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REVIEWS: CURRENT TOPICS

Therapeutic properties of green tea against environmental insults

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Abstract

Pesticides, smoke, mycotoxins, polychlorinated biphenyls (PCBs), 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 nonoxidized and nonfermented 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, antiinflammatory, antimutagenic, hepatoprotective and neuroprotective, and anticarcinogenic activities. In addition, green tea modulates signaling pathway including NF-κB and ERK pathways, preserves mitochondrial membrane potential, inhibits caspase-3 activity, down-regulates proapoptotic 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, PCBs, and arsenic are reviewed in this paper. 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

1. 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 [EDCs; *e.g.*, polychlorinated biphenyl (PCB)], 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, chlorfenvinphos, demeton-*S*-methyl, methiocarb, permethrin, chlorpyriphos, triazophos, and pirimicarb cause structural and functional changes in mammalian and avian

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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 *Aspergillus parasiticus*, are a subcategory of mycotoxins that, much like alcohol, often possess hepatotoxic properties [3]. Aflatoxin B1 (AFB_1) exposure has been shown to cause acute, subacute, and chronic liver failure [14]. Furthermore, AFB_1 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 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 PCBs. PCBs are a major class of highly persistent organic pollutants [pentachlorophenols (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 nonoxidized and nonfermented 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 antioxidative 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.

2. Bioavailability and metabolism of GTCs

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 kilogram 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, 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 [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.

3. 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 that 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 enzymes. The nephrotoxic effects include the formation of calculi, renal dysfunction, renal tubular acidosis, crystalluria, and hematuria. Additional adverse effects induced by pesticides, such as cyromazine, 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,