA ligase III, DNA protein kinase (catalytic subunit), XRCC 4, DNA ligase IV, and DNA topoisomerase II β , in Swiss albino mice [127]. GTE (10 mg/ml aqueous) restored arsenic-induced mutagenic DNA breaks and liver damages in rats via upregulation of cytosolic SOD [117]. Similarly, supplementation of tea extracts (10 mg/mL water) with NaAsO₂ (0.6 ppm)/100 g b.w. for 28 days in rats protected against arsenic-induced oxidative damages to DNA and small intestinal tissues by upregulation of antioxidant systems. In addition, in situ incubation of rat intestinal loop with NaAsO₂ alone (250 μ M) or with aqueous GTE (250 mg/mL) for 24 h showed that small intestinal epithelial cells were significantly protected by tea extract against arsenic-associated necrotic/mutagenic damages, suggesting that GTE have a direct role in free radical scavenging; the latter is associated with protection against mutagenic DNA breakages and tissue necrosis induced by arsenic [118]. Arsenic is metabolized to monomethylated arsenic (MMA), and subsequently becomes dimethylated arsenic (DMA). It was also reported that the incidence of lung tumors induced by lung tumor initiators (4NQO) and dimethylarsinic acid (DMA(V)), and 8-oxodG, were suppressed by co-treatment with EGCG [131].

Conclusions and summary

Figure 1 summarizes the working mechanism of green tea in its protection against the five most common environmental toxins and toxicants. Green tea and its extracts reduce the environmental toxicant-induced oxidative stress and damages to DNA and cellular structures by down-regulation of HO-1, MMP12, NF κ B, PI3K and ERK and up-regulation of antioxidant enzymes such as SOD and GSH, resulting in ROS quenching and lowering of oxidative products, including 8-OHdG. Green tea also suppresses toxicant-mediated carcinogenesis by preventing carcinogen-induced DNA damage, inhibiting cellular proliferation, inducing apoptosis and restoring connexin levels. On the other hand, green tea protects normal tissues and cells from toxicant-induced apoptosis by down-regulating caspases-3 and up-regulating SDO and GSH, thereby maintaining mitochondrial integrity. In addition, green tea attenuates signaling pathways such as NF κ B and ERK pathways triggered by toxicants.

The emerging evidence shows the promising protective/detoxifying impacts of green tea on environmental toxins. The lack of clinical evidence contributes to the need for such future studies. For instance, the development of predictive biomarkers for green tea consumption in the human population will offer a better understanding of the interaction between green tea and endogenous and exogenous factors that affect its bioavailability, and help to establish the safe doses of green tea consumption. Further development of molecular markers for the biological effects of green tea will also help to elucidate its underlying mechanisms of action. The interaction of green tea ingredients and other dietary factors with similar toxicant-modulating activities may also warrant further investigation.

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Figure 1.

Schematics representing the mechanisms of action for green tea in its protection against the five most common environmental toxins and toxicants. Green tea and its extracts suppress toxicant-induced cell proliferation and tumorigenesis by blocking carcinogen-mediated DNA damage. Green tea also quenches ROS and reduces oxidative stress by down-regulating MMP12, Bax/Bcl, HO-1, and NFκB, PI3K and ERK pathways and up-regulating SOD and GSH; the latter effects, coupled with down-regulation of caspases-3, offer additional protection of normal tissues from toxicant-induced apoptosis.

