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Targeting the tumor immune microenvironment with "nutraceuticals": From bench to clinical trials

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ABSTRACT

The occurrence of immune effector cells in the tissue microenvironment during neoplastic progression is critical in determining tumor growth outcomes. On the other hand, tumors may also avoid immune system-mediated elimination by recruiting immunosuppressive leukocytes and soluble factors, which coordinate a tumor microenvironment that counteracts the efficiency of the antitumor immune response. Checkpoint inhibitor therapy results have indicated a way forward via activation of the immune system against cancer. Widespread evidence has shown that different compounds in foods, when administered as purified substances, can act as immunomodulators in humans and animals. Although there is no universally accepted definition of nutraceuticals, the term identifies a wide category of natural compounds that may impact health and disease statuses and includes purified substances from natural sources, plant extracts, dietary supplements, vitamins, phytonutrients, and various products with combinations of functional ingredients.

In this review, we summarize the current knowledge on the immunomodulatory effects of nutraceuticals with a special focus on the cancer microenvironment, highlighting the conceptual benefits or drawbacks and subtle cell-specific effects of nutraceuticals for envisioning future therapies employing nutraceuticals as chemoadjuvants.

Abbreviations: 4-MU, Coumarin 4-methylumbelliferone; APCs, Antigen presenting cells; ARG1, Arginase 1; ATRA, All-*trans* retinoic acid; BG, β-1,3/1,6-glucans derived from Saccharomyces cerevisiae; BMDCs, Bone marrow dendritic cells; CAFs, Cancer associated fibroblasts; CAPE, Caffeic acid phenethyl ester; ConA, Concanavalin A; COX, Cyclooxygenase; CR3, Complement receptor 3; CRC, Colorectal cancer; CTL, Cytotoxic T lymphocytes; CTLA4, Cytotoxic T-lymphocyte antigen-4; CUR, Curcumin; DATS, Diallyl trisulfide; DCs, Dendritic cells; DHA, Docosahexaenoic acid; DIM, 3,30-diindolylmethane; DMXAA, 5,6-dimethylxanthenone-4-acetic acid; DOX, Doxorubicin; DSS, Dextran sulphate sodium; EAT, Ehrlich ascites tumor; ECM, Extracellular matrix; EGCG, Epigallocatechin-3-*O*-gallate; EGF, Epidermal growth factor; EMT, Epithelial-to-mesenchymal-transition; EPA, Eicosapentaenoic acid; FA, Fatty acids; GA, Gallic acid; GIST, Gastrointestinal stromal tumor; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; GpS, Gynostemma pentaphyllum; GTE, Green tea extract; HA, Hyaluronan; HIF-1α, Hypoxia-inducible factor 1-alpha; HUVECs, Human umbilical vein endothelial cells; I3C, Indole-3-carbinol; ICAM-1, Intercellular adhesion molecule 1; IDO, Indoleamine 2,3-dioxygenase; IFN, Interferon; IgA, Immunoglobulin A; IL, Interleukin; ITCs, Isothiocyanates; LPS, Lipopolysaccharide; M1 or M2, Polarized macrophages; Man-3DG, α-mangostin 3-*O*-β-D-2-deoxyglucopyranoside; Man-6DG, α-mangostin 6-*O*-β-D-2-deoxyglucopyranoside; MCP-1, Monocyte chemoattractant protein-1; MDSCs, Myeloid-derived suppressor cells; MMPs, Matrix metalloproteinases; MVD, Microvessel density; NK, Natural killer; NO, Nitric oxide; Nrf2, Nuclear factor erythroid 2; NSCLC, Non-small cell lung cancer; P2Et, Gallotannin-rich standardized fraction; PBMC, Peripheral blood mononuclear cell; PIC, Piceatannol; PD-(L)1, Programmed death-1 and ligand; PFA, Poly-ferulic acid; PGE2, Prostaglandin E2; PMA, Phytoemoagglutinin; PMN, Polymorphonuclear; PPP, Picropodophyllin; PPP-40, Pinus koraiensis; PUFAs, Polyunsaturated fatty acids; RA, Retinoic acid; RES, Resveratrol; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; SCFA, Short-chain fatty acids; SDG, Secoisolariciresinol diglucoside; SFN, Sulforaphane; SOD, superoxide dismutases; STING, Stimulator of IFN genes; TAMs, Tumor-associated macrophages; tBregs, Tumor-evoked regulatory B cells; TGF-β, Transforming Growth Factor-β; TILs, Tumor infiltrating lymphocytes; TIMP, Tissue inhibitor of MMPs; TLRs, Toll-like receptor; TNF-α, Tumor necrosis factor-α; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; Tregs, Regulatory T cells; VEGF, Vascular endothelial growth factor; α-TEA, α-tocopheryloxyacetic acid; α-TOS, α-tocopheryl succinate.

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Contents

1. Introduction

The term "nutraceutical" was created by Dr. DeFelice from "nutrition" and "pharmaceutical" in 1989 (DeFelice, 2002; Kalra, 2003). To date, there is no international consensus on the definition of "nutraceutical" (Aronson, 2017). The Foundation for Innovation in Medicine (FIM), of which Dr. DeFelice is the founder and chairman, defines "nutraceuticals" as a comprehensive term that includes foods, dietary supplements [as defined in the Dietary Supplement Health and Education Act (DSHEA)] and medical foods that have a health-medical benefit, including the prevention and/or treatment of disease (DeFelice, 2002). On the other hand, widespread evidence has shown that different compounds in foods, when administered as purified substances, can act as immunomodulators in humans and animals. An immunomodulator is a substance or agent that modifies immune responses through its immunomodulatory properties by regulating immune cells and their released products (Spelman et al., 2006).

In this review, we summarize the current knowledge on the immunomodulatory effects of nutraceuticals with a special focus on the cancer microenvironment, highlighting the conceptual benefits or drawbacks and subtle cell-specific effects of nutraceuticals for envisioning future therapies employing nutraceuticals as chemoadjuvants.

1.1. Classification of nutraceuticals

Although there is no universally accepted definition of nutraceuticals (Aronson, 2017; Aryee and Boye, 2015), the term usually describes a wide category of natural compounds that may impact health and disease statuses and includes purified substances from natural sources, plant extracts, dietary supplements, vitamins, phytonutrients, and various products with combinations of functional ingredients (Schmitt & Ferro, 2013). Zeisel proposed the definition of nutraceuticals to be "diet supplements that deliver a concentrated form of a presumed bioactive agent from a food, presented in a nonfood matrix, and used to enhance health in dosages that exceed those that could be obtained from normal foods. (A good example is genistein purified from soybeans and delivered in a pill in dosages greater than could be consumed in soy)" (Zeisel, 1999). Nutraceuticals have been proposed as treatments for several diseases including arthritis, sleeping disorders, certain cancers (preventative), osteoporosis, hypertension, hypercholesterolemia, depression and diabetes (Das, Bhaumik, Raychaudhuri, & Chakraborty, 2012). Although the majority of nutraceuticals are of plant origin (phytochemicals), some are present in foods of animal origin (Pesce, Iacobini, & Menini, 2018). Nutraceuticals can be classified using different approaches. Some of the most common classification methods are based on food sources (dietary fiber, probiotics, prebiotics, polyunsaturated fatty acids, antioxidant vitamins, polyphenols and spices) (Verma & Mishra, 2016); oral bioavailability, which classifies nutraceuticals according to their bioaccessibility, absorption, and transformation characteristics (McClements, Li, & Xiao, 2015); food availability: (a) traditional nutraceuticals including nutrients, herbals, phytochemicals, probiotic microorganisms and nutraceutical enzymes and (b) nontraditional nutraceuticals including fortified and recombinant nutraceuticals (Chanda, Tiwari, Kumar, & Singh, 2019); or biochemical structure (Das et al., 2012). Biochemical nutraceutical categories include phenols, lipids, organic acids and polysaccharides, organosulfurs, phytic acid, phytosterols, and terpenes (Nwanodi, 2017) (Table 1).

2. Tumor immune microenvironment

The occurrence of immune effector cells in the tissue microenvironment during neoplastic progression is critical in determining the outcome of tumor growth. The development of cancer cells induces an immune response driven by cells of the innate immune system (innate lymphoid cells, natural killer (NK) T cells, γδ T cells, NK cells and macrophages) and then by cytotoxic (CTL, $CD8^+$) and helper (T_H, $CD4^+$) T lymphocytes producing interferon-γ (IFN-γ) that are recruited into the tumor microenvironment and induce cell death, further activation of NK cells and macrophages, the humoral response and inflammation. CTLs can kill target cancer cells by granzyme exocytosis and Fas ligand (FasL)-mediated apoptosis induction and can secrete IFN-γ and tumor necrosis factor-α (TNF-α) to induce cytotoxicity in cancer cells (Lei et al., 2020). T_H cells are essential for CTL function and action. Among T_H cell subsets, T_H1 cells release IFN-γ and activate macrophages that are proficient in eliminating intracellular pathogens, while T_H2 cells are mainly implicated in antibody production in response to extracellular antigens and helping B cells undergo antibody class switching (Ivanova & Orekhov, 2015). The differentiation of different subsets of T cells is contingent on the patterns of cytokine and receptor expression. T_H1 cells are produced in response to IFN-γ and interleukin (IL)-12, while T_H2 cells are produced in the presence of IL-4. T_H1 cells play a significant role in the antitumor response, releasing inflammatory cytokines and supporting cell-mediated killing of tumor cells (Ivanova & Orekhov, 2015). T_H2-polarized $CD4^+$ T cells, by secreting IL-4 and IL-13, induce tumor-associated macrophages (TAMs) to secrete pro-angiogenic growth factors, proteases and protumoral survival factors, such as vascular endothelial growth factor-A (VEGF-A), matrix metallopeptidase-9 (MMP-9), epidermal growth factor (EGF) and urokinase-type plasminogen activator (Binnewies et al., 2018). Commitment to the T_H1 lineage inhibits T_H2 differentiation and *vice versa* (Caza & Landas, 2015). T_H17 polarization occurs in the presence of IL-6 or IL-21 and transforming growth factor-β (TGF-β) without IL-4 or IL-12 in the microenvironment (Ivanova & Orekhov, 2015). The role of T_H17 cells in the tumor microenvironment is controversial and might be dependent on the type of cancer. IL-17 released by T_H17 cells promotes cancer progression through T regulatory (Treg) cell-mediated immunosuppression and a decrease in $CD8^+$ T cell activation (Renaude et al., 2020). In addition, extracellular ATP depletion by T_H17 cells also induces immunosuppression. On the other hand, T_H17 cells might exert antitumoral activity by activating tumor-specific $CD8^+$ T cells and promoting dendritic cell (DC) infiltration into tumors (Renaude et al., 2020).

Table 1
Biochemical nutraceutical classes and examples.

Classes	Subclasses	Phytochemical species		Examples	Reference
ORGANIC ACIDS				Acetic, propionic, butyric, formic, citric, malic, lactic, and tartaric acids	Pearlin et al. (2020); Quitmann, Fan, and Czermak (2014)
POLYSACCHARIDES				β-glucans, schizophyllan, ganoderma, krestin (from mushrooms), ginseng, chitosan, chitin	Del Cornò, Gessani, and Conti (2020); Giavasis (2013); Santa et al. (2014); van Dam, van den Broek, and Boeriu (2017)
PHYTOSTEROLS				Daucosterol, β-sitosterol, stigmasterol, sitostanol, guggulsterone	Bradford and Awad (2007)
PHYTIC ACID				Inositol hexaphosphate	E. O. Silva and Bracarense (2016)
LIPIDS		FATTY ACIDS		ω-3 and ω-6 fatty acids; ω-3 Polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid, docosahexaenoic acid	Bartsch, Nair, and Owen (1999); Tvrzicka, Kremmyda, Stankova, and Zak (2011)
		TERPENES	Monoterpenes	Myrcene, limonene, geraniol	Wagner and Elmadfa (2003)
			Diterpenes	Triptolide	
			Triterpenes	Betulinic acid, oleanolic acid, corosolic acid, ursolic acid, saponins (ginsenosides), squalene, erythrodiol, CDDO-Me	
			Tetraterpenes	Carotenoids (beta-carotene), xanthophylls (lutein)	
ORGANOSULFURS				Cycloalliin, S-alkyl-L-cysteine sulfoxides, mono-, di-, and trisulfides, thiosulfonates, S-alkylcysteines, cysteine alkyl disulfides, 3-vinyl-4H-1,2-dithiin, 2-vinyl-4H-1,3-dithiin, *E*- and *Z*-4,5,9-trithiadodeca-l,6,11-triene 9-oxides (ajoenes), glucosinolates, isothiocyanates, goitrin, epithionitrile	Goncharov et al. (2016); Munday (2012)
POLYPHENOLS	NON-FLAVONOIDS	COUMARINS		4-hydroxycoumarin, aesculetin, 4-methylumbelliferone, scopoletin, esculetin, fraxetin	Majnooni et al. (2019); Venkata Sairam, Gurupadayya, Chandan, Nagesha, and Vishwanathan (2016)
		CURCUMINOIDS		Curcumin, demethoxycurcumin, bisdemethoxycurcumn	Amalraj, Pius, and Gopi (2017); Kita, Imai, Sawada, Kumagai, and Seto (2008)
		LIGNANS		Pinoresinol, lariciresinol, arctigenin, matairesinol, secoisolariciresinol, syringaresinol, medioresinol, 7-hydroxymatairesinol, enterolactone	Adlercreutz (2007); De Silva and Alcorn (2019)
		PHENOLIC ACIDS		Benzoic acids (vanillic acid, gallic acid, ellagic acid), cinnamic acids (caffeic acid, ferulic acid, coumaric acid), punicalagin, hydrolyzable tannins	Van Hung (2016)
		STILBENES		Resveratrol, piceatannol, astringin	Ahmadi and Ebrahimzadeh (2020); Chong, Poutaraud, and Hugueney (2009); Fantini et al. (2015); Vervandier-Fasseur and Latruffe (2019)
	FLAVONOIDS	FLAVONOLS		Quercetin, kaempferol, myricetin	Fantini et al. (2015); Marzocchella et al. (2011)
		FLAVONES		Apigenin, luteolin, baicalein, chrysin, wogonin	Fantini et al. (2015); Marzocchella et al. (2011)
		FLAVAN-3-OLS		(+)- Catechin, (−)-Epicatechin, (+)-Gallocatechin, (−) Epigallocatechin, (−)-Epicatechin-3-*O*-gallate, (−)-Epigallocatechin-3-*O*-gallate, proanthocyanidins	Fantini et al. (2015); Marzocchella et al. (2011)
		ANTHOCYANINS		Delphinidin, cyanidin, malvidin, pelargonidin, peonidin, petunidin	Fantini et al. (2015); Marzocchella et al. (2011)
		FLAVANONES		Naringenin, hesperetin, neohesperidin (hesperetin-7-*O*-neohesperidoside), naringin (naringenin-7-*O*-neohesperidoside), hesperidin (hesperetin-7-*O*-rutinoside), narirutin (naringenin-7-*O*-rutinoside)	Fantini et al. (2015); Marzocchella et al. (2011)
		ISOFLAVONES		Genistein, daidzein, glycitein	Fantini et al. (2015); Marzocchella et al. (2011)
		XANTHONES		α-, β-, and γ-mangostin, gartanin, DMXAA, mangiferin, prenylated xanthones, neobraclactones A-C, garcinone E, garcinoxanthones, indomethacin, cluvenone	Chantarasriwong, Batova, Chavasiri, and Theodorakis (2010); El-Seedi et al. (2020); Negi, Bisht, Singh, Rawat, and Joshi (2013); Pinto, Sousa, and Nascimento (2005)
VITAMINS				Vitamin D, calcitriol, vitamin E, vitamin B2, B6, B9, vitamin C, vitamin A, carotenes, all-*trans* retinoic acid (ATRA), retinoic acid (RA)	Ang, Pullar, Currie, and Vissers (2018); D'Ambrosio, Clugston, and Blaner (2011); Gruber (2016); Khammissa et al. (2018); G. Y. Lee and Han (2018); Reider, Chung, Devarshi, Grant, and Hazels Mitmesser (2020); van Poppel and van den Berg (1997)

The immune system acts during both the initial stages of neoplastic transformation that lead to the formation of the neoplastic niche and the progression of the neoplasm with the maturation of the neoplastic niche itself. Immune cells play dual roles in the tumor microenvironment, being able to eliminate cancer cells but also support tumor growth. This dichotomy is clearly elucidated by the theory of "cancer immunoediting", which hypothesizes the evolution of the immune system from a phase responsible for immune surveillance to a phase that leads to immune escape (R. Kim, Emi, & Tanabe, 2007). Three crucial phases have been proposed for cancer immunoediting: (1) elimination; (2) equilibrium; and (3) escape (R. Kim et al., 2007).

Initially, the immune system eliminates emerging cancer cells ("elimination" phase) via the activity of effector cells, including NK cells, and secreted IFN-γ. However, the elimination of transformed cells causes immune selection and immune shaping, which induce the development of cancer cell variants with decreased immunogenicity

that are resistant to immune effector cells (immunoevasion) in the "equilibrium" phase. Eventually, the immunosuppressive mechanisms built in the equilibrium phase protect cancer cells by both killing immune cells and converting immune cells into tumor growth-supporting cells ("escape" phase) (Beatty & Gladney, 2015; Vesely & Schreiber, 2013; Vinay et al., 2015), thus allowing cancer cells to progress and spread.

On the other hand, tumors may also avoid immune system-mediated elimination by recruiting immunosuppressive leukocytes and soluble factors, which coordinate a tumor microenvironment that counteracts the efficiency of the antitumor immune response (Beatty & Gladney, 2015). Thus, although the immune system can potentially be activated against cancer cells, some tumors develop a microenvironment that suppresses efficient antitumor immunity (Beatty & Gladney, 2015).

Regulatory T cells (Tregs), which are $CD4^+CD25^+CD127^{lo/-}Foxp3^+$ T cells, are a peculiar subpopulation of T cells able to suppress immune responses (Frydrychowicz, Boruczkowski, Kolecka-Bednarczyk, & Dworacki, 2017; Laplagne et al., 2019; Takeuchi & Nishikawa, 2016; Y. Wang, Fan, & Wu, 2020c). Tregs comprise two major populations: thymus-derived Tregs (tTregs/nTregs) and extrathymic Tregs, which are further classified as peripheral Tregs (pTregs) and induced Tregs (iTregs). pTregs arise from mature conventional $CD4^+$ T cells when epitopes are presented by antigen-presenting cells (APCs), such as DCs, in the presence of TGF-β, IL-10, and IL-2. Several factors, including stimulation by coinhibitory pathways (PD-1/PD-L1, CTLA-4/B7.1, and CTLA-4/B7.2), epigenetic regulation, cytokines (IL-6) and chemokines, chemokine-receptor interactions, hypoxia, lactate production, and microRNAs (miRNAs; MiR-21, MiR-155, MiR-125a, MiR-146a, MiR-181c, and MiR- 374), affect the generation and activity of Tregs (Frydrychowicz et al., 2017; Laplagne et al., 2019; Takeuchi & Nishikawa, 2016; T. Wei, Zhong, & Li, 2020). Naive Tregs have the phenotype $CD4^+CD25^{lo}Foxp3^{lo}CD45RA^+$, while effector Tregs (eTregs) have the expression pattern $CD4^+CD25^{hi}Foxp3^{hi}CD45RA^-$ (J. H. Kim, Kim, & Lee, 2020a). Tregs mediate immunosuppression through different mechanisms, including the interaction of CTLA-4 with CD80 or CD86 expressed by Tregs and APCs, respectively; the release of granzyme A and B to induce apoptosis in target immune effector cells; the release of cytokines, such as IL-10, IL-35 and TGF-β, and immunosuppressive metabolites, including adenosine, whose receptor is expressed by effector T cells; and depletion of IL-2 due to expression of the high-affinity chain CD25 (IL-2 receptor). Tregs impair DC antigen presentation by secreting IL-10, promoting the degradation of MHC class II homologous peptide complexes, the expression of indoleamine 2,3-dioxygenase (IDO) and the release of kynurenine, which results in T cell inactivation. Tregs can inhibit NK cells and promote the conversion of monocytes into TAMs with an M2 phenotype, which further suppress the immune response and promote myeloid-derived suppressor cells (MDSCs) function and differentiation through TGF-β (Frydrychowicz et al., 2017; Laplagne et al., 2019; Takeuchi & Nishikawa, 2016; T. Wei et al., 2020). Accordingly, Tregs are considered crucial targets that block the development and execution of immune responses against cancer cells.

M2 macrophages participate in the wound-healing process and allergy and exhibit protumor activities (Laplagne et al., 2019). MDSCs inhibit T cell responses by secreting IL-10, TGF-β, and nitric oxide (NO); block the functions of NK cells by inhibiting NK cell IL-2 utilization; display proangiogenic properties; and induce further Treg development (B. Huang et al., 2006). TAMs promote tumor invasiveness and metastasis by releasing MMPs, which degrade the extracellular matrix (ECM) and thus foster cancer cell invasion (Galdiero, Marone, & Mantovani, 2018). M1 macrophages, which have proinflammatory properties and antitumor activity, are activated by the engagement of Toll-like receptors (TLRs) on their surface and by IFN-γ released from T_H1 cells and release proinflammatory cytokines (IL-1, IL-6, IL-12, IL-23, and TNF-α) and type-1 cell-attracting chemokines, including CXCL9 and CXCL10, which promote the recruitment of additional macrophages and leukocytes to eliminate pathogens and produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Frydrychowicz et al., 2017; Laplagne et al., 2019; Takeuchi & Nishikawa, 2016; Y. Wang, Fan, & Wu, 2020c).

The redox balance is crucial in determining T cell activation/inhibition in the tumor microenvironment. T cell activation is associated with prompt generation of ROS, thus indicating that ROS are important in T cell receptor signaling (H. Kong & Chandel, 2018). Antioxidant treatment was shown to reduce T cell expansion *in vivo* after primary viral infection (Laniewski & Grayson, 2004). On the other hand, high levels of ROS are detrimental for the activation of the T cell response and mediate this effect by decreasing T cell viability (Klemke & Samstag, 2009; H. Kong & Chandel, 2018). This setting is further complicated in the tumor microenvironment by the production of ROS by activated innate immune cells, which can have harmful effects on T and NK cells (Klemke & Samstag, 2009). In addition, high levels of ROS polarize the T helper response towards the T_H2 phenotype, while low levels of ROS promote the T_H1 and T_H17 phenotypes (Frossi, De Carli, Piemonte, & Pucillo, 2008).

MDSCs comprise granulocytic or polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (Mo-MDSCs). Different cancer cell-released factors have also been demonstrated to induce MDSCs *in vitro* (PGE2, IL-6, IL-10, IL-1β, TGF-β, stem cell factor and proangiogenic factors, such as VEGF). The crosstalk between MDSCs and cancer cells is important in tumor development. Indeed, MDSCs promote angiogenesis through the production of MMP-9 and VEGF, induce cancer cell invasiveness, promote metastasis and inhibit T cell function through the production of arginase (ARG), inducible nitric oxide synthase (iNOS) and immunosuppressive cytokines, including TGF-β and IL-10 (Groth et al., 2019; Lei et al., 2020).

Similar to macrophages, neutrophils have several effects in the different phases of cancer development. They can exert antitumoral or protumoral functions. The protumoral phenotype can be driven by TGF-β, while the antitumoral phenotype can be driven by type I IFNs. Neutrophil-produced ROS and RNS are responsible for DNA damage and thus for tumor initiation, while neutrophil release of MMPs promotes tumor invasion and metastasis. In addition, neutrophils are an important source of VEGF-A, which induces angiogenesis (Galdiero et al., 2018).

A conspicuous number of fibroblasts producing ECM components is present in the stroma of several types of human cancer. These fibroblasts are defined as tumor- or cancer-associated fibroblasts (CAFs). CAFs and the ECM contribute to cancer progression by directing and coordinating immune cell infiltration through the secretion of cytokines and surface proteins or deposition of various ECM substrates. CAFs release several soluble molecules (CXCL1, CXCL2, CXCL5, CXCL6/GCP-2, CXCL8, CXCL9, CXCL10, CXCL12/SDF1, CCL2/MCP-1, CCL3, CCL5/Rantes, CCL7, CCL20, CCL26, IL-1β, IL-6, IL-10, VEGF, TGF-β, PGE2, TNF-α and NO) that recruit and activate myeloid cells (Barrett & Puré, 2020; Miyai, Esaki, Takahashi, & Enomoto, 2020). Accordingly, CAFs can affect adaptive immune cells indirectly through myeloid cells or directly by expressing PD-L1/2 on the cell membrane, driving the expression of PD-L1/2 on tumor cells through CXCL5 or promoting the development of Tregs by presenting antigens and simultaneously releasing PGE2 in the absence of costimulatory molecules. Finally, CAFs can inhibit the activity of NK cells (Barrett & Puré, 2020; Miyai et al., 2020).

Regarding the roles of proinflammatory cytokines in the tumor microenvironment, it is always necessary to remember that chronic inflammation has a different role than acute inflammation in carcinogenesis (Bottazzi, Riboli, & Mantovani, 2018; Dinarello, 2006). The persistence of an inflammatory stimulus causes prolonged exposure to proinflammatory mediators that can contribute to cellular transformation and progression. For example, by inducing ROS production, PGE2 induces cellular DNA damage, and by decreasing the production of IFN-γ, it induces immunosuppression. IL-1β induces immunosuppression,

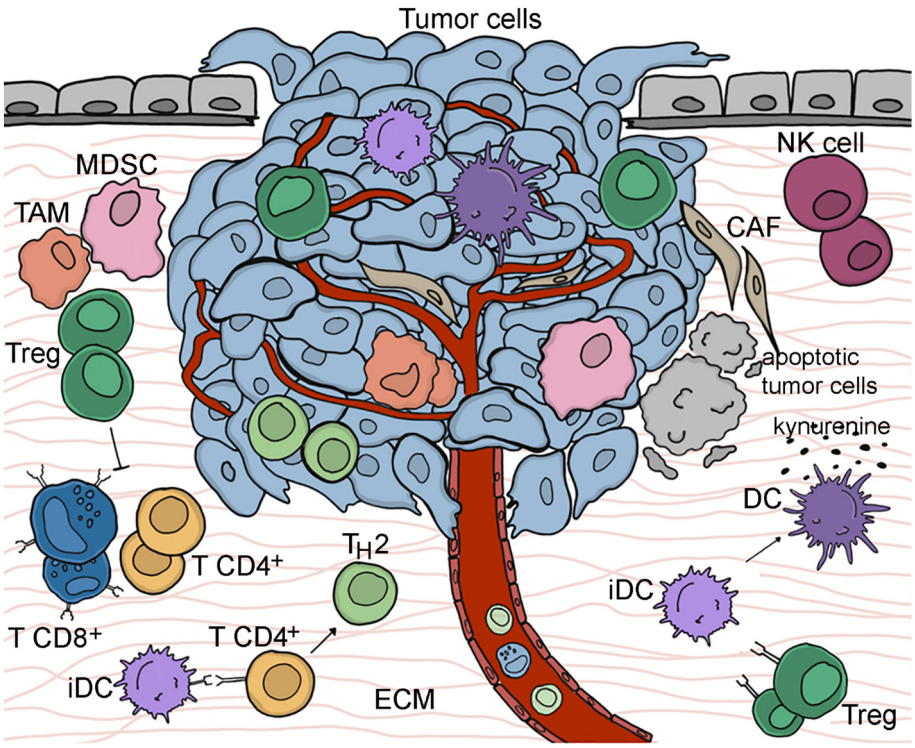

Fig. 1. Tumor microenvironment. Tumor microenvironment is made by a multifaceted network of cellular and molecular constituents including extracellular matrix (ECM), stromal cells [including cancer-associated fibroblasts (CAFs)] and immune and inflammatory cells [($CD4^+$ and $CD8^+$ T cells, T_H1 and T_H2 cells, B cells, natural killer (NK) cells, dendritic cells (DCs) and immature dendritic cells (iDCs), tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs)]. Tumor cells recruit CAFs, generate Tregs and iDCs and promote the production of TAMs. These cells suppress the immune response against cancer cells.

promotes neoangiogenesis and invasiveness and stimulates PGE2 production (Dinarello, 2006). Fig. 1 shows cellular and molecular constituents within the tumor microenvironment which play a role in the outcome of tumor growth.

In agreement with the aim of the review, the modulatory effects of the main nutraceuticals on the immune response and therefore potentially on subsets of immune or stromal cells present within the tumor microenvironment will be described. Figures and Tables report the effects of nutraceuticals on inflammatory cytokines and cells (Figs. 2, 3 and Table 2), on $CD8^+$ and $CD4^+$ T cells (Fig. 2 and Table 3), on MDSCs (Fig. 3 and Table 4) and Tregs (Fig. 4 and Table 4). Overall, accumulating evidence points to a complex scenario: nutraceutical effects are dependent on the status of target cells (e.g., resting or activated), target cell ontogeny and pathological condition (e.g., normal *vs* cancer cells or macrophages *vs* TAMs), dose, exposure time and, in *in vivo* studies, bioavailability of the nutraceutical.

3. Nutraceutical and immune cell modulation in human and animal models *in vitro* and *in vivo*

3.1. Organic acids

Organic acids have been used in food, beverages and feed preservation as feed additives (acidifiers). They are organic carboxylic acids with the structure R-COOH and are classified into different groups. They include monocarboxylic acids (acetic, propionic, butyric and formic acids) and carboxylic acids with hydroxyl groups (citric, malic, lactic and tartaric acids) (Pearlin et al., 2020; Quitmann et al., 2014).

Short-chain fatty acids (SCFAs), such as acetate, butyrate and propionate, are the most abundant active metabolites released from dietary fibers in the colon by the gut microbiota (Wong, de Souza, Kendall, Emam, & Jenkins, 2006). SCFAs are able to modulate immune cells and act as pro- or anti-inflammatory agents, depending on the stimulus (Corrêa-Oliveira, Fachi, Vieira, Sato, & Vinolo, 2016). SCFAs modulate neutrophil recruitment and the production of inflammatory cytokines (Rodrigues, Takeo Sato, Curi, & Vinolo, 2016) and enhance the production of IL-8 by human neutrophils when incubated with a TLR2 agonist (Mirmonsef et al., 2012). Acetate was shown to enhance the recruitment of neutrophils and T_H17 cells and the degree of inflammation in the intestines of mice after infection with *Citrobacter rodentium* (M. H. Kim et al., 2013). Conversely, other studies reported decreased recruitment of neutrophils and reduced inflammation in animal models of colitis (Maslowski et al., 2009; Mishiro et al., 2013) and peritonitis (Vinolo et al., 2011) after treatment with SCFAs. Acetate, butyrate and propionate have shown anti-inflammatory activities and decreased LPS-stimulated TNFα release from human blood-derived neutrophils, TNFα-stimulated NF-κB activity in human colon adenocarcinoma cells and IL-6 release from colon organoid cultures (Tedelind et al., 2007).

SCFAs can also modulate macrophages, DCs and T cells. SCFAs have been shown to produce anti-inflammatory effects by increasing the production of PGE2 and inhibiting the lipopolysaccharide (LPS)-induced production of TNF-α and IFN-γ in human monocytes and PBMCs (Cox et al., 2009). Anti-inflammatory effects on bone marrow-derived macrophages were reported for butyrate (P. V. Chang et al., 2014). Butyrate (0.5 and 1 mM) also inhibited the maturation of DCs, decreased the secretion of IL-12p40 and IFN-γ, and increased that of IL-10, thus inhibiting the activation of T cells (L. Liu et al., 2012; Millard et al., 2002). SCFAs affect the functions of immature and mature human monocyte-derived DCs by modulating leukocyte trafficking and inducing anti-inflammatory effects (Nastasi et al., 2015). Butyrate and propionate were also shown to inhibit the activation of antigen-specific $CD8^+$ T cells stimulated with MART1 peptide-pulsed DCs by modulating the secretion of IL-12 from the DCs (Nastasi et al., 2017). Treatment with butyrate and propionate was also found to lead to an increase in the expression of IDO and aldehyde dehydrogenase 1A2 (Aldh1A2) in DCs, which promoted the differentiation of naive T cells into

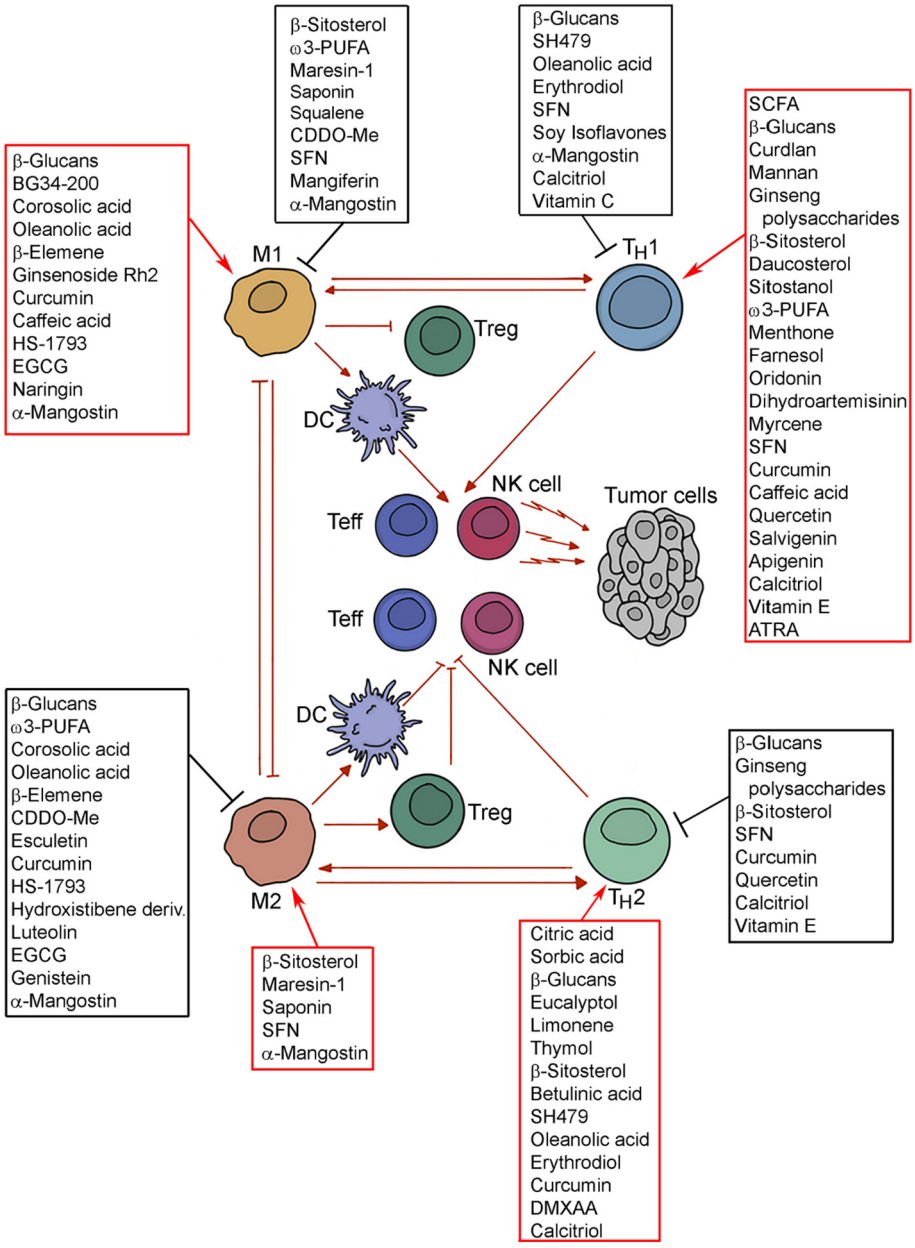

Fig. 2. M1 and M2 macrophages differentiation by nutraceuticals. The arrow and the inhibition arc indicate a positive and a negative activity of the nutraceutical reported in the boxes, respectively. M1 and M2 macrophages affect T_H1 and T_H2 immune responses which differentially affect T effector cells (Teff) response, regulatory T cells (Tregs), dendritic cells (DCs) and natural killer (NK) cells. Abbreviations: ATRA, All-*trans* retinoic acid; CDDO-Me, Methyl-2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oate; DMXAA, 5,6-Dimethylxanthenone-4-acetic acid; EGCG, Epigallocatechin-3-*O*-gallate; PUFA, Polyunsaturated fatty acids; SCFA, Short-chain fatty acids; SFN, Sulforaphane.

immunosuppressive $Foxp3^+$ Tregs (Gurav et al., 2015). Other studies have described the generation of Tregs in the colon by SCFAs, which is mediated through the inhibition of histone deacetylases (Arpaia et al., 2013; Furusawa et al., 2013; Smith et al., 2013). On the other hand, it was shown that SCFAs promote T cell differentiation into both effector (T_H1 and T_H17 cells) and Tregs ($IL\text{-}10^+$ cells) in a manner dependent on the immunological milieu. $IL\text{-}10^+$ T cell numbers were increased by acetate under steady conditions *in vivo*, whereas effector T cell numbers were increased during active immune responses induced by infection (J. Park et al., 2015). Another study reported that orally administered butyrate promoted the expression of effector molecules in $CD8^+$ T cells in mice (Luu et al., 2018). Propionate (10 mM) induces the expression of the NKG2D ligands MICA/B on activated T cells and different cancer cells and strong NKG2D-dependent NK cell-mediated killing of propionate-exposed cancer cells (Andresen et al., 2009).

Other organic acids exert anti-inflammatory and immunomodulatory effects. A diet supplemented with organic acids (citric, formic, and lactic acids) was found to inhibit the inflammation caused by influenza vaccine H9N2 vaccination by inducing $CD4^+CD25^+$ Tregs, which led to a decrease in H9N2-specific antibody titers in chickens (I. K. Lee et al., 2017). It was also reported that a combination of probiotic and organic acid (citric and sorbic acid) supplementation in chickens downregulated early cecal tonsil TLR2, ileal IL-12p35 and IFN-γ levels and enhanced later cecal tonsil IFN-γ and ileal IL-6 and IL-10 levels, suggesting an anti-inflammatory effect induced via T_H2 pathway activation (Rodríguez-Lecompte et al., 2012). Lactic acid suppresses mast cell activation via IL-33 and cytokine secretion in LPS-activated bone marrow-derived mast cells (Abebayehu et al., 2016; Caslin et al., 2019). Ferrara et al. also reported that short-chain organic acids, which are employed as feed additives in piglet diets [diet containing 1.05% of short-chain

Table 2
Effect of nutraceuticals on inflammatory cytokines and cells.

