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Mini-review

Modulation of regulatory T cells by natural products in cancer

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ABSTRACT

Tumor tolerance is known as a condition of systemic immune unresponsiveness or immunosuppression against cancers, in which malignant cells escape from the immune surveillance. Among the elements of immune tolerance orchestra, the $CD4^+CD25$ + forkhead box protein3+ (Foxp3+) regulatory T cells (Tregs) have a great importance. Moreover, increased Treg populations and, particularly, reduced proportions of effector T cells to Tregs in tumor-infiltrating lymphocytes are closely linked to worse prognosis in different tumors. In the last years, several drugs for cancer immunotherapy have been developed with very promising results; however, different resistance mechanisms to immunotherapy may limit their effectiveness. Plant-derived natural agents are emerging as an innovative therapeutic field. Particularly, a number of phytochemicals, by altering diverse immune signaling pathways, have shown to possess immunomodulating features; hence, they have been tested in multiple cancer experimental models in order to contrast the tumor-induced immunosuppressive behavior, particularly Tregs-mediated immune evasion in the tumor microenvironment. In this review, recent advances on the anti-cancer effect of natural agents, either alone or in combination with traditional drugs, due to the modulation of classic Treg cells, have been resumed with the aim to guide researchers for their potential future clinical use.

1. Introduction

Tumor-infiltrating lymphocytes are considered as a repercussion of the cancer-associated immune response which plays a crucial role in host anti-tumor response [1]. Despite immune cells are recruited in the tumor microenvironment (TME) during carcinogenesis, cancer cells are able to develop variable degrees of immunotolerance. Tumor tolerance is known as a condition of systemic immune unresponsiveness or immunosuppression against cancers which plays an important role in tumor growth and development and by which malignant cells escape from the immune surveillance, immune recognition and eradication [2]. Among the elements of immune tolerance orchestra, the $CD4^+CD25$ + forkhead box protein3+ (Foxp3+) regulatory T cells (Tregs) have a great importance. Through the release of immunosuppressive molecules, i.e. transforming growth factor (TGF)-β, interleukin-10 (IL-10) and other cytokines, Tregs inhibit the tumor specific immune effector cells, including $CD4^+$ T cells, cytotoxic $CD8^+$ T cells, dendritic cells (DCs), natural killer (NK) cells and B cells [3], and consequently disrupt the host anti-tumor response [4,5]. In addition, Tregs have been found to increase angiogenesis [6], which is known to amplify cancer aggressiveness [7].

Cancer immunotherapy is described as a specific way to promote immune responses against tumor cells [8]. Cancer immunotherapy and chemoprevention through plant-derived natural agents is emerging as an innovative therapeutic field. In fact, some natural products, by altering the immune signaling pathways [9], have demonstrated to exert immunomodulating effects, so that they have been tested as a novel complementary anti-cancer approach. In this review, we mentioned the advances in recent years on the anti-cancer effect of natural agents through the modulation of classic regulatory $CD4^+CD25$ + Foxp3+ T cells (Treg cells), with the aim to guide researchers for its future clinical use. The present review is not only limited to the anti-tumoral efficacy of phytochemicals, but also includes their synergistic effects in combination with other chemotherapeutic regimens.

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1.1. Regulatory T cells (Treg)

Tregs are a heterogeneous subpopulation of T lymphocytes accounting for 5–10% of the total $CD4^+$ T cells in humans. These cells are critical for the inhibition of auto-reactive T cells in the circulation, immune homeostasis and the suppression of immune responses after the resolution of infections [10,11]. Tregs modulate the performance of the immune system, preserves immunological self-tolerance and inhibits autoimmunity [12]. Tregs are able to suppress proliferation and production of other T cell types as well as interferon gamma (IFN-γ), a cytokine promoting the adaptive immune system responses. Two groups of Tregs have been identified: those developed within the central lymphoid organ, the thymus (natural; nTregs), and those undergoing peripheral differentiation (induced; iTregs or adaptive Tregs). The nTregs are $CD4^+$ T cells with high-affinity T cell receptor (TCR) which fundamentally express CD25 along with transcription factor FoxpP3, coreceptor cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), glucocorticoid-induced tumor necrosis factor receptor (GITR; TNFRSF18) and CD134 (OX40) [13–17]. Overexpression of Foxp3 in conventional T cells leads them to obtain Tregs characteristics with immunosuppressive capacity [18,19]. The adaptive Tregs are stimulated peripherally after antigenic induction in a tolerogenic microenvironment and are involved in the progression of an antigen-specific immunosuppression by the secretion of soluble factors, like IL-10 and TGF-β [20]. The secretion of monocyte chemo-attractant protein 1 (MCP-1) and TGF-β1 enhances metastasis through the switching of T cells into Tregs, which provides condition for the escape of tumor cells from immunosurveillance [21,22]. On the other hand, proliferation of tumor cells stimulates TGF-β1 secretion, further amplifying metastatic behavior [23]. Tregs are also able to up-regulate the IL-2 receptor alpha (CD25), which can recruit IL-2 from the environment, therefore decreasing the availability of IL-2 for effector T cells [24].

The infiltration of myeloid-derived suppressor cells (MDSC) and Tregs with high Foxp3 expression in the TME is closely correlated with a lower proportion of cytotoxic $CD8^+$ T cells to Tregs, the escape of malignant cells from immune system, a decreased immunosurveillance, cancer progression, and poor prognosis in several solid tumors [25–30]. However, in some malignancies, an elevated infiltration of Foxp3 + Tregs is linked with better prognosis, thus highlighting the complicated role of Tregs in tumors. In order to explain the latter association, it has been suggested that since tumorigenesis is an inflammatory-related disease, the anti-inflammatory role of Tregs may exert also an anti-cancer effect [31].

It is well-known that suppressing the activity of Tregs in cancer is a convincing and practical therapeutic approach. Previous studies demonstrated that depleting Tregs of cancer patients improved the prognosis, but was also able to simultaneously arouse autoimmune disorders [32]. More recently, it has been suggested that functionally inactivating Tregs seems to be an effective therapeutic strategy in cancer patients.

2. Anti-cancer effects on natural products in preclinical studies

Targeting molecules and signals aimed at inactivating Tregs by using phytochemicals has been evaluated in several studies as a promising anti-cancer approach (Tables 1 and 2).

2.1. Polyphenolic compounds

Polyphenols are a large group of plant-derived secondary metabolites naturally available in plant-based foods, like tea, vegetables, wine, soy, nuts, fruit, spices, legumes, seeds, liquids, whole-grain cereals, olives, and cocoa [33,34]. Dietary polyphenols include a large family of extremely various compounds from small molecules, *i.e.* phenolic acids, to highly polymerized compounds, i.e. proanthocyanidin polymers [35]. Polyphenols are categorized into five main groups: flavonoids, phenolic acids, lignans, stilbenes as well as other polyphenols (e.g. coumarins, curcuminoids, tannins, etc) [33,34]. Some important examples include anthocyanins [from blueberry], epigallocatechin gallate (EGCG) [from green tea], curcumin [from curry], resveratrol (RSV) [from grapes and berries] and isoflavones [from soy]. Polyphenols display beneficial effects on human health such as antimicrobial, anti-inflammation, antioxidant, detoxification, immunomodulation and anti-cancer functions [36].

Polyphenols present many anti-carcinogenic features due to the their ability to interrupt multiple intracellular signaling pathways; in addition they may exert inhibitory effects on several key steps of tumorigenesis, including cell proliferation, differentiation, survival, apoptosis and migration, angiogenesis, inflammation, and immunosuppression [37,38]. For instance, green tea constituents have anti-cancer potency on hematologic malignancies such as chronic lymphocytic leukemia (CLL) through their immunomodulatory effect. It has been shown that green tea administration significantly reduced lymphocytosis and frequency of circulating Tregs, as well as decreased the serum values of IL-10 and TGF-β in CLL patients. These finding suggest that green tea has a promising therapeutic potential *via* modulating circulating Tregs [39].