Table 1

Green tea and pesticide-related injury

First author, yr [ref]	Study design	Preparation of extract or GTP Used	Treatments	Effects of green tea
<i>Cellular studies</i>				
Cho, 2008 [9]	SH-SY5Y cells (neuroblastoma)	Not available	Rotenone Rotenone+ L-theanine	↑ Cell proliferation ↓ DNA fragmentation and apoptosis ↓ Heme oxygenase-1 up-regulation ↑ ERK1/2 phosphorylation ↑ GDNF and BDNF production
Hou, 2008 [41]	PC12 cells (pheochromocytoma cells)	Pure EGCG	Paraquat Paraquat+EGCG	↓ Apoptosis via maintaining mitochondrial membrane potential ↓ Caspase-3 activity ↓ expression of SMAC in cytosol
Kamalden, 2012 [42]	RGC-5 cells (retinal ganglion cells)	Pure EGCG and EC	Rotenone Rotenone+EGCG Rotenone+EC	↓ Rotenone-induced toxicity via JNK and p38 pathways ↓ Lipid peroxidation
Ruch, 1989 [47]	Mouse hepatocytes Human keratinocytes (NHEK cells)	GTE extracted with methanol	Paraquat Paraquat+GTE	↓ Apoptosis ↓ Inhibition of intercellular communication
Tai, 2010 [49]	SHSY-5Y cells	Pure EGCG	DDT DDT+EGCG	↓ DDT-induced toxicity
Tanaka, 2000 [50]	CNL cell (chronic neutrophilic leukemia)	Purchased from Kurita industry Company, Tokyo, Japan	Paraquat Paraquat+EGCG Paraquat+catechin Paraquat+EGCG+catechin	↓ Cell cycle rate ↓ ROS ↓ Paraquat-induced genotoxicity
Moldzio, 2010 [45]	Mesencephalic cultures Organotypic striatal cultures	Pure EGCG	Rotenone EGCG Rotenone+EGCG	↓ Nitric oxide production ↓ Rotenone-induced toxicity
Pan, 2003 [46]	Embryonic mesencephalic cells	Green tea polyphenols	Dopamine Dopamine+GTP	↓ Dopamine uptake ↓ MPP-induced dopamine neuron injury
<i>Animal studies</i>				
Pan, 2003 [46]	Male C57BL/6 mice	Green tea polyphenols	Control GTP	↓ Dopamine uptake in striatal synaptosomes ↓ MPP-induced dopamine neuron injury
Kim, 2006 [43]	Rats	Green tea leaves extracted with ethanol, concentrated, diluted with water, and extracted with ethyl acetate	Sham Paraquat Paraquat+GTE	↓ Paraquat-induced pulmonary fibrosis ↓ MDA, ET-1, and prepro-ET-1 mRNA expression ↓ Catalase activity
Sai, 2000 [48]	Male B6C3F1 mice 5-week-old	2% w/v green tea leaves were brewed with boiled water for 30 mins	Control PCP GT infusion PCP+green tea infusion	↓ PCP-induced hepatocarcinogenesis ↑ Cell proliferation ↑ Production of GJIC and connexin32
Umemura, 2003 [51]	Male B6C3F1 mice 5-week-old	2% w/v green tea leaves were brewed with boiled water for 30 mins	Drinking water DEN DEN+GT infusion DEN+PCP DEN+PCP+GTE	↓ DEN-induced hepatocarcinogenesis
Korany, 2011 [44]	Adult male Wistar rats	Film coated tablets contains 30%	Drinking water PCP GT PCP+GTE	↓ PCP-induced 8-oxodG levels in liver ↓ PCP-induced ALT activity in serum
			Control Fenitrothion Fenitrothion+GTE	↓ Fenitrothion-induced toxicity in rat parotid gland

First author, yr [ref]	Study design	Preparation of extract or GTP Used	Treatments	Effects of green tea
		polyphenol which produced by Arab Co.		↑ Caspase-3 cleaved activity Preservation of normal architecture Condensation of the chromatin

ALT, alanine aminotransferase; BDNF, brain-derived neurotrophic factor; DDT, dichlorodiphenyl-trichloroethane; DEN, diethylnitrosamine; EC, epicatechin; EGCG, (–)-epigallocatechingallate; ERK, extracellular signal-regulated kinase; ET-1, endothelin-1; GDNF, glial cell line-derived eurotrophic factor; GJIC, gap junction intercellular communication; GTE, green tea extract; GTP, green tea polyphenols; JNK, c-Jun N-terminal kinases; MDA, malondialdehyde; MPP, 1-methyl-4-phenylpyridinium; 8-oxodG, 8-oxodeoxyguanosine; PCP, pentachlorophenol; ROS, reactive oxygen species; SMAC, second mitochondria-derived activator of caspases. ↑ increase; ↓ decrease.

