Chapter 12

Cancer Chemoprevention by Dietary Polyphenols

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Chemopreventive agents

Chemoprevention is a promising and relatively new approach to cancer prevention that has precedence in cardiology, in which cholesterol lowering antihypertensive, and antiplatelet agents are administered to prevent coronary heart disease in high-risk individuals [1]. Chemoprevention can be defined as "the use of natural or synthetic chemical compounds to reverse, suppress or to prevent one or more of the biological events leading to the development of invasive cancer"

A chemopreventive strategy could potentially either prevent further DNA damage that might enhance carcinogenesis or suppress the appearance of the cancer phenotype [2]. Chemopreventive agents inhibit or reverse cellular events associated with tumor initiation, promotion, and/or progression. The mechanism of chemoprotective activities might correlate and balance between phase I + phase II enzymes levels, and influence cellular macromolecules, transporters, release of carcinogens, or DNA adducts and DNA repair [3].

More than 1000 potential chemopreventive agents have been identified in dietary sources, and many are being tested *in vitro* and *in vivo* systems with a variety of cancer types. Identification and testing of a successful chemopreventive agent is a long process, requiring *in vitro* studies, animal efficacy and toxicity studies, and eventually lengthy human clinical trials [4].

1.2. Mechanisms of action of chemopreventive agents

Broadly defined on the basis of their mechanisms of action, chemopreventive agents can be grouped into two general classes: blocking agents and suppressing agents. Blocking agents (e.g., flavonoids, oltipraz, indoles, and isothiocyanates) prevent carcinogenic compounds

from reaching or reacting with critical target sites by preventing the metabolic activation of carcinogens or tumor promoters via enhancing detoxification systems and by trapping reactive carcinogens [5]. Suppressing agents (e.g., vitamin D and related compounds, nonsteroidal anti-inflammatory drugs [NSAIDS], vitamin A and retinoids, DFMO (2-difluoromethylornithine), monoterpenes and calcium) prevent the evolution of the neoplastic process in cells that would otherwise become malignant. Mechanisms of action for suppressing agents are not well understood. Some produce differentiation, some counteract the consequences of genotoxic events such as oncogene activation, some inhibit cell proliferation, and some have undefined mechanisms [5].

An ideal chemopreventive agent should have 1. Little or no toxic effects 2. High efficacy against multiple sites 3. Capability of oral administration 4. a known mechanism of action 5. Human acceptance [6]. A chemopreventive program identifies and accesses specific chemical substances, many naturally occurring in foods, with the potential to prevent cancer initiation and to either slow or reverse the progression of premalignant lesions to invasive cancer.

1.3. Types of chemopreventive agents:

Promising chemopreventive agents being investigated include micronutrients (e.g. vitamin A, C and E, β-carotene, molybdenum, and calcium), phytochemicals (e.g. indoles, polyphenols, isothiocyanates, flavonoids, monoterpenes, and organosulfides), and synthetics (e.g. vitamin A derivatives, piroxicam, tamoxifen, 2-difluoromethylornithine [DFMO] and oltipraz). More than 40 promising agents and agent combinations are being evaluated clinically as chemopreventive drugs for major cancer targets [7].

1.3.1. Synthetic chemopreventive agents (Non-Steroidal-anti-inflammatory drugs):

Several studies have reported a 40-50% decrease in the relative risk of colorectal cancer in persons who are continuous users of aspirin or other non steroidal anti-inflammatory drugs (NSAIDS) [8], suggesting that these drugs can serve as effective cancer chemopreventive agents. Hixson *et al.,* [9] showed that the synthesis of prostaglandins is limited by cyclooxygenase. NSAIDS reversibly interrupted prostaglandin synthesis by inhibiting cyclooxygenase. NSAIDS can prevent tumor formation by their actions on prostaglandins, which can have an immune modulating effect. High levels of prostaglandin E2 can suppress the immune system, which keeps malignant cells in check.

Other mechanisms that can explain the antiproliferative antitumor effects of NSAIDS include: interference with membrane-associated processes, such as G-protein signal transduction and transmembrane calcium influx, and inhibition of other enzymes, such as phospho-diesterase, folate-dependant enzymes, and cyclic adenosine-5`-monophosphatase-dependent protein kinase, as well as enhancement of immunologic responses and cellular apoptosis [10].

At a macroscopic level, NSAIDS prevent incident neoplasia (adenomas and carcinomas), and suppress the growth of carcinomas. Therefore, NSAIDS are effective when given

"early" (proceeding adenoma-formation), as well as "late" (following the emergence of adenomas) [11]. An alternative explanation for the efficacy of NSAIDS in the prevention of colorectal cancer is their ability to scavenge reactive oxygen species [12].

1.3.2. Naturally-occurring chemopreventive agents:

Frequent consumption of fruits and vegetables has been associated with lower incidence of cancers at different organ sites. Several factors can contribute to this association, first, the nutrients in fruits and vegetables, notably vitamin C, vitamin E, folic acid, provitamin A, selenium and zinc, are essential for normal cellular functions, a deficiency in these nutrients can enhance the susceptibility of an individual to cancer, second, some nutrients, such as vitamin C, vitamin E, selenium and β-carotene, at levels above nutritional needs, can display inhibitory activities against carcinogenesis. A third factor is that non-nutritive constituents, such as polyphenols, organosulfur compounds, and indoles have anticarcinogen activities. Finally, fruits and vegetables contribute fibers and bulkiness to the diet. Persons who consume large amounts of fruits and vegetables can eat smaller amounts of meat and other animal products that can contribute to higher cancer incidence in the western countries. Supplementation with these antioxidant nutrients apparently produces a protective effect against cancer.

Comprehensive reviews of case-control and prospective cohort studies found that the relationship between high vegetable and fruit intake and reduced cancer risk appears to be strongest for cancers of the alimentary and respiratory tracts (cancers of the colon, esophagus, oral cavity and lung) and weakest for hormone related cancers (cancers of the breast, ovary, cervix, endometrium and prostate) [13-15]. Reduced cancer risk has been linked primarily to consumption of raw vegetables and fresh fruits (citrus, carrots, green leaf vegetables, cruciferous vegetables, soy products, and whole grain wheat products) [13-15]. The beneficial effect of vegetables, fruits and whole grains can be due to either individual or combined effects of their constituents, including, fiber, micronutrients and phytochemicals.

2. Dietary polyphenols and cancer chemoprevention

Polyphenols constitute one of the largest and ubiquitous groups of phytochemicals. One of the primary functions of these plant-derived polyphenols is to protect plants from photosynthetic stress, reactive oxygen species, and consumption by herbivores. Polyphenols are also an essential part of the human diet, with flavonoids and phenolic acids being the most common ones in food. Not surprisingly, there is a growing realization that lower incidence of cancer in certain populations can probably be due to consumption of certain nutrients, and especially polyphenol rich diets. Consequently, a systematic dissection of the chemopreventive potential of polyphenolic compounds in the recent years has clearly supported their health benefits, including anti-cancer properties. Given the challenges of cancer therapy, 'chemoprevention'-which uses pharmacological or natural agents to impede, arrest or reverse carcinogenesis at its earliest stages' remains the most practical and promising approach for the management of cancer patients [16].

