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The immunomodulatory potential of natural compounds in tumor-bearing mice and humans

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Abstract

Cancer is considered a fetal disease caused by uncontrolled proliferation and progression of abnormal cells. The most efficient cancer therapies suppress tumor growth, prevent progression and metastasis, and are minimally toxic to normal cells. Natural compounds have shown a variety of chemo-protective effects alone or in combination with standard cancer therapies. Along with better understanding of the dynamic interactions between our immune system and cancer development, nutritional immunology—the use of natural compounds as immunomodulators in cancer patients—has begun to emerge.

Cancer cells evolve strategies that target many aspects of the immune system to escape or even edit immune surveillance. Therefore, the immunosuppressive tumor microenvironment is a major obstacle in the development of cancer therapies. Because interaction between the tumor microenvironment and the immune system is a complex topic, this review focuses mainly on human clinical trials and animal studies, and it highlights specific immune cells and their cytokines that have been modulated by natural compounds, including carotenoids, curcumin, resveratrol, EGCG, and β -glucans. These natural compounds have shown promising immune-modulating effects, such as inhibiting myeloid-derived suppressor cells and enhancing natural killer and cytolytic T cells, in tumor-bearing animal models, but their efficacy in cancer patients remains to be determined.

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Keywords

cancer immunology; carotenoids; curcumin; resveratrol; EGCG; β -glucans

Introduction

Cancer is caused by uncontrolled proliferation and progression of abnormal cells, which could eventually lead to mortality. The most efficient cancer therapies suppress tumor growth, and prevent progression and metastasis. Advanced medical technologies and modern cancer therapies, including chemotherapy, radiotherapy, and immunotherapy, have achieved successful clinical outcomes in certain types of cancer. In addition, early detection programs, such as mammography, prostate cancer screening, and colonoscopy, lead to precise diagnosis of precancerous lesions. All of these advances improve overall survival of cancer patients. However, we now appreciate the existence of heterogeneity among cancer types and even among individual patients. Therefore, targeted therapies based on molecular signatures of cancer cells can significantly enhance therapeutic responses in selected subpopulations. Two well-documented examples are ErbB2-targeted therapies for ErbB2-positive breast cancer (Shepard et al. 1991) and estrogen antagonists for estrogen receptor-positive breast cancer (Heiser et al. 2012).

The host's immune system, which continuously monitors the body for pathogens and invading antigens, also plays an important role in the tumor microenvironment and contributes to cancer heterogeneity. The immune editing that permits tumor development and progression consists of three phases: elimination, equilibrium, and escape. First, cancer cells prevent the immune system from eliminating new cancer cells; then they achieve an equilibrium with immune cells; and last, they escape immune surveillance. Efficient immune-therapies should be able to rescue the dysregulated immune cells at all three stages and enhance the potency of cancer-combatting cells. For example, T cells, which normally recognize and kill cancer cells, can become exhausted and dysfunctional, as evidenced by the upregulation of a programmed cell death marker (PD-1), on their surface. Blocking PD-1, or its ligand PD-L1, which is expressed on cancer cells, has restored T cell function against many types of cancer (Thommen and Schumacher 2018).

An efficient cancer therapy regimen also needs to minimize toxicity to normal cells, as many cancer patients respond to cytotoxic treatments but succumb to side effects such as cachexia, weight loss, fatigue, and cytokine storm. Therefore, there is growing interest in supplementing standard cancer therapies with natural compounds and dietary components to improve quality of life during chemotherapy (Bjorklund et al. 2018, Serna-Thome et al. 2018). Importantly, the potential capabilities of these natural compounds and dietary components to inhibit tumor growth have begun to be explored. Accumulating evidence is demonstrating that natural compounds can have a wide variety of effects against cancer, such as anti-proliferation, anti-angiogenesis, anti-migration, and pro-apoptosis (Hussain, Kumar, and Ghosh 2016, Zang et al. 2014, Ferraz da Costa, Fialho, and Silva 2017, Rather and Bhagat 2018, Ko et al. 2017, Lee 2017, Rauf et al. 2017).

Nutritional immunology is also drawing more attention, given the recent success with immunotherapy. Natural compounds and dietary components have been shown to influence immune cells *in vitro* and to enhance immune responses against multiple conditions, such as inflammatory diseases (viral infection, obesity, and diabetes) and cancer (Sultan et al. 2014, Kim et al. 2015, Chirumbolo 2012, Ferguson and Philpott 2007, del Corno et al. 2016, Baraya, Wong, and Yaacob 2017, Janakiram et al. 2016, Burkard et al. 2017, Zheng et al. 2012, Ghiringhelli et al. 2012, Casey et al. 2015, Mohamed, Jantan, and Haque 2017). For instance, our group demonstrated that berries, which contain multiple chemopreventive compounds, enhanced the function of natural killer (NK) cells and decreased the infiltration of neutrophils in animal models and human patients with colorectal cancer (Pan, Kang, et al. 2017, Pan, C, et al. 2017, Pan et al. 2015). Because of the complexity of the tumor microenvironment and immune system, this review will focus on human clinical studies (Table 1 and Figure 1) and tumor-bearing animal studies (Table 2 and Figure 2). In addition, it will highlight specific immune cells and their cytokines in tumors that have been shown to be modulated by natural compounds.

We performed a PubMed search using the following key words: cancer immunity, natural compounds, diet, polyphenols, and human clinical trials. Research articles, clinical trials, and reviews that investigated and compared the immune-modulating effects of natural compounds against cancer were first screened according to abstracts and titles. Full texts of selected articles were then assessed. Reference lists from studies selected by the electronic search were manually searched to identify further relevant reports and to select the best-studied natural compounds. Therefore, this review summarizes the immune-modulating effects of carotenoids and retinoic acid (RA), curcumin, resveratrol, (–)-epigallocatechin-3-gallate (EGCG), and β -glucans.

