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Modulation of the tumor microenvironment by natural agents: implications for cancer prevention and therapy

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Abstract

The development of cancer is not just the growth and proliferation of a single transformed cell, but its surrounding environment also coevolves with it. Indeed, successful cancer progression depends on the ability of the tumor cells to develop a supportive tumor microenvironment consisting of various types of stromal cells. The interactions between the tumor and stromal cells are bidirectional and mediated through a variety of growth factors, cytokines, metabolites, and other biomolecules secreted by these cells. Tumor-stromal crosstalk creates optimal conditions for the tumor growth, metastasis, evasion of immune surveillance, and therapy resistance, and its targeting is being explored for clinical management of cancer. Natural agents from plants and marine life have been at the forefront of traditional medicine. Numerous epidemiological studies have reported the health benefits imparted on the consumption of certain fruits, vegetables, and their derived products. Indeed, a significant majority of anti-cancer drugs in clinical use are either naturally occurring compounds or their derivatives. In this review, we describe fundamental cellular and non-cellular components of the tumor microenvironment and discuss the significance of natural compounds in their targeting. Existing literature provides hope that novel prevention and therapeutic approaches will emerge from ongoing scientific efforts leading to the reduced tumor burden and improve clinical outcomes in cancer patients.

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1. Introduction

Cancer is one of the significant causes of death, affecting millions of people globally. About 1,806,590 new cancer diagnoses and nearly 606,520 cancer-related deaths are expected in 2020 in the United States alone [1]. To address this significant clinical problem, we have made extensive efforts on several fronts, including the basic biology of cancer. Over the past several years, we have witnessed significant progress in our understanding of cancer genetics and relevant signaling pathways affecting tumor phenotypes. We have also learned that tumors are not just a mass of transformed cells but are comprised of other non-malignant cells as well, ranging from fibroblasts, endothelial cells, and immune cells to even microbes [2–8]. As tumor cells progress to become highly malignant, their microenvironment also co-evolves. Indeed, tumor cells continue to corrupt the non-malignant stromal cells as they grow and use them to support their growth, metastasis, therapy resistance, and to evade the immune defense [9–15]. Tumor-stromal interactions are driven by growth factors, cytokines, metabolites, and other biomolecules secreted by the cells within the tumor microenvironment (TME). These interactions are often bidirectional and essential for optimal tumor growth, and thus provide targeting opportunities for effective clinical management.

Natural products are generated in abundance by plants and marine organisms and have been utilized for centuries in traditional medicines [16, 17]. Most of the bioactive natural products are secondary metabolites that aid in survival by often serving as mediators of innate defense mechanisms [18]. These compounds gained significant attention after different epidemiological studies reported the health benefits of the consumption of certain fruits, vegetables, and their derived products [19–22]. It also renewed the interest in ancient literature from Middle Eastern and South Asian countries that reports healing powers of natural compounds and associated practices. Over the years, bioactive constituents from natural sources have been isolated and experimentally validated for their anti-viral, anti-bacterial, anti-inflammatory, anti-fungal, and anti-cancer properties [21, 23–25]. Indeed, about forty-seven percent of all anti-cancer drugs in clinical use are derived from the naturally-occurring compounds [26]. These natural compounds exhibit significant diversity in structure, function, and biosynthesis, and therefore it is hard to classify them under strict categories. However, they are broadly put under four structural classes that include terpenoids and steroids, alkaloids, fatty acid derivatives and polyketides, and phenylpropanoids [27]. While the majority of the earlier studies investigated the effect of natural compounds on the tumor cells [28, 29], the focus later expanded to include TME components as well. These efforts resulted in the demonstration of TME-modulating effects of natural agents in multiple cancer types, as reviewed in [30–35]. Recent years have witnessed significantly increased efforts towards understanding the roles of TME in cancer pathogenesis after the reported success of immunotherapy in some cancer types [36–38].

Driven with this impetus, more and more natural compounds are now being evaluated for their TME-modulating properties in parallel investigations [39–41]. In light of the new data emerging from these efforts, it has become imperative that we revisit natural compounds to understand their broader significance in the modulation of TME as well as associated mechanisms. This review provides a comprehensive summary of the current literature on TME, especially highlighting its fundamental cellular and acellular components, and discusses their functions as well as the factors regulating the behavior and functional properties of the stromal cells. After that, we discuss the natural products of plant and marine origin that target TME via different mechanisms to confer their anti-cancer activity. The expectation is that the presented discussion would encourage cancer biologists and cancer chemoprevention and therapy experts to engage in cross-disciplinary collaborations to allow future translational advancements.

2. The cellular component of the tumor microenvironment

Principal non-malignant cells within the TME are fibroblasts, endothelial cells, and immune cells (macrophages,myeloid-derived suppressor cells (MDSCs), and lymphocytes. It has also recently been recognized that microbial cells are present within the TME and play an active role in pathobiology and therapy-resistance (Figure 1). Below we discuss in more detail about these cells, their functions, and their characteristics.

2.1. Cancer-associated fibroblasts

Fibroblasts are the quiescent mesenchymal cells that are present within the extracellular matrix (ECM) and play important roles in tissue repair. Upon injury, these cells are activated and differentiate into myofibroblasts through paracrine signaling [42, 43]. Their excessive proliferation can result in organ fibrosis and may have unwanted consequences [44, 45]. Within the context of the tumor, these myofibroblasts are referred to as cancer-associated fibroblasts (CAFs) [3, 6]. In some cases, CAFs can also be derived from other precursor cells, such as endothelial cells, smooth muscle cells, and myoepithelial cells [2, 46]. Differentiation into the CAF phenotype is facilitated by factors derived from tumor cells or other cells within the TME, such as IL-6, transforming growth factor-beta (TGF-β), sonic hedgehog (SHH), and platelet-derived growth factor (PDGF) [12, 47, 48]. Microenvironmental stress (extracellular pH, hypoxia, radiation, and chemotherapy) can further aggravate this process likely to protect and support the tumor cells [49–51]. Recently, the role of tumor-derived exosomes in CAFs generation has also been reported [52].

Morphologically, CAFs have a large spindle shape and express a cytoskeletal protein, α-smooth muscle actin (α-SMA). Some other markers, such as fibroblast activation protein (FAP), platelet-derived growth factor receptor-β, and S100 calcium-binding protein A4, are also used to identify CAFs [53, 54]. None of these markers are expressed exclusively by the CAFs because of their heterogeneous nature within tumor tissues [54, 55]. CAFs abundantly produce collagens, fibronectins, and hyaluronan, and these proteins, along with other ECM components, form a highly dense fibrotic covering around the cancer cells [55, 56]. Studies have suggested that CAFs can regulate tumor progression and therapy resistance by inducing EMT, metabolic reprogramming, activation of survival pathways, modulating anti-oxidant

system, or stemness in tumor cells [38, 55, 57]. CAFs also help in the recruitment of monocytes to the TME and promote their differentiation into immunosuppressive MDSCs [58].

2.2. Tumor-associated endothelial cells

To meet their high demand for oxygen and nutrients, actively dividing cancer cells recruit and activate the endothelial cells into the TME to facilitate the formation of new blood vessels from pre-existing blood capillaries [4]. Endothelial cells form the inner lining of the blood and lymphatic vessels [59, 60]. Single-cell RNA sequencing data has suggested that tumor-associated endothelial cells (TECs) are distinct from the normal ECs [61]. Normal ECs form uniform monolayer with few cytoplasmic projections, whereas TECs are irregular in shape and size with long fragile, or thin cytoplasmic projections extending across the vessel lumen [4]. TECs are $CD31^+$ and $CD105^+$ and appear in a mosaic pattern within the tumor tissues [62]. TME- derived cytokines and growth factors such as interleukin-8 (IL-8), vascular endothelial growth factor A (VEGF-A), and basic fibroblast growth factor (bFGF) aberrantly activate the TECs, which makes resultant blood vessels fragile, leaky and of irregular shape [59, 63]. Tumor cell-derived VEGFA, IL-10, and prostaglandin E2 also induce Fas ligand (FasL) expression in TECs, which causes FasL- mediated apoptosis of $CD8^+$T cells. However, regulatory T cells (Tregs) are not affected much since they express a high level of anti-apoptotic protein, cellular FADD-like IL-1β-converting enzyme (FLICE)-inhibitory protein [64].

2.3. Tumor-associated macrophages

Macrophages are part of the innate immune system and play active and diverse roles due to their highly flexible nature. Based on the environmental stimuli, they can differentiate either into M1 (classical-activated macrophages, anti-tumor) or M2 (alternative-activated macrophages, pro-tumor) phenotypes; a process often referred as macrophage polarization [65, 66]. Innate or adaptive immune cell-derived interferon-γ (IFN-γ) or bacterial cell-derived lipopolysaccharide (LPS) induces M1 polarization, while Th2-type cytokines (IL-4, IL-10, and IL-13) polarize macrophages into M2 phenotype [67]. In the context of cancer, M2 macrophages are often referred to as tumor-associated macrophages (TAMs), and they are the significant component of tumor-infiltrating immune cells within the TME [67, 68]. Unlike M1 macrophages that rely mostly on glycolytic metabolism and produce pro-inflammatory signals [69, 70], M2 macrophages display oxidative phosphorylation and secrete anti-inflammatory cytokines [71, 72]. Moreover, it is possible to convert M2 macrophages into the M1 subtype by altering mitochondrial respiration [70, 72]. Both M1 and M2 macrophages express different markers. M1 subtype expresses inducible nitric oxide synthase (iNOS), suppressor of cytokine signaling 3 (SOCS3), CD68, CD80, CD86, IL-1, IL-16, IL-12, IL-23, TNF-α, IFN-γ, and CXCL-10 whereas M2 macrophages express arginase 1 (Arg-1), CD163, CD200R, IL-10 and TGF-β [73].

2.4. Lymphocytes

Lymphocytes are white blood cells that include T cells, B cells, and natural killer (NK) cells. T-and B- cells are the part of adaptive immune responses, whereas NK cells are part of the innate arm of the immune system [74, 75]. T lymphocytes play a critical

role in cancer immunity and are divided into four subtypes, $CD4^+$ T helper cell, $CD8^+$ cytotoxic T cell, memory T cells, and natural killer T cells (NKT) [76–78]. $CD4^+$ T cells help in B cell maturation and can also activate macrophages and cytotoxic T cells [79]. They become functionally active after recognizing the antigen presented by major histocompatibility complex (MHC) class II molecules [79, 80]. On the other hand, $CD8^+$ T cells respond through MHC class I molecules and involve in the killing of infected or malignant tumor cells [80, 81]. Tumor cells and TME factors desensitize tumor-infiltrating lymphocytes (TILs), and they, in turn, build a tumor supportive immune microenvironment [5, 82]. The direct anti-tumor activity of $CD4^+$ T cells is less explored because a majority of the solid tumor cells do not express MHCII [79, 80]. However, these cells confer anti-tumor activity indirectly either by secreting type I cytokines or activating cytotoxic $CD8^+$ T cells [79, 83]. More importantly, a subset of tumor supportive $CD4^+$ T cells, Tregsarefound within the TME. The normal biological function of Treg cells is to distinguish between self and non-self-antigens that helps in the prevention of autoimmunity. Treg cells express the IL-2 receptor (CD25) and Forkhead Box P3 (FoxP3) transcription factor, which is a master regulator of Tregs functions [84]. Treg cells cause immune suppression in several ways. Notable among these are; i) secretion of immunosuppressive cytokines, IL-10, TGF-β and IL-35; ii) consumption of IL-2 from cellular milieu; and iii) cytotoxic T lymphocyte-associated protein-4 (CTLA-4)-mediated suppression of antigen-presenting cells or by induction of T cell exhaustion [84]. Recently, it was demonstrated that Treg cells indirectly induce the M2 population of macrophages in TME by inhibiting IFN-γ secretion [85]. B cells infiltrated into the TME induce memory $CD4^+$ T cell formation, promote proliferation and survival of activated $CD8^+$ T cells, and can also directly induce apoptosis in tumor cells by secreting granzyme B [86]. Indeed, a high density of tumor-infiltrating B cell subtypes correlates with increased survival [87]. NK cells are innate immune cells, express CD56, and are involved in boosting the host immune defense against pathogens [88]. Overall, these cells mediate anti-tumor and anti-viral immune response by executing cytotoxic action through perforin and granzyme [89].

2.5. Myeloid-derived suppressor cells

Myeloid cells are derived from bone marrow and can be either mononuclear (MN) comprising of monocytes, macrophages, and dendritic cells, or polymorphonuclear (PMN) consisting of neutrophils, basophils, eosinophils and mast cells [90, 91]. During chronic inflammation, pro-inflammatory cytokines activate myeloid progenitor cells to proliferate and differentiate into MDSCs [92]. Therefore, the accumulation of MDSCs is usually seen when a pathological condition exists, and they are mostly absent in a healthy body [91]. MDSCs induce immune suppression and help cancer progression in several ways. These cells either enhance Treg cell recruitment into the TME or differentiate into TAMs [92–94]. MDSCs also promote the differentiation of fibroblasts into CAFs. Monocytic-MDSCs (M-MDSCs) are recruited to TME by CCL-5 and CSF-1, while the TME infiltration of PMN-MDSCs is stimulated by a different set of cytokines including chemokine (C-X-C motif) ligand 12 (CXCL-12), CXCL-1, CXCL5, CXCL-6 and CXCL-8 [90, 91, 95]. Interestingly, cytokine CCL-2 has the ability to attract both M-MDSCs and PMN-MDSCs [96]. Relatively larger extent of M-MDSCs is present in TME as compared to PMN-MDSCs. In solid tumors, hypoxia is shown to induce the differentiation of MMDSCs into TAMs in order

to sustain immune suppression [94]. Studies havealso correlated the increased chance of cancer-associated death in patients who had greater abundance of circulating MDSCs [97–99].

2.6. Microbiome

A microbiome is the community of microorganisms or microbes (bacteria, fungi, protozoa, and viruses) residing in a specific niche such as the human gut. The microbiome can modulate multiple cellular events such as host physiology, cellular metabolism, and immune function. Disturbance in the host-microbiota is often associated with pathological conditions such as inflammatory bowel diseases and cancer [7]. Microbiota regulates mucosal immunity and tissue remodeling, which collectively modulate TME to promote tumor growth [8, 100]. Microbes are associated with approximately 10–20% of human malignancies [101]. The effect of the intratumoral microbiome in cancer progression is not yet well explored. However, a study suggests that *Fusobacterium nucleatum*-derived Fap2 protein interacts with the immune receptor, T-cell immunoglobulin, and ITIM domains (TIGIT), and inhibits the activity of TIGIT-expressing NK and T cells [102].

3. Non-cellular components of the tumor microenvironment

In addition to cellular components, TME is also highly abundant in the secreted material consisting of mostly matrix proteins, cytokines, growth factors, nucleic acid, and metabolites [103]. This acellular material is derived from various cell types and supports the growth of the tumor by enabling bi-directional tumor-stromal interactions [103, 104]. ECM makes the scaffold of tissues and organs and is a collection of biomolecules secreted by different cell types and provides structural and biochemical support to the microenvironment. Specialized ECM (basement membrane) is enriched with fibronectin, collagen, and laminin, whereas the other ECM (interstitial matrix) mostly contains proteoglycans, glycoproteins, and collagen. Importantly, a proteoglycan such as hyaluronic acid (HA) abundantly present in ECM of some solid cancers has gained significant interest as a drug target due to its direct and indirect roles in tumor growth and chemoresistance [105, 106]. Other ECM proteins such as fibulins, secreted protein acidic and rich in cysteine (SPARC), osteopontin, periostin, tenascin(s), and thrombospondins also have an active involvement in tumor pathobiology besides serving as a scaffold for ECM structural proteins [107–109].

4. Role of the tumor microenvironment in cancer pathobiology and therapy-resistance

Several lines of evidence suggest that TME plays a critical role in tumor growth, metastatic progression, and failure of the therapeutic intervention [13, 110, 111]. Tumor cells develop a bidirectional functional association with the surrounding stromal cells during their malignant progression[10, 14, 112]. For instance, pancreatic tumor cells utilize CXCL12, a chemokine secreted by the stromal cells, to not only promote tumor growth and metastasis but also resist the cytotoxic effects of chemotherapy [10, 111, 113]. Interestingly, activation of the CXCL12/CXCR4 pathway in pancreatic tumor cells also promotes synthesis and secretion of sonic hedgehog (SHH) that preferentially acts on the stellate cells to promote

desmoplasia [10]. Desmoplastic TME plays a diverse and significant role in pancreatic cancer pathobiology and chemoresistance [9, 114–116]. In a study on breast cancer, CAFs were shown to induce proliferation of $CD44^{+}CD24^{-}$ cancer stem-like cells via the activation of CXCL12/CXCR4 signaling [117]. Tumor cells also utilize CAFs to fulfill their energy requirements in a limited or nutrient deficient TME. CAFs-derived alanine provides an alternate carbon source to the pancreatic tumor cells under a nutrient-deprived environment [118]. In another report, CAFs-derived IL-6 is shown to induce epithelial to mesenchymal transition (EMT) and confers resistance to cisplatin in non-small cell lung carcinoma [119]. CAFs exposed to chemotherapy have significantly increased the release of exosomes that enhance the expression of Snail in the recipient tumor cells and promote gemcitabine resistance [11]. Exosome-mediated transfer of miR-221 from stromal cells to breast cancer cells triggers the generation of hormonal therapy-resistant metastatic breast cancer [120]. Interestingly, it is shown that gemcitabine is preferentially taken and metabolized by CAFs, limiting its availability to the tumor cells [121]. Moreover, CAFs also secrete various pro-inflammatory molecules (IL-6, CCL2, and TGF-β), which help in the recruitment of immunosuppressive cells [122, 123]. In another study, CXCL12 secreted from FAP^{+}-CAFs was shown to induce CTLA-4- and PD-L1-mediated immunosuppression in pancreatic cancer [124].

High accumulation of TAMs and other immune-suppressive cells in the TME has been suggested to induce aggressive cancer progression and therapy-resistance. $CD163^{+}$ TAMs induce immune suppression, and their depletion promotes robust infiltration of cytotoxic T cells into the TME, leading to the inhibition of melanoma growth [125]. In multiple myeloma patients, high $CD163^{+}$TAMs in TME correlate with worse clinical parameters [126]. In breast cancer, TAMs enhance aerobic glycolysis in tumor cells by transferring hypoxia-inducible factor-1alpha (HIF-1α) stabilizing lncRNA (HISLA) through extracellular vesicles [127]. In clinical settings, HISLA expression associated with inadequate drug response and reduced survival of breast cancer patients [127]. Likewise, pancreatic tumors exhibit increased infiltration of TAMs and low presence of cytotoxic T cells in their TME [128, 129]. TAMs induce the expression of cytidine deaminase, a gemcitabine catabolizing enzyme, in pancreatic tumor cells leading to decreased chemotherapeutic efficacy [130]. Pancreatic tumor educated-TAMs also produce different pyrimidine species, of which deoxycytidine competes with gemcitabine for uptake and metabolism and compromises the therapeutic outcome [131]. In hepatocellular carcinoma (HC), EMT hotpots are the sites of high TAMs infiltration, and HC cells co-cultured with TAMs exhibit induced expression of EMT related genes [132]. Itis also reported that TAMs induce the expression of SPARC, which is a crucial mediator for tumor cell growth, migration, and chemoresistance [133].

The role of TAMs in angiogenesis has also been elucidated. The depletion of TAMs results in a significant reduction in vessel density [134]. TAMs also promote lymphangiogenesis, which is critical for the dissemination of tumor cells to lymph nodes and metastasis via the VEGF-C/VEGFR-3 signaling axis [135]. TAMs secrete various MMPs and interleukins, VEGF, PDGF, and TGF-β in TME that facilitate the vascularization in the tumor tissues [136]. In some cases, NK cells are shown to secrete tumor supportive cytokines and activate pro-angiogenic response [137]. TME of glioblastoma is heavily infiltrated with MDSCs,

which activate B cell-induced immune suppression by blocking $CD8^+$ T-cell activation [138]. MDSCs in breast TME promote metastasis by supporting EMT of tumor cells [139]. In osteosarcoma, the majority of the MDSCs are CXCR4 positive, and activation of this signaling axis promotes their survival and hamper with the programmed death ligand-1(PDL-1) targeted immunotherapy [140]. PDL-1 expressing tumor cells interact with its receptor, programmed death-1 (PD-1) present on the T cells leading to their desensitization and a suppressed host immune response. Emerging studies also provide compelling evidence for a significant role of TME microbiome in cancer pathogenesis and therapeutic outcome. The intra-tumoral burden of *F.nucleatum* correlates with poor response to neoadjuvant chemotherapy in esophageal squamous cell carcinoma patients [141]. Moreover, the comparative analysis of the tumor microbiome associated with the short- and long-term survival of pancreatic cancer patients suggested that the intra-tumoral signature of microorganisms can be used as a prognostic marker [142].

Non-cellular components of the TME also play important roles in cancer progression, aggressiveness, and chemoresistance. ECM stiffness upregulates integrin signaling and promotes tumor cell survival and proliferation [104]. The high amount of osteopontin in the TME of triple-negative breast cancer patients serves as a prognostic marker and promotes growth and metastasis [143, 144]. Hyaluronic acid, abundantly present in TME of various cancers, is a receptor for CD44, and their interaction leads to the activation of several cancer-promoting signaling pathways and upregulation of various non-coding RNA species (miR-10b/miR-302/miR-21 and lncRNAs) [106, 145]. Pancreatic cancer stroma is highly reactive and contains a large amount of HA, which creates extensive interstitial fluid pressures leading to the collapse of vasculature and poor outcome of chemotherapy [146]. Indeed, enzymatic targeting of pancreatic tumors with recombinant hyaluronidase, which degrades HA, is shown to provide therapeutic enhancement by decreasing metastasis and increasing survival [146].