2.1.1. Curcumin

Turmeric (*Curcuma longa*), the main source of the polyphenolic compound curcumin, is a natural pleiotropic agent that is well-known for its medicinal qualities. *C. longa* has been traditionally utilized in Asian countries as a medicinal plant for its antioxidant, anti-inflammatory, anti-mutagenic, anti-bacterial, anti-lipidemic and anti-neoplastic characteristics [40–44]. Curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] derived from rhizome of *C. longa* has been frequently used as a food color additive, spice or dietary yellow pigment (Fig. 1). The presence of methoxy groups upon the phenyl rings of curcumin substantially have advantageous effects for ameliorating a wide range of human diseases such as allergic disorders, liver disease, hyperlipidemia, bronchial hyperactivity, anorexia, arthritis, coryza, metabolic syndrome, psychiatric diseases and proliferative disorders [45–49]. Curcumin can modulate the expression of numerous proteins, such as pro-inflammatory cytokines and transcription factors [50–53]. Also much attention has been devoted to the potential role of curcumin as a possible treatment for different immune-related complications [54–56]. Curcumin is on the Food and Drug Administration (FDA) list as a safe agent. Therapeutic effective curcumin doses up to 8 g daily have been excellent in clinical trials without considerable adverse effects [57]. Curcumin has a low bioavailability; peak circulating level has been reached 1–2 h after oral supplementation of 4 g or more [58]. For this reason, severla curcumin analogues have been introduced with increased bioavailability and/or metabolicstability [42,186].

Preclinical experiments revealed that curcumin has the potential to suppress the activity of Tregs by three main pathways: i) preventing cell–cell interaction *via* down-regulating the expression of immunosuppressive molecules (*e.g.*, CTLA-4), ii) attenuating inhibitory cytokine secretion and, iii) reducing the capability of IL-2 to be consumed and/or stopping IL-2 production (Fig. 2). Indeed, curcumin treatment significantly reduced the expression of Foxp3 and nuclear translocation of both p65 and c-Rel, which are essential for Foxp3 and CD25 transcriptions, in Tregs [59]. Similarly, in animal model of oral cancer (*e.g.* 4NQO mouse), curcumin administration successfully decreased the Treg frequency in peripheral blood/lymph nodes and the number of MDSCs in spleen of mice [60].

The absolute number of Foxp3 + Treg was lowered, but the frequency of T helper (Th) 1 cells was remarkably increased after curcumin treatment in colon cancer patients. Indeed, curcumin therapy inhibited the *Foxp3* gene expression in Tregs; subsequently the Tregs were switched to Th1 cells in periphery. Moreover, curcumin supplementation induced IFN-γ production by $CD4^+$ T cells through

Table 1
Modulatory effects of natural products on regulatory T cells in preclinical studies.

Natural products	Agent (dose)	Source of experimental evidence	Type of cancer	Main finding	Ref.
Polyphenolic compounds					
Curcumin	- Curcumin (5, 10, 20 μM)	- Male BALB/c mice	–	- Suppression of the activity of Tregs through preventing cell–cell interaction via CTLA-4 down-expression, attenuating inhibitory cytokine secretion and reducing the capability of IL-2 to be consumed and/or stopping IL-2 production - Reduction of Foxp3 expression of by Tregs - Decreased nuclear import of both p65 and c-Rel by Tregs	[59]
	In vitro: - Curcumin (5 μM and 10 μM) *In vivo*: - Curcumin (4 weeks)	- Cal 27 and FaDu cell lines - 4NQO mouse	- OC	- Decreased Tregs frequency in peripheral blood/lymph node and number of MDSCs in spleen of mice	[60]
	- Curcumin (50 mg/kg)	- Tumor bearing-Swiss albino mice	- Any tumor	- Prevention of Treg augmentation in tumor-arrying host - Restricted loss of T cells - Increased frequency of both memory T cell and effector memory T cells - Overturn of the type 2 immune shift - Prevention of suppressive action of Tregs through down-expression of TGF-β and IL-10	[63]
	- Curcumin–PEG (40 mg/kg)	- B16F10 tumor–bearing mice	- Melanoma	- Inhibition of STAT3 activation in the tumor location by reduction of the expression of immunosuppressive cells(i.e., MDSCs and Tregs) - Facilitated recruitment of CD8 + T cells	[67]
Resveratrol	- Resveratrol (25–75 μM)	- EG7 tumor-bearing C57BL/6 mice - CT-26 tumor bearing BALB/c mice	- Lymphoma and CC	- Decreased proportion of $CD4^+CD25^+$ cells among $CD4^+$ T cells - Attenuation of proportion of Foxp3 + expressing cells among $CD4^+CD25^+$ T cells - Abrogation of the release of TGF-β in $CD8^+$ activated cells - Increased mRNA transcription of IFN-γ in $CD8^+$ activated cells	[85]
	- Resveratrol (1, 2.5, and 5 mg/kg/day for 22 days)	- BALB/c Renca renal cancer-bearing mice	- RC	- Overturn of cancer growth depending on $CD8^+$ T lymphocyte cells - Reduced frequency of Tregs - Accumulation of activated $CD8^+$ T cells within TME - Shif of the Th2 response toward Th1 response - Inhibition of tumor angiogenesis through reduction of VEGF	[86]
	HDIL-2 (75,000 units of IL-2) + Resveratrol (100 mg/kg for 4 days)	- C57BL/6 tumor bearing mice	- Melanoma	- Reduction of endothelial cell damage and reduced progression to VLS - Repression of the HDIL-2-induced enlargement of Tregs - Prevention of the progression of VLS via proliferation of MDSCs - Promotion of the vulnerability of melanoma to the cytotoxic effect of IL-2-activated killer cells - Up-regulation of Foxo1	[87]
	- Resveratrol(20 or 50 mg/mouse)	- BALB/c and C57BL/6 tumor bearing mice	- BC	- Block of lung metastasis through inactivation of STAT3 - Inhibited production/activity of tBregs and TGF-β expression - Inactivation of tBreg-induced bias to Foxp3 + Tregs	[91]
	- HS-1793 (0.3, 0.6, 1.3 and 2.5 μM)/(0.5, 1 and 1.5 mg/kg) twice a week for 30 days	- FM3A breast tumor-bearing mice	- BC	- Decreased frequency of Tregs and production of TGF-β inducing Treg in the spleen and tumor tissues of mice - Increased number of IFN-γ-regulating CD8 + cells - Elevation of IFN-γ stimulation and production - Promotion of the cytotoxicity of splenocytes to tumor cells	[93,94]
				- Abrogation of IL-2 secretion and stimulation of IL-4 release by Con A-induced lymphocytes	[94]

(*continued on next page*)

Table 1 (*continued*)