Human Mouse	Cell Type	Treatment	*In vitro* Model	*In vivo* Model	Effects on immune system	Reference
Organic acids						
Human	Neutrophils	SCFA (20 mM)	PBMCs from HDs		↑ IL-8, IL-6, IL-1β release; ↑ TLR2 ligand-induced IL-8 production	Mirmonsef et al. (2012)
Mouse	Neutrophils	Acetate (200 mM in drinking water, for 4 weeks, before infection with *C. rodentium*)		WT, GPR41$^{-/-}$, GPR43$^{-/-}$ C57BL/6 mice infected with *C. rodentium*	↑ *IL-6*, *CXCL1*, and *CXCL2* in the cecum; ↑ Neutrophils and T_H17 cells recruitment	M. H. Kim, Kang, Park, Yanagisawa, and Kim (2013)
Mouse	Neutrophils	Butyrate (100 mM/day, i.r., for 10 days)		DSS-treated WT and MFGE8KO C57BL/6N mice	↓ MPO, TNF-α, IL-1β, IL-6; ↓ Neutrophils infiltration	Mishiro et al. (2013)
Rat	Neutrophils	Propionate (0.4-12 mM) and butyrate (*in vitro*: 0.4-3.2 mM; *in vivo*: 3.6 g/kg of tributyrin, p.o., before i.p. injection with oyster glycogen)	LPS-stimulated rat neutrophils	Wistar rats	↓ TNF-α, CINC-2αβ and NO production; ↓ Neutrophils recruitment to peritoneum	Vinolo et al. (2011)
Human/mouse	Neutrophils, Colon cells	Acetate, propionate, or butyrate (30 mM, each)	LPS stimulated-Human-blood derived neutrophils; TNFα-stimulated colorectal cancer cells (Colo320DM); Colitic mouse colon from DSS-treated C57BL/6J mice		↓ LPS-stimulated TNF-α release from neutrophils; ↓ TNF-α-stimulated NF-κB activity in COLO320DM cells; ↓ IL-6 release in colon organ cultures	Tedelind, Westberg, Kjerrulf, and Vidal (2007)
Human	Monocytes, neutrophils	SCFA (0.2-20 mM)	Human monocytes and PBMCs		↑ PGE2; ↓ MCP-1 production; ↓ LPS-induced IL-10 production; ↓ LPS-induced TNF-α and IFN-γ	Cox et al. (2009)
Mouse	Macrophages	n-Butyrate (100 μM-2 mM)	BMDM from C57BL/6 mice		↓ LPS-induced NO, IL-6 and IL-12p40	P. V. Chang, Hao, Offermanns, and Medzhitov (2014)
Human	DCs	SCFA (1 mM)	Monocytes-derived DCs isolated from HDs		↓ LPS-induced expression CD83; ↓ CCL3, CCL4, CCL5, CXCL9, CXCL10, CXCL11 release; ↓ LPS-induced IL-6 and IL-12p40 expression	Nastasi et al. (2015)
Mouse	Mast cells	Lactic acid (*in vitro*: 12.5 mM; *in vivo*: 4 mg/kg of 4% (w/v) of lactic acid, i.p., before injection with IL-33, 16 h later)	Mouse-BMMC and peritoneal mast cells from C57BL/6 mice	LPS-induced endotoxemia mouse model	↓ IL-33-mediated IL-6, IL-13, MIP-1α, and MCP-1 production; ↓ LPS-induced IL-6, TNF and MCP-1; Suppression of cytokines induced by TLR-2, 3, 4; Suppression of LPS-induced plasma IL-6, TNF, and MCP-1 *in vivo*	Abebayehu et al. (2016); Caslin et al. (2019)
Polysaccharides						
Mouse	Macrophages	β-glucans (800 μg/mouse, p.o., from day 8 after tumor formation, every day)	Macrophages	C57BL/6	M2→M1; ↑ Proinflammatory cytokines	M. Liu et al. (2015a)
Human/mouse	Macrophages	Lentinan (400 μg/day, p.o., for 29 days, starting when tumor mass reached 0.7-0.8 cm) (+anti-tumor MAbs)		Human xenografts nu/nu mice	CR3-DCC	Cheung, Modak, Vickers, and Knuckles (2002)
Mouse	Neutrophils, Macrophages	β-glucans (10 μg were mixed with tumor cells before inoculation)		C57BL/6 mice bearing lung carcinoma cells (LLC)	↑ Macrophages and neutrophils infiltrating tumor	Ning et al. (2016)
Human/mouse	Macrophages	BG136 (β-1,3/1,6-glucan) (*in vitro*: 0.1-100 μg/ml for 24 h; *in vivo*: 4 mg/kg i.v., twice a week)	RAW264.7	DLD1 colorectal cancer xenograft and AOM/DSS-induced tumor models	↑ Phagocytosis; ↑ Cytokines/chemokines	Su et al. (2019)
Mouse	NK cells	β-1,3/1,6-glucan from *G. frondosa* (1.4 or 8 mg/kg/day, i.p., for 16 days from 48 h before injection of cells)		BALB/c mice bearing colorectal cancer cells (Colon-26)	Activation of NK cells; ↑ IL-12	Masuda, Murata, Hayashi, and Nanba (2008)
Human	NK cells	β-glucans from *P. ostreatus* (5 mg/ml for 3 days)	NK cells		↑ Cytotoxic activity; ↑ IFN-γ, NO; ↑ IFN-γ, NO	El-Deeb et al. (2019)
Mouse	Macrophages, NK cells	BG34-200 (β-(1-3)-(1-4)-glucan) (25 mg/kg/day, i.p., 5 days or twice or thrice a week)		C57BL/6 mice bearing melanoma cells (B16F10)	↑ M1; ↑ Proinflammatory cytokines/chemokines	M. Zhang et al. (2018a)
Mouse	Macrophages	β-glucans (mice were continuously tube-fed for 12 days)		C57BL/6JNarl mice bearing lung cancer (LLC1)	M2→M1	W. J. Wang, Wu, Chen, Liu, and Chen (2015b)

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Table 2 (*continued*)

Human Mouse	Cell Type	Treatment	*In vitro* Model	*In vivo* Model	Effects on immune system	Reference
Phytosterols						
Human	NK cells, T cells	BSS and/or BSSG (1 μg/ml)	T cells prepared from the mononuclear cell fraction		↑ IL-2 and IFN-γ; ↑ Cytotoxic activity of NK cells	Bouic et al. (1996)
Human	NK cells	(−)-β-sitosterol-3-*O*-β-D-(6-*O*-palmitoyl) glucopyranoside 10 μM)	Human primary NK cells isolated from PBL		↑ NK cells function	Ren et al. (2015)
Human/Mouse	Keratinocytes and macrophages	BSS (7.5-60 μM)	HaCaT and J774A.1		↓ TNF-α, IL-1β, IL-6, IL-8 and ROS	P. C. Liao et al. (2018b)
Mouse/Rat	Blood sample	Stigmasterol (10-100 mg/kg, i.p., for 21 days after the first immunization)		ICR mice and Wistar rats with TPA-induced dermatitis	↓ Serum levels of TNF-α	Antwi et al. (2018)
Rat	Beta cells	Guggulsterone (12.5-25 μM)	RINm5F		↓ NF-κB	Lv et al. (2008)
Human	Epithelial cells	Guggulsterone (5-25 μM)	MCF10A		↑ HO-1	Almazari et al. (2012)
Mouse	Immune cells	Daucosterol (10 mg/kg, p.o., thrice a week, for 23 days, starting 2 weeks before DSS-treatment)	Immune cells from lymph nodes and spleen	DSS-induced colitis in C57BL/6J mice	↓ ROS, TNF-α, IL-6, and IL-1β; ↓ Macrophages infiltration; ↑ NK cells activity	J. Jang et al. (2019)
Mouse	Macrophages	BSS (1 μM)	RAW264.7		↓ (PMA)-induced NO release	Moreno (2003)
Mouse	Macrophages	BSS (50 μM)	RAW264.7		↓ ROS	Vivancos and Moreno (2005)
Mouse	Macrophages	BSS (20 or 50 mg/kg, i.p., every 2 days, for 19 days, starting 21 days after CIA induction)		C57BL/6 mice with collagen-induced arthritis (CIA)	Switch M1 to M2 phenotype; ↓ IL-10	R. Liu et al. (2019b)
Mouse	T cells, NK cells	BSS (4 μM/mouse, p.o., for 7 days, starting after 24 h of fast)		C57BL/6 mice bearing melanoma cells (B16BL6)	↑ NK cells activity; ↑ IL-12, IL-18	Imanaka et al. (2008)
Mouse	Macrophages	BSS (50 mg/kg, i.p., for 21 days, starting on day 7 after injection of cells)		BALB/c mice bearing melanoma cells (B16-F10)	↑ Macrophages lysosomal activity; ↑ NO	Boubaker et al. (2018)
Phytic acid						
Human	Intestinal epithelial cells	Phytic acid (1 mM)	Caco-2 cells		↓ IL-8 secretion	Wawszczyk, Orchel, Kapral, Hollek, and Weglarz (2012)
Human	Intestinal epithelial cells	Phytic acid (0.1-5 mM)	Caco-2 cells		↓ IL-8; ↑ IL-6	Weglarz, Wawszczyk, Orchel, Jaworska-Kik, and Dzierzewicz (2007)
Human	Intestinal epithelial cells	Phytic acid (2.5 mM)	Caco-2 cells		↓ Transcriptional activity of iNOS gene	Kapral, Wawszczyk, Sośnicki, and Węglarz (2015)
Rat	Cytokines	Phytic acid + myo-inositol (in oral diet daily for 21 days; 2.04% dodecasodium phytate, or 0.4% myo-inositol, or 1.02% dodecasodium phytate plus 0.2% myo-inositol)		Male Sprague-Dawley rats	↓ TNF-α; ↓ IL-6	Okazaki and Katayama (2014)
Rat	Cytokines	Phytic acid (0.25, 0.5 and 1.0 g/kg/day, p.o., for 4 weeks, followed by DMH injection)		DMH-induced colorectal cancer in Wistar rats	↓ TNF-α, IL-1β and IL-6	C. Liu et al. (2018)
Rat	NK cells	Phytic acid (basal diet plus 2% sodium inositol hexaphosphate in drinking water; DMH 20 mg/kg, s.c., once a week for 20 weeks)		DMH-induced colorectal cancer in Wistar rats	↑ NK cells activity	Z. Zhang, Song, and Wang (2005)
Lipids						
Mouse	Immune cells	ω-3 PUFAs (liquid ω-3 diet consisted of 8.4 g/L olive oil and 20 g/L of fish oil, for 10-16 weeks followed by injection of cells)		BALB/c mice bearing mammary carcinoma (4T1)	↑ Neutrophils; ↑ Macrophages; ↑ Lymphocyte $CD3^+$; ↑ IL-10	Khadge et al. (2018)
Mouse	Macrophages	ω-3 PUFAs (diet consisted of 134 g/kg menhaden oil, for 35 days)		FVB mice bearing prostate cancer cells (MycCaP)	↓ Macrophages; ↓ CCL2, IL-6, IL-10, and TNF-α	P. Liang et al. (2016)
Human	Prostate cancer cells	ω-3 PUFAs (100 μM)	DU-145 and PC-3		↓ IFN-γ; ↓ IL-18BP	X. Wang, Breeze, and Kulka (2015c)
Mouse	Colon tissue	ω-3 PUFAs [Modified AIN-76A diet in which 5% corn oil was substituted with 10% safflower oil, with an energy composition of protein 20%, carbohydrate 58% and fat 22%), high in ω -6 and low in ω-3 PUFA]		AOM/DSS-treated transgenic Fat-1 mice	↓ NF-κB activity; ↓ iNOS; ↑TGF-β	Nowak et al. (2007)

Mouse	Colon tissue	Maresin-1 (0.1, 0.3, and 1 mg/mouse/day, i.v., for 7 days)		DSS- and TNBS-induced colitis in CD1 mice	↓ IL-1β, TNF-α, IL-6, and INF-γ; ↓ NF-κB; ↓ M1 macrophage activity; ↑ M2 differentiation	Marcon et al. (2013)
Mouse	Melanoma cells	Fish oil and soybean oil (*in vitro*: 5-40 μl fish oil or soybean oil; *in vivo*: 20 or 40 μl/day, p.o.)	B16F10 cells	C57BL/6 mice bearing melanoma cells (B16F10)	↓ LTB_4 and PGE2; ↓ PGE2/PGE3; ↓ CXCL1; ↑ IL-10 release	Almeida et al. (2019)
Mouse	Macrophages	ω-3 PUFA (different HDF [60 kJ% fat] diets with ω-3/ω-6 ratio of 1:1 or 5:1; starting at 28 days of age until sacrifice at 12 or 20 weeks)		Streptozotocin/high fat diet mouse model	↑ Macrophages; ↓ TNF-α	Liebig, Dannenberger, Vollmar, and Abshagen (2019)
Human	Cancer cells	Fish oil (42% EPA, 21 % DHA) (31.25-1000 μg/ml)	Squamous cell carcinoma cells (A431), basal cell carcinoma cells (TE354.T)		↑ IL-10; ↓ IL-6 and TNF-α	Rehman, Mohd Amin, Yuen, and Zulfakar (2016)
Human	Glioblastoma cells	Oleic acid (0.01-100 μM)	Glioblastoma cells (U-87 MG)		↓ TNF-α; ↓ COX-2 expression; ↓ PGE_2	Lamy, Ben Saad, Zgheib, and Annabi (2016)
Human	Neutrophils	Oleic acid (1-100 μM)	Human Neutrophils		↑ Neutrophils; ↑ ROS	Carrillo, Del Mar Cavia, Roelofs, Wanten, and Alonso-Torre (2011)
Terpenes						
Human	Macrophages	Corosolic acid and oleanolic acid (*in vitro*: 30 μM; *in vivo*: 17.5 mg/kg, p.o., twice a week, starting 7 days before injection of cells, for 21 days)	HMDMs	C3H mice bearing osteosarcoma cells (LM8)	M2 → M1	Fujiwara, Takeya, and Komohara (2014)
Mouse	Macrophages	β-elemene (20-140 μg/ml)	RAW264.7		M2 → M1	X. Yu et al., 2017)
Human/Mouse	Macrophages	Ginsenoside Rh-2 (60-140 μM)	RAW264.7, THP-1		M2 → M1	H. Li et al. (2018)
Mouse	NK cells	Ginsenoside F1 (*in vitro*: 5-20 μM; *in vivo:* 50 mg/kg, i.p., for 3 days before i.v. injection of cells and thrice a week thereafter)	Lymphoma cells and melanoma (B16F10) cells	C57BL/6 mice	↑ NK cells cytotoxicity; ↑ IFN-γ	Kwon et al., 2018)
Mouse	Macrophages	Saponin (500 mg/kg/day, p.o., for 8 weeks, starting at 6 weeks of age before the appearance of spontaneous intestinal polyps)		C57BL/6J-$Apc^{Min/+}$ and C57BL/6J mice	↑ IL-4; ↓ TNF-α, IL-1β and IL-18; ↑ M2 markers; ↓ M1 markers	L. Chen, Brar, Leung, and Hsiao (2016)
Human	Macrophages	Squalene (1-100 μM)	THP-1		↑ IL-10, IL-13, and IL4; ↓ M1 macrophages; ↓ TNF-α and NF-κB	Sánchez-Quesada, López-Biedma, Toledo, and Gaforio (2018)
Mouse	Macrophages	D-limonene (added in diet 24 h before injection of cells)		BALB/c mice bearing leukemia cells (L-5178-Y)	↑ NO	Del Toro-Arreola et al. (2005)
Mouse	Macrophages	Triptolide (2.7-55.5 nM)	RAW264.7		↓ COX2, iNOS and IL-1β; ↓ NF-κB	Ma et al. (2007); Premkumar, Dey, Dorn, and Raskin (2010)
Organosulfurs						
Mouse	Macrophages	I3C (60 and 120 mg/kg/day, p.o., for up to 2 weeks)	Macrophages	BALB/c mice bearing leukemia cells (WEHI-3)	↓ Macrophages; ↑ Phagocytosis	H. F. Lu et al. (2012)
Human	Monocytes, Macrophages	I3C DIM (5 μM)	THP-1		↓ IL-1β in monocytes	T. T. Y. Wang, Pham, and Kim (2018b)
Mouse	Monocytes, Macrophages	I3C (25-100 μM)	RAW264.7		↓ NO, IL-6, and IL-1β	J. Jiang et al. (2013)
Mouse	Macrophages	I3C (1.5 and 15 mg/kg, i.p., 12 and 2 h before being treated with LPS)	Macrophages	BALB/c mice	↓ IL-6, TNF-α	J. Jiang et al. (2013)
Mouse	Macrophages	PEITC (0.12% PEITC-enriched mouse-diet for 16 weeks)		AOM/DSS-induced colitis in C57BL/6J mice	↓ Inflammatory cells	Y. Liu and Dey (2017)
Mouse	Monocytes, Macrophages	PEITC (10 μM)	RAW264.7		↓ CCL2, CXCL10, CD40, NF*k*B1, REL, REL*β*	Y. Liu and Dey (2017)
Mouse	Immune cells	DIM (30 mg/kg/day, p.o., for 8 days)		C57BL/6 mice	↑ IL-6, G-CSF, IL-12, IFN-γ	Xue, Pestka, Li, Firestone, and Bjeldanes (2008)
Mouse	Monocytes, Macrophages	DATS (100-200 μM)	RAW264.7		↓ IL-6, IL-10, IL-12(p70), MCP-1, TNF-α	You et al. (2013)
Human	Neutrophils	Dipropyl disulfide (13.1 μM), allyl propyl disulfide (22.5 μM), DADS (9.8 μM), and AITC (7.9 μM)	Neutrophils from human blood		↑ Ca^{2+} flux	Schepetkin, Kirpotina, Khlebnikov, Balasubramanian, and Quinn (2019)

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Table 2 (*continued*)

Human Mouse	Cell Type	Treatment	*In vitro* Model	*In vivo* Model	Effects on immune system	Reference
Mouse	Macrophages, NK cells	SFN (285, 570 or 1.140 mg/kg, p.o., for 20 days)		BALB/c mice bearing leukemia cells (WEHI-3)	↑ Phagocytosis of macrophages; ↑ Activity of NK cells	Shih et al. (2016)
Mouse	Immune cells	SFN (12.8, 63.8, and 318.8 mg/ml/kg/day, i.p., for 5 weeks)		BALB/c mice with induction of CAIA	↓ IL-17, TNF-α, IL-6, and IFN-γ	J. S. Kong et al. (2010)
Mouse	DCs, Macrophages	SFN (500 μg/kg, s.c. prior immunization and 250 μg/kg, 2 h after immunization)	DCs and macrophages	BALB/c or C57BL/6 mice	↓ IL-6, IL-1 and TNF-α	Shin, Hyun, Lim, and Lee (2011)
Mouse	NK cells	SFN (500 μg/mouse/day, i.p., for 5 days)		C57BL/6 mice bearing melanoma cells (B16F-10)	↑ IL-2 and IFN-γ; ↑ ADCC; ↓ IL-1β, IL-6, TNF-α, and GM-CSF	Thejass and Kuttan (2007)
Mouse	Serum	SFN (25 mg/kg, p.o., 24 h before and 6 h after i.d. injection of LPS)		Female C57BL/6 mice	↓ TNF-α, IL-1β, and IL-6	Youn et al. (2010)
Mouse	Inflammatory cells	SFN (10 or 25 mg/kg/day, i.p., from days 17 to 20)	Inflammatory cells bronchoalveolar lavage fluid	OVA-sensitized BALB/c mice	↓ T_H2 response	J. H. Park et al. (2012)
Human	Neuroblastoma cells	SFN (5 μM)	Neuroblastoma cells (SH-SY5Y)		↓ IL-1β, TNF-α	de Oliveira, Brasil, and Fürstenau (2018)
Mouse	Macrophages	SFN (5-40 μM)	Peritoneal macrophages	$Nrf2^{-/-}$ and $Nrf2^{+/+}$	↓ TNF-α, IL-1β, COX-2 and iNOS	W. Lin et al. (2008)
Porcine	DCs	SFN (10 μM)	mDCs		↓ IL-1β, TNF-α	Qu et al. (2015)
Human	Monocytes	SFN (10 μM)	THP-1		M1 → M2	Pal and Konkimalla (2016)
Polyphenols						
Non-Flavonoids						
Mouse	Macrophages	Esculetin, Fraxetin (*in vitro*: 10-100 μM; *in vivo*: 3 or 10 mg/kg, i.p., for 35 days, starting 12 h after injection of cells)	Osteosarcoma cells (LM8)	C3H7H2 mice bearing osteosarcoma cells (LM8)	↓ TGF-β1, IL-10, MCP-1	Kimura and Sumiyoshi (2015)
Mouse	Macrophages	CUR (+RES) (1-20 μM, each)	Splenocytes from BALB/c mice		↓ IL-1, IL-6 and TNF-α; ↑ IL-10; ↓ CD80, CD86	Sharma, Chopra, Kulkarni, and Agrewala (2007)
Mouse	BMDCs	CUR (1-25 μM)	DCs from C57BL/6 mice		↓ BMDCs maturation; ↓ CD80, CD86, MHCII; ↓ IL-1, IL-6, TNF-α	G. Y. Kim et al. (2005)
Human	NK cells	CUR (2-20 μM)	Melanoma cells (A375, FO1), BMCs		↓ IFN-γ, GrB	Bill et al. (2009)
Human/Mouse	Macrophages	Micellar CUR (+Baicalin) (*in vitro*: 1-10 μg/ml; *in vivo*: multiple doses equivalent to 1 μg/g (Cur:Bai, 3.75:1.25), i.v.)	Lung cancer cells (A549), RAW264.7	Nude mice bearing lung cancer cells (A549)	M2 → M1; ↑ IL-6, TNF-α	B. Wang et al. (2019)
Mouse	Macrophages	Dendrosomal nano-CUR (40 and 80 mg/kg, i.p., from day 3 up to day 38)		BALB/c mice bearing mammary cancer cells (4T1)	M2 → M1; ↓ STAT3, IL-10, ARG1; ↑ STAT4, IL-2	Shiri et al. (2015)
Mouse	NK cells	γ-oryzanol (esters of transferulic acid with phytosterols) (0.2%-1% w/w diet supplementation)		BALB/c mice bearing colon cancer cells (CT-26)	↑ NK cells cytotoxicity; ↑ Macrophages; ↑ NO; ↑ Phagocytosis; ↑ Proinflammatory cytokines (TNF-α, IL-1β, IL-6); ↓ VEGF, COX-2, PGE2	S. P. Kim, Kang, Nam, and Friedman (2012)
Mouse	Macrophages	Caffeic Acid (100-400 μM)	RAW264.7		↓ NO, PGE2; ↓ TNF-α, COX-2, iNOS	W. S. Yang et al. (2013)
Mouse	Macrophages	Caffeic Acid (40 and 80 mg/kg/day, i.p., for 10 days)		Swiss albino mice bearing EAT	↑ T_H1 cytokines (IL-2, IL-12, IFN-γ); ↓ IL-4, IL-10, Arg1; ↑ M1 macrophages	Oršolić, Kunštić, Kukolj, Gračan, and Nemrava (2016)
Mouse	Macrophages	WSPD (Caffeic acid, quercetin, naringenin, chrysin, pinocembrin, galangin) (50 mg/kg, p.o., for 7 days)		Swiss albino mice bearing EAT	↑ PMN cells numbers; ↓ Macrophages numbers in the mouse peritoneal cavity; ↑ Phagocytosis	Orsolić and Basić (2005)
Mouse	Macrophages	*Eryngium foetidum* extract (kaempferol, chlorogenic acid, Caffeic Acid, lutein and β-carotene) (35-140 μg/ml)	RAW264.7		↓ COX-2, TNF-α, IL-6; ↓ iNOS, NO; ↓ ROS	Mekhora et al. (2012)
Mouse	Macrophages	*Centipeda minima* extract (protocatechu aldahyde, vanillic acid, protocatechuic acid, chlorogenic acid, ferulic acid caffeic Acid) (12.5-100 μg/ml 24 h after treatment with 100 ng/ml LPS)	RAW264.7		↓ NO, TNF-α, IL-1β; ↓ iNOS, COX-2	S. S. Huang et al. (2013b)
Mouse	Macrophages	Goji berries (hydroxycinnamic acid amide) (1-50 μM with 100 ng/ml LPS)	RAW264.7		↓ NO	S. Wang, Suh, Zheng, Wang, and Ho (2017)
Mouse	Macrophages	*Neonauclea reticulata* fractions	RAW264.7		↓ NO	F. P. Chang et al. (2019)

		(protocatechic acid, *trans*-caffeic acid, syringic acid, FA) (6.25-100 μg/ml)				
Mouse	Macrophages	KM1608 (*Saussurea lappa* + *Terminalia chebula* + *Zingiber officinale*) (25-100 μg/ml)	RAW264.7		↑ IFN-α, IFN-β; ↑ TNF-α, IL-1β, IL-6, IL-10; ↑ iNOS, COX2, NO	Trinh et al. (2020)
Human/Mouse	Macrophages	*Cinnamomum japonicum* (Cinnamic acid, cinnamaldehyde) (25-100 μg/ml)	Intestinal cells (Caco-2) and RAW264.7 co-culture		↓ PGE2, IL-6, IL-8, TNF-α; ↓ NO	M. S. Kim and Kim (2019)
Human	Macrophages	RosA (40 μM) +ATRA (10 μM)	Acute promyelocytic leukemia cells (NB4)		↑ CD11b, CD14; ↑ CCR-1, CCR-2; ↑ ICAM-1	Heo et al. (2015)
Human	NK cells	RES (3 mM)	NK cells from HDs		↑ NK cells cytotoxicity; ↓ Platelets aggregation	Toliopoulos, Simos, Oikonomidis, and Karkabounas (2013)
Human/Mouse	Macrophages	RES (6.25-50 μM)	RAW264.7, THP-1, PBL, HUVEC		↓ NO, COX-2, PGE2; ↓ IL-1β, IL-6, IL-12p70; ↓ TNF-α, CCL5/RANTES IL-6, ICAM-1, VCAM-1, CCL2/MCP-1, CXCL8/IL-8, CXCL10/IP10	Schwager, Richard, Widmer, and Raederstorff (2017)
Human	Macrophages	Dihydroxystilbene derivatives (*in vitro*: 50 μM; *in vivo*: 10 or 25 mg/kg, p.o., twice daily, for 30 days, starting 12 h after injection of cells)	THP-1, lymphatic endothelial cells (HLECs)	C3H/He mice bearing osteosarcoma cells (LM8)	↓ MCP-1, IL-10; ↑ TGF-β	Kimura, Sumiyoshi, and Baba (2016)
Human/Mouse	Macrophages	RES analogue HS-1793 (*in vitro*: 1.25-5 μM; *in vivo*: 1.5 mg/kg, i.p., twice a week, for 30 days)	THP-1, breast cancer cells (MDA-MB-231)	C3H/He mice bearing mammary carcinoma cells (FM3A)	↓ $CD206^{+}$ macrophages, IL-10, TGF-β; ↑ M1 macrophages; ↑ IL-12p40, IL-1β, IL-6, TNF-α, IFN-γ	S. K. Jeong et al. (2014a)
Mouse	Macrophages	PIC (0.25 or 1 μM in 0.2 ml acetone, topically onto the dorsal skin 30 min before TPA 10 nM)		HR-1 mice treated with TPA	↓ COX-2, iNOS; ↓ NF-κB, AP-1	L. Liu, Li, Kundu, and Surh (2014)
Flavonoids						
Mouse	Macrophages, NK cells	Quercetin (2 or 4 mg/kg/day, p.o., for 3 weeks, after injection of cells)		BALB/c mice bearing leukemia cells (WEHI-3)	↑ Phagocytosis; ↑ NK cells activity	C. S. Yu et al. (2010)
Mouse	Macrophages	Rutin (6 or 12 mg/kg/day, p.o., for 3 weeks, after injection of cells)		BALB/c mice bearing leukemia cells (WEHI-3)	↑ Phagocytosis	J. P. Lin et al. (2009)
Mouse	NK cells	Myricetin (165 μM)	NK 92 cells		↑ NK cells activity	Lindqvist, Bobrowska-Hägerstrand, Mrówczyńska, Engblom, and Hägerstrand (2014)
Human/mouse	Macrophages and NK cells	Kaempherol-3,7-bisrhamnoside (100 and 200 μg/ml)	PBMCs from healthy volunteers and murine splenocytes		↑ Phagocytosis; ↑ NK cells activity	Alonso-Castro et al. (2012)
Human	Cancer cells	Quercetin (50 μM for K562 cells; 30 μM for SNU1 cells)	Chronic myelogenous leukemia cells (K562); Stomach adenocarcinoma cells (SNU1)		↑ NKG2D ligands (ULBP1, ULBP2, MICB); ↑ NK cell-mediated cytotoxicity	Bae, et al., (2010)
Human	Prostate cancer cells, DCs	Quercetin and kaempferol (5-20 μM)	Prostate cancer cells (PC-3); Human DCs treated with conditioned medium derived from PC-3-treated cells		↑ GM-CSF release by cancer cells; ↑ Chemotaxis of DCs	Bandyopadhyay, Romero, and Chattopadhyay (2008)
Mouse	Macrophages	Extracts of water dropwort (*Oenanthe javanica;* 1.3, 2.5, 5.0%); isorhamnetin (20, 100 and 200 μM) and hyperoside (20, 100 and 200 μM)	LPS-primed BMDMs from C57BL/6 mouse		↓ Activation of NLRP3, NLRC4, and AIM2 inflammasomes; ↓ IL-1β, TNF-α, IL-6	Ahn and Lee (2017)
Mouse	Macrophages	Quercetin (0.02% incorporated in a grain-based diet, for 16 weeks)		$Apc^{Min/+}$ C57BL/6 mouse model of intestinal carcinogenesis	↓ Macrophage infiltration in the intestinal villi	Murphy, Davis, McClellan, and Carmichael (2011)
Rat	Macrophages	Quercitrin (1 or 5 mg/kg/day, p.o., for 8 days, simultaneously with DSS administration or on established colitis)		DSS-induced colitis in Wistar rats	↓ Macrophages; ↓ Inflammation	Camuesco et al. (2004)
Human/mouse	Breast cancer cells	Apigenin (*in vitro*: 20 and 40 μM; *in vivo*: 25 or 50 mg/kg/day, p.o., for 2 weeks, starting 14 days after injection of cells)	Breast cancer cells (MDA-MB-231)	BALB/c nude mice bearing breast cancer cells (MDA-MB-231)	↓ IL-6; ↓ pSTAT3	H. H. Lee, Jung, Moon, Kang, and Cho (2019)
Human/mouse	Colon cancer cells	Wogonoside (*in vitro*: 50, 100 and 150 μM; *in vivo:* 100 mg/kg/day, p.o., for 106 days, starting 7 days before the AOM injection)	Colorectal cancer cells (HCT-116, HT29)	AOM/DSS-treated C57BL/6 mice	↓ NF-κB activation; ↓ Neutrophil and macrophage tumor infiltration; ↓ IL-1β, IL-6 and TNF-α	Y. Sun et al. (2016)

(continued on next page)

Table 2 (*continued*)

Human Mouse	Cell Type	Treatment	*In vitro* Model	*In vivo* Model	Effects on immune system	Reference
Mouse	NK cells	Apigenin (5, 10 and 25 μM), luteolin (1, 5 and 10 μM)	Splenocytes from BALB/c mice		↑ NK cells activity	Kilani-Jaziri et al. (2016)
Rat	NK cells	Chrysin (3.12 μM), hesperetin (3.12 μM)	Splenocytes from Wistar rats		↑ NK cells activity	Sassi et al. (2017)
Mouse	NK cells, Macrophages	Chrysin (50 mg/kg, p.o., every 2 days, for 14 or 21 days, starting 1 week after injection of cells)		BALB/c mice bearing melanoma cells (B16F10)	↑ NK cells activity; ↑ Macrophages cytotoxicity	Sassi et al. (2018)
Human/mouse	Macrophages	Luteolin (1-30 μM)	RAW264.7, THP-1, and lung cancer cells (LLC)		↓ M2-like phenotype of TAM (↓ IL-4); ↓ CCL-2 expression	H. J. Choi, Chung, and Ha (2016)
Human	Prostate cancer cells	EGCG (40 μg/ml)	Prostate cancer cells (DU145, PC3, LnCap)		↓ IL-6, IL-8, CXCL-1, IP-10, CCl-5, TGF-β1; ↓ NF-κB	Mukherjee, Siddiqui, Dayal, Ayoub, and Malathi (2014)
Human	Keratinocytes	EGCG (0.03, 0.15 and 0.3 mM)	UV-treated HaCaT cells		↓ IL-6 and NF-κB	Xia, Song, Bi, Chu, and Wan (2005)
Mouse	Epidermal cells, Lymph nodes	EGCG (3 mg/mouse, topically, on the dorsal surface of the right ear, before UVB exposure)		C3H/HeN mice UV-exposed	↓ $CD11b^+$ monocytes/ macrophages and neutrophils; ↓ IL-10 in skin and DLN; ↑ IL-12 in DLN	Katiyar, Challa, McCormick, Cooper, and Mukhtar (1999)
Human	Pancreatic adenocarcinoma cells	EGCG (50-200 μM)	Pancreatic adenocarcinoma cells (Colo357)		↓ IL-1RI expression; ↓ IL-6, IL-8	Hoffmann et al. (2011)
Human	Macrophage-like cells	EGCG, EGC, ECG (25-100 μg/mL)	VD3-differentiated HL-60 human acute promyelocytic cells		↑ Phagocytosis	Monobe, Ema, Tokuda, and Maeda-Yamamoto (2010)
Mouse	DCs, Macrophages	Procyanidin (PC) (+B16F10 antigen vaccine) (*in vitro*: 80 μg/ml PC; *in vivo:* B16F10 cells with 1.2 mg PC/mouse, i.m. twice on day 0 and 14, before injection of cells at 7 days after the second immunization)	DC2.4 and RAW264.7	C57BL/6 mice bearing melanoma cells (B16F10)	↑ APC activation; ↑ CD80, CD86, MHC I and MHC II levels	L. Zhang, Wang, Liu, and Wang (2017)
Mouse	Immune cells	EGCG absorbed- nanogold particles (pNG) (2 mg/mouse/day, p.o., starting 2 weeks after injection of cells)		C3H/He mice bearing bladder cancer cells (MBT-2)	↑ NK cells cytotoxicity; ↓ IL-4 and IL-6; ↑ IL-2 and IFN-γ	D. S. Hsieh et al. (2011)
Rat	Lung cells	EGCG (20 mg/kg/day, i.p., for 28 days, after bleomycin injection)		Bleomycin-induced pulmonary fibrosis in albino Wistar rats	↓ ROS, LPO, MPO; ↑ GST and NQO1; ↓ TNF-α, IL-1β and NF-κB	Sriram, Kalayarasan, and Sudhandiran (2009)
Mouse	Macrophages, NK cells	EGCG (5, 20 or 40 mg/kg/day, p.o., for 2 weeks, starting 2 weeks after injection of cells)		BALB/c mice bearing leukemia cells (WEHI-3)	↑ Macrophages phagocytosis; ↑ NK cells activity	A. C. Huang et al. (2013a)
Mouse	Macrophages	EGCG (10 mg/kg, i.p., on days 7, 9 and 11, after injection of cells)		BALB/c mice bearing mammary carcinoma cells (4T1)	↓ TAM infiltration; M2→ M1; ↓ IL-6 and TGF-β; ↑ TNF-α	J. Y. Jang, Lee, Jeon, and Kim (2013)
Mouse	Macrophages	BR-WG-P (50-150 μg/ml)	RAW264.7		↓ NO production, iNOS and COX2 expression; ↓ TNF-α, IL-6 secretion	Limtrakul, Yodkeeree, Pitchakarn, and Punfa (2015)
Mouse	Immune cells	Anthocyanins from *Lonicera caerulea* 'Beilei' fruit (50, 100 and 200 mg/kg/day, p.o., for 15 days, starting 24 h after injection of cells)		Kunming mice bearing liver cancer cells (H22)	↑ Activities of antioxidant enzymes (SOD, GSH-Px, GSH); ↑ IL-2, IFN-γ and TNF-α in serum and liver	L. Zhou et al. (2018)
Mouse	Colon cancer cells	Dietary lyophilized (freeze-dried) strawberries (*Fragaria x ananassa*) (AIN-76A diet enriched with 2.5%, 5% or 10% lyophilized strawberries, for 20 weeks, starting 4 weeks after AOM injection)		AOM/DSS-induced colitis in Crj: CD-1 (ICR) mice	↓ TNF-α, IL-1β, IL-6, COX-2 and iNOS expression	Shi et al. (2015)
Rat	Immune cells, Esophageal cancer cells	Black raspberries (AIN-76A diet enriched with 6.1% freeze-dried black raspberries (BRB) powder or with 3.8 μmol/g of an anthocyanin-rich fraction of BRBs, for 15, 25 or 35 weeks, starting after injection of NMBA)		NMBA-treated F-344 rats	↓ IL-2, IL-1β, RANTES (CCL5), TNF-α, IL-4, IL-6, and VEGF expression in plasma; ↑ IL-10, IL-5, IL-12, IL-17A, IL-18, GM-CSF, IFN-γ, and MIP-1α (CCL3) expression in plasma; ↓ IL-1β in tumor; ↑ IL-12 in tumor; ↑ NK cells activity; ↓ infiltration of macrophages and neutrophils in tumor	Peiffer et al. (2016)
Mouse	Melanoma, lung cancer cells	Naringenin + asiatic acid (50 mg/kg/day naringenin + 10 mg/kg/day asiatic acid, i.p.,		C57BL/6 mice bearing melanoma cells (B16F10) or	↑ NK cell-mediated cytotoxicity	Lian et al. (2018)

		for 23 days, starting when tumor volumes reached 50 mm^3)		lung carcinoma cells (LLC)		
Mouse	DCs, Macrophages	Hesperetin (Hes) (+B16F10 antigen vaccine) (*in vitro*: 125 μg/ml Hes; *in vivo*: B16F10 cells with 0.8 mg Hes/mouse, i.m., twice on day 0 and 7, before injection of cells at 7 days after the second immunization)	DC2.4 and RAW264.7; splenocytes from immunized mice	C57BL/6 mice bearing melanoma cells (B16F10)	↑ Activation of APCs; ↑ CD80/CD86, and MHC I molecules on APC; ↑ IL-6 secretion	S. Jiang et al. (2020)
Human/mouse	Macrophages	Naringin, aculeatiside A (*in vitro*: 30 μM; *in vivo*: 100 μM, s.c. injected into the right shank of mice)	Human (HMDMs) and murine peritoneal macrophages; Mouse LNs	C57BL/6N mice	↑ $CD169^+$ macrophage; Induction M1-like phenotype; ↑ Secretion IL-1β and IL-12; ↑ mRNA expression of IL-1β and IL-12 in mice LN	Fujiwara et al. (2018)
Mouse/ Rat	Macrophages, Prostate cancer cells	Genistein (*in vitro*: 37 and 100 μM; *in vivo*: 80 μmol/kg/day, s.c., for 3 weeks, starting when tumor volumes reached 0.1 cm^3)	RAW264.7	Copenhagen rats bearing prostate cancer cells (R-3327, MAT-Lu)	↓ TNF-α and GM-CSF production; ↓ TAMs number in tumors	Joseph and Isaacs (1998)
Human/mouse	Immune cells	Phenoxodiol (*in vitro*: 0.05-10 μg/ml; *in vivo*: 10 mg/kg/day, i.p., for 10 days, starting when tumors were palpable at day 6)	PBMCs from HDs and cancer patients; Murine splenocytes	BALB/c mice bearing colorectal cancer cells (CT-26WT)	↑ NK cells activity	Georgaki et al. (2009)
Mouse	Immune cells	Genistein (20 mg/kg/day, p.o., for 1-4 weeks, before DMBA administration or injection of cells)		B6C3F1 mice bearing melanoma cells (B16F10); B6C3F1 mice treated with DMBA	↑ NK cells activity and IFN-γ secretion	T. L. Guo, Chi, Hernandez, Auttachoat, and Zheng (2007a); T. L. Guo et al. (2001)
Human/mouse	Breast cancer cells	Genistein (*in vitro*: 10 nM; *in vivo*: AIN-93G diet with 500 ppm genistein, for 23 weeks)	Breast cancer cells (MCF-7)	Athymic BALB/c (nude) mice bearing breast cancer cells (MCF-7)	↓ Lytic activity of NK cells; ↑ Induction of PI-9	X. Jiang et al. (2008)
Human	DCs	Genistein (100 μM)	Human monocyte-derived DCs		↓ LPS-induced DC maturation markers, B7 costimulatory molecules and MHC molecules expression; ↓ LPS-induced TNF-α, IL-10, IL-6, and IL-12 secretion	J. Wei, Bhatt, Chang, Sampson, and Masilamani (2012)
Mouse	DCs	Genistein (5 μM)	BMDCs	C57BL/6 mice	↓ LPS-induced IL-12p70 secretion	Pfarr et al. (2015)
Human	Monocytes; Colon cancer cells	GEN-27 (10 μM)	LPS-stimulated THP-1 cells; THP-1 co-cultured with colon cancer cells (HCT-116)		Suppression of LPS-induced NF-κB; ↓ LPS-induced IL-6 and IL-1β secretion in THP-1	Y. Wang et al. (2016)
Human	Macrophages	Genistein (10, 20 and 40 μM)	THP-1 co-cultured with ovarian cancer stem-like cells		Suppression of M2 polarization; ↓ IL-10, IL-8; ↑ IL-12 and NO	Ning et al. (2019)
Human	Monocytes; Lung cancer cells	Tectorigenin (10-50 μM)	THP-1 co-cultured with lung cancer cells (A-549)		↓ Release of TNF-α and IL-6 from THP-1	Amin et al. (2015)
Xanthones						
Human	Macrophages	Mangiferin (12-200 μM)	THP-1		↓ M1 macrophages activation; ↓ TNF-α, IL-1β, IL-6, IL-8, IRF5 expression	Z. Wei, Yan, Chen, Bao, and Deng (2016)
Mouse	Macrophages	DMXAA (250 μg/ml)	ANA-1		↑ NF-κB translocation; ↑ p-STAT1, p-STAT3; ↑ IL-6, TNF-α, IFN-β	Ching, Young, Eberly, and Yu (1999)
Mouse	Macrophages	DMXAA (18 mg/kg, i.p.)		BALB/c mice bearing mesothelioma cells (Ab12) or broncoalveolar carcinoma cells (L1C2); C57BL/6 mice bearing lung cancer cells (LLC)	↑ IP-10, RANTES, IL-6, IFN-γ, TNF-α, MIP-1a, MCP-1, iNOS, Mig, ICAM; ↑ CXCL1, MIP-2, MCP-1, RANTES	Jassar et al. (2005)
Mouse	Macrophages	DMXAA (18 mg/kg, i.p.; 1-125 μg/ml on DCs)		C57BL/6 or SCID mice bearing thymoma cells (E. G7)	↑ MCP-1, TNF-α, RANTES, MIP1a, KC, IL-6, IP-10; ↑ CD86, ICAM, CD80 on DCs	Wallace et al. (2007)
Mouse	Macrophages	DMXAA (+immunotherapy models) (18 mg/kg, i.p. alone or combined with immunotherapy)		C57BL/6 mice bearing lung epithelial cells (TC1), or lung cancer cells (LLC); BALB/c mice bearing broncoalveolar carcinoma cells (L1C2)	↑ Immunotherapy effect; ↑ DCs, neutrophils; ↑ $CCR7^+CD127^+$M1 macrophages; ↑ TNF-α, IFN-γ, CCL5, ICAM-1	Fridlender et al. (2013)
Human	Macrophages	α-mangostin (3.125-25 μM)	293T, THP-1, $STING^{-/-}$ THP-1, leukemia cells (U937)		↑ Type I IFNs; ↑ ISG15, CXCL10; ↑ TNF-α, CD80; ↑ Switch M2 to M1; ↑ IRF3, NF-κB	Y. Zhang et al. (2018c)
Mouse	Macrophages	α-mangostin (10-80 μM)		Collection of peritoneal	↓ LRP3 inflammasome, Caspase-1; ↑ M2	Ge, Xu, Liang, Xu, and

