Chapter

Targeting Tumor-Associated Macrophages by Plant Compounds

Alice Grigore

Abstract

Macrophages play an important role in cancer development, as they represent almost half of the cells forming the tumor microenvironment. They are called tumor-associated macrophages (TAMs) and most of them are alternative activated macrophages (M2 polarized), promoting cancer progression, angiogenesis and local immunosuppression. Blocking the macrophages recruitment, preventing their activation or turning M2 cells toward M1 phenotype (classic activated macrophage promoting an efficient immune response) is a modern immunotherapeutic approach for fighting cancer. Several studies showed that plant compounds (phenolics, triterpenes, coumarins, etc.) exert antitumor properties, not only by a direct toxical effect to malignant cells but also by influencing macrophage phenotypic differentiation.

Keywords: macrophage polarization, phenolic compounds, saponins, polysaccharides, coumarins, anthraquinones, alkaloids, tumor microenvironment

1. Introduction

Macrophages represent up to 50% of the cells infiltrating into the tumor microenvironment (TME) and modulation of macrophage polarization is an interesting and novel therapeutic approach in preclinical or clinical cancer research.

An increasing number of studies have also shown that tumor-associated macrophages (TAMs) can antagonize, augment or mediate the antitumor effects of cytotoxic agents, tumor irradiation, anti-angiogenic/vascular damaging agents and checkpoint inhibitors [1].

In the tumor microenvironment, TAMs are one of the major contributors in angiogenesis by secreting pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), adrenomedullin (ADM), platelet-derived growth factor (PDGF), tumor growth factor-beta (TGF-β) and matrix metalloproteinases (MMPs). Also, TAMs promote tumor cell invasion and metastasis by modifying the composition of extracellular matrix and cell-cell junctions and promoting basal membrane disruption. It was demonstrated that macrophages facilitate the metastasis by enhancing the ability of cancer cells to enter a local blood vessel and also are involved in immunosuppression by inhibiting the T-cell response or by secreting immunosuppressive cytokines and proteases such as IL-10, TGF-β, arginase-1 and prostaglandins, which inhibit T-cell activation and proliferation [2].
TAMs often exhibit an array of activation states. In general, they are skewed away from the “classically” activated, tumoricidal phenotype (sometimes referred to as M1) toward an “alternatively” activated tumor-promoting one (M2) [1]. The classically activated M1 macrophages are stimulated by microbial substrates such as lipopolysaccharide, Toll-like receptor ligands and cytokines such as IFN-γ. They are characterized by secretion of pro-inflammatory cytokines such as interleukins IL-6, IL-12, IL-23 and TNF-α and express high levels of major histocompatibility complex class II (MHC-II), CD68, and CD80 and CD86 costimulatory molecules. The alternatively activated M2 macrophages are stimulated by IL-4 and IL-13, secrete IL-10 and TGF-β and express low levels of MHC-II and feature expression of CD163 and CD206 [3].

Unfortunately, M2 cells are the most representative cells of the TAM population within the tumor promoting genetic instability, local immunosuppression and stem cell nurturing [4] and providing essential support for a malignant phenotype [5].

In the early stages of cancers of the lung, colon and stomach, the macrophages in the normoxic milieu display an M1 phenotype and are associated with good prognosis, but within avascular areas of the tumor, TAMs alter the gene expression profile, favoring a protumor M2 phenotype, correlated with a bad prognosis [6]. In Table 1 are showed recent conclusions concerning the correlation between TAMs and clinical prognostics in several tumor types. In human breast carcinomas, high TAM density is also associated with poor prognosis [7]. TAMs in renal cell carcinoma show a mixed M1/M2 phenotype. CD68 alone has a poor predictive value, while low CD11+ and high CD206+ as single variables correlated with reduced survival [8]. There is strong evidence for an inverse relationship between TAM density and clinical prognosis in solid tumors of the breast, prostate, ovary and cervix. Type I and II endometrial carcinomas had significantly higher macrophage density in both epithelial and stromal compartments than benign endometrium [9]. Type II cancers have nearly twice the TAM density of type 1 cancers and this difference may be due to M1 macrophage predominance in the stroma of type II cancers [10].

TAMs’ distribution pattern could be an independent prognostic factor for the overall survival of gastric cancer patients, invasive front-/stroma-dominant pattern having worse outcomes [11]. Studies have shown that the amount of TAMs in tumor stroma predicts the size, stage and metastasis of the gastric tumor [12]. In lung cancer, M2 subset and TAMs in tumor stroma were associated with worse survival, while M1 subset and TAMs in tumor islet were associated with favorable survival of lung cancer [13].

