Nutrition, Immunity, and Cancer

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Key Points

- Under special circumstances and defects in resolution process or if its underlying factors continue, then inflammation will turn into chronic inflammation.
- Chronic inflammation can increase the risk of cancer through promoting tumor initiation, the rate, and extent of cell division, neovascularization, and angiogenesis.
- Chronic inflammation results in an overload of reactive oxygen species (ROS), which, in turn, may lead to the development and progression of cancer.
- Immune escape mechanisms are a hallmark of tumor progression.
- Bioactive dietary components that antagonize immune escape mechanisms would have potential to prevent tumor development or enhance tumor regression.

Dietary Components, Immunity, and Cancer

Acetylsalicylic acid is a nonsteroidal anti-inflammatory drug (NSAID) that has shown chemopreventive effects in animal models and to

reduce both inflammation and cancer risk in humans [1]. Salicylic acids exist in a wide range of fruits, vegetables, herbs, and spices. It has been shown that regular intake of salicylates may be causally associated with reduced incidence of certain cancers, especially colon cancer [2].

Macronutrients and Immune System Modulation

Amino Acids

Arginine and glutamine are depleted during the immune response. Arginine is a precursor of polyamine, which is necessary for fidelity of DNA transcription. In addition, arginine is the only substrate for iNOS. Because of reduced arginine concentrations in plasma, T-cells are downregulated by the accumulation of myeloid-derived suppressor cells (MDSCs) and arginase-1 secretion. Glutamine plays a role to sustain lymphocyte proliferation, increase phagocytosis by onocytes/macrophages, and enhance neutrophil cytotoxicity [3]. On the other hand, sulfur amino acids are essential for the generation of glutathione, acting against prooxidant effects of inflammation and aiding cytotoxic T (T_C)-cell activation [4].Tryptophan is another important anti-inflammatory molecule, which is found in various types of vegetables and fish. Tryptophan is converted into indole-3-aldehyde, the ligand of aryl hydrocarbon receptor (AhR), by bacterial enzymes (e.g., lactobacilli). AhR functions as a receptor for dietary components and as a transcription factor expressed in epithelial and immune cells and some tumor cells. Several phytochemicals and plants from the Brassicaceae family have been shown to influence AhR ligands. Anti-inflammatory effects of tryptophan can occur through conversion of indoleamine-2,3-dioxygenase to kynurenine. Both indoleamine-2,3-dioxygenase (IDO) and kynurenine modulate T-cell function. Moreover, kynurenine which is produced by cancer cells can suppress antitumor immune responses [5, 6]. AhR can mediate the effects of diet to produce anti-inflammatory effects by affecting microbiota and gut immunity.

Lipids

Increasing the ratio of n-3 to n-6 polyunsaturated fatty acids (PUFA) (n-3/n-6) is generally in favor of human health. High n-3/n-6 ratio has been associated with increased anti-inflammatory responses and decreased risk of cancer. Inflammatory cells display high proportions of n-6 PUFA and low proportions of n-3 PUFA; thus, enhancing the dietary intake of n-3 PUFA could affect the amount and type of endogenously produced eicosanoids [7]. High intake of n-3 PUFA causes replacement of arachidonic acid (AA) in inflammatory cell membranes by eicosapentaenoic acid (EPA) and decreased generation of AA-derived mediators that regulate the secretion of cytokines. Other possible effects may occur through modification of membrane fluidity and lipid rafts and also changes in the gene expression and antigen production associated with signal transduction [8]. For instance, a highly purified form of n-3 PUFA, docosahexaenoic acid (DHA), not only altered the composition of T-cell membrane but also downregulated signaling pathways of activator protein-1 (AP-1), NF-κB, and IL-2 and lymphoproliferation. Also, it has been reported that omega-3 can decrease the expression of pro-inflammatory adhesion molecules, including vascular cell adhesion molecule (VCAM)-1, intracellular adhesion molecule (ICAM)-1, and E-selectin [9]. Short-chain fatty acids (SCFAs), e.g., acetate, butyrate, and propionate, which are produced by colonic bacteria appear beneficial for regulatory T (T_{reg})-cell proliferation [10, 11]. Phase III clinical trials have been published confirming the efficacy of omega-3 supplementation in some types of cancer.

Minerals

Trace elements, in particular, zinc, iron, and selenium, play a key role in the regulation of immune responses [12]. Zinc deficiency can cause a shift from T_H1 to T_H2 immune responses, result in the activation of macrophages and monocytes, and increase the production of pro-inflammatory cytokines (tumor necrosis factor-alpha (TNF-α), IL-1β, IL-6, and IL-8) [13, 14]. Selenium has been most strongly associated with cancer risk [15]. Selenium not only does act as an antioxidant by participating in the structure of

glutathione peroxidase but also can decrease the sensitivity of lymphocytes to oxidative stress (OS). Its deficiency decreases neutrophil chemotactic activity and antibody generation by B-cells. By contrast, supplementation with selenium would increase phagocytosis, NK cell activity, and T-cell responses [16].

Vitamins

Retinoic acid, the active metabolite of vitamin A, contributes to the activation of nuclear factor receptors-α (RARα), RARβ, and RARγ, which are essential for the stability of T_H1 cells and for controlling conversion from T_H1 cells to T_H17 cells. Antioxidant vitamins like vitamins C and E are able to scavenge free radicals [17]. Vitamin B6 significantly affects the expression of iNOS and COX-2 induced by lipopolysaccharide (LPS). This vitamin inhibits the induction of NF-κB by LPS and leads to a reduction of LPS-induced I-B degradation in RAW cells. Vitamin D and calcium deficiencies interfere with cellular functions in multiple tissues and organs, including the immune system [18]. Betaine (trimethylglycine) is a vitamin-like substance that acts as a methyl donor. Study of aged Sprague Dawley (SD) rats showed that this nutrient has the ability to reduce renal expression of genes encoding inflammatory mediators such as NF-κB, COX-2, iNOS, VCAM-1, and ICAM-1 [19].

The relation of vitamin D3 to immune function and cancer has been the subject of numerous studies. Besides immune cells (macrophages, monocytes, dendritic cells (DCs), and dermal cells), the 25-hydroxyvitamin D3 is metabolized to 1,25-dihydroxyvitamin D3 in the kidneys. Genes that show differential expression in response to vitamin D include nuclear factor of activated T-cells (NFAT), nuclear factor of activated B-cells (NFAB), epidermal growth factor receptor (EGFR), c-myc, and keratin (K16). Vitamin D as an alternative to classical immunosuppressive agents is used in secondary malignancies. Vitamin D supplement has been beneficial for patients with prostate, breast, and colorectal cancer (CRC) and melanoma. Studies support its potential as an adjuvant for cancer [20, 21]. Vitamin D supplement improved disease-free survival in patients with early-diagnosed breast cancer and metastatic CRC. There was a positive association between disease-free survival and plasma 25-(OH) D3 levels [22].

Vitamin E improves immune function through its antioxidant property. Antioxidant parameters including superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) enzyme family, and vitamins C and E have the potential to serve as biomarkers of prostate cancer [23]. Daily intake of greater than 100 IU vitamin E has been demonstrated to reverse T-cell function impaired by senescence [24]. Additionally, a Bayesian meta-analysis has clearly proved the safety of vitamin E [25]. In vitamin C deficiency, phagocytic activity is impaired because of low neutrophil numbers and reduced NK cell functions [26]. Results from a meta-analysis point to the benefit of decreased mortality that patients diagnosed with breast cancer obtain from vitamin C supplement.

Dietary Bioactive Compounds and Cancer Prevention Through γδ-T-Cells

About 30% of all malignancies in the Western world are estimated to be diet related, where overconsumption of definite food items or not enough of others in whole diet may contribute to cancer incidence [27]. Thus, cancer appears to be potentially preventable or modifiable by suitable dietary interventions. For example, fruit and vegetable consumption reduces the risk of bladder [28, 29] and gastric cancer [30, 31]. Also, reduced risk of prostate cancer has been reported to be in association with cruciferous vegetable consumption and high vitamin C intake [32, 33]. Dietary components can modify the risk of cancer by affecting various processes, including DNA repair, differentiation, apoptosis, angiogenesis, and modification of immune responses. As suppression of immunity is associated with increased risk of cancer, maintenance of immune homeostasis may have the potential to decrease cancer risk [34]. This part will address **γδ**-T-cells, their ability against malignant cells, and diet-mediated changes in **γδ**-T-cell function. Several in vivo and in vitro studies reported that certain food

components might modify **γδ**-T-cell differentiation and function. We will discuss the possible effect of dietary bioactive compounds in preventing cancer through **γδ**-T-cell-based mechanisms.

Based on the T-cell receptor (TCR) on their surface, there are two main subgroups of T-cells: αβ-T-cells that account for about 95% of T-cells in peripheral blood and γδ-T-cells that account for 0.5–5% of all T-lymphocytes [35, 36]. αβ-T-cells commonly express CD4 or CD8 lineage markers [35]. **αβ**-T-lymphocytes mostly belong to helper or cytotoxic/effector subsets [37, 38]. On the contrary, γδ-T-cells do not generally express CD4 or CD8 lineage markers. T-lymphocytes usually recognize antigenic peptides by major histocompatibility complex (MHC). However, γδ-T-cells do neither require conventional MHC antigen presentation [35] nor recognize peptide antigens on antigen-presenting cell (APC) surfaces. In fact, these cells are activated in the way similar to that of the innate immune cells, meaning through recognition of pathogen-associated molecular patterns (PAMPs) [39, 40], damaged tissue [41, 42], and targets of NK-associated receptors [43, 44]. Phosphorylated uridine and thymidine compounds [45], non-protein prenyl pyrophosphates [46, 47], bisphosphonates [47, 48], and alkylamines [49, 50] have all been reported to activate or prime γδ-T-lymphocytes. Alkylamines can be obtained from the diet and include compounds such as ethylamine, butylamine, and propylamine. Other PAMPs include heat shock proteins [51] and intermediates from the mevalonate pathway which is induced in response to self's distress signals [52]. The mevalonate pathway is common to all cells, particularly malignant cells, which can be influenced by several dietary factors such as cholesterol, isoprenoids, and genistein [53].

There are two main subsets of γδ-T-cells in mammalian species: Vδ2-T-cells which are mainly found in circulation and Vδ1-T-cells which are specific to mucosal surfaces lining the respiratory, gastrointestinal, urinary, and reproductive tracts [54]. Circulating γδ-T-cells produce effector functions against invading pathogens and malignant cells and could migrate to sites of infection [55]. The mucosal population assists in the maintenance of epithelial barrier integrity through diminishing inflammatory responses and healing of the damaged tissue [56–58]. γδ-T-cells are on the frontline to respond to invading pathogens and pave the way for the rest of the immune cells to participate in the elimination of invading pathogens.

γδ-T-cells share features of both innate and adaptive immune cells [59]. These cells produce high amounts of cytokines, chemokines, and growth factors. In this respect, the most important cytokine is interferon (IFN)-γ which is involved in antitumor immune responses [60]. In addition, γδ-T-cells support humoral immunity by the production of IgA, IgM, and IgG antibodies [61]. Other important roles include recruiting macrophages and inducing cytotoxicity in malignancies by producing a variety of chemokines like perforin-granzyme and TNF-related apoptosis-inducing ligand (TRAIL)/TRAIL receptor (TRAILR) system [62].

γδ-T-Cells in Cancer

γδ-T-cells can directly reject tumor cells through different ways. They have the ability to secrete cytokines such as IL-4, IL-10, TNF-α, and IFN-γ [61, 63, 64] which promote antitumor immunity. By increasing the expansion of $CD8^+$ T-cell, monocytes, and neutrophils and upregulating the expression of Fas ligand (FasL) and TRAIL, γδ-T-cells enhance tumor killing activity in the Fas- or TRAIL receptor-sensitive tumors [65, 66]. CD16 is a receptor for the Fc portion of immunoglobulin G (Fcγ receptors). γδ-T-cells by expression of CD16 can increase antibody-dependent cellular cytotoxicity (ADCC) [67]. In addition, γδ-T-cells elicit the release of granzymes and perforin that mediate cellular apoptosis [68] and interact with professional APCs that process antigens important for the killing of target cells [69]. Another function of the γδ-T-cells is the ability to moderate or end inflammation by inhibition of macrophage activation [70, 71]. Interestingly, antigens in bioactive dietary compounds that resemble PAMPs can prime γδ-T-cells, thereby attenuating inflammation and cell damage, which have been implicated in cancer.

Bioactive Dietary Compounds and Possible γδ-T-Cell Activity Against Cancer

The modified function of γδ-T-cells by dietary bioactive compounds may cause favorable immunological response. Information regarding the effect of dietary compounds on differentiation of γδ-T-cells is limited. Vitamins A and D have been reported to play a role in γδ-T-cell differentiation [72]. Vitamin D receptor on the surface of γδ-T-cells is upregulated via a protein kinase C (PKC)-related mechanism [73]. The relationship between diet and γδ-T-cells was first drawn in 1999 [74], when drinking tea increased γδ-T-cell proliferation and IFN-γ secretion compared with coffee. L-Theanine is a bioactive compound available in tea. L-Theanine is hydrolyzed to glutamic acid and ethylamine, a nonmicrobial antigen that interacts with γδ-T-cells [75, 76]. Two classes of plant metabolites have been characterized with defined effects on γδ-T-cells, including non-protein prenyl pyrophosphates [77] and procyanidins [78] that induce Vδ2-T- and Vδ1-T-cells, respectively. Many other bioactive compounds are being investigated.

The hypothesis of nonmicrobial priming implies that though food phytochemicals cannot activate cells, they can prime the cells to respond better and more rapidly to a secondary antigen [79]. Previous in vitro experiments indicated that proanthocyanidins interact with γδ-T-cells and increase their proliferation and activation [80].

In a previous study, consumption of fruit and vegetable concentrate increased γδ-T-cells in the blood while decreasing circulating IFN-γ concentrations [81]. In another study, a capsule containing a standardized mixture of tea components, L-theanine and catechins, was reported to influence γδ-T-cell function. People consumed a distinct amount of L-theanine and catechins for 10 weeks. White blood cells (WBC) from the participants were incubated ex vivo, with the compound responsible for priming, ethylamine. Greater activation and proliferation of γδ-T-cells and greater concentration of IFN-γ were observed in subjects consuming L-theanine compared with placebo. As a side note, subjects taking the capsule experienced fewer cold and flu symptoms during the study [82, 83].

Mistletoe has been reported to increase levels of IL-12 [84], a cytokine that supports the proliferation and cytotoxicity of γδ-T-cells [85]. In another study, mistletoe extracts (50–500 mg/L) increased proliferation of γδ-T-lymphocytes in vitro in a dose-dependent manner [86]. In two strains of mice, at first food allergy was established with ovalbumin sensitization; and then feeding apple condensed tannins (ACT) resulted in much less severe anaphylaxis, lower histamine levels, and decreased serum levels of IgE, IgG1, and IgG2a. γδ-T-lymphocytes were significantly increased in the intestinal epithelium of those consuming ACT [87]. In another in vitro experiment, a quite low concentration (20–40 mg/ml) of apple polyphenols upregulated CD11b on γδ-T-cells [88].

Dietary nucleotides have been indicated to change the percentage of intestinal intraepithelial γδ-T-cells [89]. Adding 0.4% nucleotides to the regular diets of weanling mice for 2 weeks increased γδ-T-cell proportion from 50.6% to 58.7% and increased secretion of IL-7, but not IL-2 or IFN-γ.

Different dietary oils have been investigated regarding their possible effect on γδ-T-cells. In one study, splenic γδ-T-cells were statistically higher in the safflower oil diet compared with the fish oil diet. The possible response to n-6/n-3 fatty acid ratio has been suggested [90]. Conjugated linoleic acid (CLA) has also been reported to almost double the number of γδ-T-cells in pigs fed 1.33 g CLA/100 g diet for 72 days [91]. Vaccination combined with CLA increased γδ-T-cell numbers largely (sixfold).

Alkylamine compounds produced by gut microbiota have been shown to prime γδ-T-cells [50, 92]. Furthermore, they can be obtained from dietary sources, such as kola nuts [93], tea, apple skins, mushrooms, and cucumbers [92]. Drinking tea increases urinary ethylamine [75]. When mixed with peripheral blood mononuclear cells (PBMCs), ethylamine could cause a 15-fold increase in the number of γδ-T-cells [92]. In addition, the secretion of IFN-γ in PBMCs incubated with ethylamine and challenged with bacteria was shown to be stimulated by alkylamines [50, 92]. Consumption of tea caused a two- to threefold increase in the capacity of γδ-T-cells to

secrete IFN-γ in response to bacterial pathogens or nonpeptide antigens.

A trial in healthy individuals showed that regular consumption of Concord grape juice for 9 weeks significantly increased the number of circulating γδ-T-cells [94]. Consumption of *Lentinula edodes* (shiitake) mushrooms for 4 weeks also led to an increase in ex vivo proliferation of γδ-T- and NK T-cells and in sIgA production [95]. Studies also investigated the effects of aged garlic extract (AGE) in healthy subjects [96] and patients with cancer [97]. Although not many γδ-T-cells were found in the serum, they were expanded in the epithelial linings of the gastrointestinal, respiratory, and genitourinary tracts [96]. A trial in healthy subjects revealed that the proliferation index of γδ-T-cells was almost five times increased after a 10-week cranberry juice consumption [98]. Other plant preparations with γδ-T-cell agonist activity include compounds from *Funtumia elastica* bark, *Angelica sinensis* root, cocoa, cat's claw bark, grape seed extract, and safflower oil [99–102]. Recent evidence reveled that grape seed extract has potent γδ-T-cell agonist activity. On the other hand, cocoa extracts caused expansion of rat γδ-T-cells in vivo [101] to some degree similar to that observed with apple-derived procyanidins [87]. Of note, the expansion of γδ-T-cell population particularly occurred in intestinal and Peyer's patches after oral administration of procyanidins. Rats feeding cocoa showed an increase in intestinal γδ-T-cells and a decrease in production of secretory IgA [87, 101].

In one study in mice, the effect of methanol extract from *Chelidonium majus* was investigated in collagen-induced arthritis. *Chelidonium majus* decreased B-cell and γδ-T-cell numbers (in spleen) while increasing the proportion of $CD4^+CD25^+$ T_{reg} cells [103]. The production of cytokines (TNF-α, IL-6, and IFN-γ) and the levels of IgG and IgM RA factors were decreased as well [103]. One experiment showed that condensed tannins derived from the unripe peel of the apple fruit act as agonist for both human Vδ1- and Vδ2-T-cells and increase the expression of IL-2R and cell proliferation. Previous studies reported that glutamine prevents apoptosis of small intestinal γδ-T-cells and downregulates the expression of inflammatory mediators by γδ-T-cells in septic mice [104, 105].

However, it has been discussed that many of the bioactive compounds in diet are only absorbed minimally, and their ability to influence immune responses throughout the body is therefore argued. However, it must be noted that several bioactive compounds do not need to be absorbed by the body to modify immune cells. For example, such compounds may be metabolized by the microbiota, and intermediates which are absorbed in the colon influence circulating immune cells. However, this has not been proven yet. Furthermore, Peyer's patches and intraepithelial cells lining the microvilli contain several immune cells, many of which express γδ-TCR. In addition, gut immune cells are able to move in and out of tissues via the circulation and the lymphatic system [106]. In this manner, blood-borne γδ-T-cells would be influenced by bioactive compounds which have not yet been absorbed.

Although tumoricidal activity of bioactive food compounds has not been clearly shown, certain food components are known to prime γδ-T-cells. When primed cells encounter a malignant cell, they can respond faster and more efficiently in terms of increased production of cytokines. However, enhancement of immune function is not always favorable; it is associated with decreased risk of cancer on one side, and on the other side, it has the potential to increase the risk of autoimmune diseases such as inflammatory bowel disease [107] and celiac disease [108]. Further research is necessary to investigate the relevance of using bioactive food components as regulators of γδ-T-cell function. If results support the hypothesis of priming γδ-T-cells, then this would propose a mechanism by which dietary factors can reduce the risk of cancer.

