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Natural Bioactive Compounds in Foods: Modulation of Mast Cells and Tumor Microenvironment for Health Promotion and Management

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ABSTRACT: Natural compounds, including polysaccharides, alkaloids and polyphenols, have been shown to regulate immune responses within the tumor microenvironment (TME). These compounds achieve this by activating immune cells, inhibiting tumor cell proliferation, and promoting apoptosis. Furthermore, they modulate both immunosuppressive and immunoactivated states in the TME by influencing the activity of mast cells (MCs). MCs, as early and persistent infiltrating cells, play a pivotal role in allergic diseases and participate in various physiological and pathological processes. Their functions are primarily mediated through angiogenesis, tissue remodeling, and immunomodulation within the immune microenvironment. However, the role of MCs in tumorigenesis remains controversial. Depending on the tumor type, MCs exhibit remarkable plasticity and secrete a diverse array of signaling molecules that can significantly influence tumor progression. This review seeks to offer new insights into the role of MCs in tumorigenesis and development. Additionally, it explores the impact of natural compounds on the TME through MCs, contributing to a more comprehensive understanding of cancer therapy. Ultimately, this research aims to provide a scientific foundation for the development of novel tumor treatment strategies and to advance cancer therapy.

Keywords: Mast cells; Tumor microenvironment; Natural active compounds; Cancer

1. Introduction

Food serves not only as a source of essential nutrients but also as a reservoir of active substances and plant-derived compounds, such as polyphenols, flavonoids, and terpenoids. These compounds not only contribute to the unique flavors and colors of food but also play a crucial role in maintaining human health and preventing diseases [1, 2]. Several antitumor compounds that directly target tumor cells have been identified, such as paclitaxel, vincristine, and vinblastine. These components interfere with spindle formation by modulating tubulin dynamics in tumor cells, thereby disrupting the cell cycle [3]. Additionally, certain

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polyphenols and flavonoids have been shown to induce apoptosis in tumor cells [4]. Given the close relationship between tumors and their microenvironment, a comprehensive exploration of the bioactivities and mechanisms of these plant-derived bioactive compounds is essential to elucidate the complex interactions between food and health.

The role of mast cells (MCs) in the tumor microenvironment (TME) is intricate and multifaceted [5]. MCs are involved in processes such as angiogenesis, tissue remodeling, and immunomodulation [6]. Increasing evidence suggests that MCs in the TME significantly influence tumor progression [7]. Depending on their subpopulations and 'micro-localizations' within the same tumor, MCs can exert both anti-tumor and tumor-promoting effects, as illustrated in Figure 1. Studies indicate that an increase in MC density is associated with the prognosis of various cancers, including lung cancer, melanoma, and esophageal cancer [8]. Clinical evidence has shown a negative correlation between the number of infiltrating MCs and tumor prognosis in pancreatic cancer and Hodgkin's lymphoma [9] . For example, Michael *et al.,* observed elevated levels of tryptase in the blood of women with advanced breast cancer [10], which may enhance the morphometric transition of benign epithelia mediated by MCs [11]. In most human tumors, higher MC numbers linked to increased vascularity and, in some cases, reduced patient survival [12]. Moreover, MCs have been found to significantly enhance the migration and invasion of gastric cancer cells and promote their viability when co-cultured [13].

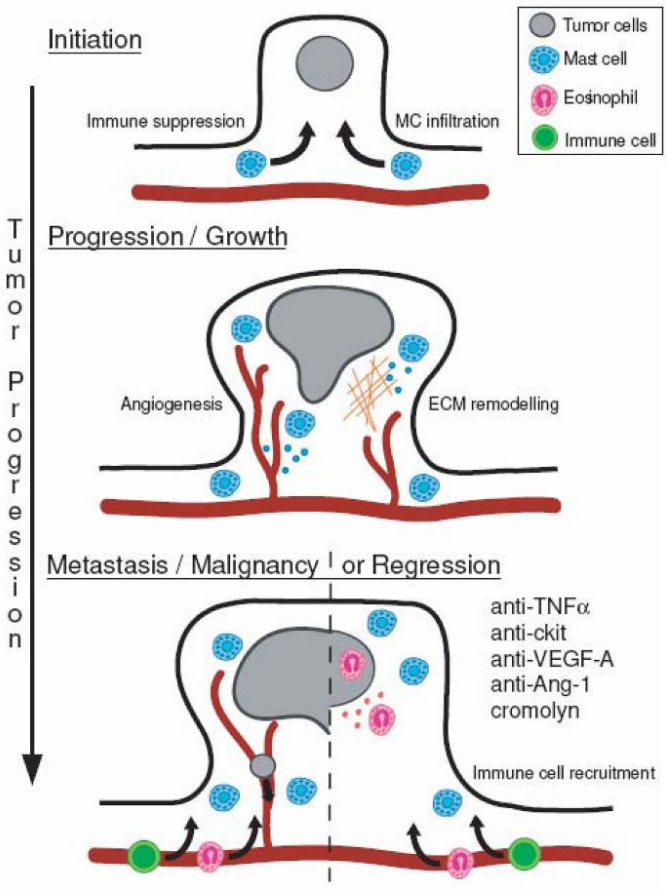


Figure 1 Schematic diagram of mast cell function at different stages of tumor progression. In the early stages of tumor growth, MCs play an active role in promoting angiogenesis and tissue remodeling. In the advanced stage, MCs induce immunosuppression, promote tumor growth, and may recruit mature immune effector cells, leading to tumor suppression.

However, MC infiltration in tumors or draining lymph nodes does not always indicate poor cancer prognosis [14]. In certain cancers, such as colorectal cancer [15], prostate cancer [16] and breast cancer [17], the findings are contradictory. Large-scale tissue microarray studies have revealed that MC infiltration is associated with improved survival in prostate cancer [18] and breast cancer [19]. MCs infiltrate rapidly after tumor initiation, accumulating at the interface between healthy tissue and the tumor. Therefore, the location and activation state of MCs within the TME are likely critical determinants of tumor prognosis. Regulating MC behavior through natural bioactive compounds holds significant potential for cancer therapy.

Actually, many plant-derived bioactive components (The compound structures and CAS numbers presented in the article are shown in Annexes S1 and S2), such as polysaccharides, polyphenols, glycosides, alkaloids, terpenoids, and quinones, can target various pathways to directly inhibit cancer growth and modulate the host immune system [20]. Given the complex role of MCs in tumor progression, this review aims to examine the signaling molecules released by MCs in the TME and explore how natural bioactive compounds influence the TME through MCs. These insights can help identify dietary interventions that mitigate tumor development, providing a deeper understanding of cancer therapy.

2. The anti-tumor effect of MCs

MCs, as important regulators of tissue homeostasis and sentinel cells that enhance immune responses in cancer patients, play a crucial role in inhibiting tumor growth. After local or systemic administration of innate immune activators, MCs may release various of signaling molecules [21], promoting immunosuppression and thus inhibiting tumor development. These effects include directly impacting tumor cell growth and recruiting and activating immune cells to exert anti-tumor effects.

2.1. MCs directly inhibit tumor cell growth and promote apoptosis through signaling molecules such as IL-4, IL-6 and TNF-α

Cytokines including interleukin(IL)-1, IL-3, IL-4, IL-6 and tumor necrosis factor-α (TNF-α) secreted by MCs, can directly inhibit tumors and induce tumor cell apoptosis[22]. Studies have shown that IL-1, IL-4, IL-6, TNF-α and proteolytic enzymes secreted by tumor-associated MCs surrounding breast cancer are detrimental to tumor cells[23]. In addition, IL-4 can bind to the IL-4 receptor (IL-4R) expressed on human breast cancer cells, potentially inducing apoptosis. Anchorage-dependent and -independent growth of breast cancer cell lines MCF-7 and MDA-MB-231 was inhibited by IL-4 treatment, with this effect requiring IL-4R[24]. In a randomized prospective study, Bhattacharya K et al., compared cardiac tissue susceptibility and serum IL-6 changes between MC-deficient (W/Wv) mice and their normal littermates (+/+). The results showed that serum IL-6 levels were higher in +/+ sham mice than in W/Wv mice[25]. Some studies have also indicated that MCs exhibit direct tumor cytotoxicity. Activation of Toll-like receptors (TLR) 2 in MCs and subsequent release of IL-6 may inhibit tumor growth both in in vitro and in vivo[7]. Moreover, N Ahmed et al. reported a role for IL-3 play a role in inducing apoptosis in oncogene-transformed, bone marrow derived 32D cells[26].

2.2. MCs recruit NK cells, T cells and other immune cells by secreting chemokines CCL3, CXCL8

Requires the recruitment of various immune effector cells and the suppression of immunosuppressive cells. Activated MCs selectively recruit immune effector cells to tumor tissue through a multi-step process involving chemokines. Studies have shown that TLR2-activated mouse MCs secrete CCL3 in vitro, which recruited natural killer (NK) cells and T cells[27]. Similarly, C-X-C motif chemokine ligand (CXCL)8 effectively induce NK cell recruitment when human MCs are activated by viruses. Primary cultures of human cord blood-derived MCs (CBMC) stimulated with poly(I:C) or reovirus produced several chemokines including CCL4 and CXCL8. The recruitment of NK cells and multiple T cell subsets was dependent on CXCL8[27]. Burke et al. suggested a novel role for MCs in recruiting of human NK cells to sites of early viral infection via CXCL8[28]. In addition, human MCs activated by viruses may also recruit $CD56^+$ T cells via CCR3 and CCR5 ligands, including invariant NK and cytotoxic T cells. MCs are abundant sources of CCL4, CCL5 and CXCL10[29]. Mast cell-derived CCL3, CCL5, and CXCL10 played roles in recruiting T cells to tumor sites. Upon contact with activated T cells, human MCs induced migration of neutrophils via CXCL8[30].

2.3. MCs promote the immune response by secreting signaling molecules

The inhibitory effect of MCs on tumors also involves the recruitment and activation of other immune cells, enhancing their anti-tumor activity. MCs can enhance T cell activation through cell contact-dependent mechanisms and TNF release[31]. In addition, mast cell-derived histamine may influence the production of effective T cell responses[32]. Activated MCs might also recruit NK cells to tumor sites and enhance their anti-tumor activity[27]. In co-culture experiments, MCs activated by TLR3, 4 or 9 activators might enhance NK cell Interferon (IFN)-γ secretion in a cell-dependent manner, stimulating an effective immune response[33].

MCs not only regulate immune cells but also modulate immunosuppressed cells. The interaction of MCs with the local Treg population within the TME is particularly important. MCs and Treg cells can mutually regulate each other's activity. Treg cells may regulate MCs activity to inhibit their degranulation in a contact-dependent manner through OX40/OX40L cells, and enhance IL-6 secretion via TGF-β1, thereby promoting their full anti-tumor effect [34]. Conversely, histamine released by MCs degranulation may inhibit the suppressive function of Treg cells through H1 receptors, inhibit immunosuppression during tumor progression, and thus inhibit tumor growth [32]. MCs may also bias Treg cells toward the pro-inflammatory Th17 phenotype through IL-6-dependent or independent mechanisms. While Th17 cells can promote tumor growth induced by chronic inflammation, in some cases, they act as are effective antitumor effector cells[35]. Therefore, MCs activation provides a potential approach to reduce Treg cells function at tumor sites, enhancing the development of anti-tumor immunity.

3. The role of MCs in promoting tumors

While there is significant evidence supporting the anti-tumor effects of MCs, studies have also reported a substantial presence of MCs in various tumors, which is associated with poor prognosis [6]. Clinical evidence has shown that the number of infiltrating MCs is significantly elevated in pancreatic cancer and Hodgkin's lymphoma, potentially contributing to the poor outcomes observed in these cancers [36]. This suggests that the aggregation of MCs at tumor sites may promote tumor development. Research on the

tumor-promoting mechanisms of MCs signaling molecules primarily focuses on their roles in angiogenesis, tumor tissue remodeling, and immunosuppression.

3.1. MCs promote tumor angiogenesis through secretion of signaling molecules

Tumor angiogenesis is a complex process influenced by angiogenic and anti-angiogenic factors, angiopoietins, proteases and their inhibitors, as well as adhesion molecules[36]. Previous studies have demonstrated that higher microvessel density (MVD) values in primary tumors are associated with worse prognose in various cancers, including lung cancer, esophageal squamous cell carcinoma, and pancreatic cancer[16, 37]. Moreover, increased MCs number at tumor sites have been linked to higher microvessels density in tumors [38]. This indicates that MCs may promote tumors growths by enhancing angiogenesis, which in turn worsens cancer outcomes[39]. As shown in Figure 1, in the early stage of tumor growth, MCs accumulate at tumor site and play a curcial role in promoting angiogenesis.

Further research indicates that MCs promote angiogenesis by secreting signaling molecules. Firstly, heparin analogues secreted by MCs enhance tumor angiogenesis, and heparin might further promote the formation of new blood vessels and promote tumor metastasis through its anticoagulant effect. It has been demonstrated that MCs tryptase was also involved in the angiogenesis of the cells a large extent[40]. Tryptase released by MCs might degrade connective tissue and activate PAR-2 expressed on endothelial cells, induced endothelial cells to form luminal structures, and promote angiogenesis[41]. Secondly, angiogenesis during tumor growth might also be attributed to a variety of pro-angiogenic factors secreted by MCs. Activation of mouse bone marrow-derived MCs, human bone marrow-derived MCs, and human mast cell (HMC-1), MCs secreted vascular endothelial growth factor (VEGF) and vascular permeability factor (VPF). A previous study found that histamine also promoted the production of VEGF, and the density of blood vessels in melanoma tissue was significantly increased, but the use of H1 receptor antagonists can inhibit this phenomenon[42]. MCs can also synthesize and secrete cytokines IL-8, which acted as an angiogenic factor as well as a tumor cell chemokine and a tumor cell mitogen. In addition, mediators present in MCs particles include basic fibroblast growth factor (bFGF), TNF-a, TNF-b, and histamine, all of which were potent inducers of angiogenesis[37, 43, 44]. Therefore, it is speculated that the infiltration of MCs into tumor tissues and the release of histamine increases the tumor neovascularization.

3.2. MCs promote tumor tissue remodeling by secreting proteolytic enzymes, metalloproteinases and histamine

Beyond promoting angiogenesis, MCs contribute to tumor tissue remodeling by degrading the extracellular matrix, directly influencing tumor cell growth, and altering the tumor miccroenvironment [37]. This process involves the secretion of cytokines and proteolytic enzymes, which remodel the extracellular matrix and consequently affect MC function, number, and phenotype. Studies have shown that tryptase may stimulate tumor growth, especially through activation of PAR-2, MAPK, and release of prostaglandin E2[45]. Moreover, MCs are also rich in metalloproteinases, a proteolytic enzyme component that was required for tumor invasion and remodeling of tumor stroma tissue, and interfered with normal stromal-epithelial

signaling, such as some matrix degradation causing tumor invasion and metastasis[46]. Besides, a previous study found that histamine induced tumor proliferation through the H1 receptor and suppressed the immune system through the H2 receptor. Histamine-activated H2 receptors can cause NMU-induced proliferation of breast tumor cells and promote remodeling of breast tumors, which may be involved in human carcinogenesis[47, 48]. Additionally, Bowrey *et al.,* demonstrated that histamine content in breast cancer was positively correlated with the number of MCs in tumor tissue, suggesting that MCs were indeed the source of histamine in tumor tissue[49]. Thus, histamine might play a role in the progression of tumor tissue.

4. MCs as potential therapeutic targets

The role of MCs in tumor growth may depend on the specific tumor type and the location of MCs in the tumor tissue. At present, studies have shown that in patients with colon cancer, the number of MCs around the tumor tissue was significantly higher than the internal tumor[50]. Upon activation and accumulation, MCs can secrete a large number of pre-formed and newly synthesized signaling molecules after activation and accumulation of MCs, affecting the TME. In the TME, activated MCs might initiate multiple responses by interacting with tumor cells, stromal cells, and immune cells.