While most cancer research has focused upon these changes and most therapeutics are directed against these tumor cells, it is now apparent that the non-malignant cells in the microenvironment evolve along with the tumor and provide essential support for their malignant phenotype [5]. The knowledge of TAM activation status may allow the therapeutic targeting of TAMs, once TAMs’ targeting/modulating agents pass clinical trials and become widely available [6, 29]. The role of macrophages in tumor progression remains to be fully elucidated, in part due to the contrasting roles they play depending on their polarization [30]. Both the systemic and local environments play a tumor-initiating role through the generation of persistent inflammatory responses to a variety of stimuli [31]. To support this correlative data between macrophage-mediated inflammation and cancer induction, genetic ablation of the anti-inflammatory transcription factor STAT3 in macrophages results in a chronic inflammatory response in the colon that is sufficient to induce invasive adenocarcinoma. However, it is unclear whether macrophages in some inflammatory situations can kill aberrant cells before they become tumorigenic and thus be antitumoral [32].
| Cancer type         | TAMs as prognostic factors                                                                                                                                                                                                                                                                                                                                 | Reference |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Breast             | CD68 as a biomarker for TAMs to evaluate the risk is better than CD163 or CD206 alone; high infiltration of TAMs was significantly associated with negative hormone receptor status and malignant phenotype                                                                                                                                                   | [14]      |
| Gastric            | The amount of TAMs in tumor stroma predicts the size, stage and metastasis of the gastric tumor Invasive front-/stroma-dominant pattern having worse outcomes Although CD68+ TAMs infiltration has the neutral prognostic effects on OS, the M1/M2 polarization of TAMs are predicative factors of prognosis in gastric cancer patients | [11, 12, 15] |
| Lung               | The prognostic value of tumor-infiltrating TAMs in lung cancer is still controversial. M2 subset and TAMs in tumor stroma were associated with worse survival, while M1 subset and TAMs in tumor islet were associated with favorable survival of lung cancer. CD204-positive TAMs are the preferable marker for prognostic prediction in NSCLC Although the density of total CD68+ TAMs is not associated with overall survival, the localization and M1/M2 polarization of TAMs are potential prognostic predictors of NSCLC | [13, 16, 17] |
| Cervix             | Tumor-infiltrating CD204+ M2 macrophages may predict poor prognosis in patients with cervical adenocarcinoma                                                                                                                                                                                                                                             | [18]      |
| Ovarian            | CD163+ TAM infiltration was associated with poor prognosis of ovarian cancer and high M1/M2 macrophage ratio in tumor tissues predicted better prognosis                                                                                                                                                                                                   | [19]      |
| Pancreatic         | Although TAM populations in tumor stroma are high, marking them as a probable prognostic factor, the multiple roles that TAMs play in pancreatic cancer progression have not yet been delineated. Additional mechanistic insight into the pathways that regulate the differentiation of TAMs from monocytes is required The density of TAMs has an impact on the overall survival of pancreatic cancer patients. M2-TAMs can be recognized as a prognostic indicator in pancreatic cancer | [20, 21] |
| Renal              | CD68 alone has a poor predictive value, while low CD11+ and high CD206+ as single variables correlated with reduced survival                                                                                                                                                                                                                               | [8]       |
| Glioblastoma       | TAM, accounting for approximately 30% of the GBM bulk cell population, may explain, at least in part, the immunosuppressive features of GBMs                                                                                                                                                                                                                       | [22]      |
| Hepatocellular carcinoma | The prognostic value of TAMs in patients with hepatocellular carcinoma (HCC) is still controversial. TAMs could serve as independent predictive indicators and therapeutic targets for HCC. Further trials are needed to elucidate the exact relationship and the underlying mechanism  | [23]      |
| Melanoma           | Independent of their intratumoral distribution, the prevalent accumulation of M2 TAMs in MM is statistically confirmed to be a poor indicator of patients’ outcome                                                                                                                                                                                                 | [24]      |
| Non-Hodgkin’s lymphoma | High-density CD68+ and CD163+ TAMs, and also high CD163+/CD68+ TAMs ratio is significantly correlated with poor overall survival                                                                                                                                                                                                                           | [25]      |
| Hodgkin’s lymphoma | High density of either CD68+ or CD163+ TAMs is a robust predictor of adverse outcomes in adult cHL                                                                                                                                                                                                                                                             | [26]      |
| Colorectal (CRC)   | The role of tumor-associated macrophages (TAMs) in predicting the prognosis of CRC remains controversial. Still, high-density CD68+ macrophage infiltration can be a good prognostic marker                                                                                                                                                                                                 | [27]      |
| Squamous cell carcinoma of the head and neck (SCCHN) | CD68+ marker has no prognostic utility in patients with SCCHN; the M2-like marker CD163+ predicts poor prognosis                                                                                                                                                                                                                                          | [28]      |