The cancer-immunity cycle

The lymphoid compartment of the immune system includes NK cells, NKT cells, CD4⁺ T cells, CD8⁺ T cells, and B cells. It can exert antigen-specific cytotoxicity, mainly with T cells, or non-specific cytotoxicity, mainly with NK cells, against cancer cells. CD8⁺ T cells are the major anti-cancer effector cells. They can differentiate into cytotoxic T lymphocytes in lymphoid organs upon encountering antigen-presenting cells (APCs). Dendritic cells (DCs) are the major APCs that present tumor-specific peptides to CD8⁺ T cells (Palucka and Coussens 2016). T cells can also secrete different types of cytokines to promote their functions, and they can interact with other immune cells. For example, Th1-polarized CD4⁺ T cells secrete interleukin-2 (IL-2), tumor necrosis factor alpha (TNF- α), and interferon gamma (IFN- γ), which can enhance the cytotoxic activities of macrophages and the antigen-presenting functions of DCs (Palucka and Coussens 2016). In the immunosuppressive tumor microenvironment, however, chronic inflammation can promote cancer cell growth and survival, and switch the Th1-like immune response to the Th2-like response. Th2-type cytokines, such as IL-4, IL-10, and transforming growth factor beta (TGF- β), are dominant, and they can recruit Foxp3⁺ T regulatory (Treg) cells, M2-polarized macrophages and monocytes, as well as B regulatory (Breg) cells. These cells further promote cancer angiogenesis, migration, and metastasis (Chen and Mellman 2013, Thommen and Schumacher 2018, Ribas 2015, Godfrey et al. 2018). In addition, NK cells are the major

components of the innate immune response. They recognize pathogens, harmful agents, and cancer cells by “missing-self” signals (Malmberg et al. 2017). Thus, NK cells can select and lyse “non-self” cells that fail to express major histocompatibility complex (MHC) class I molecules on their surface. The cytotoxicity of NK cells is also controlled by activation receptors, such as natural cytotoxicity receptors (NCRs), and by inhibitory receptors, such as killer cell inhibitory immunoglobulin-like receptors (KIRs). These receptors recognize stress signals and self-MHC class I ligands, respectively, to determine NK cell functions (Woo, Corrales, and Gajewski 2015, Iannello et al. 2016, Marcus et al. 2014). However, the functions of NK cells can be suppressed by Treg cells and myeloid-derived suppressor cells (MDSCs), as well as by their cytokines, including IL-10 and TGF- β , in the immunosuppressive tumor microenvironment (Malmberg et al. 2017).

The myeloid compartment of the immune system includes macrophages, DCs, granulocytes, and monocytes. The most important feature of these cells is their functional plasticity in the microenvironment. DCs can capture and display cancer-derived antigens to allow recognition by T lymphocytes. Therefore, DCs are key initiators of the immune response against cancer cells. However, Treg cells and high levels of IL-10 can suppress DC maturation so those cells remain immature and become subgroups of MDSCs (Veglia and Gabrilovich 2017). Macrophages are differentiated cells of the mononuclear phagocytic lineage. “Activated” macrophages, or M1-like macrophages, are involved in the Th1-type response to pathogens. Upon activation by IFN- γ and Toll-like receptors (TLRs), M1-like macrophages secrete IL-12, TNF- α , reactive oxygen species (ROS), and nitric oxide (NO) to kill pathogens and abnormal cells. “Alternatively activated” macrophages, or M2-like or tumor-associated macrophages (TAMs), have been found in the tumor microenvironment. They secrete vascular endothelial growth factors (VEGFs), IL-10, and TGF- β to recruit Treg cells, as well as to suppress CD8⁺ T cells and NK cells (Ruffell and Coussens 2015, Noy and Pollard 2014, Ostuni et al. 2015, Qian and Pollard 2010). Neutrophils, the first defense against bacteria and virus, are responsible for acute inflammation and wound healing. Like TAMs, tumor-associated neutrophils can generate VEGFs, IL-10, arginase 1 (Arg-1), and matrix metalloproteinase (MMP) to promote angiogenesis, migration, and metastasis of cancer cells (Powell and Huttenlocher 2016, Sionov, Fridlender, and Granot 2015). MDSCs are regarded as the most potent immunosuppressive cells in the tumor microenvironment. The two main types are polymorphonuclear MDSCs (PMN-MDSCs), which are morphologically and phenotypically close to neutrophils, and monocytic MDSCs (M-MDSCs), which resemble monocytes (Kumar et al. 2016, Marvel and Gabrilovich 2015). These cells are characterized by their functions: suppressing T cells and NK cells and secreting cytokines such as Arg-1, inducible NOS (iNOS), TGF- β , and IL-10 (Tcyganov et al. 2018, Gabrilovich 2017).

Carotenoids and Retinoic acid (RA)

Carotenoids are liposoluble pigments belonging to the tetraterpene family (C₄₀-based isoprenoids), and they impart yellow, orange, or red colors to fruits, leaves, and flowers (Milani et al. 2017). More than 600 carotenoids with natural structural variants have been identified. The major carotenoids in the diet and human body include β -carotene, α -

carotene, lycopene, lutein, and cryptoxanthin. Lycopene is the red pigment in ripe tomatoes, and β -carotene is the orange pigment in carrots (Milani et al. 2017).

Vitamin A (retinol) and its bioactive metabolite, retinoic acid (RA), share a polyene backbone structure with β -carotene. During the development of our immune system, RAs are critical checkpoint immune-modulators for maintaining the immune system (Carratu et al. 2012, Brown and Noelle 2015). RA-induced Foxp3⁺ Treg cells maintain the stable immune tolerance against innocuous antigens, thus preventing excessive, self-destructive immune responses that could lead to the development of inflammatory bowel disease and autoimmune disease. RAs have also been shown to regulate the differentiation of CD4⁺ T cells, Th1 lineage stability, and the balance of the Th1/Th17 versus the Th2 response (Brown and Noelle 2015).