Cocoa, Immunity, and Cancer

Cocoa, the dried, roasted, and either unfermented or fermented seeds derived from *Theobroma cacao* tree, has been consumed by ancient civilizations such as the Mayans and Aztecs [109, 110]. Cocoa or cacao contains the highest flavanol

content of all foods on a weight basis and is a significant contributor to total dietary flavonoid intake [111]. It is worth mentioning that manufacturing processes increase flavonoid contents of cocoa four times greater than in conventional cocoa powder [112]. In this respect, fermented cocoa contains high quantities of flavonoids, flavanols (also called flavan-3-ols), (−)-epicatechin (EC), and (+)-catechin and to a lesser extent other polyphenols such as quercetin, naringenin, luteolin, and apigenin [113]. When compared to other flavonoid-containing foodstuffs, cocoa and its derivatives contain high concentrations of procyanidins, which are weakly absorbed through the gut barrier [114, 115]. The procyanidins in cocoa are unique because they exist as long polymers, prepared through polymeric condensation by two, three, or up to ten linked units of catechin or epicatechin [116] formed during fermentation [117]; thus, their favorable effects would be restricted to the gastrointestinal tract. These compounds represent 60% of the total polyphenol content in cocoa products [118, 119]. Cocoa and its products are generally consumed around the world because of highly attractive organoleptic characteristics [118]. Absolutely, cocoa and its derivatives constitute a larger proportion of the diet of many individuals than green tea, wine, or soybeans [118]. However, health benefits of cocoa flavonoids depend on their bioavailability (absorption, metabolism, and elimination) [120]. Of note, oligomers and polymers of flavanols that are not absorbed in the intestine can be metabolized by gut microbiota into various metabolites with low molecular weight, which tend to be well-absorbed through the colon and possess biological properties [121].

Intake of flavonoid-rich foods that possess antioxidant properties can have health effects [122]. Over the last few years, evidence emerged suggesting health benefits of cocoa phenolics, especially prominent for their metabolic and cardiovascular effects. These effects may be due to antioxidant and antiradical properties of cocoa bioactive compounds. Along with their antiplatelet effects [123], cocoa phenolics can be protective against heart diseases [124]. In addition, they have the capacity to modify the immune responses and produce anti-inflammatory and anticarcinogenic effects [125].

Below is an overview of evidences suggesting cocoa products as a cancer-protective factor. In particular, data from epidemiological studies support protective effects of cocoa and chocolate against cancer. Then, it would be also interesting to unravel potential biologic mechanisms through which cocoa phenolics can modify immune processes, thereby protecting against cancer. The focus is mainly to show anti-inflammatory and antioxidant effects of cocoa, which are known to decrease cancer risk. Inflammation provides a microenvironment appropriate for angiogenesis and therefore tumor growth [126]. Consistently, prospective studies have linked high levels of pro-inflammatory mediators such as IL-6, CRP, and TNF-α to increased risk of cancer in [127, 128]. An inflammatory response can result in the overproduction of ROS, which, in turn, would exacerbate the condition through oxidative stress.

Epidemiological Studies

Exposure to low doses of carcinogens may happen continuously during a lifetime. Furthermore, the body's response to carcinogens and chemoprotective agents depends upon several factors such as genetic polymorphisms and epigenetic modifications [129]. Few epidemiological studies have investigated the link between cancer-related mortality and cocoa, and consequently there is a limited support for the efficacy of cocoa for cancer-related mortality. Therefore, large-scale and long-term controlled trials are necessary to confirm cancer preventive effects of foodstuffs. Below provides a summary of existing studies by type. A review of epidemiological studies on polyphenols has previously addressed the link between catechin intake and cancer risk [130].

Case-Control Studies

Data supporting cancer preventive effects of cocoa in humans come mostly from the Kuna tribe in Panama. Kuna islanders drink flavanol-rich cocoa as their major cocktail. Studies have found lower mortality rates for cancer and other

chronic diseases among islanders than in mainland Panama. However, the finding should be treated with caution due to uncertainties arising from confounding factors [131]. Case-control studies have frequently investigated the relation between cocoa and cancer. They linked flavonoid consumption and procyanidin intake to decreased risk of gastric cancer [132]. In addition, higher catechin intake reported to be associated with lower rectal cancer incidence in postmenopausal women [133]; and higher consumption of epicatechin, anthocyanidin, and procyanidin was protective against non-Hodgkin lymphoma [134]. Although intake of these phenolic compounds has been associated with reduced risk of cancers [130, 135], the nutrition source for these bioactive compounds remains to be identified. Moreover, there are studies that failed to show the efficacy of cocoa intake in decreasing risk of cancer. For example, there was no relation between chocolate and cocoa intake and the incidence of any stage of colorectal diseases ranging from polyps and adenomas to CRC [136]. Lack of correlation might lie in the lower intake of flavanols (with a small percentage of cocoa-like milk chocolate) and/or low study power [136]. In another study, CRC risk was decreased by about 26% for epicatechin and by about 22% for procyanidins [136]. In a case-control study, procyanidins were associated with a lower risk of CRC. Interestingly, the higher the degree of polymerization of procyanidins, the lower the risk of CRC [137].

Cohort Studies

Four prospective cohort studies assessed the effect of cocoa and chocolate intake on mortality and cancer outcomes: Iowa Women's Study [133], the Zutphen Elderly Study from the Netherlands [138], the Harvard Alumni Study [139], and the Leisure World Cohort Study [140]. In the first study, no separate risk estimates of rectal cancer were shown for chocolate [133]. In the study [141], no association was found between chocolate intake and non-Hodgkin lymphoma, though total procyanidin consumption was protective, with a 30% lower hazard for the category with the highest consumption. Overall catechin consumption was associated neither with epithelial cancer nor with lung cancer after adjustment for confounders. However, nonsignificant inverse association was present between intake of catechins from cocoa and chocolate and incidence of lung and all epithelial cancers. In the Harvard Alumni Study, individuals who consumed candy 1–3 times per month had a 27% lower risk of mortality [139]. In the study [140], frequent chocolate consumption was not associated with lower mortality risk, but mortality seemed to decrease (about 6%) in people with occasional chocolate intake.

Intervention Studies

To our knowledge, no clinical trial on the effectiveness of cocoa and chocolate intake for cancer prevention is available. However, few human studies report that cocoa favorably affects intermediary factors in cancer progression, in particular inflammation and oxidative stress [142–145]. Recent studies focused on the modification of antioxidant and anti-inflammatory status by consumption of cocoa derivatives. One trial [146] has demonstrated that dark chocolate intake significantly improved DNA resistance against oxidative stress. Cocoa consumption reduced NF-κB activation in PBMCs of healthy volunteers [147]; but other biomarkers of inflammation, including IL-6, remained unaltered in a group of patients with cardiovascular diseases after cocoa powder intake [146].

Evidence for cancer chemoprevention by flavonoids comes from different study types. Antitumoral effects of flavonoids occur through induction of apoptosis and inhibition of several kinases and transcription factors, angiogenesis, and cell proliferation. Further, cocoa and its bioactive compounds have shown antitumoral effects independent of antioxidant function [115, 148, 149]. However, whether it works in humans remains to be addressed. Below different pathways and molecular targets whereby cocoa and their bioactive compounds interfere with cancer cells are reviewed.

Antioxidant and Antiradical Activities of Cocoa

Polyphenols are able to capture ROS which have been implicated in carcinogenesis. One serving of cocoa or chocolate has antioxidant capacity (AOC) that exceeds the antioxidant capabilities of many foodstuffs [118]. The cocoa procyanidins, epicatechin, and catechin have important antioxidant abilities [150, 151]. Genome analysis of human colon adenocarcinoma cell line (Caco-2 cells) revealed that polyphenolic cocoa extract can modulate the expression of numerous genes involved in cellular response to OS [152]. Phenolic compounds from cocoa inhibit lipid peroxidation in microsomes and liposomes. The polyphenolic cocoa extract increased mRNA levels, protein levels, and enzymatic activity of CYP1A1 in MCF-7 and SKBR3 breast cancer cells [153]. The cocoa polyphenolic extract led to inhibition of ROS generation and xanthine oxidase activity in stimulated myelocytic leukemia HL-60 cells [154]. In vivo studies also demonstrated the protective effect of cocoa in rodent models of CRC and lung cancer and liver injury [155, 156]. In a lymphoma model, the albumin fraction of semifermented dry cacao showed free radical scavenging capacity [157]. The cacao is, therefore, the source of potential antitumor agents. Upregulation of cytoprotective enzymes like Kelch-like ECH-associated protein 1 (Keap1) and its binding partner, transcription factor NF-E2-related factor-2 (Nrf2), which are involved in antioxidant response element (ARE), by therapeutic agents like cocoa and its phenolic compounds can subsequently activate ARE [158]. Epicatechin has been described to act through this pathway as well [159]. Human studies also showed similar results with an increase in plasma AOC and a decrease in plasma lipid oxidation [143, 160].

Cocoa and Immunity

Several studies of cocoa's effects on the immune system have been published in recent years. In vitro and in vivo models have investigated both the innate and adaptive immunity. Most in vitro experiments of cocoa and its components have focused on inflammatory mediators released by macrophages. Some studies tested the effects of cocoa administration in several models of inflammation. Human studies investigating the relation between cocoa and innate immune responses are scarce and provide inconsistent results. One study showed no significant effect of cocoa on inflammatory markers in a group of healthy subjects [142]. However, another study reported that regular intake of dark chocolate by healthy humans was inversely associated with serum C-reactive protein (CRP) concentrations [161]. In vitro, on cultured lymphoid cells or PBMCs, and in vivo models also have investigated the influence of cocoa on adaptive immune response.

An Overview of Inflammation in Cancer

Inflammation is a feature of innate immunity, and chronic inflammation is a contributing factor to the initiation and progression of cancer. Chronic inflammation acts as a trigger for premalignant and malignant transformation of cells. About 20% of all cancers are related to chronic inflammation resulting from infections and autoimmune diseases [162]. The association between inflammation and cancer involves key inflammatory mediators. Several inflammatory mediators, like NF-κB, TNF-α, and COX-2, have been related to cell proliferation, antiapoptotic activity, angiogenesis, and metastasis [163, 164]. Inflammatory cytokines and cells have been broadly recognized in cancers of the stomach, colon, skin, liver, breast, lung, and head/neck [165]. Inhibition of COX-2 and iNOS has shown protective effects against tumor development in animal models, suggesting that they are crucial targets for tumorigenesis. Inflammation can enhance mutation rates and proliferation of mutated cells. Inflammatory cells are sources of ROS that are able to induce genomic instability and DNA damage. More precisely, cells may use cytokines such as TNF-α to increase ROS in adjacent epithelial cells [166, 167]. On the other

hand, NF-κB, which regulates the expression of iNOS and COX-2, is constitutively active in neoplastic cells, posing a hazard to the development of cancer. The pro-tumorigenic function of TNF-α and IL-6 released by immune cells is well established. The role of TNF-α and IL-6 as master regulators of tumor-associated inflammation and tumorigenesis makes them striking targets for adjuvant therapy in cancer [163]. Diet can also contribute to chronic inflammation that facilitates the development of gastrointestinal cancers. Chronic consumption of alcohol activates mast cells, causes polyp formation, and enhances tumor formation and invasion in a mouse model of colon cancer. In addition, red meat contains high levels of N-glycolylneuraminic acid. This foreign antigen can get incorporated into tissue and attract inflammatory cells [165]. Inflammation can also modulate composition of the gut microbiota, assisting growth of harmful bacteria such as *Escherichia coli*, which are present in higher concentrations in patients with CRC. Colitis can cause tumorigenesis by changing microbiome toward a population more capable of inducing gene damage and mutagenesis [165]. Therefore, the use of chemopreventive substances that decrease inflammation seems to be a helpful approach to control the development and progression of cancers. For example, NSAIDs or selective blockers by inhibition of COX activity, which fuels cancer-related inflammation through prostaglandin E2, decrease the risk of some type of cancers including colon and lung cancer. However, further clinical studies are necessary to determine the possible benefits and risks of long-term NSAID use for cancer prevention and treatment [165]. For more information about the role of inflammation in cancer, see comprehensive reviews [162, 164, 168].

Anti-inflammatory Effects of Cocoa and Cancer

Different anti-inflammatory effects of cocoa extracts have been reported. Cocoa extract and EC decreased TNF-α, IL-1a, IL-6 expression and NO secretion in different cells. Cocoa phenolic extract inhibited phosphorylation of AKT and ERK induced by TNF-α and suppressed MEK1 (mitogen-activated protein kinase kinase-1) and phosphatidylinositol-3-kinase (PI3K) activity induced by TNF-α, suggesting a potential chemopreventive effect against pro-inflammatory cytokine-mediated skin cancer and inflammation [169]. Cocoa polyphenols reduced phosphorylation of TNF-α-induced c-Jun N-terminal kinase (JNK) and nuclear translocation of NK-κB [170]. High-molecular-weight polymeric procyanidins from cocoa decreased TNF-α-induced IL-8 in human colon cancer HT-29 cells [171]. Cocoa flavanols have demonstrated a critical role in the prevention of neoplastic lesions in CRC [172]. Feeding animals with a 12% cocoa-enriched diet suppressed intestinal inflammation induced by AOM through the inhibition of NF-κB signaling and downregulation of COX-2 and iNOS [170]. These effects suggest the chemopreventive effect of a cocoa-rich diet on colon inflammation and preneoplastic lesions. In another study, supplementation with dark chocolate decreased cell proliferation and downregulated transcription levels of COX-2 and RelA resulting in a lower number of preneoplastic lesions [173].

Other studies reported several possible immunological effects of cocoa and cocoa flavonoids on cancer models.

Cancer Immunity Cycle

The immune system is able to recognize tumor antigens. However, mechanisms for immune escape are a hallmark of cancer progression [174]. Antitumoral activity of the immune system involves different immune cells such as NK cells, dendritic cells (DCs), macrophages, and T-cells [175]. DCs capture tumor antigens, leading to activation and priming of effector T-cells (Teff) against tumor-specific antigens in lymph nodes [176]. DCs present antigens bound to major histocompatibility complex (MHC) molecules. Activated Teff infiltrate in tumor, recognize malignant cells, and kill them. DCs capture antigens from dying tumor cells, and this would trigger the cycle over again. Naïve T-cells cannot be

activated exclusively by recognition of cancer-specific peptide-MHC I complexes by T-cell receptor (TCR). Additional activator signals must be present involving pro-inflammatory cytokines (e.g., TNF-α, IL-1, IFN-α) [177], factors released by killed cancer cells such as high mobility group box 1 (HMGB1) and cyclic dinucleotide (CDN) [178], and Toll-like receptor (TLR) signaling. Because killing of cancer cells is accompanied by release of tumor-associated antigens and increased activation of Teff, it is expected that antitumor responses should occur repeatedly. However, different mechanisms help tumor cells to escape the immune system. For example, many tumors suppress MHC expression, thus masking their presence from TCR. In addition, after infiltration of Teff into cancer cells, activation of inhibitory signaling pathways in local microenvironment would reduce T-cell function. Inhibition of these pathways by immunological drugs removes cell intrinsic inhibitory pathways that block effective antitumor cell response [179–181].

Recent studies have suggested paradoxical roles of regulatory T (T_{REG}) cells in cancer [182]. FOXP3C CD4C CD25C/high T_{REG} cells are involved in the modulatory action of the immune system and, in particular, are valuable for coordinating control of peripheral immunological tolerance [183, 184]. The transcription factor FOXP3 is a critical regulator of T_{REG} cell function. T_{REG} cells provide the machinery for immune homeostasis during infections by inducing useful inflammatory responses while minimizing collateral tissue injury. However, T_{REG} cell function in cancers is widely regarded as negative [185–187]. In fact, an increased number of T_{REG} cells have been reported in patients with head and neck, pancreatic, stomach, breast, and liver cancers [181]. Tumor-associated T_{REG} cells pose a major challenge in vaccine therapy for cancers [185, 187, 188]. Therefore, several anti-T_{REG} regimens have been developed that rely on depletion of T_{REG} cells and inhibition of their suppressive function, their residence into tumors, and/or their differentiation/proliferation [185, 186]. For instance, anti-CTLA-4 (cytotoxic T-lymphocyte-associated antigen-4) immunotherapy that has shown promising results [189] depletes T_{REG} cells from tumor tissues [189]. Chronic inflammation mediated by cytokines and ROS may cause cell injury in target cells and therefore may contribute to cancer development. Mounting evidence suggests that tumor-associated inflammation is a tumor-promoting event. The reason is that inflammation can support cancer cell survival through DNA damage and development of a tumor stroma.

Almost immediately after birth, the gastrointestinal (GI) tract changes from sterility to a large ecosystem with hundred trillion microbial organisms, representing the most densely populated ecosystem known so far [190]. The overall population of intestinal colonies including bacterial, fungal, and viral communities is referred to as the gut microbiota. The microbiota include more than 1500 bacterial species, which are estimated to encode more than 150 times more genes than human genome. The gut microbiota is in intricate and reciprocal interaction with the human host and nutrients, providing a metabolic engine important for GI health and disease. This highly regulated and complex ecosystem plays an important role in priming the immune system and maintenance of intestinal immune homeostasis [191, 192]. Besides metabolic effects, the gut microbiota affects tissue development and inflammation [193–196]. Providing a physical barrier against pathogens and supplying immunological surveillance signals are other functions of the gut microbiota. There should be an ability to maintain the balance between tolerance toward microbiota and surveillance against pathogens. Such ability comes from the cross talk between the intestinal microbiota and host that involves both innate and adaptive immunity [197–199]. The hygiene hypothesis reflects the fact that the lack of exposure of the gut to harmless microorganisms, called “old friends,” in infancy causes certain deficiencies in the immune system at later age. A number of immunological disorders such as allergic diseases, inflammatory bowel diseases, type 1 diabetes, and multiple sclerosis are thought to result from an imbalance in the function of the regulatory immune system. Proper discrimination between harmful and

harmless pathogens involves a family of cell surface and cytosolic receptors of the innate immunity, called pattern recognition receptors (PRRs). PRRs including Toll-like receptors (TLRs), C-type lectin receptors (CLRs), and nucleotide-binding oligomerization domain proteins (NOD proteins) recognize PAMPs and damage-associated molecular pattern (DAMPs). Interestingly, both harmful and harmless bacteria express these PAMPs. In this manner, pathogenic bacteria can pass through the epithelial barrier and activate inflammatory cascade through increased NF-κB translocation, on one side, and on the other side, commensal bacteria do not invade epithelial cells and do not stimulate inflammatory responses [200–203].

Commensal bacteria colonization results in Paneth cell expression of an antimicrobial peptide, regenerating islet-derived 3 gamma (Reg III-γ) [204, 205], which is involved in innate immune protection against enteric pathogens [206]. Moreover, the gut microbiota helps with maintaining the balance between Teff and Treg cell function. Expansion and differentiation of T-cells into T_{REG} cells occur in the colon in the presence of microbiota. T_{REG} cells suppress inflammatory response via the production of anti-inflammatory cytokines IL-10 and transforming growth factor (TGF)-β. A mixture of *Clostridia* strains induces the accumulation of T_{REG} cells in the colon and expression of IL-10 and CTLA-4 by Treg cells. *Lactobacillus reuteri*, *L. murinus, and Helicobacter hepaticus* have also been implicated in T_{REG} function [207–210].