Till date, A substantial number of studies in cultured cells, animal models and human clinical trials have illustrated a protective role of dietary polyphenols against different types of cancers [17–20]. Polyphenols are present in fruits, vegetables, and other dietary botanicals. Some estimates suggest that more than 8000 different dietary polyphenols exist, and these can be divided into ten different general classes based on their chemical structure [21]. Phenolic acids, flavonoids, stilbenes and lignans are the most abundantly occurring polyphenols that are also an integral part of everyday nutrition in populations worldwide. Some of the common examples of the most studied and promising cancer chemopreventive polyphenols include EGCG (from green tea), curcumin (from curry) and resveratrol (from grapes and berries). Significant gains have been made in understanding the molecular mechanisms underpinning the chemopreventive effects of polyphenols, and consequently, a wide range of mechanisms and gene targets have been identified for individual compounds. Various mechanistic explanations for their chemopreventive efficacy include their ability to interrupt or reverse the carcinogenesis process by acting on intracellular signaling network molecules involved in the initiation and/or promotion of cancer, or their potential to arrest or reverse the promotion stage of cancer [22; 23]. Polyphenolic compounds can also trigger apoptosis in cancer cells through the modulation of a number of key elements in cellular signal transduction pathways linked to apoptosis (caspases, *bcl-2* genes) [17; 22; 23]. Several elegant reviews have described in detail specific genetic and signaling mechanisms that are targeted by different polyphenols, and this is beyond the scope of this review article [24–26]. However, recent research has suggested that some of the chemopreventive potential of dietary polyphenols can in part be due to their ability to modulate epigenetic alterations in cancer cells. This is of interest; as epigenetic modifications occur early and are potentially reversible, making dietary polyphenol-induced chemoprevention of various human cancers an attractive possibility from a clinical standpoint. However, the mechanism of how flavonoids do regulate and effect various epigenetic modifications in cancer cells is a topic that is still in its infancy. Nevertheless, increasing number of reports has repeatedly shown the promise of epigenetic prevention and possibly therapy by dietary polyphenols.

2.1. Tea

Tea (*Camellia sinensis*), next to water, is the most popular beverage consumed by over two thirds of the world's population. The Chinese used tea as a medical drink as early as 3000 BC, and by the end of the sixth century as a beverage. Tea essentially signifies two or three leaves and the terminal apical buds of the shrubs *C. sinensis*, *Camellis asamica* and other southern varieties. The cultivation area of the tea has gradually expanded in the world, especially in tropical countries, and the total cultivation area has expanded to 2,300,000 ha with a total amount of production of 2,600,000 t [27].

An estimated 2.5 million metric tons of dried tea are manufactured annually. Of this amount about 20% is green tea, mainly consumed in Asian countries where tea is a major beverage. About 78% is black tea mainly consumed in the western nations and some Asian countries and about 2% is oolong tea mainly produced and consumed in South Eastern China.

2.1.1. Chemistry and mechanism of action of tea polyphenols:

Manufacture of black tea takes place by crushing the leaves causing polyphenol oxidase-dependent oxidative polymerization that leads to the formation of theaflavins, thearubigins and other oligomers in a process known as fermentation. Theaflavins (about 1% - 2% of the total dry matter of black tea) including theaflavin, theaflavin-3-O-gallate, theaflavin-3′-O-gallate and theaflavin-3-3′-O-digallate, possess benzotropolone rings with dihydroxy or trihydroxy substitution systems which give the characteristic color and taste of black tea. About 10 - 20% of the dry weight of black tea is due to thearubigens, which are even more extensively oxidized and polymerized, have a wide range of molecular weights and are less well characterized.

Oolong tea, a partially fermented tea, contains monomeric catechins, theaflavins and thearubigins. Some characteristic components, such as epigallocatechin esters, theasinensins, dimeric catechins and dimeric proanthocyanidins are also found in oolong tea.

Commercial green tea is made by steaming or drying fresh tea leaves at elevated temperature. Its chemical composition is similar to that of fresh tea leaves. Green tea contains polyphenols that include flavanols, flavandiols, flavonoids and phenolic acids. These compounds can account for up to 30% of the dry weight. Most of the green tea polyphenols are flavonols commonly known as catechin. Some major green tea catechins are epigallocatechin-3-gallate (EGCG), (-) - epigallocatechin (EGC), epicatechin-3-gallate (ECG), - (-) -epicatechin (EC), (+) -gallocatechin and (+)-catechin (Figure 1). Caffeine, theobromine and theophylline the principal alkaloids account for about 4% of the dry weight.

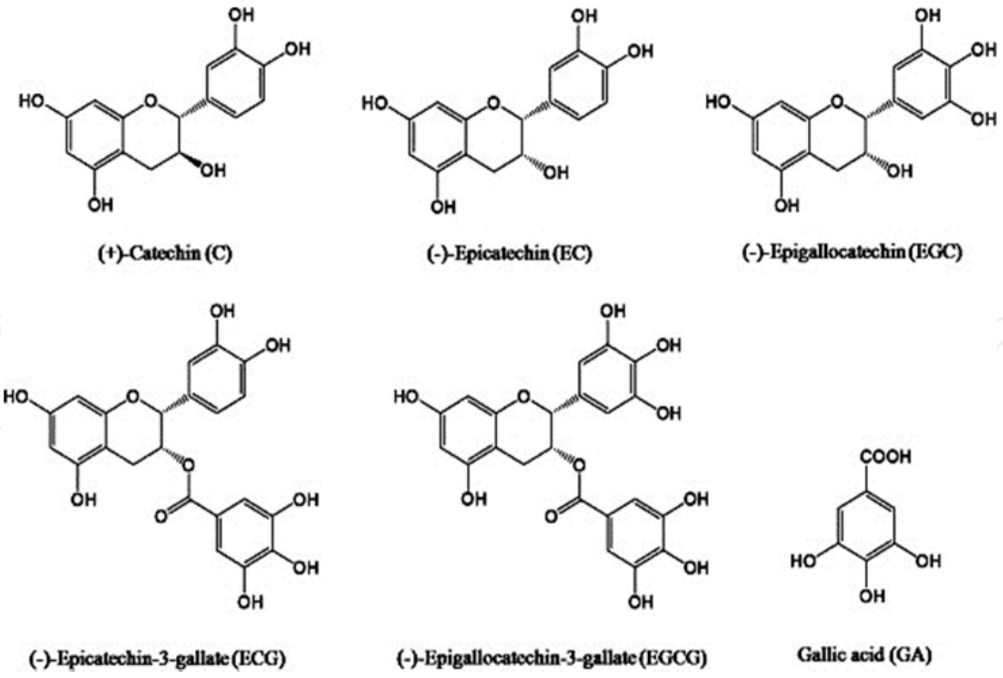

Figure 1. Components of green tea

It has been stated that a cup (200 ml) of green tea contains about 142 mg EGCG, 65 mg EGC, 17 mg EcC and 76 mg caffeine. The most important chemicals present in tea, which are of

considerable pharmacological significance, are the polyphenols and caffeine [28]. Polyphenols are present to the extent of 30-35% in the dry tea leaf and determine the quality of the beverage. The amount of polyphenols depends on the genetic make up of tea and environmental factors such as climate, light, rainfall, temperature, nutrient availability and leaf age [27].

Because the mechanisms of antimutagenesis and anticarcinogenesis by tea polyphenols vary for different cancers and for the same cancer in different population, tea consumption can affect carcinogenesis only in selected situations. Many laboratory studies have demonstrated inhibitory effects of tea preparation and tea polyphenols against tumor formation and growth. This inhibitory effect is believed to be mainly due to the antioxidative and possible antiproliferative effects of polyphenolic compounds in green and black tea. These polyphenolics can also inhibit carcinogenesis by blocking the endogenous formation of N-nitroso compounds, suppressing the activation of carcinogen and trapping of genotoxic agents. Yang and Wang [28] showed that tea polyphenols also have high complexation affinity to metals, alkaloids and biologic macromolecules such as lipids, carbohydrates, proteins and nucleic acids.

Work of Kuroda and Hara [27] illustrates that the polyphenols in tea have a strong radical scavenging and reducing activity. They capture and detoxify radicals of various promoters of carcinogenesis and radicals produced in the process of exposure to radiation and light. Since tea polyphenols inactivate enzyme and virus activity, they could be effective against carcinogenesis caused by some viruses. Tea polyphenols exert their inhibitory actions via various mechanisms at different stages of mutagenesis, carcinogenesis, invasion and metastasis of tumor cells; they act extracellularly as desmutagens and intracellularly as bio-antimutagens. Tea polyphenols modulate metabolism, block, suppress, or affect DNA replication and repair effects.

2.1.2. The health effects of green tea

Green tea has been extensively studied in people, animals, and laboratory experiments. Results from these studies suggest that green tea can be useful for the several health conditions.