(continued on next page)

Table 2 (*continued*)

Human Mouse	Cell Type	Treatment	*In vitro* Model	*In vivo* Model	Effects on immune system	Reference
				macrophages and experimental sepsis in BALB/c mice	macrophages; ↓ TNF-α, IFN-γ, IL-1β; ↑ IL-10, TGF-β1; ↓ Inflammation and vital organ injuries	Huang (2019)
Mouse	Macrophages	β-mangostin (*in vitro*: 0.78-12.5 μg/ml; *in vivo:* pre-treatment with 0.01-100 mg/kg, i.g.)	RAW264.7	Carrageenan-induced peritoneal inflammation in IRC mice	↓ PGE2, COX-2; ↓ TNF-α, IL-6; ↓ NF-κB; ↓ Peritoneal leukocytes infiltration; ↓ Peritoneal neutrophils; ↓ TNF-α, IL-1β	Syam et al. (2014)
Vitamins						
Mouse	Macrophages	Calcitriol (50 nM)	Alveolar macrophages from $Vdr^{-/-}$ and WT mice		↓ GM-CSF	G. Hu, Dong, Wang, Jing, and Chen (2019)
Human	Cytokines	Calcitriol (4 μg, for each of 3 sequential days followed by 4 days of no treatment, enteric administration, 3 cycles)	Cytokines	Head and neck cancer patients	↑ IL-2, IFN-γ; ↑ IL-6 and IL-10 in the serum and tumor of the patient; ↓ TNF-α in the tumor; ↑ VEGF, IL-1α in the serum; ↓ IL-8 in the tumor	Walker, Reeves, de Costa, Schuyler, and Young (2012)
Human	Macrophages	Calcitriol (10 nM)	THP-1		↑ CXCL8, CXCL6, CXCL1	Ryynänen and Carlberg (2013)
Mouse	Cytokines	Calcitriol (0.1 μg/kg/day)		1α(OH)ase KO BALB/c mice ($1\alpha(OH)ase^{-/-}$)	↓ IL-6 and TNF-α	J. Guo et al. (2013)
Human	Monocytes/macrophages	Calcitriol (1 μM)	Monocytes/macrophages		↑ IL-1β in monocytes; ↓ IL-1, IL-6; ↑ TNF-α in macrophages	Di Rosa et al. (2012)
Human	Monocytes	Calcitriol (0.1-10 nM)	Monocytes		↓ IL-6 and TNF-α	Y. Zhang et al. (2012)
Human	Prostate cancer cells	Calcitriol (10-100 nM)	LNCaP, PC-3, DU145 and RWPE-1 cells		↓ IL-8	Bao et al. (2006)
Human	Prostate cancer cells	Calcitriol (50 nM)	Normal and cancer prostatic cells		↓ IL-6	Nonn, Peng, Feldman, and Peehl (2006)
Mouse	Monocytes, Macrophages	Vitamin E (vitamin E-rich nanoemulsion: 0.01%, 2.4%, 4.8%, 7.2%, or 10% w/v)	RAW264.7 cells		↑ IFN-γ, IL-12; ↓ IL-10	Ye et al. (2017)
Human	Neutrophils	Vitamin C (two kiwifruit/day containing 162 ±8 mg vitamin C per 100 g fruit without the skin, for 4 weeks)	Neutrophils		↑ Superoxide production and chemotaxis	Bozonet, Carr, Pullar, and Vissers (2015)
Human	Neutrophils	Vitamin C (3 mM)	Neutrophils		↓ NET formation	Mohammed et al. (2013)
Human	NK cells	Vitamin C (50 μg/ml)	PBMCs containing NK cells		↑ NK cells proliferation	Huijskens et al. (2015)
Mouse	BMDCs, NK cells	ATRA (1 μM)	BMDCs and NK cells from BALB/c mice		↑ IFN-γ	Chau et al. (2013)
Human	Monocytes	ATRA (100 nM)	$CD14^+$ human monocytes		↑ DCs apoptosis in the absence of inflammatory signals; ↑ differentiation of immature DCs into mature DCs via a cross talk with inflammatory cytokines	Geissmann et al. (2003)
Calves	Neutrophils	Vitamin A (2000 IU/kg, i.m.)	Neutrophils	Holstein calves	↑ O_2^-, phagocytosis	Higuchi and Nagahata (2000)
Mouse	Macrophages	ATRA (1 μM)	Peritoneal Macrophages	Outbred ICR strain mice	↓ TNF-α, NO	Mehta, McQueen, Tucker, Pandita, and Aggarwal (1994)

↓: decrease; ↑: increase; → shift

ADCC, Antibody dependent cellular cytotoxicity; AITC, Allyl isothiocyanate; AOM, Azoxymethane; AP-1, Activator protein-1; APC, Antigen presenting cells; ARG1, Arginase 1; ATRA, all-*trans* retinoic acid; BMDC, Bone marrow dendritic cells; BMMC, Bone marrow-derived mast cells; BR-WG-P, Polar fraction of black rice whole grain extracts; BSS β-sitosterol; BSSG, β-sitosterol glycoside; CAIA, Collagen antibody-induced arthritis; CCL, C-C Motif Chemokine Ligand; CCR, Chemokine receptor; COX, Cyclooxygenase; CR3-DCC, (CR3)-dependent cellular cytotoxicity; CUR, Curcumin; CXCL, Chemokine (C-X-C motif) ligand; DATS, Diallyl trisulfide; DCs, Dendritic cells; DIM, 3,30-diindolylmethane; DLN, Draining lymph nodes; DMH, 1,2-dimethylhydrazine; DSS, Dextran sulphate sodium; EAT, Ehrlich ascites tumor; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; GST, Glutathione S-transferases; HD, Healthy donor; HLEC, Human lymphatic endothelial cells; HMDMs, Human monocyte-derived macrophages; HO-1, Heme oxygenase 1; I3C, Indole-3-carbinol; ICAM-1, Intercellular adhesion molecule 1; IFN, Interferon; IL, Interleukin; iNOS, Inducible nitric oxide synthase; IP6, Inositol hexaphosphate; i.d., Intradermal; i.g. Intragastric; i.m., Intramuscular; i.p., Intraperitoneal; i.r., Intrarectal; IRF-1, Interferon regulatory factor-1; ISG, Interferon-stimulated gene; i.v., Intravenous; LPO, Lipid peroxidation; LPS, Lipopolysaccharide; M1 or M2, Polarized macrophages; MCP-1, Monocyte chemoattractant protein-1; MIP-1α, Macrophage inflammatory protein 1-alpha; MPO, Hydroxyproline levels and myeloperoxidase; NET, Neutrophil Extracellular Traps; NF-κB, Nuclear factor kappa B; NK, Natural killer; NLRC4, NLR Family CARD Domain Containing 4; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NMBA, Nitrosomethyl-N-butylamine; NO, Nitric oxide; NQO1, NAD(P)H Quinone Dehydrogenase 1; PBLs, peripheral blood leukocytes; PBMCs, Peripheral blood mononuclear cells; PEITC, Phenethyl isothiocyanate; PGE2, Prostaglandin E2; PI-9, proteinase inhibitor; PMN, Polymorphonuclear; p.o., Per os; RES, Resveratrol; ROS, Reactive oxygen species; RosA, Rosmarinic acid; s.c., Subcutaneous; SCFA, Short-chain fatty acids; SFN, Sulforaphane; SOD, Superoxide dismutases; STAT, Signal transducer and activator of transcription; STING, Stimulator of IFN genes; TAMs, Tumor-associated macrophages; TGF-β, Transforming Growth Factor-β; T_H, T helper; TLRs, Toll-like receptor; TNF-α, Tumor necrosis factor-α; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; VCAM, Vascular cell adhesion molecule; Vdr, Vitamin D receptor; VEGF, Vascular endothelial growth factor; WSPD, Water-soluble propolis derivatives; WT, Wild type.

Table 3
Effect of nutraceuticals on $CD4^+$ and $CD8^+$ T cells, B cells and DCs.

Human Mouse	Cell Type	Treatment	*In vitro* Model	*In vivo* Model	Effects on immune system	Reference
Organic acids						
Human	DCs, T cells	Butyrate (1 mM)	Human monocyte-derived DCs		↓ DCs maturation (↓ expression of CD80, CD83 and MHC II; ↓ IL-12p40 and IFN-γ; ↑ IL-10 secretion); ↓ T cells activation	L. Liu et al. (2012)
Human	DCs, T cells	Propionate (1 mM), butyrate (1 mM)	Monocyte-derived DCs and $CD8^+$ T cells isolated from HDs PBMCs		↓ IL-12 secretion; ↓ $CD8^+$ T cells activation	Nastasi et al. (2017)
Mouse	T cells	Butyrate (0.5 mM), Propionate (1 mM), Acetate (*in vitro*: 10 mM; *in vivo*: 200 mM in drinking water, for 6-8 weeks, before infection with *C. rodentium*)		C57BL/6 mice infected with *C. rodentium*	Promotion of T cells differentiation; ↑ T_H1 and T_H17 cells; ↑ IL-10 producing CD4 or CD8 T cells	J. Park et al. (2015)
Mouse	T cells	Butyrate (150 mM in drinking water, for 4 weeks)		C57BL/6 mice	↑ Effector function $CD8^+$ T cells; ↑ IFN-γ and granzyme B expression in CTLs	Luu et al. (2018)
Polysaccharides						
Mouse	DCs, T cells	β-glucan (800 μg/day, p.o., for 2 weeks starting when tumors were palpable)		C57BL/6 mice bearing lung carcinoma cells (LLC)	↑ DCs infiltrating tumor; ↑ T_H1; ↑ CTLs	Tian et al. (2013)
Mouse	DCs	Curdlan and mannan (100 μg of lyposome loaded with glucans at 4 g/mol, s.c., at day 5 and 15 in tumor bearing mice)	DC2.4 cells	C57BL/6 mice	DCs activation; ↑ T_H1 cytokines production	Yuba, Yamaguchi, Yoshizaki, Harada, & Kono, 2017)
Human/mouse	DCs	β-glucan (*in vitro*: 1-10 μg/ml for 24 h; *in vivo*: 25 mg/kg/day, i.p., for 5 days or twice or thrice a week)	Human/mouse monocyte-DCs	C57BL/6 mice	DCs activation; ↑ T_H1 cytokines production	H. Huang et al. (2009), M. Zhang, Chun, et al. (2018a)
Mouse	DCs, T cells	β-glucan (10 μg were mixed with tumor cells before inoculation)		C57BL/6 mice bearing lung carcinoma cells (LLC)	↑ DCs infiltrating tumor; T_H1 differentiation; ↑ CTLs responses	Ning et al. (2016)
Human	DCs	Polysaccharides purified from *G. lucidum* (1-1000 μg/ml for 24-48-72 h)	Monocytes from PBMCs		↑ DCs maturation	W. K. Chan, Law, Lin, Lau, and Chan (2007)
Mouse	T cells	Polysaccharides purified from *G. lucidum* (25 or 100 mg/kg/day, p.o., for 14 days starting when tumor volumes reached 50 mm^3)		C57BL/6 mice bearing lung carcinoma cells (LLC)	↑ $CD4^+$ cells; ↑ $CD8^+$ cells; ↑ T_H1 cytokines production	Y. Wang, Fan, and Wu (2020c)
Mouse	DCs, T cells	BG34-200 (β-(1-3)-(1-4)-glucan) (25 mg/kg/day, i.p., for 5 days, or twice or thrice a week)		C57BL/6 mice bearing melanoma cells (B16F10)	DCs activation; ↑ tumor infiltration of $CD4^+$ and $CD8^+$	M. Zhang, Chun, et al. (2018a)
Mouse	DCs, T cells	β-glucan from *G. frondosa* (20 mg/kg/day, p.o., once every 19 days after injection of cells)		BALB/c mice bearing colon carcinoma cells (Colon-26)	DCs activation; ↑ Tumor infiltration of T cells	Masuda et al. (2013)
Mouse	T cells	β-glucan (diet containing 50% of mushrooms micelia for 14 weeks)		Swiss Webster bearing sarcoma 180 tumor	↑ $CD4^+$ cells; ↑ $CD8^+$ cells; ↓ $CD19^+$ cells	Rubel et al. (2018)
Mouse	T cells	β-glucan from *S. cerevisiae* (300 μg/day, p.o.)	PBMCs	C57BL/6	↑ IL-10, TGFβ and T_H2; ↓ T_H1	Jin, Li, and Wang (2018)
Mouse	T cells	β-glucan from mushrooms (17-170 mg/kg/day, p.o., for 42 days)		B6 mice	↓ T_H2; ↑ T_H1	Jin et al. (2018)
Phytosterols						
Human	T cells	BSS and/or BSSG (1 μg/ml)	T-cells prepared from the mononuclear cell fraction		↑ T cells proliferation	Bouic et al. (1996)
Mouse	T cells	BSS 5 μg/ml)	Splenocytes from C57BL/6 mice		↓ T_H2 cells activity (IL-4 and IL-10); ↓ T cells proliferation	Le et al. (2017)
Human	Monocytes	BSS and/or BSSG (1 μg/ml)	Monocytes		↓ T_H2 (IL-6 and TNF-α)	Bouic and Lamprecht (1999)
Human/Mouse	Monocytes	BSS (2-250 μM)	THP-1		↓ T_H17 (IL-17, IL-22, IL-23)	N. Ma et al. (2018b)
Mouse	T cells	BSS (50 mg/kg/day, i.p., for 21 days, starting on day 7 after injection of cells)		BALB/c mice bearing melanoma cells (B16-F10)	↑ CTLs activity	Boubaker et al. (2018)
Mouse	T cells	Daucosterol (10 mg/kg, p.o., thrice a week, for 23 days, starting 2 weeks before DSS administration)		BALB/c mice	↑ T_H1 (IL-2 and IFN-γ)	J. H. Lee et al. (2007)
Mouse	T cells	Phytosterols diet (2% phytosterol-enriched		$ApoE^{-/-}$ and C57BL/6J mice	↑ T_H1 (IL-2 and IFN-γ)	Calpe-Berdiel

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Table 3 (*continued*)

Human Mouse	Cell Type	Treatment	*In vitro* Model	*In vivo* Model	Effects on immune system	Reference
		Western-type diet for 4 weeks)				et al. (2007)
Mouse	T cells	Guggulsterone (30 mg/kg/day, i.p., for 5 days)		BALB/c and SCID mice with induced colitis	↓ IL-2, IL-4 and IFN-γ in $CD4^+$ T cells from lamina propria	Mencarelli, Renga, Palladino, Distrutti, and Fiorucci (2009)
Phytic acid						
Chicken	Immunocytes	Phytate and phytase (oral diet with 22 or 44% phytate and 0, 500, or 1000 phytase units/kg of feed)		One-day-old female broilers (Cobb 500)	↑ $CD4^+$ and $CD8^+$ T cells	N. Liu, Ru, Cowieson, Li, and Cheng (2008)
Lipids						
Mouse	Splenic immune cells	Fish Oil (oral diet with 22.5% of energy as menhaden fish oil)		Her2/neu FVB transgenic mice mammary tumor	↑ IL-2; ↑ INF-γ driving a T_H1 response	Turbitt et al. (2015)
Rat	Immune cells	Long-chain ω-3 fatty acids (diet containing 200 g/kg of fat of which 5% ω-3, for 21 days, followed by injection of cells)		Fischer 344 rats bearing mammary tumor cells (R3230AC)	↑ $CD25^+$ $CD4^+$ T_H cells; ↑ IL-2, NO; ↑ NK cells	Robinson, Clandinin, and Field (2002)
Rat	Immune cells	ω-6:ω-3 (ratio 6:1) (diet rich in fats of which 66% represented by a mixture of fish oil and sunflower oil, for 8 weeks, followed by injection of cells)		Wistar rats bearing Walker rat mammary carcinoma cells (256)	↑ T lymphocytes proliferation; ↓ $CD8^+$ and NO	Pizato et al. (2006)
Mouse	T cells	ω-3 (ω-3-enriched diet consisted of 1% sunflower oil and 9% menhaden fish oil, for 28 days, followed by injection of cells)		Eugonadal and castrated C57BL/6 mice bearing prostate tumor (TRAMP-C2)	↑ T_H1 response (↑ IL-12, IFN-γ and GM-CSF)	Gevariya et al. (2019)
Terpenes						
Mouse	T cells	Terpenoid compounds (0.002-500 μM)	Splenocytes from BALB/c mice		↓ IL-2 (T_H1) and IL-10 (T_H2); ↑ IFN-γ	Ku and Lin (2013)
Mouse	T cells	Artemisinin (100 mg/kg, i.p., for 20 days, starting 5-7 days after injection of cells)		BALB/c mice bearing mammary cancer cells (4T1)	↑ $CD4^+$ IFN-γ^+ T cells and CTLs	Y. Cao et al. (2019b)
Rat/Mouse	T cells	Dihydroartemisinin (*in vitro*: 25-50 μM; *in vivo*: 4.85 μg/mouse/day, i.p., for 6 days, starting 17 days after injection of cells)	Pancreatic cells (RIN)	BALB/c mice bearing mammary tumor (SMMT)	↑ T_H1	Noori and Hassan (2011)
Mouse	T cells	Myrcene (0.8 mg/ml, i.p., at 3-week intervals for 6 weeks, starting at the same time of immunization)		BALB/c mice immunized with OVA and Ag85B	↑ T_H1	Uyeda et al. (2016)
Mouse	T cells	CDDO-Me (5 mg/kg, i.p. or i.v., for a total of three injections starting 13 days after injection of cells)		C57BL/6 mice bearing melanoma cells (B16F10)	↑ CTLs; ↓ M1 and M2 cytokines	Y. Zhao, Huo, Xu, Wang, and Huang (2015a)
Mouse	DCs, T cells	Betulin (5-100 μM)	BMDCs and primary spleen cells of C57BL/6 mice		↑ IL-12p70, IFN-γ and IL-2	Pfarr et al. (2015)
Mouse	T cells	Betulinic acid (200 mg/kg)		Kunming mice bearing mouse cervical carcinoma (U14)	↑ $CD4^+$ lymphocytes; ↑ IL-2 and TNF-α	P. Wang et al. (2012b)
Mouse	T cells	Betulinic acid (25-50 mg/kg/day, p.o., for 7 days)		BALB/c and C57BL/6 psoriatic mice	↓ T_H17 (IL-17A-expressing $CD4^+$ and γδ T cells); ↓ IL-10	C. Liu et al. (2019a)
Mouse	T cells	SH479 (20 mg/kg/day, i.p., starting 23 days after immunization)		DBA/1J mice	↓ T_H17 and T_H1; ↑ T_H2 (IL-10 and IL-4)	S. Chen et al. (2017)
Mouse	T cells	Oleanolic acid and erythrodiol (50 mg/kg/day, i.p., before, at the same time or post immunization)	Murine BV-2 microglial cells	C57BL/J6 mice with induced EAE	↓ T_H17 and T_H1 (TNF-α, IFN- γ and IL-6); ↑ T_H2 (IL-10 and IL-4)	Martín, Hernández, Córdova, and Nieto (2012)
Human	T cells	Corosolic acid and oleanolic acid (*in vitro*: 30 μM; *in vivo*: 17.5 mg/kg, p.o., twice a week, starting 7 days before injection of cells, for 21 days)	HMDMs	C3H mice bearing osteosarcoma cells (LM8)	↑ $CD4^+$ and $CD8^+$	Fujiwara et al. (2014)
Human/Mouse	Colorectal cancer cells	Ginsenoside Rg3 (*in vitro*: 20-80 μM; *in vivo*: 25 mg/kg/day, i.g., for 12 days)	Human CRC cells (LoVo, SW620, HCT116)	BALB/c athymic nude mice bearing human CRC cell lines (LoVo, SW620, HCT116)	↑ B7-H1 (PD-L1) and B7-H3	Y. C. Tang et al. (2018)
Organosulfurs						
Mouse	T cells	DATS (50 mg/kg/day, p.o., for 21 days)		C57BL/6 mice bearing melanoma cells (B16F10)	↑ $CD8^+$ T cells	De Cicco et al. (2020)
Human	Untransformed human T-cells	SFN (10 μM)	Untransformed human T-cells derived from healthy donors or RA patients		↓ T_H17 cytokines	J. Liang et al. (2018)

	derived from healthy donors or RA patients					
Mouse	Ear tissue	SFN (9 μmol/day, p.o.)	Ear tissue	*Nrf2*$^{+/+}$ and *nrf2*$^{-/-}$ mice with contact hypersensitivity	Restore T_H1 immunity (↑ IFN-γ)	H. J. Kim, Barajas, Wang, and Nel (2008)
Mouse	T cells	SFN (diet containing 0.003% SFN starting 10 days before immunization)	T cells from draining LNs	SJL mice with induced EAE	↓ IL-17 and IFN-γ in draining lymph nodes	Geisel et al. (2014)
Mouse	T cells	SFN (5 mg/kg, i.p., for 1-5 days)		Swiss male mice	↓ T cells proliferation	Checker, Gambhir, Thoh, Sharma, and Sandur (2015)
Human	T cells	SFN (10-100 μM for T cells proliferation; 0.01-10 μM for cytokines production)	T cells from patients with rheumatoid arthritis		↓ T cells proliferation; ↓ IL-17, TNF-α	J. S. Kong et al. (2010)
Polyphenols						
Non-Flavonoids						
Mouse	T cells	CUR (50 mg/kg, p.o., every alternate day; from day 7 after injection of cells)		Swiss albino mice bearing EAT	↑ CD4, CD8, T_{CM}, T_{EM}, GrB, perforin,	Bhattacharyya et al. (2010)
Mouse	T cells	CUR (+RES) (100 mg/kg, p.o., 2 weeks prior or with injection of cells)		BALB/c mice bearing salivary gland tumor cells (SALTO-5)	↔ Lymphocytes and granulocytes frequencies	Masuelli et al. (2014)
Mouse	T cells	CUR (+RES) (1-20 μM, each)	Splenocytes from BALB/c mice		↓ Proliferation; ↓ CD28, IFN-γ, IL-4; ↑ CTLA-4	Sharma et al. (2007)
Mouse	T cells	CUR (*in vitro*: 5-20 μM; *in vivo*: 1-8 μM)	Cytotoxic T lymphocyte cells (CTLL-2)	C57BL/6 mice	↓ IL2/IL-2Rα; ↓ naive T cells differentiation	Oh, Hwang, and Heo (2018)
Mouse	T cells	CUR (25-100 mg/kg/day, i.p., for 10 days)		BALB/c or nude mice bearing lung carcinoma cells (LLC)	↑ CD8 cytotoxicity; ↑ IFN-γ	Luo, Song, Zhang, and Chu (2011)
Mouse	T cells	CUR (100 mg/kg, p.o., thrice a week)	Mammary carcinoma cells (TUBO)	BALB/c mice bearing mammary carcinoma cells (TUBO)	↑ CD8	Masuelli et al. (2017b)
Mouse	T cells	CUR (50 mg/kg/day, p.o., from day 14 and for 14 days) (+Metformin)		BALB/c mice bearing mammary tumor cells (EMT6/P)	↑ IFN-γ, IL-4; ↔ IL-2, IL-10	Falah, Talib, and Shbailat (2017)
Mouse	T cells	CUR (100 mg/kg, p.o.) (+anti-HER2/neu vax)		BALB/neuT mice bearing salivary gland carcinoma cells (SALTO-5)	↑ Anti-Neu humoral response; ↑ CD4, CD8; ↑ IFN-γ, IL-2	Focaccetti et al. (2020)
Mouse	T cells	CUR (20 or 50 mg/mouse, p.o., before or after injection of cells; before or after vax) (+Listeria^{at}-Mage-b vax)		BALB/c mice bearing mammary cancer cells (4T1)	↑ CD4, CD8; ↑ IFN-γ	M. Singh et al. (2013)
Mouse	T_{FH} cells, B cells	CUR (200 μg/mouse/day, i.p., for 7 days) (+NP-OVA vax)		C57BL/6 mice	↑ BCL-6^{+}CXCR5^{+}T_{FH} cells; ↑ CD95+ GL-7+ germinal center B cells	D. H. Kim, Lee, and Choi (2019a)
Mouse	T cells	CUR (*in vitro*: E.G7 pretreated with 10 μM; *in vivo*: 70 mg/kg/day, i.p., for 5 days)	Mouse thymic lymphoma cells (E.G7)	C57BL/6 mice treated CD8^{+} T cells adoptive therapy	↓ TGF-β, IDO; ↑ CD8, IFN-γ	Y. F. Chang et al. (2012)
Human	T cells	CUR (pretreatment at 20 μM for 6 h; IFN-α 10^4 U/ml or IFN-γ 10 ng/ml)	Human melanoma cells (A375, FO1 +IFNα/γ), PBMCs		↓ IRF1, ISG-15 PBMCs; ↓ p-STAT1, p-STAT3, p-STAT5	Bill et al. (2009)
Mouse	T cells	CUR (5 or 10 μM/kg/day, for 4 weeks, after 4NQO administration)		C57BL/6 mice bearing 4NQO-induced oral carcinoma	↑ CD8 TILs; ↓ PD-L1, p-STAT3	F. Liao, Liu, Luo, and Hu (2018a)
Mouse	T cells	BDMC (3 mg/kg, i.v., every 3 days for 2 or 4 weeks, starting 1 week after injection of cells) (+anti-PD-L1)		C57BL/6 mice bearing bladder carcinoma cells (MB49)	↑ CD8 TILs; ↑ IFN-γ; ↑ GrB and perforin; ↓ PD-1	Shao et al. (2017)
Human	T cells	Nano-CUR (50 μM)	Esophageal adenocarcinoma cells (OE33, OE19)		↑ CD86 on DCs; ↓ TNF-α, IL-8, IL-6, IL-10, IL-1β; ↑ IFN-γ	Milano et al. (2013)
Mouse	T cells	CUR-based micelles (40 mg/kg/day, i.v., for 5 injections, starting when tumor volumes reached 150 mm^3)		C57BL/6 mice bearing melanoma cells (B16F10)	↑ CD8^{+}; ↑ IFN-γ	Y. Lu et al. (2016)
Mouse	T cells	Nanocarrier CUR (*in vitro*: 10 μM; *in vivo*: 2 mg/kg, i.v., every 3 days) (+anti-PD-1)	Melanoma cells (B16F10)	C57BL/6 mice bearing melanoma cells (B16F10)	↑ CD8, IFN-γ; ↓ CCL-22, TGF-β, IL-10	Z. Xiao et al. (2020)
Mouse	T cells	pCaA, pFA, pCoA (4-100 μg/ml)		C57BL/6 splenocytes	↑ IFN-γ, GM-CSF	Yamanaka et al. (2012)
Mouse	T cells	*Ananas comosus* vinegar (GA, other phenolic acids) (*in vitro:* 0.25 and 0.32 mg/ml; *in vivo*: 0.08 and 2 ml/kg, p.o., for 4 weeks)	Mammary cancer cells (4T1)	BALB/c mice bearing mammary cancer cells (4T1)	↑ CD4^{+}, CD8^{+}, NK1.1^{+}; ↑ IFN-γ, IL-2; ↓ IL-1β, IL-10; ↓ NF-κB, COX-2	Mohamad et al. (2019)

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Table 3 (*continued*)

Human Mouse	Cell Type	Treatment	*In vitro* Model	*In vivo* Model	Effects on immune system	Reference
Mouse	T cells	CAPE (0.47 or 23.5 or 47 mg/kg in the diet)		BALB/c irradiated mice	↑ $CD8^+$ TIL; ↓ TGF-β, COX-2, $PD\text{-}L1^+$; ↓ $CD11b^+GR1^+$	Omene et al. (2020)
Mouse	T cells	P2Et (*Caesalpina spinosa*) (*in vitro:* 3.4 or 17 or 34 μg/ml; *in vivo*: 9.3-18.7 mg/kg, i.p., twice a week)	Mammary cancer cells (4T1)	BALB/c mice bearing mammary cancer cells (4T1)	↓ Leukocytes; ↓ Leukemoid reaction; ↓ MCP-1, IL-6	Urueña et al. (2013)
Mouse	T cells	RosA (75-150-300 mg/kg/day, i.g., for 10 days)		Kunming mice bearing liver cancer cells (H22)	↑ $CD8^+$ T, IL-2, IFN-γ; ↑ Ratio $CD4^+/CD8^+$ TILs; ↓ IL-1β, IL-6, TNF-α, TGF-β	Cao, Hu, Wu, Xu, and Jiang (2016); W. Cao et al. (2019a)
Mouse	T cells	RES (1, 2.5, and 5 mg/kg/day, i.p.)		BALB/c mice bearing renal carcinoma cells (Renca)	↑ Activated $CD8^+$ T cells; ↓ Density of NK cells; ↑ Perforin, GrB: ↑ IFN-γ; ↓ IL-6, IL-10	L. Chen, Yang, Liao, and Xiong (2015)
Human/Mouse	T cells	RES (*in vitro*: 25 and 50 μM; *in vivo*: 50 or 100 mg/mouse/day, i.p.)	Human ovarian cancer cell (SKOV3, A2780); murine ovarian surface epithelial cells (ID8)	C57BL/6 mice bearing murine ovarian surface epithelial cells (ID8)	↑ CRT, HMGB1, ATP; ↑ DCs, T cells; ↑ IL-12p70, IFN-γ; ↓ TGF-β	Y. Zhang, Yang, Yang, and Liu (2019b)
Mouse	T cells	RES analogue HS-1793 (0.3-2.5 μM)		C3H/He mice bearing mammary carcinoma cells (FM3A)	↓ IL-2; ↑ IL-4; ↑ CD8, ↔ CD4; ↑ IFN-γ	Y. J. Choi et al. (2012); M. H. Jeong et al. (2012)
Flavonoids						
Mouse	T cells	Quercetin (2 mg/mouse/day added to the rodent chow, starting when tumors reached 1 cm in diameter) (+DOX)		BALB/c mice bearing mammary cancer cells (4T1) in the mammary fat pad	↑ T cells proliferation; ↑ Type 1 cytokines IL-2 and IFN-γ; ↓ Type 2 cytokines IL-4 and IL-10; Induction of persistent T cell tumor-specific responses	Du et al. (2010)
Rat	Glioblastoma cells	Apigenin (100 μM)	Glioma cells (C6)		$T_H2 \rightarrow T_H1$	Coelho et al. (2016)
Human/mouse	T cells	Apigenin (30 μM), luteolin (30 μM)	Human breast cancer cells (MDA-MB-468, SK-BR-3); Murine mammary cancer cells (4T1); immortalized human T lymphocyte cells (Jurkat) co-cultured with MDA-MB-468, IFN-γ and apigenin		↓ IFN-γ-induced PD-L1 upregulation; ↑ T cells proliferation; ↑ IL-2 synthesis by T cells co-cultured	Coombs, Harrison, and Hoskin (2016)
Human, Mouse	T cells, Hepatocellular carcinoma cells	Baicalein (*in vitro*: 10 μM; *in vivo*: 50 mg/kg/day, i.p., for 12 days, starting 24 h after injection of cells), baicalin (*in vitro:* 40 μM; *in vivo*: 80 mg/kg/day, i.p., for 12 days, starting 24 h after injection of cells)	Human hepatocellular carcinoma cells (SMMC-7721, HepG2); immortalized human T lymphocyte cells (Jurkat) co-cultured with cancer cells, IFN-γ and baicalein or baicalin	BALB/c mice bearing liver cancer cells (H22)	↓ IFN-γ-induced PD-L1 expression; ↑ IL-2 synthesis by T cells co-cultured; ↑ $CD8^+$ cytotoxicity; ↑ $CD8^+$ T cells numbers in tumor tissues; ↓ PD-L1 in tumor tissues	Ke et al. (2019)
Human, mouse	T cells, Melanoma cells	Apigenin (*in vitro:* 30 μM; *in vivo:* 150 mg/kg/day, p.o., for 12 days, starting 4 days after injection of cells) +CUR (*in vitro*: 25 μM; *in vivo*: 50 mg/kg/day, p.o., for 12 days, starting 4 days after injection of cells)	Human melanoma cells (A375, A2058, RPMI-7951)	C57BL/6 mice bearing melanoma cells (B16F10)	↓ IFN-γ-induced PD-L1 expression; ↑ IL-2 synthesis by T cells; ↑ T cell-mediated melanoma cell killing; ↑ $CD4^+$ and $CD8^+$ T cells in tumors and spleens; ↓ PD-L1 in tumor tissues	L. Xu et al. (2018)
Mouse	T cells	Apigenin (25 mg/kg, i.p., thrice a week, starting when tumors were palpable)		C57BL/6N mice bearing pancreatic ductal adenocarcinoma cells (Panc02)	↑ $CD4^+$ and $CD8^+$ T cells; ↑ IFN-γ by $CD8^+$ from mice splenocytes	Nelson et al. (2017)
Mouse	T cells	Salvigenin (9.68 μg/mouse/day, i.p., for 12 days, starting when tumor volumes reached 1.5 cm^3)		BALB/c mice bearing mammary tumor cells (SMMT)	↓ IL-4; ↑ IFN-γ; ↑ T_H1 immunity	Noori, Hassan, Yaghmaei, and Dolatkhah (2013)
Mouse	T cells	Apigenin (5, 10 and 25 μM), luteolin (1, 5 and 10 μM)	Splenocytes from BALB/c mice		↑ CTL activity	Kilani-Jaziri et al. (2016)
Rat	T cells	Chrysin (3.12 μM), hesperetin (3.12 μM)	Splenocytes from Wistar rats		↑ CTL activity	Sassi et al. (2017)
Mouse	T cells	Chrysin (50 mg/kg, p.o., every 2 days, for 14 or 21 days, starting 1 week after injection of cells)		C57BL/6 mice bearing melanoma cells (B16F10)	↑ CTL activity	Sassi et al. (2018)
Human	T cells, Lung cancer cells, Melanoma cells	EGCG, green tea extract (*in vitro:* EGCG 10 and 50 μM; GTE 50 and 100 μg/ml; *in vivo*: GTE 0.3% in drinking water for 16 weeks, starting 2 days after injection of NNK)	Lung cancer cells (A549, H1299, Lu99); F10-OVA melanoma cells co-cultured with tumor-specific $CD3^+$ T cells	A/J mice bearing NNK-induced lung tumors	↓ IFN-γ- and EGF-induced PD-L1 expression in lung cancer cells; ↓ $PD\text{-}L1^+$ cells in tumor tissues; ↓ PD-L1 mRNA expression in F10-OVA cells; Restore of IL-2 mRNA expression in tumor-specific $CD3^+$ T cells	Rawangkan et al. (2018)

Mouse	DCs, T cells	EGCG (25 and 50 μM)	BMDCs from C57BL/6 mice; OVA-specific $CD8^+$ T cells incubated with DCs		↓ IFN-γ-induced IDO expression and activity in DC cells; Restore of the IDO-mediated T cell suppression	Y. I. Jeong et al. (2007)
Human	Oral cancer cells	EGCG (20 and 40 μM)	Oral cancer cells (HSC-3, SAS, Ca-922, SCC-4, Cal-27)		↓ IDO expression and activity	C. W. Cheng et al. (2010)
Human	Colorectal cancer cells	EGCG (10-100 μM)	CRC cells (HT29, SW837)		↓ IFN-γ-induced IDO mRNA and protein expression; ↓ IDO activity	Ogawa et al. (2012)
Mouse	T cells	EGCG (0.5 mg/ml in drinking water for 5 or 11 days, starting 10 days after injection of cells)		C57BL/6 mice bearing E7-expressing tumors (TC-1 cells)	↑ $CD8^+$ and $CD4^+$ T cell-mediated immune responses specific for the E7 oncoprotein; ↑ IFN-γ	Kang et al. (2007); C. K. Song et al. (2007)
Mouse	T cells	Procyanidin (PC) (+B16F10 antigen vaccine) (B16F10 cells with 1.2 mg PC/mouse, i.m. twice on day 0 and 14, before injection of cells at 7 days after the second immunization)		C57BL/6 mice challenged with melanoma cells (B16F10)	↑ $CD8^+$ T cell response; ↑ Perforin, IFN-γ, and TNF-α	L. Zhang et al. (2017)
Mouse	T cells	EGCG (5, 20 or 40 mg/kg/day, p.o., for 2 weeks, starting 2 weeks after injection of cells)		BALB/c mice bearing leukemia cells (WEHI-3)	↑ $CD3^+$ T cells; ↑ T cells proliferation	A. C. Huang, Cheng, et al. (2013a)
Mouse	T cells	*Pinus koraiensis* (PPP-40) (150 mg/kg/day, p.o., for 10 days, starting 24 h after injection of cells)		KM mice bearing sarcoma cells (S180)	↑ Splenic $CD4^+$ and $CD8^+$ T cells; ↑ IL-2, IL-12 and TNF-α	Yi et al. (2017)
Mouse	T cells	Poliphenon E (0.3% in drinking water, starting from the day of injection of cells)		Transgenic TH-MYCN mice; A/J mice bearing neuro 2A tumor	↑ Tumor-infiltrating $CD8^+$ and $CD4^+$ T cells	Santilli et al. (2013)
Human	Colorectal cancer cells	Delphinidin-3-*O*-glucoside, cyanidin-3-*O*-glucoside and its metabolites (delphinidin chloride and GA) (100–600 μg/ml)	CRC cells (HCT-116, HT29); PBMCs pre-treated with anthocyanins and co-cultured with HCT-116 and HT-29 cells		↓ PD-L1 expression; ↓ PD-1 expression; ↓ Binding of PD-L1 to PD-1	Mazewski, Kim, and Gonzalez de Mejia (2019)
Mouse	T cells	Naringenin + asiatic acid (50 mg/kg/day naringenin + 10 mg/kg/day asiatic acid, i.p., for 23 days, starting when tumor volumes reached 50 mm^3)		C57BL/6 mice bearing melanoma cells (B16F10) or lung carcinoma cells (LLC)	↑ $CD4^+$ and $CD8^+$ T cells	Liang et al. (2018)
Mouse	T cells	Hesperetin (Hes) (+B16F10 antigen vaccine) (B16F10 cells with 0.8 mg Hes/mouse, i.m., twice on day 0 and 7, before injection of cells at 7 days after the second immunization)		C57BL/6 mice challenged with melanoma cells (B16F10)	↑ CTL and $CD4^+$ T cell-mediated responses; ↑ IL-4, IFN-γ and TNF-α	S. Jiang et al. (2020)
Mouse	T cells	Phenoxodiol (10 mg/kg/day, i.p., for 10 days, starting when tumors were palpable)		BALB/c mice bearing CRC cells (CT-26.WT)	↑ Tumor-specific T cell lytic activity	Georgaki et al. (2009)
Mouse	T cells	Genistein (20 mg/kg/day, p.o., for 1-4 weeks, before DMBA administration or injection of cells)		B6C3F1 mice bearing melanoma cells (B16F10); B6C3F1 mice treated with DMBA	↑ CTLs activity	T. L. Guo, Chi, et al. (2007a); T. L. Guo et al. (2001)
Xanthones						
Mouse	Splenocytes, Thymocytes	Mangiferin (5-40 μg/ml)		Healthy mice; Swiss mice bearing sarcoma cells (S-180)	↑ Proliferation of thymocytes and splenocytes	Chattopadhyay, Das, Guha, and Ghosal (1987)
Mouse	Macrophages	DMXAA (18 mg/kg, i.p.)		BALB/c mice bearing mesothelioma cells (Ab12) or broncoalveolar carcinoma cells (L1C2); C57BL/6 mice bearing lung cancer cells (LLC)	↑ Tumor-specific $CD8^+$	Jassar et al. (2005)
Mouse	Macrophages	DMXAA (18 mg/kg, i.p.; 1-125 μg/ml on DCs)		C57BL/6 or SCID mice bearing thymoma cells (EG7)	↑ Tumor-specific $CD8^+$	Wallace et al. (2007)
Mouse	Macrophages	DMXAA (+immunotherapy models) (18 mg/kg, i. p. alone or combined with immunotherapy)		C57BL/6 mice bearing lung epithelial cells (TC1), or lung cancer cells (LLC); BALB/c mice bearing broncoalveolar carcinoma cells (L1C2)	↑ $CD8^+$ TILs (4-1BB$^+$ or CD25$^+$)	Fridlender et al. (2013)
Mouse	T cells	DMXAA (25 and 300 mg/kg, i.p.) (+CD80 costimulation)		C57BL/6 mice bearing thymic lymphoma cells (EL-4) or lung carcinoma cells (LLC)	↑ Tumor-specific CTLs activity, NK cells; ↑ Protection from tumor rechallenge	Kanwar, Kanwar, Pandey, Ching, and Krissansen (2001)

(continued on next page)

Table 3 (*continued*)