Cancer Prevention and Treatment, Immunity, and Probiotics

Epidemiological Studies

The preventive effect of probiotics or fermented products containing probiotics on animal and human cancers has been frequently investigated. However, epidemiological evidence is scarce. Studies on humans showed a reverse association between yogurt intake and the risk of breast cancer [211]. In another case-control study in the United States, yogurt consumption was reported to be protective against colon cancer [212]. Similar results were found by Dutch researchers for breast cancer [213]. There are clinical trials investigating the possible role of probiotics in cancer prevention. In one trial, recurrence rate of superficial bladder cancer was lower in subjects who received *L. casei* Shirota (LcS) in comparison with subjects receiving placebo [214]. However, it must be clarified if long-term supplementation of probiotics can significantly reduce the risk of CRC in humans. A cohort study with 12 years of follow-up on 45,241 volunteers determined that high yogurt consumption was significantly related to lower risk of CRC [215]. However, these studies have limitations concerning selection and standardization of microorganisms, control of food intake, time, and dosing of microorganism administration.

Clinical studies have also investigated the beneficial effect of probiotics in preventing GI disorders, including viral diarrhea and chemotherapy, radiotherapy, or antibiotic-associated diarrhea. In addition, chronic treatment with probiotics effectively reduced the urinary excretion of aflatoxin B(1)-N(7)-guanine (AFB-N(7)-guanine), a marker for hepatocyte carcinogenesis, and the risk of CRC [216]. It is commonly believed that probiotic supplementation can decrease the risk of breast cancer in perimenopausal women. However, clinical studies report inconsistent results. It seems that long-term use of probiotics is needed to achieve chemopreventive effect on the development of malignant tumors. For instance, *L. casei* supplementation for 4 years could prevent atypical CRC [217]. Usual consumption of *L. casei* Shirota (LcS) and soy isoflavone in adolescents was inversely related to the incidence of breast cancer in Japanese women [218]. In contrast, the 3-month yogurt consumption could not improve cell-mediated immune function in women [219]. Altogether, evidence for the efficacy of probiotics in human tumorigenesis is ambiguous. However, there is mounting evidence from experimental models indicating antineoplastic effects of probiotics. In addition, as shown through a meta-analysis study, data from epidemiological

studies reveal a decreased risk of CRC and precursor lesions in association with consumption of probiotics. However, interventional studies are necessary to confirm the efficacy of probiotics [220]. Coupled to the above is the need for long-term high-quality studies that assess the efficacy of probiotics in subjects with different types and stages of cancer.

Cancer Prevention

Study of proto-oncogene human epidermal growth factor receptor-2 (HER2)/neu-driven transgenic mice showed that extended contact to metronidazole in combination with ciprofloxacin increases the risk of breast cancer [221]. In fact, altered composition of the gut microbiota may influence the development and progression of cancer through inflammatory and metabolic pathways [222, 223]. However, not all probiotics have the ability to modulate the immune system and thereby play a role in cancer prevention. Previously, it has been reported that a dose of 10^8–10^9 colony-forming unit (CFU)/day of a strain with immunomodulatory effect and a duration of 48–72 h is required to influence the host immune homeostasis [224, 225].

Maintenance and Enhancement of Intestinal Barrier Function

Mucin 2 (MUC2) is the main mucin secreted by intestinal goblet cells. MUC2-deficient mice have increased risk for CRC [226]. Treatment with probiotics was reported to be effective to promote the restoration of colonic tissue through an increased MUC2 expression, extracellular mucin secretion, and inhibition of enteropathogenic adherence. Increased epithelial permeability has been implicated in early stages of CRC. *L. plantarum* MB452 was shown to enhance Caco-2 tight junction (TJ) integrity, possibly through encoding TJ-related genes including occludin and scaffold protein zonula occludens [226–228]. Probiotics are also capable of preventing epithelial barrier damage by stimulating the production of cytoprotective heat shock proteins in stressed epithelial cells to maintain hemostasis [229] and promote cell survival [230]. Components of *E. coli* strain Nissle 1917 can decrease intestinal permeability by restoring a disrupted epithelial barrier [231]. Combination of *L. rhamnosus* GG (LGG) and *B. lactis* Bb12 could also improve epithelial integrity in patients with CRC [232].

Recognition of Probiotics by the Immune System: Toll-Like Receptors

TLR2 plays a protective role in colitis-associated CRC. TLR2-deficient mice demonstrated increased inflammation and elevated serum levels of inflammatory markers such as IL-6 and IL-17A. Probiotics can modify the risk of CRC through a TLR2-dependent pathway. TLR2 recognizes gram-positive bacteria, such as lactobacilli and bifidobacteria [233, 234]. Peptidoglycan from lactobacilli blocks the production of pro-inflammatory cytokine IL-12 by macrophages via TLR2 [235]. In addition, mixture of *L. plantarum* and *L. casei* synergistically stimulate IL-10 production in macrophages through a TLR2-dependent pathway [233].

Modulation of DCs

IL-10 suppresses the production of pro-inflammatory cytokines while promoting the development of T_{REG} cells. Studies showed a strong association between probiotics and induction of IL-10 by DCs [236]. Administration of probiotics also induced regulatory DCs, which, in turn, could promote the induction of CD4+Foxp3+ T_{REG} cells in vivo [237]. Thereby, mice showed a reduction in the production of pro-inflammatory cytokines IL-17, IFN-γ, and TNF-α and an amelioration of disease progression. In the study [238], the authors investigated the ability of three *Lactobacillus* species to influence DC to drive T_{REG} cell development. Human monocyte-derived DC matured in the presence of *L. rhamnosus* showed decreased capacity to support T-cell proliferation and attenuate CD3/CD28-induced cytokine production.

L. rhamnosus GG, *B. lactis* Bb12, and/or inulin enriched with oligofructose demonstrated immune stimulatory effects by inducing the maturation of DC [239], supporting the immune response against tumor cells [240]. Activation of IL-10-secreting cells was accompanied by the induction of apoptosis in colon cancer cells and suppression of pro-carcinogenic factors [241]. *Bifidobacterium* in a mice model has been shown to alter DC activity, leading to improved tumor-specific $CD8^+$ T-cell function.

NK Cell Proliferation and Activity

Probiotics are also able to increase NK cell numbers and their cytotoxic activity [242]. Oral administration of *L. casei* Shirota (LcS) to tumor-bearing mice stimulated splenic NK cell activity, thus leading to postponed tumor formation [243–245]. Probiotics exert desmutagenic effects on myeloid DC maturation through IL-12 production and shifting T-cell activity toward T_H1, T_H2, or even T_{REG} type of responses [244, 246, 247]. Later, this molecule, IL-12, activates NK cells to produce IFN-γ [248]. In this manner, LcS is able to suppress murine tumorigenesis via increased IL-12 production by bone marrow-derived cells in vitro [249] and inhibition of IL-6 production in the colonic mucosa [250, 251]. Previous studies demonstrated that *Lactobacillus* strains with a firm cell wall resistant to intracellular digestion can stimulate high levels of IL-12 [252].

Lactobacillus and *Bifidobacterium* strains and their mixture differentially initiated NK/DC interactions via induction of DC maturation and cytolytic potential of NK cells [253]. NK cells play a critical role in tumor surveillance and production of IFN-γ and TNF-α, which induce cell-mediated immunity and lead to further activation of APCs (DCs and macrophages) [248]. NK cells also are indirectly activated by DCs which secrete soluble factors, such as IL-12, IL-18, and type I interferons. Probiotic *Lactobacillus* strains can induce secretion of pro-inflammatory cytokines, IL-12 and TNFα [254], which are positively correlated with NK cell activity.

IL-12 produced by DC and APC primes NK cell activation and subsequent secretion of TNF-α. Therefore, LcS and *Lactobacillus* strains may indirectly activate NK effector cells through DCs and APCs, respectively. NK-derived IFN-γ secretion has been implicated not only in innate antitumor immune responses but also in cell-mediated antitumor immune responses [253, 255]. In one trial, intake of fermented milk containing LcS enhanced NF-κB activity in subjects. The effect was reduced in the presence of anti-IL-12 monoclonal antibody [256]. DCs, T_{REG} cells, and NK cells are important immune cells in defense against cancer [251, 257]. However, supplementation with synbiotics containing LGG, *B. lactis*, and oligofructose for 12 weeks showed little effects on systemic immune responses in patients with CRC [239].

Inhibitory Effect of Probiotics on TLR4 and COX-2 Expression

COX-2 has been implicated in inflammatory diseases and CRC. TLR4 is mandatory for the induction of COX-2 and therefore CRC development [258]. Overexpression of TLR4 upregulates NF-κB activation and COX-2 expression [259]. The probiotic combination VSL#3 has been reported to downregulate COX-2 expression in Colo320 and SW480 intestinal epithelial cells (IECs). COX-2 has been associated with an increased risk of CRC because it stimulates cell proliferation and triggers inflammatory pathways [35]. Milks fermented with different strains of probiotics have been investigated in HT-29 colon cancer cells. Almost all of them induced a significant, although variable, reduction in the growth of HT-29 cells [260, 261].

Probiotics Enhance Innate Immune Functions

Defensins through membrane lysis and DNA damage exert cytotoxic activity on tumor cells. Murine b-defensin 2 has been shown to promote DC maturation, which initiates type I polarized immune responses through the production of pro-inflammatory cytokines such as IL-12, IL-1α, IL-1β, and IL-6 [262]. Treatment of Caco-2 colorectal adenocarcinoma cells with *L. plantarum* through the induction of TLR2 significantly upregulated the mRNA expression and secretion of human b-defensin 2 (HBD-2) in a

dose-dependent manner [263]. A probiotic mixture, including several *E. coli* strains, VSL#3, and lactobacilli, increased HBD-2 synthesis in human and Caco-2 cells [264]. In addition, probiotic products enhanced host immune function by increasing phagocytic activity of macrophages [265].

Immunoglobulins

IgA exerts anti-inflammatory and also cytotoxic effects on tumor cells [266]. It is resistant to proteolysis and can limit contact between potentially carcinogenic compounds and colon cells [225]. A study of mice treated with carcinogen showed that consumption of yogurt containing probiotics was efficient to downregulate cancer progression in the large intestine through upregulation of IgA, T-cell function, and colonic macrophage activities [234]. However, the effect of probiotic supplementation on the production of IgA remains controversial [265, 267]. LcS has been shown to inhibit tumor development and IgE production in mice [268].

Administration of *L. acidophilus* SNUL, *L. casei* YIT9029, and *B. longum* HY8001 improved the survival of tumor-bearing mice. The effect was associated with enhanced cellular immune responses as reflected in increased numbers of total T-cells, NK cells and MHC class II^+ cells, and $CD4^-CD8^+$ T-cells [269]. *Lactobacillus rhamnosus* strain GG (LGG) was reported to delay the onset of cancer through mitigating CD3 T-cell depletion in tumor-bearing mice while enhancing activation of CD8 and $CD4^-$ T-cells without significant effect on NK cell function [270]. Furthermore, *L. acidophilus* suppressed MHC class I expression and also induced a decrease in mRNA expression of stromal-derived factor-1 receptor, CXCR4, suggesting a role in cancer metastasis prevention [271]. In DSS-induced CRC mice, *Lactobacillus* and the VSL#3 mixture increased levels of angiostatin, an endogenous inhibitor of angiogenesis and regulatory T-cells [272]. In contrast, there was an increase in the number of memory $CD4^+$ T-cells and pro-inflammatory cytokines IL-17 and TNF-α [272].

Pre-inoculation with *L. plantarum* significantly reduced tumor growth and activated innate immunity while increasing the intratumoral levels of $CD8^+$ T-cells and NK cells in the tumor microenvironment [273]. Probiotic administration significantly increased the $CD8^+/CD4^+$ T-lymphocyte ratio. CD4 cells induce production of cytokines such as IL-6 and IL-10. Thus, increasing the CD8+/CD4+ T-lymphocyte ratio might explain lowering of IL-6 and delayed tumor growth by probiotics [274]. Indeed, *L. reuteri* was shown to delay the onset of neoplastic features through the induction of anti-inflammatory $CD4^+CD25^+$ T_{REG} cells. Stimulated T_{REG} cells would direct immune networks in a manner to resist against inflammatory diseases, including early stage of malignant transformation [275]. *L. rhamnosus* GG has been demonstrated to be effective in reducing the recurrence of bladder cancer [276]. The effect may be mediated by increased levels of chemokine (C motif) ligand (XCL1); this chemokine produced by activated $CD8^+$ cells and γδ-T-cells, NK cells, and master cells, which helps in chemotaxis by T-cells and NK cells and thus assists in tumor regression [276]. Activation of phagocytes by probiotics can inhibit cancer cells in early stage. Kefir consumption caused stimulation of phagocytes present in Peyer's patches and in the peritoneum [277].

Researchers have argued that stimulation rather than suppression of the innate immune system can contribute to cancer development. Yogurt feeding was correlated with altered levels of cytokines, such as TNF-α, IFN-γ, and interleukins [278, 279]. Intrapleural injection of LcS in mice could improve immunity against tumor development through release of TNF-α, an antitumor agent. In line with these observations, other studies also noted that intrapleural administration of LcS in tumor-bearing mice induced the production of IFN-γ, IL-1β, and TNF-α, leading to the inhibition of tumor growth and therefore an increased survival [280, 281]. Similar results have been reported for *L. acidophilus* SNUL, *L. casei* YIT9029, and *B. longum* HY8001 strains [269]. Urbanska and colleagues [279] investigated the effect of microencapsulated probiotic *Lactobacillus acidophilus* in a model of CRC. Daily oral administration of the microorganism significantly

induced suppression in tumor growth, tumor multiplicity, and tumor size. In a study by de Leblanc et al. [282], LcS induced the secretion of inflammatory cytokines such as TNF-α, IL-1β, and IFN-γ, resulting in reduced tumor development and improved survival of mice treated with a carcinogen [281]. IFN-γ is involved in activation of NK cells and macrophages. Consequently, it plays a significant role in cancer prevention. Humans and animals continuously produce IFN-γ in the defense against cancer [283]. Excessive inflammatory response is not desirable, and probiotics are able to induce and control T_{REG} cell function [284]. Direct immune modulatory effects of *B. lactis* and *L. rhamnosus* have been reported to be mediated through reduction of IL-2 and inducible NO synthase [285, 286]. Antitumoral and immunoregulatory effects of LcS have been investigated in various models. Of note, oral administration of LcS has demonstrated antitumoral activity against bladder cancer cells in clinical trials [287].

Modulation of Inflammatory Response

Chronic inflammation has been recognized as a risk factor for cancer. Inflammation plays a causative role in colitis-associated colon cancer, sporadic colon cancer, and hepatocellular carcinoma (HCC) [288–290]. Previous studies have reported antitumoral and anti-inflammatory effects of probiotics [291, 292]. LGG was reported to prevent colon cancer, accompanied by suppression of NF-κB pathway [293]. Li et al. showed a reduction in the level of IL-17 by probiotics in an HCC model. It suggests an association between immunomodulatory and antitumoral effects of probiotics [290]. Mounting evidence suggests the IL-6-lowering effect of *L. casei* CRL431. The proangiogenic role of IL-6 is consistent with impaired tumor growth by probiotic supplementation [274].

The *Lactobacillus casei* BL23, recognized for its anti-inflammatory characteristics, was tested for its protective effects on CRC in mice [294]. Mice in probiotic group substantially showed reduced levels of the monocyte chemoattractant protein-1 (MCP-1) and TNF-α with high levels of anti-inflammatory ones, such as IL-10 [294].

IL-17A produced by T_H17 cells would assist angiogenesis. Although the role of T_H17 cells and IL-17 in cancer is still inconsistent, but it has been suggested that reduction of T_H17 cell population and IL-17 level may inhibit progression of cancer [295, 296]. Noteworthy, ex vivo studies on splenic cells incubated with *L. casei* BL23 showed reduced numbers of T_{REG} cells and increased percentage of T_H17 cells and higher production of IL-17, IL-6, and TGF-β, together providing a microenvironment favorable to T_H17 differentiation [294]. As mentioned before, a probiotic mixture led to reduction in the proportion of T_H17 cells and in the production of IL-17 in an HCC model. In contrast, *L. casei* BL23 caused an increase in the proportion of T_H17 cells and in the production of IL-17 in a model of CRC [290]. However, both studies revealed an increase in the levels of anti-inflammatory cytokine IL-10 and anti-angiogenic cytokine IL-22. This would reflect a T_H17-mediated response.

IFN-γ plays a role in cancer immunity by increasing MHC I expression, T-cell infiltration, differentiation to cytotoxic T-lymphocytes, and T_H1 polarization, orchestrating different antitumoral immune responses [297, 298]. IFN-γ also has been used clinically for its antitumoral effect, leading to improved survival. Studies of mice reveal the role of IFN-γ in mediating the protective effect of probiotics against cancer [299, 300].

Production of Active Compounds Which May Be Involved in Immunity

Short-chain fatty acids (SCFAs) are the products of bacterial fermentation of nondigestible carbohydrates. Butyrate is a SCFA that can contribute to cancer prevention in different ways. It has the ability to increase mucus production and improve intestinal barrier function. It is also able to stimulate the production of anti-inflammatory cytokines, such as IL-10, while decreasing the production of pro-inflammatory cytokines by inhibiting the activation of NF-κB. More interestingly, butyrate can increase the immunogenicity of tumor cells by monitoring neutrophils and antigen-presenting cells and through regulation of chemotaxis by neutrophils, DCs, and macrophages [301] and suppressing COX-2 activity

[302, 303]. Other SCFAs like acetic and propionic acids also exhibit the same anti-inflammatory activity through suppression of NF-κB signaling pathway [304, 305].

Some species of probiotic bacteria, such as *Lactobacillus acidophilus*, are able to produce conjugated linoleic acid (CLA) from linoleic acid. CLA can suppress the production of eicosanoids in colon cells through replacement of arachidonic acid by CLA in the cell membrane and through interference with cyclooxygenase and lipoxygenase (LOX) enzymes. Probiotic supplementation can increase the production of CLA to promote antitumor immunity in a dose-dependent manner [241, 306].

Immunological Effects of Probiotics Combined with Chemotherapy

Probiotics also can be used in combination with conventional cancer therapies. In particular, disruption of the gut microbiota can impair the cancer cell response to platinum salts as chemotherapy. Supporting this, mice treated with an antibiotic mixture (including vancomycin, imipenem, and neomycin) displayed reduced therapeutic response to oxaliplatin and cisplatin in a colon carcinoma (MC38) and lymphoma (EL4) model, respectively. Interestingly, it has been reported that combination antibiotic therapy reduces oxaliplatin-induced DNA damage and apoptosis in tumor-bearing mice. In addition, *Ruminococcus*, *Alistipes*, and *Lactobacillus fermentum* are capable of affecting tumor response to CpG oligodeoxynucleotide (ODN), probably through regulation of TNF production [307, 308].

The study [309] proved that the efficacy of cyclophosphamide as an anticancer immunomodulatory agent, at least in part, relies on the gut microbiota. Tumor-bearing mice that were either germ-free or antibiotics-treated showed a reduction in "pathogenic" T-helper (pT_H17) responses, and their tumors were more resistant to cyclophosphamide-based therapy. It seems that this cyclophosphamide would stimulate pT_H17 cells through a complex circuitry that involves the gut microbiota [309]. More precisely, treatment with cyclophosphamide causes a reduction in the abundance of lactobacilli and enterococci in the gut [309]. Gram-positive bacteria, such as *L. johnsonii* and *E. hirae*, promote differentiation of $CD4^+$ T-cells into T_H1 and T_H17 cells. Broad-spectrum antibiotics suppressed cyclophosphamide-induced production of IL-17 and IFN-γ [309]. Consistently, another study [310] showed that two bacterial species, *Enterococcus hirae* and *Barnesiella intestinihominis*, are involved in response to cyclophosphamide therapy. After cyclophosphamide treatment, *E. hirae* migrates to secondary lymphoid organs, followed by mounting pT_H17 immune responses and accumulation of IFN-γ^+ IL-17^+ cells and $CCR6^+$ $CXCR3^+$ $CD4^+$ T-cells and T_{REG} cells in the spleen [309].