5. Natural anti-cancer agents and their TME targeting properties

Natural products have been widely explored for their multi-targeted mechanisms of actions on the tumor cells and the TME (Table 1). Several lines of evidence from laboratory and preclinical studies demonstrate the anti-tumor potential of natural agents, of which some have also been evaluated in clinical trials (Table 2). The following section discusses some of the most promising plant- and marine-based natural agents that confer anti-cancer properties through their targeting of not only the tumor cells but also the TME (Figure 2).

5.1. Plant-based products

Several plant-derived molecules possess a broad spectrum of pharmacological properties. The principal components recognized to impart the health benefits are the secondary metabolites. Plants have an almost limitless ability to synthesize secondary metabolites, which mainly serve as a defense mechanism against predation. Some of these that have been shown to alter TME and have undergone extensive preclinical evaluation are discussed below:

5.1.1. Honokiol—Honokiol is a small lignan with two phenolic rings. It is isolated from various parts of the plants of *Magnolia* species and has been used in traditional medicine to treat anxiety, stroke, and gastrointestinal conditions [147]. The extensive attention to honokiol's anti-cancer property stems from its desirable spectrum of bioavailability and high potency in preclinical studies [148]. We have demonstrated that honokiol induces cell cycle arrest and apoptosis, and sensitizes the pancreatic cancer cells to chemotherapy by targeting the NF-κB activation [149]. Honokiol enhances the therapeutic efficacy of other anti-cancer drugs as well both *in vitro* and *in vivo* [149–151]. Honokiol induces autophagy in KRAS mutant cancer cells through the modulation of the AMPK-mTOR signaling pathway [152]. It inhibits the growth and aggressiveness of breast cancer cells *in vitro* and *in vivo* through the activation of the AMPK/LKB axis [153, 154]. An earlier study reports the modulation of TME upon exogenous expression of KRAS in mouse ovarian cancer cells [155]. Enhanced levels of immunomodulatory cytokines (IL-6 and TNF-α) and neutrophils were found in the ascetic fluid of mice injected with KRAS-expressing mouse ovarian cancer cells [155]. Another preclinical study suggested that c-Rel, a subunit of NF-κB, controls the activity of Tregs, which are vital contributors in immunosuppressive TME. In another study, the role of mTOR signaling in modulating immune cell response by regulation of differentiation/activation of TAMs, T cells, and antigen-presenting cells has also been demonstrated [156]. Thus, targeting mTOR signaling by honokiol could be useful in activating the immune response. Honokiol also induces cholangiocarcinoma cell apoptosis and increases the release of damage-associated molecular patterns (DAMPs). These DAMPs have the potential to stimulate T-lymphocyte proliferation and type I cytokine production suggesting yet another mechanism for immune modulation by honokiol [157]. In an orthotopic mouse model of pancreatic cancer, we demonstrated that honokiol inhibited tumor growth and metastasis by targeting the crosstalk of tumor and stromal cells [151]. Pancreatic tumor cells treated with honokiol showed reduced synthesis and secretion of sonic hedgehog (SHH) as well as decreased expression of CXCR4 in the tumor cells, which was associated with decreased desmoplastic reaction in the TME [151]. In other studies, honokiol and its derivative (H2P) are shown to alter the TME by inhibiting angiogenesis [158–161]. These findings indicate that honokiol is an important modulator of TME and should be explored further in various combination therapies to improve the therapeutic outcome.

5.1.2. Hydroxytyrosol—Olive oil, a major constituent of the Mediterranean diet, is considered one of the healthiest dietary supplements with multiple proven health benefits [162]. The major components identified to impart these health benefits potentially are the phenolic alcohols, particularly the 3,4-dihydroxyphenyl ethanol, also referred to as hydroxytyrosol (HT). HT is found in red wines and may also be produced endogenously as well, through dopamine metabolism [163, 164]. Multiple preclinical studies have demonstrated the anticancer properties of HT in various cancers including prostate [165], breast [166–168], pancreas [169], liver [170, 171], leukemia [172, 173], and colon [174–176]. HT possesses significant reactive oxygen species (ROS) scavenging ability, which decreases oxidative DNA damage in mammary cells [177]. In contrast, HT was shown to increase the ROS levels in human colon and prostate cancer cells and inhibited their growth [178]. ROS acts as a double-edged sword. At low levels, it promotes cancer pathogenesis, but at higher levels, it induces cell death by causing DNA damage or other cellular

mechanisms [179–181]. All tumors exhibit a variable degree of hypoxia and the anti-oxidant action of HTis particularly effective under the hypoxic TME [182]. Furthermore, it is shown that the TME-dependent action of HT involves differences in mRNA translation by a yet undefined mechanism. Thus, HT not only affects the TME, but its response is modulated by different TME conditions as well. Studies from our group and others have demonstrated that HT inhibits Akt phosphorylation, leading to suppression of NF-κB activation [165, 170]. Anti-cancer activity of HT against prostate tumor cells has also been reported *via* inhibition of other cancer-relevant signaling pathways, including STAT3 and androgen receptor [165, 183–186]. It is significant as published data also demonstrate that olive oil components could inhibit pro-angiogenic and pro-inflammatory signaling in prostate cancer by modulating the IL-6/STAT3 axis and downregulating the expression of growth factors and cytokines (CXCL8, VEGF, CXCL12) [182]. Tumor-derived CXCL8 augments CCL2 and CXCL12 secretion by stromal cells, which in turn promote the growth and invasion of prostate cancer cells [187]. It is shown that HT interferes with the tumor-stromal interaction by inhibiting CCL5 expression in fibroblasts [188]. Further, the role of CXCL8, CCL2, CCL5, and CXCL12 in immune modulation is also reported in several cancers [189]. Thus, HT can potentially abrogate tumor cell-TME crosstalk to exert its diverse anti-tumor activity.

5.1.3. Resveratrol—Resveratrol (3,4′,5-trihydroxy-trans-stilbene), a phytoalexin isolated from the grapevine, peanuts, and pines, exhibits chemopreventive and therapeutic properties against several cancers [190, 191]. A preclinical study also demonstrated that resveratrol could reduce high-fat diet-induced obesity, improve insulin sensitivity, and lower glucose levels in blood [192]. Multiple mechanisms are proposed for the anti-tumor activities of resveratrol including (i) acting as an anti-oxidant/pro-oxidant and anti-mutagen, (ii) inducing activation of phase II drug-metabolizing enzymes, (iii) mediating anti-inflammatory effects, (iv) inhibiting cyclooxygenase (COX) and hydroperoxidase functions, and (iv) inducing tumor cell differentiation [24, 193–196]. With regard to its effect on TME, resveratrol is shown to counter the upregulation of carbonic anhydrase through the modulation of metastasis-associated lung adenocarcinoma transcript 1expression [197]. CA regulates the intracellular pH in cancer cells under hypoxia or during intense glycolytic dependence to maintain it at physiological levels [197]. Resveratrol also imparts anti-cancer properties through copper-mediated inter-nucleosomal DNA fragmentation at low pH that mimics stringent cancer cell growth conditions [198]. Resveratrol could suppress hypoxia-driven ROS-induced pancreatic cancer progression by inhibiting SHH upregulation, thus supporting its potential role in the interference of the tumor-stromal crosstalk [199]. In addition, resveratrol is shown to induce the activation of transient receptor potential ankyrin 1 in prostate CAFs leading to an increase in the intracellular calcium and secretion of HGF and VEGF [200]. Resveratrol also alters the “senescence-associated secretory phenotype” of senescent stromal fibroblasts associated with melanoma by reducing expression of TGF-β, CXCR4, and others [201]. In another study, resveratrol inhibited the proliferation and aggressiveness of human breast cancer cells treated with CAF-CM through downregulation of several growth- and EMT- promoting genes and signaling pathways [202]. Resveratrol treatment of spleen cells isolated from the tumor-bearing mice exhibited a dramatic decrease in the number of $CD4^+CD25^+$ cells, along with a significant reduction in the ratio of $CD4^+CD25^+$ to $CD4^+$ cells. In addition, the $FoxP3^+$ cells within the $CD4^+CD25^+$ cell

population also decreased in numbers [203]. Treatment of a breast cancer preclinical model with resveratrol analog, HS-1793, significantly inhibited the growth of implanted tumor cells with a substantial increase in IFN-γ-secreting cells in the splenocytes and decreased $CD206^+$ macrophage infiltration in the TME [204]. Resveratrol also reduced lung cancer growth by inhibiting macrophage infiltration and its polarization into M2 like phenotype [205]. Thus, resveratrol controls tumor growth through its direct effect on the tumor cells as well as by targeting the pro-tumorigenic TME.

5.1.4. Curcumin—Curcumin (diferuloylmethane) is a polyphenolic compound isolated from *Curcuma longa* (the turmeric plant). Turmeric powder has been widely used in Ayurvedic therapies for its potent anti-oxidant, anti-inflammatory, anti-viral, anti-bacterial, and anti-fungal activities [23, 206, 207]. Studies suggest that the hydroxyl groups in curcumin are essential for its anti-oxidant activity, while methoxy groups are required for anti-inflammatory and anti-proliferative activities [208]. Curcumin has also been used as a lead molecule to generate semi-synthetic derivatives exhibiting improved anti-cancer efficacy and desired pharmacological properties [209, 210]. In colorectal cancer, curcumin administration caused the apoptosis of tumor cells in a p53-mediated manner and also improved the general health of the patients [211]. On the contrary, in a lymphoma cell line, curcumin-induced the growth arrest via downregulation of p53, c-Myc, and early growth response 1 [212]. This context-dependent action could be cell-specific or attributed to TP53 mutational status. Studies from switchable mouse models of Myc-induced β-cell and skin malignancies suggest that Myc regulates tumorigenesis by impacting the tumor cell as well as by remodeling the tumor stroma and angiogenesis [213, 214]. Activation of Myc in β-cell tumors induces the secretion of chemoattractant cytokines and promotes the infiltration of inflammatory immune cells and mast cells to the islet-associated stroma. Furthermore, Myc-induced β-cells fail to expand in mice lacking mast cell function, thus suggesting an essential role for tumor-stromal crosstalk [215]. Treatment of pancreatic cancer cells with curcumin also decreases the secretion of inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8, due to the repression of NF-κB [216]. Curcumin also inhibits the expression of matrix metalloproteinases, which are responsible for ECM degradation to facilitate cellular movement and promote tumor angiogenesis [217]. The anti-inflammatory property of curcumin is also attributed to its ability to modulate the expression of COX-2 within the TME cells [218, 219]. Recently, single-cell transcriptome analysis of primary prostate tumor and lung metastases from an orthotopic mouse model was performed to delineate the role of tumor-stromal interaction in tumorigenesis. It was demonstrated that tumor-derived COX-2 product, prostaglandin E2, induced upregulation of prolactin in lung stromal cells, and in return, prolactin promoted proliferative signaling in tumor cells [220].

It has also been demonstrated that the anti-tumor activity of curcumin in metastatic breast cancer involves the infiltration of macrophages at the tumor site, predominantly of the M1 phenotype [221]. Similarly, in glioblastoma, curcumin treatment led to an increase in macrophage polarization towards the $Arginase\text{-}1^{low}$, $iNOS^{high}$ M1-type tumoricidal microglia with high activation of microglial NF-κB and STAT1 [222]. Curcumin also improved anti-tumor immunity in lung cancer patients by decreasing Tregs in TME with a concomitant increase in Th1 cells [223]. It was determined *ex vivo* that potential conversion

of Tregs to Th1 cells by curcumin resulted from the repression of FoxP3 and an increase in IFN-γ [223]. Curcumin also increased the accumulation and function of $CD8^+$ T cells in the TME by blocking multiple immunosuppressors [224]. In another study, curcumin treatment of tumor-bearing mice prevented the overall loss of T cells with an expansion of the central memory T cell/effector memory T cell populations. Curcumin treatment also inhibited the suppressive activity of Tregs cells by downregulating the production of TGF-β and IL-10 [225].

5.1.5. Berberine—Berberine is a bioactive isoquinoline alkaloid found in many herbal substances. It is a common part of the Indian and Chinese traditional medicine and possesses multiple desirable pharmacological properties [226, 227]. Despite low plasma bioavailability of berberine, its metabolic derivatives are capable of exerting similar biological activities [228]. Berberine's chemopreventive properties have been reported in colon cancer, where it inhibits the growth of intestinal polyp in animals as well as in patients with familial adenomatous polyposis [229]. Chemopreventive efficacy of berberine is also attributed to its ability to regulate macrophage polarization, as evidenced in the Apc (min/+) mouse model. Treatment of berberine in these mice led to a decrease in the number and size of polyps with a concomitant decrease in the levels of F4/80, mannose receptor (MR), and COX-2 and increase in the level of iNOS [229]. Berberine has been shown to promote chemotherapeutic efficacy in hypoxic breast cancer cells by inducing the downregulation of AMPK and HIF-1α [230]. AMPK is activated in hypoxic TME and maintains energy homeostasis [220]. In a study, berberine was predicted to bind Lys395 and Tyr394/Phe484 of Smo, a downstream effector of hedgehog signaling, through hydrogen bonding and π- π interactions, respectively [231]. In a similar approach, candidates for immunotherapy potentiation were tested for their ability to repress IFNγ-induced indoleamine 2,3-dioxygenase (IDO) promoter activity. IDO regulates the activation of Tregs cells in the TME and IDO^+plasmacytoid dendritic cells (pDCs) from mouse tumor-draining lymph nodes. It activates resting $CD4^+CD25^+Foxp3^+$ Tregs and upregulates PD-L1 and PD-L2 expression on DCs[232]. Twenty-five new berberine derivatives tested *in silico* and structure-activity assays identified a subgroup to have potential anti-cancer activity. These compounds could decrease IDO expression and enhanced NK cell-mediated specific lysis of A549 cells [233].

5.1.6. Epigallocatechin-3-gallate—Next to water, tea is the most served beverage around the globe. Catechins are the bioactive constituents of tea and considered to be one of the most active molecules for cancer chemoprevention and therapy [21]. Among these, epigallocatechin-3-gallate (EGCG) is the most potent apoptosis-inducer in cancer cells. EGCG has both anti-oxidant and pro-oxidant properties and is capable of inducing cell cycle arrest, apoptosis, and autophagic cell death in multiple cancer cell lines [234–237]. EGCG inhibits the proliferation and aggressiveness of thyroid carcinoma cells *in vitro* and in a mouse xenograft model by downregulating proteins of the EGFR and RAS signaling pathways [238]. Another mechanism of anti-cancer actions of EGCG is their ability to alter the expression of long, non-coding RNAs and mRNAs [239]. In a study with the endometrial cancer xenograft model, EGCG-treatment reduced VEGFA expression through downregulation of the HIF-1α protein. Moreover, in the host stromal cells, EGCG

induced a reduction in CXCL12 expression and release, which, in turn, led to a decrease in macrophage infiltration and polarization [240]. miR-16 was found to be abundantly present in exosomes from EGCG-treated cancer cells, which reversed the polarization of TAMs to the M1 phenotype by inhibiting IKKα [241]. In another study, EGCG-treatment improved the immunotherapeutic response in a leukemic xenograft mouse model [242]. Furthermore, EGCG treatment increased the percentage of $CD3^+$ T-cells, CD19 B-cells, and Mac-3 macrophages. In a more direct effect on immunotherapy response, EGCG was shown to inhibit the expression of PD-L1 in non-small cell lung cancer cells [243]. These findings suggest that EGCG holds significant potential as a combination therapy drug to improve the clinical outcome.

5.1.7. Zerumbone—Zerumbone, a sesquiterpene isolated from the rhizomes of *Zingiber zerumbet*, has been shown to possess immunomodulatory and anti-cancer properties [244]. It inhibits the inflammatory response by several means, such as by suppression of MAPK and NF-κB signaling, and reduced ROS production [245–247]. Zerumbone reduces TPA-induced ROS generation in leukemic and Chinese hamster ovary cells and induces the killing of tumor cells. Simultaneously, it also inhibits the expression of pro-inflammatory molecules (COX-2, TNF-α, and iNOS) in LPS- and IFN-γ- induced RAW macrophages [248]. Studies have shown that zerumbonecan block Toll-Like Receptors (TLRs)/MyD88-dependent NF-κB activation leading to the downregulation of pro-inflammatory response in LPS-induced macrophages [249, 250]. Zerumbone inhibits ovarian tumor cell growth and reduces the secretion of IL-6 [251]. Zerumbone also downregulates the expression of CD1d by blocking the antigen presentation pathway, and treatment with anti-CD1d antibody augments the zerumbone-mediated killing of breast cancer cells [252]. An antiangiogenic role of zerumbone has also been reported in liver cancer, where it abrogates the expression of VEGF/VEGFR and matrix metalloproteinase-9 [253]. Similarly, another study demonstrates zerumbone-mediated inhibition of angiogenesis due to reduced expression and secretion of VEGF and IL-8 resulting from NF-Kb downregulation [254]. Recently, it was found that the oral administration of zerumbone in enterotoxigenic *Bacteroides fragilis* (ETBF)-colonized mice reduced colon carcinogenesis by decreasing ETBF-colonization and intestinal inflammation [255].

5.1.8. Genistein—Genistein is an isoflavone present in soybeans and soy food and confers immunomodulatory role in various pathological conditions [256, 257]. It induces an anti-tumor immune response (NKT cell activation) in ovarian cancer by reducing VEGF-mediated upregulation of ganglioside [258]. In glioblastoma cells, genistein induces the upregulation of C/EBP homologous protein that impedes C/EBPβ interaction with IL-6 promoter leading to the downregulation of IL-6 expression and release tumor growth reduction [259]. Further, genistein can inhibit the release of urokinase-type plasminogen activator (uPA), which is a promoter of ECM remodeling and angiogenesis. As a result, its intraperitoneal administration in mice implanted with melanoma or mammary tumor cells reduces angiogenesis and tumor cell migration [260]. Genistein also influences the expression of multiple matrix metalloproteinases (MMPs) in fibroblast and T-cells suggesting its broader functional impact [261, 262]. Besides, genistein inhibits the expression of multiple essential genes associated with cell cycle, DNA replication, and

growth in fibroblasts [263]. Treatment of transgenic mouse prostate adenocarcinoma mice with genistein decreased osteopontin expression in TAMs and prevented the development of advanced-stage prostate cancer [264]. Pancreatic tumor-bearing rats treated with genistein also exhibited a decrease in TAMs and reduced blood vessel density [265]. Genistein also abrogates M2 polarization of TAMs and decreased accumulation of IL-10, IL-8, and nitric oxide in the conditioned media of the macrophages and ovarian cancer cells co-culture with [266]. Another study demonstrated that genistein derivative, GEN-27, decreased LPS-induced secretion of IL-6 and IL-1β from THP-1 cells, which, in turn, reduce the proliferation of colon cancer cells [267].

5.1.9. Onionin A—Onionin A, a sulfur-containing compound isolated from *Allium cepa* (onion), has been used in the prevention of various chronic diseases [268, 269]. Oral administration of aqueous extract of onion boosts the immune response in the rat by increasing the immune cell count, especially white blood cell and $CD4^+$T cells [270]. In other studies, onionin A is shown to inhibit macrophage polarization into the M2 phenotype by reducing the expression of CD163 as well as reduced the immunosuppressive functions of MDSCs by enhancing T cell activity [268, 271]. Onionin A also blocks the macrophage-induced ovarian cancer cell proliferation by inhibiting M2 polarization of human monocyte-derived macrophages (HMDMs) and reduces LPS-induced PDL-1 expression in HMDMs [272].

5.1.10. Naringenin—Naringenin is a flavonoid found in various citric fruits such as lemons, oranges, grapefruits, and tangerines [273]. It has emerged as a potent chemopreventive and therapeutic agent due to its anti-inflammatory, anti-cancer, and neuroprotective properties. Like other phytochemicals, it has an anti-oxidant property and can activate anti-oxidant signaling pathways [274, 275]. Naringenin ameliorated experimental autoimmune encephalomyelitis in mice by blocking effector T cell proliferation and secretion of IL-6, IFN-γ, and IL-17 [276]. Naringenin also inhibited the production of pro-inflammatory mediators such as TLR4, iNOS, COX-2, and NADPH oxidase-2 in LPS-treated murine macrophages and protected the mice from endotoxemia [277]. Naringenin prevented breast cancer metastasis by reducing the secretion of TGF-β1 from tumor cells and inhibits TGF-β1-mediated immunosuppression in tumor-bearing mice via increased T cell activation [278]. A similar study demonstrated that naringenin inhibited lung metastases and increased the survival of tumor-bearing mice by attenuating immunosuppressive TME through the downregulation of TGF-β1 and Tregs [279]. Naringenin can also act as an antifibrogenic phytochemical and reduce the secretion of ECM proteins through downregulation of TGF-β1/Smad3 signaling axis in the rat hepatic stellate cells [280]. Moreover, naringenin could inhibit VEGF-mediated angiogenesis by blocking intracellular calcium signaling in the endothelial cells [281]. In another study, naringenin inhibited angiogenesis by upregulating SOCS-3 and inhibiting IL-6/STAT3 signaling in vascular endothelial cells [282].

5.2 Marine-based products

Like the plant world, the biological and chemical diversity of marine life is also immense, and therefore, it also serves as an excellent source for the discovery of anti-cancer agents

[283, 284]. In recent years, there has been an increase in the number of anti-cancer compounds from marine life being tested in preclinical studies and clinical trials [285, 286]. This brief section is intended to showcase some of these marine natural products that target the TME as a mechanism of their anti-cancer ability.