Human Mouse	Cell Type	Treatment	*In vitro* Model	*In vivo* Model	Effects on immune system	Reference
Mouse	T cells	DMXAA (+OVA) (2 i.d. immunizations with 10 μg OVA plus 100 μg DMXAA)		Ifnar$^{-/-}$ C57BL/6 or Irf3$^{-/-}$ C57BL/6 mice immunized; IL33$^{-/-}$ BALB/c mice immunized	↑ T_H2 response; ↑ IRF3 mediated type-I-IFN induction	C. K. Tang et al. (2013)
Human	T cells	DMXAA (AAV-STING) (10 μg/ml)	Merkel cell polyomavirus infected or not cells; Human dermal fibroblasts		↑ CD4, CD8 TILs; ↑ STING activity; ↑ IFN-β, CCL5, CXCL10, TNF-α, IL-6, IL-29; ↑ PD-L1	W. Liu et al. (2020)
Human/Mouse	T cells	α-mangostin (*in vitro*: 0.25-4 μM; *in vivo*: 50 mg/kg, i.p.)	RORγt –Jurkat reporter cells	CD4$^+$CD25$^-$ from C57BL/6 mice and differentiated	↓ RORγt on Jurkat; ↓ T_H17 cells differentiation; ↓ T_H1, IFN-γ	X. Zhou et al. (2020)
Mouse	T cells	α-mangostin (13.9 mg/kg, i.v., every other day) (+CD258)		C57BL/6 mice bearing pancreatic ductal adenocarcinoma (KPC1199, Panc02)	↑ CD8$^+$, CD4$^+$, B cells	Y. Huang et al. (2020)
Human	T cells	Cluvenone (0.3 μM)	T cell acute lymphoblastic leukemia cells (CEM); Prostate cancer cells (PC3)		↑ T cells activation pathways	Batova et al. (2010)
Vitamins						
Mouse	DCs	Calcitriol analog, Rocaltrol® (40 nM)	BMDCs from BALB/c mice		↓ T_H1 and CTLs activation	Matsuzaki et al. (2006)
Mouse	T cells	Calcitriol (2.4×10^{-8} M)	T cells from BALB/c mice		↓ IFN-γ, IL-4	Staeva-Vieira and Freedman (2002)
Human	Mononuclear cells	Calcitriol (1×10^{-10}—1×10^{-8} M) and analogues of calcitriol (1×10^{-13}—1×10^{-15} M)	T cells from human healthy donors		↓ IL-2 from activated T cells	Binderup et al. (1991)
Mouse	Immune cells from LNs	Calcitriol (0.5 μg/kg, s.c., thrice a week from the day 7 after injection of cells)		BALB/c mice bearing mammary cancer cells (4T1)	↑ T_H2 (IL-4, IL-5, IL-9, IL-13); ↓ CD8$^+$ cells	Pawlik et al. (2018)
Mouse	T cells, Macrophages	Vitamin E (diet containing 500 ppm of vitamin E for 8 weeks)		C57BL/6NCrl mice	↑ T_H1 (↑ IFN-γ and IL-2); ↓ IL-1β, TNF-α, PGE2	Han et al. (2000)
Mouse	T cells	Vitamin E (diet containing 500 ppm of vitamin E for 4 weeks)		C57BL/6NIA mice	↑ T_H1; ↑ IL-2 production	Han et al. (2006)
Mouse	T cells	Vitamin E [diet with 1 mg of the vitamin E isomers (α- tocopherol, δ- tocotrienol, or Tocotrienol-rich fraction (TRF) containing: α-tocopherol (32%), α-tocotrienol (25%), γ-tocotrienol (29%), and δ-tocotrienol (14%)]		BALB/c mice	↑ T_H1 (↑ IFN-γ and IL-2)	Radhakrishnan, Mahalingam, Selvaduray, and Nesaretnam (2013)
Mouse	T cells	Vitamin E (diet containing 20 or 200 mg of vitamin E throughout the course of experiments)		SL mice	↑ T_H cells activity	Tanaka, Fujiwara, and Torisu (1979)
Mouse	DCs, T cells	Semisynthetic vitamin E derivative α-TEA (α-TEA (20 mmol/l)-generated autophagosome-enriched supernatant fraction was pulsed onto DCs which were used as vaccine)		BALB/c mice bearing mammary cancer cells (4T1)	↑ Cross-priming of CD8$^+$ T	Y. Li et al. (2012)
Mouse	T cells	α-TOS (200 mg/kg, i.p. or i.t., on days 10, 14, and 18 after injection of cells)		C57BL/6 mice bearing Lewis lung carcinoma cell line 3LLD122	↑ IFN-γ production	Ramanathapuram et al. (2004)
Mouse	T cells	Vitamin C (0.3-800 μM)	Bone marrow-derived progenitor cells from C57BL/Ka-Thy-1.1 mice		↑ T cells maturation	Manning et al. (2013)
Mouse	DCs, T cells	Vitamin C (0.08, 0.4, or 2 mM)	BMDCs and T cells from BALB/c and C57BL/6 mice		↑ IL-12p70; ↑ IFN-γ and IL-2	Y. J. Jeong et al. (2011)
Mouse	DCs, T cells	Vitamin C (0.08, 0.4, or 2 mM for tumor lysate-loaded DCs treatment)		C57BL/6 mice vaccinated with B16F10 melanoma cells lysate-loaded DCs	↑ CD44^{hi}CD62L^{lo}CD8$^+$ effector and effector memory T cells	Y. J. Jeong et al. (2014b)
Mouse	T cells	Vitamin C (0.625 or 5 mg/day, i.p., for 26 days)		BALB/c mice	↑ IL-2, TNF-α, and IFN-γ; ↓ IL-4	Noh et al. (2005)
Mouse	B cells	Vitamin C (0.625 or 5 mg/mouse/day, i.p., for 3 days before primary immunization and every day after primary immunization for 10 more days)		BALB/c mice	↓ Antigen-specific IgG1 antibody	A. Woo et al. (2010)
Pig	DCs Lymphocytes	ATRA (1000 nM)	DCs from PBMC	Swiss White Landrace pigs	↑ TGF-β and IL-6; ↑ Specific IgG and IgA	Saurer, McCullough, and Summerfield (2007)
Mouse	T cells	Vitamin A/ATRA (diet containing 20,000 IU	T cells	B6.SJL (CD45.1) mice; OTII	↑ T_H1 and T_H17	Hall et al. (2011)

		vitamin A/kg until use or i.p. injection of 250 μg of ATRA)	mice; DEREG mice; Rara$^{-/-}$ mice		
Mouse	T cells	ATRA (0.15 g ointment, rubbed on the tumor and the skin adjacent to the tumor every day)	C57BL/6 mice bearing B16F10 melanoma cells	↑ Frequency of tumor infiltrating CD8+ T cells; ↓ Frequency of tumor-infiltrating MDSCs ($CD11b^+$ $Gr\text{-}1^{++}$)	W. Yin, Song, Liu, Wu, and He (2017)

↓: decrease; ↑: increase; → shift; ↔ stable

AAV, Adeno-associated viruses; ApoE, Apolipoprotein E; ATP, Adenosine TriPhosphate; ATRA, all-*trans* retinoic acid; BMDCs, Bone marrow-derived dendritic cells; BSS, β-sitosterol; BSSG, β-sitosterol glycoside; CAPE, Caffeic acid phenethyl ester; CCL22, C-C Motif Chemokine Ligand 22; COX, Cyclooxygenase; CRC, Colorectal cancer; CRT, Calreticulin; CTL, Cytotoxic T lymphocyte; CTLA-4, Cytotoxic T-Lymphocyte Antigen 4; CUR, Curcumin; DATS, Diallyl trisulfide; DCs, Dendritic cells; DMBA, 2,4-Dimethoxybenzaldehyde; DMXAA, 5,6-dimethylxanthenone-4-acetic acid; DOX, Doxorubicin; EAE, Experimental autoimmune encephalomyelitis; EAT, Ehrlich ascites tumor; EGCG, Epigallocatechin gallate; EGF, Epidermal growth factor; GA, Gallic acid; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; GrB, Granzyme B; HD, Healthy donor; HMDMs, Human monocyte-derived macrophages; HMGB1, High Mobility Group Box 1; HNSCC, Head and neck squamous cell carcinoma; i.d., Intradermal; IDO, Indoleamine 2, 3-dioxygenase; IFN, Interferon; i.g., Intragastric; IL, Interleukin; i.m., Intramuscular; IRF3, Interferon regulatory factor 3; i.p., Intraperitoneal; i.t., Intratumoral; LLC, Lewis lung carcinoma; LN, Lymph node; M1 or M2, Polarized macrophages; MCP-1, Monocyte chemoattractant protein-1; MHC, Major histocompatibility complex; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NK, Natural killer; NNK, 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone; NO, Nitric oxide; NP, Nanoparticle; OVA, Ovalbumin; PBMCs, Peripheral blood mononuclear cell; pCaA, Polymerized caffeic acid; pCoA, Polymerized coumaric acid; pFA, Polymerized ferulic acid; PGE2, Prostaglandin E2; p.o., Per os; ppm, Part per million; RES, Resveratrol; RosA, Rosmarinic acid; s.c., Subcutaneous; SCFA, Short-chain fatty acids; SCID, Severe Combined Immunodeficiency; SFN, Sulforaphane; SMMT, Spontaneous mouse mammary tumor; STING, Stimulator of interferon genes; TGFβ, Transforming growth factor β; T_H, T helper; TIL, Tumour infiltrating lymphocytes; TNF, Tumor Necrosis Factor; ω-3/6, omega-3/6 fatty acids.

organic acids (with 39.8% fumaric acid and 31% lactic acid) for 28 days], increased the quantity of intraepithelial lymphocytes, specifically $CD2^-CD8^-$ γδ T cells, in the jejunum epithelium and hence could increase local immunity (Ferrara, Tedin, Pieper, Meyer, & Zentek, 2017).

Overall organic acids are able to act as pro- or anti-inflammatory agents, depending on the stimuli (Figs. 2–4 and Tables 2–4).

3.2. Polysaccharides

Polysaccharides or glycans are polymeric carbohydrate structures composed of simple sugars linked together by glycosidic bonds. Polysaccharides are the most widespread class of carbohydrates in nature and are contained in dietary fibers. They constitute the cell wall in plants and seaweeds, but they are also contained in the cell wall of bacteria, yeast and fungi (Giavasis, 2013; van Dam et al., 2017). Most cell wall polysaccharides exhibit immunomodulatory, antitumor, anti-inflammatory, antioxidant and antimicrobial effects. Based on their effects on the immune system, cell wall plant polysaccharides can be classified as "biological response modifiers" (BRMs), since they are able to stimulate and potentiate several immune responses (Giavasis, 2013; Santa et al., 2014). The biological activities of polysaccharides depend on their molecular weight, monosaccharide composition, glycosidic bond types and sulfate content (Hou, Chen, Yang, & Ji, 2020).

Polysaccharides from the cell wall of some pathogenic yeasts and bacteria strongly contribute to microorganism recognition and clearance, as they are recognized by the innate immune system as pathogen-associated molecular patterns (Devi & Maiti, 2016; Zipfel & Robatzek, 2010).

Among polysaccharides with relatively high biological activity, β-glucans show strong immunomodulatory activity (Del Cornò et al., 2020; Santa et al., 2014). They are consumed as part of the daily diet or can be taken orally as food supplements. β-glucan intake is generally safe and well tolerated (Del Cornò et al., 2020). Bioactive β-glucans consist of D-glucose monomers linked through β-glycosidic bonds with a β-(1→3) configuration and β-(1→6) or β-(1→4) linkages (F. Zhu, Du, & Xu, 2016). They show different properties depending on their origin. Indeed, β-glucans derived from mushrooms demonstrate antitumor and immunity-boosting activities, while those derived from cereals are more effective in regulating hematic cholesterol and sugar levels (Jin et al., 2018; F. Zhu et al., 2016).

The innate immune cells targeted by β-glucans are macrophages, neutrophils, DCs, and NK cells. β-glucans are able to induce the expression of proinflammatory cytokines and chemokines, enhancing the oxidative burst during the activation of these cells (Del Cornò et al., 2020) (Figs. 2, 3 and Tables 2, 3). β-glucans can be recognized by several membrane-bound immune receptors in a manner dependent on the structure and nature of the β-glucan. Among these receptors, several cell-surface receptors (pattern recognition receptors, PRRs), including scavenger receptors, lactosylceramide (LacCer), complement receptor 3 (CR3; CD11b/CD18), and dectin-1, are able to specifically recognize β-glucans (Camilli, Tabouret, & Quintin, 2018).

The ability of β-glucans to affect cytokine release has been reported (Gründemann et al., 2015; Smiderle et al., 2013). However, the β-glucan-mediated cytokine response can be pro- or anti-inflammatory depending on the nature and source of the β-glucans and the nature of the pathogen. For example, β-glucans purified from mushrooms can stimulate the secretion of proinflammatory cytokines in the tumor microenvironment, but the same β-glucans can exert anti-inflammatory activities when the inflammatory response is triggered by lipopolysaccharides (Jin et al., 2018). The recognition of β-glucans by PRRs modulates host immune responses through stimulation of innate immune cells, mainly neutrophils, macrophages and DCs, by upregulating the expression of proinflammatory cytokines (de Graaff, Govers, Wichers, & Debets, 2018; M. Zhang, Chun, et al., 2018a). In the tumor microenvironment, β-glucans mediate the activation of macrophages through dectin-1-mediated release of proinflammatory cytokines (M. Liu, Luo,

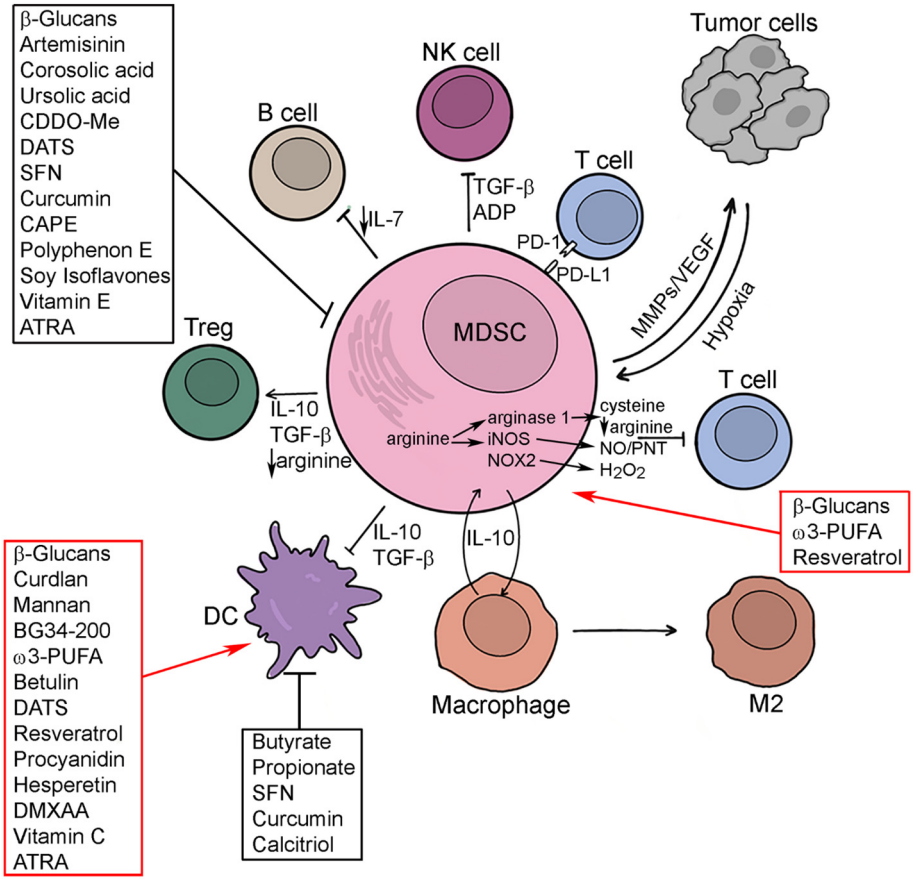

Fig. 3. Targeting MDSCs and DCs by nutraceuticals. Effects of nutraceuticals on myeloid-derived suppressor cells (MDSCs) and dendritic cells (DCs). The arrow and the inhibition arc indicate a positive and a negative activity of the nutraceutical reported in the boxes, respectively. MDSCs block B cells, natural killer (NK) cells, T cells and DCs and promote regulatory T cells (Tregs) development and M2 macrophages. Abbreviations: ADP, Adenosine diphosphate; ATRA, All-*trans* retinoic acid; CAPE, Caffeic acid phenethyl ester; CDDO-Me, Methyl-2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oate; DATS, Diallyl trisulfide; DMXAA, 5,6-Dimethylxanthenone-4-acetic acid; IL, Interleukin; iNOS, Inducible nitric oxide synthase; MMPs, Matrix metalloproteinases; NO, Nitric oxide; NOX2, NADPH oxidase 2; PD-1, Programmed cell death protein 1; PD-L1, Programmed death ligand 1; PNT, Plasma nitrotyrosine; PUFA, Polyunsaturated fatty acids; SFN, Sulforaphane; TGF-β, Transforming growth factor-β; VEGF, Vascular endothelial growth factor.

et al., 2015a). In addition, β-glucans improve phagocytosis by priming the iC3b receptor for cytotoxicity against iC3b-opsonized target cells (200 μg/day, i.p. or i.v., for 9-14 days) (Yan et al., 1999) and mediate CR3-dependent cellular cytotoxicity by neutrophils (10 μg/ml) (Zen, Liu, Cairo, & Parkos, 2002; M. Zhang, Kim, & Huang, 2018b). In addition, in preclinical studies, Lentinan, a β-glucan extracted from Shiitake mushroom, has been shown to have similar activity in combination with the anti-HER2 antibody trastuzumab in a HER2-positive breast cancer murine xenograft model (Cheung et al., 2002). Similarly, a β-1,3/1,6-glucan derived from the seaweed *Durvillaea antarctica* (BG136) was able to induce proinflammatory responses in macrophages *in vitro* by increasing macrophage phagocytic activity. BG136 administration increased the antitumor effects of an anti-PD-1 antibody on a B16 syngeneic melanoma tumor model and was able to inhibit tumor growth in a murine tumor xenograft model. BG136 treatment induces strong activation of systemic and intratumoral immune cells by enhancing the phagocytic activity of tumor-infiltrating macrophages and the production of proinflammatory cytokines and chemokines and by supporting immune cell infiltration into the tumor microenvironment (Su et al., 2019). In addition to enhancing the phagocytic activity of macrophages and stimulating NK cell activity in mice, lentinan increased IgG secretion by B lymphocytes (G. Wang, Lin, Zhao, & Lin, 2008). Accordingly, β-glucans have been used for cancer treatment and have been studied as adjuvants and immunomodulators in anticancer immunotherapy (Choromanska et al., 2018; Jin et al., 2018).

β-glucans also affect the immunological functions of NK cells. Maitake β-glucan from the edible mushroom *Grifola frondosa* inhibited lung metastasis in two experimental murine models of metastatic colon cancer and melanoma when given by intraperitoneal injection by enhancing IL-12 production and activating NK cells (Masuda et al., 2008). β-glucans purified from *P. ostreatus* induced NK cell-mediated cytotoxic effects on lung and breast cancers. This effect was associated with the upregulation and induction of IFN-γ and NO production and was stimulated by IL-2 (El-Deeb et al., 2019). Finally, polysaccharides purified from *Cantharellus cibarius*, which were mainly composed of O-2 and O-3 branched (1→6)-linked mannan, increased the proliferation and viability of NK cells activated against lung or colon cancer cells (10-250 μg/ml) (Lemieszek, Nunes, & Rzeski, 2019).

Recent studies suggest that β-glucans can affect the immune response in the tumor microenvironment by improving the response to cancer immunotherapies and inhibiting the immunosuppressive status of the tumor microenvironment (Zhang, Chun, et al., 2018a). β-glucans from different sources are able to promote the maturation of MDSCs, reducing their immunosuppressive activity and tumor infiltration in mice (Albeituni et al., 2016; Masuda et al., 2013; Rui et al., 2016). Yeast-derived particulate β-glucan treatment was found to promote the differentiation of Mo-MDSCs into a mature $CD11c^{+}F4/80^{+}Ly6C^{lo}$ population through an interaction with the receptor dectin-1, which resulted in a decrease in the suppressive function of M-MDSCs. In addition, this treatment increased the numbers of infiltrated DCs and

Table 4
Effect of nutraceuticals on MDSCs and Tregs.

Human Mouse	Cell Type	Treatment	*In vitro* Model	*In vivo* Model	Effects on immune system	Reference
Organic acids						
Mouse	DCs, T cells	Butyrate (0.5 mM), Propionate (0.5 mM)	Mature DCs from murine spleen		↑ Expression of IDO1 and Aldh1A2 in DCs; Naïve T cells → Foxp3$^+$ Tregs	Gurav et al. (2015)
Mouse	T cells	SCFA (150 mM in drinking water, for 3 weeks)		Germ-free and SPF BALB/c mice	↑ Colonic Tregs frequency and numbers; ↑ IL-10	Smith et al. (2013)
Mouse	T cells	Butyrate (0.5 mM), Propionate (1 mM), Acetate (*in vitro:* 10 mM; *in vivo*: 200 mM in drinking water, for 6-8 weeks, before infection with *C. rodentium*),	Splenocytes from C57BL/6 mice	C57BL/6 mice infected with *C. rodentium*	↑ IL-10 producing CD4$^+$ or CD8$^+$ T cells	J. Park et al. (2015)
Chicken	T cells	Formic, lactic, citric acids (diet supplemented with 0.15% organic acids)		Broilers (ROSS) immunized with a H9N2 inactivated oil vaccine	↑ CD4$^+$CD25$^+$ Tregs	I. K. Lee et al. (2017)
Polysaccharides						
Mouse	MDSCs, T cells	β-glucans (*in vitro:* 100 μg/ml; *in vivo*: 800 μg, p.o., for 14 days starting when tumors were palpable)	MDSCs	C57BL/6 mice bearing lung carcinoma cells (LLC)	↑ Differentiation in CD11c$^+$ F4/80$^+$ Ly6C^{low}; ↓ Immunosuppressive activity	Tian et al. (2013)
Mouse	T cells	Curdlan (50 μg/ml)	Foxp3$^+$ T cell population		Tregs →T_H17	Osorio et al. (2008)
Mouse	T cells	β-glucans (10 μg were mixed with tumor cells before injection of cells)		C57BL/6 mice bearing lung carcinoma cells (LLC)	↓ Tregs	Ning et al. (2016)
Mouse	MDSCs, T cells	β-glucan from *G. frondosa* (20 mg/kg/day, p.o., once every 19 days after injection of cells)		BALB/c mice bearing colon carcinoma cells (Colon-26)	↓ MDSC; ↓ Tregs	Masuda et al. (2013)
Phytosterols						
Human	T cells	Sitostanol (1.2 μM)	PBMCs		↑ Tregs and IL-10	Brüll et al. (2012)
Mouse	Immune cells	Daucosterol (10 mg/kg, p.o., thrice a week, for 23 days, starting 2 weeks before DSS administration)		DSS-induced colitis in C57BL/6J mice	↑ Foxp3$^+$CD4$^+$ Tregs	J. Jang et al. (2019)
Lipids						
Mouse	T cells	DHA (10-200 μM)	Foxp3$^+$ Treg cells isolated from C57BL/6J WT		↓ Tregs activity	M. Song et al. (2016)
Mouse	T cells			Collagen antibody-induced arthritis in Fat-1 transgenic mice	↓ IL-6, IL-23 and IL-17; ↑ Tregs (Foxp3$^+$)	J. Y. Kim et al. (2018)
Terpenes						
Mouse	MDSCs, T cells	Artemisinin (100 mg/kg i.p., for 20 days, starting 5-7 days after injection of cells)		BALB/c mice bearing mammary carcinoma cells (4T1)	↓ MDSCs; ↓ Tregs	Y. Cao, Feng, et al. (2019b)
Mouse	T cells	Dihydroartemisinin (*in vitro*: 25-50 μM; *in vivo*: 4.85 μg/mouse, i.p., for 6 days, starting 17 days after injection of cells)	Pancreatic cells (RIN)	BALB/c mice bearing mammary tumor (SMMT)	↓ CD4$^+$CD25$^+$Foxp3$^+$ Tregs	Noori and Hassan (2011)
Human/Mouse	MDSCs	CDDO-Me (*in vivo*: 60-150 mg/kg chow, for 7-14 days, starting 14 days after injection of cells; n patients: 150-300 mg/day, p.o., every 28 days)	PBMCs from patients with metastatic renal cell carcinoma or soft tissue carcinoma	C57BL/6 mice bearing colon carcinoma cells (MC38), lung carcinoma cells (LLC) thymoma (EL-4)	↓ MDSCs	Nagaraj et al. (2010)
Mouse	MDSCs, T cells	CDDO-Me (5 mg/kg, i.p. or i.v., for a total of three injections starting 13 days after injection of cells)		C57BL/6 mice bearing melanoma cells (B16F10)	↓ MDSCs; ↓ Tregs	Y. Zhao, Huo, et al. (2015a)
Mouse	T cells	SH479 20 mg/kg/day, i.p., starting 23 days after immunization)		DBA/1J mice	↑ Tregs	S. Chen et al. (2017)
Human/Mouse	MDSCs, T cells	Ursolic acid (*in vitro:* 50-1000 μM; *in vivo*: 10 mg/kg, i.v., for a total of 5 times, starting when tumor volumes reached 80-100 mm^3)	Mammary carcinoma cells (4T1) and lung cancer cells (A549)	C57BL/6 mice and BALB/c mice	↓ CD25$^+$Foxp3$^+$ Tregs; ↓ IL-10 and IL-6; ↓ MDSCs	N. Zhang et al. (2020)
Organosulfurs						
Mouse	MDSCs	DATS (50 mg/kg/day, p.o., for 21 days)		C57BL/6 mice bearing melanoma cells (B16F10)	↓ MDSCs	De Cicco et al. (2020)
Human	MDSCs	SFN (5-10 μM for 48 h under hypoxic conditions)			↓ MDSC frequency and PD-L1 expression in monocytes exposed to glioma conditioned media	Kumar et al. (2017)
Polyphenols						
Non-Flavonoids						
Mouse	T cells	CUR (5-20 μM)	Splenocytes from BALB/c mice		↓ Tregs, IL-2, TGF-β; ↓ CTLA-4, Foxp3	G. J. Zhao et al. (2012)
Mouse	T cells	CUR (50 mg/kg, p.o., every alternate day; from		Swiss albino mice bearing	↓ Tregs, TGF-β, IL-10	Bhattacharyya

(continued on next page)

Table 4 (*continued*)

Human Mouse	Cell Type	Treatment	*In vitro* Model	*In vivo* Model	Effects on immune system	Reference
		day 7 after injection of cells)		EAT		et al. (2010)
Mouse	MDSCs	CUR (50 mg/kg/day, p.o.)		BALB/c mice bearing lung carcinoma cells (LLC)	↓ MDSCs; ↓ ARG1, iNOS, ROS; ↑ F4/80, MHCII, CD80, CD11c; ↓ IL-6 in tumor microenvironment	D. Liu et al. (2016)
Mouse	T cells	CUR (100 mg/kg, p.o., thrice a week)	Mammary carcinoma cells (TUBO)	BALB/c mice bearing mammary carcinoma cells (TUBO)	↓ Tregs	Masuelli, Granato, et al. (2017b)
Human	T cells	CUR (1.5 g/capsule, twice a day for 2 weeks between diagnosis and surgery)		Lung cancer patients	↓ $Foxp3^+$ Tregs; ↑ Tbet, Th1, IFN-γ	J. Y. Zou et al. (2018)
Human	T cells	CUR (3 g oral capsules divided in 2 doses daily for one month after the surgery)		Post-surgery colorectal cancer patients	↓ Tregs, Th1, IFN-γ	B. Xu, Yu, and Zhao (2017)
Mouse	MDSCs	CUR (+$Listeria^{at}$-Mage-b vaccine) (20 or 50 mg/mouse, p.o., before or after injection of cells; before or after vax)		BALB/c mice bearing mammary carcinoma cells (4T1)	↓ IL-6, MDSCs IL-12	M. Singh et al. (2013)
Mouse	T cells	CUR (5 or 10 μM/kg/day, for 4 weeks, after 4NQO administration)		C57BL/6 mice bearing 4NQO-induced oral carcinoma	↓ Tregs ($CD4^+CD25^+Foxp3^+$); ↓ MDSCs ($CD11b^+GR1^+$); ↓ PD-L1, p-STAT3	F. Liao, Liu, et al. (2018a)
Mouse	T cells	CUR-based micelles (40 mg/kg/day, i.v., for 5 injections, starting when tumor volumes reached 150 mm^3)		C57BL/6 mice bearing melanoma cells (B16F10)	↓ MDSCs; ↓ Tregs	Y. Lu et al. (2016)
Mouse	T cells	CUR (*in vitro*: 10 μM; *in vivo:* 70 mg/kg/day i.p., for 5 days) (+ CD8 T cells adoptive therapy)	T cell lymphoma cells (E.G7)	C57BL/6 mice	↓ Tregs; ↓ TGF-β, IDO	Y. F. Chang et al. (2012)
Mouse	T cells	Nanocarrier CUR (+antiPD-1) (*in vitro:* 10 μM; *in vivo:* 2 mg/kg, i.v., every 3 days)	Melanoma cells (B16F10)	C57BL/6 mice bearing melanoma cells (B16F10)	↓ Tregs; ↓ CCL-22, TGF-β, IL-10	Z. Xiao et al. (2020)
Mouse	T cells	RES (1, 2.5, and 5 mg/kg/day, i.p.)		Mice bearing renal cell carcinoma cells (Renca)	↓ Tregs; ↑ MDSCs; ↓ IL-6, IL-10	L. Chen et al. (2015)
Mouse	T cells	RES (50 mg/mouse, i.p., every other day from days 3 to 11 after injection of cells)		BALB/c mice bearing mammary carcinoma cells (4T1)	↓ tBregs; ↓ STAT3, TGF-β	Lee-Chang et al. (2013)
Mouse	T cells	RES analogue HS-1793 (0.3-2.5 μM)		C3H/He mice bearing mammary carcinoma cells (FM3A)	↓ $CD4^+CD25^+$ $Foxp3^+$ Tregs; ↓ TGF-β; ↓ IL-2, IL-4, IL-1β, IL-10	Y. J. Choi et al. (2012); M. H. Jeong et al. (2012)
Mouse	T cells	*Ananas comosus* vinegar (GA, other phenolic acids) (*in vitro*: 0.25 and 0.32 mg/ml; *in vivo:* 0.08 and 2 ml/kg, p.o., 4 weeks)	Mammary carcinoma cells (4T1)	BALB/c mice bearing mammary carcinoma cells (4T1)	↑ IFN-γ, IL-2; ↓ Macrophages; ↓ NO, MDA, iNOS; ↓ NF-κB, COX-2	Mohamad et al. (2019)
Flavonoids						
Mouse	T cells	Apigenin (25 mg/kg, i.p., thrice a week, starting when tumors were palpable)		C57BL/6N mice bearing pancreatic ductal adenocarcinoma cells (Panc02)	↓ Tregs	Nelson et al. (2017)
Mouse	T cells	Salvigenin (9.68 μg/mouse/day, i.p., for 12 days, starting when tumor volumes reached 1.5 cm^3)		BALB/c mice bearing mammary tumor cells (SMMT)	↓ $CD4^+CD25^+Foxp3^+$ Tregs	Noori et al. (2013)
Rat	T cells	*Scutellaria ocmulgee* leaf extract (SocL) (100 mg/kg, p.o., 5 days a week, for 2 weeks, starting when tumors were palpable)		F344 rats bearing malignant glioma cells (F98)	↓ TGF-β1-induced Treg activity	Dandawate, et al., (2012)
Mouse	MDSCs, T cells	Poliphenon E (0.3% in drinking water, starting from the day of injection of cells)		Transgenic TH-MYCN mice; A/J mice bearing neuro-2A tumor	↓ MDSCs; ↓ Tregs	Santilli et al. (2013)
Mouse	T cells	Delphinidin chloride (*in vitro*: 5-40 μM; *in vivo:* 1.5 or 3 mg/kg, i.p., thrice a week, for 5 weeks, starting 1 week after injection of cells) or GA (*in vitro*: 5-40 μM; *in vivo*: 10 or 20 mg/kg, i.p., thrice a week, for 5 weeks, starting 1 week after injection of cells)	$CD4^+$ T cells from spleen of C57BL/6 mice	C57BL/6 mice bearing mastocytoma cells (P815)	↑ T cells → Tregs; ↑ TGF-β and IL-2 pathways; ↑ Tregs in allograft model	Hyun, Gil, Kim, Park, and Hwang (2019)
Mouse	T cells	Naringenin + asiatic acid (50 mg/kg/day naringenin + 10 mg/kg/day asiatic acid, i.p., for 23 days, starting when tumor volumes reached 50 mm^3)		C57BL/6 mice bearing melanoma cells (B16F10) or lung carcinoma cells (LLC)	↓ $CD4^+$ $Foxp3^+$ Tregs	Lian et al. (2018)
Mouse	T cells	Hesperetin (Hes) (+B16F10 antigen vaccine) (B16F10 cells with 0.8 mg Hes/mouse, i.m., twice on day 0 and 7, before injection of cells at 7 days after the second immunization)		C57BL/6 mice challenged with melanoma cells (B16F10)	↓ Tregs	S. Jiang et al. (2020)
Mouse	T cells	Genistein (20 mg/kg/day, p.o., for 1-4 weeks, before DMBA administration or injection of cells)		B6C3F1 mice bearing melanoma cells (B16F10); B6C3F1 mice treated with DMBA	↓ $CD4^+CD25^+$ T cells	T. L. Guo, Chi, et al. (2007a); T. L. Guo et al. (2001)
Xanthones						
Mouse	T cells	α-mangostin (13.9 mg/kg, i.v., every other day) (+CD258)		C57BL/6 mice bearing pancreatic cancer cells (KPC1199 or Panc02)	↓ Tregs, $F4/80^+$ macrophages	Y. Huang et al. (2020)

Table 4 (*continued*)

Human Mouse	Cell Type	Treatment	*In vitro* Model	*In vivo* Model	Effects on immune system	Reference
Vitamins						
Mouse	T cells	Calcitriol (125 ng painted onto a clean-shaven 8 cm^2 dorsal skin surface of mice, equivalent to 3 μM)		BALB/c mice transgenic for OVA	↑ $CD4^+CD25^+$ T cells suppressive activity	(Gorman et al., 2007)
Mouse	T cells	Calcipotriol (50 μg/g ointment applied 30 mg/mouse on the shaved dorsal skin of mice before immunization)		C57BL/6, OT-I, OT-II, $Foxp3^{GFP}$ mice, VDR^{KO} mice	↑ Tregs	Ghoreishi et al. (2009)
Mouse	Immune cells from LNs	Calcitriol (0.5 μg/kg, s.c., thrice a week from the day 7 after injection of cells)		BALB/c mice bearing mammary cancer cells (4T1)	↑ Tregs in spleen and regional LNs; ↓ T $CD4^+CD25^+$ cells in the blood	Pawlik et al., 2018
Mouse	MDSCs	Vitamin E (2 mg/kg, i.p., thrice every two days)		C57BL/6 mice bearing E7-expressing tumors (TC-1 cells)	↓ % MDSCs	Kang et al. (2014)
Mouse	T cells	Semisynthetic vitamin E derivative α-TEA (diet containing 300 mg/kg/day)		BALB/c mice bearing mammary cancer cells (4T1)	↑ $CD4^+$/Tregs and $CD8^+$/Tregs	Hahn, Jagadish, Mash, Garrison, and Akporiaye (2011)
Mouse	T cells	Vitamin C (0.1 mg/ml)	Peripheral $CD4^+$ T cells from pooled spleen and LNs from mice	BALB/c, $Foxp3^{RFP}$, congenic CD45.1 $Foxp3^{hCD2}$ reporter mice (C57BL/6 background)	↑ *In vitro* generation of alloantigen-induced Tregs	Nikolouli et al. (2017)
Human/Mouse	T cells	Vitamin C (100 μg/ml for iTregs treatment)	$CD4^+$ T cells from mouse spleen and lymph nodes (LNs) or human PBMCs	BALB/c AJc1, $Foxp3^{hCD2\text{-}hCD52}$ mice (C57BL/6 genetic background)	↑ Stabilization of iTregs	Kasahara et al. (2017)
Mouse	T cells	Vitamin C (*in vitro*: 50 μM; *in vivo:* 0.86 mg/ml/day, in drinking water)	$CD4^+$ T cells	C57BL/6 mice WT, C57BL/6 x BALB/c (F1), $Foxp3^{GFP}$ and RAG^{KO} mice	↑ Tregs, but not suppression of $CD4^+$ T cells	Oyarce, Campos-Mora, Gajardo-Carrasco, and Pino-Lagos (2018)
Mouse	T cells	ATRA (1 μM)	Peripheral T cells from spleens and LNs from mice	C57BL/6 mice	↑ $Foxp3^+$ T cells	Elias et al. (2008)
Mouse	T cells	ATRA (10 nM)	$CD4^+Foxp3^-$ cells from spleens and peripheral and mesenteric LNs from mice	C57BL/6, C57BL/6 CD45.1 ($Ly5.2^+$), C56BL/6 $CD40^{-/-}$ mice	↑ Tregs	Benson, Pino-Lagos, Rosemblatt, and Noelle (2007)
Mouse	T cells	ATRA (1-10 nM)	T lymphocytes from secondary LNs from mice	C57BL/6, B6.SJL, OT-II TCR transgenic mice $Ly5.2^+$, OT-II transgenic RAG-$1^{-/-}$ mice, $Foxp3^{GFP}$ mice	↑ Tregs in the presence of TGF-β	C. M. Sun et al. (2007)
Mouse	T cells	ATRA (2.5 nM)	Naïve T cells from mice	C57BL/6J, C57BL/6-$IL4^{-/-}$ mice	↑ Tregs	Nolting et al. (2009)
Human	T cells	ATRA (0.1 μM)	nTregs from PBMCs		Tregs stabilization in the presence of inflammatory cytokines	L. Lu et al. (2014)
Mouse	DCs, T cells	ATRA (diet containing 250 IU/g until 14 weeks)	$CD4^+$ T cells from spleens and LNs from mice	10BiT. $Foxp^{3gfp}$ mice	↓ IL-10-competent Tregs	Maynard, et al., (2009)
Mouse	MDSCs	ATRA (0.15 g ointment, rubbed on the tumor and the skin adjacent to the tumor every day)	MDSCs	C57BL/6 mice bearing B16F10 melanoma cells	↓ Frequency of tumor-infiltrating MDSCs ($CD11b^+$ $Gr\text{-}1^+$)	W. Yin et al. (2017)

↓: decrease; ↑: increase; → shift

4NQO, 4-Nitroquinoline 1-oxide; Aldh1A2, Aldehyde Dehydrogenase 1 Family Member A2; ATRA, all-*trans* retinoic acid; BM, Bone marrow; BMDCs, Bone marrow-derived dendritic cells; CUR, Curcumin; DATS, Diallyl trisulfide; DCs, Dendritic cells; DHA, Docosahexaenoic acid; DMBA, 7, 12-Dimethylbenz[a]anthracene; DSS, Dextran sulphate sodium; EAT, Ehrlich ascites tumor; GA, Gallic acid; GFP, Green fluorescent protein; IDO, Indoleamine 2,3-dioxygenase; IL, Interleukin; i.p., Intraperitoneal; IU, International unit; i.v., Intravenous; KO, Knock out; LLC, Lewis lung carcinoma; LN, Lymph node; MDSCs, Myeloid-derived suppressor cells; MHC, Major histocompatibility complex; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; OVA, Ovalbumin; PBMCs, Peripheral blood mononuclear cells; p.o., Per os; ppm, Part per million; RA, Retinoic acid; RFP, Red fluorescent protein; s.c., Subcutaneous; SCFA, Short-chain fatty acids; SFN, Sulforaphane; SMMT, Spontaneous mouse mammary tumor; SPF, Specific-pathogen-free; TGF-β, Transforming Growth Factor-β; Tregs, Regulatory T cells; WT, Wild type.

macrophages in tumor-bearing mice, thus eliciting CTL and T_H1 responses and inhibiting the suppressive activity of Tregs, which resulted in tumor growth inhibition (Tian et al., 2013). *In vitro* and *in vivo* treatment with Curdlan caused the conversion of Tregs into T_H17 effector cells and increased $CD8^+$ T cell priming in mice (Osorio et al., 2008). β-glucan can interfere with the DC-mediated induction of proinflammatory cytokine secretion (Zhang, Chun, et al., 2018a) and the initiation of T_H1 $CD4^+$ T cell responses to enhance antigen recognition and anticancer immunity (H. Huang et al., 2009). Polysaccharides purified from the medical mushroom *Ganoderma lucidum* also induce DC maturation (W. K. Chan et al., 2007). Curdlan and mannan, two microorganism-derived bioactive polysaccharides, were found to activate DCs, promote the production of T_H1 cytokines and induce relatively strong antigen-specific immune responses and antitumor effects in tumor-bearing mice

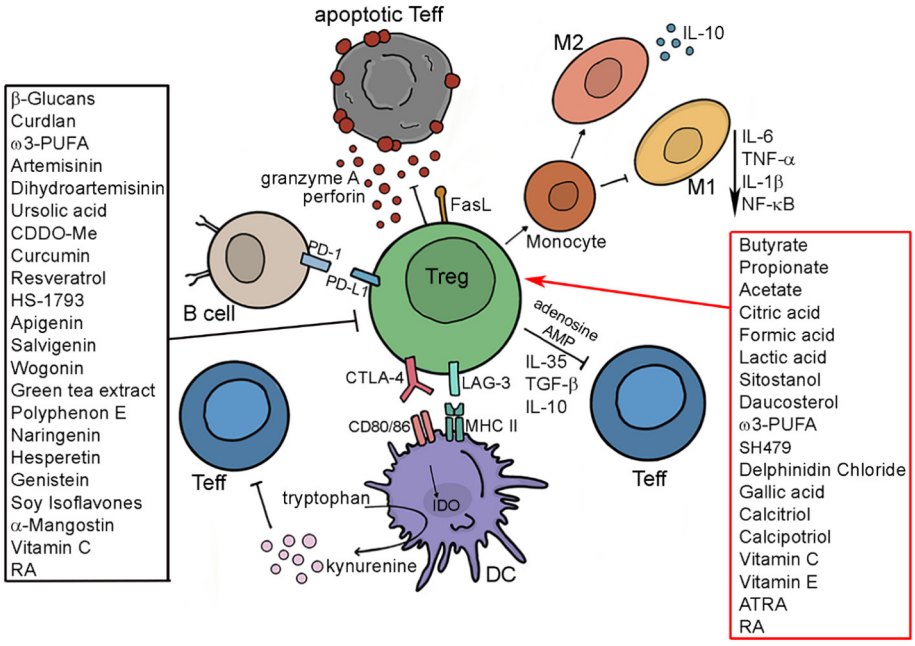

Fig. 4. Targeting Tregs by nutraceuticals. The arrow and the inhibition arc indicate a positive and a negative activity of the nutraceutical reported in the boxes, respectively. Regulatory T cells (Tregs) inhibit T effector cells (Teff) and induce Teff apoptosis, induce kynurenine production in dendritic cells (DCs) by IDO (indoleamine-2,3-dioxygenase) activation, inhibit B cells and promote M2 differentiation. Abbreviations: AMP, Adenosine monophosphate; ATRA, All-*trans* retinoic acid; CDDO-Me, Methyl-2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oate; CTLA-4, Cytotoxic T-lymphocyte antigen-4; FasL, Fas ligand; IL, Interleukin; LAG-3, Lymphocyte activation gene-3; MHC, Major histocompatibility complex; NF-κB, Nuclear factor kappa B; PD-1, Programmed cell death protein 1; PD-L1, Programmed death ligand 1; PUFA, Polyunsaturated fatty acids; RA, Rtinoic acid; TGF-β, Transforming growth factor-β; TNF-α, Tumor necrosis factor-α.