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Table 2

Green tea and smoke-related injury

First author, yr [ref]	Study design	Preparation of Extract or GTP Used	Treatments	Results
<i>Cellular studies</i>				
Misra, 2003 [22]	Guinea pig tissue microsomal suspension	1g green tea added to 10 mL of boiling water and brewed for 5 min.	Control Smoke Smoke+tea infusion	↓ Smoke-induced oxidative damage of protein
Holzer, 2012 [62]	Primary human osteoblasts	GTE (Sunphenon, Japan)	Smoke Smoke+GTE Smoke+catechins	↑ Viability ↓ ROS formation
Rathore, 2012 [71]	MCF10A cells MCF7 cells (human breast epithelial cells)	Pure EC, ECG, EGC, ECGC (Sigma-Aldrich Ltd., St. Louis, MO)	NNK+B[a]P NNK+B[a]P+EC NNK+B[a]P+ECG NNK+B[a]P+EGC NNK+B[a]P+ECGC	↓ NNK+B[a]P-induced carcinogenesis ↓ NNK+B[a]P-induced ROS production ↓ Phosphorylation of ERK1/2 ↓ DNA damage
Syed, 2007 [77]	Normal human bronchial epithelial cells	EGCG (>98% pure) (Mitsui Norin Co., Ltd Shizuoka, Japan)	Smoke Smoke+EGCG	↓ Smoke-induced cell proliferation ↓ Smoke-induced activation of NF- κ B, ↓ NF- κ B-regulated proteins cyclin D1, MMP-9, IL-8, iNOS ↓ Smoke-induced phosphorylation of ERK1/2, JNK, p38 MAPK
Leanderson, 1997 [66]	A549 cells (human lung adenocarcinoma cells)	Green tea extracted in 75°C water, 80% ethanol, chloroform, and ethyl acetate	Control Smoke+H ₂ O ₂ +Iron Smoke+H ₂ O ₂ +Iron+EGCG	↓ Smoke- and H ₂ O ₂ -induced toxicity and DNA strand breaks ↓ Production of lipid peroxidation
Weitberg, 1999 [80]	A549 cells	Pure EGCG (Sigma-Aldrich Ltd., St. Louis, MO)	Control NNK NNK+EGCG	↓ NKK-induced tumor promotion ↓ NKK-induced single-strand DNA breaks
Zhou, 2000 [83]	Human peripheral blood lymphocytes	20 g of dry green tea leaves extracted in 400 mL of distilled water at 80°C, 90°C, and 100°C for 10, 30, and 60 min, respectively	ERP/ETS ERP/ETS+GTE	↓ Smoke-induced mutations
Takahashi, 2004 [78]	MDCK cells (Mardin-Darby canine kidney cells)	Pure EGCG (Sigma-Aldrich Ltd., St. Louis, MO)	Control DMN EGCG DMN+EGCG	↑ Production of GJIC and connexin43 ↑ Phosphorylation of connexin43
Khoi, 2013 [64]	Human endothelial ECV304 cells	Pure EGCG (Sigma-Aldrich Ltd., St. Louis, MO)	Nicotine Nicotine+EGCG	↓ Nicotine-induced ROS production ↓ Nicotine-induced cell invasion and MMP-9 activity ↑ Nicotine-induced NF- κ B and AP-1 activation
<i>Animal studies</i>				
Umemur, 2003 [51]	Male B6C3F1 mice 5-week-old	2% w/v green tea leaves brewed with boiled water for 30 mins	Drinking water DEN DEN+Green tea infusion DEN+PCP DEN+PCP+Green tea	↓ DEN-induced hepatocellular tumors Arrest the progression of cholangiocellular tumors