A number of studies have examined the effects of β -carotene and other carotenoids on immune function in healthy volunteers (Hughes 2001). They have used β -carotene doses ranging from levels achievable from the diet (15 mg/day) to pharmacologic doses (180 mg/day) for periods of 14 to 365 days. Many immune-modulating effects have been observed, such as increases in the number of CD4⁺ T cells and the ratio of CD4⁺/CD8⁺ cells, as well as expression of activation markers, including IL-2 receptors and transferrin receptors on lymphocytes (Bryant and Prasad 1991, Watson et al. 1991, Murata et al. 1994). In addition, Santos et al observed that supplementation with β -carotene (50 mg on alternate days) significantly increased NK cell activity compared with that in the placebo group. Interestingly, after β -carotene supplementation for 10–12 years, elderly male participants (65–86 years old) had similar levels of NK cell activity as younger male subjects (51–64 years old), suggesting that β -carotene might be able to maintain a strong immune system in older people (Santos et al. 1996). Another interesting study compared the effects of different dietary carotenoids on the expression of antigen-presenting molecules (the MHC class II molecule (HLA-DR), intercellular adhesion molecule-I, and leukocyte function-associated antigen-3) on the surface of monocytes (Hughes et al. 2000). Hughes et al found that lycopene (found in tomatoes) and lutein (found in peas, watercress, and other vegetables) were less able than β -carotene to regulate the expression of antigen-presenting molecules on the surface of monocytes (Hughes et al. 2000), which is not surprising, given their low plasma levels after supplementation with 15 mg of lycopene or lutein daily. However, lycopene was found to reach higher concentrations in the prostate than in serum (Gerster 1997), which could contribute to the reduced risk of prostate cancer associated with the consumption of tomato-based foods (Clinton et al. 1996). Outcomes of human studies can also be influenced by many other confounding factors, such as age, gender, race, and baseline levels of carotenoids in the participants' plasma. Santos et al also conducted two studies in elderly subjects: a short-term, high-dose study (90 mg/day for 21 days) in women and a longer-term, lower-dose trial (50 mg on alternate days for 10 to 12 years) in men. Neither study showed significant changes in the functions or numbers of lymphocyte subsets (CD3⁺, CD4⁺, CD8⁺ T cells, and CD19⁺ B cells) (Santos et al. 1997). Another intervention study, in Ireland, gave elderly volunteers (>65 years old) either placebo, 8.2 mg of β -carotene, or 13.3 mg of lycopene daily for 12 weeks. This study found no changes in T cell subsets or their expression of functional surface molecules despite significant increases in plasma levels of these carotenoids, suggesting that supplementing with relatively low levels of carotenoids in

a well-nourished population may not substantially affect the immune system (Corridan et al. 2001). This may also explain inconsistent observations between epidemiologic studies (Ziegler, Mayne, and Swanson 1996, Sommer and Vyas 2012) and intervention trials (Alpha-Tocopherol 1994, Hennekens et al. 1996, Omenn et al. 1996, Watkins et al. 2000) regarding the effects of β -carotene intake on lung cancer risk.

In light of the essential role of RAs in the immune system, all-trans RAs have been used to treat cutaneous T cell lymphoma (Zhang and Duvic 2003, 2006, Huen and Kim 2015) and hematological malignancies (Montrone et al. 2009), including acute promyelocytic leukemia (APL) (Castaigne et al. 1990, Tallman et al. 1997, Tallman et al. 2002). Human clinical trials have shown that supplementation with all-trans RAs significantly improve disease-free and overall survival of patients compared to chemotherapy alone. The mechanisms could involve promoting differentiation and maturation of leukemic promyelocytes (Castaigne et al. 1990, Tallman et al. 1997, Tallman et al. 2002). In addition, in a mouse model of APL, all-trans RAs in combination with DNA vaccination effectively boosted the production of IFN- γ and increased the number of cytotoxic T cells (CD4⁺ and CD8⁺) (Furugaki et al. 2010).

Furthermore, several studies, including animal studies (Kusmartsev et al. 2003, Song et al. 2009) and human clinical trials (Recchia et al. 2005, Recchia et al. 2001, Recchia, Cesta, and Rea 2003, Recchia et al. 2006, Mirza et al. 2006, Haque, Banik, and Ray 2007), have reported that RA exerts certain immune-modulating effects on solid tumors. For example, 13-*cis* RA combined with IL-2 significantly prolonged overall survival when 44 patients with advanced ovarian cancer were compared with 82 well-matched patients receiving standard therapies (102 versus 29 months). IL-2/RA treatment strongly increased the number of NK cells and the CD4⁺/CD8⁺ ratio after 1 and 2 years of treatment (Recchia et al. 2005). Similar results were observed in two other clinical trials. One involved patients with metastatic solid tumors who had undergone aggressive surgery and chemotherapy (Recchia et al. 2001, Recchia, Cesta, and Rea 2003), and the other was a multicenter phase II study of patients with non-small-cell lung cancer (Recchia et al. 2006). RAs also dramatically suppressed the number of immature myeloid suppressor cells (ImC) (Lin⁻HLA-DR⁻CD33⁺) and significantly increased the tetanus-toxoid-specific T cell response in patients with metastatic renal cell carcinoma. However, these RA-mediated effects were observed only in patients with high plasma concentrations of RAs (>150 ng/ml) but not in patients with lower concentrations (<135 ng/ml) (Mirza et al. 2006). In addition, a combination of RAs and IFN- γ showed promise as chemoimmunotherapy for patients with glioblastoma (Haque, Banik, and Ray 2007).

In summary, baseline levels of carotenoids in plasma should be taken into account when designing clinical trials, giving that this effect has contributed to discrepancy of study outcomes. Encouragingly, the combination of RA with IL-2 demonstrated promising anti-cancer and immune-modulating effects in patients with solid tumors, making RA a potential adjuvant agent.

Curcumin

Curcumin (diferuloylmethane), also a carotenoid, is the primary active polyphenolic component of turmeric, a yellowish powder derived from *Curcuma longa* of the *Zingiberaceae* (ginger) plant family (Bose et al. 2015, Jagetia and Aggarwal 2007, Gautam, Gao, and Dulchavsky 2007, Srivastava et al. 2011). Curcumin has been widely used in traditional Indian and Chinese medicine for centuries, mainly to treat inflammatory diseases including viral infection, arthritis, colitis and hepatitis (Bose et al. 2015, Jagetia and Aggarwal 2007, Gautam, Gao, and Dulchavsky 2007, Srivastava et al. 2011, Mollazadeh et al. 2017). Given its anti-inflammatory effects, curcumin has also been intensively studied as an anti-cancer agent in the past several decades, and promising anti-tumorigenic potential has been reported. Importantly, many animal studies have revealed that curcumin can modulate cancer immunology by enhancing the cytolytic function of immune cells and inhibiting the immunosuppressive cancer microenvironment (Bhattacharyya et al. 2010, Shao et al. 2017, Singh et al. 2013, Lu et al. 2016, Liu et al. 2016, Churchill et al. 2000, Luo et al. 2011, Chang et al. 2012, Bhattacharyya et al. 2007, Mukherjee, Hussaini, et al. 2018, Mukherjee, Baidoo, et al. 2018, Pal et al. 2005, Shiri et al. 2015, Bose et al. 2015).