It has been found that green tea consumption is significantly associated with a lower risk of mortality due to stroke [29] and pneumonia [30] and imparts a lower risk of cognitive impairment [31], depression [32], and psychological distress [33]. These results have been confirmed by other researchers [34–37]. In addition, other epidemiologic studies have indicated that green tea consumption is associated with a lower risk of osteoporosis [38, 39], and randomized placebo-controlled trials have indicated that green tea is effective in lowering cardiovascular risk factors [40, 41]. Because all of the above conditions are major causes of functional disability [42–44], it is expected that green tea consumption would contribute to disability prevention. Green tea consumption is associated with a lower risk of developing functional disability.

Atherosclerosis

Population-based clinical studies indicate that the antioxidant properties of green tea can help prevent atherosclerosis, particularly coronary artery disease. (Population-based studies mean studies that follow large groups of people over time or studies that are comparing groups of people living in different cultures or with different dietary habits.) Researchers are not sure why green tea reduces the risk of heart disease by lowering cholesterol and triglyceride levels. Studies show that black tea has similar beneficial effects. In fact, researchers estimate that the rate of heart attack decreases by 11% with consumption of 3 cups of tea per day [45].

High cholesterol and cardiovascular Disease

Research shows that green tea lowers total cholesterol and raises HDL ("good") cholesterol in both animals and people. One population-based clinical study found that men who drink green tea are more likely to have lower total cholesterol than those who do not drink green tea. Results from one animal study suggest that polyphenols in green tea can block the intestinal absorption of cholesterol and promote its excretion from the body. In another small study of male smokers, researchers found that green tea significantly reduced blood levels of harmful LDL cholesterol.

Substantial evidence from *in vitro* and animal studies indicates that green tea (GT) preparations inhibit cardiovascular disease (CVD) processes [46-49]. In a previous observational study, it has been shown that GT consumption was associated with a significantly lower risk of mortality due to CVD among middle-aged adults [50]. The study also indicated that GT consumption was associated with reduced mortality from cerebral infarction but not with mortality from cerebral hemorrhage. These associations were consistent with those reported in another observational study [51].

Obesity

Obesity and its related metabolic abnormalities, including insulin resistance, alterations in the insulin-like growth factor-1 (IGF-1)/IGF-1 receptor (IGF-1R) axis, and the state of chronic inflammation, increase the risk of colorectal cancer (CRC) and hepatocellular carcinoma (HCC). However, these findings also indicate that the metabolic disorders caused by obesity might be effective targets to prevent the development of CRC and HCC in obese individuals. Green tea catechins (GTCs) possess anticancer and chemopreventive properties against cancer in various organs, including the colorectal and liver. GTCs have also been known to exert anti-obesity, antidiabetic, and anti-inflammatory effects, indicating that GTCs might be useful for the prevention of obesity-associated colorectal and liver carcinogenesis. Further, branched-chain amino acids (BCAA), which improve protein malnutrition and prevent progressive hepatic failure in patients with chronic liver diseases, might be also effective for the suppression of obesity-related carcinogenesis because oral supplementation with BCAA reduces the risk of HCC in obese cirrhotic patients. BCAA shows these beneficial effects because they can improve insulin resistance. Here, we review the detailed relationship between metabolic abnormalities and the development of CRC and

HCC. We also review evidence, especially that based on our basic and clinical research using GTCs and BCAA, which indicates that targeting metabolic abnormalities by either pharmaceutical or nutritional intervention can be an effective strategy to prevent the development of CRC and HCC in obese individuals [52].

Diabetes

Several studies have reported a protective effect for tea consumption on incident diabetes, and the results of a recent meta-analysis indicated that drinking more than 3–4 cups of tea (black, green or oolong) per day decreases the risk of Diabetes Mellitus by 20% [53]. Despite very high intake of black tea, no significant association for black tea consumption was observed, but an inverse correlation was found between green tea drinking and diabetes prevalence. Several animal and human studies have shown an antidiabetic effect for green tea polyphenols, specifically epigallocatechin gallate (EGCG) [54-57]. EGCG induces its antidiabetic effects mostly through reduced hepatic glucose production and enhanced pancreatic function [56]. Green tea has been shown to improve glucose tolerance and has been suggested as a prophylactic agent against diabetes [55].

Weight loss

Clinical studies suggest that green tea extract can boost metabolism and help burn fat. One study confirmed that the combination of green tea and caffeine improved weight loss and maintenance in overweight and moderately obese individuals. Some researchers speculate that substances in green tea known as polyphenols, specifically the catechins, are responsible for the herb's fat-burning effect.

Cancer

Many studies suggest an inverse relationship between green tea intake and the risk of a variety of cancers, although other studies have found no association. Clinical trials have been small and heterogenous with contradictory results. Dietary, environmental, and population differences can account for these inconsistencies [58].

Several population-based clinical studies have shown that both green and black teas help protect against cancer. For example, cancer rates tend to be low in countries such as Japan where people regularly consume green tea. However, it is not possible to determine from these population-based studies whether green tea actually prevents cancer in people. Emerging clinical studies suggest that the polyphenols in tea, especially green tea, can play an important role in the prevention of cancer [59].

Bladder Cancer. Only a few clinical studies have examined the relationship between bladder cancer and tea consumption. In one study that compared people with and without bladder cancer, researchers found that women who drank black tea and powdered green tea were less likely to develop bladder cancer. A follow-up clinical study by the same group of researchers revealed that bladder cancer patients (particularly men) who drank green tea had a substantially better 5-year survival rate than those who did not. Other study has demonstrated the anti-oxidant properties of green tea extract (GTE) against human bladder

uroepithelial cells. The data demonstrate that under *in vitro* conditions, green tea extract can afford both normal and tumorigenic human bladder urothelial cells protection (i.e., prevent apoptosis) to various degrees after chemical insult with H_2O_2 [60].

Breast Cancer. Although tea has been extensively investigated in *in vitro* and *in vivo* studies, few epidemiologic studies have evaluated the relationship between green tea and breast cancer risk. The results from these studies are inconsistent [61-63]. In general, the cohort studies, all based in Japan, report no significant association [61] and the case-control studies [62, 63], based on Asian-American or Chinese populations, all report an inverse relationship between green tea and breast cancer risk [62]. Previous studies have not evaluated the relationship between green tea consumption and pre- and postmenopausal breast cancer.

The most recent meta-analysis included 7 (2 cohort, 1 nested case–control and 4 case–control) epidemiological studies of green tea and breast cancer that were published as of December 2008 [64]. An inverse association between green tea and breast cancer risk was reported from case–control data, while no association was observed from cohort data [64]. The nested case–control study reported no association [65], so even if it had been included as a cohort study in the pooled analyses, the overall finding would have remained the same.

In summary, green tea could exert beneficial effects on breast carcinogenesis through inhibition of estrogen's pro-carcinogenic activity either alone by itself or in combination with other estrogen-inhibiting factors. Black tea does not appear to have protective effects on breast cancer incidence, and can increase risk of hormone-dependent tumors. Future research is needed to elucidate the interactive role of tea catechins and other dietary cancer-inhibitory compounds in mammary carcinogenesis in humans.

Ovarian Cancer. In a clinical study conducted on ovarian cancer patients in China, researchers found that women who drank at least one cup of green tea per day survived longer with the disease than those who did not drink green tea. In fact, those who drank green tea lived the longest. Other studies found no beneficial effects [66, 67]. In view of the variations in rates of breast cancer and tea-drinking practices, one case–control study was conducted in Southeast China to evaluate the association between breast cancer and tea consumption measured by type, duration, frequency and quantity of tea and the interactions between tea consumption and other lifestyle factors.

Esophageal Cancer. In the Indian studies [68-70], some results indicated that tea (presumably black tea) consumption could be responsible for the development of esophageal cancer. The authors indicated that this result could be due to drinking hot tea, which was shown to occur a couple of decades before in a Chinese cohort. The other possibility could be that Indians drink their black tea with milk, which was shown before to counteract positive effects of tea.

The higher content of tea catechins present in green tea than in black tea can explain the more consistent inverse association between tea and esophageal cancer risk in studies conducted in China and Japan than in European and American countries. The putative protective effect of tea consumption, if any, on esophageal cancer development could be

confounded and/or overshadowed by the thermal effect of tea beverages, if consumed at high temperature, as well as cigarette smoking or alcohol intake. Future prospective cohort studies are required to collect detailed information on tea temperature and histories of tobacco and alcohol use that can then be adjusted for when evaluating the protective effect of tea on esophageal cancer.