Natural products	Agent (dose)	Source of experimental evidence	Type of cancer	Main finding	Ref.
Flavonoids	- Scutellaria barbata D. Don extract (50, 100, and 150 mg/kg/day for 30 days)	- Hepatoma H22-bearing mice - HepG2 cells	- HCC	- Reduced HepG2 cell proliferation - Inhibition of growth of implanted tumor in hepatoma-bearing mice - Decreased frequencies of Th17 cells and Tregs in TME - Lowered serum values of IL-10, and TGF-β in hepatoma-carrying mice - Elevation of IL-2 and IFN-γ amounts in hepatoma-carrying mice	[112]
	- *In vitro: Scutellaria* ocmulgee leaf extract (250 μg/ml) plus wogonin (60 μM) - *In vivo*: *Scutellaria ocmulgee* leaf extract (100 mg/kg/day, 5 days a week, for 2 weeks)	- F98 rat glioma cell line - Transposable F98 gliomas in F344 rats	- Malignant gliomas	- Suppression of TGF-β1-induced Treg function - Attenuation of tumoral TGF-β1 and Treg populations - Reduced release of IL-10 - Inhibition of Smad-3, GSK-3β and ERK1/2 axis in Tregs - Promotion of P38 MAPK phosphorylation - Prevention of T cell response to TGF-β1 through mediating both Smad and non-Smad cascades	[114]
	Naringenin (100 mg/kg)	- Lewis lung carcinoma and 4T1 BC cell lines - Bleomycin-treated C57BL/6 and BALB/c mice	Lung fibrosis and metastasis	- Abrogation of lung metastases in pulmonary fibrotic mice - Decreased expression of TGF-β1 and frequency of Tregs - Reduced TGF-β1 amounts in bleomycin-induce pulmonary fibrosis mice - Increased ratio of T cells able to respond to fibrosis and cancer - Recovered functions of CTLs and IFN-γ release	[116]
	Naringenin (100 mg/kg/day for 24 days)	- 4T1 murine mammary cancer cells - Orthotopic 4T1 breast cancer resection BALB/c mice	- Lung metastasis in a BC resection model	- Increased number of IFN-γ and IL-2 regulating T cells - Reduced TGF-β1-stimulated Treg proliferation - Decreased rate of TGF-β1-induced differentiation of naive $CD4^+$ T cells to Tregs	[117]
	Naringenin (200 mg/kg/daily for 30 days)	- Murine breast cancer cell line 4T1 - 4T1/TGF- β1 bearing mice - Control (4T1/RFP cells)	- Pulmonary metastases of BC	- Reduced TGF-β1 transportation from the trans-Golgi network through repressing PKC activation - Decreased TGF-β1 secretion - Inhibition of transformation of lymphatic T cells into Tregs	[119]
	GSPs (0.5%, w/w)	- C3H/HeN mice exposed to UVB (150 mJ/cm2) radiation	- Photocarcinogenesis	- Inhibited development and function of Tregs - Diminished ability of the Tregs to enhance production of IL-10 and TGF-β in UVB-exposed mice - Induction of Tregs to promote IFNγ production by T cells - Postponed UVB-induced skin tumor development - Inactivation of Treg cells by enhancing DNA repair in dendritic cells	[136]
Tannins	Prophylactic-P2Et (75 mg/kg; 2 times per week for 21 or 32 days)	- Healthful C57BL/6 or BALB/c mice	–	- Increased frequency of $CD4^+$ and $CD8^+$ T cells, NK cells, Tregs, DCs and MDSCs	[127]
	Preincubation-P2Et (75 mg/kg; 2 per week)	- Transplantable models of B16-F1 melanomas, and 4T1 breast tumor	- Melanoma - BC	- Increased number of Tregs, MDSCs, and proinflammatory cytokines - Decrease of $CD4^+$ and $CD8^+$ active T cells	
PUFA					
Fish oil	Fish oil and selenium yeast (1 g/mice/day)	- Male BALB/cByJ tumor bearing mice	- LC	- Reduced number of Tregs and MDSCs - Alleviation of cachexia in tumor-bearing mice	[146]
	Fish oil [180 mg EPA and 120 mg DHA/ml] and corn oil [58.8% linoleic acid, 26.4% oleic, 1.3% linolenic, and 12.8% saturated fatty acid]	- Male Wistar rats	- CC	- Elevation of nTregs and iTregs - Decreased IL-10 and IL-6 levels	[141]
n-3 PUFAs	DHA (100 μM)	- C57BL6/J mice	–	- Overexpression of Tregs markers such as Foxp3 at both transcription and translation levels - Down-expression of immunosuppressive factors such as IL-10	[140]
Mushroom Extract					
Lentinula edodes mycelia	*Lentinula edodes* mycelia extract (1% or 2% equivalent to 0.08 g)	- B16 melanomas in C57BL/6 mice - B16 melanomas in BALB/c mice	- Melanoma	- Reduction in Treg populations - Decreased transcription levels of Foxp3 and slightly TGF-β - Enhanced immune response to MHC class I-restricted and tumor-reactive CD8+T cells	[153]
Others					

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Table 1 (*continued*)

Natural products	Agent (dose)	Source of experimental evidence	Type of cancer	Main finding	Ref.
Ginger	6-Gingerol (50, 500 or 5000 μg/kg/day)	- Different mouse tumor models (B16-F1 melanoma cells, CT26 colon carcinoma cells, and Renca renal cancer)	- Melanoma - RC - CC	- Recruitment of $CD4^+$ and $CD8^+$ T cells and also B220 + B cells - Decreased Treg populations - Expression of IFN-γ, and CD107a by intratumoral CD8 infiltrating T cells - Expression of chemokine receptors (CCR5 and CXCR3) by Th1 cells	[158]
Devil's club	Devil's club root extract (20 μg/ml)	- Murine C1498 cells, human U937 cells, and human HL-60/VCR cells - C57BL/6JFoxp3-RFP mice	- AML	- Mitigation of Tregs - Increased $CD8^+$ T cell activity	[162]
Polysaccharide	*Ganoderma lucidum* polysaccharides extract (10, 50, 100 and 200 mg/kg; every 2 days for 4 weeks)	- Hepatoma H22 in Kunming and BALB/c male mice	- HCC	- Elevated proportion of effector T cell to Tregs - Abolished inhibitory effect of Tregs on effector T cell production *via* enhanced secretion of IL-2 - Block of Notch1 pathway and *Foxp3* gene amplification *via* overexpression of miR-125b	[178]
Bitter melon	Bitter melon extract (100 μl; 5 days/week)	- C3H/HeNTac tumor-bearing mice	- HNC	- Attenuation of Treg infiltration through hindering FoxP3+ populations - Diminished Th17 cell population within the tumor	[183]
	Bitter melon extract (1% v/v)	- Human NK-cell line (NK3.3)	- HNSCC	- Increased cytotoxic capability of human NK-cell line to kill HNSCC cells through promotion of granzyme B accumulation and modulation of CD107a/LAMP1 - Enhanced expression of CD16 and NKp30 in NK3.3 cells-cocultured with HNSCC cells	[184]
	Bitter melon extract (30% v/v, 600 mg/mouse)	- C57BL/6 mice	- OSCC	- Inhibited expression of immune system-related genes (*s100a9, IL-23α, IL-1β, and PDCD1/PD1*)	[185]

Abbreviations: Acute myeloid lymphoma (AML), breast cancer (BC); concanavalin A (Con A); colon cancer (CC); CXC chemokine receptor 3 (CXCR3); cytotoxic T-lymphocyte antigen 4 (CTLA4); dendritic cells (DCs); docosahexaenoic acid (DHA); gallotannin-rich fraction of *Caesalpinia spinosa* (P2Et); forkhead transcription factor FKHR (Foxo1); forkhead box protein-3 (Foxp3); grape seed proanthocyanidins (GSPs); head and neck cancer (HNC); head and neck squamous cell carcinoma (HNSCC); hepatocellular carcinoma (HCC); high-dose cytokine IL-2 (HDIL-2); interferon gamma (IFN-γ); interleukin (IL); lung cancer (LC); natural killer (NK); myeloid-derived suppressor cells (MDSCs); oral cancer (OC); oral squamous cell carcinoma (OSCC); programmed cell death (PDCD1); polyethylene glycol conjugate (PEG); polyunsaturated fatty acids (PUFAs); protein kinase C (PKC); renal cancer (RC); regulatory T cells (Tregs); signal transducer and activator of transcription 3 pathway (STAT3); tumor-evoked regulatory B cells (tBregs); T helper (Th); tumor microenvironment (TME); transforming growth factor (TGF); ultraviolet B (UVB); vascular leak syndrome (VLS).

Table 2
Modulatory effects of natural products on regulatory T cells in clinical studies.