One group gave daily curcumin to Swiss albino mice who bore Ehrlich's ascites carcinoma cells. They observed significantly less tumor growth and enhanced survival rates. Curcumin prevented the loss of CD4⁺ T helper cells and CD8⁺ cytolytic T cells and diminished the Treg cell population (CD4⁺CD25⁺Foxp3⁺) in circulating blood, lymph nodes, and tumors. Curcumin also switched the Th2-type response to the Th1-type response by increasing IFN- γ secretion and decreasing the production of IL-4, TGF- β , and IL-10 (Bhattacharyya et al. 2010). In another study, C57BL/6 mice bearing Lewis lung carcinoma (LLC) received 50 mg/kg curcumin, which restored levels of CD4⁺ and CD8⁺ T cells and inhibited the production of Arg-1, ROS, and IL-6 by MDSCs (Liu et al. 2016). Also, a cocktail of natural compounds—1.28 mM⁺ TriCurin (1.28 mM curcumin:0.32 mM epicatechin gallate:4 mM resveratrol)—increased levels of tumor-infiltrating NK cells and CD8⁺ cytolytic T cells in C57BL/6 mice bearing HPV⁺ mouse lung cancer (TC-1 cells). In addition, TriCurin repolarized M2-like TAMs (Arg-1^{high}IL-10^{high}IL-12^{low}) to M1-like TAMs (iNOS^{high}IL-10^{low}IL-12^{high}) in the tumors (Mukherjee, Hussaini, et al. 2018).

Many other studies involving either genetic models (Churchill et al. 2000) or xenograft models of other types of cancer (Luo et al. 2011, Chang et al. 2012, Bhattacharyya et al. 2007, Pal et al. 2005, Shiri et al. 2015) have demonstrated that curcumin can reverse the tumor-favoring microenvironment, leading to further investigations of curcumin combined with standard cancer therapies. One study combined the anti-PD-L1 antibodies with bisdemethoxycurcumin (BDMC), a natural dimethoxy derivative of curcumin, in C57BL/6 mice with metastasized bladder cancer (MB49 cells) (Shao et al. 2017). They observed that BDMC alone increased levels of tumor-infiltrating CD8⁺ T cells, IFN- γ secretion in the blood, and decreased the number of tumor-infiltrating MDSCs. Importantly, the combination of anti-PD-L1 antibodies with curcumin further enhanced the secretion of IFN- γ , granzyme B, and perforin from CD8⁺ T cells. Furthermore, curcumin has been combined with vaccines against tumor development. For instance, one group applied two vaccination strategies to BALB/c mice bearing triple-negative breast tumors (4T1 cells) (Singh et al. 2013). One

strategy gave the mice curcumin and all the vaccinations after tumors had developed. The other treated the mice with curcumin before they were inoculated with tumor cells and then vaccinated the animals after tumors developed. For the vaccine, they used attenuated *Listeria monocytogenes* encoding tumor-associated antigen against metastasis (*Listeria*^{at}-Mage-b). Interestingly, the second strategy was more effective against metastasis than the first, as it decreased the production of MDSCs and IL-6, and increased levels of IL-12 and IFN- γ .

Despite the accumulating evidence that curcumin is an anti-cancer agent, research in this area is still challenged by one main obstacle: curcumin's low bioavailability (Panda et al. 2017). To overcome this problem, curcumin molecules have been modified. For example, curcumin liposomes were prepared and given to C57BL/6 mice bearing glioblastoma (GL261 cells) (Mukherjee, Baidoo, et al. 2018). A larger number of activated NK cells were recruited into the tumors, and TAMs were repolarized from M2-like (Arg-1^{high}) to M1-like (iNOS^{high}). However, this study found that TriCurin produced stronger immune-modulating effects than curcumin liposomes alone. Another study investigated the anti-tumor effects of a curcumin–polyethylene glycol conjugate (CUR-PEG, an amphiphilic CUR-based micelle) combined with a lipid-based Trp2 peptide vaccine in melanoma (B16F10 cells)-bearing C57BL/6 mice (Lu et al. 2016). The resulting synergistic effect associated with increased CD8⁺ cytolytic T cells, TNF- α secretion, and IFN- γ production along with decreased levels of tumor-infiltrating MDSCs and Treg cells.

In summary, curcumin is one of the most widely studied natural anti-cancer compounds. Strong evidence from *in vitro* and *in vivo* studies have demonstrated its promising chemoprotective effects. Its potential to modulate cancer immunology has been proposed as one of the mechanisms. However, successful transition from the lab to the clinic will need a solution to the issue of its low bioavailability.

Several human clinical trials have used new drug delivery systems to optimize plasma levels of curcumin when investigating the potential effects of curcumin in cancer patients. Curcumin was found to improve quality of life and reduce the systemic inflammation induced by chemotherapy (Kanai et al. 2013, Hejazi et al. 2016, Pan, Skaer, et al. 2017, Dhillon et al. 2008, Epelbaum et al. 2010, Parsons et al. 2016, Mahammedi et al. 2016, Panahi et al. 2014). Only a few studies have examined the potential immune-modulating effects of curcumin in humans, however. For example, 2 weeks of curcumin treatment increased the number of Th1 cells but decreased the number of Treg cells in peripheral blood of lung cancer patients (Zou et al. 2018). Similar results were observed in colorectal cancer patients (Xu, Yu, and Zhao 2017). Thus, further investigations of combining curcumin with standard cancer therapies could be a new field of cancer research.

Resveratrol

Resveratrol (3,4',5-trihydroxy-trans stilbene) is a non-flavonoid polyphenolic antioxidant found predominantly in grapes (*Vitis vinifera*) but also in many other natural sources, including peanuts, soy, and berries (Varoni et al. 2016, Udenigwe et al. 2008). The suggestion that the “French paradox”—the interesting observation that the mortality rate from coronary heart disease is much lower in France than in other European countries and

the USA—could be attributed to the high consumption of red wine in that country drew close attention to resveratrol, red wine's primary active ingredient. Since then, many potential benefits of resveratrol, such as antioxidation, anti-inflammation, neuroprotection, anti-proliferation, and immune-modulation, have been discovered (Katiyar 2008, Leischner et al. 2016, Soto et al. 2011, Tong et al. 2011).