Prostate Cancer. Among all cancers, prostate cancer is an ideal candidate disease for chemoprevention because it is typically diagnosed in men ages >50 years and has a high latency period [71, 72]. Therefore, even a slight delay in the progression of this disease by chemopreventive intervention could result in a substantial reduction in the incidence of the disease and, more importantly, improve the quality of life of the patients [71, 72]. Evidences collected from geographic, epidemiologic, and migration studies suggest that frequent consumption of green tea is associated with lower frequencies of prostate cancer in Asian populations in general compared with those in western societies [73-77]. Laboratory and preclinical animal studies also indicate a protective role of green tea against prostate cancer [78-82].

In summary, observational studies do not provide strong evidence for a protective effect of green tea or black tea intake against the development of prostate cancer. There is some suggestive evidence that green tea intake can reduce the risk of advanced prostate cancer. The phase II clinical trials have provided encouraging evidence in the development of green tea catechins as a chemopreventive agent against prostate carcinogenesis.

Skin Cancer. There has been considerable interest in the use of naturally occurring plant products, including polyphenols, for the prevention of UV-induced skin photodamage primarily including the risk of skin cancer. Polyphenols, specifically dietary, possessing anti-inflammatory, immunomodulatory and anti-oxidant properties are among the most promising group of compounds that can be exploited as ideal chemopreventive agents for a variety of skin disorders in general and skin cancer in particular. In this respect, chemoprevention offers a realistic strategy for controlling the risk of cancers. Furthermore, a chemopreventive approach appears to have practical implications in reducing skin cancer risk because, unlike the carcinogenic environmental factors that are difficult to control, individuals can modify their dietary habits and lifestyle in combination with a careful use of skin care products to prevent the photodamaging effects in the skin. Studies from our laboratory have shown the efficacy of naturally occurring polyphenols, such as green tea polyphenols (GTPs), silymarin from milk thistle and proanthocyanidins from grape seeds (GSPs), against UV radiation-induced inflammation, oxidative stress, DNA damage and suppression of immune responses [83].

Stomach cancer. Recently, Myung et al. conducted a meta-analysis investigating the quantitative association between the consumption of green tea and the risk of stomach cancer in humans [84]. The analysis included 13 (5 cohort and 8 case–control) studies, all conducted in Japanese or Chinese populations. An inverse association was seen in case–control studies only, but not in cohort studies. However, in a recent pooled analysis of 6 cohort studies that included more than 218,000 Japanese men and women aged 40 years or

older and more than 3500 incident stomach cancer cases found a statistically significant, inverse association between green tea consumption and stomach cancer risk in women, but not in men [85]. Compared with those drinking <1 cup/day, women with the consumption of ≥5 cups/day green tea had an approximately 20% decreased risk of stomach cancer. This protective effect was primarily seen among female nonsmokers [85].

In the study by Kinlen et al., the positive association between black tea consumption and stomach cancer death could be, at least partly, due to the effects of smoking and social class [86]. Whereas in the cohort analysis by Khan et al. that included approximately 3100 Japanese men and women, black tea consumption was associated with a statistically significantly increased risk of stomach cancer for women [87]. Given the small sample size and low intake of black tea in a population that usually consumed green tea, this positive association could be a chance finding.

Both case–control and cohort studies demonstrated an inverse association between green tea consumption and risk of stomach cancer. The protection can be stronger for women than men since the former are less likely to smoke cigarettes or drink alcoholic beverages. There is lack of evidence in support of a protective role of black tea consumption against the development of stomach cancer.

Cervical Cancer. Cancer of the cervix is the third most common malignancy worldwide in women, and the most common gynecologic cancer in the developing world. In developed countries, prevention of cervical cancer achieved by the widespread and systematic use of cervical cytologic screening, has contributed to the successful decrease in the incidence of invasive cervical carcinomas. In the developing world, cervical cancer remains a common malignancy impacting the lives of women during their period of highest productivity. Especially in low-resource settings, an inexpensive dietary chemo-preventive intervention would be an attractive adjunct to existing cervical cancer prevention programs It is well-known that the regular consumption of fruits and vegetables is highly associated with the reduced epidemiologic risk of different types of cancer [88-91] and green tea consumption is associated with lowering certain cancer incidences including cervical cancer [92].

Lung Cancer. Numerous epidemiological studies examined the association between green tea or black tea consumption and risk of lung cancer. A systematic review was conducted to evaluate the association between the consumption of green tea or black tea and lung cancer risk among 19 studies (13 case–control, 6 prospective cohort) that were published prior to September 2007 [93]. Among the 8 studies examining green tea and lung cancer risk, 3 reported a significantly lower risk while one reported a significantly increased risk of lung cancer with high green tea consumption. The remaining 4 studies reported no association [93]. More recently, Tang et al. conducted a similar meta-analysis for green tea or black tea consumption with lung cancer risk [94]. This analysis included 22 studies published from 1966 to November 2008 and 12 of them also were included in the analysis by Arts [93]. Twelve studies examined the association between green tea and lung cancer risk. A statistically significant 18% decreased risk of lung cancer was associated with every 2 cups/day of green tea consumption. This inverse green tea-lung cancer association was

slightly stronger for prospective cohort studies than retrospective case–control studies. The protective effect of green tea consumption on lung cancer risk was confined to nonsmokers [94].

In the same review by Arts [93], 11 of the 19 studies included examined the association between black tea consumption and lung cancer risk. Among them, two reported a statistically significantly reduced risk while one reported an increased risk for lung cancer associated with black tea intake. The remaining 8 studies reported a null association [93]. In a more recent meta-analysis by Tang et al., no statistically significant association was observed between black tea consumption and lung cancer risk based on 14 studies included [94]. Not included in the meta-analyses was a case–control study in Los Angeles, CA with 558 cases and 837 controls. The results showed that high consumption of dietary epicatechin, mainly from black tea, was associated with significantly reduced risk of lung cancer, especially among smokers [95].

One potential mechanism for the chemopreventive effect of tea on carcinogenesis is the strong antioxidant effect of tea polyphenols. Hakim et al. conducted a phase II randomized controlled tea intervention trial to evaluate the efficacy of regular green tea drinking in reducing DNA damage as measured by urinary 8-hydroxydeoxyguanosine among heavy smokers [96]. After consuming 4 cups/day of decaffeinated green tea for 4 months, smokers showed a statistically significant 31% decrease in urinary 8-hydroxydeoxyguanosine compared with the baseline value. In the same study, no change in urinary 8-hydroxydeoxyguanosine was seen among smokers assigned to the black tea group [96]. These findings support that tea catechins, with highest levels in green tea, exert their antioxidative role in reducing the formation of 8-hydroxydeoxyguanosine. However, a lack of inverse association between green tea consumption and lung cancer risk in smokers suggest that the antioxidation mechanism plays a limited role in reducing the risk of lung cancer development. Furthermore, the protective effect of tea consumption on lung cancer development for nonsmokers, especially among women, indicates an alternative cancer-preventive mechanism of tea that is not driven by antioxidation. Additional experimental studies that utilize animal models to elucidate the cancer-preventive mechanisms of tea catechins on lung carcinogenesis are needed.

Pancreatic Cancer. Similar to other gastrointestinal organs, epidemiological studies have provided mixed results on the association between tea consumption and risk of pancreatic cancer. There are a limited number of studies that examined the association between green tea consumption and pancreatic cancer. From an early hospital-based case–control study in Japan (124 cases and 124 matched controls), no association was observed for pancreatic cancer risk with green tea drinking [97]. In contrast, analyses from a population based case–control study conducted in Shanghai, China (451 cases and 1552 controls) demonstrated a statistically significant inverse association with increased green tea consumption and pancreatic cancer risk [98]. A prospective cohort study in Japan involved more than 100,000 Japanese adults with up to 11 years of follow-up and 233 incidents of pancreatic cancer cases did not find an association between green tea intake and pancreatic cancer risk [99]. In another prospective cohort study with up to 13 years of follow-up and 292 incident

pancreatic cancer cases in Japan, Lin et al. reported a higher percentage of dying from pancreatic cancer for subjects who consumed ≥7 cups/day of green tea compared with those <1 cup/day [100].