5.2.1. Trabectedin—Trabectedin was first isolated from the marine ascidian, *Ecteinascidia turbinate,* and can now be prepared synthetically. It is the first marine-derived anti-cancer drug currently being used in advanced soft-tissue sarcoma (STS) after the failure of anthracyclines and ifosfamide in STS patients [287, 288]. It is also used to treat patients with relapsed, platinum-sensitiveovarian cancer [289]. The most widely studied mechanisms of its anti-cancer property include the inhibition of active transcription by direct blocking of the transcribing RNA polymerase II. It can also act by causing the displacement of the transcription factors mediated through the structural changes in the DNA that hinder the recognition of transcription factor- specific DNA consensus sequence [290]. Trabectedin has targets the key members of the TME. A recent study showed that trabectedin-treated multiple myeloma cells had upregulation of NK activating receptor ligands leading to the activation of the NK cells [291]. In a study utilizing *in vitro* assays and four tumor models, trabectedin caused selective depletion of mononuclear phagocytes as well as splenic and tumor-infiltrated macrophages with a simultaneous decrease in angiogenesis [292]. Moreover, sub-cytotoxic concentrations of trabectedin significantly inhibited macrophage differentiation *in vitro* and reduced the production of inflammatory mediators, IL-6, and CCL2 [292]. Similar to solid tumors, leukemic cells also enhance the frequency of immunosuppressive cells to create a favorable microenvironment [293–295]. Trabectedin conferred cytotoxicity to human primary leukemic cells by inhibiting the myeloid and lymphoid immunosuppressive microenvironment mainly through the upregulation of the TRAIL/TNF pathway. Trabectedin also targeted the PD-L1^{+} CLL cells, PD-L1^{+} monocytes/macrophages, and PD-1^{+}T cells [296]. Similar to this observation, trabectedin induced the infiltration of CD8^{+}T cells in the osteosarcoma site, and its co-treatment with α-PD-1 mAb led to a stronger anti-tumor immune response [297].

5.2.2. Plitidepsin—Plitidepsin is a cyclodepsipeptide that was first isolated from the Mediterranean tunicate *Aplidiumalbicans*. It is currently marketed by PharmaMar (Madrid, Spain) under the trade name Aplidin. Plitidepsin demonstrates intense anti-cancer activity against multiple types of human cancer cells *in vitro* and in preclinical mouse models [298–301]. It inhibits proliferation by inducing cell cycle arrest and mediate apoptosis through Rac1/JNK activation [298]. JNK knockout (Kras; JNK1$^{-/-}$) mice develop low weight pancreatic tumors, and tumor-induced JNK activation in stroma reduces infiltration of effector T cells (CD8^{+}) cells in the TME through downregulation of CCL20 [302]. Plitidepsin targets the eukaryotic elongation factor 1A2, which is frequently overexpressed in multiple myeloma cells [303]. Additionally, plitidepsin activates p38 and c-Jun signaling-mediated Fas/CD95 translocation to lipid rafts, ultimately causing the caspase activation [299–301]. The therapeutic activity of plitidepsin in chronic lymphocytic leukemia (CLL) is mediated through a direct effect on the leukemic cells as well as an indirect effect on monocyte-derived nurse-like cells [304]. The nurse-like cells protect the CLL cells from undergoing apoptosis by increasing CXCL12-mediated ERK activation [305]. Additionally,

plitidepsin inhibits angiogenic signaling by reducing the expression of VEGF and VEGFR [306–308].

5.2.3. Fucoidan—Fucoidan is a natural sulfated polysaccharide that exists in the cell wall matrix of various brown seaweed. It has multiple biological properties such as anti-viral, anti-arthritic, and immunomodulatory potency, and its anti-cancer property has gained much attention in recent years. Fucoidan polymers induce cell cycle arrest and apoptosis in cancer cell lines [309–313]. They also induce the loss of mitochondrial membrane potential, release of cytochrome c, and increase ROS generation and ER stress, leading to DNA damage-induced apoptosis [309–311, 314]. Additionally, oligo-fucoidan has been shown to inhibit the expression of DNA methyltransferases, which leads to the upregulation of p21, a cell cycle inhibitor [315]. Fucoidan also enhances the expression of filamin A (FLNA)-derived circular RNA, which leads to the alteration of multiple genes associated with cell cycle, proliferation, and survival [313]. Similarly, fucoidan has been demonstrated to elevate the expression of miRNA29b that inhibits EMT, and lncRNA-Saf and lncRNA-p21 that target apoptosis and cell cycle pathways in hepatocellular carcinoma cells [316]. Treatment of M2 macrophages with fucoidan resulted in the downregulation of chemokines, CCL22, which mediated the growth and aggressiveness of cancer cells through its interaction with the CCR4 [317]. Elevated expression of CCL2 is associated with poor prognosis in multiple cancers [318–320]. In another study, RAW macrophages stimulated with fucoidan had an increased anti-cancer potential against S-180 cells due to the ability of fucoidan to induce nitric oxide production through upregulation of nitric oxide synthase (NOS) [317]. Fucoidan-mediated decrease of M2 macrophages in the TME is synergistic with the p53 wild type status of the cancer cells [321].

6. Conclusion and future perspective

Clinical management of cancer has been challenging due to the complex genetics and biology of cancer cells. Therefore, significant efforts have shifted towards the cancer microenvironment, which is relatively less diverse and yet plays essential roles in successful cancer progression and its resistance to therapies. In recent years, reactivation of the immune system has met remarkable success for some cancer types and has opened new avenues for cancer management. The studies briefly discussed in the above sections highlight the benefits of natural agents in cancer chemoprevention and therapeutic intervention either as a stand-alone treatment or through their enhancement of the efficacy of currently employed clinical therapies. There is substantial literature to suggest that natural agents target not only the transformed malignant cells but also effectively modulate the tumor-supportive microenvironment. It is, in most cases, achieved by blocking the bi-directional tumor-stromal crosstalk and by empowering the body's immune system. Clearly, the potential for their future clinical exploitation is immense in terms of the development of novel preventive and therapeutic approaches against cancer. It is, however, important to mention that most of the currently available information discussed here has been generated either *in vitro*, *ex vivo* or in preclinical mouse models. There is still a lot to be achieved before we could successfully translate this knowledge from the lab to the bedside.

A major limitation with most natural agents is their low aqueous solubility leading to poor absorption and delivery to the tumor cells. Also, most compounds get quickly metabolized in the systemic circulation [322]. Also, although rare, some natural agents can pose toxicity concerns at pharmacological doses along with instances leading to the development of secondary diseases. For example, chronic consumption of a 2% caffeic acid-containing diet in rats led to the development of forestomach squamous cell papilloma with toxic lesions seen in the kidneys [323]. Similarly, high consumption of green tea catechins (1%) enhanced tumor development in rat colon [324]. Some dietary flavonoids also exhibit structural similarity to thyroid hormones and can interfere with hormone biosynthesis [325]. Epidemiological data also caution that the consumption of flavonoids by pregnant mothers could increase the risk of developing acute myeloid leukemia (MLL^+) in the offspring [326]. To overcome these limitations, multiple approaches are being employed. One of them is to develop novel semi-synthetic derivatives of natural compounds to enhance their bioavailability and retention. In other cases, novel strategies are being developed to achieve their tumor-targeted, protected delivery using nanosystems. It is also being suggested that the use of natural compounds should also be tailored based on the molecular characteristics of the tumor. Of course, this requires a more in-depth understanding of their mechanisms of action. Despite these hurdles, discoveries are continuously being made to identify novel bioactive natural compounds and to highlight their molecular targets and underlying mechanisms. Furthermore, several natural agents and/or their derivatives have entered and/or continue to enter in clinical trials as new drugs or for therapeutic enhancement of existing drugs in combination therapiesIt is hoped that we will witness novel therapies and prevention approaches emerging from the scientific efforts being made with natural agents in not very distant future.

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References

[1]. Siegel RL, Miller KD, Jemal A, Cancer statistics, 2019, CA Cancer J Clin 69(1) (2019) 7–34. [PubMed: 30620402]

[2]. Radisky DC, Kenny PA, Bissell MJ, Fibrosis and cancer: do myofibroblasts come also from epithelial cells via EMT?, J Cell Biochem 101(4) (2007) 830–9. [PubMed: 17211838]

[3]. Omary MB, Lugea A, Lowe AW, Pandol SJ, The pancreatic stellate cell: a star on the rise in pancreatic diseases, J Clin Invest 117(1) (2007) 50–9. [PubMed: 17200706]

[4]. Dudley AC, Tumor endothelial cells, Cold Spring Harb Perspect Med 2(3) (2012) a006536. [PubMed: 22393533]

[5]. Fridman WH, Pages F, Sautes-Fridman C, Galon J, The immune contexture in human tumours: impact on clinical outcome, Nat Rev Cancer 12(4) (2012) 298–306. [PubMed: 22419253]

[6]. Yin C, Evason KJ, Asahina K, Stainier DY, Hepatic stellate cells in liver development, regeneration, and cancer, J Clin Invest 123(5) (2013) 1902–10. [PubMed: 23635788]

[7]. Whisner CM, Athena Aktipis C, The Role of the Microbiome in Cancer Initiation and Progression: How Microbes and Cancer Cells Utilize Excess Energy and Promote One Another's Growth, Curr Nutr Rep 8(1) (2019) 42–51. [PubMed: 30758778]

[8]. Wei MY, Shi S, Liang C, Meng QC, Hua J, Zhang YY, Liu J, Zhang B, Xu J, Yu XJ, The microbiota and microbiome in pancreatic cancer: more influential than expected, Mol Cancer 18(1) (2019) 97. [PubMed: 31109338]

[9]. Olive KP, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, Madhu B, Goldgraben MA, Caldwell ME, Allard D, Frese KK, Denicola G, Feig C, Combs C, Winter SP, Ireland-Zecchini H, Reichelt S, Howat WJ, Chang A, Dhara M, Wang L, Ruckert F, Grutzmann R, Pilarsky C, Izeradjene K, Hingorani SR, Huang P, Davies SE, Plunkett W, Egorin M, Hruban RH, Whitebread N, McGovern K, Adams J, Iacobuzio-Donahue C, Griffiths J, Tuveson DA, Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer, Science 324(5933) (2009) 1457–61. [PubMed: 19460966]

[10]. Singh AP, Arora S, Bhardwaj A, Srivastava SK, Kadakia MP, Wang B, Grizzle WE, Owen LB, Singh S, CXCL12/CXCR4 protein signaling axis induces sonic hedgehog expression in pancreatic cancer cells via extracellular regulated kinase- and Akt kinase-mediated activation of nuclear factor kappaB: implications for bidirectional tumor-stromal interactions, J Biol Chem 287(46) (2012) 39115–24. [PubMed: 22995914]

[11]. Richards KE, Zeleniak AE, Fishel ML, Wu J, Littlepage LE, Hill R, Cancer-associated fibroblast exosomes regulate survival and proliferation of pancreatic cancer cells, Oncogene 36(13) (2017) 1770–1778. [PubMed: 27669441]

[12]. Pietras K, Pahler J, Bergers G, Hanahan D, Functions of paracrine PDGF signaling in the proangiogenic tumor stroma revealed by pharmacological targeting, PLoS Med 5(1) (2008) e19. [PubMed: 18232728]

[13]. Roma-Rodrigues C, Mendes R, Baptista PV, Fernandes AR, Targeting Tumor Microenvironment for Cancer Therapy, Int J Mol Sci 20(4) (2019).

[14]. Thomas D, Radhakrishnan P, Tumor-stromal crosstalk in pancreatic cancer and tissue fibrosis, Mol Cancer 18(1) (2019) 14. [PubMed: 30665410]

[15]. Lin Y, Xu J, Lan H, Tumor-associated macrophages in tumor metastasis: biological roles and clinical therapeutic applications, J Hematol Oncol 12(1) (2019) 76. [PubMed: 31300030]

[16]. Salehi B, Stojanovic-Radic Z, Matejic J, Sharifi-Rad M, Anil Kumar NV, Martins N, Sharifi-Rad J, The therapeutic potential of curcumin: A review of clinical trials, Eur J Med Chem 163 (2019) 527–545. [PubMed: 30553144]

[17]. Prakash Mishra A, Sharifi-Rad M, Shariati MA, Mabkhot YN, Al-Showiman SS, Rauf A, Salehi B, Zupunski M, Sharifi-Rad M, Gusain P, Sharifi-Rad J, Suleria HAR, Iriti M, Bioactive compounds and health benefits of edible Rumex species-A review, Cell Mol Biol (Noisy-le-grand) 64(8) (2018) 27–34.

[18]. Zaynab M, Fatima M, Abbas S, Sharif Y, Umair M, Zafar MH, Bahadar K, Role of secondary metabolites in plant defense against pathogens, Microb Pathog 124 (2018) 198–202. [PubMed: 30145251]

[19]. Bishayee A, Thoppil RJ, Waghray A, Kruse JA, Novotny NA, Darvesh AS, Dietary phytochemicals in the chemoprevention and treatment of hepatocellular carcinoma: in vivo evidence, molecular targets, and clinical relevance, Curr Cancer Drug Targets 12(9) (2012) 1191–232. [PubMed: 22873222]

[20]. Bishayee A, Haskell Y, Do C, Siveen KS, Mohandas N, Sethi G, Stoner GD, Potential Benefits of Edible Berries in the Management of Aerodigestive and Gastrointestinal Tract Cancers: Preclinical and Clinical Evidence, Crit Rev Food Sci Nutr 56(10) (2016) 1753–75. [PubMed: 25781639]

[21]. Zubair H, Azim S, Ahmad A, Khan MA, Patel GK, Singh S, Singh AP, Cancer Chemoprevention by Phytochemicals: Nature's Healing Touch, Molecules (Basel, Switzerland) 22(3) (2017).

[22]. Mokbel K, Wazir U, Mokbel K, Chemoprevention of Prostate Cancer by Natural Agents: Evidence from Molecular and Epidemiological Studies, Anticancer research 39(10) (2019) 5231–5259. [PubMed: 31570421]

[23]. Chainani-Wu N, Safety and anti-inflammatory activity of curcumin: a component of tumeric (Curcuma longa), Journal of alternative and complementary medicine (New York, N.Y.) 9(1) (2003) 161–8.

[24]. Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, Fong HH, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto JM, Cancer chemopreventive activity of resveratrol, a natural product derived from grapes, Science 275(5297) (1997) 218–20. [PubMed: 8985016]

[25]. Goyal MR, Ayeleso AO, Bioactive Compounds of Medicinal Plants: Properties and Potential for Human Health, Apple Academic Press2018.

[26]. Newman DJ, Cragg GM, Natural products as sources of new drugs over the last 25 years, J Nat Prod 70(3) (2007) 461–77. [PubMed: 17309302]

[27]. Hanson JR, A hundred years in the elucidation of the structures of natural products, Sci Prog 100(1) (2017) 63–79. [PubMed: 28693673]

[28]. Zhang J, Zheng Z, Wu M, Zhang L, Wang J, Fu W, Xu N, Zhao Z, Lao Y, Xu H, The natural compound neobractatin inhibits tumor metastasis by upregulating the RNA-binding-protein MBNL2, Cell Death Dis 10(8) (2019) 554. [PubMed: 31320607]

[29]. Ranjan A, Ramachandran S, Gupta N, Kaushik I, Wright S, Srivastava S, Das H, Srivastava S, Prasad S, Srivastava SK, Role of Phytochemicals in Cancer Prevention, Int J Mol Sci 20(20) (2019).

[30]. Casey SC, Amedei A, Aquilano K, Azmi AS, Benencia F, Bhakta D, Bilsland AE, Boosani CS, Chen S, Ciriolo MR, Crawford S, Fujii H, Georgakilas AG, Guha G, Halicka D, Helferich WG, Heneberg P, Honoki K, Keith WN, Kerkar SP, Mohammed SI, Niccolai E, Nowsheen S, Vasantha Rupasinghe HP, Samadi A, Singh N, Talib WH, Venkateswaran V, Whelan RL, Yang X, Felsher DW, Cancer prevention and therapy through the modulation of the tumor microenvironment, Semin Cancer Biol 35 Suppl (2015) S199–S223. [PubMed: 25865775]

[31]. Deepak KGK, Vempati R, Nagaraju GP, Dasari VR, N. S, D.N. Rao, R.R. Malla, Tumor microenvironment: Challenges and opportunities in targeting metastasis of triple negative breast cancer, Pharmacological research 153 (2020) 104683. [PubMed: 32050092]

[32]. Bruno A, Pagani A, Magnani E, Rossi T, Noonan DM, Cantelmo AR, Albini A, Inflammatory angiogenesis and the tumor microenvironment as targets for cancer therapy and prevention, Cancer Treat Res 159 (2014) 401–26. [PubMed: 24114493]

[33]. Sharma SH, Thulasingam S, Nagarajan S, Chemopreventive agents targeting tumor microenvironment, Life Sci 145 (2016) 74–84. [PubMed: 26679106]

[34]. Pistollato F, Giampieri F, Battino M, The use of plant-derived bioactive compounds to target cancer stem cells and modulate tumor microenvironment, Food Chem Toxicol 75 (2015) 58–70. [PubMed: 25445513]

[35]. Cheng YT, Yang CC, Shyur LF, Phytomedicine-Modulating oxidative stress and the tumor microenvironment for cancer therapy, Pharmacological research 114 (2016) 128–143. [PubMed: 27794498]

[36]. Kansara RR, Speziali C, Immunotherapy in hematologic malignancies, Curr Oncol 27(Suppl 2) (2020) S124–S131. [PubMed: 32368182]

[37]. Minopoli M, Sarno S, Di Carluccio G, Azzaro R, Costantini S, Fazioli F, Gallo M, Apice G, Cannella L, Rea D, Stoppelli MP, Boraschi D, Budillon A, Scotlandi K, De Chiara A, Carriero MV, Inhibiting Monocyte Recruitment to Prevent the Pro-Tumoral Activity of Tumor-Associated Macrophages in Chondrosarcoma, Cells 9(4) (2020).

[38]. Khan MA, Srivastava SK, Zubair H, Patel GK, Arora S, Khushman M, Carter JE, Gorman GS, Singh S, Singh AP, Co-targeting of CXCR4 and hedgehog pathways disrupts tumor-stromal crosstalk and improves chemotherapeutic efficacy in pancreatic cancer, J Biol Chem (2020).

[39]. Chen CY, Lin YJ, Wang CCN, Lan YH, Lan SJ, Sheu MJ, Epigallocatechin-3-gallate inhibits tumor angiogenesis: involvement of endoglin/Smad1 signaling in human umbilical vein endothelium cells, Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 120 (2019) 109491. [PubMed: 31586903]

[40]. Ba P, Xu M, Yu M, Li L, Duan X, Lv S, Fu G, Yang J, Yang P, Yang C, Sun Q, Curcumin suppresses the proliferation and tumorigenicity of Cal27 by modulating cancer associated fibroblasts of TSCC, Oral Dis (2020).

[41]. Verdura S, Cuyas E, Cortada E, Brunet J, Lopez-Bonet E, Martin-Castillo B, Bosch-Barrera J, Encinar JA, Menendez JA, Resveratrol targets PD-L1 glycosylation and dimerization to enhance antitumor T-cell immunity, Aging (Albany NY) 12(1) (2020) 8–34. [PubMed: 31901900]

[42]. Yao L, Conforti F, Hill C, Bell J, Drawater L, Li J, Liu D, Xiong H, Alzetani A, Chee SJ, Marshall BG, Fletcher SV, Hancock D, Coldwell M, Yuan X, Ottensmeier CH, Downward J, Collins JE, Ewing RM, Richeldi L, Skipp P, Jones MG, Davies DE, Wang Y, Paracrine signalling during ZEB1-mediated epithelial-mesenchymal transition augments local myofibroblast differentiation in lung fibrosis, Cell Death Differ 26(5) (2019) 943–957. [PubMed: 30050057]

[43]. Bochaton-Piallat ML, Gabbiani G, Hinz B, The myofibroblast in wound healing and fibrosis: answered and unanswered questions, F1000Res 5 (2016).