(Yuba et al., 2017). Oral administration of β-glucan purified from mushrooms or yeast was able to induce M2 to M1 switching, thus decreasing immunosuppression in the tumor microenvironment and reducing the tumor burden in an experimental model of lung carcinoma (Camilli et al., 2018; M. Liu, Luo, et al., 2015a; W. J. Wang, Wu, et al., 2015b).

Systemic administration of BG34-200, an oat-derived β-(1-3)–(1-4)-glucan, reverted the immunosuppressive melanoma tumor microenvironment to an immunogenic microenvironment through the activation of M1 macrophages and the production of proinflammatory cytokines/chemokines. In primary and lung metastatic B16F10 melanoma models, BG34-200 potentiated the antitumor response by increasing tumor infiltration by $CD4^+$ and $CD8^+$ T cells and elevated IFN-γ expression in tumor sites and the activation of macrophages, DCs, T cells and NK cells (Zhang, Chun, et al., 2018a). Local β-glucan treatment of mice bearing lung cancer promoted the maturation and migration of tumor-infiltrating DCs, decreased the number of Tregs, increased the infiltration of macrophages and granulocytes into the tumor microenvironment and triggered T_H1 differentiation and cytotoxic T lymphocyte responses, thus leading to a delay in tumor growth (Ning et al., 2016). A homogeneous polysaccharide purified from the fruiting bodies of *Ganoderma lucidum* was able to inhibit tumor growth in a mouse Lewis lung cancer (LLC) model, decreasing the accumulation of MDSCs and increasing the percentages of $CD4^+$ and $CD8^+$ T cells and production of T_H1 cytokines (Y. Wang, Fan, & Wu, 2020c). Masuda et al. demonstrated that oral or intraperitoneal administration of a β-glucan derived from *Grifola frondosa* (an oriental edible mushroom) to mice bearing colon cancer was able to inhibit tumor growth by inducing a systemic tumor antigen-specific T cell response via dectin-1-dependent activation of DCs, which increased the infiltration of activated intratumoral T cells and decreased the number of tumor-induced immunosuppressive cells (Tregs and MDSCs) (Masuda et al., 2013; Masuda, Inoue, Miyata, Mizuno, & Nanba, 2009). Rubel et al. reported the antitumoral effects of the addition of β-glucans from *A. brasiliensis* and *G. lucidum mycelia* to the diet in a murine osteosarcoma experimental model. Tumor growth inhibition was accompanied by increases in $CD4^+$ and $CD8^+$ cell populations and a decrease in the $CD19^+$ cell population, promoting the T cell dominance necessary to inhibit tumor growth (Rubel et al., 2018). It is worth noting that β-1,3-glucan from *Saccharomyces cerevisiae* promotes an anti-inflammatory response by releasing IL-10 and TGF-β, thus stimulating the T_H2 immune response and inhibiting the T_H1 response. Conversely, mushroom β-1,3-glucan decreases the T_H2 immune response and supports the T_H1 immune response (Jin et al., 2018).

Overall, these results indicate that employing β-glucans from food as adjuvants to revert the immunosuppressive status in the tumor microenvironment has a strong potential, as β-glucans are able to potentiate both innate and adaptive immunity against cancer cells (Figs. 2–4 and Tables 2–4).

3.3. Phytosterols

Phytosterols are bioactive components found in plants that are structurally similar to cholesterol. They are not synthesized in the human body; thus, they are totally derived from the diet. Phytosterols are present in vegetable oils, such as corn and rice oil. The most common phytosterols in the human diet are β-sitosterol, campesterol, and stigmasterol. They are important not only for their ability to reduce cholesterol levels but also for their role in inhibiting the growth of cancer cells (Bradford & Awad, 2007). Several studies have demonstrated the actions of phytosterols as immunomodulatory compounds. The first studies that demonstrated this activity were reported by Bouic et al., who demonstrated that β-sitosterol and its glucoside derivative enhanced the cytotoxic activity of NK cells; proliferation of T lymphocytes, in particular the T_H1 population; secretion of IL-2 and IFN-γ; and inhibition of IL-4 secretion (Bouic et al., 1996; Bouic & Lamprecht, 1999). The ability to stimulate NK cell function in the presence of IL-12 was also found for (−)-β-sitosterol-3-*O*-β-D-(6-*O*-palmitoyl)glucopyranoside extracted from *Phyllanthus songboiensis* (Ren et al., 2015). In general, phytosterols promote T_H1 cell differentiation. The increased secretion of T_H1 cytokines induced by phytosterols was demonstrated in $apoE^{-/-}$ mice

Table 5
Immunomodulatory effects of nutraceuticals employed in clinical trials.

Nutraceutical	Type of trial	Number of patients	Type of cancer	Immunomodulatory effects	Reference
β-glucan	Phase I trial	30 healthy volunteers		Complement activation, production of cytokines and chemokines, expansion of anticancer effector cells, neutrophils and monocytes, and changes in the expression of early innate immune response genes	Bose et al. (2019)
Maitake extract containing β-glucan	Phase I/II dose-escalation trial	34	Postmenopausal women with resected stage I, II, or III breast cancer currently free of disease	Both immunologically stimulatory and inhibitory measurable effects in peripheral blood	Deng et al. (2009)
1-3, 1-6, D-β glucans	Prospective trial	23 cancer patients; 16 healthy volunteers	Advanced breast cancer	↑ Proliferation and activation of monocytes	Demir, Klein, Mandel-Molinas, and Tuzuner (2007)
β-glucan	Randomized double-blind placebo-controlled trial	30	Breast cancer undergoing chemotherapy	↓ WBC counts in beta-glucan group was less than control group; ↓ IL-4 serum levels; ↑ IL-12 serum levels	Ostadrahimi et al. (2014)
Maitake β-glucan	Phase II open-label, non-randomized trial	21	Myelodysplastic syndromes	↑ Neutrophil and monocyte functions	Wesa et al. (2015)
Lentinan	Controlled Trial	50	Esophageal carcinoma	↑ IL-2, IL-6 IL-12; ↓ IL-4, IL-5, IL-10	J. L. Wang, Bi, Zou, and Gu (2012a)
Lentinan	Trial	28	Digestive tract cancers	Balance of T_H1 and T_H2 cells	Yoshino et al. (2000)
Ginseng polysaccharides plus DCs	Randomized trial	96	Non-small cell lung cancer	↑ T_H1 cytokines (INF-γ, IL-2); ↑ T_H1/T_H2 cytokines (INF-γ/IL-4, IL-2/IL-5); ↓ T_H2 cytokines (IL-4, IL-5)	Ma, Liu, and Wang (2014)
IP6	Double-blind, randomized controlled trials	20	Breast cancer patients after lumpectomy and during chemotherapy	↓ Chemotherapy-induced side effects; Normal level of blood parameters	Proietti et al. (2017)
EFA	Trial	30	Colorectal cancer	↓ $CD4^+$ and $CD8^+$ T lymphocytes	Purasiri, Ashby, Heys, and Eremin (1994)
ω-3 PUFAs plus vitamin E	Trial	60	Generalized solid tumors	↑ TNF-α; ↑ T_H/T suppressor cells	Gogos et al. (1998)
ω-3 PUFAs derived from soybean and fish oils	Prospective, double-blind, randomized, controlled trial	42	Colorectal cancer	↓ IL-6 and TNF-α; ↑ $CD3^+$ and $CD4^+$ lymphocytes	B. Liang et al. (2008)
ω-3 PUFAs and strain-specific probiotic	Double-blind randomized trial	140	Colorectal cancer	↓ IL-6 and TNF-α; ↓ CRP	Golkhalkhali et al. (2018)
Fish oil supplementation	Randomized trial	38	Gastrointestinal cancer	↑ PMN cells	Bonatto et al. (2012)
ω-3 PUFAs	Pilot study	60	Esophageal cancer	↓ Inflammation; ↑ $CD4^+/CD8^+$ ratio	Long, Yang, Lin, Situ, and Liu (2013)
ω-3 PUFAs	Randomized, open, controlled, and longitudinal trial	68	Gastric cancer	↓ Inflammatory response; ↓ CRP and IL-6	Feijó et al. (2019)
Enteral diet rich in ω-3 PUFAs	Randomized trial	195	Oesophagogastric cancer	No difference in HLA-DR expression in leukocyte; No difference in clinical outcome	Sultan et al. (2012)
Enteral nutrition enriched with EPA	Double-blind, randomized, controlled trial	53	Esophageal cancer	↓ IL-8, IL-10 and TNF-α	Ryan et al. (2009)
EPA	Prospective, randomized double-blind	23	Esophageal carcinoma	↓ IL-6	Furukawa et al. (1999)
EPA and DHA from fish oil	Double-blind, randomized trial	40	Stage III non-small cell lung cancer	↓ IL-6 and CRP	van der Meij et al. (2010)
EPA and DHA	Double-blind trial	148	Colorectal cancer	↑ LTB_5; ↓ LTB_4	Sorensen et al. (2014)
EPA and DHA from fish oil	Randomized Controlled Trial	23	Colorectal cancer	↓ CRP/Albumin	J. e. A. Silva et al. (2012)
EPA and DHA from fish oil	Randomized Controlled Trial	12	Colorectal cancer	↓ CRP; ↓ CRP/Albumin	Mocellin et al. (2013)
EPA and DHA enriched fish oil	Randomized double-blind trial	45	Breast cancer	↑ $CD4^+$ T lymphocytes; ↑ hsCRP	Paixão et al. (2017)
ω-3 PUFAs	Double-blind trial	44	Colorectal cancer	↑ Infectious complications	Bakker, van den Helder, Stoutjesdijk, van Pelt, and Houdijk (2020)
ω-3 PUFAs	Randomized,	38	Carcinoma of the esophagus, stomach, or	No difference in IL-6 or TNF-α levels	McCarter,

(continued on next page)

Table 5 (*continued*)

Nutraceutical	Type of trial	Number of patients	Type of cancer	Immunomodulatory effects	Reference
	double-blind trial		pancreas		Gentilini, Gomez, and Daly (1998)
Immunonutrition enriched with arginine, fatty acids and nucleotide	Randomized trial	42	Gastrointestinal tumors	No difference in T lymphocyte subpopulation counts	Gunerhan, Koksal, Sahin, Uzun, and Ekşioglu-Demiralp (2009)
Immunonutrition enriched with ω-3 fatty acids, glutamine and arginine	Randomized trial	40	Gastric carcinoma	↑ $CD4^+$ and $CD4^+/CD8^+$ ratio; ↑ IL-2; ↓ IL-6 and TNF-α	D. W. Chen, Wei Fei, Zhang, Ou, and Xu (2005)
Immunonutrition enriched with ω-3 fatty acids, glutamine and arginine	Randomized trial	71	Esophageal cancer	↓ CRP and TNF-α	Sunpaweravong et al. (2014)
ω-3 fish oil fat emulsion-based parenteral nutrition	Prospective, randomized, controlled trial	48	Gastric cancer	↓ IL-1, IL-6 and TNF-α	Z. Wei et al. (2014)
Immunonutrition (arginine, glutamine, ω-3 PUFAs)	Prospective, randomized, double-blind trial	34	Gastric adenocarcinoma or gastrointestinal stromal tumor (GIST)	Absence of variation in nutritional status as compared to normal formula; Absence of significant anti-inflammatory effect; Presence of mild inflammation	C. Ma et al. (2018a)
Arginine, EPA, DHA and nucleotides	Double-blind trial	28	Head or neck cancer	↔ $CD4^+/CD8^+$ ratio; ↑ Polymorphonuclear CD62L and CD15 cells; ↑ ROS	Talvas et al. (2015)
Arginine, RNA, and ω-3 PUFAs (IMPACT®)	Randomized trial	26	Duct, pancreatic, gastric, or esophageal cancer	↓ TXB_2; ↓ hsCRP, PMN-elastase, AAG	Nakamura et al. (2005)
IMPACT®: immune-enhancing diet (ID) containing arginine, RNA, and ω-3 PUFAs	Randomized trial	60	Gastric cancer underwent elective curative surgery	Short duration of SIRS; ↔ $CD4^+$ T cells counts; ↓ Incidence of postoperative infectious complications	Okamoto et al. (2009)
Immunonutrition with arginine, ω-3 fatty acids and RNA	Prospective trial	36	Colorectal cancer	T_H1/T_H2 balance	Matsuda et al. (2006)
Immunonutrition with arginine, ω-3 fatty acids and RNA	Randomized double-blind trial	18	Liver cancer	No improvement in immune functions	Seguin et al. (2016)
Immunonutrition with arginine, ω-3 fatty acids and RNA	Prospective, randomized trial	109	Gastric cancer	↓ $CD4^+$ T cells	Marano et al. (2013)
Immune-modulatory diet	Prospective observational intervention	37	Gastric cancer	Maintenance of the nutrition and immune status of patients up to the surgery; ↑ CD4: CD8 ratio after surgery	Dias Rodrigues et al. (2017)
Immunonutrition	Prospective multicenter randomized single-blind trial	264	Colorectal cancer	↓ After-surgery complications; ↑ WBC count; ↓ Lymphocytes as compared to preoperative values	Moya et al. (2016)
Ginsenoside Rg3 (Shenyi capsule) plus chemotherapy	Prospective, randomized, controlled trial	133	Non-small cell lung cancer	↑ NK cells; ↔ $CD4^+/CD8^+$ ratio	P. Lu et al. (2008)
Resveratrol	Phase 1 randomized trial	9 healthy volunteers		↓ Proinflammatory cytokines; ↑ Circulating γδ T cells and Tregs; ↑ Plasma antioxidant activity compared to baseline and controls	Espinoza et al. (2017)
Gnetin C	Randomized, double-blind, placebo-controlled trial	6 healthy volunteers		↑ Circulating activated ($NKG2D^+$ and $NKp46^+$) NK cells; ↑ Cytotoxic activity as compared to baseline and controls; ↓ Neutrophils absolute count in blood	Nakagami et al. (2019)
Polyphenon E	Phase I-II trials	33 (I)- 42 (II)	Early stage (Rai stage 0 to II) CLL	↓ Absolute lymphocyte count and/or lymphoadenopathy	Shanafelt et al. (2009); Shanafelt et al. (2013)
Green tea extract	Trial	12 cancer patients; 12 healthy volunteers	Rai stage 0 CLL	↓ Lymphocytosis; ↓ Absolute number of circulating Tregs; ↓ IL-10 and TGF-β serum concentrations	D'Arena et al. (2013)
Immune-enhancing formula (containing also soy isoflavones)	Pilot study	20	Stage IV and end-stage cancer (1 bladder, 5 breast, 2 prostate, 1 neuroblastoma, 2 non-small cell lung, 3 colon, 1 mesothelioma, 2 lymphoma, 1 ovarian, 1 gastric, 1 osteosarcoma)	↑ NK cells function	See, Mason, and Roshan (2002)
Soy isoflavones supplements	Double-blind randomized placebo- controlled trial	25	Prostate cancer	↓ PGE_2	Swami et al. (2009)
Soy isoflavones-enriched bread	Randomized phase II trial	32	Prostate cancer	↓ Plasma T_H1 cytokines (IL-1β, IL-2, IL-12, IFN-γ, TNF-α); ↓ MDSC-associated cytokines (IL-6, GM-CSF, G-CSF, M-CSF);	Lesinski et al. (2015)

Table 5 (*continued*)

Nutraceutical	Type of trial	Number of patients	Type of cancer	Immunomodulatory effects	Reference
				↓ Tregs and MDSCs percentages; ↑ $CD56^+$ NK cells percentage	
Aged garlic extract	Randomized double-blind trial	42	Advanced cancer (liver, pancreatic, colon)	↑ NK cells number and activity	Ishikawa et al. (2006)
Curcumin	Phase II trial	25 cancer patients; 48-62 healthy volunteers	Pancreatic cancer	↑ Cytokines (IL-6, IL-8, IL-10, IL-1RA) in all patients before therapy; After treatment: cytokines levels variably changed; ↓ NF-κB, COX-2, STAT-3 levels and PBMCs	Dhillon et al. (2008)
Curcumin	Controlled trial	160	Solid tumors or haematological malignancies	↑ Anti-oxidative response; ↓ Inflammatory pathways; ↓ Side effects	Belcaro et al. (2014)
Curcumin	Double-blind placebo-controlled trial	96	Solid tumors	↑ Quality of life; ↓ Serum levels of inflammatory mediators and biomarkers	Panahi, Saadat, Beiraghdar, and Sahebkar (2014)
Infla-kine	Short-term study	24 healthy volunteers		↓ Inflammatory markers; ↓ IL-8, IL-6, NF-κB, TNF-α mRNA transcripts	Mikirova, Kesari, Ichim, and Riordan (2017)
ATRA plus DC vaccine	Randomized phase II trial	41	Extensive stage small cell lung cancer (SCLC)	↓ MDSC	Iclozan, Antonia, Chiappori, Chen, and Gabrilovich (2013)
ATRA plus Ipilimumab	Randomized phase II trial	8	Advanced-stage melanoma	↓ MDSC; ↑ Mature HLA-DR^+ myeloid cells; ↑ Activated $CD8^+$ T cells	Tobin et al. (2018)
13-cis retinoic acid	Phase II non-randomized trial	126	Advanced ovarian cancer	↓ VEGF; ↑ Lymphocytes count (NK and $CD4^+/CD8^+$ cells); ↑ PFS and OS	Recchia et al. (2005)
13-cis retinoic acid	Multicenter phase II trial	125	Non-Small Cell Lung Cancer	↓ VEGF; ↑ Lymphocytes count (NK and $CD4^+/CD8^+$ cells)	Recchia et al. (2006)
13-cis retinoic acid	Extended phase II trial	100	Metastatic solid tumors (including colorectal, ovary, lung, stomach, kidney and head and neck)	↓ VEGF; ↑ Lymphocytes count (NK and $CD4^+/CD8^+$ cells); CR in 18 patients enrolled with PR and 6 enrolled with SD	Recchia et al. (2009)
13-cis retinoic acid	Prospective non-randomized multicenter trial	30	Stage IIIC breast cancer treated with HDCT, PBPCT, followed by IL-2 immunotherapy	↑ Lymphocytes and NK cells counts; ↑ $CD4^+/CD8^+$ ratio; ↓ VEGF levels; ↑ Clinical outcome	Recchia et al. (2010)
ATRA	Trial	18 cancer patients; 8 healthy volunteers	Metastatic clear cell kidney cancer	↓ Immature myeloid suppressor cells; ↑ Myeloid/lymphoid DC ratio; ↑ DCs function; ↑ Antigen specific immune response	Mirza et al. (2006)
Vitamin E	Pilot study	7	Colorectal cancer	↑ Cytolytic activity of NK cells	Hanson et al. (2007)
Calcitriol	Randomized controlled trial	92	Colorectal adenocarcinoma	↓ TNF-α, IL-6 IL-1β, and IL-8	Hopkins et al. (2011)
Calcitriol	Phase 1B	18	Head and neck cancer	↓ $CD34^+$ cells; ↑ IL-12 and IFN-γ	Lathers, Clark, Achille, and Young (2004)
Calcitriol	Randomized trial	32	Head and neck cancer	↑ $CD8^+$ T cells	Walsh, Clark, Day, Gillespie, and Young (2010)

↓: decrease; ↑: increase; ↔: stable

AAG, α1-acid glycoprotein; ATRA, all-*trans* retinoic acid; CLL, Chronic lymphocytic leukemia; COX, Cyclooxygenase; CR, Complete response; CRP, C reactive protein; DHA, Docosahexaenoic acid; EFA, Essential fatty acids; EPA, Eicosapentaenoic acid; G-CSF, Granulocyte colony-stimulating factor; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; HDCT, High-dose chemotherapy; hsCRP, High sensitivity C reactive protein; IFN, Interferon; IL, Interleukin; IP6, Inositol hexaphosphate; LTB, Leukotriene; M-CSF, Macrophage colony-stimulating factor; MDSC, Myeloid-derived suppressor cells; NF-κB, Nuclear factor kappa B; NK, Natural killer; OS, Overall survival; PBMCs, Peripheral blood mononuclear cells; PBPCT, Peripheral progenitor cell transplantation; PFS, Progression free survival; PGE_2, Prostaglandin E_2; PMN, Polymorphonuclear leukocyte; PR, Partial response; PUFA, Polyunsaturated fatty acid; SD, Stable disease; SIRS, Systemic inflammatory response syndrome; T_H, T helper cells; TNF-α, Tumor necrosis factor-α; TXB_2, Thromboxane B2; VEGF, Vascular endothelial growth factor; WBC, White blood cells.

subjected to turpentine-induced inflammation (Calpe-Berdiel et al., 2007). Daucosterol, a β-sitosterol glycoside isolated from *Astragalus membranaceus,* produced immunoregulatory effects on candidiasis by inducing T_H1 cytokine production (J. H. Lee et al., 2007). On the other hand, although the plant sterol sitostanol was found to induce a T_H1 cell shift, it increased the number of Tregs and IL-10 production by PBMCs from asthma patients (Brüll et al., 2012). Another study reported that β-sitosterol isolated from *Clinacanthus nutans* (Burm. f.) Lindau also exhibited immunosuppressive activity; it inhibited concanavalin A (ConA)-stimulated T cell proliferation and suppressed T_H2 cell activity by blocking the secretion of T_H2 cytokines in mouse splenocytes (Le et al., 2017). In addition, Mencarelli et al. showed how guggulsterone [4,17(20)-pregnadiene-3,16-dione], a phytosterol derived from the gum resin of the tree *Commiphora mukul* and known for its anti-inflammatory activity, could prevent T cell-induced colitis in two models of intestinal inflammation. *Ex vivo* exposure of T helper cells derived from the lamina propria of mice to *cis*-guggulsterone (10 μM) inhibited IL-2, IL-4 and IFN-γ production by these cells (Mencarelli et al., 2009). In addition, β-sitosterol and its glucoside derivative were found to exert anti-inflammatory effects on monocytes by inhibiting IL-6 and TNF-α production (Bouic & Lamprecht, 1999). The inhibition of TNF-α, IL-1β, IL-6, and IL-8 secretion and ROS generation was also demonstrated for β-sitosterol isolated from *Moringa oleifera*, which was used to treat stimulated keratinocytes and macrophages (P. C. Liao, Liu, et al., 2018a). Moreover, β-sitosterol improved intestinal immune function by reducing jejunal TNF-α concentrations in broiler

chickens fed a basal diet supplemented with this phytosterol (40-100 mg/kg, for 42 days) (Y. Cheng et al., 2020). Sitosterol-3-*O*-β-D-glucoside from *M. oleifera* seeds (2-250 μM) also suppressed the expression of T_H17 cytokines (IL-17, IL-22, and IL-23) in LPS-stimulated THP-1 cells and in 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced psoriasis-like skin lesions in mice (N. Ma, Tang, et al., 2018b). In a similar experimental model, stigmasterol, a natural steroid alcohol, significantly reduced serum TNF-α levels, thus downregulating cutaneous allergic responses in rats with dermatitis (Antwi et al., 2018). Guggulsterone administration to RIN rat insulinoma cells prevented the damage caused by treatment with IL-1β and IFN-γ (Lv et al., 2008). Accordingly, guggulsterone could be employed as a chemopreventive agent because it induced heme oxygenase-1 (HO-1) expression through Nrf2 transcription factor. HO-1 conferred protection against oxidative stress and inflammation, in human mammary epithelial cells (Almazari et al., 2012). Another phytosterol, daucosterol, reduced the production of ROS, infiltration of macrophages, and secretion of proinflammatory cytokines and increased the $Foxp3^+$ cell count and NK cell activity in a mouse model of dextran sulfate sodium (DSS)-induced colitis (J. Jang et al., 2019).

β-Sitosterol and campesterol also modulated the function of macrophages, as shown by the observations of a decrease in phorbol ester (PMA)-induced NO release from RAW264.7 macrophages (Moreno, 2003) and inhibition (8-16 μM) of PGE2 and PGI2 release from LPS-stimulated macrophages (Awad, Toczek, & Fink, 2004). Vivancos et al. also reported a reduction in ROS levels induced by β-sitosterol through the modulation of antioxidant enzyme activities in PMA-stimulated RAW264.7 macrophages (Vivancos & Moreno, 2005). Liu et al. demonstrated that β-sitosterol (5-50 μM) modulated macrophage polarization by repressing M1 polarization and increasing M2 polarization in bone marrow-derived macrophages *in vitro*. Furthermore, β-sitosterol inhibited the production of proinflammatory cytokines in a collagen-induced arthritis mouse model (R. Liu, Hao, et al., 2019b).

A recent study reported that β-sitosterol and palmitic acid, the major components of *Nitraria retusa*, exerted antitumoral effects by stimulating immune responses in a murine melanoma model. Indeed, these compounds enhanced splenocyte proliferation, CTL activities, macrophage lysosomal activity and NO production in tumor-bearing mice (Boubaker et al., 2018). Moreover, liposomal β-sitosterol inhibited the formation of tumor metastasis in melanoma cell-bearing mice by enhancing mucosal immunity, NK cell activity and IL-12 and IL-18 production in the intestinal epithelium (Imanaka et al., 2008).

All these findings demonstrate the importance of phytosterols for their abilities to not only control plasma cholesterol levels but also potentiate innate and adaptive immunity in cancer models (Fig. 2, 4 and Tables 2–4).

3.4. Phytic acid

Phytic acid, also known as inositol hexaphosphate (IP6) or myo-inositol-1,2,3,4,5,6-hexaphosphate, is a natural antioxidant that is found in cereals, vegetables, nuts, and natural oils and composed of 6 phosphate groups linked to inositol. For years, IP6 has been considered an antinutritional component because it chelates iron, copper, zinc, and calcium and reduces the absorption of these minerals**.** However, its preventive and therapeutic effects, which are mainly related to its antioxidant potential, have been demonstrated in several diseases, including cancer (E. O. Silva & Bracarense, 2016).

Several studies have reported the immunomodulatory function of phytic acid, especially in the intestinal mucosa (Tables 2, 3). In particular, phytic acid regulates the secretion of cytokines by epithelial cells in response to different stimuli. Phytic acid was found to decrease IL-8 and IL-6 secretion during acute inflammation induced in colon epithelial cells (Wawszczyk et al., 2012; Weglarz et al., 2007) and to downregulate the expression of iNOS stimulated by proinflammatory factors in intestinal cells (Kapral et al., 2015). Okazaki et al. also observed that a dietary phytic acid improved the colonic luminal environment (composition of organic acids, microflora and mucins) in rats fed a high-fat diet and decreased the serum levels of TNF-α and IL-6 (Okazaki & Katayama, 2014). Similar effects were reported in the intestinal mucosa in a rat colorectal cancer (CRC) model. Phytic acid decreased the tumor incidence, improved the mucosal barrier function and reduced the serum levels of proinflammatory cytokines (C. Liu et al., 2018). Moreover, IP6 increased *in vivo* blood NK cell activity in the same animal model (Z. Zhang et al., 2005). IP6 and inositol prevented liver CRC metastasis *in vivo* by modulating the tumor microenvironment. Combined treatment (40 mg/kg/day each, p.o., for 20 days) altered the expression of the ECM proteins, the adhesion factor receptor integrin β1, the proteolytic enzyme MMP-9 and angiogenic factors (Fu, Song, Wen, Lu, & Cui, 2016).

Moreover, an *in vivo* study demonstrated the immunomodulatory function of IP6 in B cells. Indeed, IP6 (80 μM) activated T cell-independent humoral immunity by improving B cell antigen receptor (BCR) signaling (W. Kim et al., 2019b).

An *in vivo* study employing female broiler chickens fed nutritionally marginal diets reported several effects exerted by phytase on cellular and humoral immunity in the gastrointestinal tract. The addition of phytase to the animal diet increased the percentages of $CD4^+CD8^+$ T cell subsets and the intestinal levels of secretory IgA (N. Liu et al., 2008).

3.5. Lipids

3.5.1. Fatty acids

Lipids are a group of chemically heterogeneous compounds, most of which are fatty acids (FAs). FAs can have different roles; they have the functions of composing cell membranes, serving as storage materials in cells and acting as signaling molecules (de Carvalho & Caramujo, 2018). FAs are carboxylic acids with carbon chains varying between 2 and 36 carbon atoms in length and can be either saturated or unsaturated. Polyunsaturated FAs (PUFAs) have a pentadiene configuration of double bonds. FA composition is species and tissue specific, and the most abundant FAs in animal and plant tissues are those with 16 and 18 carbon atoms, i.e., palmitic, stearic, oleic and linoleic acids (Tvrzicka et al., 2011).

The differential roles of ω-3 and ω-6 PUFAs in immunity are the subject of numerous studies. Indeed, several studies have highlighted that high intake of ω-6 PUFAs stimulates carcinogenesis in mammary, colon and prostate cancer, mainly because of the increase in oxidative DNA damage and promotion of proinflammatory response. Conversely, fish oil-derived ω-3 fatty acids appear to protect individuals from the carcinogenic process. Thus, it is important to balance the dietary intake of ω-3 and ω-6 fatty acids (Bartsch et al., 1999).

Khadge et al. compared the effects of a diet containing ω-6 or ω-3 PUFAs on the tumor microenvironment in mice transplanted with mammary tumor cells. The results showed that the ω-3 diet delayed tumor growth and reduced metastasis by decreasing angiogenesis, tumor infiltration by myeloid cells (neutrophils and macrophages), and $CD3^+$ lymphocyte accumulation compared to the ω-6 diet (Khadge et al., 2018). Similarly, in a Her2/*neu* mouse breast cancer model, a diet with a high content of ω-3 PUFAs derived from fish oil prevented the development of tumors by increasing the numbers of splenic immune cells ($CD3^+$ T cells, $CD3^+CD4^+$ T cells, NK cells, DCs and $Gr\text{-}1^+CD11b^+$ cells) and tumor immune cell infiltrates (NK cells, $F4/80^+$ macrophages and $Gr\text{-}1^+CD11b^+$ cells) and driving a T_H1 antitumor response (Turbitt et al., 2015). Moreover, Robinson et al. demonstrated that long-chain ω-3 fatty acid supplementation in a low-polyunsaturated fat diet enhanced antitumor immune defense by increasing the cytotoxicity of NK cells, NO and IL-2 production of splenocytes and number of activated ($CD25^+$) $CD8^+$ and $CD28^+$ cells in rats transplanted with breast cancer cells (Robinson et al., 2002). It has been reported that supplementation with fish oil, which is rich in ω-3 polyunsaturated fatty acids, reduces the growth of breast tumors

in rats by improving macrophage-mediated host defense against tumors rather than T cell proliferation (Pizato et al., 2006; Togni et al., 2003).

The balance between ω-6 and ω-3 fatty acids can also modulate inflammation in prostate cancer. A diet rich in ω-3 PUFAs counteracted tumor growth by increasing the T_H1 immune response and eosinophil recruitment in tumor tissues in a mouse model of prostate cancer (Gevariya et al., 2019). By comparing the effects of ω-3 and ω-6 diets, Liang et al. also demonstrated that a diet rich in fish oil (ω-3) reduced tumor growth by altering inflammatory and immune cell infiltration into tumors in an allograft mouse model of androgen-sensitive prostate cancer. Tumors from ω-3 PUFA-treated mice showed reduced gene expression of markers for M1 and M2 macrophages compared to those from ω-6 PUFA-treated mice (P. Liang et al., 2016). It was also reported that ω-3 PUFAs are able to inhibit the production by prostate cancer cells of IFN-γ-induced IL-18-binding protein, whose enhanced production is associated with resistance to antitumor immune responses and a poor prognosis in prostate cancer patients (X. Wang, Breeze, & Kulka, 2015c).

The modulation of inflammation by ω-3 PUFAs was also investigated in CRC, and the results confirmed a protective role for ω-3 PUFAs in the development of this type of cancer. It was reported that an increased tissue level of ω-3 PUFAs reduced the incidence of colon tumors induced by inflammation in transgenic Fat-1 mice through the inhibition of NF-κB activity and iNOS and an increase in TGF-β expression in colonic tissues (Nowak et al., 2007). Anti-inflammatory activity was also reported for the docosahexaenoic acid (DHA)-derived lipid mediator maresin-1 in similar murine models of colitis. Maresin-1 protected mice against colitis by reducing the levels of inflammatory mediators and increasing the differentiation of M2 macrophages (Marcon et al., 2013). A prospective cohort study reported that the antitumor effect of marine ω-3 PUFAs on CRC was, at least in part, mediated through immunomodulatory effects on Tregs (M. Song et al., 2016). In addition, it was reported that marine eicosapentaenoic acid (EPA; 50-200 μM) inhibits the expression of IDO and indirectly increases T cell survival in mouse melanoma and breast tumor cells (C. C. Wang et al., 2018a).

Almeida et al. demonstrated the anti-inflammatory effects of a mixture of ω-3-rich fish oil and ω-6-rich soybean oil on a melanoma mouse model. The mixture reduced tumor growth and the levels of proinflammatory mediators and CXCL1 and increased the levels of IL-10 in the tumor microenvironment (Almeida et al., 2019). Liebig et al. compared the effects of three high-fat diets, which differed in their ω-3 and ω-6 PUFA contents and ratios, on nonalcoholic fatty liver disease-related liver fibrosis and tumorigenesis in streptozotocin/high-fat diet-treated mice. The diet with ω-3 PUFAs reduced hepatic lipid accumulation and tumor growth and induced an increase in the number of macrophages with a simultaneous decrease in TNF-α expression in liver tissues (Liebig et al., 2019). The immunomodulatory properties of ω-3 PUFAs in fish oil capable of attenuating the proinflammatory side effects of the anticancer drug imiquimod in human nonmelanoma skin carcinoma cells were reported by Rehman et al. Indeed, ω-3 PUFAs increased the expression of IL-10 and suppressed the expression of IL-6 and TNF-α (Rehman et al., 2016). ω-3 PUFAs can also be useful for the treatment of rheumatoid arthritis; they were found to attenuate arthritis in an anti-collagen antibody-induced arthritis mouse model by increasing the number and differentiation of Tregs and reducing IL-17, IL-6 and IL-23 production in the spleen and joint tissues (J. Y. Kim et al., 2018).

Moreover, the monounsaturated fatty acid oleic acid, which is found in olive oil, also showed anti-inflammatory effects on an *in vitro* human glioblastoma model (Lamy et al., 2016). In addition, oleic acid is able to activate neutrophils and neutrophil production of ROS (Carrillo et al., 2011).

Accordingly, PUFAs both protect tissues from chronic inflammatory stimuli and enhance the cell-mediated immune response in cancer models (Figs. 2–4 and Tables 2–4).

3.5.2. Terpenes

Terpenes are a class of hydrocarbon compounds present in essential oils. They are made of different numbers of five-carbon isoprene units that are combined to form a variety of structures. There are five main classes of terpenes: monoterpenes (2 isoprene units), sesquiterpenes (3 isoprene units), diterpenes (4 isoprene units), triterpenes (6 isoprene units) and tetraterpenes (8 isoprene units). The most studied terpenes are those produced by plants, but other organisms, such as fungi, also produce these molecules. Some examples of the most important terpenes are geraniol, squalene, isoprenol, limonene and menthol (Wagner & Elmadfa, 2003). Several studies have shown that terpenes are effective in developing antitumor immune responses. Ku & Lin demonstrated that 27 selected terpenoids modulated the T_H1/T_H2 cytokines secretion profile in mouse primary splenocytes with different modalities. In particular, most of the terpenoids (e.g., eucalyptol, limonene, thymol, β-sitosterol, and betulinic acid) showed anti-inflammatory properties *in vitro*, inducing strong T_H2 responses or inhibiting T cell responses through simultaneous suppression of the production of both IL-2 and IL-10. Other terpenoids showed a predisposition toward T_H1 skewing (menthone, farnesol and oridonin) (Ku & Lin, 2013). Recently, it was discovered that artemisinin (0.01-100 μM) and its derivatives were able to inhibit the growth of several types of cancer cells by modulating antitumor immunity. The administration of artemisinin to mice bearing breast tumors enhanced the antitumor immune response by decreasing MDSCs, Tregs and TGF-β levels and increasing $CD4^+$ IFN-γ^+ T cell and CTL numbers in splenic and tumor samples (Y. Cao, Feng, et al., 2019b). Treatment with dihydroartemisinin also reduced breast cancer tumor growth by enhancing T_H1 immune responses and decreasing the $CD4^+CD25^+Foxp3^+$ Treg frequency in splenocytes derived from tumor-bearing mice (Noori & Hassan, 2011). Uyeda et al. showed that myrcene increased IgG titers in immunized mice (Uyeda et al., 2016). The triterpenoid methyl-2-cyano-3,12-dioxooleana-1,9 (11)-dien-28-oate (CDDO-Me) is a synthetic oleanane triterpenoid with anti-inflammatory properties. It was reported that CDDO-Me improves antitumor immune responses by abrogating the immunosuppressive activity of MDSCs in mice bearing different tumors (thymoma, lung carcinoma or colon carcinoma) and in cancer patients (Nagaraj et al., 2010). Furthermore, it was demonstrated that the delivery of CDDO-Me modulates the tumor microenvironment and enhances the antitumor effect elicited by a Trp2 peptide vaccine in a melanoma mouse model. CDDO-Me reduced the levels of Tregs and MDSCs in the tumor microenvironment and increased $CD8^+$ T cell infiltration and CTL killing efficiency after vaccination. In addition, this triterpenoid changed the stromal tumor microenvironment and decreased the levels of M2 and M1 cytokines in the tumor, facilitating the activity of the vaccine (Y. Zhao, Huo, et al., 2015a).

Pfarr et al. showed the specific immunostimulatory activities of the pentacyclic triterpene betulin, the precursor of betulinic acid, in increasing IL-12 release from TLR4-stimulated bone marrow-derived dendritic cells (BMDCs). The activation of DCs by betulin resulted in enhanced T lymphocyte stimulation in the spleen, which led to decreased melanoma B16 cell viability in an antigen-specific model system (Pfarr et al., 2015). The antitumor effect of betulinic acid was also studied in cervical carcinoma tumor-bearing mice, and the results showed that this triterpene increased the levels of IL-2 and TNF-α as well as the numbers of different $CD4^+$ lymphocyte subsets (P. Wang, Li, et al., 2012b).