First author, yr [ref]	Study design	Preparation of Extract or GTP Used	Treatments	Results
Chan, 2009 [57]	Sprague-Dawley rats	60 g dried Lung Chen tea leaves brewed in 600 mL hot water (not boiling) for 30 minutes	Sham Smoke Sham+tea Smoke+tea	↓ Serum 8-isoprostane level ↓ Lung SOD activity ↓ Catalase activity
Fiala, 2005 [60]	Male Hartley guinea pigs 3-week-old	EGCG (~94% pure)	Sham Smoke Smoke+p-XSC Smoke+EGCG	↔ Smoke-induced lung cancer
Witschi, 1998 [81]	Male and female strain A/J mice	Boiling deionized water poured over 62.5 g green tea leaves and left to stand for 15 min.	Sham Smoke Smoke+GTE	↔ Smoke-induced lung tumor multiplicity
Lu, 2006 [68]	Female A/J mice 4–6 weeks old N=11–24	Polyphenon E containing 65% EGCG, 7% ECG, 3% EGC, 9% EC, 3% GCG	Control NNK NNK+Polyphenon E	↓ Cell proliferation of adenomas ↑ Cell apoptosis of adenomas ↓ c-Jun and ERK1/2 phosphorylation
Lubet, 2007[69]	Female Fisher-344 rats and Sprague-Dawley rats 28-day-old	Polyphenon E containing 64.3% EGCG, 3.1% EGC, 9.1% EC, 8.1% ECG, other polyphenols	OH-BBN OH-BBN+Polyphenon E MNU MNU+Polyphenon E	↓ OH-BBN-induced urinary bladder tumors ↓ MMN-induced mammary cancer
Sato, 2003 [75]	Male Wistar rats 7-week-old	Powdered green tea leaves	BBN BBN+Green tea	↓ BBN-induced urinary bladder tumors
Shimizu, 2011 [76]	Male db/db mice	Pure EGCG (Mitsui Norin Co. Ltd., Tokyo, Japan)	Control EGCG DEN DEN+EGCG	↓ Tumor incidence and multiplicity ↓ Serum levels of insulin, IGF-1, IGF-2 ↓ p-IGF-1R protein ↓ Phosphorylation of ERK and Akt ↓ Serum levels of free fatty acids
Maliakal, 2011 [70]	Female Wistar rats	Boiled tap water added to tea powder (2% w/v) with intermittent stirring for 10 min and filtered	NMBA NMBD+GTE	↓ Tumour multiplication, size, volume ↔ Tumour incidence
Chan, 2012 [59]	Sprague-Dawley rats	60 g dried Lung Chen tea leaves brewed in 600 mL hot water (not boiling) for 30 minutes	Sham Smoke Sham+tea Smoke+tea	↓ Lung lipid peroxidation marker ↓ Smoke-induced serum MDA ↓ Neutrophil elastase concentration ↓ Smoke-induced MMP-12
Kaneko, 2003 [63]	Female Syrian golden hamsters 6-week-old	Not available	Control BOP BOP+Catechin	↓ BOP-induced formation of 8-oxodG in the pancreas
Abe, 2008[58]	Male Br/Han:WIST@Jcl (GALAS) rats 5-week-old	Green tea extract product Sunphenon BG (Taiyo Kagaku Company, Limited, Mie, Japan)	DMBDD DMBDD+GTC	↓ DMBDD-induced liver and stomach cancers
Kim, 2009[65]	Male albino rats	Green tea leaves extracted with 80% ethanol	Control DMN Hepatic fibrosis control Hepatic fibrosis+GTE	↓ DMN-induced hydroxyproline ↓ DMN-induced MDA
Yang, 2009[82]	Female Wistar rats	Decaffeinated catechins containing EGCG, ECG, GCG, EC, EGC, GC, catechin	Non-cooking-oil-fumes Non-cooking-oil-fumes+catechins Cooking-oil-fumes (COF) Cooking-oil-fumes+catechins	✓ COF-enhanced ROS level ✓ COF-enhanced lung dityrosine ✓ COF-enhanced 4-HNE Level ↑ COF-decreased Bcl-2 and HSP70 Expression