Resveratrol has been shown to enhance cytolytic immune responses and reverse immune suppression in the tumor microenvironment (Lee-Chang et al. 2013, Chen et al. 2015, Yang et al. 2008, Pan, Shen, et al. 2017, Zhang et al. 2005, Chang et al. 2016, Li et al. 2007, Guan et al. 2012). For example, one group investigated the immune-modulating effects of resveratrol in the triple-negative breast cancer (4T1 cells)-bearing BALB/c mice and in the melanoma (B16F10 cells)-bearing C57BL/6 mice (Lee-Chang et al. 2013). Resveratrol significantly reduced levels of Breg cells (CD25⁺CD81^{high} cells within CD19⁺ B cells) and Foxp3⁺ Treg cells, though it did not affect MDSCs. In addition, resveratrol activated CD8⁺ cytolytic T cells. In renal cancer (Renca cells)-bearing BALB/c mice, resveratrol significantly increased the number and activity of CD8⁺ cytolytic T cells, but not NK cells, as well as decreased the percentage of Treg cells, but not MDSCs, in tumors. Resveratrol also switched the Th2-like immune response (IL-6 and IL-10 secretion) to favor the Th1-like response (IFN- γ secretion) in the tumor microenvironment (Chen et al. 2015). Moreover, enhanced NK cell cytotoxicity was observed during resveratrol treatment in skin lymphocytic leukemia (L1210 cells)-bearing BALB/c mice (Li et al. 2007). Furthermore, grape seed proanthocyanidins have been reported to significantly increase NK cell cytotoxicity, as well as the percentages of CD4⁺ T helper cells and CD8⁺ cytolytic T cells in sarcoma (S180 cells)-bearing BALB/c mice (Zhang et al. 2005). Interestingly, that study observed that grape seed proanthocyanidins enhanced the anti-tumor effects of doxorubicin. They completely reversed the side effects induced by doxorubicin treatment, which included reduced levels of IFN- γ and IL-2 and suppressed NK cell function (Zhang et al. 2005).

Clinical studies with healthy volunteers have demonstrated that resveratrol can be safely administered (Brown et al. 2010, Chow et al. 2010, Boocock et al. 2007, Espinoza et al. 2017). Importantly, a recent study that examined the effects of resveratrol on circulating T cell subsets in healthy volunteers found that it significantly increased the number of circulating Treg cells (CD3⁺CD4⁺CD25⁺CD127⁻) and CD3⁺NKG2D⁺ T cells while decreasing plasma levels of proinflammatory cytokines such as TNF- α and monocyte chemoattractant protein (MCP-1) (Espinoza et al. 2017). Though several clinical trials have given resveratrol to cancer patients (van Die et al. 2017, Paller et al. 2015, Howells et al. 2011, Patel et al. 2010), the results are not yet available.

In summary, the benefits of red wine are widely recognized, but most studies of resveratrol have focused on cardiovascular diseases and diabetes. Therefore, more studies are needed to evaluate the effects of resveratrol, alone or in combination with standard therapies, in cancer patients.

(-)-Epigallocatechin-3-gallate (EGCG)

Tea plants (*Camellia sinensis*) have been grown in Asia for thousands of years, and tea consumption has become the second-most common beverage worldwide. This high popularity can be attributed to tea's charming smell and flavor as well as to its multiple health benefits, including antioxidative, anti-inflammatory, antimicrobial, anti-carcinogenic, anti-hypertensive, neuroprotective, cholesterol-lowering, and thermogenic properties (Hayat et al. 2015, Crespy and Williamson 2004, Katiyar, Elmets, and Katiyar 2007). Moreover, many epidemiologic studies have suggested that green tea consumption associates with chemoprotective effects against cancer (Shirakami, Shimizu, and Moriwaki 2012). The primary active ingredients in green tea are epigallocatechin-3-gallate (EGCG), epicatechin, epicatechin-3-gallate, and epigallocatechin (Butt and Sultan 2009). Multiple anti-cancer mechanisms have been reported, such as induction of apoptosis, promotion of cell growth arrest, alteration of cell cycle regulatory proteins, activation of killer caspases, and suppression of the nuclear factor kappa-B (NF- κ B) pathway (Butt and Sultan 2009, Shirakami, Shimizu, and Moriwaki 2012). Several animal studies have shown that EGCG modulates the immune system in tumor-bearing mice (Santilli et al. 2013, Kang et al. 2007, Huang et al. 2013, Mantena, Roy, and Katiyar 2005, Hsieh et al. 2011).

One group used two xenograft models, SHSY5Y tumor-bearing NOD/SCID mice and neuro 2A tumor-bearing A/J mice, to investigate the immune-modulating effects of Polyphenon E, a clinical-grade mixture of green tea catechins, against neuroblastoma (Santilli et al. 2013). Polyphenon E shifted the balance from monocytic MDSCs (CD11b⁺Ly6G⁻Ly6^{high}) toward granulocytic MDSCs (CD11b⁺Ly6G⁺Ly6^{low}) by enhancing myeloid cell maturation and upregulating the secretion of granulocyte colony stimulating factor (G-CSF) in monocytic MDSCs. These effects rescued the MDSC-suppressed production of IFN- γ in T cells and increased the number of tumor-infiltrating CD8⁺ cytolytic T cells (Santilli et al. 2013). In a model of mice bearing E7-expressing tumors (TC-1 cells), EGCG significantly increased the E7-specific (antigen-specific) CD8⁺ T-cell immune response (IFN- γ secretion) in tumors (Kang et al. 2007). E7 is an oncoprotein in the human papilloma virus. It induces and maintains cancer cell transformation, making it a perfect candidate for a targeted vaccine. Moreover, EGCG has been reported to increase NK cell cytotoxicity in leukemia (WEHI-3 cells)-bearing BALB/c mice (Huang et al. 2013) and in bladder cancer (MBT-2 cells)-bearing C3H/He mice (Hsieh et al. 2011).

In several human clinical trials, evidence for EGCG-mediated benefits against solid tumors was largely lacking (Lazzeroni et al. 2017, Gee et al. 2017, Zhao et al. 2016, Zhao et al. 2014, Crew et al. 2012). In contrast, one group evaluated the safety and clinical efficacy of Polyphenon E in patients with early stage chronic lymphocytic leukemia (CLL) (Shanafelt et al. 2009, Shanafelt et al. 2013). Polyphenon E was well tolerated, and reduction in absolute lymphocyte count and/or lymphadenopathy was observed in the majority of patients. Similarly, another group found that green tea extract reduced or stabilized lymphocytosis and lowered the number of circulating Treg cells in 90% of CLL subjects. In addition, both IL-10 and TGF- β levels in the serum decreased during the period of green tea consumption (D'Arena et al. 2013). These studies highlight the possibility that green tea could become a

chemopreventive agent against hematological malignancies. However, the effects of green tea on solid tumors are yet to be determined.

β -Glucans

β -glucans are a group of polysaccharides found in the cell walls of bacteria, fungi (including mushrooms), and cereals such as barley and oats. All β -glucans are glucose polymers that share a β 1–3 linear glycosidic chain core but differ in length and branching structures. Two main types of branching are β 1–4 glycosidic chains in β -glucans from bacteria and β 1–6 glycosidic chains in β -glucans from fungi (Aleem 2013). Epidemiological studies show that diets containing β -glucans may prevent or slow the development of cancer, including gastric cancer and breast cancer. However, β -glucans are administered mostly to improve quality of life and overall survival in patients undergoing chemotherapy or radiation treatment (Aleem 2013).