[44]. J.I. Jun, L.F. Lau, Resolution of organ fibrosis, J Clin Invest 128(1) (2018) 97–107. [PubMed: 29293097]

[45]. Kramann R, Schneider RK, The identification of fibrosis-driving myofibroblast precursors reveals new therapeutic avenues in myelofibrosis, Blood 131(19) (2018) 2111–2119. [PubMed: 29572380]

[46]. Zeisberg EM, Potenta S, Xie L, Zeisberg M, Kalluri R, Discovery of endothelial to mesenchymal transition as a source for carcinoma-associated fibroblasts, Cancer Res 67(21) (2007) 10123–8. [PubMed: 17974953]

[47]. Chen X, Song E, Turning foes to friends: targeting cancer-associated fibroblasts, Nat Rev Drug Discov 18(2) (2019) 99–115. [PubMed: 30470818]

[48]. Albrengues J, Bertero T, Grasset E, Bonan S, Maiel M, Bourget I, Philippe C, Herraiz Serrano C, Benamar S, Croce O, Sanz-Moreno V, Meneguzzi G, Feral CC, Cristofari G, Gaggioli C, Epigenetic switch drives the conversion of fibroblasts into proinvasive cancer-associated fibroblasts, Nat Commun 6 (2015) 10204. [PubMed: 26667266]

[49]. Straub JM, New J, Hamilton CD, Lominska C, Shnayder Y, Thomas SM, Radiation-induced fibrosis: mechanisms and implications for therapy, J Cancer Res Clin Oncol 141(11) (2015) 1985–94. [PubMed: 25910988]

[50]. Libura J, Bettens F, Radkowski A, Tiercy JM, Piguet PF, Risk of chemotherapy-induced pulmonary fibrosis is associated with polymorphic tumour necrosis factor-a2 gene, Eur Respir J 19(5) (2002) 912–8. [PubMed: 12030733]

[51]. Ammirante M, Shalapour S, Kang Y, Jamieson CA, Karin M, Tissue injury and hypoxia promote malignant progression of prostate cancer by inducing CXCL13 expression in tumor myofibroblasts, Proc Natl Acad Sci U S A 111(41) (2014) 14776–81. [PubMed: 25267627]

[52]. Fang T, Lv H, Lv G, Li T, Wang C, Han Q, Yu L, Su B, Guo L, Huang S, Cao D, Tang L, Tang S, Wu M, Yang W, Wang H, Tumor-derived exosomal miR-1247–3p induces cancer-associated fibroblast activation to foster lung metastasis of liver cancer, Nat Commun 9(1) (2018) 191. [PubMed: 29335551]

[53]. Togo S, Polanska UM, Horimoto Y, Orimo A, Carcinoma-associated fibroblasts are a promising therapeutic target, Cancers (Basel) 5(1) (2013) 149–69. [PubMed: 24216702]

[54]. Kalluri R, The biology and function of fibroblasts in cancer, Nat Rev Cancer 16(9) (2016) 582–98. [PubMed: 27550820]

[55]. Liu T, Zhou L, Li D, Andl T, Zhang Y, Cancer-Associated Fibroblasts Build and Secure the Tumor Microenvironment, Front Cell Dev Biol 7 (2019) 60. [PubMed: 31106200]

[56]. McCarthy JB, El-Ashry D, Turley EA, Hyaluronan, Cancer-Associated Fibroblasts and the Tumor Microenvironment in Malignant Progression, Front Cell Dev Biol 6 (2018) 48. [PubMed: 29868579]

[57]. Fiori ME, Di Franco S, Villanova L, Bianca P, Stassi G, De Maria R, Cancer-associated fibroblasts as abettors of tumor progression at the crossroads of EMT and therapy resistance, Mol Cancer 18(1) (2019) 70. [PubMed: 30927908]

[58]. Xiang H, Ramil CP, Hai J, Zhang C, Wang H, Watkins AA, Afshar R, Georgiev P, Sze MA, Song XS, Curran PJ, Cheng M, Miller JR, Sun D, Loboda A, Jia Y, Moy LY, Chi A, Brandish PE, Cancer-Associated Fibroblasts Promote Immunosuppression by Inducing ROS-Generating

Monocytic MDSCs in Lung Squamous Cell Carcinoma, Cancer Immunol Res 8(4) (2020) 436–450. [PubMed: 32075803]

[59]. Schaaf MB, Garg AD, Agostinis P, Defining the role of the tumor vasculature in antitumor immunity and immunotherapy, Cell Death Dis 9(2) (2018) 115. [PubMed: 29371595]

[60]. Hida K, Maishi N, Annan DA, Hida Y, Contribution of Tumor Endothelial Cells in Cancer Progression, Int J Mol Sci 19(5) (2018).

[61]. Sun Z, Wang CY, Lawson DA, Kwek S, Velozo HG, Owyong M, Lai MD, Fong L, Wilson M, Su H, Werb Z, Cooke DL, Single-cell RNA sequencing reveals gene expression signatures of breast cancer-associated endothelial cells, Oncotarget 9(13) (2018) 10945–10961. [PubMed: 29541388]

[62]. di Tomaso E, Capen D, Haskell A, Hart J, Logie JJ, Jain RK, McDonald DM, Jones R, Munn LL, Mosaic tumor vessels: cellular basis and ultrastructure of focal regions lacking endothelial cell markers, Cancer Res 65(13) (2005) 5740–9. [PubMed: 15994949]

[63]. Baeriswyl V, Christofori G, The angiogenic switch in carcinogenesis, Semin Cancer Biol 19(5) (2009) 329–37. [PubMed: 19482086]

[64]. Motz GT, Santoro SP, Wang LP, Garrabrant T, Lastra RR, Hagemann IS, Lal P, Feldman MD, Benencia F, Coukos G, Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors, Nat Med 20(6) (2014) 607–15. [PubMed: 24793239]

[65]. Biswas SK, Mantovani A, Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm, Nat Immunol 11(10) (2010) 889–96. [PubMed: 20856220]

[66]. Orecchioni M, Ghosheh Y, Pramod AB, Ley K, Macrophage Polarization: Different Gene Signatures in M1(LPS+) vs. Classically and M2(LPS-) vs. Alternatively Activated Macrophages, Front Immunol 10 (2019) 1084. [PubMed: 31178859]

[67]. Najafi M, Hashemi Goradel N, Farhood B, Salehi E, Nashtaei MS, Khanlarkhani N, Khezri Z, Majidpoor J, Abouzaripour M, Habibi M, Kashani IR, Mortezaee K, Macrophage polarity in cancer: A review, J Cell Biochem 120(3) (2019) 2756–2765. [PubMed: 30270458]

[68]. Dwyer AR, Greenland EL, Pixley FJ, Promotion of Tumor Invasion by Tumor-Associated Macrophages: The Role of CSF-1-Activated Phosphatidylinositol 3 Kinase and Src Family Kinase Motility Signaling, Cancers (Basel) 9(6) (2017).

[69]. O'Neill LA, A Metabolic Roadblock in Inflammatory Macrophages, Cell Rep 17(3) (2016) 625–626. [PubMed: 27732839]

[70]. Tan Z, Xie N, Cui H, Moellering DR, Abraham E, Thannickal VJ, Liu G, Pyruvate dehydrogenase kinase 1 participates in macrophage polarization via regulating glucose metabolism, J Immunol 194(12) (2015) 6082–9. [PubMed: 25964487]

[71]. Khan MA, Zubair H, Anand S, Srivastava SK, Singh S, Singh AP, Dysregulation of metabolic enzymes in tumor and stromal cells: Role in oncogenesis and therapeutic opportunities, Cancer letters 473 (2020) 176–185. [PubMed: 31923436]

[72]. Van den Bossche J, Baardman J, Otto NA, van der Velden S, Neele AE, van den Berg SM, Luque-Martin R, Chen HJ, Boshuizen MC, Ahmed M, Hoeksema MA, de Vos AF, de Winther MP, Mitochondrial Dysfunction Prevents Repolarization of Inflammatory Macrophages, Cell Rep 17(3) (2016) 684–696. [PubMed: 27732846]

[73]. Aras S, Zaidi MR, TAMeless traitors: macrophages in cancer progression and metastasis, Br J Cancer 117(11) (2017) 1583–1591. [PubMed: 29065107]

[74]. Gasteiger G, Rudensky AY, Interactions between innate and adaptive lymphocytes, Nat Rev Immunol 14(9) (2014) 631–9. [PubMed: 25132095]

[75]. Hamerman JA, Ogasawara K, Lanier LL, NK cells in innate immunity, Curr Opin Immunol 17(1) (2005) 29–35. [PubMed: 15653307]

[76]. Hadrup S, Donia M, Thor Straten P, Effector CD4 and CD8 T cells and their role in the tumor microenvironment, Cancer Microenviron 6(2) (2013) 123–33. [PubMed: 23242673]

[77]. Nair S, Dhodapkar MV, Natural Killer T Cells in Cancer Immunotherapy, Front Immunol 8 (2017) 1178. [PubMed: 29018445]

[78]. Maimela NR, Liu S, Zhang Y, Fates of CD8+ T cells in Tumor Microenvironment, Comput Struct Biotechnol J 17 (2019) 1–13. [PubMed: 30581539]

[79]. Zhu J, Paul WE, CD4 T cells: fates, functions, and faults, Blood 112(5) (2008) 1557–69. [PubMed: 18725574]

[80]. Konig R, Huang LY, Germain RN, MHC class II interaction with CD4 mediated by a region analogous to the MHC class I binding site for CD8, Nature 356(6372) (1992) 796–8. [PubMed: 1574118]

[81]. Andersen MH, Schrama D, Thor Straten P, Becker JC, Cytotoxic T cells, J Invest Dermatol 126(1) (2006) 32–41. [PubMed: 16417215]

[82]. Badalamenti G, Fanale D, Incorvaia L, Barraco N, Listi A, Maragliano R, Vincenzi B, Calo V, Iovanna JL, Bazan V, Russo A, Role of tumor-infiltrating lymphocytes in patients with solid tumors: Can a drop dig a stone?, Cell Immunol 343 (2019) 103753. [PubMed: 29395859]

[83]. Zhang S, Zhang H, Zhao J, The role of CD4 T cell help for CD8 CTL activation, Biochem Biophys Res Commun 384(4) (2009) 405–8. [PubMed: 19410556]

[84]. Christoffersson G, von Herrath M, Regulatory Immune Mechanisms beyond Regulatory T Cells, Trends Immunol 40(6) (2019) 482–491. [PubMed: 31101537]

[85]. Liu C, Chikina M, Deshpande R, Menk AV, Wang T, Tabib T, Brunazzi EA, Vignali KM, Sun M, Stolz DB, Lafyatis RA, Chen W, Delgoffe GM, Workman CJ, Wendell SG, Vignali DAA, Treg Cells Promote the SREBP1-Dependent Metabolic Fitness of Tumor-Promoting Macrophages via Repression of CD8(+) T Cell-Derived Interferon-gamma, Immunity 51(2) (2019) 381–397 e6. [PubMed: 31350177]

[86]. Nelson BH, CD20+ B cells: the other tumor-infiltrating lymphocytes, J Immunol 185(9) (2010) 4977–82. [PubMed: 20962266]

[87]. Zhang Z, Ma L, Goswami S, Ma J, Zheng B, Duan M, Liu L, Zhang L, Shi J, Dong L, Sun Y, Tian L, Gao Q, Zhang X, Landscape of infiltrating B cells and their clinical significance in human hepatocellular carcinoma, Oncoimmunology 8(4) (2019) e1571388. [PubMed: 30906667]

[88]. Cooper MA, Caligiuri MA, Isolation and characterization of human natural killer cell subsets, Curr Protoc Immunol Chapter 7 (2004) Unit 7 34.

[89]. Olsen Saraiva Camara N, Lepique AP, Basso AS, Lymphocyte differentiation and effector functions, Clin Dev Immunol 2012 (2012) 510603. [PubMed: 23251218]

[90]. Kawamoto H, Minato N, Myeloid cells, Int J Biochem Cell Biol 36(8) (2004) 1374–9. [PubMed: 15147715]

[91]. Gabrilovich DI, Myeloid-Derived Suppressor Cells, Cancer Immunol Res 5(1) (2017) 3–8. [PubMed: 28052991]

[92]. Ugel S, De Sanctis F, Mandruzzato S, Bronte V, Tumor-induced myeloid deviation: when myeloid-derived suppressor cells meet tumor-associated macrophages, J Clin Invest 125(9) (2015) 3365–76. [PubMed: 26325033]

[93]. Nagaraj S, Youn JI, Gabrilovich DI, Reciprocal relationship between myeloid-derived suppressor cells and T cells, J Immunol 191(1) (2013) 17–23. [PubMed: 23794702]

[94]. Kumar V, Cheng P, Condamine T, Mony S, Languino LR, McCaffrey JC, Hockstein N, Guarino M, Masters G, Penman E, Denstman F, Xu X, Altieri DC, Du H, Yan C, Gabrilovich DI, CD45 Phosphatase Inhibits STAT3 Transcription Factor Activity in Myeloid Cells and Promotes Tumor-Associated Macrophage Differentiation, Immunity 44(2) (2016) 303–15. [PubMed: 26885857]

[95]. Kumar V, Patel S, Tcyganov E, Gabrilovich DI, The Nature of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment, Trends Immunol 37(3) (2016) 208–220. [PubMed: 26858199]

[96]. Chun E, Lavoie S, Michaud M, Gallini CA, Kim J, Soucy G, Odze R, Glickman JN, Garrett WS, CCL2 Promotes Colorectal Carcinogenesis by Enhancing Polymorphonuclear Myeloid-Derived Suppressor Cell Population and Function, Cell Rep 12(2) (2015) 244–57. [PubMed: 26146082]

[97]. Solito S, Falisi E, Diaz-Montero CM, Doni A, Pinton L, Rosato A, Francescato S, Basso G, Zanovello P, Onicescu G, Garrett-Mayer E, Montero AJ, Bronte V, Mandruzzato S, A human promyelocytic-like population is responsible for the immune suppression mediated by myeloid-derived suppressor cells, Blood 118(8) (2011) 2254–65. [PubMed: 21734236]

[98]. Romano A, Parrinello NL, Vetro C, Forte S, Chiarenza A, Figuera A, Motta G, Palumbo GA, Ippolito M, Consoli U, Di Raimondo F, Circulating myeloid-derived suppressor cells correlate with clinical outcome in Hodgkin Lymphoma patients treated up-front with a risk-adapted strategy, Br J Haematol 168(5) (2015) 689–700. [PubMed: 25376846]

[99]. Zhang S, Ma X, Zhu C, Liu L, Wang G, Yuan X, The Role of Myeloid-Derived Suppressor Cells in Patients with Solid Tumors: A Meta-Analysis, PLoS One 11(10) (2016) e0164514. [PubMed: 27780254]

[100]. Neish AS, Mucosal immunity and the microbiome, Ann Am Thorac Soc 11 Suppl 1 (2014) S28–32. [PubMed: 24437401]

[101]. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, Plummer M, Global burden of cancers attributable to infections in 2008: a review and synthetic analysis, Lancet Oncol 13(6) (2012) 607–15. [PubMed: 22575588]

[102]. Gur C, Ibrahim Y, Isaacson B, Yamin R, Abed J, Gamliel M, Enk J, Bar-On Y, Stanietsky-Kaynan N, Coppenhagen-Glazer S, Shussman N, Almogy G, Cuapio A, Hofer E, Mevorach D, Tabib A, Ortenberg R, Markel G, Miklic K, Jonjic S, Brennan CA, Garrett WS, Bachrach G, Mandelboim O, Binding of the Fap2 protein of Fusobacterium nucleatum to human inhibitory receptor TIGIT protects tumors from immune cell attack, Immunity 42(2) (2015) 344–355. [PubMed: 25680274]

[103]. Walker C, Mojares E, Del Rio Hernandez A, Role of Extracellular Matrix in Development and Cancer Progression, Int J Mol Sci 19(10) (2018).

[104]. Pickup MW, Mouw JK, Weaver VM, The extracellular matrix modulates the hallmarks of cancer, EMBO Rep 15(12) (2014) 1243–53. [PubMed: 25381661]

[105]. Chen JE, Pedron S, Shyu P, Hu Y, Sarkaria JN, Harley BAC, Influence of Hyaluronic Acid Transitions in Tumor Microenvironment on Glioblastoma Malignancy and Invasive Behavior, Front Mater 5 (2018).

[106]. Misra S, Heldin P, Hascall VC, Karamanos NK, Skandalis SS, Markwald RR, Ghatak S, Hyaluronan-CD44 interactions as potential targets for cancer therapy, FEBS J 278(9) (2011) 1429–43. [PubMed: 21362138]

[107]. Yu B, Wu K, Wang X, Zhang J, Wang L, Jiang Y, Zhu X, Chen W, Yan M, Periostin secreted by cancer-associated fibroblasts promotes cancer stemness in head and neck cancer by activating protein tyrosine kinase 7, Cell Death Dis 9(11) (2018) 1082. [PubMed: 30348980]

[108]. Zhao H, Chen Q, Alam A, Cui J, Suen KC, Soo AP, Eguchi S, Gu J, Ma D, The role of osteopontin in the progression of solid organ tumour, Cell Death Dis 9(3) (2018) 356. [PubMed: 29500465]

[109]. Patel H, Nilendu P, Jahagirdar D, Pal JK, Sharma NK, Modulating secreted components of tumor microenvironment: A masterstroke in tumor therapeutics, Cancer Biol Ther 19(1) (2018) 3–12. [PubMed: 29219656]

[110]. Wang M, Zhao J, Zhang L, Wei F, Lian Y, Wu Y, Gong Z, Zhang S, Zhou J, Cao K, Li X, Xiong W, Li G, Zeng Z, Guo C, Role of tumor microenvironment in tumorigenesis, J Cancer 8(5) (2017) 761–773. [PubMed: 28382138]

[111]. Singh S, Srivastava SK, Bhardwaj A, Owen LB, Singh AP, CXCL12-CXCR4 signalling axis confers gemcitabine resistance to pancreatic cancer cells: a novel target for therapy, Br J Cancer 103(11) (2010) 1671–9. [PubMed: 21045835]

[112]. Bremnes RM, Donnem T, Al-Saad S, Al-Shibli K, Andersen S, Sirera R, Camps C, Marinez I, Busund LT, The role of tumor stroma in cancer progression and prognosis: emphasis on carcinoma-associated fibroblasts and non-small cell lung cancer, J Thorac Oncol 6(1) (2011) 209–17. [PubMed: 21107292]

[113]. Arora S, Bhardwaj A, Singh S, Srivastava SK, McClellan S, Nirodi CS, Piazza GA, Grizzle WE, Owen LB, Singh AP, An undesired effect of chemotherapy: gemcitabine promotes pancreatic cancer cell invasiveness through reactive oxygen species-dependent, nuclear factor kappaB- and hypoxia-inducible factor 1alpha-mediated up-regulation of CXCR4, J Biol Chem 288(29) (2013) 21197–207. [PubMed: 23740244]

[114]. Neesse A, Algul H, Tuveson DA, Gress TM, Stromal biology and therapy in pancreatic cancer: a changing paradigm, Gut 64(9) (2015) 1476–84. [PubMed: 25994217]

[115]. Rhim AD, Oberstein PE, Thomas DH, Mirek ET, Palermo CF, Sastra SA, Dekleva EN, Saunders T, Becerra CP, Tattersall IW, Westphalen CB, Kitajewski J, Fernandez-Barrena MG, Fernandez-Zapico ME, Iacobuzio-Donahue C, Olive KP, Stanger BZ, Stromal elements act to

restrain, rather than support, pancreatic ductal adenocarcinoma, Cancer Cell 25(6) (2014) 735–47. [PubMed: 24856585]

[116]. Ozdemir BC, Pentcheva-Hoang T, Carstens JL, Zheng X, Wu CC, Simpson TR, Laklai H, Sugimoto H, Kahlert C, Novitskiy SV, De Jesus-Acosta A, Sharma P, Heidari P, Mahmood U, Chin L, Moses HL, Weaver VM, Maitra A, Allison JP, LeBleu VS, Kalluri R, Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival, Cancer Cell 25(6) (2014) 719–34. [PubMed: 24856586]

[117]. Huang M, Li Y, Zhang H, Nan F, Breast cancer stromal fibroblasts promote the generation of CD44+CD24- cells through SDF-1/CXCR4 interaction, J Exp Clin Cancer Res 29 (2010) 80. [PubMed: 20569497]

[118]. Sousa CM, Biancur DE, Wang X, Halbrook CJ, Sherman MH, Zhang L, Kremer D, Hwang RF, Witkiewicz AK, Ying H, Asara JM, Evans RM, Cantley LC, Lyssiotis CA, Kimmelman AC, Pancreatic stellate cells support tumour metabolism through autophagic alanine secretion, Nature 536(7617) (2016) 479–83. [PubMed: 27509858]

[119]. Shintani Y, Fujiwara A, Kimura T, Kawamura T, Funaki S, Minami M, Okumura M, IL-6 Secreted from Cancer-Associated Fibroblasts Mediates Chemoresistance in NSCLC by Increasing Epithelial-Mesenchymal Transition Signaling, J Thorac Oncol 11(9) (2016) 1482–92. [PubMed: 27287412]

[120]. Sansone P, Berishaj M, Rajasekhar VK, Ceccarelli C, Chang Q, Strillacci A, Savini C, Shapiro L, Bowman RL, Mastroleo C, De Carolis S, Daly L, Benito-Martin A, Perna F, Fabbri N, Healey JH, Spisni E, Cricca M, Lyden D, Bonafe M, Bromberg J, Evolution of Cancer Stem-like Cells in Endocrine-Resistant Metastatic Breast Cancers Is Mediated by Stromal Microvesicles, Cancer Res 77(8) (2017) 1927–1941. [PubMed: 28202520]

[121]. Hessmann E, Patzak MS, Klein L, Chen N, Kari V, Ramu I, Bapiro TE, Frese KK, Gopinathan A, Richards FM, Jodrell DI, Verbeke C, Li X, Heuchel R, Lohr JM, Johnsen SA, Gress TM, Ellenrieder V, Neesse A, Fibroblast drug scavenging increases intratumoural gemcitabine accumulation in murine pancreas cancer, Gut 67(3) (2018) 497–507. [PubMed: 28077438]

[122]. Kim JH, Oh SH, Kim EJ, Park SJ, Hong SP, Cheon JH, Kim TI, Kim WH, The role of myofibroblasts in upregulation of S100A8 and S100A9 and the differentiation of myeloid cells in the colorectal cancer microenvironment, Biochem Biophys Res Commun 423(1) (2012) 60–6. [PubMed: 22634002]

[123]. Yang X, Lin Y, Shi Y, Li B, Liu W, Yin W, Dang Y, Chu Y, Fan J, He R, FAP Promotes Immunosuppression by Cancer-Associated Fibroblasts in the Tumor Microenvironment via STAT3-CCL2 Signaling, Cancer Res 76(14) (2016) 4124–35. [PubMed: 27216177]

[124]. Feig C, Jones JO, Kraman M, Wells RJ, Deonarine A, Chan DS, Connell CM, Roberts EW, Zhao Q, Caballero OL, Teichmann SA, Janowitz T, Jodrell DI, Tuveson DA, Fearon DT, Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer, Proc Natl Acad Sci U S A 110(50) (2013) 20212–7. [PubMed: 24277834]

[125]. Etzerodt A, Tsalkitzi K, Maniecki M, Damsky W, Delfini M, Baudoin E, Moulin M, Bosenberg M, Graversen JH, Auphan-Anezin N, Moestrup SK, Lawrence T, Specific targeting of CD163(+) TAMs mobilizes inflammatory monocytes and promotes T cell-mediated tumor regression, J Exp Med (2019).