A large body of evidence suggests that MCs play a role in promoting or inhibiting tumors depending on local matrix conditions. At different sites, different tumor types, and different stages of tumors, MCs selectively release signaling molecules to exert tumor-promoting or anti-tumor effects. Selective inhibition of tumor-promoting molecules and promotion of cytotoxic signaling molecule secretion may effectively control the tumor-promoying effects of MCs. Therefore, activation of the immune pathway targeting MCs may make the combination therapy involving MCs become a new direction for cancer treatment. Due to their long survival time and slow rate of cell division, MCs may serve as effective targets for cancer treatments aimed at inhibiting the rapid division of tumor cells. Promising therapeutic effects have been demonstrated in some pre-clinical studies using experimental models, such as anti-cKit antibody[51], anti-TNFα antibody[52], or cromoglycate (cromolyn),a disodium MC stabilizer[53]. Through multi-intervention therapy of MCs, transform MCs pro-tumor action into tumor suppression to initiate and enhance effective anti-tumor immunity and inhibit the occurrence and development of tumors, thereby acting as an effective cancer immunotherapy.

5. MCs regulation based on natural active ingredients and its application potential in the TME

Natural active ingredients regulate the tumor microenvironment by mast cells, and the regulatory effect on tumor immunity has been gradually recognized [54]. MCs interact with multiple components in the TME, affecting tumor angiogenesis, invasion, and metastasis, as well as tumor immunity [55]. The difference in composition produces opposite functional properties: inhibition and promotion of tumor progression [56-58]. This means that it is necessary to identify the effects of specific natural active ingredients on mast cells. For example, some plant polysaccharides regulate mast cells by regulating TLR4-MAPK/NF-κB signaling pathway, thus playing a role in tumor inhibition [59]. Based on mast cell tumor homing characteristics [60], It can be used as the target carrier of anti-tumor drugs, and the immune regulation of natural active ingredients

on tumors and mast cells can be used to further improve the therapeutic effect of drugs. This provides a new strategy for targeting mast cells to treat tumors.

The interaction between bioactive components, MCs and TME constitutes a complex regulatory network. Bioactive components can significantly affect the composition and function of TME by regulating the activity of mast cells, thus exerting anti-tumor effects. For instance, active ingredients extracted from medicinal plants and marine organisms, such as terpenoids, alkaloids, polysaccharides, essential oils, and polypeptides, can effectively inhibit tumor cell growth[61, 62]. In particular, certain natural products such as curcumin and resveratrol have been found to modulate the behavior of MCs, thereby affecting the TME[63, 64]. These components show potential application value in cancer treatment by inhibiting the release of tumor-promoting mediators from MCs or by promoting anti-tumor immune responses.

Furthermore, therapeutic strategies targeting MCs have shown clinical significance in cancer treatment. By modulating the activity of MCs, tumor occurrence and progression can be limited, offering new insights for cancer therapy[65]. Furthermore, by utilizing the immunomodulatory effects of natural active ingredients, new therapeutic strategies can be developed to improve the TME and enhance anti-tumor immune responses.

Finally, although existing studies have revealed the role of MCs in the TME, further research is needed to clarify how to effectively utilize natural active ingredients to regulate MCs and their specific mechanisms in tumor treatment[55].Future research needs to focus on the interaction between MCs and the TME, and how to optimize these interactions through natural active ingredients to develop more effective cancer treatment strategies[55].

6. Dietary components that affect MCs

Plant-derived active compounds often exhibit multi-target functionality and a wide range of actions. These compounds can directly target tumor cells and also modulate various components of the TME. Plant-derived active compounds often exhibit multi-target functionality and a wide range of actions. These compounds can directly target tumor cells and also modulate various components of the TME. MCs play a crucial role in the development of allergic diseases, including allergic rhinitis, asthma, atopic dermatitis, food allergies, drug allergies, and the severe systemic reaction known as anaphylaxis [66]. MCs is not only involved in allergic diseases, but also affects the inflammatory state of TME by releasing inflammatory mediators such as TNF-α and IL-6. Thus, dietary components that target MCs may interfere with both allergy and tumor progression. In the context of managing or preventing allergic diseases, an alternative to traditional treatments could be the use of "nutraceuticals." The term "nutraceutical" was first used by DeFelice in 1989, combining "nutrition" and "pharmaceutical," and it refers to a food or food component that offers medical or health benefits, including the prevention and treatment of diseases [67]. According to this definition, nutraceuticals can include a range of products such as isolated nutrients, dietary supplements, herbal remedies, and even processed items like soups and drinks[67]. It is hypothesized that, beyond their nutritional content, these substances might also possess medicinal benefits[68]. The food items that serve as nutraceuticals can be categorized into dietary fiber, prebiotics/probiotics, polyunsaturated fatty acids, antioxidant vitamins,

polyphenols, and spices [69]. A variety of naturally occurring secondary plant compounds and other dietary elements are recognized for their impact on MCs activation. these include dietary components such as specific fatty acids and amino acids, vitamins, antioxidant plant compounds like carotenoids and flavonoids, as well as an array of spices.

6.1 Carotenoid

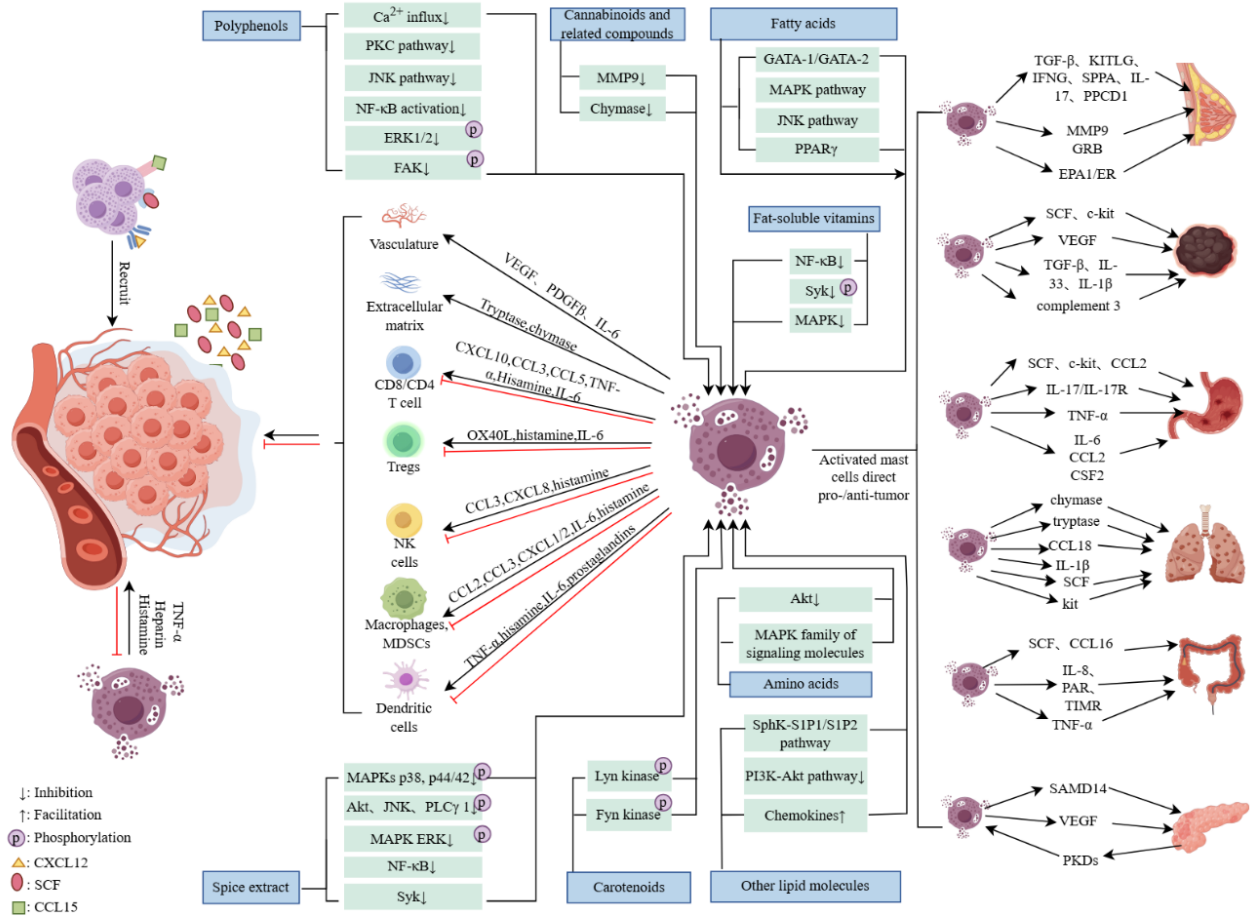
Carotenoids, a tetraterpene compound derived from carrots, reduce the polarization of tumor-associated M2 macrophages by activating the IL-6/STAT3 signaling pathway. Additionally, they inhibit the expression of tumor stem cell properties and epithelial-mesenchymal transition (EMT)-related markers induced by the TME, thereby effectively reducing the aggressiveness and migration ability of colon cancer cells. Studies have also shown that IL-6 derived from MCs can inhibit tumor growth by remodeling MCs in vivo. Carotenoids enhance the tumor suppressive effects by promoting IL-6 release from MCs while directly targeting tumor inhibition. Carotenoid inhibit FcεRI-mediated intracellular signaling, reducing mast cell degranulation and histamine release [70].The table 1 highlights some active substances affecting MCs.

Table 1. Food Bio-active Ingredients Impacting Mast Cells: Regulatory Mechanisms and Health Benefits.

Active ingredient	Research model	Regulatory mechanism	Health-related impacts	Applied food types	Efficacy	Ref.
Alpha-linolenic acid	LAD2 in vitro, C57BL/6 male mice in vivo	Through the Lyn-PLCγ-IP3R-Ca2+ and Lyn-p38/NF-κB signaling pathways.	Reduce the percentage of serum histamine release, chemokines, vasodilation, eosinophil infiltration, and degranulation of MCs.	Flaxseed oil, perilla oil	Anti-allergic, anti-inflammatory, improves skin condition, cardiovascular health	[48]
Eicosapentaenoic acid / Docosahexaenoic acid	LAD2 in vitro	Inhibit FcεRI signal transduction by disrupting the distribution of FcεRI in lipid rafts.	Alleviate allergic diseases by regulating the immune response through reducing the production of pro-inflammatory mediators.	Deep-sea fish, flaxseed oil, walnuts, etc.	Anti-inflammatory, immune regulation, improvement of cardiovascular health.	[50]
Butyric acid	Precision cutting lung slice models, BMCMCs, PBCMCs	By inhibiting histone deacetylase (HDACs) activity, altering histone acetylation levels, thereby regulating gene expression.	Butyric acid inhibits allergic reactions, reduces allergic contraction, and suppresses diseases mediated by MCs.	Foods rich in short-chain fatty acids, such as fermented foods (kimchi, yogurt, etc.)	Regulate immune response, anti-inflammatory, improve allergy symptoms	[51]
Vitamin D	Person LAD2	Vitamin D reduces VEGF expression by inhibiting the PI3K/Akt/p38 MAPK/HIF-1α signaling pathway.	VD deficiency is associated with various autoimmune and allergic diseases (chronic urticaria).	Fish, fish liver oil, egg yolks, etc.	Immune regulation, improvement of chronic urticaria symptoms	[52]
Kaempferol	C57BL/6 mouse model, LAD2	By inhibiting the phosphorylation of PLCγ (phospholipase Cγ) and subsequent intracellular calcium ion (Ca2+) mobilization to suppress MCs activation.	Alleviates local skin inflammation and systemic allergic reactions in mice, and reduces the concentration of histamine, trypsin, tumor necrosis factor α (TNF-α), interleukin 8 (IL-8), and monocyte chemoattractant protein-1 (MCP-1) in serum.	Tea, broccoli, cabbage, grapes, honeysuckle, etc.	Anti-allergic, anti-inflammatory, possibly used for the treatment of IgE-mediated allergic or inflammatory diseases.	[53, 54]
Kaempferol	BMMCs	Decreasing FcεRI expression inhibited mast cell (MCs) activation, while increasing SHIP1 expression also inhibited MCs activation.	Inhibit IgE-mediated MCs activation, suppress IL-6 production induced by LPS and IL-33.	Strawberries, broccoli, green tea, propolis, honeysuckle, etc.	Anti-allergic, anti-inflammatory, possibly used for the prevention or treatment of IL-33-mediated allergic diseases.	[56]
Quercetin	C57BL/6mouse model,LAD2	By inhibiting the Lyn/PLCγ/IP3R-Ca2+ signaling pathway to reduce MCs activation.	Alleviate clinical and histopathological symptoms of allergic conjunctivitis in OVA-induced mice, reduce the concentration of IgE, histamine, IL-4, TNF-α in serum.	Apples, onions, green tea, red wine, dark chocolate.	Anti-allergic, anti-inflammatory, treatment for non-IgE-mediated allergic diseases or inflammation.	[177]

Myricetin	BALB/c mouse model, LAD2 cells	Inhibition of MCs activation and degranulation through the PI3K/Akt/NF-κB signaling pathway.	Alleviates the symptoms of immune contact urticaria, including reducing wind and itchy behavior, inhibiting ear swelling, and lowering serum IgE, histamine, IL-4, TNF-α, and MCP-1 levels	Berries, vegetables, tea, wine.	Anti-inflammatory, anti-epileptic, anti-ulcer, etc.	[55]
Myricetin	RBL-2H3 cell	Reduce the release of β-hexosaminidase, alleviate the increase of intracellular calcium, inhibit MCs degranulation, and suppress the production of IL-4 and TNF-α.	Alleviate allergic reactions, including allergic asthma, food allergies, anaphylaxis, and atopic dermatitis, etc.	Extracted from the fruit of Myrtaceae plants.	Anti-inflammatory, antioxidant, anticancer, anti-atherosclerotic, etc.	[57]
Hesperidin	HMC-1.2	Inhibition of IL-31mRNA and protein expression, inhibition of MAPK and NF-κB signaling pathway.	IL-31 and IL-33 are expressed in various inflammatory and pathological diseases, including atopic dermatitis, inflammatory bowel disease, and asthma, among others.	Celery, perilla, onion, etc.	Treatment for hypertension, inflammatory diseases, cancer, etc.	[58]
Epicatechin	HMC-1	Block the RANKL/RANK signaling pathway to prevent MCs degranulation.	Alleviate inflammation mediated by RANKL, including allergic inflammation, autoimmune diseases, etc.	Alleviate inflammation mediated by RANKL, including allergic inflammation, autoimmune diseases, etc.	Helps treat inflammatory diseases	[59]
Resveratrol	BMMCs,C57BL/6	Inhibiting MCs activation by suppressing the MK2/3-PI3K/Akt axis.	Helps prevent and treat IgE dependent and non-dependent allergic inflammation	Red grapes, etc.	Anti-inflammatory, anti-cancer, anti-allergic, etc.	[60]
	C57BL/6	Inhibiting MCs activation by suppressing the MK2/3-PI3K/Akt axis	Relieving symptoms of allergic diseases may be effective for conditions such as asthma, chronic urticaria, etc.	Red wine	Anti-inflammatory, anti-cancer, and neuroprotective effects	[61]
	LAD2	By modulating the Nrf2 signaling pathway, inhibition of MRGPRX2-mediated MCs activation.,	Relieving symptoms of allergic diseases may be effective for conditions such as asthma, chronic urticaria, etc.	Red wine	Anti-inflammatory, anti-cancer, and neuroprotective effects.	[62]
L-Glutamic acid	Sprague-Dawley	Activate intestinal mucosal MCs (MMCs), increasing the release of RMCPII (Rat Mucosal MCs Protease II), histamine, and prostaglandin D2 (PGD2).	May affect gut health and repair "leaky gut," possibly related to gut inflammation and lipid absorption.	As a supplement, it promotes gut health and repair.	Promotes fat absorption, activates intestinal mucosal MCs, which may affect intestinal barrier function and inflammatory responses.	[178]
Astaxanthin	HR-1	Reduce ear thickness, lower MCs count, decrease IgE concentration in the blood.	Improve atopic dermatitis symptoms, regulate immune response	Lobster, salmon, trout, eggs, and red marine life, etc.	Protect the skin from ultraviolet damage, anti-cancer, activate immune function.	[179]
	SKH-1	Reduce epidermal thickness and MCs infiltration, alleviate oxidative stress and restore antioxidant protein expression.	Improve atopic dermatitis symptoms, regulate immune response	Microalgae, crustaceans	Protect the skin from ultraviolet damage, anti-cancer, activate immune function.	[180]

Active plant compounds have garnered significant attention for their potential to modulate immune responses and mitigate chronic inflammation. These compounds influence MC functions through various mechanisms Figure 2, thereby enhancing immunity and reducing chronic inflammation[71].