Various β -glucan extracts have been investigated in clinical studies, including Lentinan from shiitake mushrooms (*Lentinus edodes*), Schizophyllan (SPG) from *Schizophyllum commune*, Krestin (PSK and PSP) from *Trametes (Coriolus or Polyporus) versicolor*, Maitake from *Grifola frondosa*, *Agaricus sylvaticus*, and *A. blazei*. These fungal extracts have had beneficial effects on patients with cancers, including gastric cancer, colorectal cancer, esophageal cancer, hepatocellular carcinoma, pancreatic cancer, breast cancer, lung cancer, stomach cancer, and leukemia (Aleem 2013, Roudi et al. 2017, Ramberg, Nelson, and Sinnott 2010, Chan, Chan, and Sze 2009, Murphy, Davis, and Carmichael 2010, Jin et al. 2012, Roupas et al. 2012, Standish et al. 2008). For example, enhanced number and/or activity of NK cells were reported in studies of an extract from *Agaricales* mushrooms—*Agaricus blazei* Murill Kyowa (ABMK)—in patients with different types of cancer, including cervical, ovarian, endometrial (Ahn et al. 2004), and breast cancer (Novaes et al. 2011). Similar results were obtained with Ganopoly, a polysaccharide extract of *Ganoderma lucidum* (Lingzhi), in advanced-stage cancer patients (Gao et al. 2003, Chen et al. 2006); with *Lentinula edodes* mycelia (LEM) extract in breast cancer patients (Nagashima et al. 2013) and gastrointestinal cancer patients (Okuno and Uno 2011, Yamaguchi, Miyahara, and Hihara 2011, Ina, Kataoka, and Ando 2013); with PSK in stage II–III colorectal cancer patients (Ohwada et al. 2006, Ohwada et al. 2004); and with SPG in stage III–IV head and neck cancer patients (Kano, Kakuta, and Hashimoto 1996). Moreover, evidence of glucan-mediated effects on T cells and their cytokine secretions have also been observed. Intratumoral SPG administration augmented tumor-infiltrating T cells in patients with stage II–III invasive cervical cancers (Nakano et al. 1996). SPG also increased CD4⁺ T helper cell and IL-2 production in regional lymph nodes of patients with stage III–IV head and neck cancer (Kano, Kakuta, and Hashimoto 1996). Ganopoly (Chen et al. 2006) and LEM (Okuno and Uno 2011) increased the number of CD3⁺, CD4⁺, and CD8⁺ T cells, as well as plasma levels of IL-2, IL-6, and IFN- γ , in advanced-stage cancer patients.

A two-stage model has been proposed to explain the mechanism of immune modulation by β -glucans (Murphy, Davis, and Carmichael 2010, Albeituni and Yan 2013, Wasser 2017). The first stage is initiated when β -glucans bind to dectin-1 and TLRs that are expressed on macrophages and DCs. β -glucans are then taken up by macrophages into endosomes, where

they are fragmented and transported to the spleen, lymph nodes, and bone marrow for release. The second stage is achieved by NK cells or granulocytes that express complement receptor 3 (CR3) on their surface. The β -glucan fragments released by macrophages are recognized by CR3, which triggers signaling pathways that eventually release cytokines and stimulate adaptive immune responses, such as CR3-dependent cellular cytotoxicity (CR3-DCC).

In summary, glucans, with largely diverse structures, are becoming promising adjuvant anti-cancer agents. Some have been standardized and clinically approved, such as Lentinan, which has been used clinically against several types of cancer in Japan since the early 1980s. However, most of the abovementioned mushrooms grow in Asia, where most of the clinical trials were conducted. This could limit their use in other regions of the world.

Summary

The current review summarizes some immune-modulating effects of natural compounds as determined in human clinical trials and tumor-bearing animal models. Promising results have been observed mainly in animal studies, and mostly in xenograft mouse models where the tumor microenvironment could be significantly different from that in cancer patients and genetically modified models (Olive et al. 2009). Therefore, further investigations need to consider the similarity of the tumor microenvironment in cancer patients and proposed animal models. Ultimately, efficacy in cancer patients needs to be fully examined.

Large epidemiologic studies have suggested that diet could influence the risk of at least certain types of cancer. For example, a higher intake of fruits and vegetables might associate with a lower risk of colorectal cancer (Pan, Yu, and Wang 2018). Indeed, fruits and vegetables are enriched in many well-studied chemopreventive agents, such as curcumin and resveratrol. However, the relationship between diets that might lower cancer risk and their effects on the immune system remains largely unknown. It certainly would be valuable to investigate whether natural compounds and dietary components could strengthen the immune system in populations at high risk for cancer.

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Abbreviations:

ABMK	<i>Agaricus blazei</i> Murill Kyowa
APCs	antigen-presenting cells
APL	acute promyelocytic leukemia
Arg-1	arginase 1
BDMC	bisdemethoxycurcumin

Breg	B regulatory
CLL	chronic lymphocytic leukemia
CR3	complement receptor 3
CR3-DCC	CR3-dependent cellular cytotoxicity
CUR-PEG	curcumin–polyethylene glycol conjugate
DCs	dendritic cells
EGCG	(–)-epigallocatechin-3-gallate
G-CSF	granulocyte colony stimulating factor
IFN-γ	interferon gamma
IL-2	interleukin-2
ImC	immature myeloid suppressor cells
iNOS	inducible NOS
KIRs	killer cell inhibitory immunoglobulin-like receptors
LEM	<i>Lentinula edodes</i> mycelia
LLC	Lewis lung carcinoma
MCP-1	monocyte chemoattractant protein
MDSCs	myeloid-derived suppressor cells
MHC	major histocompatibility complex
M-MDSCs	monocytic MDSCs
MMP	matrix metalloproteinase
NCRs	natural cytotoxicity receptors
NF-κB	nuclear factor kappa-B
NK	natural killer
NO	nitric oxide
PD-1	programmed cell death marker
PMN-MDSCs	polymorphonuclear MDSCs
RA	retinoic acid
ROS	reactive oxygen species
TAMs	tumor-associated macrophages

TLRs	Toll-like receptors
TNF-α	tumor necrosis factor alpha
Treg	T regulatory
VEGFs	vascular endothelial growth factors

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Figure 1: The schematic summary of immune-modulating effects of natural compounds in humans.