Available epidemiological data are insufficient to conclude that either green tea or black tea can protect against the development of pancreatic cancer. Given the short survival and rapid progression of pancreatic cancer, the low participation rates of pancreatic cancer patients in retrospective case–control studies or the use of proxy respondents in interview for collection of information on tea consumption and other risk factors could bias the results of case–control studies. Prospective cohort studies offer methodological advantages over case–control studies. Additional data from well-designed and well-executed prospective cohort studies are required before any conclusion on the protective effect of green tea and/or black tea against the development of pancreatic cancer can be reached.

Oral cavity and pharynx Although numerous epidemiological studies examined the association between dietary factors and risk of oral and pharyngeal cancers [101], there are limited data on the effect of tea consumption on these malignancies. Combining a series of case–control studies in Italy with a total of 119 patients with cancer of the oral cavity and 6147 hospital controls, La Vecchia et al. reported a reduced, but statistically non-significant, risk of oral cancer with black tea consumption [102]. Using a similar approach, Tavani et al. combined datasets of two hospital-based case–control studies conducted in Italy and Switzerland, respectively, and reported no association between black tea consumption and oral cancer risk [103]. Recently, Ren et al. examined the association between black tea consumption and the risk of developing oral and pharyngeal cancers in the National Institutes of Health (NIH)-American Association of Retired Persons (AARP) Diet and Health Study [104].

The NIH-AARP cohort study enrolled 481,563 AARP members aged 51–71 years who resided in eight states of the United States in 1995–1996. After up to 8 years of follow-up, 392 study participants developed oral cancer and 178 developed pharyngeal cancer. The study demonstrated a statistically significant positive relationship between consumption of hot tea and risk of pharyngeal cancer. There was a suggestive positive relationship between hot tea intake and risk of oral cancer [104]. Consumption of iced tea was not associated with risk of oral or pharyngeal cancer.

There was one prospective cohort study that examined the association between green tea consumption and risk of oral cancer in the Japan Collaborative Cohort Study. The cohort consisted of 50,221 Japanese men and women aged 40–79 years at baseline and identified 37 incident oral cancer cases after 10.3 years of follow-up. The inverse association was slightly stronger for women than for men [105]. The inverse relation did not reach statistical significance due to the relatively small number of cancer cases included in the analysis.

A randomized, placebo-controlled, phase II clinical trial was conducted to examine the effect of green tea extract on the oral mucosa leukoplakia, a well established precancerous lesion of oral cancer [106]. Fifty-nine patients were randomly assigned to either the treatment group, who were given 3 g/day of a mixed green tea product composed of dried water

extract, polyphenols and pigments, or the placebo group. After 6 months, 37.9% patients in the green tea treatment arm showed reduced size of oral lesions whereas 3.4% patients had increased lesion size. In contrast, 6.7% patients in the placebo group had decreased and 10% patients had increased size of oral mucosa leukoplakia. The differences in the changes of lesion sizes between the treatment and placebo arms are statistically significant [106]. Recently, Tsao et al. completed another randomized, placebo-controlled phase II trial to evaluate the oral cancer prevention potential of green tea extract [107]. Forty-two patients with one or more histologically confirmed, bidimentionally measurable oral premalignant lesions with high-risk features of malignant transformation that could be sampled by biopsy were randomly assigned to receive 500, 750, or 1000 mg/m2 of green tea extract per day or placebo orally. The efficacy was determined by the disappearance of all lesions (a complete response) or 50% or greater decrease in the sum of products of diameters of all measured lesions (a partial response). At 12 weeks after the initiation of the treatment, 39 patients who completed the trial were evaluated; 14 (50%) of the 28 patients in the three combined green tea extract groups had a favorable response whereas only 2 (18.2%) of the 11 patients in the placebo group showed the similar response. A dose-dependent effect was observed; the favorable response rates were 58% in patients given 750 or 1000 mg/m2 green tea extract and 36.4% in those given 500 mg/m2, but only 18.2% in those assigned to the placebo arm [107].

Although limited, data from the prospective cohort study suggest a moderate protective effect of green tea consumption against the development of oral cancer. Both phase II clinical trials further support a protective role of green tea extract against the progression of precancerous lesions in the oral cavity towards malignant transformation. Phase III clinical trials with large number of patients are required to confirm the efficacy of green tea extract against the formation of oral cancer in humans. Data on the effect of black tea consumption against the development of oral cancer are too limited to draw any conclusion. One prospective study showed a statistically significant inverse association between black tea consumption and risk of pharyngeal cancer, more epidemiological studies are warranted to evaluate the potential protective effect of either green tea or black tea on the development of pharyngeal cancer in humans.

Large bowel. Numerous epidemiological studies have examined the association between tea consumption and colorectal cancer. Sun et al. conducted a meta-analysis that included 25 epidemiological studies evaluating tea consumption and risk of colorectal cancer in 11 countries [108]. The inverse association between green tea intake and colon cancer risk was mainly observed in 4 case–control studies, but not in 4 cohort studies. There was no relationship between green tea intake and rectal cancer risk in 6 case–control or cohort studies.

Following the meta-analysis, several studies examined and published the results on the green tea consumption and colorectal cancer risk. After analyzing the database of the Singapore Chinese Health Study, a prospective cohort study of diet and cancer involved over 60,000 Chinese men and women aged 45–74 years, Sun et al. found that subjects who drank green tea daily had a statistically non-significant increased risk for colorectal cancer relative to nondrinkers of green tea. This association was confined to men and was stronger for colon cancer than rectal cancer, especially for the advanced stage of colon cancer [109].

These data suggest that substances in green tea can exert an adverse, late-stage effect on the development of colorectal cancer.

Yang et al. prospectively evaluated the association between green tea consumption and colorectal cancer risk in a cohort of 69,710 Chinese women aged 40–70 years, most of which were Lifelong nonsmokers (97.3%) or nondrinkers of alcoholic beverages (97.7%). Information on tea consumption was assessed through inperson interviews at baseline and reassessed 2–3 years later in a follow-up survey. During the first 6 years of follow-up, 256 incident cases of colorectal cancer were identified. Regular tea drinkers had significantly reduced risk of colorectal cancer compared with nondrinkers. The reduction in risk was most evident among those who consistently reported to drink tea regularly at both the baseline and follow-up surveys [110].

There were two recent prospective studies on green tea consumption and colorectal cancer incidence and mortality in Japan [111, 112]. The first consisted of 96,162 Japanese men and women, and 1163 incident cases of colorectal cancer [111]. There was no statistically significant association between green tea consumption and incidence of colon and rectal cancers combined or separately in either men or women or both. The second cohort consisted of 14,001 Japanese men and women. After up to 6 years of follow-up, 43 subjects died from colorectal cancer. Given the small number of cases, the results should be interpreted with caution. Using validated biomarkers of specific tea polyphenols, Yuan et al. prospectively examined the urinary levels of specific tea catechins and their metabolites and the risk of developing colorectal cancer in the Shanghai Cohort Study as described above [113]. EGC, 4_-O-methyl-epigallocatechin (4_-MeEGC) and EC, and their metabolites in baseline urine samples were measured in 162 incident colorectal cancer cases (83 colon and 79 rectal cancer cases) and 806 matched controls. Individuals with high prediagnostic urinary catechin levels had a lower risk of colon cancer. There was no association between urinary green tea catechins or their metabolites and risk of rectal cancer. This study provided a direct evidence for the chemopreventive effect of tea catechins against the development of colon cancer in humans [113].

In terms of black tea, the meta-analysis by Sun et al. [108] included 20 studies that examined black tea consumption and colorectal cancer risk and found no association. No association was found separately in case–control studies or prospective cohort studies. In our analysis of the Singapore Chinese Health Study, we did not find any association between black tea consumption and risk of colon cancer and rectal cancer combined or separately [109]. More recently, Zhang et al. conducted a pooled analysis for black tea intake and colon cancer risk on the combined dataset of 13 cohort studies conducted in North America or Western Europe. The analysis included 731,441 subjects and 5604 incident colon cancer cases [114]. Compared with nondrinkers, consumption of 900 g/day tea (approximately four 8-oz cups/day) was associated with a modest, but statistically significantly increased risk of colon cancer. This increased risk for colon cancer was only in women, but not in men.