Conversely, it was shown that in the context of an inflammatory disorder such as psoriasis, betulinic acid suppresses the T_H17 cell response by reducing the frequencies of IL-17-expressing $CD4^+$ and γδ T cells and inhibiting the gene expression of proinflammatory mediators in the skin lesions of psoriatic mice (C. Liu, Chen, et al., 2019a). Additionally, a derivative of betulinic acid, SH479, showed anti-inflammatory effects on a collagen-induced arthritis mouse model by inhibiting T_H1 and T_H17 polarization and increasing anti-inflammatory cytokine and Tregs levels. In this way, SH479 shifted the T_H17/T_H1 response to a T_H2/Treg

phenotype (S. Chen et al., 2017). Similarly, oleanolic acid and erythrodiol were able to switch cytokine production to a T_H2 profile, with reductions in T_H17 and T_H1 cytokine levels and increases in T_H2 cytokine levels in the serum and spinal cord, in experimental autoimmune encephalomyelitis (Martín et al., 2012). Weber et al. investigated the role of betulinic acid (1-20 μg/mL) in triple-negative breast cancer cell lines, confirming its antiproliferative and anti-inflammatory functions (Weber et al., 2014).

Another function of terpenes that allows them to participate in the antitumor immune response is their ability to direct the polarization of macrophages from the M2 phenotype to the M1 phenotype. In particular, a study found that corosolic acid and oleanolic acid inhibited the polarization of human monocyte-derived macrophages into the M2 phenotype. In addition, CA increased the levels of $CD4^+$ and $CD8^+$ lymphocytes and reversed the immunosuppressive activity of MDSCs in tumor tissue in a mouse sarcoma model (Fujiwara et al., 2014). The same function was observed for β-elemene, which was found to regulate the polarization of macrophages from M2 to M1. In this way, β-elemene inhibited M2 macrophage-induced migration, invasion and epithelial-mesenchymal transition (EMT) in lung cancer cells (X. Yu et al., 2017). Similarly, ginsenoside Rh-2 polarized macrophages towards the M1 phenotype and hence affected the migration of non-small cell lung cancer (NSCLC) cells *in vitro* and *in vivo* (40 mg/kg/day, i.p., for 21 days, starting after injection of cells) (H. Li et al., 2018). The immunoregulatory properties of other ginsenosides were recently discovered. Ginsenoside F1 was shown to enhance the functions of NK cells by stimulating their cytotoxicity and the release of IFN-γ. NK cell functions were also improved by Ginsenoside F1 treatment in mouse models of syngeneic lymphoma and pulmonary metastatic melanoma (Kwon et al., 2018). Ginsenosides, in particular ginsenoside Rg3, were also found to promote antitumor immunity by decreasing the levels of B7-H1 (PD-L1) and B7-H3 in CRC tissues. High expression of B7-H1 and B7-H3 was associated with worse outcomes in CRC patients (Y. C. Tang et al., 2018). Another triterpenoid with immunoregulatory ability is ursolic acid, which improves (250 mg/kg/day, p.o., for 4 weeks, starting one week after orthotopic implantation) the efficacy of gemcitabine in pancreatic cancer by suppressing the inflammatory microenvironment in orthotopically implanted pancreatic tumors (Prasad et al., 2016). Moreover, *in vitro* administration of ursolic acid-liposomes to primary $CD4^+$ T cells obtained from breast cancer tumor-bearing mice was found to reduce the number of $CD25^+$ $Foxp3^+$ Tregs and secretion of IL-10 and IL-6. *In vivo* administration of ursolic acid-liposomes also confirmed these results, as shown by the decreased numbers of Tregs and MDSCs in tumors, thus indicating a change in the tumor microenvironment that was associated with reduced tumor size (N. Zhang et al., 2020). A study on the host gut microbiota in a colon carcinogenesis $Apc^{Min/+}$ mouse model showed the cancer-preventing effects of the triterpenoid saponin isolated from *Gynostemma pentaphyllum* (GpS) mediated by modulating the inflammatory intestinal microenvironment. GpS upregulated the expression of the anti-inflammatory cytokine IL-4 and downregulated that of proinflammatory cytokines in the gut epithelium. In addition, GpS stimulated M2 macrophage markers expression and inhibited M1 macrophage markers expression, thus enhancing intestinal tissue repair (L. Chen et al., 2016). Similarly, Sánchez-Quesada et al. described that squalene, the major component of the unsaponifiable fraction of virgin olive oil, promoted wound healing by exerting immunomodulatory effects on proinflammatory M1 macrophages. Squalene increased the production of anti-inflammatory cytokines and decreased proinflammatory signals in M1 macrophages (Sánchez-Quesada et al., 2018). Moreover, the monocyclic monoterpene D-limonene increased macrophage phagocytosis and microbicidal activity but did not affect T cell subpopulation counts ($CD4^+$, $CD8^+$ and $CD4^+CD25^+$) in lymphoma-bearing mice (Del Toro-Arreola et al., 2005). Several studies have shown the activity of the diterpene triptolide under inflammatory conditions. It inhibited the expression of inflammatory cytokines in mouse RAW264.7 macrophages stimulated with LPS and suppressed TLR-induced NF-κB activation by targeting the TLR4 and TRIF proteins (Ma et al., 2007; Premkumar et al., 2010). Similarly, it was reported that triptolide (1 mg/kg, p.o., 5 days/week, for 2 months) prevents the development of inflammation-associated cancer (Zheng et al., 2017). Jayachandran et al. reported that geraniol (100 mg/kg, p.o., for 12 weeks) also exerted anti-inflammatory effects on atherogenic diet-fed experimental hamsters (Jayachandran, Chandrasekaran, & Namasivayam, 2015). Moreover, the tetraterpenoids β-carotene and lutein (20 μM) were demonstrated to inhibit the H_2O_2-induced activation of NF-κB and expression of IL-8 in gastric epithelial cells (Y. Kim, Seo, & Kim, 2011).

Overall, terpenes stimulate the secretion of proinflammatory cytokines and potentiate the adaptive immune response (Figs. 2–4 and Tables 2–4).

3.6. Organosulfurs

Organosulfur compounds from vegetable sources are very valuable compounds in the human diet, and their consistent ingestion has been suggested to have a beneficial role in human health (Goncharov et al., 2016). These compounds are mainly derived from the *Allium* (garlic, onion, shallot, leek, and chives), *Eruca* (rucola), and *Brassica* (cabbage, cauliflower, Brussels sprouts, kale) genera. The chemical classes of these organosulfur compounds include cycloalliin; S-alkyl-l-cysteine sulfoxides; mono-, di-, and trisulfides; thiosulfonates; S-alkylcysteines; cysteine alkyl disulfides; 3-vinyl-4H-1,2-dithiin; 2-vinyl-4H-1,3-dithiin; *E*- and *Z*-4,5,9-trithiadodeca-l,6,11-triene 9-oxides (ajoenes); glucosinolates, isothiocyanates, goitrin, and epithionitriles (Goncharov et al., 2016; Munday, 2012). Glucosinolates are hydrolyzed by myrosinase to produce sulfate ions, d-glucose, and degradation products, including isothiocyanates (ITCs) (sulforaphane and erucin), epithionitriles, thiocyanates, nitriles, and goitrin. Several organosulfur compounds have been shown to inhibit cancer cell growth (Goncharov et al., 2016). The cancer cell toxicity of some sulfides can be attributed to their ability to produce ROS (Munday, 2012). Benzyl isothiocyanate (BITC), phenethyl isothiocyanate (PEITC) and sulforaphane ([1-isothiocyanato-4-(methyl-sulfinyl)butane], SFN) are important ITCs widely analyzed for their effects on cancer cell growth (Soundararajan & Kim, 2018). Indole-3-carbinol (I3C), a breakdown product of indole-3-ylmethylglucosinolate, is one of the most widely distributed glucosinolates and was investigated for its effect on the immune response in human and animal models. I3C was observed to increase the number of T cells and decrease the number of macrophages, although it promoted macrophage phagocytic activity, in an *in vivo* leukemia mouse model (H. F. Lu et al., 2012). I3C and 3,30-diindolylmethane (DIM), which is a major condensation product of I3C, were found to inhibit the induction of IL-1β in monocytes but not in macrophages while I3C was found to suppress immune cell infiltration into the lungs and cytokine release in an LPS-induced acute lung injury mouse model (J. Jiang et al., 2013; T. T. Y. Wang, Pham, & Kim, 2018b). Similarly, PEITC has shown anti-inflammatory properties in colon epithelial cells and macrophages in mice with DSS-induced colitis-associated colon carcinogenesis (Y. Liu & Dey, 2017). Conversely, DIM induces the proliferation of splenocytes (5-20 μM) and ROS production by peritoneal macrophages (10-40 μM). Different serum cytokines (IL-6, granulocyte colony-stimulating factor (G-CSF), IL-12 and IFN-γ) are also increased upon mice DIM treatment (Xue et al., 2008). Anti-inflammatory effects were also reported for diallyl trisulfide (DATS), which was found to inhibit cyclooxygenase and inducible NO synthase and reduce the levels of LPS-induced IL-6, IL-10, IL-12p70, MCP-1, and TNF-α in RAW264.7 cells (You et al., 2013). On the other hand, dipropyl disulfide, allyl propyl disulfide, diallyl disulfide (DADS), and allyl isothiocyanate (AITC) can activate human neutrophil functions (Ca^{2+} flux) (Schepetkin et al., 2019). The most promising result for the use of a sulfide to positively modify the immune response was observed by De Cicco et al., who showed that DATS inhibited tumor growth, reduced the frequency of MDSCs and increased $CD8^+$ T cell and DC

numbers in the tumor microenvironment, spleen and blood of melanoma-bearing mice (De Cicco et al., 2020).

SFN is a member of the isothiocyanate group of organosulfur compounds and naturally occurs in cruciferous vegetables, such as broccoli, Brussels sprouts and cabbages (Jabbarzadeh Kaboli et al., 2020). SFN has shown antitumor effects mediated by activating apoptosis, affecting chromatin remodeling, and inhibiting angiogenesis, the cell cycle, P-450-mediated drug metabolism (phase 1 biotransformation), drug conjugation (phase 2 biotransformation), the NF-κB pathway and cyclooxygenase (COX)-2, thus reducing inflammation (Jabbarzadeh Kaboli et al., 2020). SFN is considered an antioxidant compound that is a potent Nrf2 agonist (Bayat Mokhtari et al., 2018). Considering the low bioavailability of SFN, it is unlikely that SFN can efficiently destroy tumor cells; it could therefore be important to investigate the effect of SFN on the anticancer immune response. Unfortunately, despite the proven antitumor effects of SFN, the role of SFN in the adaptive immune response under healthy and pathological conditions has been poorly analyzed in humans. Recently, Liang et al. analyzed the effects of SFN on untransformed human T cells. Surprisingly, they showed that SFN induced a pro-oxidative state in T cells derived from healthy donors or rheumatoid arthritis patients. In addition, although SFN did not impair T cell/APC immune synapse formation, it downregulated the expression of T_H17 cytokines and IL-22, which play major roles within the pathophysiology of many chronic inflammatory/autoimmune diseases (J. Liang et al., 2018). Quite a few studies have been performed to assess the effects of SFN on immunity in mouse models. SFN treatment increased the number and proliferation of T and B cells in a leukemia mouse model *in vivo*, but it had no effect on the numbers of monocytes and macrophages (Shih et al., 2016). A different study showed that SFN could restore T_H1 immunity in old mice with a decreased contact hypersensitivity response. This effect could be attributed to the antioxidant properties of SFN (H. J. Kim et al., 2008). Park et al. reported that SFN attenuated T_H2 cytokine levels rather than T_H1 cytokine levels in a murine model of asthma (J. H. Park et al., 2012). Suppression of T_H1 and T_H17 cell differentiation in T cells primed by SFN-treated DCs was observed in mice with experimental autoimmune encephalomyelitis fed SFN (Geisel et al., 2014). The ability of SFN to inhibit T cell-mediated immunity both *in vitro* and *in vivo* was confirmed by Checker et al., who showed that SFN (10-20 μM) inhibited mitogen-induced mouse T and B lymphocyte proliferation and activation *in vitro* and homeostatic proliferation of T cells and exhibited potent anti-inflammatory effects *in vivo* (Checker et al., 2015). Similarly, SFN inhibited T cell proliferation and cytokine secretion *in vitro* and *in vivo* in mice with experimental rheumatoid arthritis (J. S. Kong et al., 2010). Given all these observations, it appears that SFN inhibits rather than activates the specific immune response, although one study reported that SFN increased the class II- but not class I-restricted presentation of an exogenous antigen in both DCs and peritoneal macrophages in mice both *in vitro* (1.25-20 μM) and *in vivo* (Shin et al., 2011) (Figs. 2, 3 and Tables 2–4).

The role of SFN in innate immune cells is even more controversial. Several studies have shown proinflammatory activity for SFN, while others have reported the opposite function. The dual opposing effects of SFN might be dependent on the target cell type and undoubtedly on the tumor microenvironment created by the interactions of different cell types, growth factors and pro- and anti-inflammatory mediators. Indeed, it was reported that the administration of SFN significantly enhances NK cell activity, antibody-dependent cellular cytotoxicity, and IL-2 and IFN-γ expression in metastatic tumor-bearing animals. However, the same study reported a downregulation of the serum levels of proinflammatory cytokines during metastasis (Thejass & Kuttan, 2007). Increased NK cells cytotoxicity against a prostate cancer cell line and increased T cell infiltration into the tumor were also observed after SFN treatment (6 μmol, p.o., thrice a week, for 17 to 19 weeks) in TRAMP mice (S. V. Singh et al., 2009). Increased macrophages phagocytosis and NK cells activity were reported for an *in vivo* leukemia mouse model treated with SFN (Shih et al., 2016). Conversely, SFN reduced the population of inflammatory cells in a murine model of asthma (J. H. Park et al., 2012). Similarly, the anti-inflammatory effects induced by SFN were demonstrated by reduced secretion of IL-1β and TNF-α and decreased levels of COX-2 in H_2O_2-treated human neuroblastoma cells (de Oliveira et al., 2018); by inhibition of TLR4 signaling *in vitro* (10 and 20 μM) which was paralleled by reduced production of inflammatory cytokines *in vivo* in experimental inflammatory animal models (Youn et al., 2010) and by inhibition of the LPS-stimulated production of TNF-α, IL-1β, COX-2 and iNOS in primary peritoneal macrophages by pretreatment with SFN (W. Lin et al., 2008). Another potential drawback related to SFN that could affect the antitumor immune response is that, at noncytotoxic concentrations, SFN was found to shift M1 polarization to M2 polarization after stimulation with soluble collagen (Pal & Konkimalla, 2016) and to inhibit monocyte-DC differentiation from immature to mature porcine DCs (Qu et al., 2015). On the other hand, it was reported that SFN inhibits the transformation of normal monocytes into MDSCs induced by glioma-conditioned medium *in vitro*, which is associated with a simultaneous increase in the mature DC frequency (Kumar et al., 2017), thus emphasizing the potential role of SFN in the antitumor immune response, considering the presence of MDSCs and immature DCs in the tumor microenvironment.

3.7. Polyphenols

3.7.1. Non-flavonoids

Non-flavonoid polyphenols are a group of molecules with antioxidant properties. They are composed of a simple C6 backbone and divided into phenolic acids (hydroxybenzoic and hydroxycinnamic acids), stilbenes, lignans, coumarins and curcuminoids (Benvenuto et al., 2020; Fantini et al., 2015).

3.7.1.1. Coumarins. Coumarin ($C_9H_6O_2$, 2H-1-benzopyran-2-one) and its derivatives constitute a class of compounds that can be isolated from the fruits, leaves, flowers, stems and roots of several plants, among which Apiaceae are the most represented. These compounds are alpha-benzopyrones and are divided into four main subgroups: simple coumarins, furanocoumarins, pyranocoumarins, and dicoumarins. Many derivative forms can be synthesized and acquire pharmacological or therapeutic properties depending on their chemical substitutions (Majnooni et al., 2019; Venkata Sairam et al., 2016).

Kimura et al. evaluated the effects of esculetin, fraxetin, and daphnetin (dihydroxycoumarins) on osteosarcoma cells *in vitro* and *in vivo*. Esculetin inhibited the expression of MMP-2, production of proangiogenic factors in tumor cells, and release of cytokines in M2 THP-1 macrophages. Conversely, fraxetin inhibited the production of MCP-1 and IL-10 but not that of TGF-β (Kimura & Sumiyoshi, 2015).

Hyaluronan (HA), a predominant component of the ECM, is reported to be involved in tumor spread. Wang et al. reported that the efficacy of coumarin 4-methylumbelliferone (4-MU) (0.25 μM) in human and murine breast carcinoma cell lines was dependent on the HA concentration (100-300 μM) (R. Wang et al., 2015a). The same effects were obtained in human prostate cancer cells (0.4 mM) (Lokeshwar et al., 2010), melanoma cells, and ovarian cancer, squamous cell carcinoma (0.2-1 mM) (-Kultti et al., 2009), murine colon carcinoma (0.125-0.5 mM) (Malvicini et al., 2015) and hepatoma cell lines (0.25-0.50 mM) (Piccioni et al., 2015; Piccioni et al., 2012). In addition, 4-MU inhibited angiogenesis, macrovascular and microvascular endothelial cell proliferation, and MMP-2 expression levels *in vivo* in a chick chorioallantoic membrane assay (25 mM) and in the intersegmental vessel sprouts of fluorescence-labeled zebrafish embryos (0.2 mM) (García-Vilas, Quesada, & Medina, 2013). The variation in HA in the tumor microenvironment of mice treated with 4-MU (200 mg/kg/day, p.o., starting from day 6 until mice sacrifice) and transplanted with colon carcinoma cells was found to result in an increase in the homing of T lymphocytes to the tumor site at the same time as decreased production of proangiogenic molecules and with increased production of

antiangiogenic molecules (Malvicini et al., 2015). These properties were further confirmed in a mouse model of liver fibrosis and hepatocarcinoma (400 mg/kg/day, p.o.) (Piccioni et al., 2015). Cumulatively, the principal action of coumarins is directed towards the stromal component of the tumor microenvironment, where the compounds reduce angiogenesis and MMPs levels.

3.7.1.2. Curcuminoids. Curcumin (CUR), together with demethoxycurcumin and bisdemethoxycurcumin, is derived from the rhizomes of *Curcuma longa* L. and *Curcuma xanthorrhiza*, perennial plants in the *Zingiberaceae* family that originate from India and are cultivated in tropical and subtropical regions. CUR is an orange-yellow crystalline compound that is poorly hydrophilic because of its structure composed of two methoxybenzene rings connected by an unsaturated chain. Traditionally, CUR is recognized as a medicinal herb used, like many others, as an antioxidant, antimicrobial, anti-inflammatory, antiaging, and antitumor agent (Amalraj et al., 2017; Kita et al., 2008; Masuelli et al., 2017a). Cumulative evidence has demonstrated an important role for CUR in affecting adaptive immunity in the tumor microenvironment, particularly in regulating the functions of Tregs and APCs and the release of immunosuppressive molecules. Alterations in the host's immune system are generated under neoplastic conditions. CUR was found to restore T cell populations ($CD4^+$, $CD8^+$) and subpopulations (central memory and effector memory) to normal frequencies and functions in a mouse model of Ehrlich's ascites carcinoma (Bhattacharyya et al., 2010) and, when administered with resveratrol, CUR preserved the normal frequencies of lymphocytes and granulocytes in salivary gland tumor-bearing mice (Masuelli et al., 2014). Diminished production of IFN-γ and IL-4 in ConA-stimulated lymphocytes (Sharma et al., 2007), systemic inhibition of Tregs suppressive activity, Treg-induced T_H2 polarization, and reduced consumption of IL-2 were demonstrated in healthy BALB/c mice after CUR treatment (G. J. Zhao et al., 2012). CUR prevents the binding of IL-2Rα (CD25) that directly sequesters IL-2 (Oh et al., 2018).

CUR alone is not sufficient to affect tumor growth. In fact, when administered to Lewis lung carcinoma-bearing immunodeficient nude mice, CUR failed to delay the increase in tumor volume. However, when CUR was administered to immunocompetent mice, it was able to boost the T cell immune response and cytokine release, leading to the inhibition of tumor growth (Luo et al., 2011). Similarly, Liu et al., using the same mouse model, reported an increase in T cell numbers accompanied by decreases in the frequency of mature MDSCs and in factors characterizing MDSCs immunosuppressive activity following CUR treatment (50 mg/kg/day, i.g.) (D. Liu et al., 2016). Similarly, an increase in effector T cell numbers and a decrease in Tregs numbers in the peritumoral area of $HER2/neu^+$ transplanted mouse mammary tumors grown in CUR-treated immunocompetent BALB/c mice were demonstrated (Masuelli, Granato, et al., 2017b). The increase in IFN-γ-producing T cell numbers and decrease in Tregs numbers have been explained in terms of cell plasticity in CUR-treated lung cancer patients by Zou et al. and in postsurgery CUR-treated CRC patients by Xu et al. The conversion of Tregs into IFN-γ^+ T_H1 cells was explained by the CUR-dependent inhibition of Foxp3 gene transcription in Tregs and activation of the T-bet promoter that activates IFN-γ production (B. Xu et al., 2017; J. Y. Zou et al., 2018).

CUR has been administered simultaneously with drugs, anticancer vaccines, adoptive T cell therapy or cytokines. CUR, when given in combination with the antidiabetic drug metformin (N',N'-dimethylbiguanide hydrochloride), was found to stimulate a T_H2 response in mice transplanted with breast cancer cells (Falah et al., 2017), while when administered in combination with a recombinant HER2/neu vaccine, it strengthened the specific humoral response and increased TIL infiltration and cytokine release in a mouse model of head and neck carcinoma (Focaccetti et al., 2020). An increased immune response triggered by administration of the $Listeria^{at}$-Mage-b vaccine with CUR was demonstrated in a triple-negative breast cancer mouse model (M. Singh et al., 2013); a similar strengthening of the immune response was observed in mice immunized with antigen 4-hydroxy-3-nitrophenylacetyl (NP)-ovalbumin, in which humoral immunity was augmented by daily CUR administration (D. H. Kim, Lee, & Choi, 2019a). When administered in combination with adoptive T cell therapy, CUR was shown to increase activated TIL numbers and reduce the percentage of Tregs and expression of TGF-β and IDO in the tumor microenvironment (Y. F. Chang et al., 2012). Conversely, when CUR was simultaneously administered with cytokines, despite the direct antitumor effects observed, it demonstrated detrimental modulation of the cellular immune response (Bill et al., 2009).

Treatment with CUR, or the natural analog bisdemethoxycurcumin, lowered PD-L1 expression on cancer cells, both *in vitro* and *in vivo*, and CUR additionally increased TIL numbers and decreased Tregs or MDSCs numbers in a mouse model of chemically induced oral squamous carcinoma (Liao, Liu, et al., 2018a), a model of bladder cancer (Shao et al., 2017) and a model of melanoma (L. Xu et al., 2018).

Similarly, CUR suppressed the immune response in LPS-activated macrophages and the complete maturation of BMDCs by reducing costimulatory molecule expression and proinflammatory cytokine production but not IL-10 production, which was increased (Sharma et al., 2007). The sustained weak costimulation during antigen presentation caused poor IFN-γ production by T cells (G. Y. Kim et al., 2005).

CUR is known to have poor bioavailability, and many different CUR formulations or combinations have been analyzed with the aim of fixing this drawback and increasing the antitumor or immunomodulatory efficacy of CUR. A nano-CUR preparation was given to activated T cells, causing a reduction in the secretion of inflammatory cytokines and therefore modifying the T cell phenotype towards conditions detrimental to tumor growth and migration (Milano et al., 2013). On the other hand, the use of an intracellular-labile amphiphilic CUR-based micelle delivery system (CUR-PEG) induced decreases in the frequencies of MDSCs and Tregs, activation of IFN-γ-producing cytotoxic T cells and a reduction in CAFs numbers in a mouse melanoma model (Y. Lu et al., 2016). A new formulation that encapsulates CUR together with epicatechin gallate and RES in liposomes was used in a mouse model of glioblastoma (encapsulated compounds 1.28 mM, i.p., for 5 days). It induced switching from an anti-inflammatory M2 TAM phenotype ($ARG1^{hi}iNOSl^{lo}IL\text{-}12^{lo}IL\text{-}10^{hi}$) to a proinflammatory M1 phenotype ($ARG1^{lo}iNOS^{hi}IL\text{-}12^{hi}IL\text{-}10^{lo}$), iNOS expression and consequent NO release (Mukherjee et al., 2018a; Mukherjee et al., 2018b). A similar micellar delivery system, encapsulating CUR and baicalin, was found to induce macrophage remodeling towards a tumor-suppressive phenotype (B. Wang et al., 2019), while dendrosomal nano-CUR induced macrophage switching from the M2 phenotype to the M1 phenotype (Shiri et al., 2015). A dual-pH-sensitive polymeric nanodrug carrying an anti-PD-1 antibody on the shell and CUR in the core was developed by Xiao et al. (Z. Xiao et al., 2020). The advantage of this formulation was the possibility to accumulate the nanoparticles in the tumor either via permeation of tissues or binding to tumor-infiltrating T cells. At the low pH in tumors, the encapsulated CUR was released and downregulated the expression of cytokines, inhibited the recruitment of Tregs and further promoted the infiltration of antitumor T cells because of PD-1 blockade (Z. Xiao et al., 2020).

Tumor-promoting CAFs are also influenced by CUR (10 mM), which was found to restore normal peritumor fibroblasts by reducing the expression of protumorigenic molecules (MMP-2, SDF-1, and TGF-β1) and characteristic molecular markers of CAFs (Ba et al., 2020).

Accordingly, cellular and soluble components of the tumor microenvironment appear to be affected by CUR administration, but it is particularly worth noting that CUR activity strongly requires contributions from the host's immune system to reach its antitumor potential (Figs. 2–4 and Tables 2–4).

3.7.1.3. Lignans. Lignans are a class of molecules that contribute to reducing cancer risk because they are endowed with antioxidative, anti-

inflammatory, antiatherosclerogenic, and antiestrogenic properties. Lignans are divided into plant lignans [pinoresinol, lariciresinol, arctigenin, matairesinol, secoisolariciresinol, syringaresinol, medioresinol, 7-hydroxymatairesinol and sesamin (a lignan precursor)] and enterolignans or mammalian lignans, which are metabolized in the large bowel from plant lignans [enterodiol (END) and enterolactone (ENL)]. Plant lignans occur mainly as glycosides in foods, including flaxseed, sesame seed, whole-grain cereals, vegetables, beans, berries, some fruits, red wines, tea, coffee and olive oil (Adlercreutz, 2007; De Silva & Alcorn, 2019).

Bowers et al. evaluated the effect of adding the lignan secoisolariciresinol diglucoside (SDG) (100 mg/kg) to the diet of tumor-bearing mice. After consumption, SDG is hydrolyzed into secoisolariciresinol, which is metabolized into the enterolignans ENL and END by intestinal bacteria. MMP-9, TNF-α and GM-CSF levels were significantly decreased in ENL-treated mammary tumor cell lines (1-10 μM) (Bowers et al., 2019). ENL was shown to remodel the tumor microenvironment of metastatic breast cancer cells (25-75 μM) by inhibiting cancer cell spread through decreasing the expression of MMPs and increasing that of tissue inhibitor of MMPs (TIMP)-1 (Mali, Joshi, Hegde, & Kadam, 2017). The function of insulin-like growth factor-1 receptor was impaired using picropodophyllin (PPP) in a mouse model of multiple myeloma. Treatment with PPP (3.2 mg in 5 g of food/day/mouse) inhibited tumor cell growth in the bone marrow and reduced the microvessel density (MVD) (Menu et al., 2007). Tetrahydrofurofuran-like lignans, which are derived from Magnoliae Flos, show a preventive or therapeutic inhibitory effect on breast cancer-mediated bone loss. Aschatin, fargesin, lirioresinol B dymethil ether, and magnolin have all been used to treat breast cancer cells (0-100 μM) and found to inhibit migration, invasion and bone resorption (Jun et al., 2014). A study showed the synthetic dihydrobenzofuran lignan methyl(E)3-[2-(3,4-dihydroxyphenyl)-7-hydroxy-3-methoxycarbonyl-2,3dihydro-1-benzofuran-5yl]-prop-2-enoate (Q2-3) enhanced the secretion of IL-25 in murine or human fibroblasts *in vitro*, establishing a strong suppressive tumor microenvironment. Q2-3 treatment (2-100 μg/kg) increased the frequency of IL-25$^+$ fibroblasts in mouse lungs and 3D cell coculture systems composed of fibroblasts, collagen and breast cancer cells (S. Y. Yin et al., 2016). Accordingly, lignans show major contributions to reducing angiogenesis and the MVD.

3.7.1.4. Phenolic acids. Phenolic acids are a group of compounds derived from benzoic (p-hydroxybenzoic, vanillic and protocatechuic acids) or cinnamic (caffeic, p-coumaric and ferulic acids) acids that possess one or more aromatic rings with one or more hydroxyl groups. They can be purified from all parts of edible plants (seeds, leaves, roots and stems of fruit, vegetable, and grain plants). The major food sources of phenolic acids are coffee, tea, berries, and nuts. Phenolic compounds possess antioxidant properties that help to remove ROS, which contribute to cancer development (Van Hung, 2016).

Phenolic acids (protocatechuic, ferulic, vanillic, and hippuric acid) (0.1-2 μM) derived from anthocyanin metabolism in the gastrointestinal tract decrease the adhesion of monocytes to TNF-α-stimulated endothelial cells (Krga et al., 2016). Zheng et al. synthesized a polyferulic acid (PFA) to be used as a drug delivery vehicle. Uniform doxorubicin-encapsulated PFA nanoparticles (PFA@DOX NPs) were created; these NPs (10 mg/ml) persisted in the circulation and specifically reached the weakly acidic tumor microenvironment where the drug could be released and accumulate with high efficiency, ensuring a higher concentration of the drug at the tumor site than elsewhere in the body (Y. Zheng et al., 2019). Ferulic acid (4-hydroxy-3-methoxycinnamic acid) treatment (2 mM) also increases the activity of superoxide dismutases (SODs) and catalases in 2D and 3D cultures of bladder cancer cells, thus protecting the cells from ROS activity (Peng et al., 2013).

Rice bran contains several bioactive components, including ferulic acid, γ-oryzanol, caffeic acid, tricin, coumaric acid, phytic acid and several vitamins, micronutrients, and essential amino acids. In particular, ferulic acid has antioxidative properties and blocks the release of TNF-α (Henderson et al., 2012). The esters of transferulic acid and phytosterols (sterols and triterpenic alcohols) are the main constituents of γ-oryzanol (Tuncel & Yilmaz, 2011). Kim et al. evaluated the effect of diet-fed γ-oryzanol on CRC-bearing mice. The compound increased NK cell cytotoxicity and restored peritoneal macrophage activity and the ability of these cells to release proinflammatory cytokines after recombinant IFN-γ and LPS priming (S. P. Kim et al., 2012). Enzymatically polymerized polyphenols derived from caffeic acid, ferulic acid and p-coumaric acid strongly induce IFN-γ and GM-CSF in murine splenic CD4$^+$ and not CD8$^+$ T cell populations (Yamanaka et al., 2012).

Yang et al. demonstrated that caffeic acid acts as an anti-inflammatory agent, reducing the levels of TNF-α, COX-2 and iNOS and suppressing the production of inflammatory molecules induced in LPS-treated RAW264.7 macrophages (W. S. Yang et al., 2013). Similarly, Oršolić et al. reported that after caffeic acid treatment, there was an increase in the number of activated T_H1 cytokine-producing M1 macrophages infiltrating the peritoneal cavity of ascites tumor-bearing mice and a decrease in the level of ARG1 activity but not NO activity. Lymphocytes and neutrophils were not changed, while the MVD and VEGF release into ascites fluid were reduced (Oršolić et al., 2016). The same authors reported the effect of two different water-soluble propolis derivatives collected from Croatian or Brazilian beehives that included 14.8% or 15.8% polyphenols, respectively, containing caffeic acid, quercetin, naringenin, chrysin, pinocembrin, and galangin in different proportions. Both water-soluble propolis derivatives were able to induce a significant increase in PMN cell numbers and a decrease in macrophage numbers (Orsolić & Basić, 2005). Immunomodulatory effects on LPS-stimulated RAW264.7 macrophages were reported for the leaf extract of *Eryngium foetidum* (containing kaempferol, chlorogenic acid, caffeic acid, lutein and β-carotene) (Mekhora et al., 2012), the aqueous extract of *Centipeda minima* (containing protocatechualdehyde, vanillic acid, protocatechuic acid, chlorogenic acid, ferulic acid, and caffeic acid in order of relative amount) (S. S. Huang, Chiu, et al., 2013b), several hydroxycinnamic acid amides (HCCA, N-*trans*-caffeoyl dopamine, N-*trans*-feruloyl phenethylamine, N-*trans*-feruloyl dopamine, and N-3,4-dihydroxyhydrocinnamoyl tyramine) identified in Goji berries (or *Lycium barbarum*) (S. Wang et al., 2017), and the purified methanol extracts and ethyl acetate fractions of *Neonauclea reticulata* (containing more than twenty compounds including phenolic acid, protocatechuic acid, *trans*-caffeic acid, syringic acid, and ferulic acid) (F. P. Chang et al., 2019). Dihydrocaffeic acid and caffeic acid (100 μM) reduce the production of ROS-induced proinflammatory cytokines in spontaneously immortalized human keratinocytes following early events after ultraviolet irradiation and TNF-α stimulation (Poquet, Clifford, & Williamson, 2008).

Gallic acid (GA), caffeic acid, and other phenolic acids are the main components of pineapple (*Ananas comosus*) vinegar. They inhibit macrophages, NO and malonaldehyde production, iNOS, NF-κB, COX-2, angiogenesis-related proteins and tumor cell migration *in vitro*, whereas they reduce anti-inflammatory cytokine production and increase IFN-γ and IL-2 levels as well as CD4$^+$, CD8$^+$ and NK1.1$^+$ cell numbers *in vivo* (Mohamad et al., 2019). The combined immunomodulatory effect of *Saussurea lappa* C. B. Clarke, *Terminalia chebula* Retz, and *Zingiber officinale* Roscoe in the formulation KM1608 was evaluated. All these medicinal plants individually possess anti-inflammatory, antioxidant, and anticancer activities (Trinh et al., 2020) due to the many phytochemicals they contain (e.g., dehydrocostus lactone, ellagic acid, and 6-gingerol). KM1608 increased interferon (IFN-α and IFN-β), cytokine (TNF-α, IL-1β, IL-6, and IL-10) and proinflammatory enzyme (iNOS and COX2) levels, and network pharmacological analyses identified several genes related to the immune response (Trinh et al., 2020).

Propolis, the resinous product collected by honeybees from plants, contains more than 300 compounds, mainly flavonoids but also aldehydes, phenolic aldehydes, ketones, and phenolic acids, principally caffeic acid phenethyl ester (CAPE). Propolis was found to completely

abolish the expression of MMP-2 and MMP-9 in human hepatocellular carcinoma (12.5 and 25 μM) (K. W. Lee et al., 2008), block angiogenesis (1-20 μg/ml) (Chung et al., 2013), reduce VEGF and MMP-9 protein levels and increase trombospondin-1 expression on human gastric cancer cells (0.01-1 μg/ml) (Kosova, Kurt, Olmez, Tuğlu, & Arı, 2016); it also was shown to inhibit migration and NO production and decrease TLR-4 protein levels in LPS-stimulated breast cancer cell (25 μg/ml) (H. Chang, Wang, Yin, Liu, & Xuan, 2017). The results reported by Omene et al. are very interesting and demonstrate the contribution of CAPE to restoring the $CD8^+$ TIL infiltration of fast-growing postirradiation primary tumors. In addition, CAPE-fed mice exhibited decreased TGF-β, COX-2, PD-$L1^+$ cell and $CD11b^+GR1^+$ myeloid cell levels (Omene et al., 2020).

Hypoxic conditions in the tumor microenvironment increase hypoxia-inducible factor (HIF)-1α expression and induce tumor cell proliferation. Vanillic acid (30 μM) limits HIF-1α expression in colon cancer, hepatic cancer and human lung carcinoma cells grown in hypoxic conditions (J. Gong, Zhou, & Yang, 2019). A new compound isolated uniquely from Brazilian green propolis, 3,5-diprenyl-4-hydroxycinnamic acid (artepillin C), is responsible for the immunomodulatory effects of propolis on activated T cells and for the inhibition of HIF-1α protein and VEGF-A expression (300 ng/chorioallantoic membrane assay) (G. C. Chan, Cheung, & Sze, 2013; Hattori et al., 2011). Cinnamic acid and cinnamaldehyde, which are from *Cinnamomum japonicum* Sieb., were shown to induce decreases in PGE2, anti-inflammatory cytokine and nitrite production after LPS stimulation in human CRC cells cocultured with murine macrophages (M. S. Kim & Kim, 2019).

The gallotannin-rich standardized fraction (P2Et) from *Caesalpinia spinosa* contains a high proportion of galloylquinic acid derivatives and pentagalloylglucose and a lower proportion of GA derivatives (gallates). P2Et has been shown to diminish the host inflammatory response in tumor-bearing mice and reduce blood leukocyte counts and the serum levels of the cancer-promoting cytokines MCP-1 and IL-6 (Urueña et al., 2013).

Rosmarinic acid (α-*O*-caffeoyl-3,4-dihydroxyphenyl lactic acid) was found to decrease the expression of anti-inflammatory cytokines and VEGF in murine hepatocarcinoma tumor tissues. In parallel, the IL-2 and IFN-γ levels, the percentage of circulating $CD8^+$ T lymphocytes and the ratio $CD4^+/CD8^+$ cells in murine hepatic carcinoma tumors were increased (Cao et al., 2016; W. Cao, Mo, et al., 2019a). When combined with all-*trans* retinoic acid (ATRA), rosmarinic acid induces markers of myeloid differentiation in human acute promyelocytic leukemia cells and increases the expression of CCR-1, CCR-2 and intercellular adhesion molecule (ICAM)-1. Increased expression of CD11b can also be detected on bone marrow cells from acute promyelocytic leukemia patients but not those from healthy donors (Heo et al., 2015).

All these studies indicate that phenolic acids constitute a rich class of molecules with pleiotropic properties within the tumor microenvironment that are mainly aimed at strengthening the immune response against the tumor (Figs. 2, 3 and Tables 2, 3).

3.7.1.5. Stilbenes. Stilbenes are phytoalexins (C_6-C_2-C_6 structure) formed by two aromatic rings linked by an ethylene bridge. They are mainly produced in plants in response to UV radiation and injury, pathogen attack or mechanical stress. Red grapes and red wine are the principal dietary sources of stilbenes, but these molecules are also produced by other edible plants (hops, peanuts, pines, plums, legumes, and herbs), berries (blackberries, blackcurrants, blueberries, and mulberries), Itadori tea, soy and the roots of Japanese knotweed (*Polygonum cuspidatum*). Absorption proceeds through diffusion or facilitated transport, and compounds are metabolized in the liver. The following molecules are part of this class: resveratrol (RES, 3,4′,5-trihydroxystilbene, present as *cis* and *trans* isomers), piceatannol (PIC), pinosylvin, pterostilbene, astringin and rhapontin. RES is principal among these compounds and is characterized by antioxidant, anti-inflammatory, antiaging and anticancer properties despite its limited bioavailability. For this reason, chemists have been encouraged to synthesize derivatives and analogs with an improved pharmacokinetic/pharmacodynamic profile (Ahmadi & Ebrahimzadeh, 2020; Chong et al., 2009; Fantini et al., 2015; Vervandier-Fasseur & Latruffe, 2019).

Warburton et al. examined the effect induced by gene expression changes associated with functional food consumption. Among other genes, RES increased the expression of those related to the immune response, DC maturation and phagosome formation and was relevant to inflammation and tumorigenesis. A strong upregulation of genes with protumorigenic action was found, in disagreement with evidence commonly reporting the contribution of RES to tumor death through apoptosis induction (Warburton, Vasieva, Quinn, Stewart, & Quinn, 2018).