First author, yr [ref]	Study design	Preparation of Extract or GTP Used	Treatments	Results
Roy, 2010[72]	Male swiss albino mice	GTP (Indfrag limited, Bangalore, India)	Control GTP BTP DEN DEN+GTP	✓ DEN-induced COX-2 expression ✓ DEN-induced activation of NFκB and Akt
Sagara, 2010[73]	Female C3H/He mice	GTP (Tokyo Kasei Industries, Tokyo, Japan)	Control BBN GTP BBN+GTP	↓ Frequency of invasive tumors ↓ Tumor volume and microvessel density of intratumoral and stromal region
Saiwichai, 2010[74]	Rats	Dried methanol extract dissolved in 500 mL of water at 50°C and washed with hexane, chloroform and ethyl acetate; residue dissolved in 50°C water and freeze dried to obtain mixture of EGCG, ECG, EGC, EC	Sham Smoke Smoke+GTE	↓ Serum HMGB1 level
<i>Human studies</i>				
Lee, 1997 [67]	Questionnaire based study, Male	Not available	Non-smokers Smokers Smokers+Green tea	↑ SCE rates in smokers group ↔ Frequency of SCE in smokers
Vermeer, 1999 [79]	Healthy female volunteers	Lyophilized green tea solids dissolved in boiling water (0.5 g in 100 mL); four cups (2 g) of tea per day in test week 4, and eight cups (4 g) of tea per day in test week 5.	Fish meal rich in amines Fish meal+Green tea	↓ Nitrosation
Hakim, 2008 [61]	RCT Smokers (N=133)	4 cups (960 mL)/d of decaffeinated green tea product consisting of EGCG, EGC, EC, ECG, total catechins, gallic acid, total flavanol glycosides.	Water Green tea	✓ Urinary 8-OHdG

4-HNE, 4-hydroxy-2-nonenal; 8-OHdG, 8-hydroxydeoxyguanosine; BBN, N-butyl-N-(4-hydroxybutyl)-nitrosamine; BOP, N-Nitrosobis(2-oxopropyl)amine; COX-2, cyclooxygenase-2; DEN, diethylnitrosamine; DMBDD, N-nitrosodiethylamine (DEN), N-methylnitrosourea (MNU), N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN), 1,2-dimethylhydrazine (DMH) and 2,2'-dihydroxy-di-n-propylnitrosamine (DHPN); DMN, dimethylnitrosamine; EC, epicatechin; ECG, epicatechin-3-gallate; EGC, epigallocatechin; EGCG, (-)-epigallocatechin gallate; ERK, extracellular arsignal-regulated kinase; ERP/ETS, extractable respirable particulate/environmental tobacco smoke; GJIC, gap junction intercellular communication; GTE, green tea extract; GTP, green tea polyphenols; HMGB1, high-mobility group protein B1; IGF, insulin-like growth factor; IL-8, interleukin-8; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinases; MAPK, mitogen-activated protein kinases; MDA, malondialdehyde; MMP, matrix metalloproteinases; MNU, methylnitrosourea; NF-κB, nuclear factor-κB; NNK, 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone; PCP, pentachlorophenol; RCT, randomized controlled trial; ROS, reactive oxygen species; SCE, sister-chromatid exchange; SOD, superoxide dismutase. ↑ increase; ↓ decrease; ↔ no difference