Studies have demonstrated the significance of *Bifidobacterium* to natural antitumor immunity and also in response to anti-PD-L1 antibody therapy and CTLA-4 therapy in tumor settings [311, 312]. Furthermore, *Bacteroides fragilis* improved response to CTLA-4 blockade, by affecting IL-12-dependent T_H1 immune response. *Bifidobacterium* in combination with anti-PD-L1 antibody enhanced antitumor immunity through activation of DCs [312].

Altogether, finding bacterial genera linking intestinal immune homeostasis and anticancer immune responses is essential to shed light on the possibility of using selected bacteria to improve cancer therapy by enriching the gut microbiota. In patients with metastatic melanoma, an increased delivery of bacteria belonging to the *Bacteroidetes* phylum is associated with an increased resistance to the development of checkpoint blockade-induced colitis [313]. Recent advances in this field such as fecal transplant open up new avenues in cancer therapy [314, 315].

Role of Microorganisms in the Development of Cancer

Tumorigenesis is a complex process. As a result, it is difficult to draw a direct association between dysbiosis, inflammation, and tumorigenesis.

Adherent/invasive *E. coli* strains are present in great quantity on the colonic mucosa of patients with CRC but not normal colonic mucosa. This indicates involvement of *E. coli* colonization in cancer pathophysiology [316]. Long-term colonization of enterotoxigenic *Bacteroides fragilis* (ETBF) led to colitis and multiple intestinal neoplasia (MIN) in mice [317]. On the other side, IL-10-deficient mice colonized with *Bacteroides vulgates* displayed low-grade inflammation and more interestingly were less likely to develop colorectal tumors as compared with conventionalized IL-10-deficient mice [318]. The results support the differential role of gut microorganisms in intestinal immune homeostasis and CRC. There is a complex interaction between the gut microbiota and IECs, where innate immune receptors including Nod-like receptors (NLRs) and TLRs play a role. It has been reported that Nod1 pathway could increase tumor-promoting effect of attenuated Wnt signaling. Furthermore, gut microbiota depletion by antibiotics decreases tumor development in Nod1-deficient mice [319]. These data highlight the complicated interaction between the microbiota, inflammation, and cancer and support the hypothesis that susceptibility to cancer would be influenced by the composition of the gut microbiota and by the repertoire of host innate sensors as well. As a result, modification of the intestinal microbiota using probiotics or prebiotics may affect the development of cancer.

Gut Microbiota Induces Potent T_{REG} Cells with Systemic Antineoplastic Properties

The association of tumor-associated cells expressing T_{REG} cell markers including FOXP3 with poor prognosis of human cancers remains inconsistent. Under certain conditions, microbial priming of T_{REG} cells not only protects against cancer development but also helps remission of already established intestinal, mammary, and prostate cancers [320]. However, T_{REG} cells play paradoxical roles in cancer [320, 321]. Actually, Treg-mediated decreased risk of cancer is dependent on microbiota-induced IL-10, which acts to maintain immune system homeostasis and support a protective anti-inflammatory and antineoplastic T_{REG} phenotype. Probiotic consumption in mice shifts immunity toward IFN-γ and CD25 to improve wound healing and promote systemic health [322]. IFN-γ levels increase during T_{REG}-mediated tumor regression in mice. Recent findings show that an unbalanced gut flora would weaken response to immune [307, 309] and non-immune chemotherapeutic regimens such as cisplatin and oxaliplatin [307].

Based on the "hygiene hypothesis," hygienic subjects are vulnerable to a redirection of unbalanced resting peripheral T_{REG} to T_H17 immune responses, putting them at higher risk of autoimmune diseases and cancer [182]. Furthermore, consumption of beneficial probiotic bacteria led to the expansion of $Foxp3^+$ cells in the periphery [275, 322], improving defense against mammary cancer [275]. Probiotics-induced enhancement of the T_{REG}-dominated arm of the immune system did not interfere with the capability to respond against invading pathogens [322]. Altogether, the gut and its cross talk with the host determine the fate of preneoplastic and neoplastic lesions arising in epithelia throughout the body. It would open up a new avenue in cancer immunotherapy through modulation of beneficial T_{REG} via diet. This concept not only could be considered for fighting cancer, but also arousing these dormant T_{REG}-mediated capabilities may give an alternative approach to reduce cancer risk and promote overall good health and longevity [320].

Lactoferrin, Immunity, and Cancer

Lactoferrin (Lf) is an iron-binding glycoprotein belonging to the transferring family. It contributes to the regulation of iron absorption in the bowel and immune responses, as well as is able to exert antimicrobial, antioxidant, antitumoral, and anti-inflammatory effects [323, 324]. Lf is produced by mucosal epithelial cells and is present in most biological fluids, including tears, saliva, vaginal fluids, semen, and most abundantly milk and colostrum [324]. Moreover, it is

present in considerable amounts in polymorphonuclear granules [323]. Recent reports have shown that this multifunctional agent essentially exerts antimicrobial effect, which can be directed against bacteria, fungi, and viruses [325]. Other Lf-mediated activities include immune modulatory functions and tumor growth inhibition [325]. Its bacteriostatic effect is mediated through iron-binding ability, which consequently restricts the use of iron by bacteria and inhibits their growth systemically. Additionally, Lf damages the external membrane of the gram-negative bacteria by interacting with the lipopolysaccharide (LPS) [323]. Therefore, knowledge of the physiological role and possible therapeutic implications of LF is hastily growing. Here, we present possible antitumoral effects of LF through immune modulatory activity.

Antitumor Activity

The first reports suggesting that Lf may possess antitumor effects through depleting tumor cells of glutathione, making them more susceptible to chemotherapy, appeared in 1995 [326]. Since then, in vitro studies have demonstrated antitumor effects of Lf in different cancer cell lines such as breast cancer [327, 328], pancreatic cancer, colon cancer, and oral squamous cell carcinoma [329–331]. Suggested mechanisms include increased NK cell cytotoxicity and inhibition of cell growth and metastatic colony formation. Chemopreventive effects of bovine Lf (bLf) also have been implicated in treatment of tumors of the colon, peritoneum, lung, esophagus, mouth, and neck. Moreover, the immune modulatory effect of Lf has been shown in mice [332–334]. Oral administration of recombinant human Lf has been investigated in head and neck squamous cell carcinoma in mice. Animals treated with Lf exhibited tumor growth inhibition of 75% concurrent with a 20-fold increase in lymphocyte ratio compared with controls. Of note, when mice were depleted of CD3+ cells, Lf-induced tumor inhibition was abrogated [335].

Other studies investigated the effects of iron-saturated (i-s) bLf on the augmentation of chemotherapy. Results showed that chemotherapy eradicated large lymphomas only in mice fed 100% i-s bLf for at least 2 weeks prior to chemotherapy, but not in mice fed lower saturated forms of bovine Lf or control mice fed no bLf. Lf was nevertheless effective in augmenting chemotherapy at the lowest dose tested, equated to a 70 kg person ingesting 3 grams of Lf per day. In addition, 100% i-s bLf decreased angiogenesis, increased apoptosis, and supported immunomodulation, as reflected in increased production of T_H1 (TNF-α, IFN-γ, and IL-18) and T_H2 (IL-4, IL-5, IL-6, and IL-10) cytokines, which are necessary for optimal antitumor immune responses. Moreover, 100% i-s bLf also restored both RBC and WBC numbers depleted by chemotherapy [336]. However, the ability of Lf to exert a protective effect at sites far away from the GI tract is less understood [337].

Evidence for Chemopreventive Potential

Anti-inflammatory Activity

Lf possesses potent modulatory properties. It can decrease the production of pro-inflammatory cytokines (IFN-γ, TNF-α, IL-1β, IL-6, and granulocyte-macrophage colony-stimulating factor (GMCSF)) [335, 338–341] while upregulating the levels of anti-inflammatory cytokines (IL-10) [342, 343]. However, other studies reported inconsistent results: (1) ex vivo upregulation of TNF-α and IFN-γ concurrent with a reduction in IL-5 and IL-10 upon induction with the exotoxin toxic shock syndrome toxin-1 [344] and (2) enhanced IL-12 production and decreased IL-10 release in human immunodeficiency virus (HIV)-infected children [345]. Together, these results indicate that Lf affects the T_H1/T_H2 cytokine balance independent of the host immune setting. Thus, Lf can increase the production of T_H1 cytokines in settings requiring an augmented ability to control infection on one hand and on the other hand may decrease the production of T_H1 cytokines to restrict excessive inflammatory responses [346]. Moreover, intravenous administration of bLf 24 h presurgery eased thymec-

tomy- and splenectomy-induced TNF-α and IL-6 generation, suggesting that Lf may have therapeutic application in cases of shock syndromes [347].

Immune Modulatory Activity

As already discussed, Lf also possesses immune-modulating properties. In vivo studies on the oral administration of bLf in mice revealed increased levels of NK cells, $CD4^+$ and $CD8^+$ cells, and IFN-γ^+ cells, in both the mucosal layer of the small intestine and the peripheral cells [348–350]. In addition, NK cell cytotoxicity is increased both in vitro and in vivo [328, 351, 352]. In humans, $CD3^+$, $CD4^+$, and $CD8^+$ T-cell activation has been observed as well [353].

Endogenous Lf belongs to the innate nonspecific immune system. However, mounting evidence shows that it may also be attributed to acquired immunity and protection against inflammation. As a powerful modulator of inflammatory and immune responses, Lf supports protection against both microbial infections such as septic shock and inflammatory diseases such as arthritis, chronic hepatitis, and cancer [354–356]. The modifying activity by Lf is connected to its capability to interfere with both specific cell receptors on a wide range of epithelial and immune cells [357] and pro-inflammatory bacterial components like LPS [358].

At the molecular level, the modulatory characteristics of Lf are mediated through iron binding and interactions with a multitude of compounds such as LPS. At the cellular level, Lf modifies the migration, maturation, differentiation, activation, proliferation, and function of immune cells. Some possible mechanisms include modulation of NF-κB and MAP kinase signaling [354]. Lf has been shown to increase the accumulation of neutrophils to sites of damage, support cell-to-cell interaction by promoting "stickiness," promote phagocytosis by polymorphonuclear leukocytes (PMNs) and monocyte/macrophages, support motility and superoxide production, reduce the release of pro-inflammatory cytokines, increase the number and activity of NK cells, and promote the maturation of lymphocytes [359–363].

In addition, a mechanism underlying antitumor effect of Lf is regulation of NK cell activity [328, 364] and inhibition of vascular endothelial growth factor (VEGF)-mediated angiogenesis [365]. It was reported that Lf has a significant effect on NK cell cytotoxicity and target cell sensitivity to lysis in hematopoietic and breast epithelial cell [328]. Other studies reported inhibition of tumor growth and lung colonization by B16-F10 melanoma experimental metastasis in mice treated with human Lf through increased NK cell activity [351].

Rodent cancer models have shown enhancement of intestinal immune homeostasis following oral administration of Lf. In particular, increased activation of NK cells, $CD4^+$ T-cells, and $CD8^+$ T-cells was demonstrated after Lf administration [348, 349].

In vivo oral administration of bLf enhanced NK cell activity and $CD4^+$ and $CD8^+$ T-cells in tumor-bearing mice [349, 350, 362] and also increased $CD3^+$ and $CD4^+$ T-cells in immunocompromised mice [366]. Activation of $CD4^+$ T-cells induces the generation of plasma B-cells, memory B-cells, and antibodies [367, 368]. Moreover, $CD4^+$ activation improves macrophage function, by inducing the release of cytokines [346]. Further activation of $CD4^+$ T-cells induces the generation of cytotoxic $CD8^+$ T-cells, which would destroy virus-invaded cells, cancer cells, and intracellular bacteria, as indicated in experimentally induced cancers [369].

Inhibition of Angiogenesis

Administration of bLf was reported to inhibit angiogenesis in rats [365] and mice [370]. In contrast, human Lf promotes angiogenesis [371]. BLf may inhibit angiogenesis through inhibition of IL-18 production [372]. Moreover, increased levels of IL-18 raise mucosal and systemic immune responses via cytokine secretion and NK cell activation [373]. In addition, Lf can reduce the levels of pro-inflammatory cytokines such as IL-6 and IL-1β as potent angiogenic inducers [374].

Clinical Trials

Few studies investigated the effect of lactoferrin on the immune system. In one study, 2 g bLf/day for 4 weeks increased phagocytic activity of

PMNs in three participants and increased $CD16^+$ T-cell counts in two of them. There was an augmentation in the percentage of NK cells, the percentage of $CD11b^+$ and $CD56^+$ T-cells, and the $CD16^+$ cell counts [375]. The oral administration of 40 mg bLf equivalent/day for 10 days in healthy participants resulted in an increased percentage of lymphocytes and immature cell forms, concurrent with a reduced percentage of neutrophils, eosinophils, and monocytes. Additionally, TNF-α levels were reduced, while changes in IL-6 were not significant [376]. The oral administration of placebo, 2, 10, or 50 mg of Lf daily, for 7 days in healthy subjects exhibited a significant, though transient, increase in the number of immature neutrophils and a significant reduction in the release of IL-6 and TNF-α by peripheral blood cells [377]. It has been suggested that a function of Lf could be to modify inflammatory reactions through the regulation of cytokine generation [378, 379].

Antitumor Immunity and Dietary Components

About ten plant-derived anticancer drugs are currently approved. They can be classified into four main classes of compounds: *Vinca* (or *Catharanthus*) alkaloids, epipodophyllotoxins, taxanes, and camptothecins. There are also a large number of phytochemicals subject to various phases of clinical trials, such as curcumin, epigallocatechin gallate (EGCG), soy isoflavones, etc. These compounds have shown anticancer effects both in vitro and in vivo. Some of them are discussed in the following section.

Resveratrol

Resveratrol is a polyphenol belonging to the stilbene class of phytochemicals. It is found in several plant species including grapes, peanuts, mulberries, cranberries, and other fruits [380, 381]. Resveratrol was found to be most abundant in the skin of grapes. It has been reported to block various cancer-related proliferative pathways making it a hopeful anticancer therapeutic candidate [382, 383]. A plant with considerably high content of resveratrol, *Polygonum cuspidatum*, is highly used in traditional Chinese medicine (TCM) to treat inflammation and cancer [384]. In 1997, resveratrol was first demonstrated to delay cancer initiation, promotion, and progression [385]. It is already used in clinical settings because of its antitumor cancer and chemopreventive activities [386]. Ongoing trials are investigating the possible effect of resveratrol on human cancers. Most clinical trials are testing the anticancer effects of resveratrol in CRC including NCT00256334, NCT00578396, NCT00920803, and NCT00433576. Two trials in GI cancers (NCT01476592) and thyroid cancers are assessing the effect of resveratrol on notch-1 signaling. The anticancer effect of resveratrol has also been investigated in leukemia, lymphoma, multiple myeloma, and prostate, breast, brain, and other nervous system cancers. In a bone cancer pain model, resveratrol was recently proposed to have palliative effects by blocking spinal glial activation and downregulating CX3CR1 [387].

Nuclear Factor-κB Pathway

Resveratrol has been shown to have anti-inflammatory and antitumor effects [388]. Resveratrol blocks cell proliferation and induces apoptosis in various cancer cell lines, such as breast, prostate, colon, and ovarian cancer cells [389]. The inhibitory effects of resveratrol on tumor growth have been attributed to its anti-inflammatory activity [389]. Aberrant regulation of NF-κB has been associated with cancer and autoimmune diseases. NF-κB is used by cells as a regulator of genes that control cell proliferation and cell survival. Many different types of human malignancies showed dysregulation of NF-κB. Resveratrol suppresses NF-κB activity mainly through blocking NF-κB inhibitor kinase (IKK) in murine and human macrophage cells along with downregulation of AP-1 [390, 391]. Resveratrol can downregulate NF-κB-induced gene products involved in inflammation, such as iNOS and COX-2, matrix metalloproteinase (MMP)-3, MMP-9, and vascular endothelial growth factor (VEGF) in macrophages and vari-

ous cancer cells [392, 393]. NF-κB-mediated transcriptional activity stimulated by EGF and TNF-α was effectively blocked by resveratrol in prostate cancer cell lines [394]. Resveratrol treatment in human multiple myeloma cell line inhibited proliferation by decreasing proliferative and antiapoptotic factors. The effect, which was mediated through suppression of NF-κB, potentiated the effects of bortezomib and thalidomide [395].

MAPK phosphatase 5 (MAPK5) is a potent inhibitor of cellular inflammatory responses because it can inhibit the enzymatic activation of MAPK, one of the upstream kinases that control the activation of NF-κB [396]. It has been reported that resveratrol could upregulate MAPK5 and block p38 pathway in prostate cancer cell lines [397]. Furthermore, resveratrol can inhibit NF-κB by blocking the upstream activator PKCδ and by activating the inhibitor SIRT1 [398].

Anti-inflammatory Implications: Focus on COX-2

Resveratrol is a potent COX suppressor, which has been confirmed in different in vivo and in vitro studies. Resveratrol can inhibit COX-2 activity through direct binding or suppression of transcription factors [399]. Resveratrol counteracts the proliferation of CRC and MCF-7 breast cancer cell line through affecting p53-COX-2 pathway. In vivo studies confirmed that resveratrol in dietary levels leads to a reduction in the formation of DMBA-induced mammary tumors through inhibition of COX-2-, MMP-9-, and NF-κB-mediated tumor cell proliferation [400].

In an interesting study, resveratrol was shown to prevent apoptosis induced in human leukemia K562 cells by H_20_2. In fact, resveratrol reversed the elevation of leukotriene B4 and prostaglandin E2 induced by H_20_2 challenge through inhibition of 5-lipoxygenase, COX, and peroxidase activity of prostaglandin H synthase [401].

Other Inflammatory Pathways

Resveratrol is also able to suppress the expression of hypoxia-inducible factor-1α (HIF-1α) through inhibition of MAPK and increased degradation of HIF-1α protein via the proteasome pathway. Resveratrol also suppressed VEGF through inhibition of HIF-1α [402, 403].

Recent studies have discussed the role of microRNAs (miRNAs) in mediating the anti-inflammatory effects of resveratrol. Resveratrol can decrease the secretion of pro-inflammatory cytokines (e.g., IL-1, IL-6, IL-8, and TNF-α), the expression of adhesion proteins including intercellular adhesion molecule (ICAM)-1, and the expression of leukocyte chemoattractants, such as MCP-1 [404]. Resveratrol suppressed TNF-α-induced signaling pathways both via NF-κB activation and by increasing transcriptional activity of p65 [405]. In addition, resveratrol induced the expression of Egr-1 from its chromosomal locus. Egr-1 has demonstrated antitumor effects upon experimental increase in TNF-α [406]. The control of transgenic expression via activation of Egr-1 promoter by resveratrol may sensitize cancer cells, expanding the use of adenovector Ad.Egr-TNF in patients resistant to radiation or chemotherapy, suggesting a new means for development of inducible gene treatments [406]. In prostate cancer cell line, resveratrol increased the production of ROS and expression of pro-apoptotic factors including TRAIL [383]. In a mouse model with prostate cancer, resveratrol significantly reduced cell proliferation and the expression of growth factors and their receptors [383].

In human colon cancer cells resistant to the cytotoxic effect of resveratrol, resveratrol was able to sensitize tumor cells to TNF, anti-CD95 antibody, and TRAIL-mediated apoptosis and led to activation of a caspase-dependent death pathway [407]. Indeed, resveratrol sensitized lung cell lines to TNF-induced apoptosis by modifying sirtuin effect, and this activity is consistent with its ability to induce activity of Sirt1, a known NF-κB transcription repressor. Polyphenols can augment TRAIL expression in gastric cancer cell lines and are able to increase TRAIL-mediated apoptosis in various cancer types such as human melanoma, prostate carcinoma, pancreatic cancer, malignant glioma, prostate carcinoma, hepatocellular carcinoma, gastric carcinoma, neuroblastoma cells,

Burkitt's lymphoma, ovarian cancer cells, renal cancer cells, and colon cancer cells [408].