Table 1. TAMs as potential predictive indicators in several tumor types.
Targeting a single signaling axis that promotes the immunosuppressive and protumoral functions of macrophages is inadequate as there are multiple signals involved in the communication between tumor cells and TAMs. Identifying and inhibiting key driver pathways, which are critical for both cancer cell survival and TAM activation, may offer therapeutic advantages as they disrupt the vicious positive feedback loop between tumor and TAMs [33]. Prevention of TAM accumulation and reduction of TAM presence by depleting existing TAMs represent novel strategies for an indirect cancer therapy specifically aimed at tumor-promoting cells within the microenvironment, but the challenge with this approach is to find ways for local administration of such drugs to the tumor [30]. Targeting TAM polarity toward an M1 phenotype also became a real immunotherapeutical approach in cancer, recalling responses from both innate and adaptive immune systems, leading to tumor regression [4].

Triple combination of anti-CTLA-4, anti-PD-1 and G47Δ-MLL12 was associated with macrophage influx and M1-like polarization in two glioma models [34]. A combination of a bivalent ganglioside and β-glucan, a yeast-derived polysaccharide, able to differentiate TAMs into an M1 phenotype is currently under investigation in a phase I clinical trial of patients with neuroblastoma [35]. Vadimezan, a fused tricyclic analog of flavone acetic acid, was found to repolarize macrophages in M1 phenotype, and it has been the subject of numerous preclinical studies and clinical trials [36]. Zoledronic acid, a clinical drug for cancer therapy, has been found to inhibit spontaneous mammary carcinogenesis by reverting macrophages from the M2 phenotype to the M1 phenotype [37].

2. Herbal compounds in TAM modulation

Research to date suggests that, despite the potency of cytotoxic anticancer agents and the high specificity that can be achieved by immunotherapy, neither of these two types of treatment is sufficient to eradicate the disease. Moreover, even in standard chemotherapy, there has been efficiency through the introduction into current practice of treatments with combinations of drugs [38]. In general, literature data show that the combination of conventional treatment with natural compounds exerts an additive effect caused by the alternative activation of signaling pathways that induce cell death or increase the activity of the chemotherapeutic agent. The involvement of these natural compounds (alone or in combination therapy) in the immunobiology of cancer is a branch that has not yet been studied but offers major therapeutic opportunities. Herbal compounds have many regulatory effects on macrophage polarization, but the specific mechanisms, signaling pathways and target genes involved remain incompletely understood [39]. Their effects, according to recent research studies, are summarized in Figure 1.

Although natural products have historically been a critical source for therapeutic drugs, sometimes natural molecules may suffer from insufficient efficacy, unacceptable pharmacokinetic properties, undesirable toxicity or reduced availability, which impedes their direct therapeutic application. Poor availability of some natural compounds, despite their pharmacological effects, limits their clinical application. In recent years, there has been an increased interest in developing nanoformulations with increased bioavailability and fewer side effects. For instance, TAM-rich tumors, due to their enhanced permeability, demonstrated an elevated retention (>700%) of the nanotherapeutic (poly(l-lactic-co-glycolic acid)-b-poly(ethylene glycol) (PLGA-PEG)), as compared to TAM-deficient tumors [29].
2.1 Saponins

Triterpenic compounds, including corosolic acid, tigogenin, timosaponin AIII, neoadsipidistrin and oleanolic acid, suppress the CD163 expression. Corosolic and oleanolic acids change M2 polarization to M1 polarization in human monocyte-derived macrophages (HMDMs) by suppressing STAT3 and NF-kB activation. The effects of these two compounds were exerted not only on macrophages but also on glioblastoma cells, suppressing tumor cell proliferation and sensitizing tumor cells to anticancer drugs [40, 41].