Epidemiological studies provided suggestive evidence to support a protective role of green tea consumption, especially in high amount and long-term duration of consumption, in

reducing the risk of colon cancer. This effect of green tea on colon carcinogenesis can depend on the time of exposure, where late exposure can promote the growth of colon tumor cells. Current epidemiological data suggest that black tea consumption can increase, instead of decrease, the risk of colorectal cancer.

Kidney. Several epidemiological studies examined the relationship between tea consumption and kidney cancer risk. Mellemgaard et al. conducted a population-based case–control study that enrolled 368 renal cell cancer cases and 396 matched controls living in Denmark [115]. The study did not find an association between black tea consumption and renal cell cancer risk. Bianchi et al. conducted a population-based case–control study of renal cell cancer in Iowa (406 cases and 2434 controls), and found no association [116].

Similarly, a more recent case–control study of renal cell cancer in Italy including 767 cases and 1534 controls did not find any association between tea consumption and risk of renal cell cancer [117]. Lee et al. analyzed datasets of the Nurses' Health Study and the Health Professionals Follow-up Study and found that consumption of >1 cup/day tea was associated with statistically non-significantly reduced risk of renal cell cancer relative to <1 cup/month [118]. In a pooled analysis, Lee et al. combined data of 13 prospective cohorts including more than 774,000 men and women and 1478 incident renal cell cancer cases. Compared with nondrinkers, individuals who consumed ≥1 cups/day of tea had a statistically borderline significant 15% risk reduction in renal cell cancer after adjustment for body mass index, cigarette smoking, hypertension and other potential confounders [119]. All these studies were conducted in North America and West Europe and examined the effect of presumably black tea on renal cell cancer risk. These findings do not support a protective role of black tea on kidney cancer. Additional prospective epidemiological studies are warranted to examine the association between green tea consumption and kidney cancer risk.

Glioma. Regular intake of tea was not associated with risk of adult glioma in a case–control study [120]. Recently Holick et al. examined the association between coffee, black tea and caffeine intake and risk of adult glioma in three prospective cohort studies in the United States. The analysis included 335 incident glioma cases. Compared with nondrinkers, there was a statistically non-significant, approximately 30% decreased risk of glioma incidence for those consuming 4 cups/week of black tea [121]. More data are warranted to draw any conclusion on the association between tea consumption and adult glioma risk.

Lymphoma. Thompson et al. examined the association between black tea consumption and risk of non-Hodgkin's lymphoma in the Iowa Women's Health Study. The analysis included 415 incident lymphoma cases during the 20 years of follow-up following baseline interview. No association was found between black tea consumption and risk of non-Hodgkin's lymphoma [122].

Leukemia. A hospital-based case–control study involving 107 adults with leukemia and 110 orthopaedic controls in China found that green tea consumption was associated with a statistically significant 50% decreased risk of leukemia. The inverse association was dose dependent with number of cups of tea per day, number of years of tea consumption, and the

amount of dry tea leaves consumed [123]. A similar case–control study enrolled 252 leukemia patients aged 0–29 years and 637 sex- and age matched control subjects in Taiwan. Compared with nondrinkers, high intake of total tea catechins was associated with approximately 50% reduced risk. This inverse association was stronger in older (16–29 years) than in the younger (0–15 years) group [124]. Given the limitations of small study size and hospital-based study design, further studies are warranted to confirm these results.

2.1.3. Possible active tea components and their tissue levels

Plasma EGCG, EGC and EC exist in free and conjugated (glucuronide and sulfate) forms. The plasma tea polyphenol levels in rats and mice in some anticarcinogenesis experiments were comparable to the peak levels in humans after consuming two or three cups of tea [125]. In a preliminary experiment, after administration of regular green tea in drinking fluid to rats, the EGCG was detected in the esophagus (410 ng/g) but not in the lung, the EGCG, EGC and EC levels in the small intestine and intestinal contents were rather high (1.5 - 5.5 mg/g) due to the unabsorbed and biliary excreted glucuronides of polyphenols in the intestine. High EGC and EC levels were also observed in the colon tissues (1.8 and 0.3 mg/g respectively). Due to possible glucuronidase and esterase activities in the colon, most of the EGC and EC were found in the free form and EGCG was found at lower levels. EGCG has been usually considered the active anticarcinogenic components in tea because it is the most abundant polyphenol in tea.

Hackett *et al.,* [126] reported that three human volunteers were given 2 g of (+)- catechin and the metabolic changes in it were then examined by looking at their blood and urine. About 55% of the labeled catechin was excreted in urine within 2 h after its uptake. The metabolites in urine were (+) - catechin, and glucuronic and sulfate compounds of 3-O-methye- (+)-catechin. These metabolites were about ¾ of the catechin uptake.

Matsumoto *et al.,* [127] determined the amount of tea polyphenols in organs and tissues to examine the fate of catechin in the digestive canal, such as the stomach; small and large intestines of rats. EGCG given orally was transferred from the stomach to the small intestine within several hours and moved to the large intestine after 8 hours. Most of the amount of catechins taken in orally moved into the digestive tract and were excreted in the feces. Some part of the catechins was metabolized by intraintestinal bacteria and about 20% of the catechin can have been absorbed by the digestive organs.

Tea catechins and crude extracts, however, have some beneficial effects on human health, such as suppression of high blood pressure [128], reduction of blood glucose levels [129] suppression of cholesterol and prevention of fat increase [130]. Tea drinking can also induce higher levels of glutathione [131], so that detoxification of reactive forms of carcinogens can occur more efficiently, other biochemical mechanisms have been hypothesized for the anticancer properties of tea e.g. induction of DNA repair, binding with activated carcinogens. Moderate tea consumption (5 cups / day an extract of about 11 g of tea) can be readily curable in some types of human cancer [132]. In other studies on the inhibitory effects of tea catechins, black tea extract and oolong tea extract and EC, EGC, ECG, EGCG

and other tea extracts (0.05 or 0.1%) showed a significant decrease in the number and area of preneoplastic glutathione S-transferase placental form (GSTP)-positive foci in the liver of rats [133].

2.1.4. Antioxidative function of tea polyphenols

The most noteworthy properties of tea polyphenols and other flavonoids are their antioxidative activities. Reactive oxygen species may play important roles in carcinogenesis through damaging DNA, altering gene expression, or affecting cell growth and differentiation. The anticarcinogenic activities of tea polyphenols are believed to be closely related to their antioxidative properties. The findings that green tea preparations inhibited 12-0-tetradecanoylphorbol- 1 3-acetate-induced hydrogen peroxide formation in mouse epidermis and NNK-induced 8-hydroxydeoxyguanosine formation in mouse lung are consistent with this concept. Inhibition of tumor promotion-related enzymes such as ornithine decarboxylase, protein kinase C, lipoxygenase, and cyclooxygenase by tea preparations has also been reported. Although inhibition of carcinogen activation by tea or green tea polyphenol fractions could be demonstrated *in vitro* and, in certain cases, *in vivo* [134], this mechanism was not demonstrated for NNK bioactivation *in vivo*. Oral administration of tea preparations to animals has been reported to moderately enhance the activities of glutathione peroxidase, catalase, glutathione S-transferase, NADPH-quinone oxidoreductase, uridine diphosphate-glucuronosyltransferase, and methoxyresorufin O-dealkylase. The effects of a mild induction of these enzymes on carcinogenesis are not clear. Mechanisms relating to the quenching of activated carcinogens, antiviral activity, and enhancing immune functions have also been suggested, but their relevance to carcinogenesis remains to be determined. Inhibition of nitrosation by tea preparations has been demonstrated *in vitro* and in humans [135]; this may be an important factor in preventing certain cancers, e.g., gastric cancer, if the endogenously formed N-nitroso compounds are causative factors. Other results suggest that the antiproliferative effect of tea is important for the anticarcinogenic activity. One may speculate that tea polyphenols inhibit growth-related signal transduction pathways [136].