[126]. Wang H, Hu WM, Xia ZJ, Liang Y, Lu Y, Lin SX, Tang H, High numbers of CD163+ tumor-associated macrophages correlate with poor prognosis in multiple myeloma patients receiving bortezomib-based regimens, J Cancer 10(14) (2019) 3239–3245. [PubMed: 31289595]

[127]. Chen F, Chen J, Yang L, Liu J, Zhang X, Zhang Y, Tu Q, Yin D, Lin D, Wong PP, Huang D, Xing Y, Zhao J, Li M, Liu Q, Su F, Su S, Song E, Extracellular vesicle-packaged HIF-1alpha-stabilizing lncRNA from tumour-associated macrophages regulates aerobic glycolysis of breast cancer cells, Nat Cell Biol 21(4) (2019) 498–510. [PubMed: 30936474]

[128]. Lankadasari MB, Mukhopadhyay P, Mohammed S, Harikumar KB, TAMing pancreatic cancer: combat with a double edged sword, Mol Cancer 18(1) (2019) 48. [PubMed: 30925924]

[129]. Stromnes IM, Burrack AL, Hulbert A, Bonson P, Black C, Brockenbrough JS, Raynor JF, Spartz EJ, Pierce RH, Greenberg PD, Hingorani SR, Differential Effects of Depleting versus

Programming Tumor-Associated Macrophages on Engineered T Cells in Pancreatic Ductal Adenocarcinoma, Cancer Immunol Res 7(6) (2019) 977–989. [PubMed: 31028033]

[130]. Weizman N, Krelin Y, Shabtay-Orbach A, Amit M, Binenbaum Y, Wong RJ, Gil Z, Macrophages mediate gemcitabine resistance of pancreatic adenocarcinoma by upregulating cytidine deaminase, Oncogene 33(29) (2014) 3812–9. [PubMed: 23995783]

[131]. Halbrook CJ, Pontious C, Kovalenko I, Lapienyte L, Dreyer S, Lee HJ, Thurston G, Zhang Y, Lazarus J, Sajjakulnukit P, Hong HS, Kremer DM, Nelson BS, Kemp S, Zhang L, Chang D, Biankin A, Shi J, Frankel TL, Crawford HC, Morton JP, Pasca di Magliano M, Lyssiotis CA, Macrophage-Released Pyrimidines Inhibit Gemcitabine Therapy in Pancreatic Cancer, Cell Metab 29(6) (2019) 1390–1399 e6. [PubMed: 30827862]

[132]. Fu XT, Dai Z, Song K, Zhang ZJ, Zhou ZJ, Zhou SL, Zhao YM, Xiao YS, Sun QM, Ding ZB, Fan J, Macrophage-secreted IL-8 induces epithelial-mesenchymal transition in hepatocellular carcinoma cells by activating the JAK2/STAT3/Snail pathway, Int J Oncol 46(2) (2015) 587–96. [PubMed: 25405790]

[133]. Brekken RA, Puolakkainen P, Graves DC, Workman G, Lubkin SR, Sage EH, Enhanced growth of tumors in SPARC null mice is associated with changes in the ECM, J Clin Invest 111(4) (2003) 487–95. [PubMed: 12588887]

[134]. Lin EY, Li JF, Gnatovskiy L, Deng Y, Zhu L, Grzesik DA, Qian H, Xue XN, Pollard JW, Macrophages regulate the angiogenic switch in a mouse model of breast cancer, Cancer Res 66(23) (2006) 11238–46. [PubMed: 17114237]

[135]. Riabov V, Gudima A, Wang N, Mickley A, Orekhov A, Kzhyshkowska J, Role of tumor associated macrophages in tumor angiogenesis and lymphangiogenesis, Front Physiol 5 (2014) 75. [PubMed: 24634660]

[136]. Dirkx AE, Oude Egbrink MG, Wagstaff J, Griffioen AW, Monocyte/macrophage infiltration in tumors: modulators of angiogenesis, J Leukoc Biol 80(6) (2006) 1183–96. [PubMed: 16997855]

[137]. Bruno A, Focaccetti C, Pagani A, Imperatori AS, Spagnoletti M, Rotolo N, Cantelmo AR, Franzi F, Capella C, Ferlazzo G, Mortara L, Albini A, Noonan DM, The proangiogenic phenotype of natural killer cells in patients with non-small cell lung cancer, Neoplasia 15(2) (2013) 133–42. [PubMed: 23441128]

[138]. Lee-Chang C, Rashidi A, Miska J, Zhang P, Pituch KC, Hou D, Xiao T, Fischietti M, Kang SJ, Appin CL, Horbinski C, Platanias LC, Lopez-Rosas A, Han Y, Balyasnikova IV, Lesniak MS, Myeloid-derived suppressive cells promote B cell-mediated immunosuppression via transfer of PD-L1 in glioblastoma, Cancer Immunol Res (2019).

[139]. Ma X, Wang M, Yin T, Zhao Y, Wei X, Myeloid-Derived Suppressor Cells Promote Metastasis in Breast Cancer After the Stress of Operative Removal of the Primary Cancer, Front Oncol 9 (2019) 855. [PubMed: 31552179]

[140]. Jiang K, Li J, Zhang J, Wang L, Zhang Q, Ge J, Guo Y, Wang B, Huang Y, Yang T, Hao D, Shan L, SDF-1/CXCR4 axis facilitates myeloid-derived suppressor cells accumulation in osteosarcoma microenvironment and blunts the response to anti-PD-1 therapy, Int Immunopharmacol 75 (2019) 105818. [PubMed: 31437795]

[141]. Yamamura K, Izumi D, Kandimalla R, Sonohara F, Baba Y, Yoshida N, Kodera Y, Baba H, Goel A, Intratumoral Fusobacterium Nucleatum Levels Predict Therapeutic Response to Neoadjuvant Chemotherapy in Esophageal Squamous Cell Carcinoma, Clin Cancer Res (2019).

[142]. Riquelme E, Zhang Y, Zhang L, Montiel M, Zoltan M, Dong W, Quesada P, Sahin I, Chandra V, San Lucas A, Scheet P, Xu H, Hanash SM, Feng L, Burks JK, Do KA, Peterson CB, Nejman D, Tzeng CD, Kim MP, Sears CL, Ajami N, Petrosino J, Wood LD, Maitra A, Straussman R, Katz M, White JR, Jenq R, Wargo J, McAllister F, Tumor Microbiome Diversity and Composition Influence Pancreatic Cancer Outcomes, Cell 178(4) (2019) 795–806 e12. [PubMed: 31398337]

[143]. Wang X, Chao L, Ma G, Chen L, Tian B, Zang Y, Sun J, Increased expression of osteopontin in patients with triple-negative breast cancer, Eur J Clin Invest 38(6) (2008) 438–46. [PubMed: 18452545]

[144]. Macri A, Versaci A, Lupo G, Trimarchi G, Tomasello C, Loddo S, Sfuncia G, Caminiti R, Teti D, Famulari C, Role of osteopontin in breast cancer patients, Tumori 95(1) (2009) 48–52. [PubMed: 19366056]

[145]. Bourguignon LYW, Matrix Hyaluronan-CD44 Interaction Activates MicroRNA and LncRNA Signaling Associated With Chemoresistance, Invasion, and Tumor Progression, Front Oncol 9 (2019) 492. [PubMed: 31293964]

[146]. Provenzano PP, Cuevas C, Chang AE, Goel VK, Von Hoff DD, Hingorani SR, Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma, Cancer Cell 21(3) (2012) 418–29. [PubMed: 22439937]

[147]. Banik K, Ranaware AM, Deshpande V, Nalawade SP, Padmavathi G, Bordoloi D, Sailo BL, Shanmugam MK, Fan L, Arfuso F, Sethi G, Kunnumakkara AB, Honokiol for cancer therapeutics: A traditional medicine that can modulate multiple oncogenic targets, Pharmacological research 144 (2019) 192–209. [PubMed: 31002949]

[148]. Arora S, Singh S, Piazza GA, Contreras CM, Panyam J, Singh AP, Honokiol: a novel natural agent for cancer prevention and therapy, Curr Mol Med 12(10) (2012) 1244–52. [PubMed: 22834827]

[149]. Arora S, Bhardwaj A, Srivastava SK, Singh S, McClellan S, Wang B, Singh AP, Honokiol Arrests Cell Cycle, Induces Apoptosis, and Potentiates the Cytotoxic Effect of Gemcitabine in Human Pancreatic Cancer Cells, PLoS ONE 6(6) (2011) e21573. [PubMed: 21720559]

[150]. Gao X, Yu T, Xu G, Guo G, Liu X, Hu X, Wang X, Liu Y, Mao Q, You C, Zhou L, Enhancing the anti-glioma therapy of doxorubicin by honokiol with biodegradable self-assembling micelles through multiple evaluations, Scientific reports 7 (2017) 43501. [PubMed: 28240249]

[151]. Averett C, Bhardwaj A, Arora S, Srivastava SK, Khan MA, Ahmad A, Singh S, Carter JE, Khushman M, Singh AP, Honokiol suppresses pancreatic tumor growth, metastasis and desmoplasia by interfering with tumor-stromal cross-talk, Carcinogenesis 37(11) (2016) 1052–1061. [PubMed: 27609457]

[152]. Luo LX, Li Y, Liu ZQ, Fan XX, Duan FG, Li RZ, Yao XJ, Leung EL, Liu L, Honokiol Induces Apoptosis, G1 Arrest, and Autophagy in KRAS Mutant Lung Cancer Cells, Front Pharmacol 8 (2017) 199. [PubMed: 28443025]

[153]. Nagalingam A, Arbiser JL, Bonner MY, Saxena NK, Sharma D, Honokiol activates AMP-activated protein kinase in breast cancer cells via an LKB1-dependent pathway and inhibits breast carcinogenesis, Breast cancer research : BCR 14(1) (2012) R35. [PubMed: 22353783]

[154]. Sengupta S, Nagalingam A, Muniraj N, Bonner MY, Mistriotis P, Afthinos A, Kuppusamy P, Lanoue D, Cho S, Korangath P, Shriver M, Begum A, Merino VF, Huang CY, Arbiser JL, Matsui W, Gyorffy B, Konstantopoulos K, Sukumar S, Marignani PA, Saxena NK, Sharma D, Activation of tumor suppressor LKB1 by honokiol abrogates cancer stem-like phenotype in breast cancer via inhibition of oncogenic Stat3, Oncogene 36(41) (2017) 5709–5721. [PubMed: 28581518]

[155]. Yoshida M, Taguchi A, Kawana K, Adachi K, Kawata A, Ogishima J, Nakamura H, Fujimoto A, Sato M, Inoue T, Nishida H, Furuya H, Tomio K, Arimoto T, Koga K, Wada-Hiraike O, Oda K, Nagamatsu T, Kiyono T, Osuga Y, Fujii T, Modification of the Tumor Microenvironment in KRAS or c-MYC-Induced Ovarian Cancer-Associated Peritonitis, PLoS One 11(8) (2016) e0160330. [PubMed: 27483433]

[156]. Thomson AW, Turnquist HR, Raimondi G, Immunoregulatory functions of mTOR inhibition, Nat Rev Immunol 9(5) (2009) 324–37. [PubMed: 19390566]

[157]. Jiraviriyakul A, Songjang W, Kaewthet P, Tanawatkitichai P, Bayan P, Pongcharoen S, Honokiol-enhanced cytotoxic T lymphocyte activity against cholangiocarcinoma cells mediated by dendritic cells pulsed with damage-associated molecular patterns, World journal of gastroenterology 25(29) (2019) 3941–3955. [PubMed: 31413529]

[158]. Bai X, Cerimele F, Ushio-Fukai M, Waqas M, Campbell PM, Govindarajan B, Der CJ, Battle T, Frank DA, Ye K, Murad E, Dubiel W, Soff G, Arbiser JL, Honokiol, a small molecular weight natural product, inhibits angiogenesis in vitro and tumor growth in vivo, J Biol Chem 278(37) (2003) 35501–7. [PubMed: 12816951]

[159]. Li Z, Liu Y, Zhao X, Pan X, Yin R, Huang C, Chen L, Wei Y, Honokiol, a natural therapeutic candidate, induces apoptosis and inhibits angiogenesis of ovarian tumor cells, European journal of obstetrics, gynecology, and reproductive biology 140(1) (2008) 95–102.

[160]. Ma L, Chen J, Wang X, Liang X, Luo Y, Zhu W, Wang T, Peng M, Li S, Jie S, Peng A, Wei Y, Chen L, Structural modification of honokiol, a biphenyl occurring in Magnolia officinalis: the evaluation of honokiol analogues as inhibitors of angiogenesis and for their cytotoxicity and

structure-activity relationship, Journal of medicinal chemistry 54(19) (2011) 6469–81. [PubMed: 21853991]

[161]. Wang T, Chen W, Wu J, H2-P, a honokiol derivative, exerts anti-angiogenesis effects via c-MYC signaling pathway in glioblastoma, J Cell Biochem 119(4) (2018) 3142–3148. [PubMed: 29080353]

[162]. Fabiani R, Anti-cancer properties of olive oil secoiridoid phenols: a systematic review of in vivo studies, Food & function 7(10) (2016) 4145–4159. [PubMed: 27713961]

[163]. Pineiro Z, Cantos-Villar E, Palma M, Puertas B, Direct liquid chromatography method for the simultaneous quantification of hydroxytyrosol and tyrosol in red wines, Journal of agricultural and food chemistry 59(21) (2011) 11683–9. [PubMed: 21950381]

[164]. de la Torre R, Bioavailability of olive oil phenolic compounds in humans, Inflammopharmacology 16(5) (2008) 245–7. [PubMed: 18815736]

[165]. Zubair H, Bhardwaj A, Ahmad A, Srivastava SK, Khan MA, Patel GK, Singh S, Singh AP, Hydroxytyrosol Induces Apoptosis and Cell Cycle Arrest and Suppresses Multiple Oncogenic Signaling Pathways in Prostate Cancer Cells, Nutrition and cancer 69(6) (2017) 932–942. [PubMed: 28718667]

[166]. Ramirez-Tortosa C, Sanchez A, Perez-Ramirez C, Quiles JL, Robles-Almazan M, Pulido-Moran M, Sanchez-Rovira P, Ramirez-Tortosa M, Hydroxytyrosol Supplementation Modifies Plasma Levels of Tissue Inhibitor of Metallopeptidase 1 in Women with Breast Cancer, Antioxidants (Basel, Switzerland) 8(9) (2019).

[167]. Lu HY, Zhu JS, Zhang Z, Shen WJ, Jiang S, Long YF, Wu B, Ding T, Huan F, Wang SL, Hydroxytyrosol and Oleuropein Inhibit Migration and Invasion of MDA-MB-231 Triple-Negative Breast Cancer Cell via Induction of Autophagy, Anti-cancer agents in medicinal chemistry (2019).

[168]. Cruz-Lozano M, Gonzalez-Gonzalez A, Marchal JA, Munoz-Muela E, Molina MP, Cara FE, Brown AM, Garcia-Rivas G, Hernandez-Brenes C, Lorente JA, Sanchez-Rovira P, Chang JC, Granados-Principal S, Hydroxytyrosol inhibits cancer stem cells and the metastatic capacity of triple-negative breast cancer cell lines by the simultaneous targeting of epithelial-to-mesenchymal transition, Wnt/beta-catenin and TGFbeta signaling pathways, European journal of nutrition (2018).

[169]. Goldsmith CD, Bond DR, Jankowski H, Weidenhofer J, Stathopoulos CE, Roach PD, Scarlett CJ, The Olive Biophenols Oleuropein and Hydroxytyrosol Selectively Reduce Proliferation, Influence the Cell Cycle, and Induce Apoptosis in Pancreatic Cancer Cells, Int J Mol Sci 19(7) (2018).

[170]. Zhao B, Ma Y, Xu Z, Wang J, Wang F, Wang D, Pan S, Wu Y, Pan H, Xu D, Liu L, Jiang H, Hydroxytyrosol, a natural molecule from olive oil, suppresses the growth of human hepatocellular carcinoma cells via inactivating AKT and nuclear factor-kappa B pathways, Cancer letters 347(1) (2014) 79–87. [PubMed: 24486741]

[171]. Tutino V, Caruso MG, Messa C, Perri E, Notarnicola M, Antiproliferative, antioxidant and anti-inflammatory effects of hydroxytyrosol on human hepatoma HepG2 and Hep3B cell lines, Anticancer research 32(12) (2012) 5371–7. [PubMed: 23225439]

[172]. Fabiani R, Rosignoli P, De Bartolomeo A, Fuccelli R, Morozzi G, Inhibition of cell cycle progression by hydroxytyrosol is associated with upregulation of cyclin-dependent protein kinase inhibitors p21(WAF1/Cip1) and p27(Kip1) and with induction of differentiation in HL60 cells, The Journal of nutrition 138(1) (2008) 42–8. [PubMed: 18156402]

[173]. Fabiani R, De Bartolomeo A, Rosignoli P, Servili M, Selvaggini R, Montedoro GF, Di Saverio C, Morozzi G, Virgin olive oil phenols inhibit proliferation of human promyelocytic leukemia cells (HL60) by inducing apoptosis and differentiation, The Journal of nutrition 136(3) (2006) 614–9. [PubMed: 16484533]

[174]. Storniolo CE, Martinez-Hovelman N, Martinez-Huelamo M, Lamuela-Raventos RM, Moreno JJ, Extra Virgin Olive Oil Minor Compounds Modulate Mitogenic Action of Oleic Acid on Colon Cancer Cell Line, Journal of agricultural and food chemistry (2019).

[175]. Terzuoli E, Nannelli G, Frosini M, Giachetti A, Ziche M, Donnini S, Inhibition of cell cycle progression by the hydroxytyrosol-cetuximab combination yields enhanced chemotherapeutic efficacy in colon cancer cells, Oncotarget 8(47) (2017) 83207–83224. [PubMed: 29137335]

[176]. Lopez MC de Las Hazas, C. Pinol, A. Macia, M.J. Motilva, Hydroxytyrosol and the Colonic Metabolites Derived from Virgin Olive Oil Intake Induce Cell Cycle Arrest and Apoptosis in Colon Cancer Cells, Journal of agricultural and food chemistry 65(31) (2017) 6467–6476. [PubMed: 28071050]

[177]. Warleta F, Quesada CS, Campos M, Allouche Y, Beltran G, Gaforio JJ, Hydroxytyrosol protects against oxidative DNA damage in human breast cells, Nutrients 3(10) (2011) 839–57. [PubMed: 22254082]

[178]. Sun L, Luo C, Liu J, Hydroxytyrosol induces apoptosis in human colon cancer cells through ROS generation, Food & function 5(8) (2014) 1909-14. [PubMed: 24953710]

[179]. Emanuele S, D'Anneo A, Calvaruso G, Cernigliaro C, Giuliano M, Lauricella M, The Double-Edged Sword Profile of Redox Signaling: Oxidative Events As Molecular Switches in the Balance between Cell Physiology and Cancer, Chemical research in toxicology 31(4) (2018) 201–210. [PubMed: 29513521]

[180]. Xu J, Wise JTF, Wang L, Schumann K, Zhang Z, Shi X, Dual Roles of Oxidative Stress in Metal Carcinogenesis, Journal of environmental pathology, toxicology and oncology : official organ of the International Society for Environmental Toxicology and Cancer 36(4) (2017) 345–376.

[181]. de Sa Junior PL, Camara DAD, Porcacchia AS, Fonseca PMM, Jorge SD, Araldi RP, Ferreira AK, The Roles of ROS in Cancer Heterogeneity and Therapy, Oxidative medicine and cellular longevity 2017 (2017) 2467940. [PubMed: 29123614]

[182]. Calahorra J, Martinez-Lara E, De Dios C, Siles E, Hypoxia modulates the antioxidant effect of hydroxytyrosol in MCF-7 breast cancer cells, PLoS One 13(9) (2018) e0203892. [PubMed: 30235254]

[183]. Kwan HY, Liu B, Huang C, Fatima S, Su T, Zhao X, Ho AHM, Han Q, Hu X, Gong RH, Chen M, Wong HLX, Bian Z, Signal transducer and activator of transcription-3 drives the high-fat diet-associated prostate cancer growth, Cell Death Dis 10(9) (2019) 637. [PubMed: 31474764]

[184]. Hellsten R, Lilljebjorn L, Johansson M, Leandersson K, Bjartell A, The STAT3 inhibitor galiellalactone inhibits the generation of MDSC-like monocytes by prostate cancer cells and decreases immunosuppressive and tumorigenic factors, The Prostate 79(14) (2019) 1611–1621. [PubMed: 31348843]

[185]. Culig Z, Santer FR, Androgen receptor signaling in prostate cancer, Cancer metastasis reviews 33(2–3) (2014) 413–27. [PubMed: 24384911]

[186]. Dai C, Heemers H, Sharifi N, Androgen Signaling in Prostate Cancer, Cold Spring Harb Perspect Med 7(9) (2017).

[187]. Maxwell PJ, Neisen J, Messenger J, Waugh DJ, Tumor-derived CXCL8 signaling augments stroma-derived CCL2-promoted proliferation and CXCL12-mediated invasion of PTEN-deficient prostate cancer cells, Oncotarget 5(13) (2014) 4895–908. [PubMed: 24970800]

[188]. Sarsour EH, Goswami M, Kalen AL, Lafin JT, Goswami PC, Hydroxytyrosol inhibits chemokine C-C motif ligand 5 mediated aged quiescent fibroblast-induced stimulation of breast cancer cell proliferation, Age (Dordrecht, Netherlands) 36(3) (2014) 9645.