M2 polarization was switched also by astragaloside IV (AS-IV, 3-O-β-D-xylopyranosyl-6-O-β-D-glucopyranosyl cycloastragenol), a natural saponin extracted from Astragali radix, by modulating the AMPK signaling pathway. In the intravenous lung cancer model, AS-IV treatment did not alter the percentage of macrophages but did significantly reduce the number of M2 macrophages [42]. In another study, G-Rh2, a monomeric compound extracted from Panax ginseng C. A.
Macrophages

Mey (ginseng), converts the differentiation of macrophages from M2 to M1 phenotype resulting in the decreased levels of MMPs and VEGF. By blocking the PI3K-Akt signaling pathway, the compound prevented the metastasis of lung cancer (NSCLC) cells [43]. Recently, a novel EV-liked ginseng-derived nanoparticle (GDNP) was tested in melanoma, and it altered M2 polarization both in vitro and in vivo, depending on TLR4 and MyD88 signaling and contributing to an antitumor response [44].

A potential role of celastrol, a pentacyclic triterpenoid in antimetastasis treatment, was suggested by Yang et al. [45], which found that this compound suppresses M2-like polarization by interfering with STAT6 signaling pathway after stimulation with IL-13. An active role in decreasing macrophage recruitment and tumor angiogenesis was showed for lupeol and stigmasterol in an in vivo model [46].

2.2 Alkaloids

Treatment with 9-hydroxycanthin-6-one, a β-carboline alkaloid isolated from the Ailanthus altissima stem bark, inhibited the levels of M2 phenotype markers and some cancer-promoting factors, such as MMP-2, MMP-9 and VEGF, in macrophages educated in ovarian cancer–conditioned medium. The compound also decreased the expressions of MCP-1 and RANTES, major determinants of macrophage recruitment at tumor sites, in ovarian cancer cells [47].

A regulatory effect on macrophage differentiation during tumor development exerts phlenumdines E, A, hupermine A and 12-epi-lycopodine-N-oxide isolated from the club moss Phlegmariurus nummulariifolius (Blume) Ching, which exhibited an inhibitory effect on IL-10–induced expression of CD163, an M2 phenotype marker, in HMDMs [48].

Sophoridine, a bioactive alkaloid extracted from the seeds of Sophora alopecuroides L, was able to reshape gastric cancer immune microenvironment by shifting TAM polarization to M1 and suppressing M2-TAM polarization through TLR4/IRF3 axis [49].

2.3 Phenolic compounds

2.3.1 Chalcones

In a model of azoxymethane (AOM)/dextran sodium sulfate (DSS)-induced colitis-associated tumorigenesis, it was showed that isoliquiritigenin (6′-deoxychalcone) inhibits M2 macrophage polarization depending on the downregulation of the IL-6/STAT3 pathway [50]. The same mechanism was proposed by Sumiyoshi et al. [51], for xanthoangelol and 4-hydroxyderricin, chalcones isolated from Angelica keiskei roots. In the in vivo study, the antitumor action of xanthoangelol was higher than that of 4-hydroxyderricin and it was proposed that the presence of a 4-free phenolic OH and/or the presence of a longer isoprene moiety in C-3 could be the cause of better activity of xanthoangelol. Reducing breast cancer cells’ migration with the aid of M2 macrophages was achieved in vitro by the total flavonoid from Glycyrrhizae Radix et Rhizoma and isoliquiritigenin. These compounds inhibited gene and protein expression of Arg-1, upregulated gene of HO-1 and protein expression of iNOS, and enhanced the expression of microRNA 155 and its target gene SHIP1 [52].

2.3.2 Catechins

Macrophage infiltration and differentiation of macrophages into tumor-promoting M2 macrophage were decreased by epigallocatechin gallate (EGCG) treatment in murine tumor models and the molecular mechanism proposed was
the downregulation of NF-κB pathway [53, 54]. EGCG can be rapidly degraded in vivo limiting its clinical application. A peracetate-protected EGCG (Pro-EGCG) synthesized by modification of the reactive hydroxyl groups with peracetate groups proved six times more stability than EGCG and showed greater efficacy in induction of cell death in leukemic cells. Treatment with Pro-EGCG inhibits differentiation of macrophages toward TAMs through decreasing CXCL12 expression in endometrial stromal cells with no influence on the expression level of CD163 and CD206 [55].