Curcumin and green tea have shown to suppress Treg cell function, and mushroom extracts (LEM, PSK, SPG, AMBK, and GLPS) have shown to enhance T and NK cell function in humans.

Figure 2: The schematic summary of immune-modulating effects of natural compounds in tumor-bearing mice.

Curcumin, all-trans retinoic acid (ATRA), resveratrol, and EGCG have shown to suppress MDSCs, TAMs and Treg cells, as well as enhance T and NK cell function.

Table 1.

Immune-modulating effects of natural compounds in human studies

Compound	Doses	Human participants	Effects	Refs
β -carotene	50 mg on alternate days for 10–12 years or placebo	38 middle-aged men 51–64 y, 21 elderly men 65–86 y	Increased NK cell activities in elderly men to levels similar to those in younger men	Santos, 1996
β -carotene	15 mg daily for 26 days or placebo	25 healthy nonsmoking men	Increased the percentages of monocytes expressing antigen-presenting molecules	Hughes, 2000
β -carotene	90 mg daily for 21 days or placebo	25 healthy elderly women 60–80 y	No differences in the profiles of lymphocyte subsets (CD3 ⁺ , CD4 ⁺ , CD8 ⁺ T cells, and CD19 ⁺ B cells)	Santos, 1997
	50 mg on alternate days for 10–12 years or placebo	50 healthy elderly men 50–86 y		
Lycopene	13.3 mg daily for 12 weeks or placebo	58 healthy volunteers >65 years	No differences in T cell subsets and their expression of functional surface molecules	Corridan, 2001
β -carotene	8.2 mg daily for 12 weeks or placebo			
Curcumin	3 g daily for 2 weeks	30 non-small-cell lung cancer patients	Increased Th1 cells, decreased Treg cells in peripheral blood	Zou, 2018
Curcumin	3 g daily for 1 month	40 advanced colon cancer patients	Increased Th1 cells, decreased Treg cells in peripheral blood	Xu, 2017
Resveratrol	1 g daily for 28 days	9 healthy volunteers	Increased the number of circulating Treg cells (CD3 ⁺ CD4 ⁺ CD25 ⁺ CD127 ⁻) and CD3 ⁺ NK G2D ⁺ T cells	Espinoza, 2017
			Decreased levels of proinflammatory cytokines in plasma, such as TNF- α and MCP-1	
Polyphenon E	400–2000 mg daily for up to 6 months	33 Rai stage 0-II CLL patients	Decreased absolute lymphocyte count (ALC)	Shanafelt, 2009
Polyphenon E	2000 mg daily for up to 6 months	42 Rai stage 0-II CLL patients	Decreased absolute lymphocyte count (ALC)	Shanafelt, 2013
Green tea extract	4 capsules daily for 1 month + 6 capsules for 5 months	12 Rai stage 0 CLL patients	Decreased lymphocytosis and circulating Treg cells	D'Arena, 2013
	6 capsules contain 4602 mg of green tea leaves, 189 mg of EGCG, and 97.5 mg of caffeine		Decreased IL-10 and TGF- β serum levels	
<i>Agaricus blazei</i> Murill Kyowa (ABMK)	9 packs daily for 9 weeks	100 gynecological cancer patients	Increased NK cell activity	Ahn, 2004

Compound	Doses	Human participants	Effects	Refs
<i>Ganoderma lucidum</i> polysaccharide (GLPS)	1800 mg daily for 12 weeks	34 advanced-stage cancer patients	Increased the absolute number of CD56+ NK cells	Gao, 2003
			Increased levels of IL-2, IL-6, and IFN- γ in plasma	
			Decreased levels of IL-1 and TNF- α in plasma	
<i>Ganoderma lucidum</i> polysaccharide extract	1800 mg daily for 12 weeks	47 advanced colorectal cancer patients	Increased the number of CD3+, CD4+, CD8+, and CD56+ lymphocytes	Chen, 2006
			Increased NK cell activities	
			Increased levels of IL-2, IL-6, and IFN- γ in plasma	
<i>Lentinula edodes</i> mycelia extract (LEM)	1800 mg daily for 3 weeks	10 breast cancer patients with nodal metastases	Decreased levels of IL-1 and TNF- α in plasma	Nagashima, 2013
			Prevented chemotherapy-induced decline in cytotoxic activities of NK and LAK cells	
			Prevented chemotherapy-induced decline in the proportion of activated NK and NK T cells in lymphocytes	
<i>Lentinula edodes</i> mycelia extract (LEM)	1800 mg daily for 4 weeks	1 gastric and 7 colorectal cancer patients	Increased IFN- γ production by CD4+ T, CD8+ T, and CD56+ NK/NKT cells	Okuno, 2011
Protein-bound polysaccharide K (PSK)	3 g daily for 2 years	139 stage III colorectal cancer patients	Increased the number of NK cells	Ohwada, 2006
Sizofiran (SPG)	20 mg injected intramuscularly at 5 and 2 days before surgery	40 stage III–IV head and neck cancer patients	Increased cytotoxic activities of NK cells and LAK cells	Kano, 1996
			Increased CD4+ T cells in lymph nodes	
			Increased IL-2 production	
Sizofiran (SPG)	0.2 mg or 20 mg injected intramuscularly 7 and 3 days before radiation therapy	45 stage II–III invasive cervical cancer patients	Increased tumor-infiltrating T cells	Nakano, 1996

Table 2.