Natural products	Agent (dose)	Source of experimental evidence	Type of cancer	Main finding	Ref.
Polyphenolic compounds					
Curcumin	- Curcumin (3 g/capsule; 2 capsules per day; 1 month)	- 40 CC patients - 30 controls	- CC	- Reduction of Foxp3+ Tregs - Elevation of Th1 cells - Inhibition of Foxp3 gene expression in Tregs - Switch of Tregs to Th1 cells in periphery - Induction of IFN-γ production by $CD4^+$ T cells	[61]
	- Curcumin (1.5 g/capsule; 2 capsules per day; 2 weeks) - Placebo	- 30 LC patients - 6 controls	- LC	- Conversion of Tregs to Th1 cells - Down-expression of Foxp3 - Overexpression of IFN-γ	[62]
Green tea	- Green tea extract (4602 mg of green tea leaves, 189 mg of EGCG and 97.5 mg of caffeine; 6 month)	- 12 untreated CLL patients - 2 controls	- CLL	- Reducedlymphocytosis and frequency of circulating Tregs - Decreased serum values of IL-10 and TGF-β	[39]
Flavonoids	-Soy bread (34 mg isoflavones/slice or almond powder)	-32 patients	- Prostate cancer	-Reduction of Th1 cells and MDSC-associated cytokines -Elevated number of NK cells -Decreased frequency of Tregs and monocytic ($CD33+HLADR-CD14^+$) MDSCs	[133]
Agaricus blazei Murill (AbM)	- Chemotherapy + stem cell transplantation + AndoSan (containing 82% AbM)	- Treatment group (19 patients) - Placebo group (21 patients)	- MM	- Increased number of Tregs and plasmacytoid DCs and elevated serum concentrations of IL-1RA, IL-5, and IL-7 in leukapheresis product	[150]

Abbreviations: colon cancer (CC); chronic lymphocytic leukemia (CLL); dendritic cells (DCs); epigallocatechin gallate (EGCG); forkhead box protein-3 (Foxp3); interferon gamma (IFN-γ); interleukin (IL); lung cancer (LC); natural killer (NK); multiple myeloma (MM); myeloid-derived suppressor cells (MDSC); regulatory T cells (Tregs); T helper (Th); transforming growth factor (TGF).

suppressing the Foxp3 binding to T-bet, the IFN-γ transcription factor [61]. Consistently, curcumin therapy in lung cancer patients yielded similar results [62]. This evidence demonstrated that curcumin can improve the anti-tumor status in cancer patients by the overexpression of IFN-γ, the decrease of the Treg frequency, and the increase of Th1 cell population [61,62].

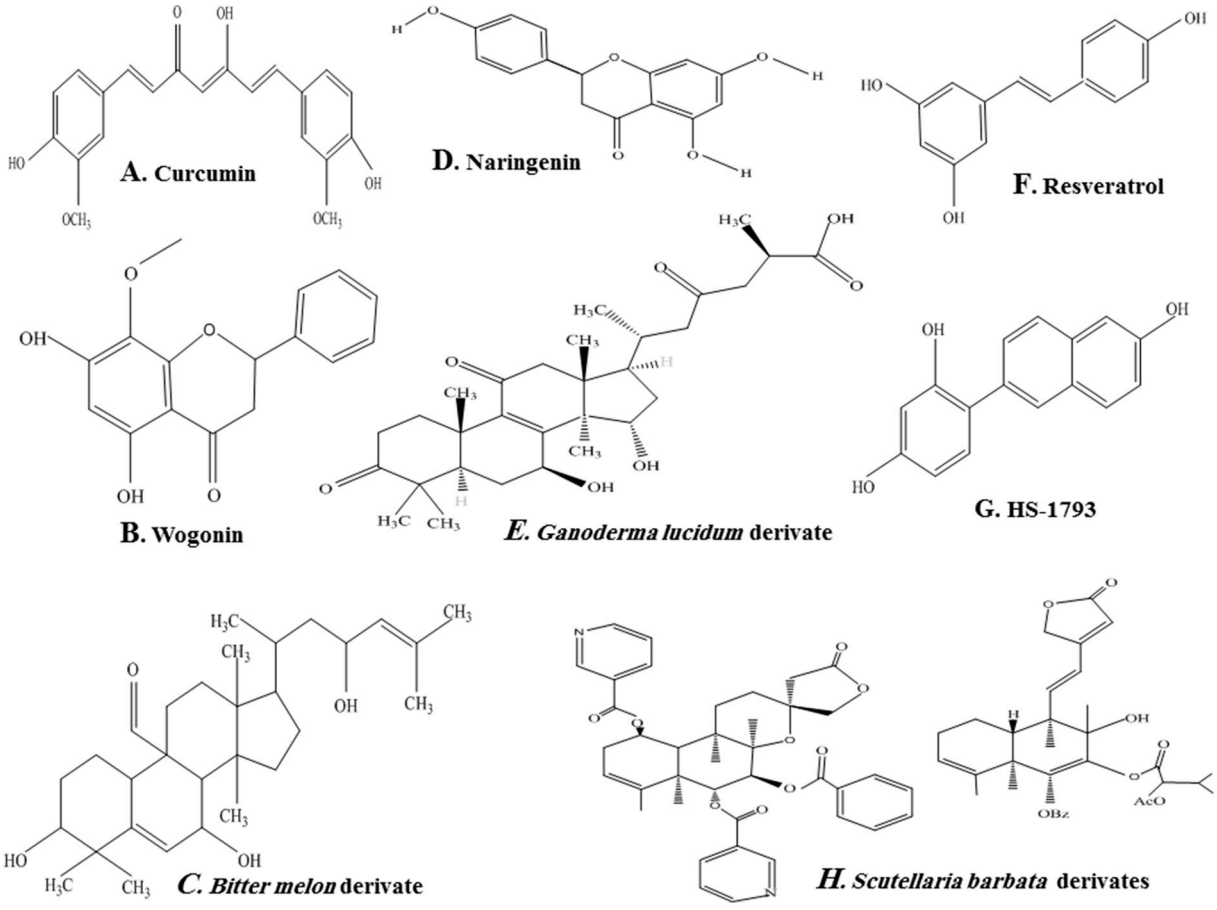

Fig. 1. Chemical structure of natural products reducing Treg populations (A, B, C, D, E, F, G and H), decreasing TGF-β levels (A, B, D, F, G and H), and enhancing IFN-γ levels (A, D, F, G and H) in tumors.

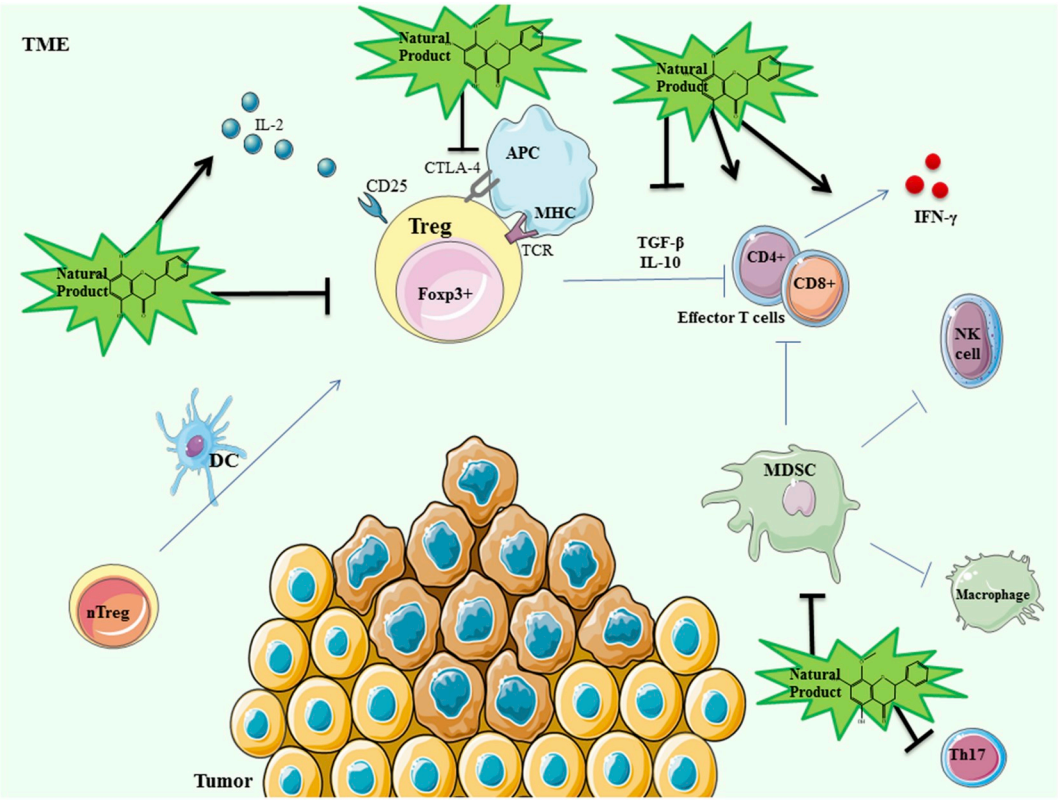

Fig. 2. Inhibitory effects of natural products on tumors through attenuating Tregs, decreasing TGF-β and IL-10 levels, elevating the proportion of effector T cell to Tregs, inducing IFN-γ production of effector T cells, reducing MDSCs, diminishing Th17 cell population, preventing cell–cell interaction of Tregs *via* the down-expression of CTLA-4, and prevention of both IL-2 consumption and IL-2 expansion. **Abbreviations:** Antigen-presenting cell (APC); cytotoxic T-lymphocyte antigen 4 (CTLA4); dendritic cells (DCs); forkhead box protein-3 (Foxp3); interferon gamma (IFN-γ); interleukin (IL); regulatory T cells (Tregs); myeloid-derived suppressor cells (MDSC); natural killer (NK); Natural regulatory T cell (nTreg); tumor microenvironment (TME); transforming growth factor (TGF).