Figures 2. Nutrient-Mediated Regulation of Mast Cells: Signaling Pathways and Molecular Interactions. This diagram illustrates how various nutrients, including polyphenols, cannabinoids, fatty acids, and fat-soluble vitamins, modulate mast cell (MC) signaling pathways such as NF-κB, MAPK, and JNK. These nutrients influence mast cell functions at multiple levels, impacting immune responses, angiogenesis, and pro-inflammatory or anti-inflammatory mediators. The regulation of these pathways plays a significant role in immune modulation, tumor progression, and inflammatory diseases.

6.2 Polyphenols

6.2.1 Flavonoid

Flavonoids constitute a class of polyphenolic compounds that are naturally present in plants, known for their antioxidant and anti-inflammatory activities. Polyphenolic compounds, especially flavonoids, suppress mast cells activation by inhibiting the expression and release of pro-inflammatory cytokines, leukotrienes, and prostaglandins [72]. Kaempferol and myricetin, both flavonols, have been found to suppress the degranulation and cytokine release in LAD2 cells that are triggered by IgE, C48/80, or streptavidin[73-75]. Kaempferol suppressed the activation of LAD2 cells induced by IgE, potentially by inhibiting Lyn kinase activity and the subsequent downstream signaling through the PLCγ-IP3R/Ca2+ pathway[73, 74]. In a study conducted by Cao et al. in 2020, it was demonstrated that kaempferol notably impeded the movement of Parkinson's disease protein 7 (DJ-1) to the plasma membrane in LAD2 cells. This action effectively blocked the activation of Lyn,

and consequently, curbed the activity of receptor-distal signaling molecules, including Syk, Btk, PLCγ, IP3R, protein kinase C (PKC), MAPK, Akt, and NF-κB[74].

A higher concentration of 50 μM kaempferol in IL-33-stimulated bone marrow-derived mast cells (BMMC) significantly reduced the cytokine release of tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), and interleukin-13 (IL-13) by nearly 80%[76]. Myricetin impeded the activation of RBL-2H3 cells induced by IgE/antigen stimulation, acting through the Syk signaling pathway[77].

Upon treatment with kaempferol, IL-33-stimulated bone marrow-derived MCs (BMMC) exhibited a time-dependent decrease in phospholipase Cγ (PLCγ) and the cell surface expression of the high-affinity IgE receptor (FcεRI), while the expression of Src homology 2 domain-containing inositol 5-phosphatase 1 (SHIP1) was enhanced. This upregulation of SHIP1 was also observed in mouse peritoneal MCs, suggesting a potential anti-allergic effect of kaempferol[76]. In response to luteolin treatment, IL-33-stimulated HMC-1.2 cells exhibited a decrease in IL-31 production by approximately 70%, likely due to the suppression of the IL-31/IL-33 signaling axis. This effect may contribute to the mitigation of diseases activated by IL-33, including asthma[78].

6.2.2 Resveratrol

Further studies have demonstrated that resveratrol, a natural polyphenol compound present in red grapes, exerts notable anti-inflammatory and anti-allergic effects in murine models of atopic dermatitis (AD). The results of several studies have demonstrated that resveratrol has the capacity to inhibit the activation of MCs and the subsequent release of inflammatory mediators. Furthermore, it has been shown to reduce skin inflammation by inhibiting the activation of Sphingosine kin-1 (SphK1), Stat3 and NF-κB p65 signaling pathways. These findings suggest that resveratrol could be a potential natural therapy for preventing and treating pathological inflammation driven by MCs [79].

In bone marrow-derived MCs (BMMC) stimulated by either IL-33 or IgE/antigen, the administration of 25 μM resveratrol led to a reduction of over 40% in the secretion of TNF-α, IL-13, and IL-6. This effect is suspected to be mediated through the modulation of the MAPK-activated protein kinase (MK)-2/3-PI3K/Akt signaling axis, as the production of IL-6 and IL-13 in MCs in response to IL-33 is known to be facilitated by the MK2/3-driven activation of the PI3K/Akt pathway[80]. Resveratrol treatment in RBL-2H3 cells activated by IL-33 resulted in the inhibition of the release of proinflammatory cytokines and chemokines, including TNF-α, IL-6, IL-4, IL-3, and MCP-1[81]. Beyond its effect on MAPK, resveratrol treatment also led to a significant decrease in the phosphorylation of p38, inhibitor of nuclear factor kappa B (IκBα), and the NF-κB subunit p65 by over 50% in RBL-2H3 cells that were stimulated with IL-33 and IgE/antigen[81].

At a higher concentration of 200 μM, resveratrol demonstrated a dose-dependent reduction in C48/80-induced β-hexosaminidase (β-hex) and histamine release by approximately 80% in the LAD2 mast cell line. The expression of cytokines MCP-1, TNF-α, and IL-1β was suppressed by resveratrol by about 40%, 60%, and 80%, respectively. Additionally, resveratrol increased the expression of the nuclear erythroid 2-related factor 2 (Nrf2) and the production of its target genes, including the transcription factor heme

oxygenase-1 (HO-1) and NADPH dehydrogenase quinone 1 (NQO1). Consequently, the Nrf2/HO-1 pathway could be a potential therapeutic target for treating MC-mediated allergic conditions[82].

6.2.3 Catechin

Epigallocatechin gallate (EGCG), a catechin derived from green tea, lessened histamine release and cytokine production—including TSLP, IL-1β, IL-6, and IL-8—in HMC-1 cells activated by receptor activator of NF-κB ligand (RANKL). This reduction was achieved by modulating the PI3K, MAPK, caspase-1, and NF-κB signaling pathways[83]. The suppression of Th2 immune responses by L-Theanine（LTA）+ EGCG inhibits the cross-linking of OVA and FcεRI, thereby reducing mast cell (MC) degranulation and decreasing serum levels of histamine (HIS) and mast cell protease-1 (mMCPT-1) via the FcεRI/Btk/PLCγ signaling pathway. Additionally, LTA + EGCG attenuates Th2 immune responses through the FcεRI/Lyn/Syk/PI3K/AKT signaling pathway, leading to reduced serum levels of IL-4 and IL-13 [84]. In addition, some studies have demonstrated that catechins, in synergy with caffeine, stabilize mast cells in a dose-dependent manner [85].

6.2.4 Curcumin

Curcumin and bisdemethoxycurcumin (BDMC) are two natural compounds found in curcuma, also known as turmeric. In RBL-2H3 cells activated by IgE/antigen, curcumin led to a significant decrease in the release of β-hexosaminidase by approximately 80% and histamine by around 60%[86].Curcumin and BDMC are likely to exert their effects by targeting the Syk pathway, which subsequently leads to the inhibition of the activation of mitogen-activated protein kinases (MAPK) such as ERK, JNK, and p38, as well as nuclear factor kappa B (NF-κB) and the translocation of protein kinase C delta (PKC-δ)[86]. Spices like curcumin and cinnamon extract/cinnamaldehyde inhibit-mast degranulation and inflammatory mediators synthesis by targeting specific enzymes and signaling pathways[87, 88].

6.2.5 Lignans

Lignans are mainly found in the seeds, fruits and wood of plants, especially in the seeds of sesame, which have a relatively high content. This is also the origin of the name "sesamin". Its metabolism can produce monocatechol and dicatechol, and the bioavailability and activity of these metabolic products in the body may be different from those of sesamin. Studies have found that sesamin and its metabolites (such as monocatechol SC-1 and dicatechol SC-2) exhibit higher binding affinity and inhibitory efficiency than traditional SYK inhibitors (such as R406) by tightly binding to the ATP-binding pocket of splenic tyrosine kinase (SYK). In vitro experiments showed that sesamin significantly inhibited the degranulation of IgE/ HSA-stimulated RBL-2H3 cells and reduced the release of β -hexosaminase and histamine. In animal models, sesamin can alleviate passive skin hypersensitivity (PCA) and active systemic hypersensitivity (ASA) reactions, reduce the levels of allergic mediators (such as IgE, IgG, histamine, IL-4 and mMCP-1) in serum, and partially correct the imbalance of Th cell differentiation in the spleen. These results indicate that sesamin effectively inhibits the degranulation of mast cells and alleviates the systemic inflammatory response by suppressing SYK and its

downstream signaling pathways[89] . It can provide relief ideas for alleviating the inflammatory symptoms of tumors. Another aspect related to sesamin is that it can not only directly inhibit the degranulation of mast cells, but also regulate the composition and function of intestinal microbiota, increase the production of short-chain fatty acids, and enhance the intestinal barrier function [90]. These studies have all demonstrated the inhibitory effects of excessive activation of mast cells and degranulation responses, indicating that they have great application potential in the treatment of clinical diseases targeting or starting from mast cells. At the same time, they also produce other beneficial effects to assist in the recovery of diseases.

6.3 Fatty acid

6.3.1 n-3 polyunsaturated fatty acids

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 fatty acids that may interact with and stimulate the G-protein coupled receptor 120 (GPR120) in MCss. This interaction could result in an elevation of cyclic adenosine monophosphate (cAMP) levels within the cells. Qiao Bai et al. verified the inhibitory effect of increased cAMP content on TNF-α, alleviating allergic symptoms and local inflammatory response through mast cell models [91]. To some extent, mast cells may influence the inflammatory response in the tumor microenvironment. The subsequent activation of protein kinase A (PKA) could then lead to the inhibition of MCs degranulation, potentially reducing the release of inflammatory mediators[92]. n-6 fatty acids, on the other hand, exhibit the opposite pro-inflammatory and pro-allergic effects of n-3 fatty acids[93], so it is necessary to pay attention to the ratio between the two during dietary intake to avoid potential accidents.

6.3.2 Short chain fatty acid

Short-chain fatty acids like butyrate inhibit the release of pro-inflammatory mediators by intestinal mast cells[94]. Butyrate modulated the activity of histone deacetylase (HDAC), echoing the effects of the HDAC inhibitor trichostatin A, which resulted in the suppression of transcription for crucial FcεRI signaling genes such as Bruton's tyrosine kinase (Btk), Syk, and LAT[95].

6.4 Vitamin

Vitamin D, a fat-soluble nutrient, possesses a range of physiological and immunomodulatory effects. It is predominantly sourced from animal-based foods, including fatty fish, egg yolks, liver, milk, and butter. Fat-soluble vitamins D3 and E stabilize mast cells, reducing the release of pro-inflammatory mediators[96, 97]. Treatment of LAD2 cells with calcidiol prior to serum stimulation effectively reduced the expression of vascular endothelial growth factor (VEGF) by inhibiting the activation of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/Akt/p38 and mitogen-activated protein kinase (MAPK)/hypoxia-inducible factor 1-alpha (HIF-1α) signaling pathways[98]. VEGF serves as a potential blood biomarker for chronic spontaneous urticaria (CSU). The results imply that proper vitamin D supplementation might curb mast cell-mediated VEGF synthesis, potentially leading to a reduction in CSU symptoms[98].

6.5 Polysaccharides

Some studies have shown that polysaccharides treated with fermentation can significantly reduce their

particle size, thereby improving their bioavailability and cell penetration. For example, studies have found that laveri polysaccharide (FPHSP-2/3), fermented by Lactobacillus plantarum, inhibits mast cell degranulation by reducing the release of β-hexosaminase in rat basophilic leukemic cells (RBL-2H3 cells) by inhibiting the Ca^{2} endogenous flow. This suggests that properly treated polysaccharides may have the potential to act directly on mast cells [21]. Interestingly, red algae polysaccharide showed the same mast cell degranulation inhibition mechanism as laver polysaccharide. Based on this, Marine algal polysaccharide may be a new raw material for mast cell degranulation inhibitors in the future.

In ovo-sensitised rat models, Astragalus polysaccharide significantly decreased the density of mast cells in skin tissue (from 180.0 to 99.7 /mm^2) and degranulation, and down-regulated the expression of CD34 in microvascular endothelial cells, thereby reducing the status of mast cells and microvessels, and thus inhibiting the inflammatory response[99].

Studies on sulfated polysaccharides (specifically Tosalvan), such as those from the Japanese river alga Sujiaonori, have demonstrated significant reductions in β-aminohexosidase release, a marker of allergic reactions, in MCs model RBL-2H3 cells, and that Sujiaonori supplementation reduced the level of epidermal water loss and improved skin barrier function[100].

Sulfated oligosaccharides (ESO) from Eucheuma cottonii was found to reduce MCs protease-1, histamine levels, and specific IgE production. ESO also induced MCs apoptosis, demonstrating its potentical in reducing allergic reactions [101].

Sulfated polysaccharide (GLSP) from Gracilaria lemaneiformis, inhibit the p38 MAPK signaling pathway, reducing mast cell activation in KU812 cells (a human stromal cell model) through the RBL-2H3 cell model, which in turn inhibits the activation and function of MCs, as well as modulating the immune response, demonstrating the potential of anti-food allergy[102].

6.6 Other plant active ingredients

Cannabidiol (CBD) and Palmitoylethanolamide (PEA) modulate the endocannabinoid system to reduce mast cell inflammatory responses [103, 104]. Amino acids, including arginine, glutamine, and asparagine, reduce mast cells by mediated pro-inflammatory cytokines production[105, 106].

Boswellic acid, particularly acetyl-11-keto-β-boswellic acid (AKBA), derived from frankincense, effectively inhibits 5-lipoxygenase (5-LOX), a key enzyme in inflammatory responses. By blocking 5-LOX, boswellic acid reduces leukotrienes production, of 5-LOX playsespecially in the production of leukotrienes, modulating inflammatory responses in the TME[34]. Additionally, frankincense extracts lower pro-inflammatory cytokines levels[35], such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), which are critical inflammation [36]. Regulating the levels of these pro-inflammatory cytokines in the TME is crucial for controlling chronic inflammation and enhancing immunity. Boswellic acid can also prevent the activation of nuclear factor-κB (NF-κB), a protein complex that controls the expression of many genes related to inflammation. By inhibiting NF-κB, boswellic acid can reduce overall inflammation and pain[37], which is significant for immune regulation and inflammation control in the TME.

Carnoic acid (CA), a polyphenol, suppresses allergic inflammatory mediators by inhibiting Syk kinase activation. CA significantly inhibited allergen-induced early responses, including Ca^{2+} mobilization, reactive oxygen species (ROS) production, and subsequent degranulation. Furthermore, CA treatment also reduced late responses, including release of all detected cytokines and chemokines after IgE stimulation, and expression of corresponding genes other than CCL 2. Importantly, CA mediates the inhibitory effect of the tyrosine kinase Syk and its downstream effectors TAK 1 (Ser412) and Akt (Ser473) and NF κ B signaling pathway, which can have some influence on the TME[107].

The mixed extract of wheat grass and wild cherry (TAAR) was verified to inhibit the activation and degranulation of MCs in vitro and in vivo, reducing the release of mediators such as histamine andβ -hexanosidase, and decreasing the production of inflammatory factors such as TNF- α and IL-6. These findings suggest that TAAR extracts may influence the TME by regulating the function of MCs, particularly in tumor-associated inflammation and immune responses. For example, by reducing the release of inflammatory mediators, TAAR extracts may help mitigate the inflammatory response in the TME, thereby affecting tumor growth and progression[108].

In their 2021 study utilizing LAD2 cells, Ding et al. demonstrated that the application of alpha-lipoic acid (ALA) led to a dose-dependent reduction in the release of β-hexosaminidase (β-hex) and histamine triggered by C48/80. Specifically, ALA treatment led to a roughly 60% reduction in histamine degranulation. Furthermore, ALA mitigated the release of cytokines including C-X-C motif chemokine ligand (CXCL)-8/IL-8, IL-13, and tumor necrosis factor α (TNF-α) by LAD2 cells in response to C48/80 stimulation. The observed decrease in MCs (MC) activity was linked to the suppression of Lck/Yes-related novel protein tyrosine kinase (Lyn) activity within LAD2 cells, which was mediated through the Lyn-phospholipase Cγ (PLCγ)-inositol trisphosphate receptor (IP3R)-Ca2+ and Lyn-p38/NF-κB signaling cascades. Consistently, ALA also showed similar effects on serum histamine and cytokine levels, and it diminished vasodilation along with the proportion of degranulated MCs in C57BL/6 mice[109].