Migrating cancer cells are protected from NK cell cytotoxicity by platelet aggregation. RES not only inhibits nonreversible platelet aggregation *in vitro* but also increases the cytotoxicity of NK cells against chronic myeloid leukemia cells used as target cells (Toliopoulos et al., 2013). When a low dose of RES was employed to treat renal carcinoma-bearing mice, IFN-γ release in the tumor microenvironment and the density of tumor-infiltrating $perforin^+/granzyme\text{-}B^+$ $CD8^+$ T cells increased. The percentage of Tregs and angiogenesis were instead decreased in the studied tumors (L. Chen et al., 2015). Similarly, a low dose of RES was found to block the generation of a unique subset of regulatory B cells, defined as tumor-evoked regulatory B cells (tBregs), involved in breast cancer metastasis. These cells produced TGF-β, which promoted the conversion of non-Treg $CD4^+$ T cells into metastasis-promoting $Foxp3^+$ Tregs. RES-induced loss of tBregs eliminated the suppression of effector immune cells, thus counteracting the invasiveness of tumor cells in a mouse model of breast cancer (Lee-Chang et al., 2013). RES treatment induces immunogenic cell death through increased calreticulin expression, high mobility group box 1 secretion and ATP release in ovarian cancer cells of either human or murine origin. Immunogenic cell death increases the frequencies of both mature DCs and $CD8^+$ T cells and modulates cytokines, greatly decreasing TGF-β levels while increasing IL-12p70 and IFN-γ levels, in the tumor microenvironment of mouse ovarian carcinoma cells (Y. Zhang, Yang, et al., 2019b). Hypoxia-induced production of ROS in pancreatic cancer cells is reduced by RES treatment, and hypoxia-induced HIF-1α expression and migratory and invasive capacities are also reduced (W. Li, Cao, Chen, Lei, & Ma, 2016). The generation of an inflammatory tumor microenvironment after chemotherapeutic treatment (5FU, 1 nM) was found to increase the malignant potential of drug-resistant CRC cells, which was reversed by RES treatment (5 μM) (Buhrmann et al., 2018). Similarly, the CAF-induced migratory and invasive capacities of breast cancer cells were shown to be inhibited by RES treatment (10, 25, 50 μM) (Suh, Kim, & Surh, 2018). RES (10-50 μM) interferes with epithelial-stromal crosstalk, inducing HGF and VEGF secretion through activation of the transient receptor potential ankyrin 1 channel in CAFs (Vancauwenberghe et al., 2017). Menicacci et al. showed that RES modulated the protumor microenvironment originating from senescent fibroblast-secreted factors ("senescence-associated secretory phenotype", SASP). Chemokine, proinflammatory interleukin, protease and corresponding receptor levels were reduced in the fetal lung fibroblast-derived cell line MRC5 by chronic treatment with RES (5 μM) *in vitro* (Menicacci et al., 2017).

TAMs have stimulatory roles in tumor growth and metastasis, especially when induced by T_H2 cytokines to polarize towards the M2 phenotype. The inflammatory profile of LPS-stimulated murine RAW264.7 macrophages was modified by RES treatment, which reduced the production of NO and secretion of PGE2 and proinflammatory cytokines. A similar effect was exerted on the human monocytic leukemia cell line THP1 and peripheral blood lymphocytes. In addition, RES increased the expression of proinflammatory molecules in HUVECs (Schwager et al., 2017). Hydroxystilbene derivatives (2,3-, 3,4-, and 4,4'-dihydroxystilbene), when incubated with human M2 macrophages, demonstrated the ability to inhibit the production of MCP-1 and IL-10, while TGF-β production was further enhanced by the tested

compounds. All derivatives analyzed also showed antiangiogenic effects on human lymphatic endothelial cells (Kimura et al., 2016).

The synthetic RES analog HS-1793 decreases IL-2 and increases IL-4 secretion by Con-A-stimulated lymphocytes from tumor-bearing mice without modifying the $CD4^+$ T cell population (Y. J. Choi et al., 2012), but it reduces Tregs levels and TGF-β production and conversely increases IFN-γ-producing $CD8^+$ T cell numbers (M. H. Jeong et al., 2012). In the murine mammary carcinoma model FM3A, both the number of IFN-γ secreting cells and the amount of cytokines released were modulated by HS-1793 treatment. As a consequence, the number and distribution of IL-10 and TGF-β-producing $CD206^+$ M2 macrophages were reduced to the advantage of classically activated M1 macrophages producing immunostimulatory cytokines (S. K. Jeong, Yang, et al., 2014a).

PIC (5, 20, 50 μM) is another stilbene that has been found to modulate the tumor microenvironment. In fact, it was shown to modify PD-L1 expression on a panel of breast and CRC cell lines, similar to RES (5, 20, 50 μM) (Lucas, Hsieh, Halicka, Darzynkiewicz, & Wu, 2018). Authors have defined this mechanism as a "search, enhance, and engage" (SEE) signal that is useful to sensitize and increase the immunogenicity of tumors that, because of low PD-L1 expression, behave as "cold, nonresponsive" tumors (T. C. Hsieh & Wu, 2019). Topically application of PIC to the dorsal skin of hairless mice before TPA treatment was shown to reduce the expression of COX-2 and iNOS linked to inflammation-associated carcinogenesis (L. Liu et al., 2014). On the other hand, PIC administered daily to tumor-bearing BALB/c mice reduced macrophage infiltration into tumor tissues and MMP-9 expression in both tumor tissue and lung tissue, therefore reducing the migratory capacity of tumor cells but increasing TIMP-2 expression in the lungs. The levels of markers of lymphangiogenesis and angiogenesis were decreased, as were the MVD and VE-cadherin expression on endothelial cells. Moreover, PIC (5, 10, 20 μM) downregulated the expression of several cytokines (H. Song et al., 2015).

Overall, RES, the main constituent of the stilbene class of compounds, is a molecule characterized by a multitude of effects on the tumor microenvironment, which are dependent on the cells, time, dose, and conditions used for study. RES contributes to the development of an antitumor immune response but also the cell migration and angiogenesis of cancer cells (Fig. 2–4 and Tables 2–4).

3.7.2. Flavonoids

Flavonoids are a large group of polyphenolic compounds and secondary metabolites of plants that are responsible for the color and flavor of fruits, flowers and vegetables and also have roles in plant defense against pathogens and signaling. Flavonoids are formed through a biosynthetic process that synthesizes flavonoids from phenylalanine and involves the shikimic acid and acylpolymalonate pathways. Flavonoids are present in edible fruits, vegetables, herbs, spices, legumes, nuts, and plant-derived beverages, such as tea and wine. Flavonoids are classified into different classes: flavonols, flavones, flavan-3-ols, anthocyanins, flavanones and isoflavones are the most important, while dihydroflavonols, flavan-3,4-diols, chalcones, dihydrochalcones and aurones represent minor classes. Classification is based on flavonoid structure, which consists of three aromatic rings named A, B, and C. The classes differ from each other based on the functional groups, the level of oxidation in the C-ring, or the connections between the B-ring and C-ring (Marzocchella et al., 2011).

Flavonoids are able to modulate innate and adaptive immune responses within the tumor microenvironment (Grivennikov, Greten, & Karin, 2010). In particular, these compounds inhibit the production of proinflammatory cytokines and chemokines (Grivennikov et al., 2010). They also can enhance the antitumor response and inhibit tumor progression (Fantini et al., 2015; Ghiringhelli, Rebe, Hichami, & Delmas, 2012). Evidence from epidemiological studies demonstrated the association between flavonoids, lignan intake and decreased cancer risk and mortality, as well as improved survival (Grosso et al., 2017; Micek et al., 2020) (Figs. 2–4 and Tables 2–4).

3.7.2.1. Flavonols. Flavonols are the most common class of flavonoids and are present mainly in fruits, plants, wine, and tea. The most abundant flavonol in plant-derived foods is quercetin, and other members of this class are kaempferol and myricetin (Marzocchella et al., 2011).

Different flavonols have been demonstrated to increase the activity of NK cells and phagocytic activity of macrophages *in vitro* and *in vivo* in leukemia (J. P. Lin et al., 2009; Lindqvist et al., 2014; C. S. Yu et al., 2010). A similar effect was demonstrated for kaempferol-3,7-bisrhamnoside (kaempferitrin) (Alonso-Castro et al., 2012). The induction of NK cell-activating ligands in tumor cells could be a way to enhance the recognition of tumor cells by NK cells. In this regard, quercetin is able to induce NKG2D ligands in tumor cells, and in this way, it could increase the susceptibility of tumor cells to NK cell-mediated cytotoxicity in studies of a human chronic myelogenous leukemia cell line and a human stomach adenocarcinoma cell line (Bae et al., 2010).

Several studies have demonstrated the capacity of flavonol members to modulate the expression of cytokines. GM-CSF activates the host immune system by enhancing the activation of antigen-presenting DCs and thus provides a strategy to develop antitumor immune responses. Quercetin and kaempferol increase GM-CSF release by human prostate cancer cells and enhance the chemotaxis of DCs (Bandyopadhyay et al., 2008). Extracts of water dropwort (*Oenanthe javanica*) and its active compounds, isorhamnetin (3-methylquercetin) and hyperoside (quercetin-3-*O*-galactoside), were shown to inhibit proinflammatory cytokine secretion by LPS-primed bone marrow-derived macrophages. Inflammasome activation is linked to chronic inflammation associated with various cancers (gastric, hepatic, and CRC). Thus, the inhibition of these complexes by flavonoids could be useful in these types of tumors (Ahn & Lee, 2017). Furthermore, quercetin and its glycoside quercitrin were found to alter tumor-associated inflammation by reducing macrophage infiltration into the intestinal villi in a mouse model of intestinal carcinogenesis (Murphy et al., 2011) and by reducing macrophage numbers and the associated inflammation in a rat model of inflammatory bowel disease (Camuesco et al., 2004). Quercetin could also be useful for the treatment of glioblastoma, which is promoted by an inflammatory microenvironment. The proinflammatory cytokine IL-6 and related downstream signaling pathways can be inhibited by quercetin in glioblastoma cells (Michaud-Levesque, Bousquet-Gagnon, & Béliveau, 2012).

The oxidative state and hypersecretion of ILs and cytokines in the tumor microenvironment are also implicated in the drug and radiation resistance of cancer cells. A novel nanohydrogel of hyaluronic acid loaded with quercetin was found to increase the anticancer efficacy of temozolomide in glioblastoma multiforme cells by reducing ROS, IL-8, IL-6 and VEGF production under proinflammatory conditions, which contributed to cell drug resistance (Barbarisi et al., 2018). Lipid-calcium nanoparticles (NPs) loaded with quercetin phosphate (LCP-QP) could remodel the tumor microenvironment in a stroma-rich bladder carcinoma model by downregulating Wnt16 expression in activated fibroblasts to enhance the antitumor effect of cisplatin NPs (LCP-QP i.v. injected to mice at a QP dose of 5.5 mg/kg, 5 injections daily, for 10 days) (K. Hu et al., 2017). The enhancement of the anticancer efficacy of DOX by quercetin was also previously demonstrated in breast cancer-bearing mice. Indeed, the combination of dietary quercetin, given as a food supplement, and intratumoral DOX injection increased mouse tumor-free survival by promoting lymphocyte proliferation, T_H1 rather than T_H2 cell proliferation and persistent T cell tumor-specific responses in mice (Du et al., 2010).

3.7.2.2. Flavones. Flavones are a class of flavonoids mainly found as 7-*O*-glycosides, and their bioavailability is very low because of their low solubility. The main flavones are apigenin, which is abundant in parsley,

onion, celery, garlic, pepper, and chamomile, and luteolin, which is found mainly in bird chili, onion leaves and celery. Less abundant flavones in foods include baicalein, wogonin, tangeretin, nobiletin and chrysin (Marzocchella et al., 2011).

Several studies have demonstrated the roles of flavones as immunomodulatory agents because they alter the expression and secretion of inflammatory cytokines within tumors. Apigenin (5,7,4′-trihydroxyflavone) induces a shift towards a T_H1 immune response in glioblastoma (Coelho et al., 2016). In addition, apigenin and baicalein (5-50 μM) inhibit the growth and invasive properties of breast cancer cells by suppressing IL-6 expression (H. H. Lee et al., 2019; Terabayashi et al., 2018). The major constituents of *Scutellaria baicalensis,* baicalin, baicalein and wogonin, were shown to inhibit cancer-associated inflammation *in vitro* by decreasing the levels of proinflammatory cytokines and MMPs (W. Y. Gong et al., 2014). Wogonin (5,7-dihydroxy-8-methoxyflavone; 15, 30 and 60 μM) also inhibits the invasion of breast cancer cells by decreasing MMPs expression and activities (P. Chen et al., 2011a) and suppresses the migration of human alveolar adenocarcinoma cells in an inflamed microenvironment. Wogonin inhibits the *in vitro* (5, 10 and 20 μM) and *in vivo* (30 and 60 mg/kg/2d, i.v., for 3 weeks) induction of EMT induced by IL-6 (Y. Zhao et al., 2015b). The main *in vivo* metabolite of wogonin, wogonoside (50, 100 and 150 μM), was also demonstrated to inhibit TNF-α-induced invasion and migration in breast cancer tumor cells by blocking the EMT process (Yao et al., 2017). The inhibition of NF-κB activation by wogonoside was also reported in colon cancer cells and in DSS-initiated and dextran sulfate sodium-induced colitis-associated tumorigenesis. This flavone inhibited neutrophil and macrophage infiltration into tumor tissues and decreased the expression and secretion of proinflammatory cytokines (Y. Sun et al., 2016). MMP-2 and MMP-9 are also modulated by other flavones. Scutellarin (5, 10 or 20 mg/kg/day, p.o., for 3 weeks, starting 7 days after injection of cells) was found to inhibit the growth and invasion of xenograft human tongue squamous carcinoma cells in nude mice (H. Li et al., 2013a). Similarly, it was found that tangeretin-zinc oxide quantum dots (Tan-ZnO QDs; 20, 30 μM) downregulate MMP-2, MMP-9 and VEGF expression in the metastatic H358 lung cancer cell line (Roshini et al., 2018).

Apigenin, baicalein and baicalin also have the potential to enhance T cell-mediated immune responses against breast cancer and hepatocellular carcinoma cells. Apigenin and its major metabolite luteolin inhibit IFN-γ-induced STAT1 phosphorylation, which prevents inducible PD-L1 upregulation in breast cancer cells (Coombs et al., 2016). Similarly, baicalein and baicalin were found to promote T cell immunity against hepatocellular carcinoma cells by inhibiting IFN-γ-induced PD-L1 expression. The same study also reported the *in vivo* stimulation of antitumor T cell responses by the two flavones, as shown by the increase in $CD8^+$ T cell numbers and downregulation of PD-L1 expression in hepatocellular carcinoma cells (Ke et al., 2019). Xu et al. also reported that apigenin and the polyphenol CUR enhanced the sensitivity of tumor cells to T cell-mediated cell killing by inhibiting IFN-γ-induced PD-L1 expression in human melanoma cells. Moreover, these findings were confirmed *in vivo* with a melanoma xenograft mouse model, which showed inhibition of tumor growth, a reduction in PD-L1 expression on tumor cells and DCs, and increases in $CD4^+$ and $CD8^+$ T cell numbers in the tumor upon treatment (L. Xu et al., 2018). Nelson et al. reported another mechanism of action for apigenin in modulating T cell responses in pancreatic cancer. Apigenin increased $CD4^+$ and $CD8^+$ T cell percentages and decreased Tregs numbers in tumor-bearing mice and improved mouse survival (Nelson et al., 2017). A decrease in splenic Tregs, along with a decrease in the level of IL-4 and an increase in that of IFN-γ, was also observed in spontaneous mouse breast cancer mammary tumor-bearing mice treated with salvigenin purified from *Tanacetum canescens*, demonstrating the stimulation of T_H1 antitumor immunity (Noori et al., 2013). Similarly, *Scutellaria ocmulgee* leaf extract, which contains wogonin, inhibits TGF-β1-induced Tregs activity in rats bearing F98 malignant gliomas, thus suggesting a new immunotherapeutic strategy to inhibit tumor-mediated immune suppression in this cancer (Dandawate et al., 2012). Furthermore, apigenin, luteolin, chrysin (5,7-dihydroxyflavone) and hesperetin were found to increase the activity of NK cells and CTLs derived from mouse and rat spleens (Kilani-Jaziri et al., 2016; Sassi et al., 2017), and chrysin inhibited B16F10 melanoma cell growth *in vivo* by increasing the cytotoxic activity of NK cells, CTLs and macrophages (Sassi et al., 2018). Choi et al. demonstrated that luteolin was also able to inhibit the tumor-supporting M2 phenotype of TAMs and the IL-4-stimulated migration of THP-1 monocytes and Lewis lung carcinoma cells through suppression of IL-4-stimulated CCL-2 expression (H. J. Choi et al., 2016).

3.7.2.3. Flavan-3-ols. The flavan-3-ol class includes a wide range of compounds with one hydroxyl group in the 3-position of the C-ring. The flavan-3-ols can be divided into monomers and polymers (monomers bind to each other to form proanthocyanidins). The simplest monomer is (−)-epicatechin; the hydroxylation of this monomer produces (+)-gallocatechin and (−)-epigallocatechin, while esterification of the 3-position of the C-ring with GA transforms monomers into (−)-epicatechin-3-*O*-gallate (ECG) and (−)-epigallocatechin-3-*O*-gallate (EGCG). Flavan-3-ols are mainly present in fruits (e.g., apple, blackcurrant, blueberry, and grape seed), cereals, nuts, wine and tea (Marzocchella et al., 2011).

Numerous studies have investigated the modulatory effects of flavan-3-ols, in particular EGCG, the major polyphenol component found in green tea, on immune responses in tumors.

Prostate tumors can be promoted by inflammation. It has been reported that EGCG may provide protection against inflammation in this type of cancer. Indeed, prostate cancer cells pretreated with EGCG show suppression of proinflammatory cytokines and chemokines, MMP-9 and MMP-2 activities and cell migration (Mukherjee et al., 2014).

The anti-inflammatory and antioxidant roles of EGCG and green tea are also important in the prevention of UV-induced skin carcinogenesis. An *in vitro* study showed that EGCG was able to attenuate the UV-induced activation of NF-κB and the proinflammatory pathway, particularly IL-6 secretion, in human keratinocytes (Xia et al., 2005). Topical application of EGCG to C3H/HeN mouse skin before UV exposure was able to inhibit the UVB-induced increase in IL-10 expression and enhance IL-12 production in the skin and draining lymph nodes. In addition, EGCG reduced the number of infiltrating $CD11b^+$ monocytes/macrophages and neutrophils, which are considered to be responsible for creating the UV-induced immunosuppressive state (Katiyar et al., 1999). Furthermore, it was reported that EGCG protects the skin against the oxidative stress induced by UV exposure by reducing UVB-induced NO and H_2HO_2 production and decreasing leukocyte infiltration, which plays a role in ROS production (Katiyar, 2003). Zhu et al. demonstrated the antiangiogenic activity of EGCG (5-50 μM) in gastric cancer cells, as shown by the inhibition of IL-6-induced VEGF expression and angiogenesis (B. H. Zhu et al., 2011). EGCG was also found to modulate IL-1, as demonstrated by the downregulation of IL-1RI expression and inhibition of IL-1-induced tumorigenic factors in human pancreatic adenocarcinoma cells. EGCG affected cell viability and inhibited IL-1-induced IL-6 and VEGF secretion and the release of MMP-2 (Hoffmann et al., 2011). Monobe et al. demonstrated that pyrogallol-type green tea polyphenols [EGCG, epigallocatechin (EGC), and ECG] enhanced the phagocytic activity of human acute promyelocytic cells (Monobe et al., 2010).

MMPs have a key role in the tumor microenvironment because tumor cells need to break down the ECM to invade other tissues. Several studies have reported that EGCG is able to modulate MMPs expression. Roomi et al. demonstrated the efficacies of EGCG, green tea extract (GTE), and a nutrient mixture (composed of lysine, proline, ascorbic acid and green tea extract) in inhibiting MMP-2 and MMP-9 expression in four different cancer cell lines, at doses of 50-500 μg/ml (Roomi, Monterrey, Kalinovsky, Rath, & Niedzwiecki, 2010). Vayalil et al.

reported the same findings in human prostate carcinoma cells by EGCG (5-40 μM) (Vayalil & Katiyar, 2004). Similarly, another study demonstrated that the combination of EGCG (5-20 μM) and GA (30-120 μM) inhibited MMP-2 and MMP-9 activity in DOX-resistant breast cancer cells (Nowakowska & Tarasiuk, 2016). The inhibition of MMPs expression and secretion by EGCG (10-60 μM) was also demonstrated in oral squamous cell carcinoma cells (P. N. Chen et al., 2011b; Chiang, Wong, Lin, Chang, & Liu, 2006; Ho, Yang, Peng, Chou, & Chang, 2007; Kato et al., 2008; Koh et al., 2011).

EGCG and GTE have been reported to modulate the expression of the immune checkpoint molecule PD-L1 induced by IFN-γ and EGF in lung cancer cells *in vitro*. In addition, A/J mice bearing 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)-induced lung tumors treated with GTE in drinking water showed reduced tumor volumes and reduced PD-L1 expression in tumors. Finally, coculture experiments using F10-OVA melanoma cells and tumor-specific $CD3^+$ T cells demonstrated that EGCG decreased PD-L1 mRNA expression in these cells and restored IL-2 mRNA expression in tumor-specific $CD3^+$ T cells (Rawangkan et al., 2018).

EGCG reverses the IDO-mediated suppression of T cell responses in tumors by suppressing STAT1 activation and COX-2/PGE2 pathway activity in murine bone marrow-derived DCs (Y. I. Jeong et al., 2007). Similarly, EGCG inhibits the expression and activity of IDO in human oral cancer cell lines and human CRC cells (C. W. Cheng et al., 2010; Ogawa et al., 2012).

Several studies have demonstrated that EGCG can modulate the tumor immune microenvironment in animal models (D. S. Hsieh et al., 2011; A. C. Huang, Cheng, et al., 2013a; J. Y. Jang et al., 2013; Kang et al., 2007; Santilli et al., 2013; C. K. Song et al., 2007; Sriram et al., 2009). Two studies reported that EGCG increased the antitumor responses induced by vaccination in C57BL/6 mice bearing E7-expressing tumors through enhancement of $CD8^+$ and $CD4^+$ T cell-mediated immune responses specific for the E7 oncoprotein (Kang et al., 2007; C. K. Song et al., 2007). Similarly, Zhang et al. demonstrated that procyanidin, which was employed as a tumor cell vaccine adjuvant in melanoma, inhibited tumor growth and increased mouse survival by enhancing APCs activation and $CD8^+$ T cell-mediated immune responses (L. Zhang et al., 2017). Hsieh et al. also reported that EGCG, when adsorbed onto the surface of nanogold particles, enhanced NK cell cytotoxicity in a mouse bladder cancer model (D. S. Hsieh et al., 2011). The anti-inflammatory effects of EGCG have also been demonstrated in bleomycin-induced rat pulmonary fibrosis, as shown by reductions in ROS, lipid peroxidation, and hydroxyproline levels and myeloperoxidase activity, by increases in the activities of Phase II enzymes and by reductions in TNF-α and IL-1β secretion (Sriram et al., 2009). The oral administration of EGCG to mice intraperitoneally injected with mouse leukemia cells was found to increase the percentages of $CD3^+$ T cells, $CD19^+$ B cells, and macrophages and promote macrophage phagocytosis, NK cell activities and T and B cell proliferation (A. C. Huang, Cheng, et al., 2013a). Jang et al. also demonstrated that EGCG suppressed tumor growth in a murine breast cancer model and inhibited TAMs infiltration and polarization into tumor-promoting M2 macrophages and M1 macrophage-associated TNF-α upregulation in tumors (J. Y. Jang et al., 2013). The immunomodulatory activities of polyphenols from pinecones of *Pinus koraiensis* (PPP-40), catechin-based flavonoids and phenolic acids were previously evaluated in spleen tissues from tumor-bearing S180 mice. PPP-40 inhibited tumor growth and ameliorated tumor-induced immunosuppression by increasing the percentages of splenic $CD4^+$ and $CD8^+$ T cells and the production of T cell-related cytokines. In addition, PPP-40 improved the levels of antioxidant enzymes (Yi et al., 2017). Polyphenon E is a green tea catechin formulation that contains 53% EGCG, 9% epicatechin, 11% (−)-EGC, 5% ECG, and 5% (−)-gallocatechin gallate. By employing transgenic TH-MYCN mice and two xenograft models (SHSY5Y tumor-bearing NOD/SCID mice and neuro 2A tumor-bearing A/J mice), Santilli et al. demonstrated that polyphenon E inhibited neuroblastoma tumor growth only in the context of a functioning immune system through an increase in tumor-infiltrating $CD8^+$ T cell numbers and the inhibition of the immunosuppressive activities of MDSCs and Tregs in tumors (Santilli et al., 2013).

3.7.2.4. Anthocyanins. Anthocyanins are a class of more than 550 water-soluble pigments, which are widespread throughout the Plantae kingdom. The most abundant anthocyanins in plants are cyanidin, pelargonidin, delphinidin, peonidin, petunidin and malvidin. The main food sources of anthocyanins are fruits (e.g., bilberry, blackberry, blueberry, and cherry), vegetables (e.g., red cabbage, and purple corn) and red wine. These compounds can occur as aglycones (anthocyanidin) or heterosides (anthocyanin), which are mainly present in nature and consist of the aglycone form with several sugars linked to the C-ring (glucose, galactose, arabinose, rhamnose, and xylose). Although the mean dietary intake of anthocyanins is higher than that of other flavonoid classes, these flavonoids are poorly absorbed in the human body so their bioavailability is very low (Marzocchella et al., 2011). Several studies have demonstrated the ability of anthocyanins to modulate the immune system, particularly inflammatory cytokines. For example, Limtrakul et al. demonstrated the anti-inflammatory effects of the polar fraction of black rice whole-grain extracts, which contain high levels of anthocyanins and other phenolic acid compounds (hydroxybenzoic acid and the hydrocinnamic acid derivatives vanillic acid, protocatechuic acid, coumaric acid, ferulic acid, and chlorogenic acid), with inhibition of LPS-induced proinflammatory mediators and proinflammatory cytokine secretion seen in RAW264.7 macrophages. In addition, the authors showed that black rice extracts inhibited inflammation induced by LPS (Limtrakul et al., 2015). The anthocyanins extracted from *Lonicera caerulea* 'Beilei' fruit (cyanidin-3,5-diglucoside, cyanidin-3-glucoside, cyanidin-3-rutinoside and peonidin-3-glucoside) possess immunoregulatory activity. They were shown to inhibit tumor growth and increase the survival of hepatoma cell-bearing mice by enhancing the activities of antioxidant enzymes and regulating the levels of immune cytokines, including IL-2, IFN-γ and TNF-α (L. Zhou et al., 2018). A preclinical animal model of colon carcinogenesis was employed by Shi et al. to investigate the anti-inflammatory effects of dietary lyophilized (freeze-dried) strawberries (*Fragaria x ananassa*). The phytochemicals contained in the strawberries were anthocyanins, ellagitannin/ellagic acid/ellagic acid derivatives and flavonols. Strawberries reduced the expression of proinflammatory mediators in a mouse colon cancer model (Shi et al., 2015). Anthocyanins derived from black raspberries were able to positively modulate cytokines and innate immune cell responses in an *in vivo* rat esophageal cancer model. In addition, they increased NK cells and $CD8^+$ T cell numbers and decreased the infiltration of macrophages and neutrophils into the esophagus of rats (Peiffer et al., 2016). Conversely, a recent study reported that delphinidin chloride and its hydrolytic metabolite GA were able to promote the differentiation of naive T cells into Tregs with immunosuppressive ability in an allograft animal model (Hyun et al., 2019).

Other studies have evaluated the effects of anthocyanin-rich extracts on immune checkpoints. It has been demonstrated that delphinidin-3-*O*-glucoside (D3G) and its metabolites (delphinidin chloride and GA) inhibit the activation of T cells in the tumor microenvironment by reducing the binding of PD-L1 to PD-1 (Mazewski et al., 2019). Similarly, it was reported that orally administered bilberry anthocyanin extracts (156 μg anthocyanins/mouse/day, p.o., for 20 days, starting 7 days after injection of cells) improve the antitumor efficiency of an anti-PD-L1 antibody *in vivo* by modulating the gut microbiota in colon adenocarcinomas (L. Wang et al., 2020b).

3.7.2.5. Flavanones. Several studies have demonstrated the modulation of the tumor immune microenvironment by flavanones. Flavanones are polyphenols present mainly in citrus fruits, such as aglycones (e.g., naringenin and hesperetin), monoglycosides, and

diglycosides (neohesperidosides: neohesperidin and naringin; rutinosides: hesperidin and narirutin). Aglycones are better absorbed in the body than glycosides (Marzocchella et al., 2011).

Naringenin has been demonstrated to modulate the tumor immune microenvironment in syngeneic mouse models of melanoma and lung carcinoma. Naringenin combined with asiatic acid (a triterpene from *Centella asiatica*) was shown to inhibit tumor progression by promoting NK cell-mediated cytotoxicity against tumor cells in the tumor microenvironment and enhancing T cell immunity against cancer, as shown by increases in both $CD4^+$ and $CD8^+$ T cell numbers and a decrease in the $CD4^+Foxp3^+$ Tregs number (Lian et al., 2018). Naringenin (50 mg/kg/day, p.o., for 4 weeks, starting 10 days after injection of cells, concurrently with the first DOX dose) has also been studied for its antioxidant properties in ameliorating DOX-induced cytotoxicity in a Dalton's lymphoma ascites tumor-bearing mouse model by preventing alterations in antioxidant enzymes (SOD, GPx, and CAT) (Kathiresan et al., 2016).

Another flavanone, hesperetin, is able to activate APCs by upregulating costimulatory marker (CD80/CD86) and MHC I molecule expression; this flavanone can also stimulate the secretion of IL-6 in DC2.4 and RAW264.7 cells. In addition, hesperetin, used as a melanoma vaccine adjuvant, suppressed tumor growth, activated APCs, enhanced CTL and $CD4^+$ T cell-mediated responses and inactivated Tregs activity *in vivo*. Hence, in this model, hesperetin induced the secretion of IL-6, which plays a role in the mobilization of antitumor T cell responses against the tumor (S. Jiang et al., 2020). Indeed, IL-6 has two roles in the tumor microenvironment as IL-6 can also act as a growth factor for tumor cells to support cancer cell proliferation, angiogenesis and metastasis (Fisher, Appenheimer, & Evans, 2014). In this respect, Berghe et al. reported that kurarinone, a lavandulyl flavanone isolated from *Sophora flavescens* Ait. roots, inhibited breast cancer cell growth by blocking NF-κB-driven IL-6 expression (Berghe et al., 2011).

A study explored the actions of natural compounds in regulating macrophage activation by assessing the $CD169^+$ phenotype in macrophages, because it has been reported that increased expression of CD169 on lymph node sinus macrophages is associated with the induction of antitumor immunity. It was found that naringin, aculeatiside A, and onionin A enhanced CD169 expression in both human and murine peritoneal macrophages and that naringin and aculeatiside A induced an antitumor M1 phenotype in murine macrophages in regional lymph nodes *in vitro* and *in vivo* (Fujiwara et al., 2018).

3.7.2.6. Isoflavones. Isoflavones possess a chemical structure similar to the estrogen structure and hence are classified as phytoestrogens and exert pseudohormonal activity. The main members of this class are genistein and daidzein, and they are mainly found in soybean products and leguminous plants. Isoflavones are highly absorbed and have the best bioavailability among flavonoids, and they can occur as aglycones (genistein and daidzein) or glycosides (genistin and daidzin) (Marzocchella et al., 2011).

Several lines of evidence have demonstrated that isoflavones can modulate the immune system and inhibit carcinogenesis. Genistein was found to reduce tumor size in rats bearing a highly metastatic rat prostate cancer cell line by decreasing the number of TAMs and inhibiting TNF-α and granulocyte monocyte-colony stimulating factor (Joseph & Isaacs, 1998). Phenoxodiol is a synthetic analog of the plant isoflavone genistein with improved anticancer efficacy. Low-dose of phenoxodiol could reduce tumor growth and improve mouse survival in a colon cancer model by stimulating both NK cell and tumor-specific T cell lytic activity (Georgaki et al., 2009). Similarly, oral administration of genistein was found to counteract the growth of mouse melanoma B16F10 tumor cells or carcinogenesis induced by DMBA in mice through increases in NK cells and CTL activities and IFN-γ secretion and through a decrease in Tregs numbers (T. L. Guo, Chi, et al., 2007a; T. L. Guo et al., 2001).

Conversely, other studies have shown contradictory results. Indeed, Jiang et al. reported that a very low concentration of genistein inhibited the lytic activity of NK cells against breast cancer cells (X. Jiang et al., 2008), and it exerted immunosuppressive activity because it reduced the LPS-induced IL-12 secretion of human monocyte-derived DCs (J. Wei et al., 2012) and BMDCs (Pfarr et al., 2015).

It has been reported that isoflavones have anti-inflammatory properties and hence can exert cancer-preventing activity. Inflammation present in the tumor microenvironment plays a critical role in the initiation and development of colon cancer (Di Caro, Marchesi, Laghi, & Grizzi, 2013). Genistein was able to decrease proinflammatory IL-6 cytokine secretion and inhibit IFN-γ-induced STAT1 and IL-6-induced STAT3 nuclear translocation in human intestinal Caco-2 cells (Paradkar, Blum, Berhow, Baumann, & Kuo, 2004). 3′-Chloro-5,7-dimethoxyisoflavone, a synthetic isoflavone derivative, inhibits TNF-α-induced CXCL10 expression, which is involved in tumor migration, invasion and metastasis in human colon cancer cells (Shin et al., 2011). Wang *et al.* reported the suppression of LPS-induced NF-κB by GEN-27, a novel synthetic derivative of genistein, in the same cancer cell line. In addition, GEN-27 inhibited the secretion of proinflammatory cytokines, which have a role in promoting the proliferation of colon cancer cells, in LPS-stimulated THP-1 cells (Y. Wang et al., 2016). The chemopreventive activity of genistein in inflammation-associated cancers was also demonstrated in ovarian cancer. Genistein blocked IL-8/STAT3 signaling and thus suppressed the M2 polarization of THP-1 macrophages cocultured with ovarian cancer stem-like cells (Ning et al., 2019).

Additionally, lipid mediators can stimulate tumorigenesis, and genistein (10 μM) is able to reduce the synthesis of prostaglandins, particularly PGE2, in human prostate cancer cells by decreasing COX-2 expression and activity (Swami et al., 2009).

The production of tumor-promoting proinflammatory cytokines in the tumor microenvironment promotes cancer cell growth, invasion, and metastasis through the activation of EMT in tumor cells. It has been reported that an *O*-methylated isoflavone, tectorigenin, inhibits the lung cancer cell-induced proinflammatory response of THP-1 monocytes by preventing the release of TNF-α and IL-6 from the monocytes in a coculture model and suppresses EMT in lung cancer cells (Amin et al., 2015). Another isoflavone, biochanin A (5,7-dihydroxy-4'-methoxy-isoflavone), also suppresses lung cancer cell migration by decreasing MMP-2 and VEGF levels *in vitro* (40 and 80 μM) and *in vivo* (0.125 mg/mouse, i.p., thrice a week, for 25 days after injection of cells) (Lai, Li, & Gao, 2018). Sehm et al. investigated the impact of dietary isoflavonoids (biochanin, SDG, and genistein) on glioma and found biochanin (50 μM) showed antiangiogenic properties by reducing the vessel density in the peritumoral areas (Sehm et al., 2014).

The isoflavone genistein inhibits human CRC cell invasion, migration and metastasis *in vitro* (10 μM) and *in vivo* (25 or 75 mg/kg/day, p.o., for 5 weeks, starting 3 days after orthotopic implantation of tumor cells) through the suppression of neoangiogenesis and downregulation of MMP-2 expression (X. Xiao et al., 2015). Liu et al. also confirmed the inhibition of angiogenesis by genistein in glioblastoma *in vitro* (0.1 mM) and *in vivo* (100 μg/mouse/day, peritumoral, starting when tumor volumes reached 150 mm^3), and the mechanism involved CHOP-mediated inhibition of C/EBPβ and reductions in VEGF and IL-6 expression (X. Liu et al., 2015b). The same effects of genistein on angiogenesis were also demonstrated in human prostate cancer cells (5-50 μM), with inhibition of basal and hypoxia-stimulated VEGF expression (Y. Guo, Wang, Hoot, & Clinton, 2007b). Genistein (15-50 μM) was also found to reduce the metastatic and invasive properties of prostate cancer cells by inhibiting the TGF-β-mediated increase in MMP-2 expression (X. Huang et al., 2005; L. Xu & Bergan, 2006) and reversing EMT (L. L. Zhang et al., 2008).

Overall, these studies suggest a role for flavonoids as immunomodulatory agents, able to modify the release of inflammatory cytokines

within the tumor. Accordingly, flavonoids affect the antitumor innate and adaptive immune responses (Figs. 2–4 and Tables 2–4).

3.7.3. Xanthones

Xanthones (9H-xanthen-9-one or dibenzo-γ-pirone) are compounds structurally related to flavonoids and are secondary metabolites of plants in particular families (Gentianaceae, Guttiferae, Moraceae, Clusiaceae, and Polygalaceae), fungi, and lichen. Some of the species that contain xanthones are *Garcinia, Gentiana, Gentianella, Hypericum, Polygala, Swertia, Aspergillus,* and *Penicillium*. When produced in fungi, xanthones are completely derived from acetate, while xanthones found in higher plants show oxygenation configurations that originate from a combination of the acetate and shikimate pathways (Chantarasriwong et al., 2010). These compounds are classified into six main groups: simple xanthones, xanthone glycosides, prenylated xanthones, xanthonolignoids, bisxanthones, and miscellaneous xanthones. Xanthones can also be synthetically generated. Xanthones possess anti-inflammatory, immunomodulatory, anticarcinogenic, antioxidant, cardioprotective and antiatherogenic activities and antimicrobial, antimalarial and antiparasitic properties. The principal compounds in the class are mangiferin, α/βmangostin, and DMXAA (El-Seedi et al., 2020; Negi et al., 2013; Pinto et al., 2005).

Mangiferin (1,3,6,7-tetrahydroxyxanthone-C_2-β-D-glucoside) is widely distributed in higher plants and has been isolated from *Cunscora decussatu* Schult (family Gentianaceae), *Swertia chirata* Buch. Ham (Gentianaceae) and *Mangifera indica* Linn. (Anacardiaceae). The first report of mangiferin immunomodulatory potential dates back to the late 1980s, when Chattoppadhyay et al. reported its effect involved in mediating the proliferation of murine thymocytes and splenocytes from tumor-free or tumor-bearing mice (Chattopadhyay et al., 1987). Since then, mangiferin has been demonstrated to be a useful compound for tumor microenvironment modification. It was reported that this compound (240 μM) inhibits the migration of murine melanoma cells and angiogenesis (Delgado-Hernández et al., 2020) and reduces migration and invasion (12.5, 25, 50 μM) by highly metastatic breast cancer cell lines (H. Li et al., 2013b). Similarly, mangiferin (400 μM) was found to suppress TNF-α-induced MMP-9 expression and nonmetastatic prostate carcinoma cell invasion and to downregulate TNF-α-induced NF-κB activity (Dilshara, Kang, Choi, & Kim, 2015). In LPS-stimulated monocyte-derived macrophages, mangiferin inhibits activation *in vitro,* decreasing proinflammatory cytokine levels and reducing the frequency of M1 macrophages after treatment (Z. Wei et al., 2016). Therefore, cumulative evidence shows that mangiferin inhibits tumor cell migration but reduces the M1 macrophage frequency.

5,6-Dimethylxanthenone-4-acetic acid (DMXAA), a simple carboxylated xanthone, has been shown to regulate the gene expression of IL-6, TNF-α and IFN-β in the ANA-1 murine macrophage cell line (Ching et al., 1999). The induction of cytokines by DMXAA in conjunction with B7.1 (CD80)-mediated immunotherapy was able to overcome immune resistance and lead to the complete rejection of tumors in mice by generating potent and prolonged tumor-specific CTL activity and vessel damage (Kanwar et al., 2001). DMXAA efficiently activates TAMs to release a variety of immunostimulatory cytokines and chemokines able to boost tumor-specific $CD8^+$ T cell immunity (Jassar et al., 2005). In DMXAA-treated tumor-bearing mice, systemic administration of this compound induces strong antigen-specific antitumor CTL responses by interacting with both the innate and acquired immune systems (Wallace et al., 2007). Tang et al. confirmed the induction of an antigen-specific immune response using DMXAA as a vaccine adjuvant. In addition, the group reported the development of a preferential T_H2 response (C. K. Tang et al., 2013). Immunotherapeutic approaches take advantage of combinations with DMXAA to produce tumor regression and immune cell infiltration. The tumor microenvironment can be adjusted, with increases in DC, neutrophil and $CCR7^+$ $CD127^+$ M1 macrophage frequencies. There is a switch from an immunosuppressive microenvironment to a proinflammatory microenvironment. $CD8^+$ TILs are expanded and activated (Fridlender et al., 2013).

DMXAA was also demonstrated to be an agonist of only murine, not human, stimulator of IFN genes (STING), which is completely silenced in tumors with poor intratumoral infiltration. STING is essential for the innate immune response in the tumor microenvironment, and $CD8^+$ T cell priming requires activation of this pathway in APCs through release of cytokines (S. R. Woo et al., 2014). DMXAA contributes to restoration of the STING activity that stimulates downstream cytokine production, T cell activation and migration, suggesting the potential of a further combination of DMXAA with anti-PD-1/PD-L1 therapy (W. Liu et al., 2020). In contrast to DMXAA, α-mangostin, a polyphenolic xanthone derivative of the fruit pericarp of *Garcinia mangostana*, was demonstrated to act as a human STING agonist. α-Mangostin induced repolarization of M2 macrophages into the proinflammatory M1 phenotype (Y. Zhang, Sun, et al., 2018c).

T_H17 cells are a peculiar T cell subset mainly involved in the development of autoimmune diseases but are also found in the peripheral blood and tumor site of cancer patients (W. Zou & Restifo, 2010). α-Mangostin inhibits the master transcription factor of T_H17 cells (RORγt) and reduces T_H17 cell differentiation and the levels of inflammatory cytokines produced in Jurkat cells. Additionally, it inhibits the differentiation of T_H1 cells and expression of IFN-γ (X. Zhou et al., 2020). α-Mangostin diminishes circulating TNF-α, IFN-γ, and IL-1β levels while enhancing systemic IL-10 and TGF-β1 levels, reducing inflammation in LPS-stimulated macrophages and experimentally induced polymicrobial sepsis (Ge et al., 2019).