It has been shown that curcumin can not only reduce Treg suppressive potency but can also prevent its augmentation in tumor-carrying host. In this regard, curcumin may potentially inhibit tumor-induced dysfunction of T cell-mediated immune responses. In tumorigenesis, the loss of effector and memory T cells, a skewing of the immune response from type 1 towards a type 2, as well as a declined production of effector T cells has been well documented. Curcumin successfully restricted loss of T cells, extended the frequency of both memory T cell and effector memory T cells, overturned the type 2 immune shift and ameliorated the tumor-induced suppression of T cell production in tumor-harboring hosts. Moreover, prevention of suppressive action of Treg cells through down-regulating gene expression of TGF-β and IL-10 in cancer cells has been achieved after curcumin therapy. Finally, curcumin boosted the capability of effector T cells to eradicate tumor cells [63].

Autophagy is a catabolic process overactivated in malignant cells and overexpressed in stressful states. Autophagy is the most frequent escape mechanism in tumor cells in order to survive [64]. However, the question whether blockage or induction of autophagy may promote the successful rate of chemotherapy-mediated anti-tumor response remains still unanswered. Recently, Masuelli et al. investigated the *in vitro* and *in vivo* anti-tumor effects of curcumin administration with or without the autophagy inhibitor chloroquine on Her2/neu-overexpressing murine mammary cancer cell lines (TUBO). Curcumin-induced cell death in TUBO was enhanced by combination with chloroquine and a little in nude mice. However, chloroquine deactivated the curcumin cytotoxic impact in immune competent mice, since absence of tumor repression and lower overall survival was observed in these mice in comparison with only curcumin-treated mice. Curcumin/chloroquine-treated mice significantly recruited Foxp3 T cell, enhancing the release of vascular endothelial growth factor (VEGF) and angiogenesis in the TME, and decreased T cytotoxic cells *versus* mice with curcumin treatment alone. These results indicate that autophagy is substantial to evoke anti-cancer immune response and that autophagy withholding by chloroquine diminishes this response also *via* infiltrating Treg cells within tumor and inhibiting the anti-cancer performance of curcumin. It has been suggested that autophagy induction instead of suppression may upgrade the beneficial effect of chemotherapy/radiotherapy [65].

Recently, it has been shown that a lipid-based tumor-associated antigen (Trp2) peptide vaccine platform was effective as immunotherapy against melanoma [66]. However, the suppressive immune status within TME is an obstacle against a successful therapeutic vaccine. The addition of curcumin–polyethylene glycol conjugate (PEG), an amphiphilic nanocurcumin-based micelle, to vaccine therapy caused a synergistic anti-tumor effect in the B16F10 tumor–bearing mice. Combination therapy could inhibit signal transducer and activator of transcription 3 pathway (STAT3) activation in the tumor by a reduction of the expression of the immunosuppressive cells, like MDSCs, and Treg, which lead to a easier CD8 + T cells recruitment. Furthermore, curcumin–PEG also reduced the MDSC population in the spleen, which could promote the vaccine efficacy by generating cytotoxic T cells [67].

2.1.2. Resveratrol (RSV)

Resveratrol (RSV) (3,5,4′-trihydroxy-trans-stilbene), a non-flavonoid polyphenol, exists in several dietary constituents such as skin of red grapes, mulberries, pomegranate, Japanese knot-weed plant, soy beans, and peanuts (Fig. 1) [68]. This natural agent is known for its important beneficial properties as an antioxidant, anti-cancer, anti-viral, anti-fungal, anti-inflammatory, immunomodulatory and anti-

aging agent [69–71]. Several *in vitro* and *in vivo* studies demonstrated that RSV may exert different cardiovascular protective effects [72,73]. There is accumulating evidence about the importance of RSV in chemoprevention and cancer therapy in different tumor types including both hematological and solid malignancies [74–81]. RSV can stimulate cell cycle arrest and trigger apoptosis in malignant cells [82,83]. Indeed, promotion of immune responses through the increase of Th1 cytokines and the expansion of T active lymphocytes was observed after RSV administration [84]. It has been speculated that RSV anti-tumor effects may be mediated by Tregs.

Both *in vitro* and *in vivo* experiments showed that RSV significantly decreased the proportion of $CD4^+CD25^+$ cells among $CD4^+$ T cells through a dose-dependent mechanism. Furthermore, Foxp3+ expressing cell populations among $CD4^+CD25^+$ T cells were substantially reduced after RSV administration. In addition, both *in vivo* and *ex vivo* studies reported that RSV abrogated the release of TGF-β, but increased mRNA transcription of IFN-γ in $CD8^+$ activated cells, thereby promoting immune responses (Fig. 2). These findings suggest that RSV has an inhibitory role on Tregs within $CD4^+$ cells and creates an undesirable peri-TME in mice model of cancer. Thus, RSV may serve as a potential adjuvant therapy in cancer immunotherapy; nonetheless, the association between RSV and Treg cells has not been clarified yet. Thus, further research in this field is needed [85].

Similarly, low doses of RSV inhibited Renca renal cancer growth by activating $CD8^+$ T lymphocytes. After RSV administration, the number of Tregs decreased, whereas the number of MDSCs did not significant change. Noteworthy, cumulating quantity of activated $CD8^+$ T cells within TME in the RSV-treated group highlighted the overexpression of Fas ligand (FasL) and a higher cytotoxicity. RSV decreased the expression of Th2 cytokines (*i.e.*, IL-6 and -10) and increased the expression of Th1 cytokines (*i.e.*, IFN-γ), thereby promoting the amplification of Fas in Renca cells. Likewise, RSV inhibited tumor angiogenesis by reducing VEGF levels in TME. RSV might be a potential agent for renal cancer immunotherapy *via* modulating the Tregs within TME [86].

Immunotherapy by high-dose cytokine IL-2 (HDIL-2) is a potent remedy for patients with advanced renal cancer and melanoma. Meanwhile, it is associated with severe toxicity, including endothelial cell damage and IL-2-induced vascular leak syndrome (VLS). Guan and colleagues demonstrated that RSV could reduce the endothelial cell damage and suppress the progress to VLS, thereby enhancing the effectiveness of HDIL-2 treatment in metastasized melanoma. In particular, RSV significantly reduced the occurrence of VLS in C57BL/6 mice undergoing HDIL-2 therapy, by supporting the integrity of endothelial cells and inhibiting endothelial cell apoptosis. More importantly, the combination of HDIL-2 and RSV treatment was significantly more successful in abrogating tumor growth and dissemination compared to HDIL-2 therapy alone. RSV induced the proliferation of MDSCs that prevented the progression to VLS, but repressed the HDIL-2-induced enlargement of Tregs. Therewith, RSV promoted the vulnerability of melanoma cells to the cytotoxic effect of IL-2-activated killer cells, and up-regulated the expression of Forkhead transcription factor FKHR (Foxo1), a tumor suppressor gene. These findings suggested the potential effects of RSV in HDIL-2 melanoma therapy through the induction of MDSC expansion and the inhibition of Tregs expansion [87].