Resveratrol inhibited epithelial-mesenchymal transition (EMT) of pancreatic cancer cells by downregulating both the PI3K/AKT/NF-κB pathway and the EMT-related gene expression (E-cadherin, N-cadherin, vimentin, MMP-2, and MMP-9), which are essential for cancer cell motility and metastasis [409, 410]. In human pancreatic cancer cell, resveratrol treatment induced transcriptional upregulation of macrophage inhibitory cytokine-1 (MIC-1), which has antitumor activity [411]. Resveratrol is capable of blocking mediators of metastasis including lysophosphatidic acid (LPA), transforming growth factor (TGF), and focal adhesion kinase (FAK) in cancer cells like ovarian carcinoma cell. LPA induces the expression of HIF-1α and VEGF and thereby promotes cell migration [403]. Additionally, resveratrol can inhibit TGF-β1 and so cause inhibition of cell adhesion, migration, and invasion of lung cancer cells in A549 lung cancer cells [412, 413]. Resveratrol could diminish cell proliferation by influencing autocrine growth modulator pathways in breast cancer cells. For instance, it can increase the expression of the growth inhibitor TGF-ß2 without affecting the expression of TGF-ß1 and TGF-ß3 [414, 415]. Resveratrol may be used to modify the immunological reaction in tumor microenvironment, including inhibition of T-cell proliferation, reduction of IFN-γ and IL-4 secretion, downregulation of B-cell proliferation and therefore production of IgG1 and IgG2a isotypes, and suppression of CD28 expression on $CD4^+$ T-cells and CD80 on macrophages [416].

Other possible antitumor effects from an immunological viewpoint include downregulation of MHC class I and II molecules; induction of tolerogenic DC phenotype; downregulation of the ability of bone marrow (BM)-derived DC to produce IL-12 p70 [417]; increasing the production of TNF-α, IL-12, and IL-1β in response to LPS stimulation; enhancing the secretion of IL-10; suppression of mucosal and systemic $CXCR3^-$-expressing effector T-cells and inflammatory cytokines in the colon [418]; and inhibition of the suppressive activity of FoxP3-expressing T_{REG} cells among $CD4^+CD25^+$ cells [416, 419–423].

Low-dose resveratrol was able to enhance cell-mediated immune responses by promoting T_H1 cytokine production, macrophage function, and also APC-induced IL-12 and IFN-γ production [424]. Resveratrol treatment downregulated the frequency of T_{REG} cells in EG7-bearing C57BL/6 mice. In addition, both $CD4^+CD25^+FoxP3^+$ to $CD4^+CD25^+$ cell ratio and $CD4^+CD25^+$ to $CD4^+$ cell ratio were reduced concurrently by resveratrol in a dose-dependent manner [425]. Resveratrol has been mostly investigated as an adjuvant agent combined with conventional chemotherapeutics to prevent or reduce the risk of multidrug resistance. Resveratrol strengthened the antitumor effect of 5-fluorouracil (5-FU) on CRC cells, thereby enhancing chemosensitization and reducing drug resistance [426]. For example, resveratrol sensitized various human cancer cell lines to chemotherapeutic agents such as doxorubicin, cytarabine, actinomycin D, Taxol, and methotrexate by suppressing the expression of survivin and enhancing apoptosis. The mechanism by which resveratrol chemosensitizes cancer cells includes inhibition of tumor cell proliferation, metastasis, and angiogenesis and induction of tumor cell apoptosis through inhibition of related signaling pathways, such as SIRT1, signal transducers and activators of transcription 3 (STAT3), Hh, AMPK/YAP, PTEN/PI3K/AKT, and NF-κB [427–430]. Moreover, NF-κB activation could upregulate the levels of some antiapoptotic genes, including TNF receptor-associated factor 1 (TRAF1) and TRAF2 [431]. Administration of resveratrol in $IL\text{-}10^{-/-}$ mice induced immunosuppressive $CD11b^+Gr^-1^+$ MDSCs in the colon. The stimulation of immunosuppressive $CD11b^+Gr^-1^+$ cells by resveratrol during colitis is distinctive and offers a novel mode of anti-inflammatory action of resveratrol [418].

AhR and Nrf2 as Inflammation-Environment-Diet Molecular Crossroads

AhR functions as a modulator of immunity (inflammation) and reaction to xenobiotics on one hand and acts as a mediator of effect of res-

veratrol on the other hand. Moreover, it is interesting to mention that the effect of resveratrol is frequently associated with upregulation or activation of Nrf2 [432, 433]. Resveratrol also augments the activation of nuclear factor E2-related factor-2 (Nrf2), which is followed by activation of antioxidant response element (ARE). Resveratrol has been reported to increase the expression of heme oxygenase-1 (HO-1) via Nrf2 activation in PC12 cells. In leukemia K562 cells, resveratrol increased NQO1 expression and stimulated Nrf2/Keap1/ARE binding to NQO1 promoter [434]. It also restored glutathione levels in human lung cancer A549 cells treated with cigarette smoke extracts by increasing the Nrf2-induced GCL expression [435]. There are some dietary AhR antagonists such as genistein, kaempferol, and EGCG. One recent agonist of AhR causes a number of anti-inflammatory responses in vitro and in vivo [436, 437]. Resveratrol assists Nrf2 and AhR in maintaining homeostasis against inflammatory insults, which may be involved in tumorigenesis. For instance, resveratrol caused inhibition of TCDD-induced recruitment of AhR and ARNT to the CYP1A1/CYP1A2 and CYP1A1/CYP1B1 promoter in hepatic cancer (HepG2) and breast cancer cell (MCF-7), respectively [438]. Therefore, resveratrol could modulate the activity of some cytochrome P450 enzymes and so act as chemopreventive compound by limiting activation of pro-carcinogens.

Immune Surveillance

Downregulation of tumor immunosurveillance involves resistance to apoptosis, production of immunosuppressive cytokines, and reduced expression of MHC class I antigens. Particularly, macrophages inhibit or increase the growth and spread of cancer based on their activation state. Synthetic resveratrol analog, HS-1793, significantly increased IFN-γ-secreting cells in splenocytes and also decreased $CD206^+$ macrophage infiltration [439]. The local augmentation of IFN-γ modified the status of tumor-associated macrophages (TAMs) associated with the cancer microenvironment that occurred coincident with increased levels of pro-inflammatory and immunostimulatory cytokines (CD206, CD204, IL-10, TGF-β, EGF, and MMP-9) and decreased levels of IL-6 and immunosuppressive and tumor progressive mediators [439]. However, further studies are necessary to clarify the mechanism of action of resveratrol. Oral resveratrol significantly improved survival of lymphocytic leukemia L1210 cell-bearing mice through normalization of CD4/CD8 ratios and enhancement of NK cell activities and antisheep RBC titers. Furthermore, resveratrol suppressed cellular content, release, and mRNA expression of IL-6 [440].

CD95 Signaling Pathway

The Fas receptor (FasR), also known as CD95, Apo-1, and tumor necrosis factor receptor superfamily member 6 (TNFRSf6), leads to apoptosis. Resveratrol induces tumor cell death by modifying the levels of Fas and its ligand, FasL [441–443]. Earlier studies have reported this effect in leukemia cell lines [441] and colon [442] and breast carcinoma cells [443]. A study in multiple myeloma and T-cell leukemia cells emphasized the role of Fas/CD95 signaling in lipid rafts in anti-myeloma and anti-leukemia chemotherapy [444]. Using leukemia lines derived from patients with malignancies pro-B t(4;l1), pre-B, and T-cell ALL, it has been demonstrated that resveratrol could induce extensive apoptotic cell death not only in CD95-sensitive leukemia lines but also in B-lineage leukemic cells that are resistant to CD95 signaling [445]. Altogether, the CD95-CD95L system and its chemotherapeutic and chemopreventive potential are interesting enough to be considered in anticancer drugs [446].

Resveratrol and Its Interplay with NK Cells

Direct influence of resveratrol on NK cells and their killing ability on different levels has been reported in previous studies. Resveratrol exerts concurrent effects on NK cells and other immune cells like $CD8^+$ and $CD4^+$ T-cells [447]. The killing ability of NK cells against human immortalized myelogenous leukemia K562 cells was increased after resveratrol treatment. Furthermore, a dose-related inhibition of lytic activity was reported at high concentrations of

resveratrol. Another study reported blocking of viability and enhanced apoptosis of NK cells upon incubation with high concentrations of resveratrol, whereas low concentrations of resveratrol resulted in upregulation of NKG2D and IFN-γ and increased killing of leukemia K562 target cells by NK cells [448]. Higher vulnerability of human lymphoblastoid T-cells (Jurkat cells) to cytotoxic effect of resveratrol also has been reported [449, 450]. Resveratrol in NK-92 cells increased the expression of perforin and phosphorylation of ERK-1/ ERK-2 and JNK, which are known to contribute NKG2D-mediated cytotoxicity [450]. Intragastric administration of resveratrol enhanced the killing ability of isolated spleen NK cells against mouse 51Cr-labeled lymphoma [451].

Furthermore, resveratrol increased the expression of NKG2D ligands on human promyeloblastic leukemia KG-1a cells, thus offering two mechanisms to potentiate cytokine-induced killer cells (CIK, a mixed phenotype between T-cells and NK cells) [452]. Stimulation of KG-1a cells susceptible to CIK-mediated cytolysis occurs via an increase in cell surface expression of NKG2D ligands and receptor DR4 and also via suppression of DcR1 along with activation of the TRAIL pathway [452]. Resveratrol may modify this axis, thereby promoting tumor surveillance by the innate immune system. Resveratrol is further capable of sensitizing cells of various cancer types, including neuroblastoma, medulloblastoma, glioblastoma, melanoma, T-cell leukemia, and pancreatic, breast, and colon cancer, to TRAIL-induced apoptotic cell death [453, 454]. In essence, resveratrol can upregulate the expression of receptors DR4 and DR5 in human prostate cells [455], thus enhancing TRAIL sensitivity and possibly facilitating NK cell-mediated killing activity. Resveratrol also considerably increased CD95L expression on HL-60 human leukemia cells and on T47D breast carcinoma cells [446], which would further help in NK cell-mediated apoptosis. Resveratrol has another therapeutic potential in defeating aggressive NK cell leukemias and lymphomas through inhibition of constitutively active signal transducers and activators of transcription 3 (STAT3) signaling [456].

Possible Interaction with T_{REG}

Resveratrol is also able to decrease the cell number and function of immune T_{REG} cells. High-dose IL-2 (HDIL-2) led to T_{REG} expansion, but it was inhibited by resveratrol which could abrogate the toxic effects of HDIL-2 on endothelial cells [457]. Resveratrol was also involved in suppression of TGF-β secretion from the spleen of tumor-bearing mice and concurrent increase in IFN-γ expression in $CD8^+$ T-cells, together resulting in immune stimulation [423]. Despite its immunostimulatory activity, IFN-γ is also reported to induce T-cell inhibitory molecule IDO in many cell types, including APCs [458]. Resveratrol can inhibit IFN-γ-induced IDO expression in bone marrow-derived dendritic cells (BMDCs) [459]. Resveratrol-mediated inhibition of EG7 thymoma tumor growth was dependent on IDO through inhibition of the Jak/Stat pathway and protein kinase C-δ (PKCδ), which both need IFN-γ-mediated IDO expression [460]. Resveratrol combined with thymoquinone was reported to decrease tumor size and increase serum levels of INF-γ in breast cancer tumor-bearing mice [461].

Regulatory B-Cells

The most fascinating antitumor immune mechanism of action of resveratrol is through inhibition of tumor-induced regulatory B-cells (tBregs), which inhibit breast cancer metastasis [462, 463]. Low concentrations of resveratrol significantly decreased tBregs (defined as CD25+ $CD81_{high}$ cells within the CD19+ population) and Treg populations in mice. It must be emphasized that resveratrol had no effect on MDSCs in the tumor models [462, 463].

Modulation of Mucosal Integrity: Implication of MUC2 and MUC1

Oral administration of resveratrol activated the expression of MUC2 and inhibited the expression of MUC1 through modification of the enzymes that initiate *o*-glycosylation of mucin in 1,2-dimethylhydrazine (DMH)-treated rats. Therefore, resveratrol assists in maintaining integrity of the colon [464] through modification of enzymes that initiate *o*-glycosylation of mucin [465].

Curcumin

Curcumin is the active polyphenol derived from the *Curcuma longa* plant, which is also known as turmeric. Two curcuminoids, demethoxycurcumin and bisdemethoxycurcumin, exhibit antiproliferative activity on various cancer cells [466–468]. Curcumin has been reported to be effective as a therapeutic and preventive agent for cancer of the colorectum, liver, lung, pancreas, breast, ovary, uterine, bladder, prostate, kidney, and brain, non-Hodgkin lymphoma, and leukemia [469–471]. It can exert effective immune responses and cytotoxic activity on different cancer cell lines, such as YAC-1 murine lymphoma, human HL-60 leukemia, and MDAMB breast carcinomas [472]. In vivo studies have shown immunostimulatory effects of curcumin [472, 473].

Mechanisms of Action of Curcumin: A Role for NF-κB

Inflammation has been implicated in the different steps of tumorigenesis, including induction, survival, proliferation, invasion, and metastasis. Primary studies described curcumin as an effective modulator of inflammation [474]. The direct effect of curcumin on inflammation has been attributed to inhibition of NF-κB signaling. NF-κB is a transcription factor that controls the expression of several genes involved in growth, inflammation, carcinogenesis, and apoptosis [475]. Curcumin can inhibit this pathway through downregulation of the activation of IκBα kinase (IKK), phosphorylation and degradation of IκBα, and phosphorylation and nuclear translocation of the p65 subunit [476, 477] in several cancer and premalignant cell types [478, 479]. The results were confirmed in cells isolated from patients with multiple myeloma [480] and advanced pancreatic cancer [481]. As NF-κB regulates several pathways like MMP, inhibition of NF-κB leads to downregulation of molecular events implicated in other signaling pathways and thus offers different opportunities for prevention and treatment [482] as indicated in several studies [483–485]. For instance, curcumin suppresses the production of CXC chemokines through inhibition of the NF-κB pathway [486]. In addition, the expression of multiple NF-κB-regulated gene products, including IL-6, IL-8, MMP-9, COX-2, and CCL2, was reduced with curcumin. Furthermore, curcumin also affects other inflammatory markers and subsequent tumor promotion [474], such as inflammatory cytokines (TNFα, IL-1, IL-6, and IL-8) [487, 488], inflammatory transcription factors (STATs), and inflammatory enzymes (COX-2, 5-lipoxygenase (LOX)) [489]. Curcumin can inhibit different invasion, cell adhesion, and extracellular matrix molecules, such as matrix metalloproteinase, CCRX4, COX-2, ELAM1, and ECAM1 [490].

Curcumin can inhibit iNOS induction and scavenge NO radicals in breast cancer cells in the promotion phase of carcinogenesis [491, 492]. TNF-α is a direct stimulator of aerobic glycolysis in malignant breast epithelial cell lines, and interestingly curcumin could reverse this effect of TNF-α [493].

Curcumin strongly prevents the generation of hematogenous metastases through suppression of the expression of NF-κB/activator protein-1 (AP-1)-dependent MMP, Egr-1, [494], and other genes involved in cell adhesion (chemokines, TNF, and Cox-2) [495, 496]. On the other hand, inhibition of NF-κB reduced the expression of prometastatic chemokine (C-X-C motif) ligand (CXCL) 1 and 2, which, in turn, decreased the expression of chemotactic receptor CXCR4 along with other prometastatic genes [486]. Decreased expression of matrix metalloproteinases, ICAM-1, and CXCR4 along with suppressed cell migration and invasion has been reported in breast cancer cell line [497].

Effect of Curcumin on Matrix Metalloproteinase-9 (MMP-9)

MMPs have been considered as one of the important molecules assisting tumor cells during metastasis [498, 499]. MMP-9 shows a major role in the breakdown of extracellular matrix in disease processes such as tumor metastasis [500]. However, curcumin shows a vital role in the inhibition of MMP-9 activities and cell invasion through downregulating NF-κB [501].

Restoration of $CD4^+$ and $CD8^+$ T-Cell Populations and Increased T_H1-Type Response

Curcumin could efficiently restore $CD4^+$ and $CD8^+$ T-cell populations in the tumor microenvironment and prevent depletion of central memory and effector memory T-cells in peripheral circulating blood and lymph nodes and at the tumor site. In this manner, curcumin can drive T_H2 cytokine response toward a T_H1-type response [502, 503]. However, results regarding this point are not consistent. These contradicting reports suggest that curcumin may be implicated in complex signaling pathways, leading to an enhanced antitumor immunity. Curcumin is able to reverse the decrease in the levels of T_H1 cytokines such as IFN-γ and the increase in T_H2 cytokines such as IL-4 during cancer progression. Although some studies suggest different outcomes in which curcumin favors a T_H2-type response, there are studies reporting that curcumin supports cancer regression by restoring T_H1 immune responses [504, 505]. The elevated population of tumor-infiltrating lymphocytes leads to increased tumor cell killing. A delayed NK cell cytotoxic response and a simultaneous increase in IL-12 secretion in the serum of treated mice were reported after curcumin treatment [472]. Curcumin might prevent T-cell depletion by inhibiting secretion of suppressive molecule PGE-2 by tumor cells [506]. PGE-2 inhibits expression of the cytokine receptor gamma chain (γc) in T-cells, which causes deactivation of the Jak/Stat pathway and reduces expression of pro-survival protein Bcl-2 in T-cells. Curcumin through inhibition of PGE-2 would restore γc and Bcl-2 expression in T-cells and so support T-cell survival and differentiation [507].

It has been reported that curcumin arrests maturation of DCs and stimulates a tolerogenic phenotype that next promotes functional $FoxP3^+$ T_{REG} cells. It has been shown that DCs generated in the presence of curcumin had minimal CD83 expression, suppressed levels of CD80 and CD86, and reduced expression of both MHC class II and CD40 in comparison with those DCs that were differentiated in the absence of curcumin. Curcumin enabled arrested maturation of DCs and induced a tolerogenic phenotype [473, 503, 508, 509]. An increase in the generation of $CD4^+CD25_{high}CD127_{low}$ $FoxP3^+$ T_{REG} cells that exert suppressive functions on naïve syngeneic T-cells has also been observed with curcumin treatment [508]. Curcumin prevented loss of effector and memory T-cells, extended central memory T-cell (TCM)/effector memory T-cell (TEM) populations, reversed T_H2 immune response, and attenuated tumor-induced inhibition of T-cell proliferation in tumor-bearing hosts [510].

Reduction of T_{REG} Cell Population

$CD4^+CD25^+FOXP3^+$ T_{REG} cells play an important part in the tumor immune evasion process. Progression of tumor coincides with an elevation in T_{REG} cells, which secrete immunosuppressive cytokines like TGF-β and IL-10 and express the high-affinity IL-2 receptor CD25, which sequesters IL-2 from the tumor milieu. It must be noted that IL-2 is necessary for proliferation of other T-cells, and so its reduction leads to effector T-cell apoptosis [511, 512].

Curcumin is able to block IL-2 signaling by decreasing accessible IL-2 and high-affinity IL-2R, as well as interfering with IL-2R signaling. Curcumin has also been demonstrated to block IL-2-induced phosphorylation of STAT5A and Janus kinase (JAK), but not JAK1, suggesting inhibition of critical proximal events in IL-2R signaling [513].

Curcumin can efficiently decrease T_{REG} cell number and the levels of IL-10 and TGF-β [514]. Other studies also reported similar results, suggesting that treatment of $CD4^+CD25^+$ T_{REG} cells with curcumin decreased their immunosuppressive activity [472, 515]. FOXP3 and CTLA-4 are essential for T_{REG} function [516]. It has been shown that curcumin can reduce the expression of CTLA-4 and FOXP3, two key transcription factors that are involved in regulating transcriptional program of T_{REG} cells and are necessary for development and function of T_{REG} [516]. Curcumin inhibited T_{REG} function by blocking cell-cell contact [514].