[189]. Nagarsheth N, Wicha MS, Zou W, Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy, Nat Rev Immunol 17(9) (2017) 559–572. [PubMed: 28555670]

[190]. Goswami SK, Das DK, Resveratrol and chemoprevention, Cancer letters 284(1) (2009) 1–6. [PubMed: 19261378]

[191]. Bishayee A, Cancer prevention and treatment with resveratrol: from rodent studies to clinical trials, Cancer Prev Res (Phila) 2(5) (2009) 409–18. [PubMed: 19401532]

[192]. Ding S, Jiang J, Wang Z, Zhang G, Yin J, Wang X, Wang S, Yu Z, Resveratrol reduces the inflammatory response in adipose tissue and improves adipose insulin signaling in high-fat diet-fed mice, PeerJ 6 (2018) e5173. [PubMed: 29967759]

[193]. Cai H, Scott E, Kholghi A, Andreadi C, Rufini A, Karmokar A, Britton RG, Horner-Glister E, Greaves P, Jawad D, James M, Howells L, Ognibene T, Malfatti M, Goldring C, Kitteringham N, Walsh J, Viskaduraki M, West K, Miller A, Hemingway D, Steward WP, Gescher AJ, Brown K, Cancer chemoprevention: Evidence of a nonlinear dose response for the protective effects of resveratrol in humans and mice, Sci Transl Med 7(298) (2015) 298ra117.

[194]. Lissa D, Senovilla L, Rello-Varona S, Vitale I, Michaud M, Pietrocola F, Boileve A, Obrist F, Bordenave C, Garcia P, Michels J, Jemaa M, Kepp O, Castedo M, Kroemer G, Resveratrol and aspirin eliminate tetraploid cells for anticancer chemoprevention, Proc Natl Acad Sci U S A 111(8) (2014) 3020–5. [PubMed: 24516128]

[195]. Lin D, Dai F, Sun LD, Zhou B, Toward an understanding of the role of a catechol moiety in cancer chemoprevention: The case of copper- and o-quinone-dependent Nrf2 activation by a catechol-type resveratrol analog, Mol Nutr Food Res 59(12) (2015) 2395–406. [PubMed: 26314862]

[196]. Hadi SM, Ullah MF, Azmi AS, Ahmad A, Shamim U, Zubair H, Khan HY, Resveratrol mobilizes endogenous copper in human peripheral lymphocytes leading to oxidative DNA breakage: a putative mechanism for chemoprevention of cancer, Pharmaceutical research 27(6) (2010) 979–88. [PubMed: 20119749]

[197]. Saghafi T, Taheri RA, Parkkila S, Emameh RZ, Phytochemicals as Modulators of Long Non-Coding RNAs and Inhibitors of Cancer-Related Carbonic Anhydrases, Int J Mol Sci 20(12) (2019).

[198]. Shamim U, Hanif S, Albanyan A, Beck FW, Bao B, Wang Z, Banerjee S, Sarkar FH, Mohammad RM, Hadi SM, Azmi AS, Resveratrol-induced apoptosis is enhanced in low pH environments associated with cancer, Journal of cellular physiology 227(4) (2012) 1493–500. [PubMed: 21678400]

[199]. Li W, Cao L, Chen X, Lei J, Ma Q, Resveratrol inhibits hypoxia-driven ROS-induced invasive and migratory ability of pancreatic cancer cells via suppression of the Hedgehog signaling pathway, Oncology reports 35(3) (2016) 1718–26. [PubMed: 26707376]

[200]. Vancauwenberghe E, Noyer L, Derouiche S, Lemonnier L, Gosset P, Sadofsky LR, Mariot P, Warnier M, Bokhobza A, Slomianny C, Mauroy B, Bonnal JL, Dewailly E, Delcourt P, Allart L, Desruelles E, Prevarskaya N, Roudbaraki M, Activation of mutated TRPA1 ion channel by resveratrol in human prostate cancer associated fibroblasts (CAF), Molecular carcinogenesis 56(8) (2017) 1851–1867. [PubMed: 28277613]

[201]. Menicacci B, Laurenzana A, Chilla A, Margheri F, Peppicelli S, Tanganelli E, Fibbi G, Giovannelli L, Del Rosso M, Mocali A, Chronic Resveratrol Treatment Inhibits MRC5 Fibroblast SASP-Related Protumoral Effects on Melanoma Cells, The journals of gerontology. Series A, Biological sciences and medical sciences 72(9) (2017) 1187–1195. [PubMed: 28329136]

[202]. Suh J, Kim DH, Surh YJ, Resveratrol suppresses migration, invasion and stemness of human breast cancer cells by interfering with tumor-stromal cross-talk, Archives of biochemistry and biophysics 643 (2018) 62–71. [PubMed: 29477771]

[203]. Yang Y, Paik JH, Cho D, Cho JA, Kim CW, Resveratrol induces the suppression of tumor-derived CD4+CD25+ regulatory T cells, Int Immunopharmacol 8(4) (2008) 542–7. [PubMed: 18328445]

[204]. Jeong SK, Yang K, Park YS, Choi YJ, Oh SJ, Lee CW, Lee KY, Jeong MH, Jo WS, Interferon gamma induced by resveratrol analog, HS-1793, reverses the properties of tumor associated macrophages, Int Immunopharmacol 22(2) (2014) 303–10. [PubMed: 25042796]

[205]. Sun L, Chen B, Jiang R, Li J, Wang B, Resveratrol inhibits lung cancer growth by suppressing M2-like polarization of tumor associated macrophages, Cell Immunol 311 (2017) 86–93. [PubMed: 27825563]

[206]. Lelli D, Sahebkar A, Johnston TP, Pedone C, Curcumin use in pulmonary diseases: State of the art and future perspectives, Pharmacological research 115 (2017) 133–148. [PubMed: 27888157]

[207]. Jurenka JS, Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research, Alternative medicine review : a journal of clinical therapeutic 14(2) (2009) 141–53. [PubMed: 19594223]

[208]. Aggarwal BB, Sethi G, Baladandayuthapani V, Krishnan S, Shishodia S, Targeting cell signaling pathways for drug discovery: an old lock needs a new key, J Cell Biochem 102(3) (2007) 580–92. [PubMed: 17668425]

[209]. Tsuda T, Curcumin as a functional food-derived factor: degradation products, metabolites, bioactivity, and future perspectives, Food & function 9(2) (2018) 705–714. [PubMed: 29206254]

[210]. Momtazi AA, Sahebkar A, Difluorinated Curcumin: A Promising Curcumin Analogue with Improved Anti-Tumor Activity and Pharmacokinetic Profile, Current pharmaceutical design 22(28) (2016) 4386–97. [PubMed: 27229723]

[211]. He ZY, Shi CB, Wen H, Li FL, Wang BL, Wang J, Upregulation of p53 expression in patients with colorectal cancer by administration of curcumin, Cancer investigation 29(3) (2011) 208–13. [PubMed: 21314329]

[212]. Han SS, Chung ST, Robertson DA, Ranjan D, Bondada S, Curcumin causes the growth arrest and apoptosis of B cell lymphoma by downregulation of egr-1, c-myc, bcl-XL, NF-kappa B, and p53, Clinical immunology (Orlando, Fla.) 93(2) (1999) 152–61.

[213]. Pelengaris S, Khan M, Evan GI, Suppression of Myc-induced apoptosis in beta cells exposes multiple oncogenic properties of Myc and triggers carcinogenic progression, Cell 109(3) (2002) 321–34. [PubMed: 12015982]

[214]. Pelengaris S, Littlewood T, Khan M, Elia G, Evan G, Reversible activation of c-Myc in skin: induction of a complex neoplastic phenotype by a single oncogenic lesion, Mol Cell 3(5) (1999) 565–77. [PubMed: 10360173]

[215]. Soucek L, Lawlor ER, Soto D, Shchors K, Swigart LB, Evan GI, Mast cells are required for angiogenesis and macroscopic expansion of Myc-induced pancreatic islet tumors, Nat Med 13(10) (2007) 1211–8. [PubMed: 17906636]

[216]. Hidaka H, Ishiko T, Furuhashi T, Kamohara H, Suzuki S, Miyazaki M, Ikeda O, Mita S, Setoguchi T, Ogawa M, Curcumin inhibits interleukin 8 production and enhances interleukin 8 receptor expression on the cell surface:impact on human pancreatic carcinoma cell growth by autocrine regulation, Cancer 95(6) (2002) 1206–14. [PubMed: 12216086]

[217]. Sun K, Duan X, Cai H, Liu X, Yang Y, Li M, Zhang X, Wang J, Curcumin inhibits LPA-induced invasion by attenuating RhoA/ROCK/MMPs pathway in MCF7 breast cancer cells, Clinical and experimental medicine 16(1) (2016) 37–47. [PubMed: 25596714]

[218]. Yang H, Huang S, Wei Y, Cao S, Pi C, Feng T, Liang J, Zhao L, Ren G, Curcumin Enhances the Anticancer Effect Of 5-fluorouracil against Gastric Cancer through Down-Regulation of COX-2 and NF- kappaB Signaling Pathways, J Cancer 8(18) (2017) 3697–3706. [PubMed: 29151957]

[219]. Zhao J, Zhu J, Lv X, Xing J, Liu S, Chen C, Xu Y, Curcumin potentiates the potent antitumor activity of ACNU against glioblastoma by suppressing the PI3K/AKT and NF-kappaB/COX-2 signaling pathways, OncoTargets and therapy 10 (2017) 5471–5482. [PubMed: 29180881]

[220]. Zheng Y, Comaills V, Burr R, Boulay G, Miyamoto DT, Wittner BS, Emmons E, Sil S, Koulopoulos MW, Broderick KT, Tai E, Rengarajan S, Kulkarni AS, Shioda T, Wu CL, Ramaswamy S, Ting DT, Toner M, Rivera MN, Maheswaran S, Haber DA, COX-2 mediates tumor-stromal prolactin signaling to initiate tumorigenesis, Proc Natl Acad Sci U S A 116(12) (2019) 5223–5232. [PubMed: 30819896]

[221]. Shiri S, Alizadeh AM, Baradaran B, Farhanghi B, Shanehbandi D, Khodayari S, Khodayari H, Tavassoli A, Dendrosomal curcumin suppresses metastatic breast cancer in mice by changing m1/m2 macrophage balance in the tumor microenvironment, Asian Pacific journal of cancer prevention : APJCP 16(9) (2015) 3917–22. [PubMed: 25987060]

[222]. Mukherjee S, Baidoo J, Fried A, Atwi D, Dolai S, Boockvar J, Symons M, Ruggieri R, Raja K, Banerjee P, Curcumin changes the polarity of tumor-associated microglia and eliminates glioblastoma, International journal of cancer 139(12) (2016) 2838–2849. [PubMed: 27543754]

[223]. Zou JY, Su CH, Luo HH, Lei YY, Zeng B, Zhu HS, Chen ZG, Curcumin converts Foxp3+ regulatory T cells to T helper 1 cells in patients with lung cancer, J Cell Biochem 119(2) (2018) 1420–1428. [PubMed: 28731226]

[224]. Chang YF, Chuang HY, Hsu CH, Liu RS, Gambhir SS, Hwang JJ, Immunomodulation of curcumin on adoptive therapy with T cell functional imaging in mice, Cancer Prev Res (Phila) 5(3) (2012) 444–52. [PubMed: 22135043]

[225]. Bhattacharyya S, Md Sakib Hossain D, Mohanty S, Sankar Sen G, Chattopadhyay S, Banerjee S, Chakraborty J, Das K, Sarkar D, Das T, Sa G, Curcumin reverses T cell-mediated adaptive immune dysfunctions in tumor-bearing hosts, Cellular & molecular immunology 7(4) (2010) 306–15. [PubMed: 20305684]

[226]. Ortiz LM, Lombardi P, Tillhon M, Scovassi AI, Berberine, an epiphany against cancer, Molecules (Basel, Switzerland) 19(8) (2014) 12349–67.

[227]. Imenshahidi M, Hosseinzadeh H, Berberis Vulgaris and Berberine: An Update Review, Phytotherapy research : PTR 30(11) (2016) 1745–1764. [PubMed: 27528198]

[228]. Wang K, Feng X, Chai L, Cao S, Qiu F, The metabolism of berberine and its contribution to the pharmacological effects, Drug metabolism reviews 49(2) (2017) 139–157. [PubMed: 28290706]

[229]. Piao M, Cao H, He N, Yang B, Dong W, Xu M, Yan F, Zhou B, Wang B, Berberine Inhibits Intestinal Polyps Growth in Apc (min/+) Mice via Regulation of Macrophage Polarization, Evidence-based complementary and alternative medicine : eCAM 2016 (2016) 5137505. [PubMed: 27493671]

[230]. Pan Y, Shao D, Zhao Y, Zhang F, Zheng X, Tan Y, He K, Li J, Chen L, Berberine Reverses Hypoxia-induced Chemoresistance in Breast Cancer through the Inhibition of AMPK-HIF-1alpha, International journal of biological sciences 13(6) (2017) 794–803. [PubMed: 28656004]

[231]. Kaboli PJ, Bazrafkan M, Ismail P, Ling KH, Molecular Modelling of Berberine Derivatives as Inhibitors of Human Smoothened Receptor and Hedgehog Signalling Pathway Using a Newly Developed Algorithm on Anti-Cancer Drugs, Recent patents on anti-cancer drug discovery 12(4) (2017) 384–400. [PubMed: 28969581]

[232]. Sharma MD, Baban B, Chandler P, Hou DY, Singh N, Yagita H, Azuma M, Blazar BR, Mellor AL, Munn DH, Plasmacytoid dendritic cells from mouse tumor-draining lymph nodes directly activate mature Tregs via indoleamine 2,3-dioxygenase, J Clin Invest 117(9) (2007) 2570–82. [PubMed: 17710230]

[233]. Wang YX, Pang WQ, Zeng QX, Deng ZS, Fan TY, Jiang JD, Deng HB, Song DQ, Synthesis and biological evaluation of new berberine derivatives as cancer immunotherapy agents through targeting IDO1, Eur J Med Chem 143 (2018) 1858–1868. [PubMed: 29133053]

[234]. Sur S, Panda CK, Molecular aspects of cancer chemopreventive and therapeutic efficacies of tea and tea polyphenols, Nutrition 43–44 (2017) 8–15.

[235]. Rao SD, Pagidas K, Epigallocatechin-3-gallate, a natural polyphenol, inhibits cell proliferation and induces apoptosis in human ovarian cancer cells, Anticancer research 30(7) (2010) 2519–23. [PubMed: 20682977]

[236]. Li P, Li S, Yin D, Li J, Wang L, Huang C, Yang X, EGCG sensitizes human nasopharyngeal carcinoma cells to TRAIL-mediated apoptosis by activation NF-kappaB, Neoplasma 64(1) (2017) 74–80. [PubMed: 27881007]

[237]. Huang J, Chen S, Shi Y, Li CH, Wang XJ, Li FJ, Wang CH, Meng QH, Zhong JN, Liu M, Wang ZM, Epigallocatechin gallate from green tea exhibits potent anticancer effects in A-549 non-small lung cancer cells by inducing apoptosis, cell cycle arrest and inhibition of cell migration, Journal of B.U.ON. : official journal of the Balkan Union of Oncology 22(6) (2017) 1422–1427. [PubMed: 29332333]

[238]. Wu D, Liu Z, Li J, Zhang Q, Zhong P, Teng T, Chen M, Xie Z, Ji A, Li Y, Epigallocatechin-3-gallate inhibits the growth and increases the apoptosis of human thyroid carcinoma cells through suppression of EGFR/RAS/RAF/MEK/ERK signaling pathway, Cancer cell international 19 (2019) 43. [PubMed: 30858760]

[239]. Hu DL, Wang G, Yu J, Zhang LH, Huang YF, Wang D, Zhou HH, Epigallocatechin3gallate modulates long noncoding RNA and mRNA expression profiles in lung cancer cells, Molecular medicine reports 19(3) (2019) 1509–1520. [PubMed: 30628683]

[240]. Wang J, Man GCW, Chan TH, Kwong J, Wang CC, A prodrug of green tea polyphenol (−)-epigallocatechin-3-gallate (Pro-EGCG) serves as a novel angiogenesis inhibitor in endometrial cancer, Cancer letters 412 (2018) 10–20. [PubMed: 29024813]

[241]. Jang JY, Lee JK, Jeon YK, Kim CW, Exosome derived from epigallocatechin gallate treated breast cancer cells suppresses tumor growth by inhibiting tumor-associated macrophage infiltration and M2 polarization, BMC cancer 13 (2013) 421. [PubMed: 24044575]

[242]. Huang AC, Cheng HY, Lin TS, Chen WH, Lin JH, Lin JJ, Lu CC, Chiang JH, Hsu SC, Wu PP, Huang YP, Chung JG, Epigallocatechin gallate (EGCG), influences a murine WEHI-3

leukemia model in vivo through enhancing phagocytosis of macrophages and populations of T- and B-cells, In vivo (Athens, Greece) 27(5) (2013) 627–34.

[243]. Rawangkan A, Wongsirisin P, Namiki K, Iida K, Kobayashi Y, Shimizu Y, Fujiki H, Suganuma M, Green Tea Catechin Is an Alternative Immune Checkpoint Inhibitor that Inhibits PD-L1 Expression and Lung Tumor Growth, Molecules (Basel, Switzerland) 23(8) (2018).

[244]. Singh SP, Nongalleima K, Singh NI, Doley P, Singh CB, Singh TR, Sahoo D, Zerumbone reduces proliferation of HCT116 colon cancer cells by inhibition of TNF-alpha, Scientific reports 8(1) (2018) 4090. [PubMed: 29511228]

[245]. Igarashi Y, Ohnishi K, Irie K, Murakami A, Possible Contribution of Zerumbone-Induced Proteo-Stress to Its Anti-Inflammatory Functions via the Activation of Heat Shock Factor 1, PLoS One 11(8) (2016) e0161282. [PubMed: 27536885]

[246]. Sf A, Maharjan R, Immunomodulation of Zerumbone via Decreasing the Production of Reactive Oxygen Species from Immune Cells, Pak J Biol Sci 21(9) (2018) 475–479. [PubMed: 30724050]

[247]. Li L, Wu XH, Zhao XJ, Xu L, Pan CL, Zhang ZY, Zerumbone ameliorates behavioral impairments and neuropathology in transgenic APP/PS1 mice by suppressing MAPK signaling, J Neuroinflammation 17(1) (2020) 61. [PubMed: 32066466]

[248]. Murakami A, Takahashi D, Kinoshita T, Koshimizu K, Kim HW, Yoshihiro A, Nakamura Y, Jiwajinda S, Terao J, Ohigashi H, Zerumbone, a Southeast Asian ginger sesquiterpene, markedly suppresses free radical generation, proinflammatory protein production, and cancer cell proliferation accompanied by apoptosis: the alpha,beta-unsaturated carbonyl group is a prerequisite, Carcinogenesis 23(5) (2002) 795–802. [PubMed: 12016152]

[249]. Haque MA, Jantan I, Harikrishnan H, Zerumbone suppresses the activation of inflammatory mediators in LPS-stimulated U937 macrophages through MyD88-dependent NF-kappaB/MAPK/PI3K-Akt signaling pathways, Int Immunopharmacol 55 (2018) 312–322. [PubMed: 29310107]

[250]. Kim MJ, Yun JM, Molecular Mechanism of the Protective Effect of Zerumbone on Lipopolysaccharide-Induced Inflammation of THP-1 Cell-Derived Macrophages, J Med Food 22(1) (2019) 62–73. [PubMed: 30383973]

[251]. Abdelwahab SI, Abdul AB, Zain ZN, Hadi AH, Zerumbone inhibits interleukin-6 and induces apoptosis and cell cycle arrest in ovarian and cervical cancer cells, Int Immunopharmacol 12(4) (2012) 594–602. [PubMed: 22330084]

[252]. Shyanti RK, Sehrawat A, Singh SV, Mishra JPN, Singh RP, Zerumbone modulates CD1d expression and lipid antigen presentation pathway in breast cancer cells, Toxicol In Vitro 44 (2017) 74–84. [PubMed: 28633979]

[253]. Samad NA, Abdul AB, Rahman HS, Rasedee A, Tengku Ibrahim TA, Keon YS, Zerumbone Suppresses Angiogenesis in HepG2 Cells through Inhibition of Matrix Metalloproteinase-9, Vascular Endothelial Growth Factor, and Vascular Endothelial Growth Factor Receptor Expressions, Pharmacogn Mag 13(Suppl 4) (2018) S731–S736.

[254]. Shamoto T, Matsuo Y, Shibata T, Tsuboi K, Nagasaki T, Takahashi H, Funahashi H, Okada Y, Takeyama H, Zerumbone inhibits angiogenesis by blocking NF-kappaB activity in pancreatic cancer, Pancreas 43(3) (2014) 396–404. [PubMed: 24622069]

[255]. Hwang S, Jo M, Hong JE, Park CO, Lee CG, Rhee KJ, Protective Effects of Zerumbone on Colonic Tumorigenesis in Enterotoxigenic Bacteroides fragilis (ETBF)-Colonized AOM/DSS BALB/c Mice, Int J Mol Sci 21(3) (2020).