On the other hand, tumor metastasis needs another player, a distinctive subset of TGF-β–generating regulatory B cells, namely tumor-evoked regulatory B cells (tBregs) [88,89]. In fact, tBregs are involved in the TGF-β-dependent switching of non-Treg $CD4^+$ T cells to metastasis-inducing Foxp3+ Treg cells [88], which inactivate NK cells and $CD8^+$ T lymphocytes and, consequently support propagation of tumor cells [89,90].

RSV can significantly block mouse lung metastasis through the inactivation of STAT3, the inhibition of the production and activity of tBregs. Consequently, it allows host anti-tumor immune responses *via* inactivation of tBreg-induced bias to Foxp3+ Tregs. However, any change in MDSC populations in tumor-bearing mice was not observed following RSV administration [91].

However, RSV only at high doses shows a significant efficacy, and its clinical utility for treating cancer is limited by its photosensitivity and metabolic instability. Therefore, a more stable and strong analogue of RSV, with a rather potent tumoricidal ability, is required. A novel synthetic RSV derivative, HS-1793, has recently been developed to more effectively abolish viability of cancer cell compared to RSV [92].

Two similar studies reported that HS-1793 displayed both preventive and therapeutic benefits against cancer. The frequency of Tregs and the production of TGF-β inducing Tregs were significantly decreased in the spleen and tumor tissues from HS-1793-treated tumor-bearing mice. By contrast, the supplementation with HS-1793 increased the number of IFN-γ-regulating $CD8^+$ cells, elevated IFN-γ stimulation and production, and also promoted the cytotoxicity of splenocytes to FM3A breast tumor cells [93,94]. Beside, HS-1793 abrogated IL-2 secretion and stimulated IL-4 release of concanavalin A (Con A)-induced lymphocytes from FM3A breast tumor-bearing mice in a dose-dependent manner [94]. These findings suggest that HS-1793 modulate the activity of cancer-derived T cells, reflecting an inhibitory impact on the Tregs, presumably being involved in promoting tumor-specific $CD8^+$ T cell cytotoxicity responses and $CD4^+$ T cells protecting action against tumor development and immunoediting.

2.1.3. Flavonoids

Flavonoids represent the most common class of polyphenols, accounting for 60% of total natural polyphenols. More than 4000 forms of natural flavonoids have been characterized, including anthocyanins, chalcones, proanthocyanidins, flavonols, flavones, isoflavones, and flavanones [95]. In last decades, flavonoids attracted scientific attention due to their potential chemo-preventive and anti-cancer properties [96,97].

2.1.3.1. Skullcap extracts. Extracts or flavonoids constituents from the traditional herb *Scutellaria* sp., which belong to the family of herbaceous crops commonly named as American skullcaps, have demonstrated encouraging efficacy against several human cancers, including malignant glioma [98,99] and breast cancer [100,101]. Skullcap (*Scutellaria lateriflora L. Lamiaceae*) consists of nearly 400 Scutellaria species in the world. The most widely used and well-studied species is baical skullcap (*S. baicalensis*), also known as Huang-qin, which have higher sterols and phenolic compounds [102]. In addition to *S. baicalensis*, other species such as *S. lateriflora*, *S. amoena*, *S. rehderiana*, *S. hypericifolia*, *S. tenax*, and *S. viscidula* are extensively used as an ataractic and for treating several disorders [103–105]. It has been reported that Baicalein can suppresses platelet 12-lipoxygenase-1 [106], and lipid peroxidation [107]. Extracts of *S. lateriflora* have anxiolytic features [108]. *S. baicalensis*, and *S. barbata,* are native to China and Korea respectively, while *S. lateriflora* is widely employed by native Americans [104,105].

Specifically, *Scutellaria barbata* D. Don (SB), a tall perennial herb, is widely found in China and Korea [109]. It has been shown that flavonoids and scutebarbatines are the major physiological active ingredients of SB (Fig. 1). SB has traditionally been utilized in China in order to treat different types of human malignancies [110,111]. It has been shown that SB extract (SBE) hindered the HepG2 cells proliferation *in vitro* in a dose-dependent manner and considerably inhibited growth of implanted tumor in hepatoma-bearing mice. SBE decreased the Treg populations and frequency of Th17 cells in TME, and lowered the serum values of IL-10, and TGF-β, while elevated IL-2 and IFN-γ in hepatoma-carrying mice (Fig. 2). Thus, it has been proposed that SBE might regulate the exploiting of Treg cells in TME [112].

A methoxyflavone, wogonin (WG; 5,7-dihydroxy-8-methoxyflvone) is isolated from the roots of *Scutellaria baicalensis* Georgi, known for its potency in inducing apoptosis in tumor cells, with high efficacy and low adverse effects [113].

WG and *Scutellaria ocmulgee* leaf extract (SocL) could suppress TGF-β1-induced Treg function in malignant gliomas. It has been detected a substantial attenuation of tumoral TGF-β1 and Treg populations as well as circulating levels of TGF-β1 in a SocL-supplemented rat model of glioma. SocL and WG impeded glioma progression, TGF-β1-mediated Tregs action, the release of IL-10 *in vitro*, whereas IL-2 levels were not influenced or only marginally increased. Additionally, SocL *plus* WG inhibited Smad-3, GSK-3β and ERK1/2 axis in Tregs, though P38 MAPK phosphorylation was significantly promoted, suggesting that SocL or WG could prevent the T cell response to TGF-β1 through mediating both Smad and non-Smad cascades [114].

2.1.3.2. Naringenin. Naringenin (NAR; 4′,5,7-trihydroxyflavanone), one of the flavanone family members, is found in vegetables and citrus fruits such as grapefruits, tomatoes, and tomato-derived products (Fig. 1). Many studies have reported different pharmacological activities for NAR, including antioxidant, anti-inflammatoty, anti-mutagenic, anti-atherogenic and anti-cancer [115].

Patients with pulmonary fibrosis have a higher risk of developing lung carcinoma, possibly because of unbalanced local immunoregulation. Accordingly, the fibrotic environment surrounding the affected lung areas increases TGF-β1 availability, promotes overproliferation of Tregs and reduces the percentage of effector T cells, thus generating immunosuppressive circumstances which facilitate tumor formation and development. NAR considerably abrogated lung metastases in pulmonary fibrotic mice *via* a decreased expression of TGF-β1 and frequency of Tregs in the TME. NAR significantly decreased TGF-β1 both in tumor tissues and circulation of mice with bleomycin-induced pulmonary fibrosis. NAR also enhanced the availability of effector T cells, but also recovered the functions of the CTLs and IFN-γ release in order to oppose to tumor and fibrosis [116].

Similarly, oral ingestion of NAR remarkably mitigated the frequency of metastatic malignant cells in the lung and prolonged the life expectancy of tumor resected mice. Elevated levels of IFN-γ and IL-2 by T cells boosted anti-tumor activity in NAR treated mice. *In vitro* experiments revealed that NAR impeded TGF-β1-stimulated Treg proliferation (Fig. 2). In fact, NAR significantly decreased the rate of TGF-β1-induced conversion of naive $CD4^+$ T cells to Tregs (from 24% to 11%). Regulation of immunosuppression induced by Tregs might be the main mechanism of NAR-mediated suppression of metastasis [117]. Previous study also provided the evidence that NAR could block TGF-β ligand interactions with its receptor, thus preventing TGF-β signaling pathway and transcription of downstream genes [118]. Consistently, NAR can block TGF-β1 transport from the trans-Golgi network through repressing protein kinase C (PKC) activation, leading to reduced TGF-β1 secretion and transformation of lymphatic T cells into Tregs in breast cancer [119]. Altogether, these findings suggest that oral ingestion of NAR can exert anti-cancer effects through restoring T cell activity.

2.1.3.3. Tannins. Tannins are a group of polyphenolic compounds found in different contents in many fruits and vegetables such as cereals, leguminous seeds, bananas, sorghum, grapes, red wine, tea, coffee, persimmons, and chocolate [120]. Tannins are categorized into hydrolysable (*syn.* catechin tannins) and condensed tannins (*syn.* proanthocyanidins). Hydrolysable tannins are secondary metabolites belonging to the family of vegetable tannins; they consist of a center hydrophobic core of polyhydric alcohol such as glucose, glucitol, shikimic acid, quercitol, as well as a hydroxyl hydrophilic shell. *Caesalpinia spinosa* is a shrub, widely known as divi-divi, which has anti-bacterial and antioxidant actions, possibly due to its hydrolysable tannins [121].