7. Natural active components affecting the TME as shown Table 2

7.1. Terpenes

Terpene compounds are a class of natural organic compounds widely found in nature. They are composed of isoprene (C5H8) units, which are linked together in various ways to form polymers. The general formula for terpenes can be written as (C5H8)n. Depending on their molecular structure, they can be classified as monoterpenes (consisting of two isoprene units, C10H16), sesquiterpenes (three isoprene units, C15H24), diterpenes (four isoprene units, C20H32), hemiterpenes (five isoprene units), triterpenes (six isoprene units, C30H48), tetraterpenes (eight isoprene units, C40H64), and polyterpenes (consisting of more than eight isoprene units)[114]. Natural monoterpenes such as borneol, extracted from the Dipterocarpaceae family, can trigger oxidative damage mediated by reactive oxygen species (ROS) and regulate mitogen-activated protein kinases (MAPKs) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathways, enhancing the anticancer effects of cisplatin[115].The key diterpene compound celastrol, found in

Tripterygium wilfordii, promotes the apoptosis of MDSCs and the polarization of TAMs from M2 to M1by inhibiting the PI3K/AKT/NF-κB pathway[116].Oridonin, a diterpene compound, can reduce the differentiation of Treg cells by lowering the expression of TGF-β receptors, thereby further inhibiting the development of breast cancer[117]. Other studies have found that oridonin at low concentrations (15 or 20 μmol/L) can induce autophagy by enhancing the expression of p62 protein and the LC3B-II/LC3B-I ratio, while high concentrations (≥30 μmol/L) induce apoptosis[118]. Notably that oridonin can form a covalent bond with Cys-813, reducing the activity of highly expressed hexokinase I in bladder cancer, thereby inhibiting the proliferation of bladder cancer cells and immune escape[119]. The sesquiterpenes cedrol, discovered in juniper, has shown anticancer activity through in vitro and in vivo experiments. Cedrol reduces the expression of minichromosome maintenance (MCM) proteins, thereby decreasing cellular density within tumors and reducing tumor vascularization[120]. The triterpenoid compound 23-hydroxybetulinic acid extracted from Chinese white-headed eagles, inhibits colon cancer growth in a mouse model , by reducing the proportion of MDSCs and the expression of the immunosuppressive factor Arg1 in MDSCs[121]. Additionally, it promotes TAM polarization of TAM from M1 phenotype to M2 phenotype [122].In both in vivo and in vitro breast cancer models, artemisinin was found to promote T cell activation in the TME, inhibit the expression of Tregs and MDSCs, and suppress the in vivo growth of breast cancer[123].

Table 2. Natural active substances that affect the tumor microenvironment.

Anti-tumor components		Source	Name	Type of tumor	Antitumor mechanism	Ref.
Terpenes	Monoterpene	Dipterocarpus	Borneol	Glioma	It can trigger ROS overproduction and affect MAPKs and PI3K/AKT signaling pathway, and enhance the anti-tumor effect of cisplatin	[65]
	Diterpenes	Thunder god vine	Triptolide	ovarian cancer	Inhibition of PI 3K /AKT/NF-κB pathway inhibited M2 macrophage polarization and promoted M1 macrophage polarization	[66]
				Breast cancer	The expression of TGF-β receptor was decreased and the differentiation of Treg cells was reduced	[67]
		Rabdosia rubescens	Oridonin	Small cell lung cancer	Autophagy was induced by activation of PERK/eIF2α/CHOP signaling pathway at low concentration, and apoptosis was induced by high concentration in small cell lung cancer	[68]
				Bladder cancer	The activity of HK1 is inhibited by covalent bonding with Cys-813 located near the HK1 glucose binding domain	[69]
	Sesquiterpenes	Needle juniper	cedrol	Colorectal cancer	Inhibiting tumor growth by suppressing MCM protein expression.	[70]
		Sweet wormwood	arteminsinin	Breast cancer	By promoting T cell activation and suppressing the expression of Tregs and MDSCs.	[71]
	Triterpenes	Pulsatilla chinensis	23-Hydroxybetulinic acid	Colon cancer	By inhibiting the differentiation of MDSCs, the immunosuppressive function of MDSCs is suppressed, thereby restoring the anti-tumor activity of CD8+ T cells.	[72]
				Colorectal cancer	Promoting TAM polarization from M1 to M2 type by activating the JAK/STAT 3/NF-κB/STAT 1 pathway.	[73]
Polyphenols	Astragalus	Grapes, berries.	Resveratrol	Oral squamous cell carcinoma	Activate the Syk signaling pathway to guide macrophages towards M1 phenotype differentiation and block their transition to the M2 phenotype.	[74]
				Esophageal squamous cell carcinoma	Inhibit the activity of TAOK1	[76]
				Pancreatic cancer	By clearing tumor-associated fibroblasts and inducing their senescence	[77]
	Flavonoids	Mulberry, Forsythia	Quercetin	Breast cancer	Enhancing the survival and suppressive properties of G-MDSCs through the ESR2/STAT3 signaling pathway.	[78]
					By inhibiting the activity of CYP3A4, it affects the metabolism of arachidonic acid.	[79]
				Melanoma	By increasing the percentage of M1 macrophages, CD8+ T cells, and CD4+ T cells to modulate the TME.	[80]

				Brain glioma	By modulating Rac1-p66Shc signaling, specifically inhibiting Rac1 activation, thereby suppressing the production of ROS and tumor growth.	[81]
		Milk thistle	Silymarin	Stomach cancer	By reducing the expression of MMP-2 and MMP-9	[82]
					By modulating MAPK signaling in cancer cells	[83]
		Turmeric, Iris	Curcumin	Colorectal cancer	Exhibits anti-tumor activity through various mechanisms including modulating the gut microbiota, enhancing gut barrier function, inhibiting inflammatory responses, promoting autophagy, and targeting cancer stem cells.	[84, 85]
				Pancreatic cancer	Targeting circular RNA pathways in pancreatic cancer cells	[86]
				Colorectal cancer	By downregulating the expression of USP4 and LAMP3 pathways.	[87]
					By adjusting the balance of gut microbiota.	[88]
		Astragalus	Astragalus Polysaccharides	Lung cancer	By modulating the S1PR1/STAT3 signaling pathway.	[93]
				Ovarian cancer	By enhancing the patient's sensitivity to PARPi through the PINK1/Parkin pathway, survival rates are improved.	[94]
				Colorectal cancer	By inducing Treg cells to differentiate into HCT-116	[95]
		Mushroom	Lentinan	Bladder cancer	By inducing macrophage activation, enhancing the proliferation of CD4+ and CD8+ T cells, upregulating the expression of IFN-γ and IL-2, while downregulating the proportion of MDSCs and Tregs, and reducing the expression of anti-inflammatory cytokines IL-10 and TGF-β.	[96]
				Lung cancer, colorectal cancer	By increasing the expression of IFN-γ	[98]
Polysaccharides		Fenugreek seeds	Plantago Seed Polysaccharides	Breast cancer	By modulating the transformation of macrophages into the M1 phenotype.	[99]
		Licorice	Licorice polysaccharides	Colorectal cancer	By inducing the differentiation of regulatory T cells, downregulating the expression of immunosuppressive molecules.	[100]
		Ganoderma lucidum	Ganoderma lucidum polysaccharides	Lung cancer	Regulate MDCSs to enhance anti-tumor immune response through the CARD9-NF-κB-IDO pathway.	[101]
				Liver cancer	Inhibition of Tregs accumulation and function by miR-125b.	[102]
		Purslane	Portulaca Oleracea Polysaccharides	Breast cancer	By increasing ACSL4-mediated ferroptosis.	[103]
		Grifola frondosa	Grifola frondosa polysaccharides	Breast cancer	By eliminating MDSCs and enhancing T cell responses.	[104]
		Barbary Wolfberry Fruit	Barbary Wolfberry Polysaccharide	Lung cancer	By inhibiting angiogenesis	[105]
Alkaloids	Isoquinolines	Coptis	Berberine	Nasopharyngeal carcinoma	By inhibiting STAT3 activation	[106]
				Colorectal cancer	By intervening in the EGFR signaling pathway	[107]
		Spatholobus	Sanguinarine	Lung cancer	By promoting cell differentiation and inhibiting the activity of	[108]

		suberectus			MDSCs.	
		Dendrobium nobile	Dendrobine	Lung cancer	By inhibiting the PD-1/PD-L1 checkpoint pathway.	[109]
	Piperidine class	Black pepper	Piperine	Head and neck cancer cells	By adjusting the related signaling pathways.	[110]
		Potato	Solanine	Liver cancer	By suppressing the TGF β/Smad signaling pathway, the proportion of TGF β is downregulated.	[111]
	Indole compounds	Baldhead fungus	N-hydroxysuccinamide	Colorectal cancer	By blocking the interaction of the TAK1-TRAF6 complex to inhibit the NF-κB signaling pathway, while also exhibiting effective cytotoxicity.	[112]
	Hydroxyanthraquinones	Reed rhizome, Rhubarb	Emodin	Macrophages	By restoring macrophage homeostasis	[113]
				Breast cancer	By modulating T cell activation mediated by the TME.	[114]
Quinones	Naphthoquinones	Comfrey	Shikonin	Colorectal cancer	By promoting the phosphorylation of Akt and ERK1/2 in NK cells	[115]
				Breast cancer	Stimulate DC cell maturation, enhance Th1 cell and cytotoxic T cell activity.	[116]
		Peony	Total Glycosides of Paeony	Melanoma	By promoting the degradation of α5-nAChR	[117]
				Liver cancer	By suppressing the BAFF-BAFF-R pathway, the proportion of Breg is downregulated.	[118]
Saponin	Glycosides	Dioscorea zingiberensis	Diosgenin	Melanoma	By activating the Cx43/STAT 1/IFN-γ pathway and inhibiting the IL-4/JAK 2/STAT 3 pathway, it promotes the polarization of TAMs from the M2 phenotype to the M1 phenotype.	[119]
			ZnS	Hepatocellular carcinoma	By adjusting the expression of TCONS-00026762	[120]
		Gotu Kola	Madecassoside	Breast cancer	Inhibition through the YAP1/VEGFA signaling pathway	[121]
		Ginseng	Rg3	Cervical cancer	By reducing AKT2 expression	[122]
			Rh4	Multiple Myeloma	By modulating SIRT2 expression	[123]
		Red Rhodiola	Salidroside	Non-small cell lung cancer	By modulating the Hsp 70/Foxp 1/Foxp 3 pathway	[124]

7.2. Polyphenols

Natural polyphenols can be divided into six groups according to their chemical structure: stilbenes, flavanols, flavonols, flavonoids, chalcones and isoflavones. Resveratrol, a polyphenol found in grapes, is an anti-tumor compound that plays an anti-cancer role by regulating the polarization state of TAMs and further inhibiting the migration and invasion of CAL 27 cells by suppressing the phosphorylation of Syk protein [124]. Crude flavonoids in rose, about 28.34%, have been confirmed to induce apoptosis of HepG2 cells by up-regulating the expression of pro-apoptotic proteins p53 and Bax, and down-regulating the expression of anti-apoptotic protein Bcl-2 [125]. A recent study found that resveratrol can directly target the overexpressed thousand and one amino-acid protein kinase 1 (TAOK1) in esophageal squamous cell carcinoma, significantly reducing cancer cell proliferation and inducing cell cycle arrest and apoptosis[64]. Furthermore, resveratrol can also target senescent tumor-associated fibroblasts, preventing their senescence while inhibiting the progression of pancreatic cancer [126]. Quercetin is a flavonoid compound extracted from plants such as mulberry and forsythia. It can promote the survival of mouse and human granulocyte myeloid-derived suppressor cells, achieving anti-tumor therapeutic effects[127].In another breast cancer study, it was found that quercetin can inhibit the activity of CYP3A4, reducing the metabolism of the arachidonic acid into epoxyeicosatrienoic acids, further affecting the nuclear translocation of signal transducer and activator of transcription 3, thereby inhibiting the development of breast cancer[128].In recent studies on inhibiting melanoma, quercetin promotes the release of IL-2 and IFN-γ by increasing the percentage of M1 macrophages, CD8+ T lymphocytes, and CD4+ T lymphocytes, further inhibiting the growth of melanoma[129].P66Shc and Rac1 are two proteins associated with tumor-related inflammation. In the study of human brain gliomas, it was found that quercetin specifically inhibits Rac1 activation by modulating Rac1-p66Shc signaling, thereby suppressing the production of ROS and the growth of gliomas [130].Silymarin, which is also a flavonoid, can inhibit the recruitment of MCs and reduce the expression of MMP-2 and MMP-9, resulting in tumor suppressive effects [131]. Silibinin can also reduce the growth of gastric cancer cells by inhibiting p-ERK and activating p-P38 and p-JNK[132].Curcumin, derived from the root and rhizome of plants such as turmeric and calamus, can increase the number of CD4+ T cells and CD8+ T cells in the TME, while reducing the number of CD4+CD25+Foxp3+ Treg cells. It promotes the secretion of interferon-γ (IFN-γ) and inhibits the production of interleukin-4 (IL-4), transforming growth factor-β (TGF-β), and interleukin-10 (IL-10), thereby facilitating the conversion of Treg cells to Th1 cells, and thus restoring the host's immune surveillance capability[133, 134].Curcumin has been proven to mediate the expression of circular RNAs to inhibit tumor development. Some studies have focused on circ_0079440 in pancreatic cancer, finding that curcumin inhibits the development of pancreatic cancer by targeting the circ_0079440/miR-522-3p/EIF4A1 pathway[135].Furthermore, in the study of colorectal cancer, it was found that curcumin exerts an inhibitory effect on tumors by downregulating the expression of USP4 and LAMP3[136]. It is interesting that curcumin can inhibit the development of colorectal cancer induced by AOM/DSS in mice by regulating intestinal homeostasis and intestinal metabolites[137]. Two kinds of tea

polyphenols (gallatechin and gallatechin gallate) can significantly reduce the level of mast cell protease in mice, alleviate certain inflammatory reactions, and the pathological changes of intestinal tract, thymus, spleen and lung can be observed in pathological sections [138]. These two polyphenols can act as inhibitors of mast cell proteases, reduce PARs activation, and further regulate the occurrence of tumor microenvironment-related responses. In recent years, there have been abundant studies on the anti-tumor effect of EGCG, and it exerts anti-cancer effects through multiple mechanisms. Recent reviews have well summarized the mechanism of EGCG in anti-tumor, mainly by regulating the expression of various cancer-related micrornas (miRNAs) to inhibit the proliferation of cancer cells and tumor growth [139]. However, their bioavailability in vivo is relatively low and most studies remain at the in vitro experimental stage. In the future, it is necessary to further explore the mechanism of action in the human body and the direction to improve bioavailability.

7.3. Polysaccharides

Over the past few decades, polysaccharides extracted from various traditional Chinese medicines have gained widespread attention in the field of cancer treatment due to their diverse mechanisms of action and minimal adverse effects[140]. For example, the inhibitory effect of angelica polysaccharide (AP) on MCs activation and its possible molecular mechanism has been demonstrated. Yaru Wu et al. orally fed rhodiola rosea polysaccharide to tumor-bearing mice, and confirmed that rhodiola Rosea polysaccharide induced tumor cell apoptosis through S-phase block of mitochondria-related pathway, and showed a dose-dependent effect [141]。 Studies found that AP significantly reduced the release of histamine, β-hexosaminidase, leukotriene C4 (LTC4), IL-1, IL-4, TNF-α, IL-6, and MCP-1/CCL2 in anti-DNP IgE-stimulated RBL-2H3 cells. In addition, AP inhibited Ca2+ inward flow and downregulated p-Fyn, p-Akt, p-P38, IL-4, TNF-α, and NF-κB p65 protein expression. These findings suggest that AP may inhibit MCs activation by suppressing the release of inflammatory factors and allergic mediators, as well as the Gab2/PI3-K/Akt and Fyn/Syk signaling pathways[113].