Table 3

Green tea and mycotoxin-related injury

First author, yr [ref]	Study design	Preparation of Extract or GTP Used	Treatments	Effects of green tea
<i>Cellular studies</i>				
Hour, 1999[92]	TA100, TA98, and TA97(Salmonella typhimurium strains)	12.5 g green tea leaves added to 500 mL boiling water and steeped for 15 min	AFB ₁ AFB ₁ +GTE AFB ₁ +EGCG	↓ AFB ₁ -induced mutagenesis
Mo, 2013 [100]	Aspergillusflavus	10 g green tea soaked in 100 mL of boiling demi-water for 0.5 h	AFB ₁ AFB ₁ +Green tea	↓ Aflatoxin production by down-regulating the transcription of aflR and aflS
Snijman, 2007 [103]	TA100 and TA98	Pure EGCG (Sigma-Aldrich, St. Louis, MO)	AFB ₁ AFB ₁ +EGCG	↓ AFB ₁ -induced mutagenesis
Wang, 1989 [107]	TA100 and TA98	100 g of green tea powder suspended in water (0.75 L, 75°C), filtered, and extracted with 80% ethanol (0.75 L, 50°C); aqueous and ethanol extracts combined, concentrated and extracted with chloroform; remaining aqueous phase extracted with ethyl acetate; residue dissolved in water and freeze-dried to obtain GTP containing EC, EGC, ECG and EGCG.he oxidation of by atmospheric oxygen	AFB ₁ AFB ₁ +GTP	↓ AFB ₁ -induced mutagenesis ↓ AFB ₁ -induced frequency of SCE ↓ AFB ₁ -induced chromosomal aberrations
<i>Animal studies</i>				
Ito, 1989 [94]	Male Wistar rats	20 g green tea added to 1 L of boiling water and steeped for 10 min	AFB ₁ AFB ₁ +GTE	↓ AFB ₁ -induced chromosome aberration
Marnewick, 2004 [98]	Male Fischer rats	Boiled tap water added to tea leaves and stems (2 g/100 mL or 4 g/100 mL)	AFB ₁ AFB ₁ +Green tea	↓ Activation of AFB ₁ -induced mutagenesis
Marnewick, 2009 [99]	Male Fischer rats	Boiled tap water added to tea leaves and stems (2 g/100 mL or 4 g/100 mL)	DMSO DEN DEN+FB1 DEN+FB1+Green tea	↑ Oxygen radical absorbance capacity ↓ Serum cholesterol ↑ GSSG level and catalase activity ↓ GSH:GSSG ratio ↔ FB1-induced lipid peroxidation
Qin, 1997 [101]	Male Fischer rats	Instant GT powder (Thomas J. Lipton, Englewood Cliffs, NJ)	AFB ₁ AFB ₁ +Green tea	↓ AFB ₁ -induced hepatocarcinogenesis by modulation of AFB ₁ metabolism ↓ AFB ₁ -DNA binding ↓ AFB ₁ -induced GST-P-positive hepatocytes
Qin, 2000 [102]	Male Fischer rats	Instant GT powder (Thomas J. Lipton, Englewood Cliffs, NJ)	DMSO DMSO+Green tea DMSO+CCl ₄ AFB ₁	↓ Initiation and promotion of AFB ₁ -induced hepatocarcinogenesis ↓ AFB ₁ -induced GST-P-positive hepatic foci and area and volume