It has been observed that the gallotannin-rich fraction of *C.spinosa* (named P2Et) is an antioxidant and anti-tumor agent, and shows cytotoxic effects against several malignancies [122–124]. Previously, it has been shown that P2Et has anti-tumor effects in both breast cancer and melanoma [123,125,126]. However, prophylactic therapy with P2Et yielded conflicting results. Prophylactic-P2Et treatment in healthful mice enhanced the frequency of $CD4^+$ and $CD8^+$ T cells, NK cells, Tregs, DCs and MDSCs in immune organs. Surprisingly, pre-incubation of P2Et and host immune cells did not result in anti-proliferation and anti-metastasis effects in transplantable models of B16-F1 melanomas and 4T1 breast tumor. A disadvantageous effect was detected in both models possibly due to the extended number of Tregs, MDSCs, and proinflammatory cytokines, together with a decrease in $CD4^+$ and $CD8^+$ active T cells. Altogether, this evidence indicates that the anti-tumoral and immunomodulatory effects of the P2Et extract crucially rely on the existence of the tumor and may potentially be mediated *via* the complicated communications between the malignant cells and the other elements and factors of the TME [127].

2.1.3.4. Other flavonoids. Legumes are known to be a source of isoflavones. Soybeans are known to enrich a high amount of bioactive gradients (*i.e.*, isoflavones, phytosterols, sphingolipids, and phenolic acids) [128,129]. Oral consumption of isoflavones is correlated with human health advantages such as reduced risk of cardiovascular disease, menopausal symptoms, osteoporosis and several tumors [104,130–132].

In a crossover randomized trial, 32 prostate cancer patients were randomly assigned to receive 2 slices of soy bread (34 mg isoflavones per slice) or soy almond bread for 8 weeks. At the end of the study the concentration of Th1 and MDSC-associated cytokines was significantly reduced, but percentages of Th2 and Th17 cytokines as well as $CD8^+$ and $CD4^+$ T cells were not influenced. Instead the number of NK cells was significantly elevated. The frequency of Tregs and monocytic ($CD33+HLADR\text{-}CD14^+$) MDSCs was declined after the intervention. Overall, soy bread can abrogate inflammation and reduce the number of Tregs and MDSCs in prostate cancer patients [133].

Grape seeds include polyphenol members belonging to the family of proanthocyanidins, which are a group of complex phytochemicals composed of polymers of polyhydroxy flavan-3-ol units [134]. IH636 grape seed proanthocyanidin (GSP) extract, which is a standardized water-ethanol extract obtained from red grape seeds, is commercially prepared as ActiVin [135].

Ultraviolet B (UVB) radiation cause to activation of Tregs and depletion of these Tregs attenuates immunosuppression and photocarcinogenesis in mice. It has been shown that consumption of GSP inhibits the development and function of Tregs, and also diminishes the capability of the Tregs to enhance the proliferation of IL-10 and TGF-β in UVB-exposed mice. In addition, GSPs also induce Tregs to promote IFN-γ production by T cells. Indeed, dietary GSP inhibited UVB-induced skin tumor formation in wild-type mice through inactivation of Treg cells by enhancing DNA repair of dendritic cells in UVB-exposed skin [136].

2.2. Polyunsaturated fatty acids

It has been reported that consumption of n-3 polyunsaturated fatty acids (PUFAs) has advantageous effects on inflammatory diseases by alleviating inflammation [137]. Preliminary researches displayed that fish oil consumption could increase Foxp3 expression and Treg population in animal models of inflammatory diseases [138,139]. Yessoufou and co-workers have also demonstrated that the treatment of Tregs with n-3 PUFAs overexpressed Treg markers such as Foxp3 at both transcription and translation levels, but reduced their immune suppressive function *via* down-expressing immunosuppressive factors such as IL-10 [140]. The competency of Tregs to impede or interdict the tumor related-inflammation relies on their ability to produce IL-10, which assert maintenance of immune balance and prepares an anti-inflammatory Treg property [140]. Patients with weaken IL-10 and Treg-mediated repressive cycle are increasingly vulnerable to inflammation-related malignancies.

In a recent study, treatment with fish oil and corn oil, as a source of

n-3 and n-6 PUFAs respectively, increased the frequency of nTregs and iTregs in colonic intraepithelial lymphocytes but also decreased IL-10 and IL-6 levels. Actually, fish oil modulates immune response on colon cancer *via* modifying Tregs and associated cytokines [141]. These findings supported previous results showing the significant reduction of IL-10 concentrations in colonic intraepithelial lymphocytes after fish oil treatment [142]. One possible mechanism by which Tregs perform their regulatory activity is through generation of the anti-inflammatory cytokine IL-10, whose levels are directly associated with worsen survival in several cancer types [143–145].

Supplementation with either fish oil or selenium yeast had small or no significant effect on the frequency of Tregs and MDSCs in murine lung carcinoma model. But, administration of both fish oil and selenium simultaneously revealed a synergetic effect, as demonstrated by the reduced number of Tregs and MDSCs and the alleviation of cachexia in tumor-bearing mice. This finding supported the hypothesis that combination of selenium with fish oil has an immunomodulatory impact on lung cancer [146].

2.3. Mushroom extract

A large number of mushrooms have been used as common folk immune potentiators against cancer and many polysaccharides and protein-polysaccharide complexes with anti-tumor potency have been derived from mushrooms [147]. The mushroom *Agaricus blazei* Murill (AbM), also known in Brazil as “Cogumelo do Sol”, has long been used as a food and for medicinal purposes. In a phase I clinical study of cancer patients, consumption doses of AbM 1.8, 3.6, 5.4 g/day (granulated powder) for six months was well tolerated [148]. This mushroom has been used in a variety of diseases, including diabetes, arteriosclerosis, allergic/asthma, hepatitis, hypercholesterolemia, heart disease and cancer. These effects are mediated by the AbM-mediated stimulation of innate immune systems [149]. In a randomized, double-blind, placebo-controlled study, AbM was tested in 40 patients with multiple myeloma undergoing intensive chemotherapy *plus* autologous stem cell transplantation; 19 patients (47.5%) received adjuvant mushroom extract AndoSan (containing 82% AbM) and 21 patients (52.5%) received placebo. At the end of study, raised numbers of Tregs and plasmacytoid DCs were found in the leukapheresis product along with elevated concentrations of IL-1RA, IL-5, and IL-7 in cases receiving AbM than in controls. Increasing Treg population after AbM supplementation may represent an immunosuppressive indicator with negative effects on prognosis [150].

Dehydrated flour from *Lentinula edodes* mycelia (L.E.M) extract has been shown to possess anti-cancer and immunomodulatory properties [151,152]. Administration of L.E.M. extract considerably suppressed tumor growth probably through contribution of T cell. Oral feeding of melanoma-bearing mice with L.E.M. extract also led to significant reduction in Treg populations and also decreased transcription levels of Foxp3 and slightly TGF-β within the tumor (Fig. 2). Oral administration of L.E.M extract enhanced MHC class I-restricted and tumor-reactive CD8 + T cells within melanoma-carrying mice, likely through the attenuation of Tregs-mediated immunosuppression [153]. L.E.M has revealed no evidence of toxicity, even at high doses > 50 mg/day for one week [154].