Increased oxidative stress in tumor inhibits NF-κB activity in thymic T-cells, which makes

T-cells vulnerable to apoptosis by TNF-α secreted from tumor cells [517, 518]. Curcumin through inhibition of oxidative stress and reduction of surface expression of TNF-α receptor (TNFR1) on thymic T-cells of tumor-bearing mice [517] prevents reduction of NF-κB activity in thymic T-cells.

Curcumin treatment can inhibit the tumor suppressor indoleamine-2,3-dioxygenase (IDO) as well as the immunosuppressive cytokine TGF-β, thereby promoting T-cell cytotoxic activity [519]. IDO exerts its immune suppressive effect by catalyzing tryptophan, which is necessary for T-cell proliferation [520].

Reduced T-Cell Apoptosis

Prolonged injections of curcumin maintained levels of T_H1 cytokines, NK cell cytotoxic activity, and production of ROS and NO by macrophages [472]. Tumor-bearing mice treated with curcumin showed improvement in immune cell numbers and tumor regression, consistent with inhibition of apoptosis in thymocytes and splenocytes [502]. Curcumin reduced T-cell apoptosis in tumor-bearing mice through activation of the JAK3-STAT5a pathway in T-cells and subsequent restoration of BCL-2 levels [506]. Inhibition of tumor-induced thymic atrophy by restoring the activity of NF-κB pathway also has been reported after curcumin treatment [517]. Eventually, although low dose of curcumin stimulated effective antitumor response by escalating $CD8^+$ cytotoxic T-cells and IFN-γ production, higher dose of curcumin was harmful for T-cells [473].

STAT Pathway

STATs modify tumor-promoting inflammation via collaboration of other transcription factors [474, 521]. Curcumin inhibits the expression of STATs, especially nuclear STAT3, STAT5a, and STAT5b in human chronic K562 leukemia cells. When used as a pretreatment, curcumin inhibited IFN-γ-induced phosphorylation of nuclear STAT1 and STAT3 [522, 523] in human K562 leukemia cells and STAT1 in human lung A549 carcinoma and melanoma cells [524]. Following treatment with curcumin and its analogs such as GO-Y030 [525], FLLL1, and FLLL12 [526], similar downregulation of STAT3 activation was also observed in Hodgkin's lymphoma [483], T-cell leukemia [527], head and neck squamous cell carcinoma [528], multiple myeloma cells [529], and $CD138^+$ cells derived from multiple myeloma patients [480].

Curcumin alone or in combination with epigallocatechin gallate (EGCG) blocked STAT3 phosphorylation and undermined the interaction between STAT3 and NF-κB through suppression of CD44 expression, together diminishing breast cancer stem cells (bCSCs) population [530, 531].

COX-2

Curcumin is an effective inhibitor of COX-2 in several cancer types [532–535]. Moreover, curcumin can inhibit COX-2 expression in PBMCs of patients with pancreatic cancer [481] and on oral premalignant cells [476]. Furthermore, fluorocurcumin, a curcumin analog, has been reported to suppress NF-κB and PGE-2, and so it was suggested to be a potential agent against COX-2-overexpressing tumors [536]. Curcumin downregulates the expression of EGFR in pancreatic and lung adenocarcinoma expressing COX-2 [537] through inhibition of ligand-induced activation of EGFR [538] or through decreasing the transcriptional activity of Egr-1.

Synergy with Drugs

Several studies investigated the potential synergistic activity of curcumin in combination with conventional chemotherapeutic agents. Curcumin combined with omega-3 fatty acid could suppress the expression and activity of iNOS, COX-2, and 5-LOX and upregulation of p21 [534] and therefore prevent or even treat pancreatic tumor xenografts [534]. Curcumin would potentiate the effect of paclitaxel-mediated chemotherapy in advanced breast cancer in vitro and in vivo. This effect has been attributed to suppression of NF-κB and serine/threonine Akt pathways, COX-2, and MMP-9 [539, 540]. Reduction of COX-2 is also reported in human colon cancer HT-29 cell lines treated with curcumin combined with 5-FU [541]. Although prostate and breast cancer cells (DU145, PC-3, and LNCaP) are typically resistant to TRAIL-induced apoptosis, they can be

sensitized with curcumin. This mixture stimulates inhibition of active NF-κB and other pathways that also were confirmed by preclinical studies performed in PC-3- and TRAIL-resistant LNCaP xenografts [542–545].

Interleukins

M2 macrophages and T_{REG} cells are two main leukocytes that secrete the anti-inflammatory cytokine IL-10 [546]. M2 macrophages play a critical role in tumor progression and development consistent with increased IL-10 concentrations in various solid tumors. M1 macrophages produce IL-12, an antitumor chemokine. So, the IL-10/IL-12 ratio might predict tumor progression [547]. IL-10 could inhibit several components of immunity, including co-stimulatory and adhesion molecules (CD86 and CD54) that induce an inflammatory response in macrophages [548] and cytokines such as IL-12, IL-23, IL-1β, and TNF-α that are involved in inflammatory immune response [548–550]. IL-10 enhances the activation and proliferation of B-cells and antibody production. Maintaining the T_H1/T_H2 balance is one of the important facets of immunomodulatory action of IL-10. IL-10 has potential anticancer effects which may be mediated through reductions in the production of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 that play important roles in neovascularization as well [551, 552].

Curcumin can increase the frequency of M1 macrophages while decreasing the frequency of M2 macrophages, resulting in a decrease in the expression of STAT3, IL-10, and arginase-1 in mice with metastatic breast cancer. Through reduction in IL-10 levels, curcumin can also block Janus kinase-STAT signaling and increase tumor cell apoptosis [547].

Curcumin can act as an antitumor agent through prevention of tumor-induced T-cell depletion by increasing the production of IFN-γ, an important T_H1 cytokine for the production and function of peripheral T-cells, and IL-2, which is crucial for differentiation of cytotoxic T-lymphocytes. Antitumor activity of curcumin could also be due to the restoration of activated/effector $CD4^+$ and $CD8^+$ T-cells, induction of tumor-infiltrating lymphocytes (TILs), and upregulation of IFN-γ expression. Curcumin also reduces the levels of TGF-β and IL-10 in T_{REG} cells and decreases the number of T_{REG} cells in the tumor microenvironment [503].

IL-8 was overexpressed in ER-negative cancer cells and showed a potential correlation with tumor progression and invasiveness. Overexpression of IL-8 is linked to progression and metastasis of cancer cells in the colon [553]. Treatment of colon cancer cells with curcumin inhibited neurotensin-induced gene expression and protein secretion of IL-8, thereby preventing migration of cancer cells [554]. Curcumin also reduced the expression of IL-8 in human pancreatic cancer cell line [555].

Exosomes and Immune Suppression in Cancer

Exosomes are small particles that are released from normal and neoplastic cells and are present in serum and other bodily fluids. Exosomes have various molecules including signal peptides, mRNA, and microRNA. Tumors also secrete exosomes which are immune suppressive bodies containing a distinct set of proteins that can affect the immune system. In cancer, signaling via exosomes affects the immune system through inhibition of T-cell and NK cell functions and an increase in the number and/or activity of immune suppressor cells, including myeloid-derived suppressor cells (MDSCs), T_{REG} cells, and $CD116^+$ HLA-DR−/low cells [556]. Curcumin reduces the inhibitory effects of exosomes on NK cytotoxicity [557]. Of note, curcumin can reverse the tumor exosome-mediated inhibition of NK cell function via the ubiquitin-proteasome pathway [558].

Green Tea and Catechins

Several epidemiological and experimental studies have reported a negative correlation between green tea and development of cancers of the bladder, cervix, breast, esophagus, colorectum, stomach, lung, liver, ovaries, oropharynx, pancreas, prostate, and skin [559]. The health benefits of

green tea could be mostly attributed to catechins, including catechin (C), epicatechin (EC), epigallocatechin (EGC), and epicatechin gallate (EGCG).

Transcription Factors

EGCG has been found to suppress the expression and/or activity of many transcription factors, such as HIF-1α, nuclear STAT1 and STAT3, NF-κB, and AP-1. In addition, different MMPs, including MMP-2, MMP-9, and MMP-14/MT1-MMP, have been downregulated by EGCG [559]. EGCG has been reported to block angiogenesis and decrease xenograft tumor growth via inhibition of IGF-1 through downregulating the protein expression of HIF-1α and VEGF in A549 lung cancer cells [560, 561] and via inhibition of HIF-1α-dependent expression of VEGF, IL-8, and CD31 in other lung NCI-H460 cell lines [562]. EGCG blocked xenograft angiogenesis and tumor growth in gastric cancer cell line BGC-823 [563]. EGCG is also able to inhibit IL-6-induced angiogenesis via inhibition of VEGF expression through downregulating Stat3 activity in human gastric carcinoma AGS cells and SGC-7901 cancer cells [564, 565]. In HeLa cervical cancer cell line, EGCG inhibited cell proliferation and invasion through suppression of MMP-9 gene expression and upregulation of TIMP-1 gene expression [566]. In SW837 CRC cell line, EGCG inhibited tumor growth by downregulating HIF-1α and several major growth factors [567]. In T-24 bladder cancer cell line and SW620 cell line, EGCG inhibited cell adhesion, migration, and invasion through suppression of MMP-9 expression via inhibition of NF-κB signaling pathway [568]. In esophageal TE-8 and SKGT-4 cancer cells, EGCG reduced cell invasion through lessening p-ERK1/p-ERK2, c-Jun, and COX-2 [569].

Overexpression of the human epidermal growth factor receptor-2 (HER2/neu) is linked to poor prognosis in various types of cancer. EGCG blocks activation of these receptors by inhibiting STAT3 and NF-κB activation. EGCG and Polyphenon E (PolyE) have been shown to decrease transcriptional activity of AP-1 and NF-κB promoters and inhibit COX-2 transcription and PGE-2 production in CRC cell lines [570].

Effect of Green Tea on Nuclear Transcription Factor NF-κB

EGCG has been reported to inhibit the activation of NF-κB in H891 human HNSCC cells, MDA-MB-231 human breast cancer cells, PC-9 human lung cancer cells, human colon cancer cells, A431 epidermoid carcinoma cells, and H891 head and neck cancer cells. EGCG decreased lipopolysaccharide (LPS)-induced TNF production in the RAW 264.7 macrophage cell line [571]. Treatment with EGCG and PolyE reduced the levels of inflammatory cytokines, such as TNF-α, in the colon epithelium and also inhibited inflammation-related colon carcinogenesis induced by AOM and DSS injection in a mouse colon cancer model [572].

Regulation of the NF-κB pathway may play a critical role in mediating chemopreventive properties of catechin in prostate cancer cells. Catechin treatment regulates NF-κB gene expression through accumulation of IκBα, repression of NF-κB phosphorylation [573], reduction in IKKα expression, inhibition of IKK activity [574] and proteasome and caspase cleavage of the p65 subunit [575], and reduction in other signaling factors, including RANK and NIK [573]. NF-κB target genes involved in carcinogenesis, including Bcl-2, Bcl-xL, survivin, MMPs, VEGF, uPA, and iNOS [576–578], are also decreased by catechin treatment. Thus, one of the probable mechanisms by which EGCG can exert antitumor effects is through suppression of the NF-κB signaling pathway.

EGCG treatment resulted in decreased COX-2 promoter activity through inhibition of NF-κB activation [579]. AP-1 serves as another potential target for anticancer effects of EGCG [580]. EGCG has been demonstrated to interfere with AP-1-induced transcriptional activity through inhibition of a JNK-dependent pathway [581].

Effect of Green Tea Catechins on Cyclooxygenase and Lipoxygenase

EGCG has been reported to inhibit mitogen-induced COX-2 expression in androgen-sensitive LNCaP and androgen-insensitive PC-3 human prostate carcinoma cells [582]. Pretreatment with green tea catechins inhibited

COX-2 expression induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) in mouse skin and reduced COX-2 expression in the SW837 human CRC cell line, colon epithelium, and LPS-induced macrophages. It has been shown that EGCG decreases the activity of COX-2 after IL-1A stimulation of human chondrocytes [583]. Recent cancer research suggests that development of compounds, which can inhibit COX-2 expression preferably without affecting COX-1, is a hopeful approach for cancer chemoprevention. The inhibition of NF-κB is suggested as a possible mechanism for inhibition of COX-2 expression. EGCG, EGC, and ECG from green tea and theaflavins from black tea have been reported to inhibit lipoxygenase (LOX)-dependent activity by 30–75% [584]. Consumption of green tea and dietary fat modulates 5-lipoxygenase-dependent pathway of arachidonic acid metabolism throughout AOM-induced colon carcinogenesis [585].

Effect of Green Tea on AP-1 Transcription Factor

AP- 1 is another transcription factor including Jun and Fos protein families that regulates expression of gene associated with apoptosis and proliferation. AP-1 has been implicated in cancer development and progression. AP-1 is induced by TNF and IL-1 as well as by a variety of environmental stimulators like UV radiation. Theaflavins and EGCG inhibited ultraviolet B (UVB)-induced AP-1 activation [586] and AP-1-dependent transcriptional activity and DNA binding activity [587, 588]. A previous study in JB6 mouse epidermal cell line demonstrated that EGCG treatment inhibits AP-1 activation and cell transformation and Ras-activated AP-1 activity in the H-ras-transformed cells. EGCG inhibits AP-1 activity through inhibition of JNK but not ERK activation [586]. EGCG or PolyE treatment causes inhibition of AP-1 and NF-κB luciferase reporter activity in the HT29 human colon cancer cell line. These findings indicate that inhibition of the NF-κB and/or AP-1 pathways is a possible mechanism underlying anticancer effects of green tea catechins [589, 590].

Effect of Green Tea on STAT3

EGCG inhibited phosphorylation of EGFR, Stat3, and ERK proteins in human HNSCC cell lines such as YCU-N861 and YCU-H891 [591]. Inhibition of activation of the EGFR, Stat3, and Akt by EGCG treatment has been shown in YCU-H891 HNSCC and MDA-MB-231 breast carcinoma cell lines [592].

EGCG-induced increase in IFN-γ secretion in a previous study has been attributed to an increase in NK and NK T-cell numbers that could be due to induced STAT1 activity. A previous clinical trial on 20 patients with stage IV cancer with a special regime containing soy extract reported increased cytotoxic activity of NK cells and TNF-α secretion [593]. An aggressive combination of immunoactive nutraceuticals was efficient in significantly increasing NK function [593].

Inflammatory Factors

Different studies reported that EGCG is able to inhibit the expression of various inflammatory factors in tumor cells including inflammatory cytokines (IL-8), inflammatory growth factors (insulin-like growth factor 1 (IGF-1) and VEGF), and inflammatory mediators (COX-2 and iNOS). In addition, it can inhibit the expression of chemokines, such as the colony-stimulating factor 1 (CSF-1) and C-C motif chemokine ligand 2 (CCL2). Therefore, targeting different inflammatory factors might play an important role in EGCG-mediated cancer inhibition [559, 594–597].

Modulation of Antitumor Immunity

Green tea has been reported to enhance humoral and cell-mediated immunity, resulting in reduced risk of certain cancers [579]. IDO, an immune regulatory enzyme, is associated with tumor immune escape. EGCG has been reported to downregulate the expression of IDO in human oral and colorectal cancer cells by inhibition of STAT1 function [579], concurrent with increased antitumor immunity. This indicates that EGCG can be a potential regulator of tumor immunity [598, 599].

Myeloid-Derived Suppressor Cells

MDSCs contribute to the negative regulation of immune responses. MDSCs downregulate T-cell

function through generation of arginase, NO, ROS, and peroxynitrate. However, in the tumor microenvironment, MDSCs are able to differentiate into tumor-associated macrophages (TAMs) and express arginase and iNOS and suppress generation of ROS [600, 601]. Besides antigens and co-stimulation, cytokines are required for T-cell activation, proliferation, and maintenance. Recent studies have shown that cytokines (IL-12 or IFN-γ) released by DCs or other APCs can act as the third signal that is responsible for activation, expansion, and appropriate production of effector and memory T-cells [602]. However, the tumor microenvironment cannot supply such inflammatory signals, leading to inappropriate activation of DCs. Furthermore, tumors produce immunosuppressive cytokines such as IL-10 and TGF-β and also increase T_{REG} cell number, which both further dampen proper DC activation [600].

Myeloid cells hamper the function of T- and NK cells. It is well known that tumor-induced T_{REG} cells blunt NK and $CD4^+/CD8^+$ T-cell-mediated immune responses. PolyE is able to promote the differentiation of MDSCs into more mature neutrophil-like cells with hypersegmented nuclei [603]. These cells are unable to inhibit the secretion of IFN-γ from $CD3^+$ splenocytes in vitro. MDSCs were less infiltrated into the neuroblastomas of mice drinking PolyE in comparison with control group. This confirms the hypothesis that catechins hinder the migration of myeloid cells to the tumor site. MDSCs interfere with the antitumor activity of $CD8^+$ T-cells. Intriguingly, another study has reported that EGCG enhances $CD8^+$ T-cell-mediated antitumor immunity as obtained by DNA vaccination. Depletion of immunosuppressive T_{REG} cells by means of a CD4-specific antibody decreases the growth of neuroblastomas in A/J mice [604]. In another report, depletion of $CD4^+$ cells failed to modify tumor growth in neuroblastoma cells of A/J mice, which received PolyE-pretreated MDSCs. These findings possibly show that MDSCs fail to stimulate $CD4^+$ T_{REG} cells when they have been exposed to PolyE. PolyE could be potentially beneficial in cancer patients by antagonizing cells that interfere with antitumor immune responses elicited by immunotherapy [604, 605].

Other investigators suggest the role of immunoregulatory cytokine IL-12 in DNA repairs and induction of cytotoxic T-cells in the tumor microenvironment in skin cancer models [606]. In fact, EGCG inhibits UVB-induced immunosuppression and induces repair in mice through stimulation of IL-12. Mechanisms of green tea for chemoprevention in lung cancer include antioxidant activity, phase II enzyme induction, and inhibition of TNF-α expression. EGCG also inhibits UVB-induced infiltration of leukocytes and APC depletion [603, 606, 607]. In addition, topical application of EGCG has been shown to inhibit UVB-induced angiogenesis while inducing cytotoxic T-lymphocytes ($CD8^+$ T-cells) in skin tumors on SKH-1 mice [608].

Synergistic Effect of EGCG Combined with Other Bioactive Compounds and Chemotherapeutics

Recent studies have found synergistic antitumor effect of EGCG in combination with other dietary bioactive compounds like ascorbic acid, curcumin, 6-gingerol, N-acetylcysteine, panaxadiol, pterostilbene, quercetin, sulforaphane, vitexin-2-o-xyloside, raphasatin, EPA-FFA, and proanthocyanidins. Combination of EGCG with these small molecules can synergistically inhibit cancer growth through enhanced bioavailability of EGCG.

Several studies reported that EGCG could sensitize cancer cells to X-irradiation and ionizing radiation in different cell lines like glioblastomas and promyelocytic leukemia HL-60 cells. In addition, EGCG can also improve the chemotherapeutic effect of various drugs such as paclitaxel, capecitabine, cisplatin, docetaxel, and doxorubicin (DOX). Therefore, considering EGCG as an adjuvant therapy can be a practical and efficient approach for cancer treatment [559].