In vivo and in vitro experiments to verify the anti-tumor effects of ginger polysaccharide (UGP1), it was found that in vivo, it can inhibit tumor proliferation, increase p53 expression and Bax/Bcl-2 ratio, and enhance the secretion of pro-inflammatory cytokines (such as TNF-α, IL-2 and IL-6). At the same time, reducing the secretion of tumor promoting cytokines (such as TGF-β) in the serum [84] may change the cytokine network formed by mast cells in the tumor microenvironment and play an anti-tumor role[142]. Astragalus polysaccharide, a major component extracted from Astragalus, has been extensively studied for its role in treating non-small cell lung cancer. It functions by inhibiting the S1PR1/STAT3 signaling pathway and promoting the differentiation of myeloid-derived suppressor cells (MDSCs) in peripheral blood[143]. In ovarian cancer research, astragalus polysaccharides, as adjunct medication, inhibit mitochondrial autophagy through the PINK1/Parkin pathway, thereby increasing the sensitivity of ovarian cancer stem cells to PARP inhibitors, reducing patient resistance, and improving survival rates[144]. Moreover, astragalus polysaccharides can inhibit the recruitment of MDSCs and regulatory T cells (Tregs), thereby reducing the

expression of IL-10, transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF)[145]. Certain immune-suppressive cytokines expressed in the TME, such as IL-10 and TGF-β, are key factors in the failure of anti-tumor immune responses. Lentinan has been shown to inhibit the progression of bladder cancer by upregulating IFN-γ and IL-2 expression while significantly decreasing IL-10 and TGF-β levels in MDSCs and Tregs[146]. In recent years, the anti-tumor effect of edible mushroom polysaccharides has gradually entered the public's attention [147], Lentinan has also been found to increase interferon gamma (INF-γ) independently of T cells, thereby inhibiting tumor blood vessels formation. Interestingly, long-term administration of lentinan can continuously suppress tumor growth[148]. Studies utilizing the breast cancer 4T1 cell model have validated that psyllium polysaccharides promote macrophage polarization into the M1 phenotype, while improving T cell accumulation in the spleen and lymph nodes, synergistically achieving tumor suppression effects[149]. Glycyrrhizin polysaccharides demonstrate the ability to inhibit IL-10 and TGF-β secretion by dendritic cells, downregulating their expression[150]. Recently, ganoderma lucidum polysaccharides have emerged as a potential anticancer agent. They activate the CARD9-NF-κB-IDO pathway in Lewis lung cancer, inducing MDSCs differentiation and inhibiting their accumulation, thereby preventing cancer development[151]. These polysaccharides have significantly inhibited tumor growth in tumor-bearing mice, by increasing the expression of miR-125b, enhancing the ratio of effector T cells (Teffs) to regulatory T cells (Tregs)[152].The anti-tumor effect of Portulaca oleracea polysaccharides have been confirmed, as they promote ferroptosis by upregulating acyl-CoA synthetase long-chain family member 4 (ACSL4), thereby inhibiting ovarian cancer development[153]. Another polysaccharide, Grifola frondosa polysaccharide, depletes MDSCs in CD8+ T cells, reducing their numbers in tumor tissues, and ultimately inhibiting tumor growth[154]. Ahomogeneous polysaccharide, PPTP80-1, isolated and purified from Barbary Wolfberry fruit, was found, activate the immune system and exhibit anti-tumor effects in zebrafish tumor models [155].

7.4. Alkaloids

Numerous studies have indicated that natural alkaloids possess significant potential in the treatment and prevention of cancer. For example, berberine inhibits the proliferation of nasopharyngeal carcinoma cells and promotes their apoptosis by suppressing the activation of STAT3 induced by tumor-associated fibroblasts[156]. Additionally, in studies of rectal cancer models, berberine has been shown to inhibit the secretion of TNF-α and the expression of downstream signaling pathways, effectively suppressing tumor progression[157].Sanguinarine blocks the Wnt/β-catenin pathway, preventing the polarization of M2-type macrophages, and thereby inhibiting angiogenesis in lung cancer. Concurrently, it promotes the differentiation of MDSCs into macrophages and dendritic cells through the NF-κB pathway[158]. Dendrobine isolated from Dendrobium alkali, has demonstrated no hepatorenal toxicity in mice with tumors and inhibits tumor immune escape by suppressing the PD-1/PD-L1 checkpoint pathway, further limiting tumor growth. However, this effect has only been observed in lung cancer tumors[159]. Piperine, found in black pepper, has shown inhibitory effects on cancer cells in vitro by regulating cell cycle arrest and promoting apoptosis. It

can also inhibit the gene expression of matrix metalloproteinases 2/9 (MMP2/9) and downregulate the levels of inflammation-related molecules (PTGS2, PTGER4). Furthermore, piperine affects cytokines release(IFN-γ, IL-8) and regulates the activity of the ERK and p38 signaling pathways, thereby exerting its anti-tumor effects at multiple levels[160].Solanine extracted from potatoes may downregulate TcB through the TGF-β/SMAD pathway and activate anti-tumor immune responses[161]. Additionally, the alkaloid N-hydroxysporamide has been confirmed to exhibit inhibitory effects on NF-κB. It also demonstrated cytotoxicity by inducing apoptosis in tumor cells, showing anti-tumor activity both in vitro and in vivo[162].

7.5. Quinones

Emodin extracted from rhubarb and giant knotweed, inhibits the polarization of M2-type macrophages. By reducing the paracrine and autocrine effects of tumor cells, emodin suppresses the migration and recruitment of macrophages to metastatic sites, thereby improving the immunosuppressive conditions within the TME[163]. In the treatment of breast cancer, emodin can regulate T cells activation and inhibit tumor angiogenesis, effectively reducing lung metastasis of cancer cells [164]. Shikonin, derived from the roots of plants in the Boraginaceae family, affects signaling pathways by promoting the phosphorylation of Akt and ERK1/2 in NK cells[165]. Shikonin also promote the maturation of DC cells while enhancing the activity of Th1 cells and cytotoxic T cells, thereby improving their tumor killing effects[166].

7.6. Saponin

Saponins are compounds composed of saponin aglycones and sugar molecules. The aglycones are typically triterpenoid or steroid structures, while the attached sugar molecules often include glucose, arabinose, rhamnose, galactose, and xylose. Due to these structural feature, saponins exhibit diverse biological activities such as anti-tumor, immune regulation, and anti-inflammatory effects. B-cell activating factor (BAFF), a member of the tumor necrosis factor (TNF) family, significantly impacts B cells survival and differentiation. Total glucosides of paeony (TGP) inhibit the phosphorylation of p38-MAPK, reduce α5-nAChR-mediated cell proliferation and migration, and induce mitochondrial dysfunction and apoptosis[167]. Paeoniflorin reduces the proportion of regulatory B cells (Bregs) by inhibiting the BAFF-BAFF-R signaling pathway[168]. Dioscin, a saponin extracted from Dioscorea zingiberensis and Dioscorea nipponica, inhibits M2 macrophages polarization in tumor-associated macrophages (TAMs) by activating the Cx43/STAT1/IFN-γ signaling pathway and suppressing the IL-4/JAK2/STAT3 pathway[169]. Recently, a new saponin ZnS, was discovered in Dioscorea zingiberensis. Its anticancer effect has been verified, demonstrating ZnS inhibits the proliferation of liver cancer cell proliferation in a dose-dependent manner. It significantly suppresses cell vitality, induces, and reduces invasion of liver cancer cells by regulating the expression of TCONS-00026762[170]. Madecassoside derived from Centella asiatica, inhibits breast cancer tumor growth and angiogenesis primarily through the YAP1/VEGFA signaling pathway[171]. Ginsenoside Rg3, extracted from ginseng, suppresses AKT2 expression in cervical cancer cells, reversing AKT-mediated cell proliferation, migration, and invasion[172]. Additionally, ginsenoside Rh4 inhibits cancer cell proliferation by regulating SIRT2, promoting cell cycle arrest, and inducing

ferroptosis[173]. Salidroside, a glucoside derived from Rhodiola, is a type of tyrosol glycoside. Recent studies have identified a novel mechanism by which it inhibits non-small cell lung cancer: salidroside suppresses the function of Treg cells via the Hsp 70/Foxp 1/Foxp 3 pathway, thereby inhibiting tumor growth[174].

8. Conclusion

The function of MCs in tumor progression depends on the specific tumor type and its stage of development, making a universal generalization impractical. As illustrated in Figure 3, MCs may serve a dual role in tumor biology by both promoting growth and inhibiting progression. Typically, in the earlystages of carcinogenesis, MCs, as sentinel cells, exert an anti-tumor effect. MC regulation of anti-tumor immunity may occur via the following mechanisms: Interleukin-4 (IL-4), secreted by MCs, has been demonstrated to inhibit the proliferation of tumor cells. Conversely, IL-1, IL-6, tumor necrosis factor-alpha (TNF-α), interferon-alpha (IFN-α), and transforming growth factor-beta (TGF-β) have been shown to promote the apoptosis of tumor cells. Additionally, MCs may regulate anti-tumor immunity through the release of pre-synthesized and newly synthesized mediators (including histamine, CCL3, CCL5, CXCL10, IL-6, etc.) stored in their granules. This may occur through the induction of activation and differentiation of immune cells, such as dendritic cells, CD4+ T cells, and NK cells, thereby enhancing anti-tumor responses. Conversely, growth factors secreted by MCs, such as PDGF, SCF, and NGF, can directly induce tumor cell proliferation and metastasis. This may occur through the expression of H1 receptors on human malignant tumors or through the H2 receptors to inhibit the immune system. New angiogenic agents, including heparin, VEGF, IL-8, and proteases, facilitate the formation of new blood vessels and metastasis, promoting angiogenesis and supplying essential nutrients for tumor growth. Additionally, matrix metalloproteinases (MMPs), selectively secreted by MCs, play a crucial role in extracellular matrix (ECM) degradation, with MMP2 and MMP9 being particularly important for tissue remodeling in the TME.

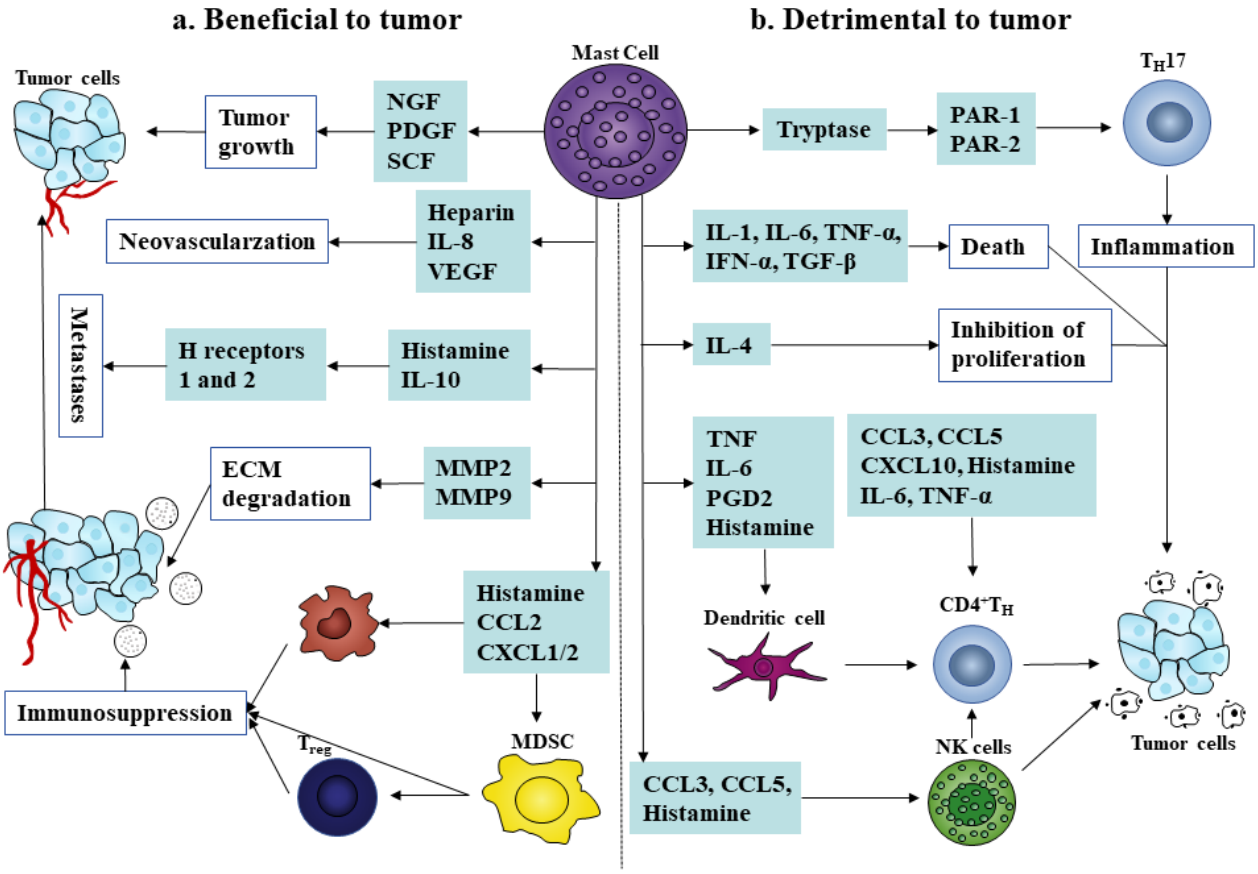


Figure 3. The main mechanism of action of mast cells in tumor progression. In the tumor microenvironment, mast cells release a series of media that affect the survival of tumor cells, as well as the remodeling of local tissues and the recruitment of immune effector cells. Local cell infiltration also produces and secretes its own molecular subpopulations, resulting in a series of complex interactions.

The complex role of MCs in tumor progression can be modulated through the intervention of natural bioactive substances. These natural bioactive substances can influence the TME, thereby regulating the behavior of MCs. For example, studies have found that curcumin can activate the innate immune system to fight against cancer and can inhibit epithelial-mesenchymal transition (EMT) in the TME.[175]Chlorogenic acid can regulate the TME and malignant behavior of cancer, inhibiting the growth of pancreatic cancer through the AKT/GSK-3β/β-catenin signaling pathway[176].

Natural active substances also affect the TME by regulating the function of immune cells. For example, polysaccharides extracted from natural resources can activate natural killer cells (NK cells), enhance their cytotoxicity against tumors, and through the TLR4/MAPKs/NF-κB signaling pathway, enhance the cytotoxicity of NK cells[177]. Furthermore, some polysaccharides can convert immunosuppressive macrophages into M1-like phenotype by inhibiting the PD-L1/PD-1 axis and activate T lymphocytes[178, 179] . Based on this, we can provide functional hints for anti-tumor food supplements [180]. The development of new combination therapies in combination with existing anti-tumor therapies, such as immune checkpoint inhibitors, chemotherapy, and radiotherapy, can further enhance the anti-tumor effects of bioactive ingredients. Future research should focus on the screening and optimization of bioactive

ingredients, further analysis of mast cell functions, and development of clinical combination therapies to provide new strategies for cancer treatment.

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Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] M. Li, M. Qian, Q. Jiang, et al., Evidence of Flavonoids on Disease Prevention, Antioxidants. 12 (2023) https://doi.org/10.3390/antiox12020527.

[2] M. El Oirdi, Harnessing the Power of Polyphenols: A New Frontier in Disease Prevention and Therapy, Pharmaceuticals. 17 (2024) https://doi.org/10.3390/ph17060692.

[3] S. Razak, T. Afsar, A. Ullah, et al., Taxifolin, a natural flavonoid interacts with cell cycle regulators causes cell cycle arrest and causes tumor regression by activating Wnt/ β -catenin signaling pathway, BMC Cancer. 18 (2018) https://doi.org/10.1186/s12885-018-4959-4.

[4] M. Singh, M. Verma, S. Pandey, et al., Anticancer Potential of Quercetin, Epigallocatechin Gallate, Kaempferol, Apigenin, and Curcumin against Several Human Carcinomas, Endocrine, Metabolic & Immune Disorders - Drug Targets. 24 (2024) https://doi.org/10.2174/0118715303320523240910072723.

[5] V. Kannen, D.M. Grant, J. Matthews, The mast cell-T lymphocyte axis impacts cancer: Friend or foe?, Cancer Lett. 588 (2024) 216805. https://doi.org/10.1016/j.canlet.2024.216805.

[6] S. Maltby, K. Khazaie, K.M. McNagny, Mast cells in tumor growth: angiogenesis, tissue remodelling and immune-modulation, Biochim Biophys Acta. 1796 (2009) 19-26. https://doi.org/10.1016/j.bbcan.2009.02.001.

[7] S.A. Oldford, I.D. Haidl, M.A. Howatt, et al., A critical role for mast cells and mast cell-derived IL-6 in TLR2-mediated inhibition of tumor growth, J Immunol. 185 (2010) 7067-7076. https://doi.org/10.4049/jimmunol.1001137.