2.1.5. Effects of tea on mutation and genotoxicty

As to the genotoxic profile of tea catechins when tested alone, Chang *et al*. [137] have shown that there is minimal genotoxic concern with a decaffeinated green tea catechin mixture (Polyphenon E) that contains about 50% epigallocatechin gallate and 30% other catechins. Isbrucker *et al.* [138] have also found no genotoxic concern with a epigallocatechin gallate (GTE) preparation, Teavigo. On the other hand, many studies have demonstrated that tea catechins could suppress the genotoxic activity of various carcinogens with both *in vitro* and *in vivo* systems.

a. *In vivo* studies

Imanishi *et al.*, [139] reported that when green tea or black tea polyphenols was administered orally 6, 12 or 18 hours before an intraperitoneal injection of mitomycin C

resulted in a statistically significant decrease of micronucleus formation in mouse bone marrow, although, post-treatment administration had no effect.

Hot water extracts of green tea effectively suppressed AFB1 (aflatoxin B1) induced chromosome aberrations in bone marrow cells in rats when given green tea extract 24 h before injection with AFB1 [140]. Rats administered green tea extract 2 h before or after the AFB1 injection showed no suppressive effect. The suppressive effect of green tea extracts on AFB1 induced chromosome aberration was directly related to the dose of green tea extract (in the range of 0.1 to 2 g/kg). Black tea or coffee given 24 or 2 h before the AFB1 injection produced no suppressive effect.

De boer, [141] showed that the mutagenic potency of several chemicals including the dietary heterocyclic amine 2-amino-1-methyl-6-phenyl-imidazo(4,5-b) pyridine (PhIP)(the environmentally important aromatic hydrocarbon benzo(a)pyrene) and the food contaminant aflatoxin B1 can be modulated by dietary compounds including green tea in lacI transgenic rodent.

Green tea effectively inhibited oxidative DNA damage and cell proliferation in liver of 2-nitropropane (2NP) treated rats [142]. It was suggested that pyrogallol-related compounds of green tea such as EGCG, ECG and EGC are antimutagenic factors in the *Escherichia coli* B/R Wp2 assay system [143-146].

Significant inhibition activity of the tea catechins ECG and EGCG, against the mutagenicity of Trp-P-2 and N-OH-Trp-P-2 has been found by [143] using *Salmonella typhimurium*, TA98 and TA100 with and without rat liver S9 mix. EGCG has also an inhibitory effect against the mutagenicity of benzo[a]pyrene (B[a]P) diol epoxide in TA100 strain without S9 mix. Green tea has potent suppressive effects against gene expression of the SOS response in *salmonella typhimurium* TA1535/psk 1002 induced by four nitroarenes [147].

A study performed by [148] reported that EGCG suppressed the direct-acting mutagenicity of 3-hydroxyamino-1-methyl-5H-pyrido-(4,3-b) indole (Trp-p-2(NHOH)) and 2-hydroxyamino-6-methyldipyrido(1,2-a:3,2-d) imidazole (Glu-p-1(NHOH)) in the Ames *salmonella* test. furthermore, they added that EGCE has also a suppressive effect in the *in vivo* Drosophila mutation assays, i.e., the wing spot test, and the DNA repair test, on several carcinogens.

Kada *et al.*, [144] showed that a homogenate of Japanese green tea gave high bioantimutagenic activity against spontaneous mutations resulting from altered DNA-polymerase III in strain NIG 1125 of *Bacillus subtilis*. They identified chemically the active principles and they obtained 0.85 g EC, 1.44 g EGC, 1.24 g ECG and 4.87 g EGCG from 12 g of a crude extract of green tea powder.

Green tea extract reduced the levels of ischemia/reperfusion induced hydrogen peroxide, lipid peroxidation and oxidative DNA damage (formation of 8-hydroxydeoxyguanosine) by pretreatment of 0.5 or 2% green tea water extract for 3 weeks, respectively in Mongolian gerbils. Moreover, green tea also reduced the number of ischemia/reperfusion- induced apoptotic cells and locomotors activity [149].

Li *et al*., [150] indicated that green tea, tea pigments, and mixed tea could effectively inhibit DMBA (7,12-dimethyl-benz(a)anthracene) induced oral carcinogenesis in hamster. Protection from DNA damage and suppression of cell proliferation could be important mechanisms of anticarcinogenic effects of the tea preparations. Another study reported that green tea consumption inhibited the formation of micronuclei in peripheral blood lymphocytes in smokers [151].

Katiyar *et al*., [152] demonstrated that green tea polyphenols (GTP) prevent ultraviolet (UV)-B-induced cyclobutane pyrimidine dimers (CPD), which are considered to be mediators of UVB induced immune suppression and DNA damage on human skin. It has been also demonstrated that standardized green tea extract protects against psoralen plus ultraviolet A-induced phototoxicity to human skin by inhibiting DNA damage and diminishing the inflammatory effects of this modality.

Binding of AFB1 to hepatic nuclear DNA was inhibited in rats given 0.5% instant green tea for 2 or 4 weeks before a single injection of AFB1 [153].

The oral administration of 0.2% green tea or 0.1% black tea for 28 days decreased the extent of chromosome damages (micronuclei) in the peripheral blood of mice subsequently treated with B[a]P [154].

The level of one of the two lung DNA adducts produced by the lung carcinogen NNK (4(methylnitrosamino)-1-(3-pyridyl)-1-butanone) during and after carcinogen treatment was reduced in mice given 2% green tea as their sole source of drinking water [155]. Green tea suppressed 8-OH-2'deoxyguanosine or 8-OH-guanosine, but not ^{6}O-methylguanine levels, in lung DNA.

Recently, it has been demonstrated that the administration of green tea extract 24 hr before the dimethylnitrosoamine (DMN) injection significantly suppressed DMN-induced chromosomal aberrations and sister chromatid exchanges. The suppression was observed 18 hr, 24 hr and 48 hr after the DMN treatment but no suppressive effect was observed at the early period (6 hr and 12 hr) after the DMN treatment. Furthermore, the suppression was observed for all doses of DMN investigated. Mice given green tea 2 hr before the DMN injection displayed no suppressive effect. Mice that were given 2% green tea extract as the sole source of drinking water for four days before sacrifice displayed significantly suppressed DMN-induced chromosomal aberrations and sister chromatid exchanges [156]. They conclude that the suppression of DMN-induced chromosomal aberrations and sister chromatid exchanges should be considered as a green tea exerting a preventive action.

b. *In vitro* studies

Studies with cell lines had demonstrated that tea polyphenols affect signal transduction pathways, inhibit cell proliferation and induce apoptosis, but the effective concentrations are usually much higher than those observed in blood and tissue [157].

Islami *et al.,* [158] described a novel observation that EGCG displayed strong inhibitory effects on the proliferation and viability of HTB-94 human chondrosarcoma cells in a dose-

dependent manner and induced apoptosis. The induction of apoptosis by EGCG via activation of caspase-3/cpp32 - like proteases can provide a mechanistic explanation for its antitumor effects.

Supplementation with green tea extract significantly decreased malondialdehyde production and DNA damage after Fe(+2) oxidative treatment in jurkat T-cell line [159]. EGCE was effective in reducing the mutagenecity of Trp-p-2(NHOH) in mouse FM3A cells in culture. EGCE was also effective in inhibiting DNA single strand breaks *in vitro* caused by Glu-p-1(NHOH) [160].

Jain *et al.,* [161] found that the extract of green tea leaves decreased the mutagenic activity of N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) to E.coli Wp2 *in vitro* in a desmutagenic manner.

In cultured mammalian cells, the frequencies of mitomycin C or ultraviolet light-induced sister-chromatid exchanges and chromosomal aberrations were suppressed by subsequent treatment with tea polyphenols in the presence of liver-metabolizing enzymes (S9 fraction). In the absence of such enzymes, however, the tea extracts suppressed sister chromatid exchanges and chromosomal aberrations at low concentrations but enhanced them at high concentration [162].

It was shown that EGCG and EGC rather than ECG and EC were found to induce apoptosis in lovo cells. Moreover, EGCG, EGC and ECG caused the arrest at the G1-phase of the cell cycle, whereas EC induced the S-phase arrest [163].