First author, yr [ref]	Study design	Preparation of Extract or GTP Used	Treatments	Effects of green tea
			AFB ₁ +CCl ₄ AFB ₁ +CCl ₄ +Green tea	↑ GSH level
Tulayakul, 2007 [105]	Female piglets	Green tea extracts (Taiyo Kagaku Co., Ltd., Mie, Japan)	AFB ₁ AFB ₁ +GTE	↑ AFB ₁ detoxification ↓ P450 enzyme activity in liver ↑ GST activity in intestine ↑ Conversion of AFB ₁ to aflatoxicol in the liver
<i>Human studies</i>				
Huang, 2004 [93]	Randomized, double blinded and placebo-controlled phase IIa chemoprevention Trial (design)	GTP consisted of EGCG, ECG, EGC, and EC (Shili Natural Product Company, Guilin, Guangxi)	Placebo Green tea (500 mg) Green tea (1000 mg) For 3 months	Green intake at 1000 mg daily for 3 months was safe
Luo, 2006 [95]	Randomized, double blinded and placebo-controlled phase IIa chemoprevention	GTP consisted of EGCG, ECG, EGC, and EC (Shili Natural Product Company, Guilin, Guangxi)	Placebo Green tea (500 mg) Green tea (1000 mg) For 3 month	↓ 8-OHdG levels
Luo, 2006 [96]	Randomized, double blinded and placebo-controlled phase IIa chemoprevention trial	GTP consisted of EGCG, ECG, EGC, and EC (Shili Natural Product Company, Guilin, Guangxi)	Placebo Green tea (500 mg) Green tea group (1000 mg) For 3 month	Metabolic profiling identified 106 metabolites, and 56 of them were chosen to construct discriminant functions.
Tang, 2008[104]	Randomized, double blinded and placebo-controlled phase IIa chemoprevention trial	GTP consisted of EGCG, ECG, EGC, and EC (Shili Natural Product Company, Guilin, Guangxi)	Placebo Green tea (500 mg) Green tea(1000 mg) For 3 month	✓ AFB-AA levels ↓ AFM ₁ ↑ AFB-NAC levels ↑ AFB-NAC:AFM ₁

8-OHdG, 8-hydroxydeoxyguanosine, AFB-AA, AFB₁-albumin adducts; AFB-NAC, aflatoxin B₁-mercapturic acid; AFB₁ aflatoxin B₁; AFM₁, aflatoxin M₁; DEN, diethylnitrosamine; EGCG, (–)-epigallocatechin-3-gallate; FB, fumonisin B; GSH, glutathione; GSSG, oxidized glutathione; GST, glutathione S-transferase; GTE, green tea extract; GTP, green tea polyphenols; SCE, sister-chromatid exchange. ↑ increase; ↓ decrease; ↔ no difference

Table 4

Green tea and PCB-related injury

First author, yr [ref]	Study design	Preparation of Extract or GTP Used	Treatments	Effects of green tea
<i>Cellular studies</i>				
Han, 2012[112]	Primary vascular endothelial cells	Pure EGCG (Cayman Chemical Co., Ann Arbor, MI)	PCB PCB+EGCG	↓ CYP1A1 mRNA and protein expression ↓ Superoxide production ↓ MCP-1 and VCAM-1 ↑ Nrf2-controlled genes (GST and NQO1)
Ramadass, 2003[115]	Endothelial cells	Pure EGCG (Sigma-Aldrich, Ltd., St. Louis, MO)	PCB 77 (3,3', 4,4' - tetrachlorobiphenyl) PCB 77+EGCG	↓ Oxidative stress↓ CYP1A1 activity
Weisburger, 1994[116]	<i>in vitro</i> systems of Jägerstad	Not available	PCB PCB+EGCG	↓ Formation of typical HCAs (MeIQx and PhIP)
<i>Animal studies</i>				
Morita, 1997[113]	Male rats	Not available	PCB PCB+GTE	↓ Liver distribution of PCB
Newsome, 2014 [114]	C57BL/6 mice	GTE (Taiyo International Inc., Minneapolis, MN)	PCB PCB+GTE	↑ SOD1, GSR, NQO1 and GST ↓ Oxidative stress

EGCG, (–)-epigallocatechingallate; GTE, green tea extract; GSR, glutathione S-reductase; GST, glutathione S transferase; HCAs, Heterocyclic amines; MCP-1, monocyte chemotactic protein-1; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline; NQO1, NAD(P)H:quinoneoxidoreductase; Nrf2, nuclear factor erythroid 2 [NF-E2]-related factor 2; PCB, polychlorinated biphenyl; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine ; SOD1, Superoxide Dismutase 1; VCAM-1, vascular cell adhesion protein-1. ↑ increase; ↓ decrease.