[8] H.Y. Lim, B.J. Seung, S.H. Cho, et al., Canine mammary cancer in overweight or obese female dogs is associated with intratumoral microvessel density and macrophage counts, Vet Pathol. 59 (2022) 39-45. https://doi.org/10.1177/03009858211040481.

[9] G.O. Elpek, T. Gelen, N.H. Aksoy, et al., The prognostic relevance of angiogenesis and mast cells in squamous cell carcinoma of the oesophagus, J Clin Pathol. 54 (2001) 940-944. https://doi.org/10.1136/jcp.54.12.940.

[10] M. Samoszuk, M.A. Corwin, Mast cell inhibitor cromolyn increases blood clotting and hypoxia in murine breast cancer, Int J Cancer. 107 (2003) 159-163. https://doi.org/10.1002/ijc.11340.

[11] B.A. Pereira, N.L. Lister, K. Hashimoto, et al., Tissue engineered human prostate microtissues reveal key role of mast cell-derived tryptase in potentiating cancer-associated fibroblast (CAF)-induced morphometric transition in vitro, Biomaterials. 197 (2019) 72-85. https://doi.org/10.1016/j.biomaterials.2018.12.030.

[12] A. Scott, O. Lian, R. Bahr, et al., Increased mast cell numbers in human patellar tendinosis: correlation with symptom duration and vascular hyperplasia, Br J Sports Med. 42 (2008) 753-757. https://doi.org/10.1136/bjsm.2007.040212.

[13] B. Zhong, Y. Li, X. Liu, et al., Association of mast cell infiltration with gastric cancer progression, Oncol Lett. 15 (2018) 755-764. https://doi.org/10.3892/ol.2017.7380.

[14] A. Rigoni, M.P. Colombo, C. Pucillo, The Role of Mast Cells in Molding the Tumor Microenvironment, Cancer Microenviron. 8 (2015) 167-176. https://doi.org/10.1007/s12307-014-0152-8.

[15] T.Y.S. Ngaha, A.V. Zhilenkova, F.E. Essogmo, et al., Angiogenesis in Lung Cancer: Understanding the Roles of Growth Factors, Cancers (Basel). 15 (2023) https://doi.org/10.3390/cancers15184648.

[16] I. Esposito, M. Menicagli, N. Funel, et al., Inflammatory cells contribute to the generation of an angiogenic phenotype in pancreatic ductal adenocarcinoma, J Clin Pathol. 57 (2004) 630-636. https://doi.org/10.1136/jcp.2003.014498.

[17] T.L. Curley, D.H. Thamm, S.W. Johnson, et al., Effects of morphine on histamine release from two cell lines of canine mast cell tumor and on plasma histamine concentrations in dogs with cutaneous mast cell tumor, Am J Vet Res. 82 (2021) 1013-1018. https://doi.org/10.2460/ajvr.20.08.0137.

[18] A. Fleischmann, T. Schlomm, J. Kollermann, et al., Immunological microenvironment in prostate cancer: high mast cell densities are associated with favorable tumor characteristics and good prognosis, Prostate. 69 (2009) 976-981. https://doi.org/10.1002/pros.20948.

[19] A.B. Rajput, D.A. Turbin, M.C. Cheang, et al., Stromal mast cells in invasive breast cancer are a marker of favourable prognosis: a study of 4,444 cases, Breast Cancer Res Treat. 107 (2008) 249-257. https://doi.org/10.1007/s10549-007-9546-3.

[20] R. Li, X. Song, Y. Guo, et al., Natural Products: A Promising Therapeutics for Targeting Tumor Angiogenesis, Frontiers in Oncology. 11 (2021) https://doi.org/10.3389/fonc.2021.772915.

[21] Z. Cheng, S.-H. Wang, L.-Y. Li, et al., Fermented
Porphyra haitanensis polysaccharides inhibit the degranulation of mast cell and passive cutaneous anaphylaxis, Food & Medicine Homology. (2025) https://doi.org/10.26599/fmh.2026.9420086.

[22] S. Ch'ng, R.A. Wallis, L. Yuan, et al., Mast cells and cutaneous malignancies, Mod Pathol. 19 (2006) 149-159. https://doi.org/10.1038/modpathol.3800474.

[23] T.C. Theoharides, P. Conti, Mast cells: the Jekyll and Hyde of tumor growth, Trends Immunol. 25 (2004) 235-241. https://doi.org/10.1016/j.it.2004.02.013.

[24] J.L. Gooch, A.V. Lee, D. Yee, Interleukin 4 inhibits growth and induces apoptosis in human breast cancer cells, Cancer Res. 58 (1998) 4199-4205. https://www.ncbi.nlm.nih.gov/pubmed/9751635

[25] J.R. Starkey, P.K. Crowle, S. Taubenberger, Mast-cell-deficient W/Wv mice exhibit a decreased rate of tumor angiogenesis, Int J Cancer. 42 (1988) 48-52. https://doi.org/10.1002/ijc.2910420110.

[26] N. Ahmed, S.M. Anderson, M.V. Berridge, IL-3 induces apoptosis in a ras-transformed myeloid cell line, Apoptosis. 4 (1999) 71-80. https://doi.org/10.1023/a:1009686220607.

[27] Q. Rao, Y. Chen, C.R. Yeh, et al., Recruited mast cells in the tumor microenvironment enhance bladder cancer metastasis via modulation of ERbeta/CCL2/CCR2 EMT/MMP9 signals, Oncotarget. 7 (2016) 7842-7855. https://doi.org/10.18632/oncotarget.5467.

[28] H. Yuan, Y.H. Hsiao, Y. Zhang, et al., Destructive impact of T-lymphocytes, NK and Mast cells on basal cell layers: implications for tumor invasion, BMC Cancer. 13 (2013) 258. https://doi.org/10.1186/1471-2407-13-258.

[29] M.G. Brown, S.M. McAlpine, Y.Y. Huang, et al., RNA sensors enable human mast cell anti-viral chemokine production and IFN-mediated protection in response to antibody-enhanced dengue virus infection, Plos One. 7 (2012) e34055. https://doi.org/10.1371/journal.pone.0034055.

[30] P. Salamon, N.G. Shoham, R. Gavrieli, et al., Human mast cells release Interleukin-8 and induce neutrophil chemotaxis on contact with activated T cells, Allergy. 60 (2005) 1316-1319. https://doi.org/10.1111/j.1398-9995.2005.00886.x.

[31] C. Demarta-Gatsi, A. Rivkin, V. Di Bartolo, et al., Histamine releasing factor and elongation factor 1 alpha secreted via malaria parasites extracellular vesicles promote immune evasion by inhibiting specific T cell responses, Cell Microbiol. 21 (2019) e13021. https://doi.org/10.1111/cmi.13021.

[32] N.A. Forward, S.J. Furlong, Y. Yang, et al., Mast cells down-regulate CD4+CD25+ T regulatory cell suppressor function via histamine H1 receptor interaction, J Immunol. 183 (2009) 3014-3022. https://doi.org/10.4049/jimmunol.0802509.

[33] X. Ma, J. Deng, L. Han, et al., Single-cell RNA sequencing reveals B cell-T cell interactions in vascular adventitia of hyperhomocysteinemia-accelerated atherosclerosis, Protein Cell. 13 (2022) 540-547. https://doi.org/10.1007/s13238-021-00904-0.

[34] K. Ganeshan, P.J. Bryce, Regulatory T cells enhance mast cell production of IL-6 via surface-bound TGF-beta, J Immunol. 188 (2012) 594-603. https://doi.org/10.4049/jimmunol.1102389.

[35] J.J. Wei, C.W. Song, L.C. Sun, et al., SCF and TLR4 ligand cooperate to augment the tumor-promoting potential of mast cells, Cancer Immunol Immunother. 61 (2012) 303-312. https://doi.org/10.1007/s00262-011-1098-z.

[36] M. Gulubova, T. Vlaykova, Prognostic significance of mast cell number and microvascular density for the survival of patients with primary colorectal cancer, J Gastroenterol Hepatol. 24 (2009) 1265-1275. https://doi.org/10.1111/j.1440-1746.2007.05009.x.

[37] A. Imada, N. Shijubo, H. Kojima, et al., Mast cells correlate with angiogenesis and poor outcome in stage I lung adenocarcinoma, Eur Respir J. 15 (2000) 1087-1093. https://doi.org/10.1034/j.1399-3003.2000.01517.x.

[38] T. Groot Kormelink, D.G. Powe, S.A. Kuijpers, et al., Immunoglobulin free light chains are biomarkers of poor prognosis in basal-like breast cancer and are potential targets in tumor-associated inflammation, Oncotarget. 5 (2014) 3159-3167. https://doi.org/10.18632/oncotarget.1868.

[39] W. Zou, N.P. Restifo, T(H)17 cells in tumour immunity and immunotherapy, Nat Rev Immunol. 10 (2010) 248-256. https://doi.org/10.1038/nri2742.

[40] D. Ribatti, G. Ranieri, Tryptase, a novel angiogenic factor stored in mast cell granules, Experimental Cell Research. 332 (2015) 157-162. https://doi.org/10.1016/j.yexcr.2014.11.014.

[41] Q. Zhou, Y.-w. Wang, P.-f. Ni, et al., Effect of tryptase on mouse brain microvascular endothelial cells via protease-activated receptor 2, Journal of Neuroinflammation. 15 (2018) https://doi.org/10.1186/s12974-018-1287-1.

[42] H.J. Jeong, H.A. Oh, S.Y. Nam, et al., The critical role of mast cell-derived hypoxia-inducible factor-1alpha in human and mice melanoma growth, Int J Cancer. 132 (2013) 2492-2501. https://doi.org/10.1002/ijc.27937.

[43] K. Milek, K. Kaczmarczyk-Sekula, A. Strzepek, et al., Mast cells influence neoangiogenesis in prostatic cancer independently of ERG status, Pol J Pathol. 67 (2016) 244-249. https://doi.org/10.5114/pjp.2016.62027.

[44] I. Lilja, C. Gustafson-Svard, L. Franzen, et al., Tumor necrosis factor-alpha in ileal mast cells in patients with Crohn's disease, Digestion. 61 (2000) 68-76. https://doi.org/10.1159/000007737.

[45] G. Dyduch, K. Kaczmarczyk, K. Okon, Mast cells and cancer: enemies or allies?, Pol J Pathol. 63 (2012) 1-7. https://www.ncbi.nlm.nih.gov/pubmed/22535614

[46] H. Yang, J. Xie, W. Mu, et al., Tea polyphenols protect learning and memory in sleep-deprived mice by promoting AMPA receptor internalization, Neuroreport. 31 (2020) 857-864. https://doi.org/10.1097/WNR.0000000000001462.

[47] P. Conti, M.L. Castellani, D. Kempuraj, et al., Role of mast cells in tumor growth, Ann Clin Lab Sci. 37 (2007) 315-322. https://www.ncbi.nlm.nih.gov/pubmed/18000287

[48] N. Matsumoto, M. Ebihara, S. Oishi, et al., Histamine H1 receptor antagonists selectively kill cisplatin-resistant human cancer cells, Sci Rep. 11 (2021) 1492. https://doi.org/10.1038/s41598-021-81077-y.

[49] P.F. Bowrey, J. King, C. Magarey, et al., Histamine, mast cells and tumour cell proliferation in breast cancer: does preoperative cimetidine administration have an effect?, Br J Cancer. 82 (2000) 167-170. https://doi.org/10.1054/bjoc.1999.0895.

[50] S. Wang, L. Li, R. Shi, et al., Mast Cell Targeted Chimeric Toxin Can Be Developed as an Adjunctive Therapy in Colon Cancer Treatment, Toxins. 8 (2016) https://doi.org/10.3390/toxins8030071.

[51] B. Huang, Z. Lei, G.M. Zhang, et al., SCF-mediated mast cell infiltration and activation exacerbate the inflammation and immunosuppression in tumor microenvironment, Blood. 112 (2008) 1269-1279. https://doi.org/10.1182/blood-2008-03-147033.

[52] M.F. Mercogliano, S. Bruni, F. Mauro, et al., Harnessing Tumor Necrosis Factor Alpha to Achieve Effective Cancer Immunotherapy, Cancers. 13 (2021) https://doi.org/10.3390/cancers13030564.

[53] L. Soucek, E.R. Lawlor, D. Soto, et al., Mast cells are required for angiogenesis and macroscopic expansion of Myc-induced pancreatic islet tumors, Nat Med. 13 (2007) 1211-1218. https://doi.org/10.1038/nm1649.

[54] J.N. Lichterman, S.M. Reddy, Mast Cells: A New Frontier for Cancer Immunotherapy, Cells. 10 (2021) https://doi.org/10.3390/cells10061270.

[55] S. Shi, L. Ye, X. Yu, et al., Focus on mast cells in the tumor microenvironment: Current knowledge and future directions, Biochimica et Biophysica Acta (BBA) - Reviews on Cancer. 1878 (2023) https://doi.org/10.1016/j.bbcan.2022.188845.

[56] R. Molfetta, R. Paolini, The Controversial Role of Intestinal Mast Cells in Colon Cancer, Cells. 12 (2023) https://doi.org/10.3390/cells12030459.

[57] D. Amre, F. Xu, S. Yan, et al., Prevalence of Childhood Atopic Dermatitis: An Urban and Rural Community-Based Study in Shanghai, China, PLoS ONE. 7 (2012) https://doi.org/10.1371/journal.pone.0036174.

[58] D. Ribatti, R. Tamma, E. Crivellato, The dual role of mast cells in tumor fate, Cancer Letters. 433 (2018) 252-258. https://doi.org/10.1016/j.canlet.2018.07.005.

[59] T. Long, Z. Liu, J. Shang, et al., Polygonatum sibiricum polysaccharides play anti-cancer effect through TLR4-MAPK/NF-κB signaling pathways, International Journal of Biological Macromolecules. 111 (2018) 813-821. https://doi.org/10.1016/j.ijbiomac.2018.01.070.

[60] A. Benito-Martin, L. Nogués, M. Hergueta-Redondo, et al., Mast cells impair melanoma cell homing and metastasis by inhibiting HMGA1 secretion, Immunology. 168 (2022) 362-373. https://doi.org/10.1111/imm.13604.

[61] H. Zhou, M. Zhang, H. Cao, et al., Research Progress on the Synergistic Anti-Tumor Effect of Natural Anti-Tumor Components of Chinese Herbal Medicine Combined with Chemotherapy Drugs, Pharmaceuticals. 16 (2023) https://doi.org/10.3390/ph16121734.

[62] W. Zhao, X.D. Zheng, P.Y.Z. Tang, et al., Advances of antitumor drug discovery in traditional Chinese medicine and natural active products by using multi-active components combination, Medicinal Research Reviews. 43 (2023) 1778-1808. https://doi.org/10.1002/med.21963.

[63] J.f. Duan, Q.j. Zhang, J. Zhu, et al., Curcumin affects autophagy of prolactinoma cells by upregulating miR-206 to exert antitumor effects, Journal of Biochemical and Molecular Toxicology. 38 (2024) https://doi.org/10.1002/jbt.23734.

[64] M. Song, Y. Qu, H. Jia, et al., Targeting TAOK1 with resveratrol inhibits esophageal squamous cell carcinoma growth in vitro and in vivo, Molecular Carcinogenesis. 63 (2024) 991-1008. https://doi.org/10.1002/mc.23703.

[65] X. Guo, M. Sun, P. Yang, et al., Role of mast cells activation in the tumor immune microenvironment and immunotherapy of cancers, European Journal of Pharmacology. 960 (2023) https://doi.org/10.1016/j.ejphar.2023.176103.

[66] N.D. Dave, L. Xiang, K.E. Rehm, et al., Stress and Allergic Diseases, Immunology and Allergy Clinics of North America. 31 (2011) 55-68. https://doi.org/10.1016/j.iac.2010.09.009.

[67] S.L. DeFelice, The nutraceutical revolution: its impact on food industry R&D, Trends in Food Science & Technology. 6 (1995) 59-61. https://doi.org/10.1016/s0924-2244(00)88944-x.

[68] A. Bergamin, E. Mantzioris, G. Cross, et al., Nutraceuticals: Reviewing their Role in Chronic Disease Prevention and Management, Pharmaceutical Medicine. 33 (2019) 291-309. https://doi.org/10.1007/s40290-019-00289-w.

[69] L. Das, E. Bhaumik, U. Raychaudhuri, et al., Role of nutraceuticals in human health, Journal of Food Science and Technology. 49 (2011) 173-183. https://doi.org/10.1007/s13197-011-0269-4.