[256]. Zhang K, Wang Y, Ma W, Hu Z, Zhao P, Genistein improves thyroid function in Hashimoto's thyroiditis patients through regulating Th1 cytokines, Immunobiology 222(2) (2017) 183–187. [PubMed: 27729167]

[257]. Mace TA, Ware MB, King SA, Loftus S, Farren MR, McMichael E, Scoville S, Geraghty C, Young G, Carson WE 3rd, Clinton SK, Lesinski GB, Soy isoflavones and their metabolites modulate cytokine-induced natural killer cell function, Scientific reports 9(1) (2019) 5068. [PubMed: 30911044]

[258]. Tiper IV, Temkin SM, Spiegel S, Goldblum SE, Giuntoli RL 2nd, Oelke M, Schneck JP, Webb TJ, VEGF Potentiates GD3-Mediated Immunosuppression by Human Ovarian Cancer Cells, Clin Cancer Res 22(16) (2016) 4249–58. [PubMed: 27076627]

[259]. Liu X, Liu K, Qin J, Hao L, Li X, Liu Y, Zhang X, Liu X, Li P, Han S, Mao Z, Shen L, C/EBPbeta promotes angiogenesis through secretion of IL-6, which is inhibited by genistein, in EGFRvIII-positive glioblastoma, International journal of cancer 136(11) (2015) 2524–34. [PubMed: 25382637]

[260]. Farina HG, Pomies M, Alonso DF, Gomez DE, Antitumor and antiangiogenic activity of soy isoflavone genistein in mouse models of melanoma and breast cancer, Oncology reports 16(4) (2006) 885–91. [PubMed: 16969510]

[261]. Latocha M, Plonka J, Kusmierz D, Jurzak M, Polaniak R, Nowosad A, Transcripional activity of genes encoding MMPs and TIMPs in breast cancer cells treated by genistein and in normal cancer-associated fibroblasts--in vitro studies, Acta Pol Pharm 71(6) (2014) 1095–102. [PubMed: 25745786]

[262]. Owen JL, Torroella-Kouri M, Iragavarapu-Charyulu V, Molecular events involved in the increased expression of matrix metalloproteinase-9 by T lymphocytes of mammary tumor-bearing mice, Int J Mol Med 21(1) (2008) 125–34. [PubMed: 18097625]

[263]. Moskot M, Jakobkiewicz-Banecka J, Smolinska E, Piotrowska E, Wegrzyn G, Gabig-Ciminska M, Effects of flavonoids on expression of genes involved in cell cycle regulation and DNA replication in human fibroblasts, Mol Cell Biochem 407(1–2) (2015) 97–109. [PubMed: 26003441]

[264]. Mentor-Marcel R, Lamartiniere CA, Eltoum IA, Greenberg NM, Elgavish A, Dietary genistein improves survival and reduces expression of osteopontin in the prostate of transgenic mice with prostatic adenocarcinoma (TRAMP), The Journal of nutrition 135(5) (2005) 989–95. [PubMed: 15867270]

[265]. Joseph IB, Isaacs JT, Macrophage role in the anti-prostate cancer response to one class of antiangiogenic agents, J Natl Cancer Inst 90(21) (1998) 1648–53. [PubMed: 9811314]

[266]. Ning Y, Feng W, Cao X, Ren K, Quan M, Chen A, Xu C, Qiu Y, Cao J, Li X, Luo X, Genistein inhibits stemness of SKOV3 cells induced by macrophages co-cultured with ovarian cancer stem-like cells through IL-8/STAT3 axis, J Exp Clin Cancer Res 38(1) (2019) 19. [PubMed: 30646963]

[267]. Wang Y, Lu P, Zhang W, Du Q, Tang J, Wang H, Lu J, Hu R, GEN-27, a Newly Synthetic Isoflavonoid, Inhibits the Proliferation of Colon Cancer Cells in Inflammation Microenvironment by Suppressing NF-kappaB Pathway, Mediators Inflamm 2016 (2016) 2853040. [PubMed: 27057094]

[268]. El-Aasr M, Fujiwara Y, Takeya M, Ikeda T, Tsukamoto S, Ono M, Nakano D, Okawa M, Kinjo J, Yoshimitsu H, Nohara T, Onionin A from Allium cepa inhibits macrophage activation, J Nat Prod 73(7) (2010) 1306–8. [PubMed: 20597533]

[269]. Zeng Y, Li Y, Yang J, Pu X, Du J, Yang X, Yang T, Yang S, Therapeutic Role of Functional Components in Alliums for Preventive Chronic Disease in Human Being, Evidence-based complementary and alternative medicine : eCAM 2017 (2017) 9402849. [PubMed: 28261311]

[270]. Mirabeau TY, Samson ES, Effect of Allium cepa and Allium sativum on some immunological cells in rats, Afr J Tradit Complement Altern Med 9(3) (2012) 374–9. [PubMed: 23983369]

[271]. Fujiwara Y, Horlad H, Shiraishi D, Tsuboki J, Kudo R, Ikeda T, Nohara T, Takeya M, Komohara Y, Onionin A, a sulfur-containing compound isolated from onions, impairs tumor development and lung metastasis by inhibiting the protumoral and immunosuppressive functions of myeloid cells, Mol Nutr Food Res 60(11) (2016) 2467–2480. [PubMed: 27393711]

[272]. Tsuboki J, Fujiwara Y, Horlad H, Shiraishi D, Nohara T, Tayama S, Motohara T, Saito Y, Ikeda T, Takaishi K, Tashiro H, Yonemoto Y, Katabuchi H, Takeya M, Komohara Y, Onionin A inhibits ovarian cancer progression by suppressing cancer cell proliferation and the protumour function of macrophages, Scientific reports 6 (2016) 29588. [PubMed: 27404320]

[273]. Patel K, Singh GK, Patel DK, A Review on Pharmacological and Analytical Aspects of Naringenin, Chin J Integr Med 24(7) (2018) 551–560. [PubMed: 25501296]

[274]. Manchope MF, Calixto-Campos C, Coelho-Silva L, Zarpelon AC, Pinho-Ribeiro FA, Georgetti SR, Baracat MM, Casagrande R, Verri WA Jr., Naringenin Inhibits Superoxide Anion-Induced Inflammatory Pain: Role of Oxidative Stress, Cytokines, Nrf-2 and the NO-cGMP-PKG-KATP Channel Signaling Pathway, PLoS One 11(4) (2016) e0153015. [PubMed: 27045367]

[275]. Nouri Z, Fakhri S, El-Senduny FF, Sanadgol N, Abd-ElGhani GE, Farzaei MH, Chen JT, On the Neuroprotective Effects of Naringenin: Pharmacological Targets, Signaling Pathways, Molecular Mechanisms, and Clinical Perspective, Biomolecules 9(11) (2019).

[276]. Wang J, Niu X, Wu C, Wu D, Naringenin Modifies the Development of Lineage-Specific Effector CD4(+) T Cells, Front Immunol 9 (2018) 2267. [PubMed: 30327657]

[277]. Liu X, Wang N, Fan S, Zheng X, Yang Y, Zhu Y, Lu Y, Chen Q, Zhou H, Zheng J, The citrus flavonoid naringenin confers protection in a murine endotoxaemia model through AMPK-ATF3-dependent negative regulation of the TLR4 signalling pathway, Scientific reports 6 (2016) 39735. [PubMed: 28004841]

[278]. Zhang F, Dong W, Zeng W, Zhang L, Zhang C, Qiu Y, Wang L, Yin X, Zhang C, Liang W, Naringenin prevents TGF-beta1 secretion from breast cancer and suppresses pulmonary metastasis by inhibiting PKC activation, Breast cancer research : BCR 18(1) (2016) 38. [PubMed: 27036297]

[279]. Du G, Jin L, Han X, Song Z, Zhang H, Liang W, Naringenin: a potential immunomodulator for inhibiting lung fibrosis and metastasis, Cancer Res 69(7) (2009) 3205–12. [PubMed: 19318568]

[280]. Liu X, Wang W, Hu H, Tang N, Zhang C, Liang W, Wang M, Smad3 specific inhibitor, naringenin, decreases the expression of extracellular matrix induced by TGF-beta1 in cultured rat hepatic stellate cells, Pharmaceutical research 23(1) (2006) 82–9. [PubMed: 16341574]

[281]. Pafumi I, Festa M, Papacci F, Lagostena L, Giunta C, Gutla V, Cornara L, Favia A, Palombi F, Gambale F, Filippini A, Carpaneto A, Naringenin Impairs Two-Pore Channel 2 Activity And Inhibits VEGF-Induced Angiogenesis, Scientific reports 7(1) (2017) 5121. [PubMed: 28698624]

[282]. Wiejak J, Dunlop J, Mackay SP, Yarwood SJ, Flavanoids induce expression of the suppressor of cytokine signalling 3 (SOCS3) gene and suppress IL-6-activated signal transducer and activator of transcription 3 (STAT3) activation in vascular endothelial cells, Biochem J 454(2) (2013) 283–93. [PubMed: 23782265]

[283]. Pereira RB, Evdokimov NM, Lefranc F, Valentao P, Kornienko A, Pereira DM, Andrade PB, Gomes NGM, Marine-Derived Anticancer Agents: Clinical Benefits, Innovative Mechanisms, and New Targets, Marine drugs 17(6) (2019).

[284]. Jimenez PC, Wilke DV, Branco PC, Bauermeister A, Rezende-Teixeira P, Gaudencio SP, Costa-Lotufo LV, Enriching cancer pharmacology with drugs of marine origin, Br J Pharmacol 177(1) (2020) 3–27. [PubMed: 31621891]

[285]. Schwartsmann G, Da Rocha AB, Mattei J, Lopes R, Marine-derived anticancer agents in clinical trials, Expert Opin Investig Drugs 12(8) (2003) 1367–83.

[286]. Alves C, Silva J, Pinteus S, Gaspar H, Alpoim MC, Botana LM, Pedrosa R, From Marine Origin to Therapeutics: The Antitumor Potential of Marine Algae-Derived Compounds, Front Pharmacol 9 (2018) 777. [PubMed: 30127738]

[287]. Ratan R, Patel SR, Trabectedin and Eribulin: Where Do They Fit in the Management of Soft Tissue Sarcoma?, Current treatment options in oncology 18(6) (2017) 34. [PubMed: 28534249]

[288]. De Sanctis R, Marrari A, Santoro A, Trabectedin for the treatment of soft tissue sarcomas, Expert opinion on pharmacotherapy 17(11) (2016) 1569–77. [PubMed: 27328277]

[289]. Prado CM, Baracos VE, Xiao J, Birdsell L, Stuyckens K, Park YC, Parekh T, Sawyer MB, The association between body composition and toxicities from the combination of Doxil and trabectedin in patients with advanced relapsed ovarian cancer, Appl Physiol Nutr Metab 39(6) (2014) 693–8. [PubMed: 24869973]

[290]. Larsen AK, Galmarini CM, D'Incalci M, Unique features of trabectedin mechanism of action, Cancer chemotherapy and pharmacology 77(4) (2016) 663–71. [PubMed: 26666647]

[291]. Cuce M, Gallo Cantafio ME, Siciliano MA, Riillo C, Caracciolo D, Scionti F, Staropoli N, Zuccala V, Maltese L, Di Vito A, Grillone K, Barbieri V, Arbitrio M, Di Martino MT, Rossi M, Amodio N, Tagliaferri P, Tassone P, Botta C, Trabectedin triggers direct and NK-mediated cytotoxicity in multiple myeloma, J Hematol Oncol 12(1) (2019) 32. [PubMed: 30898137]

[292]. Germano G, Frapolli R, Simone M, Tavecchio M, Erba E, Pesce S, Pasqualini F, Grosso F, Sanfilippo R, Casali PG, Gronchi A, Virdis E, Tarantino E, Pilotti S, Greco A, Nebuloni M, Galmarini CM, Tercero JC, Mantovani A, D'Incalci M, Allavena P, Antitumor and anti-

inflammatory effects of trabectedin on human myxoid liposarcoma cells, Cancer Res 70(6) (2010) 2235–44. [PubMed: 20215499]

[293]. Wang YT, Chen J, Chang CW, Jen J, Huang TY, Chen CM, Shen R, Liang SY, Cheng IC, Yang SC, Lai WW, Cheng KH, Hsieh TS, Lai MZ, Cheng HC, Wang YC, Chen RH, Ubiquitination of tumor suppressor PML regulates prometastatic and immunosuppressive tumor microenvironment, J Clin Invest 127(8) (2017) 2982–2997. [PubMed: 28691927]

[294]. van Attekum MH, Eldering E, Kater AP, Chronic lymphocytic leukemia cells are active participants in microenvironmental cross-talk, Haematologica 102(9) (2017) 1469–1476. [PubMed: 28775118]

[295]. Bakker E, Qattan M, Mutti L, Demonacos C, Krstic-Demonacos M, The role of microenvironment and immunity in drug response in leukemia, Biochimica et biophysica acta 1863(3) (2016) 414–426.

[296]. Banerjee P, Zhang R, Ivan C, Galletti G, Clise-Dwyer K, Barbaglio F, Scarfo L, Aracil M, Klein C, Wierda W, Plunkett W, Caligaris Cappio F, Gandhi V, Keating MJ, Bertilaccio MTS, Trabectedin reveals a strategy of immunomodulation in chronic lymphocytic leukemia, Cancer Immunol Res (2019).

[297]. Ratti C, Botti L, Cancila V, Galvan S, Torselli I, Garofalo C, Manara MC, Bongiovanni L, Valenti CF, Burocchi A, Parenza M, Cappetti B, Sangaletti S, Tripodo C, Scotlandi K, Colombo MP, Chiodoni C, Trabectedin Overrides Osteosarcoma Differentiative Block and Reprograms the Tumor Immune Environment Enabling Effective Combination with Immune Checkpoint Inhibitors, Clin Cancer Res 23(17) (2017) 5149–5161. [PubMed: 28600479]

[298]. Munoz-Alonso MJ, Gonzalez-Santiago L, Zarich N, Martinez T, Alvarez E, Rojas JM, Munoz A, Plitidepsin has a dual effect inhibiting cell cycle and inducing apoptosis via Rac1/c-Jun NH2-terminal kinase activation in human melanoma cells, The Journal of pharmacology and experimental therapeutics 324(3) (2008) 1093–101. [PubMed: 18089842]

[299]. Gajate C, Mollinedo F, Cytoskeleton-mediated death receptor and ligand concentration in lipid rafts forms apoptosis-promoting clusters in cancer chemotherapy, J Biol Chem 280(12) (2005) 11641–7. [PubMed: 15659383]

[300]. Mitsiades CS, Ocio EM, Pandiella A, Maiso P, Gajate C, Garayoa M, Vilanova D, Montero JC, Mitsiades N, McMullan CJ, Munshi NC, Hideshima T, Chauhan D, Aviles P, Otero G, Faircloth G, Mateos MV, Richardson PG, Mollinedo F, San-Miguel JF, Anderson KC, Aplidin, a marine organism-derived compound with potent antimyeloma activity in vitro and in vivo, Cancer Res 68(13) (2008) 5216–25. [PubMed: 18593922]

[301]. Gajate C, An F, Mollinedo F, Rapid and selective apoptosis in human leukemic cells induced by Aplidine through a Fas/CD95- and mitochondrial-mediated mechanism, Clin Cancer Res 9(4) (2003) 1535–45. [PubMed: 12684430]

[302]. Sato T, Shibata W, Hikiba Y, Kaneta Y, Suzuki N, Ihara S, Ishii Y, Sue S, Kameta E, Sugimori M, Yamada H, Kaneko H, Sasaki T, Ishii T, Tamura T, Kondo M, Maeda S, c-Jun N-terminal kinase in pancreatic tumor stroma augments tumor development in mice, Cancer Sci 108(11) (2017) 2156–2165. [PubMed: 28837246]

[303]. Abbas W, Kumar A, Herbein G, The eEF1A Proteins: At the Crossroads of Oncogenesis, Apoptosis, and Viral Infections, Front Oncol 5 (2015) 75. [PubMed: 25905039]

[304]. Morande PE, Zanetti SR, Borge M, Nannini P, Jancic C, Bezares RF, Bitsmans A, Gonzalez M, Rodriguez AL, Galmarini CM, Gamberale R, Giordano M, The cytotoxic activity of Aplidin in chronic lymphocytic leukemia (CLL) is mediated by a direct effect on leukemic cells and an indirect effect on monocyte-derived cells, Investigational new drugs 30(5) (2012) 1830–40. [PubMed: 21887502]

[305]. Burger JA, Tsukada N, Burger M, Zvaifler NJ, Dell'Aquila M, Kipps TJ, Blood-derived nurse-like cells protect chronic lymphocytic leukemia B cells from spontaneous apoptosis through stromal cell-derived factor-1, Blood 96(8) (2000) 2655–63. [PubMed: 11023495]

[306]. Biscardi M, Caporale R, Balestri F, Gavazzi S, Jimeno J, Grossi A, VEGF inhibition and cytotoxic effect of aplidin in leukemia cell lines and cells from acute myeloid leukemia, Annals of oncology : official journal of the European Society for Medical Oncology 16(10) (2005) 1667–74. [PubMed: 16014640]

[307]. Straight AM, Oakley K, Moores R, Bauer AJ, Patel A, Tuttle RM, Jimeno J, Francis GL, Aplidin reduces growth of anaplastic thyroid cancer xenografts and the expression of several angiogenic genes, Cancer chemotherapy and pharmacology 57(1) (2006) 7–14. [PubMed: 16001179]

[308]. Broggini M, Marchini SV, Galliera E, Borsotti P, Taraboletti G, Erba E, Sironi M, Jimeno J, Faircloth GT, Giavazzi R, D'Incalci M, Aplidine, a new anticancer agent of marine origin, inhibits vascular endothelial growth factor (VEGF) secretion and blocks VEGF-VEGFR-1 (flt-1) autocrine loop in human leukemia cells MOLT-4, Leukemia 17(1) (2003) 52–9. [PubMed: 12529660]

[309]. P A, K A, L S, M M, K M, Anticancer effect of fucoidan on cell proliferation, cell cycle progression, genetic damage and apoptotic cell death in HepG2 cancer cells, Toxicology reports 6 (2019) 556–563. [PubMed: 31249789]

[310]. Narayani SS, Saravanan S, Ravindran J, Ramasamy MS, Chitra J, In vitro anticancer activity of fucoidan extracted from Sargassum cinereum against Caco-2 cells, International journal of biological macromolecules 138 (2019) 618–628. [PubMed: 31344415]

[311]. Niyonizigiye I, Ngabire D, Patil MP, Singh AA, Kim GD, In vitro induction of endoplasmic reticulum stress in human cervical adenocarcinoma HeLa cells by fucoidan, International journal of biological macromolecules 137 (2019) 844–852. [PubMed: 31295479]

[312]. Delma CR, Thirugnanasambandan S, Srinivasan GP, Raviprakash N, Manna SK, Natarajan M, Aravindan N, Fucoidan from marine brown algae attenuates pancreatic cancer progression by regulating p53 - NFkappaB crosstalk, Phytochemistry 167 (2019) 112078. [PubMed: 31450091]

[313]. Zhang N, Gao L, Ren W, Li S, Zhang D, Song X, Zhao C, Zhi K, Fucoidan affects oral squamous cell carcinoma cell functions in vitro by regulating FLNA-derived circular RNA, Annals of the New York Academy of Sciences (2019).

[314]. Xue M, Ji X, Xue C, Liang H, Ge Y, He X, Zhang L, Bian K, Zhang L, Caspase-dependent and caspase-independent induction of apoptosis in breast cancer by fucoidan via the PI3K/AKT/GSK3beta pathway in vivo and in vitro, Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 94 (2017) 898–908. [PubMed: 28810530]

[315]. Liao CH, Lai IC, Kuo HC, Chuang SE, Lee HL, Whang-Peng J, Yao CJ, Lai GM, Epigenetic Modification and Differentiation Induction of Malignant Glioma Cells by Oligo-Fucoidan, Marine drugs 17(9) (2019).

[316]. Yan MD, Lin HY, Hwang PA, The anti-tumor activity of brown seaweed oligo-fucoidan via lncRNA expression modulation in HepG2 cells, Cytotechnology 71(1) (2019) 363–374. [PubMed: 30632031]

[317]. Sun J, Sun J, Song B, Zhang L, Shao Q, Liu Y, Yuan D, Zhang Y, Qu X, Fucoidan inhibits CCL22 production through NF-kappaB pathway in M2 macrophages: a potential therapeutic strategy for cancer, Scientific reports 6 (2016) 35855. [PubMed: 27775051]

[318]. Maolake A, Izumi K, Shigehara K, Natsagdorj A, Iwamoto H, Kadomoto S, Takezawa Y, Machioka K, Narimoto K, Namiki M, Lin WJ, Wufuer G, Mizokami A, Tumor-associated macrophages promote prostate cancer migration through activation of the CCL22-CCR4 axis, Oncotarget 8(6) (2017) 9739–9751. [PubMed: 28039457]

[319]. Fang WB, Yao M, Jokar I, Alhakamy N, Berkland C, Chen J, Brantley-Sieders D, Cheng N, The CCL2 chemokine is a negative regulator of autophagy and necrosis in luminal B breast cancer cells, Breast cancer research and treatment 150(2) (2015) 309–20. [PubMed: 25744294]

[320]. Qian BZ, Li J, Zhang H, Kitamura T, Zhang J, Campion LR, Kaiser EA, Snyder LA, Pollard JW, CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis, Nature 475(7355) (2011) 222–5. [PubMed: 21654748]

[321]. Lin J, Wang K, Wang H, Shao Q, Luan Y, Xu Y, Song X, Tan W, Liu S, Wei F, Qu X, Fucoidan reduced the invasion of oral squamous cell carcinoma cells and modified their effects to macrophages, Medical oncology (Northwood, London, England) 34(1) (2017) 9.

[322]. Vareed SK, Kakarala M, Ruffin MT, Crowell JA, Normolle DP, Djuric Z, Brenner DE, Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects, Cancer Epidemiol Biomarkers Prev 17(6) (2008) 1411–7. [PubMed: 18559556]

[323]. Hagiwara A, Hirose M, Takahashi S, Ogawa K, Shirai T, Ito N, Forestomach and kidney carcinogenicity of caffeic acid in F344 rats and C57BL/6N x C3H/HeN F1 mice, Cancer Res 51(20) (1991) 5655–60. [PubMed: 1913684]

[324]. Hirose M, Hoshiya T, Mizoguchi Y, Nakamura A, Akagi K, Shirai T, Green tea catechins enhance tumor development in the colon without effects in the lung or thyroid after pretreatment with 1,2-Dimethylhydrazine or 2,2'-dihydroxy-di-n-propylnitrosamine in male F344 rats, Cancer letters 168(1) (2001) 23–9. [PubMed: 11368873]

[325]. Ferreira AC, Lisboa PC, Oliveira KJ, Lima LP, Barros IA, Carvalho DP, Inhibition of thyroid type 1 deiodinase activity by flavonoids, Food Chem Toxicol 40(7) (2002) 913–7. [PubMed: 12065212]

[326]. Ross JA, Davies SM, Potter JD, Robison LL, Epidemiology of childhood leukemia, with a focus on infants, Epidemiol Rev 16(2) (1994) 243–72. [PubMed: 7713179]

[327]. Menon VP, Sudheer AR, Antioxidant and anti-inflammatory properties of curcumin, Advances in experimental medicine and biology 595 (2007) 105–25. [PubMed: 17569207]

[328]. Wang L, Chen X, Du Z, Li G, Chen M, Chen X, Liang G, Chen T, Curcumin suppresses gastric tumor cell growth via ROS-mediated DNA polymerase γ depletion disrupting cellular bioenergetics, Journal of Experimental & Clinical Cancer Research 36(1) (2017).