Table 5

Green tea and arsenic-related injury

First author, yr [ref]	Study design	Preparation of Extract or GTP Used	Treatments	Effects of green tea
<i>Cellular studies</i>				
Calatayud, 2011[119]	Caco-2 cells	GTE (Plantextrakt, Germany)	As(III) As(III)+GTE	↑ TEER ↓ As(III) P _{app}
Kim, 2015[120]	BAE cells	Pure EGCG	As As+EGCG	↑ Cell cytotoxicity↑ ROS formation ↑ Lipid peroxidation ↓ Catalase activity
Lee, 2011[121]	HL60 cells	Pure EGCG	ATO ATO+EGCG	↑ Mitochondria-induced apoptosis ↑ ROS formation to damage cell
Nakazato, 2005[123]	Malignant B-cell lines	Pure ECGC (WAKO Chemical Co. Tokyo, Japan)	As ₂ O ₃ As ₂ O ₃ +EGCG	↑ Apoptotic cell death ↑ ROS formation
Sinha, 2005[125]	V79 cells	Green tea leaves extracted with hot water and extracted with ethyl acetate	NaAsO ₂ NaAsO ₂ +GTE	↓ Chromatid breaks ↑ SOD and CAT
Sinha, 2007[126]	Normal human lymphocytes	Green tea leaves extracted with hot water and extracted with ethyl acetate	As(III) As(III)+GTE	↓ DNA damage and ROS formation ↓ ROS formation and lipid peroxidation ↑ CAT, SOD, and GPx
Sinha, 2003[128]	V79 cells	2.5 g of dry tea brewed in 100 ml of boiled water for 5 min. GTE consisted of ECG, EGC, EGCG	As As+GTE	↓ Apoptosis
Sinha, 2005[129]	V79 cells	Green tea leaves extracted with hot water and extracted with ethyl acetate	As As+GTE	↑ Repair activity
<i>Animal studies</i>				
Acharyya, 2014[117]	Rats	Leaf dust of green tea dried, crushed, and extracted by distilled water	As As+GTE	↓ Apoptotic hepatic degeneration ↓ DNA damage ↑ SOD1 protection
Acharyya, 2015[118]	Rats	Leaf dust of green tea dried, crushed, and extracted by distilled water	NaAsO ₂ NaAsO ₂ +GTE	↓ Intestinal tissue degeneration ↓ DNA-breakages ↓ Necrotic damage
Messarrah, 2013[122]	Rats	66 g dry leaves extracted per liter of tap water in drinking water	NaAsO ₂ NaAsO ₂ +GTE	↓ TBARS ↓ Oxidative stress ↑ Body weight
Raihan, 2009[124]	Rabbits	3.75 g green tea boiled with arsenic-free fresh drinking (100 mL) for 10 min.	As As+GTE	↑ GSH ↓ TBARS and NOx
Sinha, 2011[127]	Swiss albino mice	0.5 g of dry tea leaves boiled with milli-Q water (5 mL) for 5 min.	As(III) As(III)+GTE	↓ 8 OHdG and OGG1 ↑ DNA repair enzymes
Sinha, 2010[130]	Swiss albino mice	0.5 g of dry tea leaves boiled with milli-Q water (5 mL) for 5 min.	As(III) As(III)+GTE	↓ Lipid peroxides ↓ Protein carbonyl ↑ CAT, SOD, GPx, GR, GST, and GSH

As, arsenic; As(III), arsenite; As₂O₃, arsenic trioxide; ATO, arsenic trioxide; BAE, bovine aortic endothelial cells; Caco-2 cells, human epithelial colorectal adenocarcinoma cells; CAT, catalase; EGCG, (–)-epigallocatechingallate; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GST, glutathione-S-transferase; GTE, green tea extract; HL60, human promyelocytic leukemia cells; NaAsO₂, sodium arsenite; NOx, nitrogen oxides; OGG1, 8-oxoguanine DNA glycosylase; 8 OHdG, 8-hydroxy-2'-deoxyguanosine; P_{app}, apparent permeability; SOD, superoxide

dismutase; TBARS, thiobarbituric acid reactive substances; TEER, transepithelial resistance; V79, male Chinese hamster lung fibroblasts; ↑ increase; ↓ decrease.

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