Ginseng

Ginseng (the root of *Panax ginseng*) is a well-known herbal medicine for the treatment of various disorders. The main active components of

ginseng include a series of tetracyclic triterpenoid saponins (ginsenosides), polyacetylenes, polyphenolic compounds, and acidic polysaccharides [609]. Until now, 38 ginsenosides have been purified from ginseng roots, with seven major ones, namely, Rg1, Re, Rf, Rb1, Rc, Rb2, and Rd, comprising more than 80% of the total available ginseng [610]. Ginsenosides can be classified into three groups: the protopanaxadiol group (e.g., Rb1, Rb2, Rb3, Rc, and Rd), the protopanaxatriol group (e.g., Re, Rf, Rg1, and Rg2), and the oleanane group (e.g., Ro) [611, 612]. The acidic polysaccharides are found to be more biologically active. Preliminary studies showed that the neutral polysaccharides contain antitumor activity [613]. A case-control study in Korean population reported that long-term ginseng intake was associated with a decreased risk of different types of cancers [614]. The main active components of red ginseng for cancer prevention are ginsenosides Rg3, Rh2, Rg5, and PPD, which work synergistically [615, 616].

Acidic polysaccharides of ginseng (ginsan) isolated from the ethanol-insoluble fraction of the *P. ginseng* root have also demonstrated anticancer immune modulatory function [617, 618]. Treatment with ginsan (acidic polysaccharide fraction of ginseng) makes splenocytes isolated from unprimed normal mice to be converted into activated killer (AK) cells, which can induce cytotoxic activity on numerous tumor cells comprising NK-resistant murine mastocytoma cell line P815 and NK-sensitive murine lymphoma cell line YAC-1 [619, 620]. Ginsan can be combined with other immunotherapeutics like IL-2 to enhance antitumor effect. Ginsan can stimulate the production of cytokines IFN-γ, IL-2, IL-1, TNF-α, IL-12, GMCSF, and IL-4 to modify the function of AK cells. Macrophages are also necessary as accessory cells for the production of AK cells by ginsan [619]. The immune phenotype of these cells was described to be $Thy1^+$ (thymocyte and peripheral T-cell marker), $AsGM^+$ (NK cell and basophil marker), $CD4^+$, and $CD8^+$ [619].

Ginsan is able to convert macrophages into an M1 tumor inhibitory phenotype [617] as reported in peritoneal macrophages on murine B16 melanoma and fibroblast L929 cells. Generation of NO and ROS by macrophages is modified by inflammatory cytokines; and ginsan-treated peritoneal macrophages significantly enhance secretion of IFN-γ, TNF-α, IL-1β, and IL-6 [617].

Red ginseng acidic polysaccharide (RGAP) increased cytokine secretion by macrophages but did not stimulate their tumoricidal activity on its own [618]. RGAP combined with recombinant IFN-γ possesses an increased synergistic effect on the cytokine production and phagocytic and cytotoxic capacity of macrophages against murine B16 melanoma cells. Activation of the NF-κB pathway has been postulated to be responsible for this synergistic effect [618].

The red ginseng ginsenoside Rg3 also showed stimulatory effects on macrophages and increased the phagocytic index of peripheral blood macrophages resulting in an improved antitumor effect in a mice model of lung carcinoma [621]. Korean red ginseng (KRG) possesses no effect on the accumulation of MDSCs. However, it might inhibit suppressive function of these cells leading to immune activation mediated by T-cell proliferation and cytokines IFN-γ and IL-2 [622]. Altogether, it must be mentioned that the bioactive constituents of *ginseng* demonstrated favorable anticancer immunotherapeutic effects, which are mainly modified via production of tumoricidal macrophages and AK cells.

Anti-inflammatory Effects

Several ginsenosides have been shown to affect inflammatory signaling pathways, thereby inhibiting cancer development [623]. In a chemically induced mouse model of skin carcinogenesis, topical administration of ginsenoside Rg3 suppressed TPA-induced activation of NF-κB and AP-1 and COX-2 expression, accounting for its antitumor effects [624]. 20(S)-Rg3 can inhibit the production of ROS, but not that of NO, and decrease the production of cytokines, such as TNF-α, IL-1β, IL-6, and PGE-2 in LPS-stimulated Raw 264.7 murine macrophages and human keratinocyte (HaCaT) cells [625]. In MCF-7 cells, ginsenoside Rg1 inhibited MMP-9 activity through NF-κB-mediated suppression of breast cell migration and invasion [626].

Ginsenoside Rg5 is also able to suppress NF-κB activity in a lung inflammation model. Rg5 reduced the expression of COX-2, iNOS, IL-1β, and TNF-α in LPS-stimulated alveolar macrophages through inhibition of IL-1 receptor-associated kinases (IRAKs) and IκB kinase-β (IKKβ), subsequently blocking the phosphorylation and nuclear accumulation of NF-κB [627]. Inhibition of NF-κB and subsequent reduction in IL-8 and PGE-2 also have been demonstrated in human embryonic kidney (HEK)-293 cells and HaCaT keratinocytes [628].

Treatment of human esophageal carcinoma cells with ginsenoside Rg3 reduced expression of VEGF, which was associated with the reduced expression of HIF-1α and COX-2 and diminished NF-κB activity [629]. Rg3 combined with gemcitabine significantly reduced the growth rate of Lewis lung carcinoma cells transplanted in C57BL/6 mice by reducing the expression of VEGF [630].

P. ginseng can inhibit chemically induced aberrant crypt foci in mice maybe through anti-inflammatory activities like inhibition of COX-2. Ginseng can also inhibit MMPs and kinase pathways. In addition, it was demonstrated that ginseng activates PPAR-γ and TGF-β1, which are capable to interfere with the inflammation-to-cancer process. The following anti-inflammatory effects of ginsenosides have been reported in cancer models: inhibition of COX-2 and NF-κB in gastric cancer; inhibition of MAPK, NF-κB, and AP-1 in liver, lung, and breast cancer; and inhibition of iNOS, COX-2, and NF-κB in mammary and liver cancer [631].

Compound K (CK) significantly inhibited the secretion and protein expression of MMP-9. The inhibitory effect of compound K on MMP-9 expression was correlated with decreased MMP-9 mRNA levels and reduced MMP-9 promoter activity [632].

Red ginseng inhibited tumor growth by influencing neovascularization and angiogenesis. The angiosuppressive effect of Rg3 could be due to the differential regulation of MMP-2 and MMP-9 activities [633]. Dose-dependent downregulation of MMP-2 and MMP-9 production by Rg3 is thought to be responsible for the inhibition of endothelial cell invasiveness and angiogenesis [633]. Rg3 effectively abrogated the VEGF-dependent neovessel formation, leading to delayed tumor angiogenesis [634]. In a model for gastritis and gastric cancer, treatment of endothelial cells with KRG significantly reduced the expression of inflammatory mediators, including iNOS, COX-2, IL-8, and IL-1β, and angiogenic factors including IL-6, VEGF, platelet-derived growth factor, and MMPs [618].

Role of microRNA in Inflammation-Related Angiogenesis

Recent researches have highlighted a role for microRNAs (miRNAs) – noncoding short RNA molecules (18 to 23 nucleotides) – in controlling gene expression by directing mRNA degradation or repressing post-transcriptional translation, thereby silencing gene expression [635].

A recent study showed that ginsenoside Rh2 caused upregulation of 44 miRNAs and downregulation of 24 miRNAs in human non-small cell lung cancer cells. Interestingly, affected miRNAs were mostly involved in angiogenesis, inflammation, and cell proliferation [636]. Furthermore, Rh2 suppressed miR-21, miR-27b, and miR-31, all of which exhibit pro-angiogenic effects consistent with the reported anti-angiogenic activities of Rh2 [637]. Ginsenoside Rg3 has been shown to regulate VEGF-induced angiogenic response via miRNA modulation [635]. Red ginseng caused a synergistic effect with drug 5-FU for antiproliferative impact on a human CRC model [638]. Red ginseng significantly potentiated the anticancer activities of epirubicin and paclitaxel; thus, their dose and adverse events could be decreased [639]. Rg3 has been demonstrated to block NF-κB signaling and improve the vulnerability of prostate cancer cells to docetaxel and other chemotherapeutics. Also, protective effect of red ginseng in anticancer drug-induced toxicity was reported to be mediated via the regulation of NF-κB activities [640].

Carotenoids

β-Carotene is the main carotenoid isolated from orange and yellow fruits and vegetables.

Lycopene is the main carotenoid found in red fruits and vegetables. The correlation between the high dietary consumption of carotenoids and low risk of prostate cancer has been frequently investigated. The inhibitory effect of β-carotene on the proliferation of human cancer cell lines (PC-3, DU 145, and LNCaP) has been previously demonstrated [641]. Carotenoids have been investigated for their immune-enhancing effects mostly via induction of NK cell activities and increasing leukocyte cell number, CD4/CD8 ratio, and MHC I expression [642]. The antitumor effect of dietary lutein has been investigated in a mammary tumor-bearing mice model. Lutein showed a stimulatory effect on IFN-γ expression while suppressing the expression of IL-10 in splenocytes [643, 644].

Lycopene is a potent antioxidant that can be used as a protective anticancer agent [645]. The antiproliferative and apoptotic effects of lycopene have been shown in prostate cancer cell line (LNCaP) [646], colon cells (HT-29 and T84), and breast cancer cell lines [647]. Both lycopene and β-carotene have been shown to inhibit metastasis in experimental settings, for example, lung metastasis in B16F-10 melanoma cells in C57BL/6 mice and in human hepatoma SK-Hep1-1 cells. Lycopene also decreases the level of VEGF and MMP [648].

In vitro administration of lycopene effectively reduced inflammatory signaling. Lycopene was able to inhibit the mRNA and protein expression of the pro-inflammatory cytokine IL-8 via inactivation of the NF-κB transcription factor through inhibition of the phosphorylation of IKK and IKB and by decreasing the translocation of the NF-Bp65 subunit from the cytosol to the nucleus. Lycopene also decreased the production of TNF, COX-2, iNOS, and IL-6 [649, 650]. The effects of lycopene were correlated with reduced phosphorylation of COX-2, PGE-2, and ERK1/ERK2 [651]. Lycopene also decreased MMP-7 expression in colon cancer cells. The decrease of MMP-7 expression by lycopene was associated with diminished stability and increased E-cadherin expression, showing that MMP-7 may hydrolyze this adhesion molecule. Furthermore, lycopene decreased MMP-7 and c-myc expression by blocking AKT, GSK3, and ERK1/ERK2 phosphorylation [652].

β-Cryptoxanthin was shown to reduce the gene expression of IL-1α in mouse macrophage RAW 264 cells [653]. Both astaxanthin and canthaxanthin exhibited inhibitory activity in relation to cancer development in the urinary bladder, tongue, and colorectum through downregulation of cell proliferation. Another study demonstrated the anti-inflammatory and antitumor effects of astaxanthin in inflamed colon due to modification of the expression of inflammatory cytokines that are involved in inflammation-associated carcinogenesis [654]. Indeed, astaxanthin may aid COX-2 suppression [655]. Other studies reported that in 1,2-dimethylhydrazine (DMH)-induced colon carcinogenesis, daily administration of astaxanthin significantly blocked colon carcinogenesis by modifying the expression of NF-κB, COX-2, MMP-2, MMP-9, ERK2, and protein kinase B (Akt) [656]. Lycopene decreased the invasive ability of hepatoma cells by downregulating the activity of NF-κB [657], maybe through suppression of IGF-1 receptor. Lycopene could be efficient in treatment of benign prostate hyperplasia (BPH) via inhibition of NF-κB. On the contrary of the inhibitory effect of lycopene on NF-κB activity, β-carotene stimulated NF-κB in human leukemic (HL-60) and colon adenocarcinoma (LS-174 and WiDr) cells [658]. Astaxanthin attenuated the production of inflammatory markers and cytokines by LPS in vitro (LPS-treated RAW 264.7 cells and primary macrophages) and in vivo (LPS-treated mice) through NF-κB inhibition. Furthermore, astaxanthin thoroughly inhibited all the main signaling molecules involved in NF-κB activation, like IkB kinase phosphorylating activity, IkBa degradation, and the nuclear translocation of the NF-κB p65 subunit [659]. Anti-angiogenic effect of β-carotene was investigated by an in vivo model of B16F-10 melanoma in mice and by in vitro studies [660]. β-Carotene treatment significantly decreased the number of tumor-directed vessels concurrent with reduction of serum VEGF and pro-inflammatory cytokines, e.g., IL-1β, TNF-α, and IL-6. In addition, similar decrease of these cytokines was detected after β-carotene treatment in melanoma cells and found to result from inhibition of c-Rel subunit of NF-κB and AP-1. AP-1 transcription system has been shown to be

blocked by lycopene in MCF-7 mammary cancer cells [661]. The AP-1 complex comprises proteins from the Jun (c-Jun, JunB, and JunD) and Fos (c-Fos, FosB, Fra-1, and Fra-2) families, which are connected as homo- (Jun/Jun) or heterodimers (Jun/Fos). It is probable that lycopene and retinoic acid decrease growth factor-induced induction of AP-1 transcriptional activity by changing the composition of AP-1 complexes that bind to DNA [662, 663]. There was a three- to fourfold increase in the expression of c-Jun and c-Fos genes in the lungs of ferrets, supplemented with high-dose β-carotene and exposed to tobacco smoke. This study suggested a possible explanation for the enhancing effect of β-carotene on lung carcinogenesis in smokers, as demonstrated in large intervention studies [664].

Under basal conditions, Nrf1 and Nrf2 are present in the cytoplasm bound to the inhibitory protein Keap1. After challenge with stimulating agents, they are released from Keap1 and translocated to the nucleus [665, 666]. Studies have shown that dietary antioxidants (terpenoids [667]), flavonoids (epigallocatechin gallate (EGCG) [668, 669]), and isothiocyanates may function as anticancer agents by activating this transcription system. However, hydrophobic carotenoids such as lycopene lack any electrophilic group and, therefore, are unable to interact with Keap1. Thus, it seems that oxidative products actively play a role in the induction of the EpRE/ARE (electrophile/antioxidant response element) transcription system by carotenoids. It has been demonstrated that oxidized derivatives, isolated by ethanol from partially oxidized lycopene, transactivated EpRE/ARE in HepG2 human hepatocellular carcinoma cells [670] with a strength resembling to that observed with unextracted lycopene mixture. In contrast, the intact carotenoid exhibited a small insignificant effect [671].

Isoflavones

Isoflavones, such as daidzein and genistein, are mostly found in soybeans. Previous experimental and epidemiological studies suggest cancer protective effects of isoflavones and their metabolites. Genistein was described to downregulate direct cellular cytotoxicity and ADCC. Genistein is able to inhibit tyrosine kinase activity, which is crucially involved in NK cell activation in epidermoid carcinoma A431 cells [672]. Both genistein and daidzein are extensively metabolized in humans and found as conjugated metabolites, mainly glucuronides [673, 674]. Genistein and daidzein glucuronides could increase NK cell-mediated cytotoxicity in human PBMCs at nutritionally achievable concentrations, which were tenfold lower than concentrations of isoflavones used to inhibit tumor cell (MCF-7 and MDA-468 human breast cancer cells) growth in vitro [673, 675]. At higher concentrations, however, genistein decreased NK cell-mediated killing of K562 target cells. In the presence of IL-2, genistein increased NK cell activation at even lower concentrations. The existence of IL-2 may be essential for genistein to increase NK cell activity, and this may be correct for other flavonoids too. Factors determining the effects of genistein on NK cell activity in mice include the duration of exposure, sex, and even generation. The described effects may be of nutritional relevance as isoflavone concentrations after soy consumption are within the range (<2 μmol/L) for which NK cell activation is anticipated. The glucuronides were generally less potent than genistein and daidzein [673]. Genistein administration by oral gavage for 1–4 weeks increased NK cell-mediated cytolysis and cytotoxic T-cell activity in B6C3F1 mice [676].

Moreover, increased host resistance was shown in adult B6C3F1 mice (intravenous injection of B16F10 melanoma cells) treated with genistein, as reflected in lung tumor weight and NK cell modulatory effects [676]. Increased intake of dietary soy has been reported to reduce the severity of macroscopic lung metastasis [677]. In a study in bladder cancer, isoflavone-rich soy phytochemical concentrate (SPC) was shown to have greater anti-metastatic effect in comparison with genistein. Particularly, SPC but not genistein significantly blocked lung metastases through suppression of NF-κB expression in tumor tissues and reduction of circulating IGF-1 levels [678]. Besides decreasing the metastasis of breast cancer cell to lung [679], genistein has been shown to be a useful chemotherapeutic agent to inhibit the development and metastasis

of sex gland cancers such as prostate cancer [680]. Inhibition of MMP-9 by genistein also has been suggested as a possible mechanism for prevention of prostate cancer to bone metastasis [681, 682]. Other genes targeted by genistein in primary stages of breast cancer include MMP-2, MMP-7, and CXCL12, which support invasion and metastasis [683, 684]. Genistein also inhibited the activation of focal adhesion kinase [685] and HSP27 pathway [685], which regulate cancer cell detachment and invasion, respectively. Genistein has been reported for its cytotoxic effect in prostate cancer cell lines LNCaP and PC3 [686], hepatoma cancer cell lines (HepG2, Hep3B) [687], and A431 and Colo205 xenograft tumors, [688, 689]. Genistein can be used combined with conventional therapy such as 5-FU, all-trans retinoic acid (ATRA), and trichostatin A to improve their cytotoxicity and apoptotic activity in human pancreatic cancer cell line (MIA PaCa-2) [690] and human lung cancer cell line (A549) [691, 692]. Genistein at very low concentrations stimulated the proteinase inhibitor 9 (PI-9), which is a granzyme B inhibitor and inhibits the capability of NK cells to lyse breast cancer cells [693] with an opposite activity in high concentrations [676]. Moreover, it seems that polyphenol-stimulated NK cytotoxicity depends on the cell type. Genistein has also shown to decrease in vitro cytotoxic activity of NK cells in melanoma and breast cancer cells [524, 693] and, in contrast, was found to increase NK-mediated cytotoxicity in in vitro and in vivo tumor models [676, 694, 695].

Quercetin

Quercetin is a well-known flavanol, which has been shown to inhibit NK cell killing activity in peripheral blood lymphocytes from human donors. However, high doses of quercetin could cause pro-apoptotic or cytotoxic effects through the inhibition of Ca^{2+} channels and Na+/K+ ATPase activity [122, 696]. More clearly, indirect NK cell stimulation by quercetin resulting in augmented IFN secretion has been reported in low doses of quercetin. Quercetin improved NK cell activity in BALB/c mice treated with WEHI-3 leukemia cells and oral quercetin [697].

Quercetin stimulated NK cell activity through inhibition of protein kinase C (PKC), PI3K, and HSP70 in target cells while increasing the expression of NKG2D ligands [698, 699]. Some chemotherapeutics were reported to increase the expression of NKG2D and HSPs, thereby decreasing cell vulnerability to NK cell-mediated cytolysis. It has been reported that quercetin can induce the expression of NKG2D ligands, MHC class I-related chain B (MICB), UL16-binding protein 1 (ULBP1), and UL16-binding protein 2 (ULBP2) while downregulating the expression of HSP70 in K562 (erythroleukemia), SNU-1 (gastric carcinoma), SNU-C4 (colon cancer), and human Raji (Burkitt's lymphoma) target cells, together reflected in increasing cell susceptibility to NK-92-mediated lysis [698]. It has been suggested that increased NKG2D ligand expression was mostly responsible for the inhibitory effect of quercetin on NF-κB and PI3K [698]. Quercetin demonstrated an antiproliferative effect through the induction of apoptosis by disturbing the MMP system [700, 701]. In addition, quercetin can be administrated combined with other chemotherapeutic agents such as doxorubicin to enhance their cytotoxic effects on liver cancer cells (SMMC7721 and QGY7701) as well as to provide protection for non-tumoral liver cells from toxic effects of free radicals [702].

Quercetin is able to reduce the number and size of polyp in the Apc (Min/+) mouse through reduction in macrophage infiltration [703]. In addition, treatment with quercetin prior to intraperitoneal injection of EAT tumor cells stimulated macrophage spreading, suggesting that this compound affects the tumoricidal activity of macrophages [704]. In vivo, tumor-bearing mice treated with quercetin showed an improvement in the phagocytic activity of peritoneal macrophages [697].