Immune-modulating effects of natural compounds in tumor-bearing mice

Compound	Doses	Animal models	Effects	Refs
All-trans retinoic acid (ATRA)	Subcutaneous implantation of 5 mg ATRA + PML-RAR α DNA vaccine	Acute promyelocytic leukemia (APL)	Increased the production of IFN- γ Enhanced cytotoxic T cells (CD4+ and CD8+)	Furugaki, 2010
All-trans retinoic acid (ATRA)	Subcutaneous implantation of 5 mg ATRA (21-day release) + HA-specific vaccine/C3 peptide-specific vaccine	7,12-dimethylbenz(a)anthracene-induced mamalian adenocarcinoma (DA3-HA cells injected to BALB/c mice) Methylcholanthrene-induced sarcoma (MethA cells injected into BALB/c mice) Fibrosarcoma (C3 cells injected into C57BL/6 mice)	Decreased immature myeloid cells (ImCs)	Kusmartsev, 2003
Curcumin	Oral 50 mg/kg on alternate days for 14 days	Ehrlich's ascites carcinoma (EAC) cells injected into Swiss albino mice	Curcumin Diminished the Treg cell population (CD4+CD25+Foxp3+) Increased IFN- γ secretion, decreased production of IL-4, TGF- β , and IL-10. Reversed Th2-type immune bias	Bhattacharyya, 2010
Curcumin	Oral 50 mg/kg every day for 20–25 days	Lewis lung carcinoma (LLC) cells injected into C57BL/6 mice	Reduced the accumulation of MDSCs in spleen and tumors Promoted the maturation and differentiation of MDSCs Inhibited the expression of Arg-1 and ROS in purified MDSCs Decreased the level of IL-6 in tumor tissue and serum	Liu, 2016
TriCurin	1.28 mM+ TriCurin (1.28 mM curcumin + 0.32 mM epicatechin gallate + 4 mM resveratrol)	HPV+ mouse lung cancer (TC-1 cells injected into C57BL/6 mice) Head and neck squamous cell carcinoma (UMSCC47 cells injected into athymic nude/nude mice)	Increased tumor-infiltrating NK cells and CD8+ cytolytic T cells Repolarized M2-like TAMs (Arg-1 ^{high} IL-10 ^{high} IL-12 ^{low}) to M1-like TAMs (iNOS ^{high} IL-10 ^{low} IL-12 ^{high}) in the tumors	Mukherjee, 2018
Curcumin	0.1% in AIN-76A diet till 110 days of age	Familial adenomatous polyposis (Apc ^{Min/+} mice)	Increased mucosal CD4+ T cells and B cells	Churchill, 2000

Compound	Doses	Animal models	Effects	Refs
Bisdemethoxycurcumin (BDMC)	3 mg/kg every 3 days for 2–3 weeks, i.v. + 200 µg α-PD-L1 antibody for 2–4 weeks, i.p.	Mouse bladder carcinoma (MB49 cells injected into C57BL/6 mice)	Increased intratumoral CD8+ T cell infiltration	Shao, 2017
			Increased the level of IFN-γ	
			Decreased the number of intratumoral myeloid-derived suppressor cells	
			α-PD-L1 facilitated the secretion of IFN-γ, granzyme B, and perforin through these CD8+ T-cells	
Curcumin	Oral 0.8 or 2 g/kg curcumin daily + <i>Listeria</i> ^Δ Mage-b vaccine	Triple-negative breast cancer (4T1 cells injected into BALB/c mice)	Decreased levels of IL-6 and increased IL-12 production by MDSCs	Singh, 2013
			Improved CD4 and CD8 T cell responses	
TriCurin liposome (TrLp) or curcumin liposome (CLp)	TrLp (1.28 mM+) or CLp (5 mM) daily for 5 days or every 72 h for 60 days	Mouse glioblastoma (GL261 cells injected into C57BL/6 mice)	Increased activated NK cells in tumors	Mukherjee, 2018
			TAMs repolarized from M2-like (Arg-1 ^{high}) to M1-like (iNOS ^{high}).	
			TrLp more effective than CLp	
Curcumin–polyethylene glycol conjugate (CUR–PEG)	40 mg/kg CUR–PET every other day, i.v. + TRP2 peptide vaccine	Melanoma (B16F10 cells injected into C57BL/6 mice)	Increased cytotoxic T lymphocyte response and IFN-γ production	Lu, 2016
			Decreased levels of tumor-infiltrating MDSCs and Treg cells	
			Decreased levels of IL-6	
Resveratrol	20 mg or 50 mg/mouse on alternate days for 19 days, i.p. 50 mg or 500 mg/mouse on alternate days for 14 days, i.p.	Triple-negative breast cancer (4T1 cells injected into BALB/c mice) Melanoma (B16F10 cells injected into C57BL/6 mice)	Decreased B regulatory cells (Breg, CD25+CD81 ^{high} cells within CD19+ B cells) and Foxp3+ Treg cells	Lee-Chang, 2013
			Activated CD8+ cytolytic T cells	
Resveratrol	1, 2.5, and 5 mg/kg daily for 22 days, i.p.	Renal cancer (Rencac cells injected into BALB/c mice)	Increased the number and cytotoxicity of CD8+ T cells	Chen, 2015
			Switched from expression of Th2 cytokines (IL-6 and IL-10) to Th1 cytokines (IFN-γ)	
Resveratrol	Oral 12.5, 25, 50 mg/kg daily for 3 weeks	Mouse lymphocytic leukemia (L1210 cells injected into BALB/c mice)	Increased NK cell activity	Li, 2007

Compound	Doses	Animal models	Effects	Refs
Grape seed proanthocyanidins	Oral 200 mg/kg proanthocyanidins daily + 2 mg/kg doxorubicin on alternate days for 9 doses, i.p.	Mouse sarcoma (S180 cells injected into BALB/c mice)	Increased NK cell cytotoxicity and percentages of CD4 ⁺ T helper cells and CD8 ⁺ cytolytic T cells	Zhang, 2005
			Reversed doxorubicin-induced side effects, including lower levels of IFN- γ , IL-2 expression and NK cell function	
Polyphenon E	0.3% in the drinking water	Mouse neuroblastomas (Transgenic TH-MYCN mice; Human SHSY5Y cells injected into NOD/SCID mice; Syngeneic Neuro 2A cells injected into A/J mice)	Shifted the balance from monocytic MDSCs (CD11b+Ly6G-Ly6 ^{high}) toward granulocytic MDSCs (CD11b+Ly6G+Ly6 ^{low})	Santilli, 2013
			Rescued MDSC-suppressed production of IFN- γ in T cells	
			Increased tumor-infiltrating CD8 ⁺ cytolytic T cells	
EGCG	0.5 mg/mL in drinking water for 78 days + 2 μ g pcDNA3-Sig/E7/LAMP-1 vaccine	E7-expressing tumors (TC-1 cells injected into C57BL/6 mice)	Increased the E7-specific CD8 ⁺ T-cell immune response (IFN- γ secretion)	Kang, 2007
EGCG	Oral 5, 20, and 40 mg/kg for two weeks	Mouse leukemia (WEHI-3 cells injected into BALB/c mice)	Increased the percentages of CD3 ⁺ T cells, CD19 ⁺ B cells, and macrophages	Huang, 2013
			Increased NK cell activity Reduced the percentage of CD11b ⁺ monocyte cells	
EGCG	Oral 2 mg	Mouse bladder cancer (MBT-2 cells injected into C3H/He mice)	Increased NK cell cytotoxicity	Hsieh, 2011