Zhao *et al.,* [164] illustrated that after HL-60 cells were treated by tea polyphenols (250 micro g/ml) for 5h, DNA extracted from HL-60 cells showed a typical internucleosomal DNA degradation i.e. DNA ladder and apoptotic vehicles were observed.

Ahmed *et al*., [165] studied the effect of green tea polyphenols and the major constituent epigallocatechin-3-gallate on the induction of apoptosis and regulation of cell cycle in human and mouse carcinoma cells and found that treatment of A431 cells with green tea polyphenols and its components epigallocatechin-3-gallate, epigallocatechin and epicatechin-3-gallate resulted in the formation of internucleosomal DNA fragments, a characteristic of apoptosis. Treatment with epigallocatechin-3-gallate also resulted in apoptosis in HaCaT, L5178Y, and Du145 cells. The DNA cell cycle analysis showed that in A431 cells, epigallocatechin-3-gallate treatment resulted in arrest in the G0/G1 phase of cell cycle and a dose-dependent apoptosis. The G0/G1 arrest shown by epigallocatechin-3-gallate, therefore suggested that this agent might slow down the growth of cancer cells by artificially imposing the cell cycle checkpoint. The loss of cell cycle checkpoint results in the selection of cells that have a growth advantage and a predisposition for acquiring more chromosomal aberrations.

2.2. Coffee polyphenols

Caffeic acid and chlorogenic acid are catechol-containing coffee polyphenols that, in a similar way to the tea polyphenols, have shown to be demethylating agents. Lee et al.,

studied the modulating effects of these two compounds on the *in vitro* methylation of synthetic DNA substrates and also on the methylation status of the promoter region of *RARβ* in two human breast cancer cells lines [166]. The presence of caffeic acid or chlorogenic acid inhibited in a concentration-dependent manner the DNA methylation catalyzed by DNMT1, predominantly through a non-competitive mechanism. This inhibition, similar to other dietary polyphenols, was largely due to the increased formation of SAH. Treatment of MCF-7 and MAD-MB-231 human breast cancer cells with these two compounds partially inhibited the methylation of the promoter region of *RARβ*.

Caffeic acid phenethyl ester (CAPE), which also is a chatechol, kills various types of cancer cells but is innocuous to normal cells. There are several studies reporting the *in vitro* and *in vivo* inhibitory ef1fects of CAPE in multiple cancer models, such as colon cancer [167], lung cancer [168], melanoma [169], glioma [170], pancreatic cancer [171], gastric cancer [172], cholangiocarcinoma [173], hepatocellular carcinoma [174], and breast cancer [175, 176].

2.3. Sulforaphane

Sulforaphane, a dietary phytochemical obtained from broccoli, has been implicated in several physiological processes consistent with anticarcinogenic activity, including enhanced xenobiotic metabolism, cell cycle arrest, and apoptosis. Although the effect of sulforaphane as a demethylating agent has not been specifically studied, this compound was found to down regulate DNMT1 in CaCo-2 colon cancer cells [177].

2.4. Isothiocyanates

Isothiocyanates comprise another class of dietary compounds known to affect the epigenome. Isothiocyanates are metabolites of glucosinolates present in a wide variety of cruciferous vegetables and demonstrated to have anticancer properties. Treatment of prostate cancer cells with phenethyl isothiocyanate, a metabolite of gluconasturtin from watercress, was shown to lead to demethylation and re-expression of *GSTP1* [178]. On the other hand, treatment with different isothiocyanates prevented the esophageous tumorigenesis induced by the methylating agent *N*-nitrosomethylbenzylamine (NMBA) in male rats [179].

2.5. Curcumin

Curcumin is a polyphenolic compound derived from the dietary spice turmeric and possesses diverse pharmacological effects including antioxidant, anti-inflammatory, anti-proliferative, and anti-angiogenic activities. Curcumin has been used for centuries in Asia, both in traditional medicine and in cooking where curcumin gives natural yellow color to the food. It has been well known that curcumin possesses potent antiinflammatory activity because of its inhibitory effects on cyclooxygenases 1, 2 (COX-1, COX-2), lipoxygenase (LOX), TNF-α, interferon γ (IFN-γ), inducible nitric oxide synthase (iNOS), and NF-κB [180, 181]. Importantly, experimental evidences suggest that curcumin could exert its inhibitory

effects on cancer development and progression. The mechanisms implicated in the inhibition of tumorigenesis by curcumin are unclear but could involve a combination of anti-oxidant, anti-proliferation, pro-apoptotic, and anti-angiogenic properties through the regulation of genes and molecules that are involved in multiple signaling pathways. Moreover, preclinical animal experiments and phase I clinical trials have demonstrated minimal toxicity of curcumin even at relatively high doses (12 g/day) [182]. However, curcumin exhibits poor bioavailability because of poor absorption and rapid metabolism [182]. To improve the bioavailability of curcumin, liposomal curcumin, nanoparticle curcumin, and structural analogs of curcumin have been synthesized and investigated to determine the absorption and anti-cancer activity [183, 184]. The results are promising, which further suggest that curcumin or its novel structural analogs could serve as potent agents for the prevention and/or treatment of human malignancies, and thus requires more phase II and III clinical trials.

2.6. Rosmarinic acid

Rosmarinic acid is a natural polyphenol antioxidant carboxylic acid found in many *Lamiaceae* herbs used commonly as culinary herbs such as lemon balm, rosemary, oregano, sage, thyme and peppermint. Rosmarinic acid has been recently shown to be a potent inhibitor of DNMT1 activity in nuclear extracts from MCF7 breast cancer cells and decrease the protein levels of DNMT1. However, this compound was unable to demethylate and reactivate known hypermethylated genes such as *RASSF1A, GSTP1* and *HIN-1* in this cell line (185).

2.7. Resveratrol

Resveratrol, a phytoalexin made naturally by several plants, has been produced by chemical synthesis because of its potential anti-cancer, anti-inflammatory, blood-sugar-lowering and other beneficial cardiovascular effects. There is limited evidence about the potential demethylating activity of this compound. Resveratrol has shown to be a weak DNMT activity inhibitor in nuclear extracts from MCF7 cells, and as rosmarinic acid, was unable to reverse the methylation of several tumor suppressor genes [185]. In MCF-7 cells, resveratrol improved the action of adenosine analogues to inhibit methylation and to increase expression of RARβ2, although without significant effect on its own [186].

3. Summary and conclusions

There is traditional and widespread use of dietary polyphenols all around the world. While the anecdotal epidemiological evidence has historically supported the idea of different diet and good health, experimental evidence accumulated in the recent years from various preclinical and clinical studies clearly support the idea that dietary polyphenols have potentially beneficial effects on multitude of health conditions, including cancer. Although the health effects of dietary polyphenols in humans are generally considered promising, there are definite challenges and limitations of the current data in better understanding the

molecular mechanisms responsible for this effect, together with the possible interactions between different polyphenols and other dietary constituents. While *in vitro* models have enormously contributed to the understanding of polyphenols mediated regulation of the epigenetic network, there is still a paucity of *in vivo* data for the majority of these dietary compounds. Therefore, until sufficient preclinical and clinical data has been gathered on the epigenetic changes induced by some of the dietary polyphenols, one should be cautious while interpreting and extrapolating the significance of current *in vitro* evidence. Once such evidence is established, the next and more important step would be to determine the most effective doses of these 'dietary nutraceuticals' in order to obtain various beneficial effects in human subjects.

Additional clinical work is required to examine the safety profile of various doses of dietary polyphenols, and more basic science studies are needed to improve our understanding of the molecular mechanisms underlying the chemopreventive effect of various dietary polyphenols. It is really exciting to witness that we have at least begun to explore the molecular mechanistic underpinnings of the "goodness" of certain diets and diet-related factors, which have been in existence for centuries.

The mere fact that currently hundreds of dietary polyphenols are being characterized from an "epigenomic" perspective clearly reflects our enthusiasm and trust we pose in the concept of safe and natural agents for cancer chemoprevention. Of course, the current evidence is thin and it is a long and treacherous road ahead of us; nonetheless, given the promise and potential of these polyphenols it is realistic to fathom that some of these compounds can become integral for the cancer chemoprevention in future.

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