[70] H. Kim, Y.-T. Ahn, G.S. Lee, et al., Effects of astaxanthin on dinitrofluorobenzene-induced contact dermatitis in mice, Molecular Medicine Reports. 12 (2015) 3632-3638. https://doi.org/10.3892/mmr.2015.3892.

[71] R. Shahbazi, F. Sharifzad, R. Bagheri, et al., Anti-Inflammatory and Immunomodulatory Properties of Fermented Plant Foods, Nutrients. 13 (2021) https://doi.org/10.3390/nu13051516.

[72] T. Tanaka, A. Iuchi, H. Harada, et al., Potential Beneficial Effects of Wine Flavonoids on Allergic Diseases, Diseases. 7 (2019) https://doi.org/10.3390/diseases7010008.

[73] J. Cao, Y. Wang, S. Hu, et al., Kaempferol ameliorates secretagogue-induced pseudo-allergic reactions via inhibiting intracellular calcium fluctuation, Journal of Pharmacy and Pharmacology. 72 (2020) 1221-1231. https://doi.org/10.1111/jphp.13312.

[74] J. Cao, C. Li, P. Ma, et al., Effect of kaempferol on IgE-mediated anaphylaxis in C57BL/6 mice and LAD2 cells, Phytomedicine. 79 (2020) https://doi.org/10.1016/j.phymed.2020.153346.

[75] S. Hu, Y. Zhang, B. Dang, et al., Myricetin alleviated immunologic contact urticaria and mast cell degranulation via the PI3K/Akt/NF-κB pathway, Phytotherapy Research. 37 (2023) 2024-2035. https://doi.org/10.1002/ptr.7726.

[76] K. Nagata, S. Araumi, D. Ando, et al., Kaempferol Suppresses the Activation of Mast Cells by Modulating the Expression of FcεRI and SHIP1, International Journal of Molecular Sciences. 24 (2023) https://doi.org/10.3390/ijms24065997.

[77] T.S. Vo, T.T. Le, S.Y. Kim, et al., The role of myricetin fromRhodomyrtus tomentosa(Aiton) Hassk fruits on downregulation of FcεRI-mediated mast cell activation, Journal of Food Biochemistry. 44 (2020) https://doi.org/10.1111/jfbc.13143.

[78] D.N. Che, J.Y. Shin, H.J. Kang, et al., Luteolin suppresses IL-31 production in IL-33-stimulated mast cells through MAPK and NF-κB signaling pathways, International Immunopharmacology. 83 (2020) https://doi.org/10.1016/j.intimp.2020.106403.

[79] C.D. Carlucci, Y. Hui, A.P. Chumanevich, et al., Resveratrol Protects against Skin Inflammation through Inhibition of Mast Cell, Sphingosine Kinase-1, Stat3 and NF-κB p65 Signaling Activation in Mice, International Journal of Molecular Sciences. 24 (2023) https://doi.org/10.3390/ijms24076707.

[80] S. Nakajima, K. Ishimaru, A. Kobayashi, et al., Resveratrol inhibits IL-33–mediated mast cell activation by targeting the MK2/3–PI3K/Akt axis, Scientific Reports. 9 (2019) https://doi.org/10.1038/s41598-019-54878-5.

[81] Y. Xu, Q. Liu, X. Guo, et al., Resveratrol attenuates IL-33-induced mast cell inflammation associated with inhibition of NF-κB activation and the P38 signaling pathway, Molecular Medicine Reports. (2020) https://doi.org/10.3892/mmr.2020.10952.

[82] J. Wang, Y. Zhang, S. Hu, et al., Resveratrol inhibits MRGPRX2-mediated mast cell activation via Nrf2 pathway, International Immunopharmacology. 93 (2021) https://doi.org/10.1016/j.intimp.2021.107426.

[83] H.-Y. Kim, H.-G. Kang, S.-Y. Nam, et al., Blockade of RANKL/RANK signaling pathway by epigallocatechin gallate alleviates mast cell-mediated inflammatory reactions, International Immunopharmacology. 88 (2020) https://doi.org/10.1016/j.intimp.2020.106872.

[84] W. Xu, X. Song, Q. Qu, et al., Synergistic effects of l-theanine and epigallocatechin gallate in alleviating ovalbumin allergy by regulating intestinal immunity through inhibition of mast cell degranulation, Food & Function. 14 (2023) 2059-2073. https://doi.org/10.1039/d2fo03404b.

[85] M. Yashima, Y. Sato, I. Kazama, Catechin synergistically potentiates mast cell-stabilizing property of caffeine, Allergy, Asthma & Clinical Immunology. 17 (2021) https://doi.org/10.1186/s13223-020-00502-5.

[86] Z.-L. Kong, S. Sudirman, H.-J. Lin, et al., In vitro anti-inflammatory effects of curcumin on mast cell-mediated allergic responses via inhibiting FcεRI protein expression and protein kinase C delta translocation, Cytotechnology. 72 (2019) 81-95. https://doi.org/10.1007/s10616-019-00359-6.

[87] A. Gasbarrini, M. Grimaldi, M.V. Fogli, et al., Curcumin and Fennel Essential Oil Improve Symptoms and Quality of Life in Patients with Irritable Bowel Syndrome, Journal of Gastrointestinal and Liver Diseases. 25 (2016) 151-157. https://doi.org/10.15403/jgld.2014.1121.252.ccm.

[88] S.C. Gupta, G. Kismali, B.B. Aggarwal, Curcumin, a component of turmeric: From farm to pharmacy, BioFactors. 39 (2013) 2-13. https://doi.org/10.1002/biof.1079.

[89] Y. Li, X. Chen, L. Xu, et al., Sesamin is an effective spleen tyrosine kinase inhibitor against IgE-mediated food allergy in computational, cell-based and animal studies, Food Science and Human Wellness. 14 (2025) https://doi.org/10.26599/fshw.2024.9250081.

[90] Y. Li, F. Wu, Y. Wang, et al., Sesamin Alleviates Allergen-Induced Diarrhea by Restoring Gut Microbiota Composition and Intestinal Barrier Function, Journal of Agricultural and Food Chemistry. 73 (2025) 1965-1981. https://doi.org/10.1021/acs.jafc.4c10158.

[91] Q. Bai, X. Feng, Y. Wang, et al., Adenosine cyclic phosphate with ultrasonic-assisted pectinase extraction alleviated allergic reactions in RBL-2H3 through inhibiting the influx of intracellular Ca2+, Food Science and Human Wellness. 12 (2023) 832-841. https://doi.org/10.1016/j.fshw.2022.09.023.

[92] X. Wang, R. Ilarraza, B.P. Tancowny, et al., Disrupted Lipid Raft Shuttling of FcεRI by n-3 Polyunsaturated Fatty Acid Is Associated With Ligation of G Protein-Coupled Receptor 120 (GPR120) in Human Mast Cell Line LAD2, Frontiers in Nutrition. 7 (2020) https://doi.org/10.3389/fnut.2020.597809.

[93] L.W.J. van den Elsen, Y. Nusse, M. Balvers, et al., n-3 Long-chain PUFA reduce allergy-related mediator release by human mast cellsin vitrovia inhibition of reactive oxygen species, British Journal of Nutrition. 109 (2012) 1821-1831. https://doi.org/10.1017/s0007114512003959.

[94] C.C. Wang, H. Wu, F.H. Lin, et al., Sodium butyrate enhances intestinal integrity, inhibits mast cell activation, inflammatory mediator production and JNK signaling pathway in weaned pigs, Innate Immunity. 24 (2017) 40-46. https://doi.org/10.1177/1753425917741970.

[95] J. Folkerts, F. Redegeld, G. Folkerts, et al., Butyrate inhibits human mast cell activation via epigenetic regulation of FcεRI-mediated signaling, Allergy. 75 (2020) 1966-1978. https://doi.org/10.1111/all.14254.

[96] Z.Q. Liu, X.X. Li, S.Q. Qiu, et al., Vitamin D contributes to mast cell stabilization, Allergy. 72 (2017) 1184-1192. https://doi.org/10.1111/all.13110.

[97] J.M. Zingg. Vitamin E and Mast Cells. Vitamin E. 2007, p. 393-418. https://doi.org/10.1016/s0083-6729(07)76015-6.

[98] J.-W. Zhao, J.-D. Ping, Y.-F. Wang, et al., Vitamin D suppress the production of vascular endothelial growth factor in mast cell by inhibiting PI3K/Akt/p38 MAPK/HIF-1α pathway in chronic spontaneous urticaria, Clinical Immunology. 215 (2020) https://doi.org/10.1016/j.clim.2020.108444.

[99] S. Zhang, T. Zhang, K. Teng, et al., Effect of astragalus polysaccharide powder injection on the density of microvessels and mast cells in ovalbulmin-sensitized rat skin, Journal of China Agricultural University. 15 (2010) 67-71.

[100] N.R. Ngatu, M. Tanaka, M. Ikeda, et al., Sujiaonori-Derived Algal Biomaterials Inhibit Allergic Reaction in Allergen-Sensitized RBL-2H3 Cell Line and Improve Skin Health in Humans, Journal of Functional Biomaterials. 8 (2017) https://doi.org/10.3390/jfb8030037.

[101] S.-S. Xu, Q.-M. Liu, A.-F. Xiao, et al., Eucheuma cottonii Sulfated Oligosaccharides Decrease Food Allergic Responses in Animal Models by Up-regulating Regulatory T (Treg) Cells, Journal of Agricultural and Food Chemistry. 65 (2017) 3212-3222. https://doi.org/10.1021/acs.jafc.7b00389.

[102] Q.-M. Liu, Y. Yang, S.J. Maleki, et al., Anti-Food Allergic Activity of Sulfated Polysaccharide from Gracilaria lemaneiformis is Dependent on Immunosuppression and Inhibition of p38 MAPK, Journal of Agricultural and Food Chemistry. 64 (2016) 4536-4544. https://doi.org/10.1021/acs.jafc.6b01086.

[103] V. Martínez, A. Iriondo De-Hond, F. Borrelli, et al., Cannabidiol and Other Non-Psychoactive Cannabinoids for Prevention and Treatment of Gastrointestinal Disorders: Useful Nutraceuticals?, International Journal of Molecular Sciences. 21 (2020) https://doi.org/10.3390/ijms21093067.

[104] E.M.M. Quigley, Editorial: diet, inflammation and irritable bowel syndrome, Alimentary Pharmacology & Therapeutics. 45 (2017) 1278-1279. https://doi.org/10.1111/apt.14014.

[105] H. Zhu, D. Pi, W. Leng, et al., Asparagine preserves intestinal barrier function from LPS-induced injury and regulates CRF/CRFR signaling pathway, Innate Immunity. 23 (2017) 546-556. https://doi.org/10.1177/1753425917721631.

[106] S. Lechowski, K. Feilhauer, L. Staib, et al., Combined arginine and glutamine decrease release of de novo synthesized leukotrienes and expression of proinflammatory cytokines in activated human intestinal mast cells, European Journal of Nutrition. 52 (2012) 505-512. https://doi.org/10.1007/s00394-012-0353-1.

[107] R.W.E. Crozier, M. Yousef, J.M. Coish, et al., Carnosic acid inhibits secretion of allergic inflammatory mediators in IgE-activated mast cells via direct regulation of Syk activation, Journal of Biological Chemistry. 299 (2023) https://doi.org/10.1016/j.jbc.2022.102867.

[108] J.-H. Lee, J.-Y. Lim, Y.-D. Jeon, et al., Wheatgrass-and-Aronia-Mixed Extract Suppresses Immunoglobulin E-Mediated Allergic Reactions In Vitro and In Vivo, International Journal of Molecular Sciences. 24 (2023) https://doi.org/10.3390/ijms241511979.

[109] Y. Ding, Y. Wang, C. Li, et al., α-Linolenic acid attenuates pseudo-allergic reactions by inhibiting Lyn kinase activity, Phytomedicine. 80 (2021) https://doi.org/10.1016/j.phymed.2020.153391.

[110] I. Ulasov, S. Conti, A. Vexler, et al., Combined acetyl-11-keto-β-boswellic acid and radiation treatment inhibited glioblastoma tumor cells, Plos One. 13 (2018) https://doi.org/10.1371/journal.pone.0198627.

[111] A. Shadab, M. Abbasi-Kolli, E. Yazdanpanah, et al., Exploring the immune-modulating properties of boswellic acid in experimental autoimmune encephalomyelitis, Apmis. 132 (2024) 452-464. https://doi.org/10.1111/apm.13406.

[112] H.P.T. Ammon, Boswellic extracts and 11-keto-ß-boswellic acids prevent type 1 and type 2 diabetes mellitus by suppressing the expression of proinflammatory cytokines, Phytomedicine. 63 (2019) https://doi.org/10.1016/j.phymed.2019.153002.

[113] G.D. Park, Y.-H. Cheon, S.Y. Eun, et al., β-Boswellic Acid Inhibits RANKL-Induced Osteoclast Differentiation and Function by Attenuating NF-κB and Btk-PLCγ2 Signaling Pathways, Molecules. 26 (2021) https://doi.org/10.3390/molecules26092665.

[114] Y.-H. Miao, X. Wang, X.-M. Zhao, et al., Co-assembly strategies of natural plant compounds for improving their bioavailability, Food & Medicine Homology. 2 (2025) https://doi.org/10.26599/fmh.2025.9420022.

[115] W.-q. Cao, X.-q. Zhai, J.-w. Ma, et al., Natural borneol sensitizes human glioma cells to cisplatin-induced apoptosis by triggering ROS-mediated oxidative damage and regulation of MAPKs and PI3K/AKT pathway, Pharmaceutical Biology. 58 (2019) 72-79. https://doi.org/10.1080/13880209.2019.1703756.

[116] H. Hu, Study on the mechanism of triptolide inhibition on Cisplatin resistant
epithelial ovarian cancer based on the polarization of TAMs. , (2020) https://doi.org/10.27232/d.cnki.
gnchu.2020.000064.

[117] J. Guo, T. Chen, Z. Ma, et al., Oridonin inhibits 4T1 tumor growth by suppressing Treg differentiation via TGF-β receptor, International Immunopharmacology. 88 (2020) https://doi.org/10.1016/j.intimp.2020.106831.

[118] L. Xu, Y. Jiang, Y. Bi, et al., Suppression of PERK/eIF2α/CHOP pathway enhances oridonin-induced apoptosis by inhibiting autophagy in Small-Cell lung cancer cells, Biomedicine & Pharmacotherapy. 175 (2024) https://doi.org/10.1016/j.biopha.2024.116684.

[119] S. Liu, X. Wang, X. Sun, et al., Oridonin inhibits bladder cancer survival and immune escape by covalently targeting HK1, Phytomedicine. 126 (2024) https://doi.org/10.1016/j.phymed.2024.155426.

[120] S. Jin, J.-h. Park, H.J. Yun, et al., Cedrol, a Sesquiterpene Isolated from Juniperus chinensis, Inhibits Human Colorectal Tumor Growth associated through Downregulation of Minichromosome Maintenance Proteins, Journal of Cancer Prevention. 27 (2022) 221-228. https://doi.org/10.15430/jcp.2022.27.4.221.

[121] T. He, Chen, L., Cui, Y., and Luo, Y. , Effects of23-hydroxybetulinic acid on the growth of mouse colon cancer by inhibiting myeloid-derived suppressor cells., Chin. Tradit. Pat. Med. 46 (04) (2024) 1126–1134. https://doi.org/10.3969/j.issn.1001-1528.2024.04.010.

[122] P. Liu, Effective components of Pulsatilla regulate M1/M2 phenotype transformation of TAMs against colorectal cancer. , (2023) https://doi.org/10.27180/d.cnki.gjxzc.2023. 000022.

[123] Y. Cao, Y.-H. Feng, L.-W. Gao, et al., Artemisinin enhances the anti-tumor immune response in 4T1 breast cancer cells in vitro and in vivo, International Immunopharmacology. 70 (2019) 110-116. https://doi.org/10.1016/j.intimp.2019.01.041.

[124] W. Li, Effect of resveratrol on oral squamous cell carcinoma invasion and metastasis by regulating the polarization state ofTAMs., (2022) https://doi.org/10.27162/d.cnki.gjlin.2022. 003364.