β-Glucan

β-Glucan is a polymer made of D-glucose molecules that are connected by linear β-glycosidic bond with side branches that are different based

on their sources [705]. β-Glucans, including zymosan, laminarin, lentinan, and pleuran, are found in mushroom, barley, cereals, and seaweeds as well as bacterial and fungal cell wall. The anticancer effect of β-glucan is chiefly because of its immunomodulatory effect rather than its direct cytotoxic activity. A range of β-glucans have been described as immunomodulators [706]. β-Glucans are able to induce the immune system effector cells, mostly macrophages, monocytes, neutrophils, NK cells, and DCs via their interaction with glucan-specific receptors, such as dectin-1, TLR, and CR3 (complement receptor 3 or CD11b/CD18), expressed by these cells [707]. In addition, they can increase the phagocytic effects of neutrophils, NK cells, and cytotoxic T-lymphocytes. β-D-Glucans have been demonstrated to stimulate the secretion of pro-inflammatory cytokines (IL-1α/IL-1β, TNF-α, IL-2, IFN-γ, and IL-12) that stimulate antitumor immune response as well as NO and H_2O_2 by activated macrophages that demonstrated antitumor effect [708]. The effect of natural β-glucan, schizophyllan, combined with chemotherapy was investigated on the survival rate of patients with ovarian cancer [709]. Furthermore, Maitake D-fraction found in *Grifola frondosa* (Maitake mushroom) has been reported to decrease the size of tumors, primarily in the lung, liver, and breast, in more than 60% of treated patients [710]. Moreover, supplementation with 5.4 grams *Ganoderma* polysaccharides per day for 12 weeks boosted immune responses in patients with lung and colorectal cancer [711, 712]. β-Glucans combined with mAbs RMA-S-MUC1 subcutaneously implanted in C57Bl/6 mice improved complement receptor 3 (CR3)-mediated phagocytosis of ic3b (inactivated C3b)-opsonized tumor cells by effector granulocytes and enhanced tumor recession in treated animals [713]. Lentinan, derived from *Lentinus edodes*, was shown to induce apoptosis in hepatoma H22-bearing mice [714], cervical carcinoma HeLa cells, and hepatocellular carcinoma (HepG2 and SMMC-7721 cell). Furthermore, lentinan induced antitumor immune responses through enrollment of immune cells, mostly macrophages and T-lymphocytes, into TME to attack tumor cells and release inflammatory chemokines (TNF-α, IL-2, IL-1β, TGF-β, IP-10, M-CSF, and TREM-1). The immunomodulating effects of arabinogalactan (AG) and fucoidan (FU) in vitro have been investigated in mouse spleen lymphocytes, which turned cytotoxic after treatment with AG and FU. Novel maloyl glucans have been isolated from aloe vera gel (*Aloe barbadensis*) – veracylglucan B possesses both anti-inflammatory and antiproliferative effects, while veracylglucan C has merely shown anti-inflammatory effects and appears to complement the actions of veracylglucan B [715].

Withania somnifera

Withania somnifera (WS), also known as Ashwagandha, has been a part of Ayurvedic medicine for many centuries. WS has been reported to be efficient in arthritis, cancer, and mental disorders [716, 717]. Steroidal lactones, including withanolides and withaferins, are the most biologically active components [716]. Among them, withaferin A (WA) and withanolide A have been investigated for anticancer and immunomodulatory effects, respectively [718, 719].

Along with its antitumor effect, treatment of tumor-bearing mice with withanolide A led to the polarization of T_H1 cells and subsequent increase in the production of pro-inflammatory cytokines (IFN-γ and IL-2) while reducing the polarization of T_H2 cells [720]. Moreover, there was a significant increase in the proliferative activity of $CD4^+$ and $CD8^+$ T-cells present in the serum of WS-treated mice. In response to stimulation with concanavalin A (Con A) and LPS, proliferation of T-cells and B-cells was also significantly increased with WS treatment. Treatment with WA not only increased NK cell population in one study but also increased its cytotoxic activity. In addition, APCs purified from blood samples of tumor-bearing mice showed an enhanced maturation and expression of co-stimulation markers (CD80, CD40, and CD40L) on T-cells [720], suggesting the effective role of WS in DC-mediated activation of T-cells – all of which may be involved in antitumor function of WS. WA treatment induced tumor rejection

and protection from rechallenge. This indicates that WA can build immunological memory in Ehrlich ascites carcinoma model. A possible mechanism of tumor rejection could be attributed to macrophages because WA increased the frequency of peritoneal macrophages, and transfer of these macrophages from cured mice caused tumor rejection. In a breast cancer model, WA induced immunogenic cell death (ICD) in cancer cells through expression of HSPs such as HSP70, HSP90, and calreticulin on the membrane of tumoral cells. All of these ICD mediators bind to receptors on DCs, leading to activation and maturation of DCs and the production of inflammatory cytokine IL-12 [721]. Of note, WA could diminish the function of the tumor inhibitory immune cell type, i.e., myeloid-derived suppressor cells (MDSCs), to generate ROS known to mediate the suppressive effect of MDSCs on T-cells [722].

Flavone Acetic Acid (a Synthetic Flavonoid)

Synthetic flavone acetic acid (FAA) has been frequently investigated for its antitumor activities. In particular, it has the ability to induce NK cell activity [723]. FAA increased NK cell-mediated killing activity in both healthy and tumor-bearing mice [723] as well as cancer patients [724]. It has been postulated that an indirect mechanism (e.g., induction of cytokines), rather than a direct interaction of FAA with NK cells [725], is responsible for the discovered effect. In mouse renal cancer, intravenous or intraperitoneal administration of FAA increased NK cell activity in the spleen, liver, lungs, and peritoneum and was synergistically enhanced by co-administration of IL-2 [725]. The first report on the enhancing effect of FAA on NK cell function in humans came from a study with six cancer patients undergoing a weekly treatment with FAA. Three out of the six patients showed a considerably enhanced NK cell activity after treatment [724]. In another trial, NK cell activity not only remained unchanged after treatment with FAA in cancer patients but even significantly reduced 24 h after treatment [726]. The synergistic activity of FAA and IL-2 [725] was subsequently studied in 26 melanoma patients. In 23 of 26 patients, NK activity was significantly enhanced (2–20-fold higher cytotoxicity) during combined treatment with FAA and IL-2. However, large variations in NK cell activity were observed in patients over the duration of the trial [727]. Of nine cancer patients receiving 1–6 courses of FAA infusions, enhanced NK cell activity was reported in only three patients, while six others were unresponsive to treatment [728].

However, intravenous FAA in the abovementioned trials differed completely from the oral intake of flavonoids through diet or supplements. After intravenous injection, compounds are 100% bioavailable, which surpass the usual maximum plasma concentrations of dietary flavonoids. A possible mechanism of action by which FAA induces NK cell activity is through induction of cytokines, including IFN-α, thereby improving NK cell function.

Phenoxodiol (a Synthetic Flavonoid)

Phenoxodiol is a synthetic analog of genistein [729]. Phenoxodiol could induce NK cell function and their perforin content in human PBMCs from healthy donors, thereby increasing cytotoxicity of NK-sensitive K562 cells. The increased cytotoxicity of phenoxodiol-treated cells was more prominent in PBMCs from cancer patients than in those from healthy volunteers. On the contrary, genistein and daidzein only marginally stimulated PBMC cytotoxicity [675]. In a previous experimental in vivo study, the effects of phenoxodiol genistein and daidzein were investigated in tumor-bearing mice. Only phenoxodiol and only at high-dose of 20 mg/kg body weight was able to enhance the cytolytic activity of splenocytes against NK-sensitive target cells (CT-26 and YAC-1) [675].

Polymethoxylated Flavones

Treatment with a mixture of polymethoxylated flavones derived from orange peel oil in high doses mildly downregulated NK cell activity

with no effect on humoral immunity [730]. These findings suggest that consumption of high-dose citrus fruit during certain conditions like tamoxifen therapy of mammary tumors must be avoided. Polymethoxylated flavones, such as nobiletin, tangeretin, and sinensetin, from the peel of citrus fruits, have been reported to potentiate the cytotoxicity of KHYG-1 (NK leukemia cells that exhibit high cytolytic activity against K562 target cells [731]) by enhancing the expression of granzyme B [731]. Among them, nobiletin was also able to increase the levels of IFN-γ, perforin, granzyme A, and granzyme B in KHYG-1 cells [731]. The important role of granzyme B in nobiletin-mediated cytolysis has been confirmed in that study. It must be noted that nobiletin increased phosphorylation of cAMP response element-binding protein (CREB) while controlling the phosphorylation of ERK1/ERK2 and p38 MAPK [731].

Apigenin and Amentoflavone

Apigenin is found in common fruits and vegetables, such as parsley, onions, oranges, tea, chamomile, wheat sprouts, apple, guava, tomato, and broccoli, and in some seasonings. Studies have reported its antitumor effects. Topical application of apigenin prior to UV irradiation prevents UV-induced tumorigenesis in mice. In addition, it exhibited antiproliferative effects on breast cancer cell lines that expressed different levels of HER2/neu. It induced apoptosis in HER2/neu-overexpressing breast cancer cells. Apigenin has been shown to inhibit cancer cell proliferation and transcriptional activation of VEGF in A549 lung cancer cells [732–737]. Amentoflavone is a biflavonoid formed out of two apigenin units [738]. It is present in *Ginkgo biloba*, Saint John's wort [739], and *Nandina domestica* [740]. Treatment with amentoflavone increased NK cell activity in splenocytes in control and tumor-bearing BALB/c mice [741]. Tumor-bearing controls showed weaker and delayed NK cell activity in comparison with amentoflavone-treated mice [741]. NK cell activity was investigated in splenocytes isolated from tumor-bearing mice incubated with K562 target cells. Furthermore, antibody-dependent cellular cytotoxicity (ADCC) was significantly improved in amentoflavone-treated mice [741]. Taken together, amentoflavone effectively increased lymphoid cell proliferation and effector cell functions by inducing the production of IL-2 and IFN-γ in tumor-bearing mice [741].

Proanthocyanidins

Proanthocyanidins derived from grape seeds have different strong immunomodulatory properties. Ultraviolet B (UVB), as a part of UV irradiation, causes immunosuppression which can be inhibited by proanthocyanidins through the induction of IL-12 in mice [742]. In addition, proanthocyanidins can inhibit UVB-induced immunosuppression by inducing $CD8^+$ effector T-cells and reducing regulatory $CD4^+$ T-cells. Proanthocyanidins make UVB-exposed mice to secrete higher levels (five- to eightfold) of T_H1 cytokines from $CD8^+$ T-cells and lower levels (80–100%) of T_H2 cytokines from $CD4^+$ T-cells [743]. Of note, proanthocyanidins increase the frequency of $CD4^+CD25^+FoxP3^+$ regulatory T-cells while decreasing the frequency of $CD4^+IL\text{-}17^+$ pathogenic T-cells. Downregulation of IL-17 secretion and enhancement of Foxp3 expression because of proanthocyanidin treatment have been reported in vivo.

Organosulfur Compounds

Garlic is a rich source of organosulfur compounds (OSCs), including allicin, diallyl sulfide, and diallyl disulfide, which contain, respectively, mono-, di-, and polysulfide functional groups [744]. Garlic and its compounds are capable to facilitate stimulation of immune effector cells to promote antitumor immunity [745]. Aged garlic extract (AGE) has been reported to stimulate phagocytosis by macrophages and cytotoxic activities of T-lymphocytes [746] in sarcoma-180-bearing mice. In addition, it can increase the secretion of pro-inflammatory cytokines (IL-2,

IL-12, TNF-α, and IFN-γ) and the frequency of NK cells. However, diallyl disulfide, diallyl sulfide, and allyl methyl sulfide exhibited an inhibitory effect on the release of TNF-α, IL-10, and NO generation in LPS-stimulated RAW 264.7 macrophages [747]. Some dietary phytochemicals like sulforaphane are powerful stimulators of phase II/detoxifying genes, and this effect is dependent on nuclear factor erythroid 2-related factor 2 (Nrf2) [748]. In fact, sulforaphane is able to stabilize Nrf2 [749].

Capsaicin

Capsaicin is the dominant pungent component present in red chili pepper [750, 751]. The antiproliferative effects of capsaicin through several mechanisms including production of ROS and disruption of mitochondrial membrane and release of cytochrome c have been reported in some cancer cell lines, such as leukemic cells (NB4 and Kasumi-1 cells) [752], prostate cancer cell line PC-3 [753], and human colon adenocarcinoma Colo205 cells [754]. The anti-angiogenic effects of capsaicin have been shown via its suppressive effects on VEGF. Capsaicin is able to inhibit NF-κB and STAT3 transcriptional pathway that play a vital role in inflammation and tumor growth [755, 756].

Bromelain

Bromelain is a mixture of proteolytic enzymes purified from pineapple (*Ananas comosus*). It has been approved as an anti-inflammatory agent for post-surgical conditions and infection. Immunomodulatory effects of bromelain include (1) induction of CD2-mediated T-cell activation [757], (2) increasing T-lymphocyte proliferation in splenocytes without significant effect on purified $CD4^+$ and $CD8^+$ T-cells [758], and (3) decreasing the production of pro-inflammatory cytokines, such as IL-2, IL-6, IL-4, IFN-γ, and G-CSF, from inflamed tissues [759]. The immunostimulatory effect of bromelain was only demonstrated on the healthy immune system when combating foreign antigens [760, 761]. Also, bromelain is able to stimulate the oxidative explosion in neutrophils by increasing intracellular ROS that induce DNA destruction, thereby enhancing the cytotoxic effect of neutrophils on tumor cells [762]. The antitumor and cytotoxic effect of bromelain has been shown in mouse skin papilloma through inhibition of NF-κB and COX-2 expression [763]. Its cytotoxic effect has been shown on melanoma B16F10-Nex2 cells [764] and human cholangiocarcinoma cell lines (TFK-1, SZ-1) as well [765]. Bromelain has the ability to decrease the expression of CD44 surface marker, which is involved in tumor proliferation [766]. Of note, bromelain treatment led to a significant reduction in invasion, migration, and adhesion of glioma cells without any adverse effect on marginal cells [767].

Betulinic Acid

Betulinic acid (Bet A) is a naturally occurring triterpenoid present in several plant species such as the white birch (*Betula pubescens*). Bet A has been investigated for its cytotoxic effects on melanoma cells [768], neuroblastoma tumor cells [769], glioma cells [770], human leukemia HL-60 cells [771], malignant head and neck squamous cell carcinoma SCC25 and SCC9 cell lines [772], and colon cancer cells [773]. Of note, Bet A is able to inhibit the secretion of IL-6, COX-2, and PGE-2 in LPS-induced PBMCs via downregulation of NF-κB signaling [774, 775].

Zerumbone

Zerumbone is a sesquiterpene in the rhizomes of shampoo ginger. Zerumbone has immunomodulatory activity via modulation of MAPK and NF-κB pathways [776] and cytokine secretion [777]. It has been demonstrated to downregulate production of different inflammatory mediators, mainly NO, COX-2, PGE-2, and iNOS in macrophages [778]. Moreover, this potent immunomodulator has been investigated for its anticancer effects and suggested to be helpful in cancers of the breast, bone marrow, liver, lung, cervix, colon, prostate, pancreas, and skin [778–784].

Noni Fruit

Morinda citrifolia (noni) is a Hawaiian plant used for cancer. Its polysaccharide-rich substance has been shown to possess antitumor effect in the Lewis lung tumor model, resulting in improvement of the host immune system through affecting the production of cytokines (TNF-α and IFN-γ) and nitric oxide. Two glycosides, 6-*O*-(β-d-glucopyranosyl)-1-*O*-octanosyl-β-d-glucopyranose and asperulosidic acid, were purified as active compounds from noni juice. Both compounds were efficient in downregulating TPA- or EGF-induced cell transformation and associated AP-1 activity [785].

Flavanols

Other flavanols like myricetin have been investigated in the context of antitumor immunology. Myricetin potentiated the ability of NK-92 cells to lyse K562 erythroleukemia target cells [786].

Naringenin

Naringenin is the major flavanone in grapefruit. It was reported to increase the expression of NKG2D ligands in human Raji (Burkitt's lymphoma) cells [787]. MICA, MICB, ULBP1, and ULBP2 protein expressions were also increased compared with untreated control cells [787]. Although quercetin exhibited weaker but similar effect on NKG2D ligand expression, luteolin (flavone), kaempferol (flavonol), taxifolin (flavanonol), apigenin (flavone), and hesperetin (flavanone) did not show modulation of NKG2D ligand expression [787].

Chrysin

Chrysin is the main flavanone of *Passiflora incarnata* (also known as passion flower) [788]. It can be found in natural products like propolis and honey [789]. Chrysin has been reported to have anti-inflammatory, antioxidative, and chemopreventive activities [789]. Oral administration of chrysin in a murine leukemia mouse model increased populations of T- and B-lymphocytes and enhanced phagocytosis by macrophages as well as NK cell-mediated cytotoxicity. After chrysin treatment, the viability of WEHI-3 cells (murine leukemia cells) was reduced. Splenocytes isolated from WEHI-3-injected leukemic BALB/c mice after chrysin treatment exhibited an enhanced NK cell toxicity toward YAC-1 target cells [789].

Tangeretin

The flavone tangeretin is found in citrus fruit peel [790]. Tangeretin treatment in female C3H mice reduced lymphocyte counts, suggesting an inhibitory effect of tangeretin on cell proliferation and differentiation of NK cells [791]. Tangeretin also antagonized the tumor-suppressive effects of tamoxifen in MCF-7/MCF-6 tumor-bearing mice by reducing the number of NK cells and NK cell activation through lymphokines [790]. The in vivo antitumor effect of tangeretin has been shown in DMBA (7,12-dimethylbenz(a) anthracene)-induced breast cancer-bearing animals [792]. The antiproliferative and anti-angiogenic effects of tangeretin in A549 human lung cancer cell line have been attributed to downregulation of IL-1β-induced COX-2 expression. Moreover, it has the capability to enhance the levels of non-enzymatic antioxidants (ascorbic acid, vitamin E, and GSH) and reduce the serum levels of tumor markers [793, 794].

Silymarin

Silymarin has shown both antitumoral and cytoprotective effects. It has been reported that silymarin can inhibit NF-κB activation [795]. Another study has shown the biphasic effect of silymarin on Jurkat cells, a human peripheral blood leukemia T-cell line [796]. Low dose of silymarin increased cell proliferation, while high doses caused inhibition of DNA synthesis and significant cell death [797].

Alkaloids

Caffeine is a major phytochemical, which belongs to the alkaloid class. Using the B16F-10 melanoma cell-induced experimental metastasis model, oral and intraperitoneal caffeine administration significantly decreased tumor size [798]. Investigation using a spontaneous transgene-induced mammary tumor model provided further evidence of inhibition of metastasis by caffeine [799].

6-Gingerol

6-Gingerol is the pungent phenolic compound derived from ginger (*Zingiber officinale*). 6-Gingerol demonstrated antiproliferative effect by stimulation of apoptosis against several tumor cell lines such as OSCC and cervical HeLa [800]. Moreover, 6-gingerol showed an anti-metastasis effect on lung B16F10 melanoma in vivo. Inhibition of angiogenesis occurred through downregulation of VEGF. Also, it exhibited its inhibitory effect on COX-2 expression by downregulation of p38 MAPK and NF-κB in vivo [801].

Kaempferitrin

The antitumor and immunostimulatory effects of bioactive flavonoid kaempferitrin from *Justicia spicigera* have been reported in human cervical carcinoma cells (HeLa) [802]. More precisely, kaempferitrin is able to stimulate antitumor immune responses by inducing phagocytic activity of human macrophage in vitro, enhancing the levels of NO and generation of H_2O_2, and stimulating NK activity.

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