2.4. Ginger

6-Gingerol (1-[4′-hydroxy-3′-methoxyphenyl]-5-hydroxy-3-decanone) (6-G) is the bioactive pungent ingredient in *Zingiber officinale* Roscoe (Zingiberaceae); it is widely used as a condiment and in complementary and alternative medicine. Ginger and its gradients at doses up to 2.0 g/day have minimum toxicity and are well-tolerated in both laboratory animals and humans. Ginger is generally accepted as safe on the U.S. FDA's list [155]. The rhizome of this plant has been identified to have therapeutic benefits such as anti-inflammation, anti-bacterial and anti-tumor activity [156,157]. Specifically, 6-G suppressed tumor growth in different mouse tumor models, like B16-F1 melanoma cells, CT26 colon carcinoma cells, and Renca renal cancer, albeit it was not able to eradicate the tumor completely. 6-G administration led to an enormous recruitment of $CD4^+$ and $CD8^+$ T cells and also B220 + B cells, and decreased the Treg populations in tumor-carrying mice. After 6-G supplementation, the intratumoral CD8 infiltrating T cells increasingly expressed IFN-γ and CD107a; also, Th1 cells expressed chemokine receptors (i.e., CCR5) and CXC chemokine receptor 3 (CXCR3) in treated mice. Thus, 6-G may have the potential to be used in cancer immunotherapy in order to enhance the population of tumor-infiltrating lymphocytes [158].

2.5. Devil's club

The ethnobotanical Devil's club (*Oplopanax horridus* Miq.) as a deciduous shrub belongs to the Araliaceae family. It is associated to taxonomy of the well-known medicinals, for instance Asian ginseng (*Panax ginseng*), American ginseng (*Panax quinquefolius L.*), and Siberian ginseng (*Acanthopanax senticosus*) (Fig. 1) [159]. For centuries, the inner bark of aerial stems, root and berries of this plant has been frequently used as decoctions, poultices, chewing, and consumption of pastes for the prevention and treatment of rheumatoid arthritis, cancer, autoimmune diseases, diabetes, infections, pneumonia, dandruff, lice and colds [160,161]. Innovative *in vivo* model of acute myeloid leukemia demonstrated that Devil's club root extract increased the murine survival through mitigating Tregs and increasing $CD8^+$ T cell activity [162].

2.6. Polysaccharides

Polysaccharides are macromolecular biopolymers, composed of complex carbohydrates including at least ten monosaccharides joined through glycosidic bonds which can be linear or branched. Carbohydrates have a generalized formula $C_x(H_2O)_y$ where x would be a number in the value of 200–2500. Structurally, polysaccharides are differ according to the variation in architecture of monosaccharide residues, glycosidic bonds, molecular weights, sugar sequence, and degrees of polymerization and branching [163]. There are two types of polysaccharides: homopolymers in which polymer is made up by similar monosaccharides, or heteropolymers, in which polymer consists of more than two types of monosaccharides [164].

Polysaccharides can be categorized in 2 groups regarding to their origin. Natural polysaccharides are usually derived from different sources, such as plants, seaweed, fungal, bacterial, and animals. Instead, semi-synthetic polysaccharides are generated through the modification of the polysaccharides by chemical or enzymatic reactions [165].

Seaweed polysaccharides (hydrocolloids), as alginate, fucoidan, carrageenan, laminaran, and agarose [166], are widely used in biomedical fields [167–169]. Bacterial polysaccharides, including extracellular polysaccharides (EPS), have highly variable structures and play a key role in protection against environmental stresses, matrix stabilization and energy storage [170,171]. Five pentoses including D-ribose, D- and L-xylose, and D- and L-arabinose, 6 aldohexoses including D-glucose, D-and L-mannose, D-allose, D-galactose, and L-altrose as well as 3 heptoses including L-*glycero*-D-*manno*-heptose, D-*glycero*-D-*galacto*-heptose, and D-*glycero*-D-*manno*-heptose have been found in EPS [172].

Fungal polysaccharides, isolated from mycelium, mushroom fruiting bodies, and fermentation broth of medicinal fungi and edible mushrooms have been emerged as a promising natural source of immunoregulatory compounds [173,174]. *Ganoderma lucidum*, a derivation of edible Basidiomycete, has long been used as a pharmaceutical and complementary compound in numerous Asian countries (Fig. 1). The great biologically and functionally active components of *G. lucidum* are triterpenoids and polysaccharides. G. *lucidum* polysaccharides

(GLPS) have been reported to possess several advantageous clinical properties, such as anti-tumor, anti-inflammation, immunomodulating and antioxidant [175,176]. Orally consumption of dried hot water extract of *G. lucidum* (36/72 g; daily) was reported to be effective in healing of human lesions without any toxic events even at very high doses [177].

GLPS significantly repressed tumor growth in animal model of hepatoma through elevating the proportion of effector T cell to Tregs. Besides, GLPS abolished the inhibitory effect of Tregs on effector T cell production with an enhanced secretion of IL-2. GLPS treatment blocked Notch1 pathway and Foxp3 gene amplification *via* overexpression of miR-125b in T cells. This evidence provides an insight into the GLPS mechanisms against hepatocellular carcinoma *via* miR-125b inhibition of Tregs proliferation and action, which led to suppression of Notch1 cascade and Foxp3 expression [178].

2.7. Bitter melon

Bitter melon or bitter gourd (*Momordica charantia*) is one of dietary plants known for their biological functions in alternative therapy. This plant has antioxidant, anti-inflammatory, anti-tumor, anti-glycemic, anti-septic, and immunomodulatory effects (Figs. 1 and 2). Bitter melon-related products may abolish tumor cell growth through inhibiting tumor formation and proliferation, inducing apoptotic cell death, modulating cell cycle, autophagy and immune system [179]. In several clinical trials, tablets of dried powder of bitter melon dosage from 500 to 6000 mg/day were selected for intervention [180–182]. Particularly, oral administration of bitter melon extract (BME) significantly inhibited the head and neck cancer growth in mice *versus* control group. In addition, BME feeding attenuated the infiltrating Tregs through hindering FoxP3+ populations in the local tumor tissues and in spleens of mice. Furthermore, BME treatment diminished Th17 cell population within the tumor, but did not change Th1 and Th2 cell populations [183]. Furthermore, BME treatment increased cytotoxic capability of human NK-cell line (NK3.3) to kill head and neck squamous cell carcinoma cells through promoting granzyme B accumulation and modulating CD107a/LAMP1. BME enhanced the expression of CD16 and NKp30 in NK3.3 cells cocultured with head and neck squamous cell carcinoma cells [184]. Altogether, it seems that BME suppresses growth of head and neck carcinoma *via* modulating cell reproduction, Treg populations and NK-cell–mediating killing action. In another report, a higher expression of immune system-associated genes, *s100a9, IL-23a, IL-1β, and programmed cell death (PDCD1)/PD1*, which occurred during oral cancer progression, was inhibited *via* BME. This finding provides evidence for possible advantages of BME in preventing and repressing oral carcinoma development [185].

3. Conclusion and future perspective

The immune system has a key role in anti-tumor defense by monitoring cells with the potential to become malignant, and by eradicating them. Treg infiltration into the tumors plays a significant role in tumor immune evasion and it is considered the major obstacle for effective immunotherapy. Moreover, reduced proportions of effector T cells to Tregs in tumor-infiltrating lymphocytes are closely linked to worse prognosis in different tumors. Thus, it is a proper conditioning approach to make TME unfavorable for the growth of tumor cells through the manipulation of Tregs without hurting host tissues. Recent progresses in the knowledge about the mechanisms behind the carcinogenesis indicate that one of the best strategies for the management of tumor progression is the induction of anti-cancer immunity. From a clinical point of view, pharmacological therapy represents the only approved approach to increase immune cell activity against cancer. In this regard, significant survival results have been achieved with drug-based immunotherapy. However, resistance to conventional immunotherapy may limit its clinical effectiveness. Several natural compounds extracted from plants have the potential to be used as adjuvant therapy against tumor immune dysfunction, due to their immunomodulatory features. These plant derivatives such as curcumin, resveratrol and flavonoids not only can down-express Treg suppressive function but also can prevent their augmentation in TME. Also, the inhibition of the activity of Treg CTLA-4 by curcumin can disturb the function of Tregs. Natural compounds such as curcumin were successful effective in both preclinical and clinical studies; so they may serve in the future as a novel encouraging therapeutic regimens in cancer immunotherapy. Starting from the current knowledge on the immunomodulatory and anti-cancer effects of some phytochemicals, it should be considered to further optimize their therapeutic effects by developing novel potent tumor specific Treg cell–targeted therapies without considerable side effects.

Conflicts of interest

None.

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