[125] Z. Zhang, M. Wang, S. Xing, et al., Flavonoids of Rosa rugosa Thunb. inhibit tumor proliferation and metastasis in human hepatocellular carcinoma HepG2 cells, Food Science and Human Wellness. 11 (2022) 374-382. https://doi.org/10.1016/j.fshw.2021.11.016.

[126] H. Jiang, G.-T. Wang, Z. Wang, et al., Resveratrol inhibits pancreatic cancer proliferation and metastasis by depleting senescent tumor-associated fibroblasts, World Journal of Gastrointestinal Oncology. 16 (2024) 3980-3993. https://doi.org/10.4251/wjgo.v16.i9.3980.

[127] Z. Ma, Y. Xia, C. Hu, et al., Quercetin promotes the survival of granulocytic myeloid-derived suppressor cells via the ESR2/STAT3 signaling pathway, Biomedicine & Pharmacotherapy. 125 (2020) https://doi.org/10.1016/j.biopha.2020.109922.

[128] H. Tang, Y. Kuang, W. Wu, et al., Quercetin inhibits the metabolism of arachidonic acid by inhibiting the activity of CYP3A4, thereby inhibiting the progression of breast cancer, Molecular Medicine. 29 (2023) https://doi.org/10.1186/s10020-023-00720-8.

[129] X. Li, X. He, B. Lin, et al., Quercetin Limits Tumor Immune Escape through PDK1/CD47 Axis in Melanoma, The American Journal of Chinese Medicine. 52 (2024) 541-563. https://doi.org/10.1142/s0192415x2450023x.

[130] R.A. Baba, H.A. Mir, T.A. Mokhdomi, et al., Quercetin suppresses ROS production and migration by specifically targeting Rac1 activation in gliomas, Frontiers in Pharmacology. 15 (2024) https://doi.org/10.3389/fphar.2024.1318797.

[131] D.E.A. Komi, F.A. Redegeld, Role of Mast Cells in Shaping the Tumor Microenvironment, Clinical Reviews in Allergy & Immunology. 58 (2019) 313-325. https://doi.org/10.1007/s12016-019-08753-w.

[132] S.H. Kim, G.S. Choo, E.S. Yoo, et al., Silymarin induces inhibition of growth and apoptosis through modulation of the MAPK signaling pathway in AGS human gastric cancer cells, Oncology Reports. (2019) https://doi.org/10.3892/or.2019.7295.

[133] W. Weng, A. Goel, Curcumin and colorectal cancer: An update and current perspective on this natural medicine, Seminars in Cancer Biology. 80 (2022) 73-86. https://doi.org/10.1016/j.semcancer.2020.02.011.

[134] S. Mukherjee, J.N.E. Baidoo, A. Fried, et al., Using curcumin to turn the innate immune system against cancer, Biochemical Pharmacology. 176 (2020) https://doi.org/10.1016/j.bcp.2020.113824.

[135] R. Luo, S. Li, C. Yang, et al., Curcumin Inhibits the Development of Pancreatic Cancer by Targeting the circ_0079440/miR-522-3p/EIF4A1 Pathway, Cell Biochemistry and Biophysics. (2024) https://doi.org/10.1007/s12013-024-01466-8.

[136] H. Wei, X. Li, F. Liu, et al., Curcumin inhibits the development of colorectal cancer via regulating the USP4/LAMP3 pathway, Naunyn-Schmiedeberg's Archives of Pharmacology. 397 (2023) 1749-1762. https://doi.org/10.1007/s00210-023-02721-0.

[137] W. Deng, X. Xiong, M. Lu, et al., Curcumin suppresses colorectal tumorigenesis through restoring the gut microbiota and metabolites, BMC Cancer. 24 (2024) https://doi.org/10.1186/s12885-024-12898-z.

[138] Q. Zhang, X. Yu, L. Tian, et al., Therapeutic effects of epigallocatechin and epigallocatechin gallate on the allergic reaction of s1-casein sensitized mice, Food Science and Human Wellness. 12 (2023) 882-888. https://doi.org/10.1016/j.fshw.2022.09.018.

[139] Y. Li, Q.P. Dou, B. Li, et al., MicroRNAs as novel molecular targets of green tea polyphenol epigallocatechin-3-gallate (EGCG): relevance and importance to nutrition sciences and cancer prevention, Food Science and Human Wellness. (2024) https://doi.org/10.26599/fshw.2024.9250317.

[140] R. Shi, B. Dan, L. Lü, Bioactive effects advances of natural polysaccharides, Journal of Future Foods. 3 (2023) 234-239. https://doi.org/10.1016/j.jfutfo.2023.02.005.

[141] Y. Wu, Q. Wang, H. Liu, et al., A heteropolysaccharide from Rhodiola rosea L.: preparation, purification and anti-tumor activities in H22-bearing mice, Food Science and Human Wellness. 12 (2023) 536-545. https://doi.org/10.1016/j.fshw.2022.07.056.

[142] Y. Qian, C. Shi, C. Cheng, et al., Ginger polysaccharide UGP1 suppressed human colon cancer growth via p53, Bax/Bcl-2, caspase-3 pathways and immunomodulation, Food Science and Human Wellness. 12 (2023) 467-476. https://doi.org/10.1016/j.fshw.2022.07.048.

[143] M. Shen, Y.-j. Wang, Z.-h. Liu, et al., Inhibitory Effect of Astragalus Polysaccharide on Premetastatic Niche of Lung Cancer through the S1PR1-STAT3 Signaling Pathway, Evidence-Based Complementary and Alternative Medicine. 2023 (2023) https://doi.org/10.1155/2023/4010797.

[144] Q. Peng, Y. Yu, L. Ye, et al., Astragalus polysaccharides sensitize ovarian cancer stem cells to PARPi by inhibiting mitophagy via PINK1/Parkin signaling, iScience. 27 (2024) https://doi.org/10.1016/j.isci.2024.110376.

[145] B. Zuo, Mechanism of Astragalus polysaccharides and Glycyrrhiza polysaccharide inducing regulatory T cell differentiation to anti-tumor cell HCT-116., (2019) https://doi.org/10.27286/d.cnki.gsxzy.2019.000019.

[146] M. Sun, R. Bu, B. Zhang, et al., Lentinan Inhibits Tumor Progression by Immunomodulation in a Mouse Model of Bladder Cancer, Integrative Cancer Therapies. 19 (2020) https://doi.org/10.1177/1534735420946823.

[147] Z. Yin, D. Sun-Waterhouse, J. Wang, et al., Polysaccharides from edible fungi Pleurotus spp.: advances and perspectives, Journal of Future Foods. 1 (2021) 128-140. https://doi.org/10.1016/j.jfutfo.2022.01.002.

[148] S. Deng, G. Zhang, J. Kuai, et al., Lentinan inhibits tumor angiogenesis via interferon γ and in a T cell independent manner, Journal of Experimental & Clinical Cancer Research. 37 (2018) https://doi.org/10.1186/s13046-018-0932-y.

[149] J. Zhang, J. Cui, J. Gao, et al., Polysaccharides of Plantago asiatica enhance antitumor activity via regulating macrophages to M1-like phenotype, Biomedicine & Pharmacotherapy. 159 (2023) https://doi.org/10.1016/j.biopha.2023.114246.

[150] B. Zuo, Mechanism of Astragalus polysaccharides and Glycyrrhiza polysaccharide inducing regulatory T cell differentiation to anti-tumor cell HCT-116. , (2019) https://doi.org/10.27286/d.cnki.gsxzy.2019.000019.

[151] Y. Wang, X. Fan, X. Wu, Ganoderma lucidum polysaccharide (GLP) enhances antitumor immune response by regulating differentiation and inhibition of MDSCs via a CARD9-NF-κB-IDO pathway, Bioscience Reports. 40 (2020) https://doi.org/10.1042/bsr20201170.

[152] A. Li, X. Shuai, Z. Jia, et al., Ganoderma lucidum polysaccharide extract inhibits hepatocellular carcinoma growth by downregulating regulatory T cells accumulation and function by inducing microRNA-125b, Journal of Translational Medicine. 13 (2015) https://doi.org/10.1186/s12967-015-0465-5.

[153] L. Xia, M. Yang, Y. Liu, Portulaca oleracea L. polysaccharide inhibits ovarian cancer via inducing ACSL4-dependent ferroptosis, Aging. 16 (2024) 5108-5122. https://doi.org/10.18632/aging.205608.

[154] X. Li, Q. Ruan, W. Yang, et al., Polysaccharide isolated from Grifola frondosa eliminates myeloid-derived suppressor cells and inhibits tumor growth by enhancing T cells responses, International Journal of Biological Sciences. 20 (2024) 664-679. https://doi.org/10.7150/ijbs.85276.

[155] W. Liu, N. Li, J. Hou, et al., Structure and antitumor activity of a polysaccharide from Rosa roxburghii, International Journal of Biological Macromolecules. 273 (2024) https://doi.org/10.1016/j.ijbiomac.2024.132807.

[156] C.M. Tsang, Y.C. Cheung, V.W.-Y. Lui, et al., Berberine suppresses tumorigenicity and growth of nasopharyngeal carcinoma cells by inhibiting STAT3 activation induced by tumor associated fibroblasts, BMC Cancer. 13 (2013) https://doi.org/10.1186/1471-2407-13-619.

[157] D. Li, Y. Zhang, K. Liu, et al., Berberine inhibits colitis-associated tumorigenesis via suppressing inflammatory responses and the consequent EGFR signaling-involved tumor cell growth, Laboratory Investigation. 97 (2017) 1343-1353. https://doi.org/10.1038/labinvest.2017.71.

[158] B. Li, Y. Luo, Y. Zhou, et al., Role of sanguinarine in regulating immunosuppression in a Lewis lung cancer mouse model, International Immunopharmacology. 110 (2022) https://doi.org/10.1016/j.intimp.2022.108964.

[159] L. Li, J. Nong, J. Li, et al., Dendrobine Suppresses Tumor Growth by Regulating the PD-1/PD-L1 Checkpoint Pathway in Lung Cancer, Current Cancer Drug Targets. 24 (2024) https://doi.org/10.2174/0115680096305416240820040314.

[160] J.P. Gusson-Zanetoni, L.P. Cardoso, S.O. de Sousa, et al., Molecular Aspects of Piperine in Signaling Pathways Associated with Inflammation in Head and Neck Cancer, International Journal of Molecular Sciences. 25 (2024) https://doi.org/10.3390/ijms25115762.

[161] J. Gao, Y. Ying, J. Wang, et al., Solanine Inhibits Immune Escape Mediated by Hepatoma Treg Cells via the TGFβ/Smad Signaling Pathway, BioMed Research International. 2020 (2020) 1-10. https://doi.org/10.1155/2020/9749631.

[162] L. Feng, R.-R. Shang, X.-J. Wang, et al., The Natural Alkaloid (−)-N-Hydroxyapiosporamide Suppresses Colorectal Tumor Progression as an NF-κB Pathway Inhibitor by Targeting the TAK1–TRAF6 Complex, Journal of Natural Products. 86 (2023) 1449-1462. https://doi.org/10.1021/acs.jnatprod.3c00125.

[163] S. Iwanowycz, J. Wang, D. Altomare, et al., Emodin Bidirectionally Modulates Macrophage Polarization and Epigenetically Regulates Macrophage Memory, Journal of Biological Chemistry. 291 (2016) 11491-11503. https://doi.org/10.1074/jbc.M115.702092.

[164] Q. Liu, J. Hodge, J. Wang, et al., Emodin reduces Breast Cancer Lung Metastasis by suppressing Macrophage-induced Breast Cancer Cell Epithelial-mesenchymal transition and Cancer Stem Cell formation, Theranostics. 10 (2020) 8365-8381. https://doi.org/10.7150/thno.45395.

[165] J.C. Boulos, M. Rahama, M.-E.F. Hegazy, et al., Shikonin derivatives for cancer prevention and therapy, Cancer Letters. 459 (2019) 248-267. https://doi.org/10.1016/j.canlet.2019.04.033.

[166] T.-J. Lin, H.-T. Lin, W.-T. Chang, et al., Shikonin-enhanced cell immunogenicity of tumor vaccine is mediated by the differential effects of DAMP components, Molecular Cancer. 14 (2015) https://doi.org/10.1186/s12943-015-0435-9.

[167] X. Meng, L. Cheng, J. Jiao, et al., Total Glucosides of Paeony Induce Mitochondrial Dysfunction and Apoptosis by Promoting the Degradation of α5-nAChR in Melanoma Cells, Combinatorial Chemistry & High Throughput Screening. 27 (2024) https://doi.org/10.2174/0113862073271585231129172213.

[168] S.S. Song, P.F. Yuan, P.P. Li, et al., Protective Effects ofTotal Glucosides of Paeonyon N-nitrosodiethylamine-induced Hepatocellular Carcinoma in Rats via Down-regulation of Regulatory B Cells, Immunological Investigations. 44 (2015) 521-535. https://doi.org/10.3109/08820139.2015.1043668.

[169] Q. Sun, Dioscin induced tumor-associated-macrophages from M2 type to M1 type and its mechanism via Cx43, (2022) https://doi.org/10.27441/d.cnki.gyzdu.2022.001177.

[170] X. Liu, P. Zhou, K. He, et al., Dioscorea Zingiberensis New Saponin Inhibits the Growth of Hepatocellular Carcinoma by Suppressing the Expression of Long Non-coding RNA TCONS-00026762, Frontiers in Pharmacology. 12 (2021) https://doi.org/10.3389/fphar.2021.678620.

[171] M. Guo, Y. Ying, Y. Chen, et al., Asiaticoside inhibits breast cancer progression and tumor angiogenesis via YAP1/VEGFA signal pathway, Heliyon. 10 (2024) https://doi.org/10.1016/j.heliyon.2024.e37169.

[172] H. Liu, T. Xie, Y. Liu, Ginsenoside Rg3 inhibits the malignant progression of cervical cancer cell by regulating AKT2 expression, Heliyon. 9 (2023) https://doi.org/10.1016/j.heliyon.2023.e19045.

[173] Q. Ying, J. Lou, D. Zheng, Ginsenoside Rh4 inhibits the malignant progression of multiple myeloma and induces ferroptosis by regulating SIRT2, Clinical and Experimental Pharmacology and Physiology. 50 (2023) 757-765. https://doi.org/10.1111/1440-1681.13805.

[174] Z. Wen, T. Liu, Y. Zhang, et al., Salidroside regulates tumor microenvironment of non-small cell lung cancer via Hsp70/Stub1/Foxp3 pathway in Tregs, BMC Cancer. 23 (2023) https://doi.org/10.1186/s12885-023-11036-5.

[175] Y. Ohnishi, T. Sakamoto, L. Zhengguang, et al., Curcumin inhibits epithelial-mesenchymal transition in oral cancer cells via c-Met blockade, Oncology Letters. (2020) https://doi.org/10.3892/ol.2020.11523.

[176] X. Chen, B. Liu, J. Tong, et al., Chlorogenic Acid Inhibits Proliferation, Migration and Invasion of Pancreatic Cancer Cells via AKT/GSK-3β/β-catenin Signaling Pathway, Recent Patents on Anti-Cancer Drug Discovery. 19 (2024) 146-153. https://doi.org/10.2174/1574892818666230327134746.

[177] G. Wang, Z. Hu, Q. Fu, et al., Resveratrol mitigates lipopolysaccharide-mediated acute inflammation in rats by inhibiting the TLR4/NF-κBp65/MAPKs signaling cascade, Scientific Reports. 7 (2017) https://doi.org/10.1038/srep45006.

[178] S. Bi, W. Huang, S. Chen, et al., Cordyceps militaris polysaccharide converts immunosuppressive macrophages into M1-like phenotype and activates T lymphocytes by inhibiting the PD-L1/PD-1 axis between TAMs and T lymphocytes, International Journal of Biological Macromolecules. 150 (2020) 261-280. https://doi.org/10.1016/j.ijbiomac.2020.02.050.

[179] L.F. Zhang H, Liu E H, Resource, Chemical Structure and Immunomodulatory Activity of Natural Polysaccharides, Hans Journal of Medicinal Chemistry. 12 (2024) 227-238. https://doi.org/10.12677/hjmce.2024.123026.

[180] L. Zhou, Y. Hu, C. Gao, et al., Identification of novel targets and mechanisms of wogonin on lung cancer, bladder cancer, and colon cancer, Journal of Future Foods. 4 (2024) 267-279. https://doi.org/10.1016/j.jfutfo.2023.07.009.