[329]. Wang L, Chen X, Du Z, Li G, Chen M, Chen X, Liang G, Chen T, Curcumin suppresses gastric tumor cell growth via ROS-mediated DNA polymerase gamma depletion disrupting cellular bioenergetics, J Exp Clin Cancer Res 36(1) (2017) 47. [PubMed: 28359291]

[330]. Larasati YA, Yoneda-Kato N, Nakamae I, Yokoyama T, Meiyanto E, Kato JY, Curcumin targets multiple enzymes involved in the ROS metabolic pathway to suppress tumor cell growth, Scientific reports 8(1) (2018) 2039. [PubMed: 29391517]

[331]. He Z-Y, Shi C-B, Wen H, Li F-L, Wang B-L, Wang J, Upregulation of p53 Expression in Patients with Colorectal Cancer by Administration of Curcumin, Cancer investigation 29(3) (2011) 208–213. [PubMed: 21314329]

[332]. Shiri S, Alizadeh AM, Baradaran B, Farhanghi B, Shanehbandi D, Khodayari S, Khodayari H, Tavassoli A, Dendrosomal Curcumin Suppresses Metastatic Breast Cancer in Mice by Changing M1/M2 Macrophage Balance in the Tumor Microenvironment, Asian Pacific Journal of Cancer Prevention 16(9) (2015) 3917–3922. [PubMed: 25987060]

[333]. Bhattacharyya S, Md Sakib Hossain D, Mohanty S, Sankar Sen G, Chattopadhyay S, Banerjee S, Chakraborty J, Das K, Sarkar D, Das T, Sa G, Curcumin reverses T cell-mediated adaptive immune dysfunctions in tumor-bearing hosts, Cellular & Molecular Immunology 7(4) (2010) 306–315. [PubMed: 20305684]

[334]. Piao M, Cao H, He N, Yang B, Dong W, Xu M, Yan F, Zhou B, Wang B, Berberine Inhibits Intestinal Polyps Growth in Apc (min/+) Mice via Regulation of Macrophage Polarization, Evidence-Based Complementary and Alternative Medicine 2016 (2016) 1–8.

[335]. Tsang CM, Cheung YC, Lui VW, Yip YL, Zhang G, Lin VW, Cheung KC, Feng Y, Tsao SW, Berberine suppresses tumorigenicity and growth of nasopharyngeal carcinoma cells by inhibiting STAT3 activation induced by tumor associated fibroblasts, BMC cancer 13 (2013) 619. [PubMed: 24380387]

[336]. Karimi G, Mahmoudi M, Balali-Mood M, Rahnama M, Zamani Taghizadeh Rabe S, Tabasi N, Riahi-Zanjani B, Decreased Levels of Spleen Tissue CD4(+)CD25(+)Foxp3(+) Regulatory T Lymphocytes in Mice Exposed to Berberine, J Acupunct Meridian Stud 10(2) (2017) 109–113. [PubMed: 28483181]

[337]. Germano G, Frapolli R, Simone M, Tavecchio M, Erba E, Pesce S, Pasqualini F, Grosso F, Sanfilippo R, Casali PG, Gronchi A, Virdis E, Tarantino E, Pilotti S, Greco A, Nebuloni M, Galmarini CM, Tercero JC, Mantovani A, D'Incalci M, Allavena P, Antitumor and Anti-inflammatory Effects of Trabectedin on Human Myxoid Liposarcoma Cells, Cancer Research 70(6) (2010) 2235–2244. [PubMed: 20215499]

[338]. Nagalingam A, Arbiser JL, Bonner MY, Saxena NK, Sharma D, Honokiol activates AMP-activated protein kinase in breast cancer cells via an LKB1-dependent pathway and inhibits breast carcinogenesis, Breast Cancer Research 14(1) (2012).

[339]. Bai X, Cerimele F, Ushio-Fukai M, Waqas M, Campbell PM, Govindarajan B, Der CJ, Battle T, Frank DA, Ye K, Murad E, Dubiel W, Soff G, Arbiser JL, Honokiol, a Small Molecular Weight Natural Product, Inhibits Angiogenesisin Vitroand Tumor Growthin Vivo, Journal of Biological Chemistry 278(37) (2003) 35501–35507.

[340]. Li Z, Liu Y, Zhao X, Pan X, Yin R, Huang C, Chen L, Wei Y, Honokiol, a natural therapeutic candidate, induces apoptosis and inhibits angiogenesis of ovarian tumor cells, European Journal of Obstetrics & Gynecology and Reproductive Biology 140(1) (2008) 95–102. [PubMed: 18440692]

[341]. Wang T, Chen W, Wu J, H2-P, a honokiol derivative, exerts anti-angiogenesis effects via c-MYC signaling pathway in glioblastoma, Journal of Cellular Biochemistry 119(4) (2017) 3142–3148. [PubMed: 29080353]

[342]. Hahm E-R, Karlsson AI, Bonner MY, Arbiser JL, Singh SV, Honokiol inhibits androgen receptor activity in prostate cancer cells, The Prostate 74(4) (2013) 408–420. [PubMed: 24338950]

[343]. Zubair H, Bhardwaj A, Ahmad A, Srivastava SK, Khan MA, Patel GK, Singh S, Singh AP, Hydroxytyrosol Induces Apoptosis and Cell Cycle Arrest and Suppresses Multiple Oncogenic Signaling Pathways in Prostate Cancer Cells, Nutrition and Cancer 69(6) (2017) 932–942. [PubMed: 28718667]

[344]. Zhao B, Ma Y, Xu Z, Wang J, Wang F, Wang D, Pan S, Wu Y, Pan H, Xu D, Liu L, Jiang H, Hydroxytyrosol, a natural molecule from olive oil, suppresses the growth of human hepatocellular carcinoma cells via inactivating AKT and nuclear factor-kappa B pathways, Cancer Letters 347(1) (2014) 79–87. [PubMed: 24486741]

[345]. Sarsour EH, Goswami M, Kalen AL, Lafin JT, Goswami PC, Hydroxytyrosol inhibits chemokine C-C motif ligand 5 mediated aged quiescent fibroblast-induced stimulation of breast cancer cell proliferation, AGE 36(3) (2014).

[346]. Lissa D, Senovilla L, Rello-Varona S, Vitale I, Michaud M, Pietrocola F, Boileve A, Obrist F, Bordenave C, Garcia P, Michels J, Jemaa M, Kepp O, Castedo M, Kroemer G, Resveratrol and aspirin eliminate tetraploid cells for anticancer chemoprevention, Proceedings of the National Academy of Sciences 111(8) (2014) 3020–3025.

[347]. Hadi SM, Ullah MF, Azmi AS, Ahmad A, Shamim U, Zubair H, Khan HY, Resveratrol Mobilizes Endogenous Copper in Human Peripheral Lymphocytes Leading to Oxidative DNA Breakage: A Putative Mechanism for Chemoprevention of Cancer, Pharmaceutical Research 27(6) (2010) 979–988. [PubMed: 20119749]

[348]. Mitani T, Harada N, Tanimori S, Nakano Y, Inui H, Yamaji R, Resveratrol Inhibits Hypoxia-Inducible Factor-1^|âlpha;-Mediated Androgen Receptor Signaling and Represses Tumor Progression in Castration-Resistant Prostate Cancer, Journal of Nutritional Science and Vitaminology 60(4) (2014) 276–282. [PubMed: 25297617]

[349]. Wang Y, Romigh T, He X, Orloff MS, Silverman RH, Heston WD, Eng C, Resveratrol regulates the PTEN/AKT pathway through androgen receptor-dependent and -independent mechanisms in prostate cancer cell lines, Human Molecular Genetics 19(22) (2010) 4319–4329. [PubMed: 20729295]

[350]. Wu D, Liu Z, Li J, Zhang Q, Zhong P, Teng T, Chen M, Xie Z, Ji A, Li Y, Epigallocatechin-3-gallate inhibits the growth and increases the apoptosis of human thyroid carcinoma cells through suppression of EGFR/RAS/RAF/MEK/ERK signaling pathway, Cancer Cell International 19(1) (2019).

[351]. Wei R, Mao L, Xu P, Zheng X, Hackman RM, Mackenzie GG, Wang Y, Suppressing glucose metabolism with epigallocatechin-3-gallate (EGCG) reduces breast cancer cell growth in preclinical models, Food & function 9(11) (2018) 5682–5696. [PubMed: 30310905]

[352]. Palanisamy S, Vinosha M, Manikandakrishnan M, Anjali R, Rajasekar P, Marudhupandi T, Manikandan R, Vaseeharan B, Prabhu NM, Investigation of antioxidant and anticancer potential of fucoidan from Sargassum polycystum, International journal of biological macromolecules 116 (2018) 151–161. [PubMed: 29729339]

[353]. Vetvicka V, Vetvickova J, Fucoidans Stimulate Immune Reaction and Suppress Cancer Growth, Anticancer research 37(11) (2017) 6041–6046. [PubMed: 29061783]

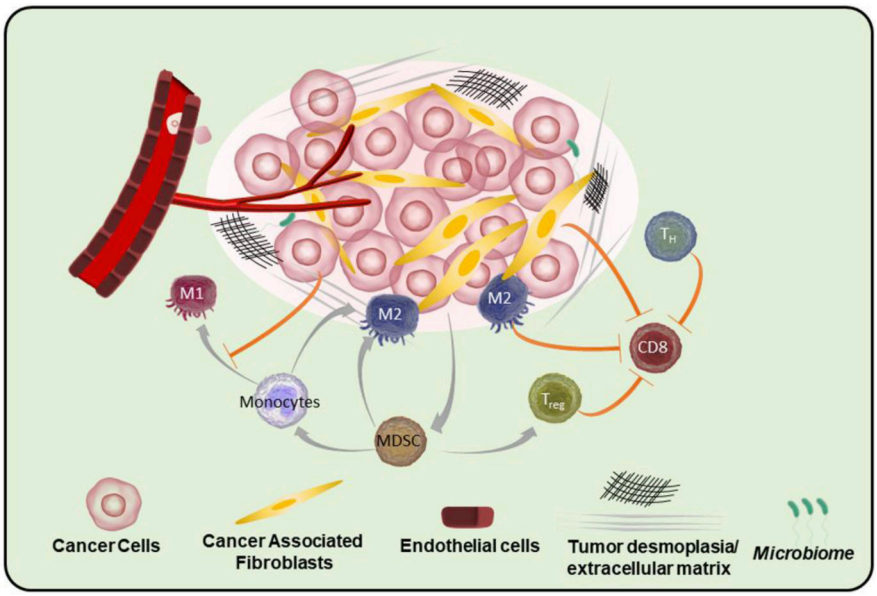

Figure 1: Components of the tumor microenvironment.

The tumor microenvironment is a complex network of stromal cells (fibroblasts, endothelial cells, lymphocytes, macrophages, and myeloid-derived suppressor cells), and other acellular entities surrounding the tumor cells. Tumor and stromal cells actively interact and influence each other to support tumor growth by promoting desmoplasia, angiogenesis, and immune suppression.

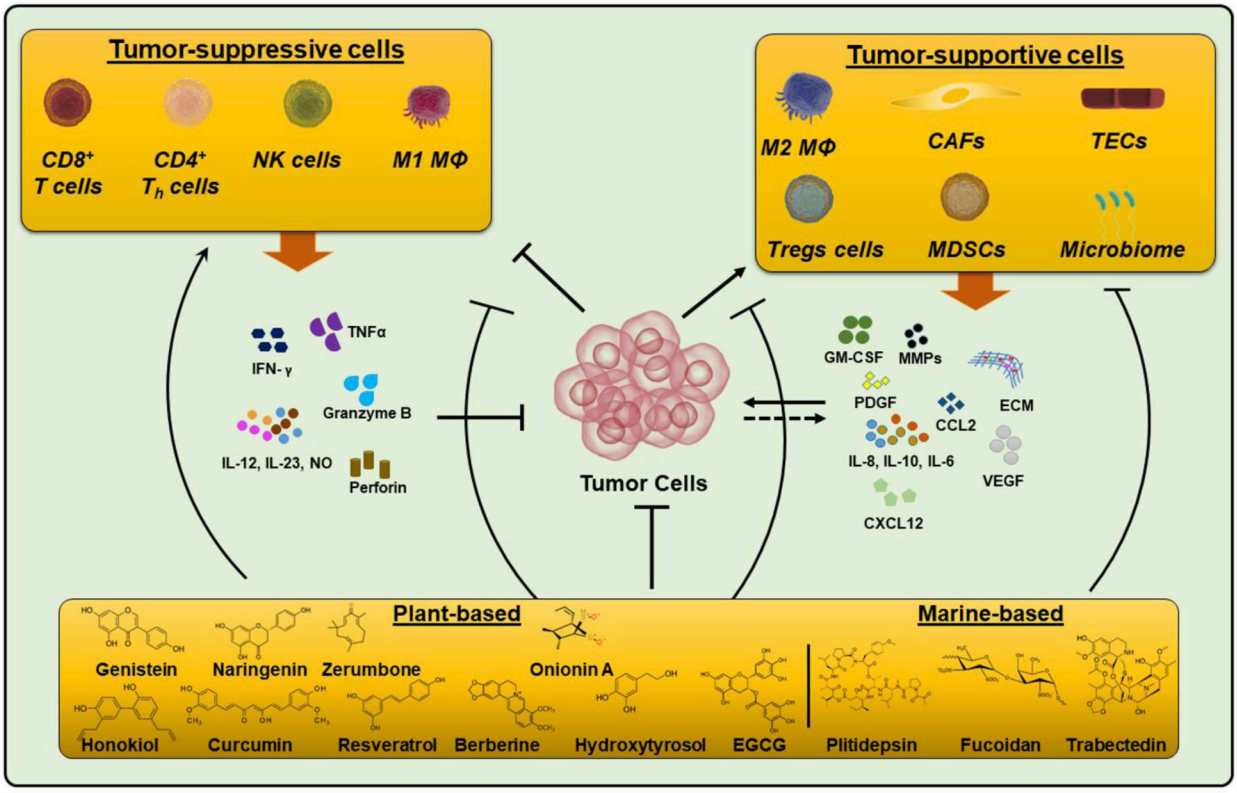

Figure 2: Targeting of the tumor and stromal cells by natural agents.

Plant- or marine-derived agents can either directly impact the tumor or stromal cells or confer their anti-tumor properties by interfering with the tumor supportive tumor-stromal interactions or both. *CAFs:*cancer-associated fibroblast cells, *NK cells:* natural killer cells, *TECs:* tumor endothelial cells, *Treg cells:* regulatory T cells, *MDSCs:* monocytes derived suppressor cells, *M1/M2 MØ*: M1/M2 macrophages.[#] *CAFs* are shown to have diverse or sometimes opposing functions. While the majority of the data suggest their tumor-supporting roles, there are indications that they could also oppose tumor growth. Solid arrows indicate direct effect, and broken arrows show likely interactions through unknown mechanisms.

Table1:

List of plant- and marine-based natural compounds and their TME targeting potential

Natural Agent (chemical category)	Source	Effect on TME	References
Terpenoids			
Zerumbone (sesquiterpene)	*Zingiber zerumbet* Sm. (Ginger)	Downregulation of CD1d Inhibition of angiogenesis via targeting VEGF/VEGFR Inhibition in the colonization of enterotoxigenic *Bacteroides fragilis*	[252, 253, 255]
Curcumin (curcuminoid)	*Curcuma longa* (Turmeric plant)	Modulation of immunomodulatory cytokines Modulation of the ECM Disruption of tumor-fibroblast interaction Polarization towards M1 macrophage phenotype Decreased Tregs cells Increased central memory T cell	[221–225, 328, 332–333]
Alkaloids			
Berberine (benzylisoquinoline alkaloids)	Berberis plants	Increased M1 macrophage polarization Active in a hypoxic microenvironment Disruption of tumor-fibroblast interaction Decreased Tregs cells Increased NK cell activity	[230, 231, 233, 334–336]
Trabectedin	*Ecteinascidia turbinate* (Marine ascidian)	Activation of NK cells Inhibition of macrophage polarization Targeting of PD-L1 positive tumor cells and immune cells Induction of CD8+ T cells infiltration	[291,292, 296, 337]
Phenylpropanoids			
Honokiol (lignan)	*Magnolia* species	Activation of immunomodulatory cytokines Inhibition of angiogenesis Inhibition of immunosuppressive Tregs Stimulation of T-lymphocytes Disruption of tumor-fibroblast interaction	[157–160]
Hydroxytyrosol (catechol)	*Oleaeuropaea* (Olive plant)	Inhibits remodeling of ECM and angiogenesis Modulation of oxidative stress Active in a hypoxic microenvironment Modulation of immunomodulatory cytokines Disruption of tumor-stromal interaction	[167, 168, 343–345]
Resveratrol (stilbenoid)	Pine trees, peanut plants, grapevines, and vaccinium shrubs	Disables immunosuppressive Tregs Active in a hypoxic microenvironment Inhibition of cancer-associated fibroblasts Modulation of oxidative stress Inhibition of M2 polarization of macrophages	[199–203]
Epigallocatechin-3-gallate (EGCG; catechin)	*Camellia sine sis* (Tea)	Inhibition of metabolic circuitry in fibroblasts Decreased M2 macrophage infiltration Inhibition of tumor angiogenesis Improvement of immunotherapy response via downregulation of PD-L1	[240, 241, 350, 351]
Genistein (isoflavone)	*Genistatinctoria*	Inhibition of tumor angiogenesis Modulation of the ECM Inhibition of fibroblast growth Disruption of macrophage-tumor cell interaction	[261–263, 266]
Naringenin (flavones)	*Grapefruit, bergamot, sour orange, tomatoes, coca and others*	Decreased accumulation of ECM AbrogatesTGF-β mediated immunosuppression Inhibitionof VEGF-mediated angiogenesis	[279–281]
Onionin A (flavonoids and phenols)	*Allium cepa (Onion)*	Inhibition of macophage polarization Inhibition of the MDSCs activity Inhibitionof PDL-1 expression	[268, 270–272]
Others *			
Plitidepsin (cyclodepsipeptide)	*Aplidiumalbica ns (Mediterranean tunicate)*	Inhibition of angiogenesis Activation of immunomodulatory cytokines Induce CD8+T cell infiltraion	[302, 304, 306]
Fucoidan (sulfated polysaccharides)	*Brown algae and brown seaweed*	Inhibition of M2 macrophage activity Activation of macrophage-induced tumor cell killing Activation of immunomodulatory cytokines	[317, 352, 353]

*Nonribosomal polypeptides and modified polysaccharides.

Table 2:

List of compounds alone or as a co-treatment with other compounds undergo clinical trials

Compound name	Type of cancer	Clinical trial phase	Current status	Clinicaltrials.gov Identifier
Hydroxytyrosol	Breast cancer	Phase 2 and 3	Active, recruiting	NCT02068092
Resveratrol	Colon cancer Liver cancer Colorectal cancer	Phase 1 Phase 1 and 2 Phase 1	Completed Withdrawn Completed	NCT00256334 NCT02261844 NCT00433576
Curcumin	Prostate cancer Breast cancer Colorectal cancer	Phase 3 Phase 1 Phase 1	Active Recruiting Unkown	NCT03769766 NCT03980509 NCT00973869
Curcumin + Avastin/FOLFIRI	Colorectal cancer	Phase 2	Active, not recruiting	NCT02439385
Curcumin + 5- Fluorouracil	Metastatic colon cancer	Early phase 1	Active, not recruiting	NCT02724202
Berberine Hydrochloride	Colorectal Adenomas	Phase 2	Recruiting	NCT03281096
	Colorectal cancer patients with ulcerative colitis remission	Phase 1	Active, not recruiting	NCT02365480
Berberine + Gefitinib	Lung adenocarcinoma and EGFR mutation	Phase 2	Not yet recruiting	NCT03486496
EGCG	Colorectal cancer	Early phase 1	Recruiting	NCT02891538
	Patients with Lung cancer receiving radical radiotherapy	Phase 2	Recruiting	NCT02577393
Trabectedin (ET 743)	Prostate cancer Pancreatic cancer	Phase 2 Phase 2	Completed Completed	NCT00147212 NCT01339754
Trabectedin+Bevacizumab	Ovarian Epithelial cancer recurrent	Phase 2	Completed	NCT01735071
Plitidepsin + Sorafenib	Advanced solid tumors	Phase 1	Completed	NCT00788099
Plitidepsin + Gemcitabine	Lymphomas			
Plitidepsin + Dexamethasone	Relapsed/Refractory Multiple Myeloma	Phase 3	Completed	NCT01102426
Oligo Fucoidan	Advanced Hepatocellular Carcinoma	Phase 2	Active	NCT04066660
Genistein + FOLFOX or FOLFOX-Avastin	Colon cancer Rectal cancer Colorectal cancer	Phase 1 and 2	Completed	NCT01985763
Genistein + Gemcitabine	Breast cancer	Phase 2	Completed	NCT00244933
Genistein	Prostate cancer	Phase 2	Recruiting	NCT02766478
Genistein + Decitabine	Non-Small Cell lung cancer	Phase 1 and Phase 2	Completed	NCT01628471