Collagen enrichment and increased stiffness at tumor sites reduce immune cell infiltration and immune cell cytotoxic activity and increase Tregs numbers (Kuczek et al., 2019). α-Mangostin (10 μM) was found to reduce the mechanical stiffness induced by lung and other cancer cells (Phan, Shahbazzadeh, & Kihara, 2020; Phan, Shahbazzadeh, Pham, & Kihara, 2018). This property was exploited to formulate a dual-mechanism-based CTL infiltration enhancer, termed “nano-sapper”. With this strategy, α-mangostin reduced stromal deposition, reversed CAFs activation and helped tumor necrosis factor superfamily 14 restore the vasculature and stimulate the recruitment of CTLs in orthotopic pancreatic ductal adenocarcinoma mouse models. After nano-sapper treatment, tumor blood vessels were normalized; $CD4^+$ and $CD8^+$ T cells and B cells accumulated in the tumor site; and Tregs and macrophage numbers were decreased (Y. Huang et al., 2020). A similar strategy combining a CAFs-targeting biodegradable polymer nanoparticle loaded with α-mangostin was developed for use in pancreatic cancer. This micellar system (10 and 20 μM) inactivated CAFs, reduced ECM production and promoted normalization of the vasculature, enhancing perfusion at the tumor site (Feng et al., 2020). Due to its low water solubility, α-mangostin has a low oral bioavailability, which suggests the need to design novel analogs to improve its poor absorption. The glycosides α-mangostin 3-*O*-β-D-2-deoxyglucopyranoside (Man-3DG) and α-mangostin 6-*O*-β-D-2-deoxyglucopyranoside (Man-6DG) were demonstrated to have a better biodistribution in tissues and better metabolic stability than α-mangostin. The two analogs (10 μM) suppressed hepatic cancer cell migration *in vitro* and inhibited angiogenesis and the hypoxia-induced accumulation of the HIF-1α protein (S. M. Kim, Han, Le, Sohng, & Jung, 2020b). Innovative biodegradable nanomicelles loaded with α-mangostin (1.56-25 μg/ml) were shown to counteract angiogenesis in a murine model of subcutaneous melanoma (S. Yang et al., 2019).

Inhibitory effects on cell migration and invasion and reductions in MMP-2 and MMP-9 levels in response to β-mangostin treatment (2.5-10 μM) were observed in hepatic cancer (C. F. Huang et al., 2017). PGE2 and COX-2 levels were decreased in LPS-stimulated RAW264.7 macrophages by β-mangostin treatment, and the release of TNF-α and IL-6 was inhibited. Moreover, pretreatment of mice with β-mangostin inhibited leukocyte infiltration and reduced TNF-α and IL-1β levels in

the peritoneal fluid in a model of carrageenan-induced peritoneal inflammation (Syam et al., 2014).

After the identification of the pharmacophoric motif of caged *Garcinia* xanthones, Batova et al. synthesized the simple analog cluvenone. Gene expression analysis was performed on T-cell acute lymphoblastic leukemia treated with cluvenone and showed upregulation of pathways involved in T cell activation (Batova et al., 2010).

Overall, xanthones act on all components of the tumor microenvironment; on the one hand, they stimulate the activation and generation of tumor-specific cells, and on the other hand, they modify the stromal components of the tumor microenvironment by damaging vessels and modifying the CAFs phenotype (Figs. 2–4 and Tables 2–4).

3.8. Vitamins

A commonly accepted notion is that enriching the diet with foods containing vitamins is a useful tool to reduce the onset of cancer and strengthen the immune system (van Poppel & van den Berg, 1997). Maintaining adequate levels of vitamin D is important for optimal immune health (Reider et al., 2020). The major function of $1,25(OH)_2D3$ (calcitriol) is to regulate calcium homeostasis. Several studies have shown a role for vitamin D deficiency in increasing cancer risk. Calcitriol inhibits cell proliferation, angiogenesis, and invasion; promotes differentiation and apoptosis (Khammissa et al., 2018); and plays an important role in the immune system mainly through inhibition of the production of cytokines production that are either required for T_H1 differentiation or produced by differentiated T_H1 cells (Staeva-Vieira & Freedman, 2002) (Figs. 2–4 and Tables 2–4).

Indeed, calcitriol was found to suppress the maturation of antigen-presenting DCs, resulting in a reduction in their capacity to present antigens to naive T lymphocytes in regional lymph nodes. The addition of a calcitriol analog greatly decreased the immunostimulatory activity of BMDC1 in stimulating the T_H1 immune response and CTL generation (Matsuzaki et al., 2006) and dramatically suppressed, at the concentration of 0.1-100 nM, the differentiation of monocytes into DCs, thus generating a subset of partially mature DCs with an impaired costimulatory capacity and low IL-12 production that could potentially increase tolerogenic T lymphocyte generation (Lyakh, Sanford, Chekol, Young, & Roberts, 2005). The effect of calcitriol on the inflammatory response mediated by monocytes/macrophages was demonstrated to be dependent on their differentiation. In the early stage of differentiation, monocytes exhibited stronger activity of their antimicrobial pathway upon treatment, whereas in the more mature stages of differentiation, this vitamin induced anti-inflammatory effects (Di Rosa et al., 2012). The decrease in antigen-specific presentation might lead to T cell anergy.

On the other hand, calcitriol might interfere with tumor cell growth by decreasing inflammatory and proangiogenic cytokine secretion in the tumor microenvironment. The anti-inflammatory effect of calcitriol was inferred from its abilities to inhibit IL-6 and TNF-α production by human monocytes (Y. Zhang et al., 2012), to inhibit IL-6 and TNF-α *in vitro* (1-1000 nM) and *in vivo* in a hepatocellular carcinoma model (J. Guo et al., 2013), to inhibit GM-CSF-induced alveolar macrophage proliferation (G. Hu et al., 2019) and to decrease IL-6 expression in primary prostatic cultures of normal and adenocarcinoma cells (Nonn et al., 2006). In addition, IL-8, a proangiogenic cytokine secreted by prostate cancer cells, was suppressed by calcitriol (Bao et al., 2006). In one human study, a decrease in the IL-8 level in the tumors of head and neck cancer patients was also found upon calcitriol treatment (Walker et al., 2012). However, calcitriol was demonstrated to increase the expression of CXCL8, CXCL6 and CXCL1 in both undifferentiated and PMA-differentiated THP-1 cells, thus promoting the recruitment and activation of neutrophils (Ryynänen & Carlberg, 2013).

It has also been found that calcitriol inhibits T cell proliferation and decreases the production of IL-2 and INF-γ by T_H1 cells. In fact, calcitriol potently inhibits T lymphocyte proliferation induced by IL-1 or an alloantigen by inhibiting IL-2 release from activated T lymphocytes (Binderup et al., 1991) and inhibits both the T_H1 cytokine IFN-γ and the T_H2 cytokine IL-4 in naive $CD62L^+CD4^+$ T cells during *in vitro* polarization (Staeva-Vieira & Freedman, 2002).

It should also be noted that calcitriol can produce a negative effect on the host immune response by inducing Tregs and T_H2 cell polarization in human and mouse models. Topical calcitriol and vitamin D analog calcipotriol significantly enhance the suppressive capacity (Gorman et al., 2007) and proliferative activity of $CD4^+CD25^+Foxp3^+$ Tregs in mice, respectively (Ghoreishi et al., 2009). Calcitriol was shown to upregulate T_H2 and Tregs numbers in the spleen and regional lymph nodes of 4T1 tumor-bearing mice; increase granulocyte and B lymphocyte numbers; to decrease $CD4^+$, $CD4^+CD25^+$, and $CD8^+$ T cell numbers, as well as $CD335^+$ NK cell numbers, in the blood; and to increase the level of IL-10 in tumors (Pawlik et al., 2018). In addition, calcitriol (0.1 μM) can increase IL-10 and TLR9 expression by human $CD3^+CD4^+$ T cells *in vitro* (Urry et al., 2009). In one human study, calcitriol was found to increase both T_H1 and T_H2 cytokine levels in the blood and tumors of head and neck cancer patients treated prior to surgery (Walker et al., 2012).

Vitamin E, a family of natural compounds divided into two broad groups (tocopherols and tocotrienols), has been shown to have many beneficial health effects, including anticancer activity and immunomodulatory properties (G. Y. Lee & Han, 2018). In different mouse models, vitamin E or its analogs [alpha-tocopheryloxyacetic acid (α-TEA) and α-tocopheryl succinate (α-TOS)] have been demonstrated to promote a shift towards a T_H1 response. In fact, vitamin E supplementation can increase the production of T_H1 cytokines following influenza infection in mice (Han et al., 2000), enhance the immune response to a specific antigen and the production of cytokines promoting the cell-mediated T_H1 immune response (Radhakrishnan et al., 2013), and increase the secretion of T_H1 cytokines but decrease the secretion of T_H2 cytokines in RAW264.7 cells of macrophage origin (Ye et al., 2017). The analog α-TEA was shown to increase the production of intratumoral IFN-γ and decrease IL-4 levels in a mouse tumor model (Hahn et al., 2011), stimulate autophagy and enhance cross-priming of $CD8^+$ T cells (Y. Li et al., 2012), while α-TOS was found to increase the effectiveness of a DC-based vaccine used to treat established tumors by increasing IFN-γ production by $CD4^+$ and $CD8^+$ T cells (Ramanathapuram et al., 2004). Notably, vitamin E was shown to decrease the suppression of $CD8^+$ T cell activation mediated by $CD11b^+$ MDSCs and reduce the percentage of $CD11b^+Gr\text{-}1^+$ MDSCs among splenocytes in TC-1 tumor-bearing mice (Kang et al., 2014), while α-TEA treatment increased the frequencies of activated T cells in the tumor microenvironment and the ratios of $CD4^+$ or $CD8^+$ T cells to Tregs among tumor-draining lymph node cells or splenocytes (Hahn et al., 2011). In addition, a diet containing vitamin E increases T helper cell activity and proliferation in mice (Han et al., 2006; Tanaka et al., 1979) (Figs. 2–4 and Tables 3, 4).

Vitamins B2, B6, and B9 are significant suppliers of nutritional support to the immune system (Gruber, 2016). These vitamins were able to inhibit pro-monocytic cell proliferation and decrease the expression of PD-L1 in these cells (vitamin B2 at 0.125 μg/ml; vitamin B6 and vitamin B9 at 125 μg/ml). On the other hand, they promoted the production of IL-10 and secretion of IL-8 by pro-monocytic cells (Mikkelsen et al., 2019).

Some evidence supports the concept that vitamin C supports the immune system (Ang et al., 2018). In one human study, it was reported that ascorbate improves innate immunity by enhancing neutrophil functions, including chemotaxis and oxidant generation (Bozonet et al., 2015). In addition, it reduced neutrophil extracellular trap formation by human PMNs (Mohammed et al., 2013); inhibited FAS-induced apoptosis in the monocytic U937 (10-13 mM) cell line and fresh human monocytes (4-14 mM) (Perez-Cruz, Carcamo, & Golde, 2003); and improved the generation and expansion of NK cell progenitors from hematopoietic stem cells and the generation of NK cell progenitors from T/NK cell progenitors (Huijskens et al., 2015). Vitamin C has also been shown to affect adaptive immune responses by decreasing antigen-specific

IgG1 titers in mouse serum (A. Woo et al., 2010), improving the differentiation of mouse bone marrow-derived progenitor cells into functional T lymphocytes *in vitro* (Manning et al., 2013), inducing higher frequencies of $CD44^{hi}CD62L^{lo}CD8^{+}$ effector and effector memory T cells upon administration of vitamin C-treated and tumor lysate-loaded DCs to mice (Y. J. Jeong, Kim, et al., 2014b), and increasing IL-12p70 secretion by DCs and thus shifting immune responses towards the T_H1 phenotype (Y. J. Jeong et al., 2011) only during T cell activation (Noh et al., 2005). On the other hand, vitamin C appears to downregulate the immune response by increasing Tregs development in mouse models. Indeed, vitamin C not only led to increased generation of $Foxp3^{+}$ allo-iTregs but also induced elevated Foxp3 stability after restimulation *in vitro* by increasing Treg-specific demethylated region demethylation in alloantigen-specific Treg induction cultures (Nikolouli et al., 2017), stabilized Foxp3 expression relatively efficiently in adoptively transferred iTregs in a graft-versus-host disease environment and facilitated the induction of stable human iTregs (Kasahara et al., 2017). However, it was also reported that vitamin C reduces the ability of natural Tregs to suppress effector T cell proliferation *in vitro* while enhancing the effect on TGF-β-induced $Foxp3^{+}$ Tregs. In addition, although vitamin C has been shown to increase iTregs generation *in vitro* and *in vivo*, no allograft tolerance was achieved in animals orally treated with vitamin C (Oyarce et al., 2018) (Figs. 2–4 and Tables 2–4).

Vitamin A and related forms are found as pro-vitamin A, preformed vitamin A, carotenes, ATRA and retinoic acid (RA). Preformed vitamin A is present mainly in animal and dairy products, while pro-vitamin A (carotenoids) is found in fruits and vegetables (D'Ambrosio, Clugston, & Blaner, 2011). Vitamin A and its metabolites are involved in innate and adaptive B and T cell responses. Vitamin A affects the functions of macrophages and neutrophils. ATRA was shown to induce TGF-β and IL-6 secretion by monocyte-derived DCs and IgA responses in cocultured lymphocytes (Saurer et al., 2007), suppress the production of NO and TNF-α by activated peritoneal macrophages (Mehta et al., 1994), activate immature DCs in the presence of moderate amounts of proinflammatory mediators (Geissmann et al., 2003), suppress the maturation of BMDCs in response to TLR stimulation and increase IFN-γ secretion by NK cells *in vitro* (Chau et al., 2013). Supplementation with vitamin A increases the phagocytic and bactericidal activities of neutrophils in cows (Higuchi & Nagahata, 2000).

Vitamin A is also able to regulate $CD4^{+}$ T cell differentiation and potentiate $CD4^{+}$ T cell conversion into Tregs. Indeed, it has been reported that ATRA inhibits the formation of T_H17 cells, promotes Foxp3 expression (Elias et al., 2008), potently induces $Foxp3^{+}$ adaptive Tregs to acquire a gut-homing phenotype (Benson et al., 2007), enhances Tregs conversion from $Foxp3^{-}$ $CD4^{+}$ T cells in the presence of TGF-β (C. M. Sun et al., 2007), increases the Tregs conversion of naive T cells in the absence of inhibitory cytokines (Nolting et al., 2009), and stabilizes nTregs in a proinflammatory milieu (L. Lu et al., 2014). On the other hand, in contrast to its potent effects on the induction of iTregs, ATRA was reported to potently inhibit the TGF-β–mediated induction of IL-10 in naive $CD4^{+}$ T cells in mice (Maynard et al., 2009), and to be necessary to elicit proinflammatory $CD4^{+}$ helper T cell responses to infection or mucosal vaccination (Hall et al., 2011). Finally, the administration of ATRA was reported to inhibit B16F10 melanoma growth *in vivo*, which was dependent on the ability of ATRA to induce antitumor $CD8^{+}$ T cell immunity and to inhibit the frequency of tumour-infiltrating MDSCs (W. Yin et al., 2017) (Figs. 2–4 and Tables 2–4).

4. Modulation of the immune response by nutraceuticals employed in clinical trials

Based on results from *in vitro* and *in vivo* studies, many clinical trials have evaluated the immunomodulatory effects of nutraceuticals on healthy volunteers and patients with different types of cancer (Table 5).

The effects of β-glucan for cancer prevention, development and survival were evaluated in several clinical trials. The yeast-derived soluble β-1,3/1,6 glucan Imprime PGG mediated immune response activation via complex formation with naturally occurring anti-β glucan IgG antibodies in phase I studies of 30 healthy volunteers, demonstrating a role in cancer prevention. Changes in immunological parameters, including the activation of complement; production of cytokines and chemokines; expansion of anticancer effector cells, neutrophils and monocytes; and expression of early innate immune response genes, were induced (Bose et al., 2019). Maitake extract containing β-glucan was orally administered in a phase I/II clinical trial of breast cancer patients, free of disease after initial treatment, which confirmed significant changes in immune functions with no serious adverse events or dose-limiting toxicity (Deng et al., 2009). Similarly, a prospective clinical trial showed that short-term oral administration of 1-3, 1-6, and D-β glucans to 23 patients with advanced breast cancer stimulated the proliferation and activation of monocytes, alleviating lymphopenia (Demir et al., 2007). A randomized, double-blinded, placebo-controlled clinical trial was conducted with 30 women with breast cancer undergoing chemotherapy to assess the effect of β-glucan on WBC counts and serum IL-4 and IL-12 levels. The results showed that β-glucan counteracted decreases in the WBC counts and IL-4 level and increased the IL-12 level, thus suggesting that beta-glucan could be useful as a nutrition adjuvant therapy in combination with cancer treatments (Ostadrahimi et al., 2014). In a phase II clinical trial of 21 patients affected by myelodysplastic syndromes (MDS), maitake-derived β-glucan was well tolerated and enhanced *in vitro* neutrophil and monocyte function with beneficial immunomodulatory potential. These findings suggested that maitake may enhance immune responses against bacterial infection in MDS patients (Wesa et al., 2015).

Lentinan has been used in combination with chemotherapy in the treatment of cancer in both China and Japan (M. Zhang, Zhang, Zhang, & Tian, 2019a). The administration of lentinan in combination with chemotherapy improves general condition, symptoms, signs, quality of life and the immune response in patients with esophageal carcinoma, increasing the serum levels of proinflammatory cytokines while decreasing the levels of anti-inflammatory cytokines (J. L. Wang, Bi, et al., 2012a). Intravenous administration of lentinan regulates the ratio of $CD4^{+}$ IL-4^{+} T cells to $CD4^{+}$ IL-6^{+} T cells by maintaining the balance between T_H1 and T_H2 cells in peripheral blood samples collected preoperatively from patients affected by cancer of the digestive tract (Yoshino et al., 2000).

A randomized clinical trial evaluated the effect of ginseng polysaccharides plus DCs administered thoracoscopically on 96 patients with NSCLC. The results showed that the combined treatment increased the expression of T_H1 cytokines, the T_H1/T_H2 ratio and improved the quality of patients life (Ma et al., 2014).

A double-blinded, randomized, controlled trial evaluated the effect of IP6 on 20 patients undergoing breast surgery and polychemotherapy. After 6 months, the patients in the group receiving IP6 topically had a reduction in chemotherapy-induced side effects and maintained a normal complete blood count, demonstrating that IP6 could be useful for improving the quality of cancer patients life (Proietti et al., 2017).

Many clinical trials have investigated the effects of fatty acids on cancer patients. Dietary EFA supplementation in 30 patients with CRC induced a marked reduction in $CD4^{+}$ $CD8^{+}$ T lymphocyte numbers and T suppressor cell subsets. The inhibition of T suppressor cells activity could be beneficial for patients with both localized and advanced CRC (Purasiri et al., 1994). Dietary ω-3 PUFAs plus vitamin E had immunoregulatory effects on 30 well-nourished and 30 malnourished patients with generalized malignancy. ω-3 PUFAs increased the lowered ratio of T helper cells to T suppressor cells, rescued the decrease in TNF-α production and appeared to prolong the survival of malnourished patients (Gogos et al., 1998). Supplementation with ω-3 PUFAs derived from soybean and fish oils in 42 postoperative CRC patients reduced the magnitude of inflammatory responses and increased the

percentages of $CD3^+$ and $CD4^+$ lymphocytes, improving the patients outcome (B. Liang et al., 2008). Similarly, the double-blinded, randomized, controlled study by Golkhalkhali et al. demonstrated that ω-3 PUFAs and strain-specific probiotics improved the quality of the life, reduced inflammatory marker levels and relieved certain chemotherapy side effects in 140 CRC patients (Golkhalkhali et al., 2018). Moreover, a randomized trial demonstrated that fish oil supplementation in 38 patients during cancer chemotherapy administration after surgical resection led to an improvement in host defense with an increased number of blood PMNs and amelioration of their functions. Fish oil supplementation may be useful in preventing chemotherapy-induced decline in neutrophil number (Bonatto et al., 2012).

ω-3 PUFA supplementation reduced inflammation in gastric cancer patients as a pre-treatment, and reduced inflammation and improved immune function by increasing the $CD4^+/CD8^+$ ratio, when applied as parenteral nutrition following esophageal cancer surgery (Feijó et al., 2019; Long et al., 2013). In contrast, the results of the randomized clinical trial conducted by Sultan et al. showed that an enteral diet rich in ω-3 PUFAs, which was administered to 195 patients undergoing esophagogastric cancer surgery, did not lead to a substantial difference in HLA-DR expression in leukocytes or clinical outcomes in the treated groups compared to control groups (Sultan et al., 2012). A double-blinded, randomized, controlled trial demonstrated that enteral nutrition enriched with EPA modulated inflammatory response in 53 patients after esophageal cancer surgery, by diminishing the postoperative production of IL-8, IL-10 and TNF-α, preserved lean body mass in patients post esophagectomy, but did not impact the short-term clinical outcome (Ryan et al., 2009). In a prospective, randomized, double-blinded trial of a cohort of 23 patients undergoing esophagectomy or thoracotomy fed parenterally with soy oil emulsion and enterally with EPA, the administration of EPA significantly reduced the serum concentration of IL-6 in the patients, reduced the stress response, and the stress-induced immunosuppression (Furukawa et al., 1999). The levels of proinflammatory cytokines were also reduced by oral nutritional supplementation with EPA and DHA from fish oil in 40 patients with stage III NSCLC during multimodality treatment. In addition, this supplementation resulted in a preservation of body weight and fat free mass during chemoradiotherapy and in the improvement of physical functioning and patients quality of life (van der Meij et al., 2010). Similarly, EPA and DHA administered to 148 patients awaiting CRC surgery resulted in neutrophil production of high amounts of leukotriene B5 and reduced production of leukotriene B4, indicating an anti-inflammatory action for the supplement. However, this effect was not associated with the reduction of the risk of postoperative complications (Sorensen et al., 2014). In two different clinical trials enrolling CRC patients, the administration of a fish oil-supplemented diet containing EPA and DHA, during chemotherapy, induced a clinically relevant reduction in the C-reactive protein/albumin ratio, plasma fatty acid profile and potentially prevented weight loss associated with disease progression and chemotherapy (Mocellin et al., 2013; J. e. A. Silva et al., 2012).

The immune-enhancing effects and the positive effects on nutritional status exerted by EPA and DHA-enriched fish oil were also observed in 45 breast cancer patients who showed an increased number of circulating $CD4^+$ T lymphocytes after supplementation started after the diagnosis of breast cancer and prior to treatment (Paixão et al., 2017). Conversely, no alterations in the expression of serum inflammatory cytokines were found in patients undergoing elective colon resection for nonmetastasized cancer after 2 intravenous injections of ω-3 PUFAs, and unexpectedly, a worse postoperative outcome was reported for the treated patients (Bakker et al., 2020). Additionally, no changes in inflammatory cytokines were observed in 38 gastrointestinal cancer patients (McCarter et al., 1998). No significant differences in T lymphocyte subpopulation counts were found among 42 patients with gastrointestinal tumors undergoing preoperative immunonutrition enriched with arginine, fatty acids and nucleotides (Gunerhan et al., 2009). On the other hand, in a randomized trial of 40 patients with gastric carcinoma who had undergone major surgery, the patients administered enteral immunonutrition enriched with ω-3 fatty acids, glutamine and arginine showed higher $CD4^+$ T cell counts, a higher $CD4^+/CD8^+$ ratio and higher IL-2 levels than those in the control group, whereas IL-6 and TNF-α levels were lower in the immunonutrition group. Thus, enteral immunonutrition could improve defence mechanisms and modulate inflammatory action after major elective surgery for gastric carcinoma (D. W. Chen et al., 2005). In a randomized study, the same combined treatment reduced the increases in inflammatory cytokine levels, but without affecting anti-tumor response, in 71 esophageal cancer patients compared to control-treated patients (Sunpaweravong et al., 2014).

Similarly, a prospective, randomized, controlled study of ω-3 fish oil fat emulsion-based parenteral nutrition in 48 patients after surgical resection of gastric cancer demonstrated the anti-inflammatory activity of fatty acids, which inhibited the release of proinflammatory cytokines and reduced the rate of inflammatory complications (Z. Wei et al., 2014). Contrasting results were reported in a prospective, randomized, double-blinded study that recruited 34 patients with gastric adenocarcinoma or gastrointestinal stromal tumor (GIST). In this cohort, the same protocol of enteral immunonutrition did not induce significant anti-inflammatory effects and resulted in mild inflammation (C. Ma, Tsai, et al., 2018a). The administration of enteral immunonutrition based on arginine, EPA, DHA and nucleotides in 28 patients with head or neck cancer undergoing radiotherapy improved the functional capacities of patients through the enhancement of the immune cell response. These patients showed a balance between $CD4^+$ and $CD8^+$ T cells, increases in the numbers of polymorphonuclear $CD62L^+$ and $CD15^+$ cells, an increase in ROS production and stimulation of the antioxidant defense capacity in PBMCs (Talvas et al., 2015). An evaluation of the effects of preoperative nutritional support with arginine, RNA, and ω-3 PUFAs (IMPACT®) on inflammation and immunity in 26 cancer patients undergoing major surgery showed decreases in the levels of inflammatory markers and cytokine receptors, improving a preoperative nutritional status and postoperative inflammatory and immune response (Nakamura et al., 2005). The same formulation, administered before surgery, shortened the duration of systemic inflammatory response syndrome and reduced the incidence of postoperative infectious complications by enhancing cellular immunity in 60 patients with gastric cancer who underwent surgery (Okamoto et al., 2009). Another prospective clinical trial investigated the effects of preoperative oral immunonutrition with arginine, ω-3 fatty acids and RNA in 36 patients undergoing elective surgery for CRC. This formulation corrected the T_H1/T_H2 impaired balance before surgey, and helped to maintain it in the postoperative period (Matsuda et al., 2006). In contrast, the same nutritional supplementation did not improve patient liver and immune functions in 18 patients with liver cancer (Seguin et al., 2016). The immunological impact of early postoperative enteral immunonutrition supplemented with the same formulation after total gastrectomy in 109 gastric cancer patients was analyzed in a prospective, randomized study. The results showed that the postoperative $CD4^+$ T cell counts decreased in both the intervention group and the control group, but the reduction was higher in the intervention group, resulting in improved clinical and immunological outcomes in patients (Marano et al., 2013). Moreover, a prospective observational intervention study involving 37 gastric cancer patients evaluated the effect of an immunomodulatory diet given to patients at baseline and protracted after surgery. This supplement diet induced a favorable nutrition and immune status, increasing the nutrition requirement and the $CD4^+/CD8^+$ T cell ratio (Dias Rodrigues et al., 2017). Perioperative immunonutrition was also administered to patients undergoing colorectal resection and under an enhanced recovery protocol, and in this case, the immunonutrient-enriched supplements reduced the incidence of postsurgery complications and induced an increase in the WBC count but decreases in lymphocyte counts compared to the corresponding preoperative values (Moya et al., 2016).

Ginsenoside Rg3 improved immune function in 133 patients with NSCLC by increasing the number of NK cells, while the $CD4^+/CD8^+$ T cell ratio was normal in the ginsenoside-treated patients compared to patients receiving chemotherapy. In addition, ginsenoside Rg3 in combination with chemotherapy improved the postoperative life span of cancer patients (P. Lu et al., 2008).

Several clinical trials have evaluated the safety and the healt-promoting effects of polyphenols in healthy subjects. In a small study enrolling 9 healthy Japanese subjects, repeated doses of resveratrol produced decreases in proinflammatory cytokine levels, increases in circulating γδ T cell and Tregs frequencies and a significant increase in plasma antioxidant activity compared to baseline levels and control treatment (Espinoza et al., 2017). A significant increase in the number of circulating activated NK cells with a simultaneous decrease in the neutrophil number was observed after administration of the naturally occurring stilbene gnetin C to 6 healthy subjects in a randomized, double-blinded, placebo-controlled phase I trial (Nakagami et al., 2019).

Other trials have evaluated the effects of polyphenolic compounds on cancer patients. The effects of polyphenon E and EGCG were investigated in untreated patients with asymptomatic early stage (Rai stage 0 to II) chronic lymphocytic leukemia. Phase I (33 patients) and II (42 patients) clinical trials demonstrated that polyphenon E (for up to 6 months) decreased the absolute lymphocyte count and/or lymphadenopathy in patients (Shanafelt et al., 2009; Shanafelt et al., 2013). Similarly, another clinical study enrolled 12 patients diagnosed with Rai stage 0 chronic lymphocytic leukemia, and each patient received 4 capsules per day of green tea extract (containing green tea leaves, EGCG and caffeine) for the first month and then 6 capsules per day for the following 5 months. Green tea extract consumption reduced lymphocytosis, the absolute number of circulating Tregs and the serum concentrations of both IL-10 and TGF-β. These results suggested that oral green tea could be useful in prolonging the early stage phase of chronic lymphocytic leukemia and the remission phase after therapy in patients (D'Arena et al., 2013). An increase in NK cell function was observed in PBMCs derived from 20 patients with stage IV or end-stage cancer (bladder cancer, breast cancer, prostate cancer, neuroblastoma, ovarian cancer, osteosarcoma, mesothelioma, lymphoma, NSCLC, colon cancer and gastric cancer) treated with a combination of immunoactive nutraceuticals containing soy extract (See et al., 2002). A reduction in the synthesis of prostaglandins, particularly PGE2, was observed in prostate specimens from prostate cancer patients treated for 2-4 weeks prior to prostatectomy with soy isoflavone supplements (Swami et al., 2009). Moreover, a randomized phase II clinical trial reported the immunomodulatory properties of soy isoflavone-enriched bread in 32 men with prostate cancer. The results showed that the soy bread decreased plasma T_H1 type cytokine and MDSC-associated cytokine levels and Tregs and MDSCs percentages but increased the percentage of $CD56^+$ NK cells in patient peripheral blood. Thus, these findings suggested that dietary soy can reduce inflammation associated with early carcinogenesis and cancer progression (Lesinski et al., 2015). The enhancing effect of aged garlic extract on the NK cell number and NK cell activity was demonstrated in a randomized, double-blinded clinical trial that enrolled 42 patients with advanced cancer (liver, pancreatic, or colon cancer). However, aged garlic extract administration caused no improvement in patient quality of life (Ishikawa et al., 2006).

Many clinical trials have employed CUR. PRIMMO (NCT03192059) is an ongoing multicenter, open-label, nonrandomized phase II trial that enrolled 3 cohorts of patients: recurrent/refractory cervical carcinoma, endometrial carcinoma, and uterine sarcoma. The protocol consisted of a 2-week induction phase with a combination of immunomodulatory drugs (vitamin D, aspirin, and lansoprazole), metronomic chemotherapy (low-dose cyclophosphamide) and food supplementation (CUR), followed by treatment with the anti-PD-1 antibody pembrolizumab and radiotherapy. The aim of the trial was to evaluate the efficacy of this complex combination after 26 weeks of administration and then determined whether clinical benefits are conferred by continuing the protocol for up to two years (Tuyaerts et al., 2019). Another phase II trial enrolled twenty-five pancreatic cancer patients to evaluate the safety of CUR administration in the absence of any other chemo- or radiotherapy. Cytokines (IL-6, IL-8, IL-10, and IL-1RA) were detected in all patients before the beginning of therapy, while a sample of 48-62 healthy volunteers showed undetectable levels. After oral treatment, the changes in cytokine levels varied, and NF-κB, COX-2, and STAT-3 expression decreased in PBMCs. Oral CUR was well tolerated in pancreatic cancer patients without toxicities (Dhillon et al., 2008). With the aim of alleviating the side effects of chemo- and radiotherapies, phytosomal Meriva CUR, which consists of curcuminoids (CUR:demethoxycurcumin:bis-demethoxycurcumin=33:8:1) combined with soy-lecithin, was administered over an 8-week period to cancer patients with solid tumors or hematological malignancies. An evaluation of oxidative stress was performed before and after the administration of the supportive agents, showing upregulation of the antioxidative response, downregulation of inflammatory pathways and a cumulative improvement in the side effects experienced by patients (Belcaro et al., 2014). In a similar double-blinded, placebo-controlled trial, the administration of Meriva to 47 patients with solid tumors (versus 49 patients in the placebo group) produced a significant improvement in the quality of life and decreases in serum levels of inflammatory mediators and biomarkers (Panahi et al., 2014). The administration of Infla-Kine, a natural supplement composed of a proprietary blend of *Lactobacillus fermentum* extract, burdock seed (arctigenin), zinc, alpha lipoic acid, papaya enzyme and an enhanced absorption bio-CUR complex (BCM-95®), administered to 24 healthy volunteers for 4 weeks led to reductions in inflammatory marker levels, with decreases in IL-8, IL-6, NF-κB, TNF-α mRNA transcript levels in PBMCs. Thus, the results supported the use of this supplement to modulate chronic inflammation associated with several diseases, including cancer (Mikirova et al., 2017).

Several trials have investigated the effects of RA on the immune response of cancer patients. A randomized phase II trial in 41 patients with advanced small cell lung cancer (SCLC) demonstrated that ATRA in combination with vaccination using wild-type p53-transduced DCs decreased MDSCs numbers compared to the vaccine alone, thus enhancing the antitumor immune response to vaccination and improving the clinical outcome of the disease (Iclozan et al., 2013). Similarly, a randomized phase II clinical trial investigated the effect of ATRA in combination with ipilimumab on MDSCs compared to that of ipilimumab monotherapy in 8 advanced-stage melanoma patients. ATRA in combination with ipilimumab decreased the frequency of circulating MDSCs and increased the frequencies of mature $HLA\text{-}DR^+$ myeloid cells and activated $CD8^+$ T cells in the melanoma patients. Thus, targeting MDSCs could be useful to augment immunotherapeutic approaches and to improve outcomes in cancer patients (Tobin et al., 2018). Forty-four patients with advanced ovarian cancer responding to chemotherapy and 82 well-matched controls were enrolled in a nonrandomized phase II clinical study designed to assess the efficacy of subcutaneous low-dose IL-2 combined with oral ATRA in decreasing serum VEGF levels and improving the immune function of patients. A significant decrease in the VEGF level was observed among the treated patients, who also exhibited NK cell number and $CD4^+/CD8^+$ T cell ratio improvement with respect to controls and to baseline levels, with significant improvements in PFS and OS over two years of treatment (Recchia et al., 2005). A similar protocol was applied to 38 NSCLC patients (and 87 controls) with stage IIIB or IV disease and a complete/partial response or stable disease after chemotherapy, and the same results were achieved in terms of VEGF level reduction and improvements in immune function (Recchia et al., 2006). A third clinical study from the same authors enrolled a total of 100 patients with metastatic solid tumors (including CRC, ovarian, lung, stomach, kidney and head and neck cancer patients) with a partial response or stable disease after chemotherapy. A self-administered combination of IL-2 and RA decreased the serum level of VEGF and increased lymphocyte counts. Eighteen of the patients who entered the study with a partial response and 6 of the patients with

stable disease achieved a complete response, maintaining a relapse-free response and an OS rate at 5 years of 96% (Recchia et al., 2009). A prospective, nonrandomized, multicenter trial was conducted by the same group with a total of 30 patients with stage IIIC breast cancer treated with high-dose chemotherapy and peripheral progenitor cell transplantation, followed by immunotherapy with IL-2 and 13-cis-RA. After a median follow-up time of 61 months, immune functions were improved, as shown by increases in lymphocyte and NK cell counts, the $CD4^+/CD8^+$ T cell ratio and decreases in VEGF levels in all patients; improved clinical outcomes were seen (Recchia et al., 2010). Another trial employing ATRA treatment followed by a subcutaneous IL-2 schedule was performed with 18 patients with metastatic clear cell kidney cancer. In the patients with higher plasma concentrations, ATRA treatment substantially reduced the presence of immature myeloid suppressor cells and improved the myeloid/lymphoid DC ratio, thus improving DC function and the antigen-specific immune response (Mirza et al., 2006).

In a pilot study, Hanson et al. analyzed short-term dietary supplementation with a high dose of vitamin E in advanced CRC patients, demonstrating the adjuvant role of this nutraceutical in cancer immunotherapy. Indeed, six of the seven patients recruited for the study showed increased cytolytic activity by NK cells (Hanson et al., 2007).

The role of calcitriol as a chemopreventive agent limiting inflammation in 92 colorectal adenoma patients was analyzed in a randomized, controlled clinical trial in which the participants of the intervention group received calcitriol supplementation over six months. The plasma levels of the proinflammatory markers TNF-α, IL-6, IL-8 and IL-1β were reduced, although these changes were not significant (Hopkins et al., 2011). However, in two different clinical trials, it was demonstrated that treatment of head and neck cancer patients with escalating doses of calcitriol could improve the immune response by decreasing the levels of immunosuppressive $CD34^+$ cells, increasing the levels of IL-12 and IFN-γ and significantly increasing the levels of $CD8^+$ T cells. Only one of the two studies reported the increase in time to tumor recurrence, while in the other one no clinical responses were observed (Lathers et al., 2004; Walsh et al., 2010).

Accordingly, although very few clinical trials have been performed when compared to the numbers of *in vitro* and animal model studies, the performed clinical trials indicate a positive immunomodulatory effect for nutraceuticals on cancer patients. However, further clinical trials with enrollment of increased numbers of participants are needed, particularly phase III trials. Only the accomplishment of phase III studies will indicate whether nutraceuticals can be employed as new therapeutic agents for cancer treatment alone or in combination with conventional therapies.

5. Summary and Conclusion

Several epidemiological studies have shown that nutrition has critical roles in the preservation of health and the pathogenesis and treatment of diseases. In diseases, there is an association between nutrition and immunity that, from an evolutionary point of view, has shown a close connection in the development and function of the immune system (Cooper & Ma, 2017). Phagocytosis is the most primordial and universal modality of food procurement and defense against foreign agents in unicellular invertebrates. Moving up the scale of development to multicellular invertebrates and vertebrates, phagocytosis acquires increasing importance for involvement in cellular and humoral immune responses. From the oral cavity to the terminal part of the intestine, there are several immune cells closely connected to each other, which while they must protect the body from attack by pathogens, they must also avoid immune responses to components present in foods or commensal microorganisms. The analysis of the roles of components in food in influencing the immune response in healthy individuals or those with pathologies has led to the conclusion that foods are able to modulate both the innate and adaptive immune responses. This evidence led to the development of a new discipline, immunonutrition. Whereas the evolution of a tumor depends enormously on the activation of the host immune system, which is evidently rendered inefficient by tumor cells in the tumor microenvironment, substantial energy is spent on modifying the immune system in the tumor microenvironment. The success of inducing immune responses to cancer cells with checkpoint inhibitor therapy in some types of tumors has created new hopes for anticancer therapy.

Accordingly, a plethora of studies have been carried out to determine the modulatory effects of individual food components on the immune response using *in vitro* or *in vivo* experiments in humans and animal models in both healthy and pathological conditions, including tumors. To analyze the effects of nutraceuticals on the anticancer immune response, clinical trials have been carried out in neoplastic patients. The results emerging from *in vitro* studies and experimental models have certainly been encouraging. It has become clear that each nutraceutical has a different effect on the immune system and this effect depends on the type of tumor and target immune cells. Sometimes the effects of nutraceuticals appear to be inconsistent and indeed even controversial. In addition, it should be considered that because nutraceuticals can have different or the same effects on the immune system when taken in combination, they could have an antagonist or additive/synergistic effect, respectively, in patients. It is therefore important to consider the cumulative effects of nutraceutical intake. On the other hand, incorrect administration of these natural compounds may interfere with the activity of conventional therapies, leading to harmful effects on humans. The other important drawback is that most phytochemicals have modest absorption and biodistribution but fast metabolism and excretion in the human body. The poor bioavailability will affect the effective dose delivered to cancer cells and the tumor microenvironment. However, one way to counteract this drawback could be combination treatment with different phytochemicals having similar effects. In addition, novel semisynthetic products based on natural compounds with enhanced bioavailability and retention could be conceived. Nanotechnologies can also help improve tissue delivery. It should also be considered that the gut microbiota is important for the bioavailability of foods polyphenols since they are not well absorbed by the small intestine. Polyphenol derivatives, enzymatically processed by bacteria in the gastrointestinal tract, are absorbed by epithelial cells of the small intestine (Pasinetti et al., 2018). On the other hand, microbiota-derived metabolites possess anti-inflammatory or proinflammatory effects (J. Wang, Chen, & Wang, 2020a).

Undoubtedly, the potential for the future clinical use of nutraceutical is enormous for both novel preventive and therapeutic approaches for cancer treatment. However, there is still much to be done before translating *in vitro* studies and animal models into a real benefit for cancer patients. Overall, the future challenge will be to find nutraceutical formulations that allow improvement of their bioavailability to enable to nutraceutical use in combination with traditional antitumor therapies without any sort of interference.

Declaration of Competing of Interest

The authors declare no conflicts of interests.

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