2.3.3 Flavonoids

Luteolin, 3,0,4,0,5,7-tetrahydroxyflavone, is a common flavonoid derived from various plants and inhibits IL-4–induced phosphorylation of STAT6 and the TAM phenotype, ameliorating the recruitment of monocytes and the migration of lung cancer cells by the reduction of chemokine CCL2 secretion from macrophages [56]. The antitumor mechanism of luteolin in non-small cell lung carcinoma (NSCLC) was mediated by downregulation of TAM receptor tyrosine kinases (RTKs), and it was found to decrease the protein levels of all three TAM RTKs in the A549 and A549/CisR cells in a dose-dependent manner [57]. In an in vitro tumor model, cobalt chloride (CoCl2) was used to simulate hypoxia and it was showed that luteolin decreased the expression of VEGF and MMP-9, which promote angiogenesis. In addition, luteolin also suppressed the activation of HIF-1 and phosphorylated-signal transducer and activator of STAT3 signaling, particularly within the M2-like TAMs [58].

The regulation of M2 macrophage repolarization through inhibiting PI3K/Akt signal pathway is the mechanism proposed for baicalein (5,6,7-trihydroxyflavone), a widely used Chinese herbal medicine derived from the root of Scutellaria baicalensis. Changing the phenotype of macrophages from M2 to M1 was supported by decreasing of M2-specific marker CD206 correlated to the increased M1-specific marker CD86. Still, the authors of the study suggested that the cytotoxic effect of baicalein on breast cancer cells directly is more pronounced than on TAMs (IC 50 of baicalein for MDA-MB-231 at 24 h, 48 h and 72 h was 79.12/50.10/34.77 μmol/L, for MCF-7 at 24 h, 48 h and 72 h was 49.76/43.73/39.44 μmol/L, for TAM at 24 h, 48 h and 72 h was 191.5/107.1/41.78 μmol/L, respectively) [59].

It has been reported that a novel chrysin (5,7-dihydroxyflavone) analog 8-bromo-7-methoxychrysin has anticancer activities with more potent bioactivity than the lead compound [60]. It also has the capacity to regulate the tumor microenvironment by inhibition of NF-κB activation, suppressing significantly the expression of the M2 macrophage marker CD163 and modulating the secretion profile of TAM cytokines [61].

According to traditional Chinese medicine (TCM) theory, herbs with Qi-tonifying character are involved in improving the defense capacity of immune system. Total flavonoids from Glycyrrhizae Radix et Rhizoma significantly inhibited the expression of Arg-1 (above 90% at 100 μg/mL), one of the phenotype markers of M2 macrophages, and suppressed M2 polarization of macrophages partly by inactivating STAT6 pathway. The regulation of M1 and M2 markers’ expressions was partly due to the enhancement of miR-155 levels [62].

Naringin (4′,5,7-trihydroxyflavanone-7-rhamnoglucoside) exert a potential inhibitory effect on tumor progression by inducing CD169-positive and M1-like macrophages, potentially correlating with cytotoxic T-cell activation [63].

2.3.4 Isoflavones

Puerarin [4H-1-benzopyran-4-one, 8-β-D-glucopyranosyl-7-hydroxy-3-(4-hydroxyphenyl)] is the major bioactive ingredient isolated from the root of
Macrophages

traditional Chinese medicine Ge-gen (*Radix Puerariae*) able to suppress the cell invasion and migration probably through inactivating MEK/ERK 1/2 pathway in a model of NSCLC. Also, it was showed that puerarin acts directly on macrophages by increasing M1 macrophage markers (CD197+, iNOS+ and CD40+) and reducing the expression of M2 markers (CD206+, Arg-1+ and CD163+) [64].

Another isoflavone, genistein, can inhibit the increased M2 polarization of macrophages and stemness of ovarian cancer cells by co-culture of macrophages with ovarian cancer stem-like cells through disrupting IL-8/STAT3 signaling axis [65].

### 2.3.5 Phenolic acids

Chlorogenic acid (5-caffeoylquinic acid, CA), the ester of caffeic acid, is a phenolic compound widely found in plants. It was showed that this compound inhibits growth of G422 glioma *in vivo*, an effect associated with a decrease of M2-like TAMs and recruitment of M1-like TAMs into tumor tissue. Low dose (1 μM) of CA could significantly inhibit the M2 macrophage-induced proliferation of glioma and breast cancer cells, mainly via STAT1 and STAT6 signaling pathways [66]. Oršolić et al. [67] concluded that the antitumor activity of CA is the result of the synergistic activities of different mechanisms by which CA acts on proliferation, angiogenesis, immunomodulation and survival. Mice with Ehrlich ascites tumor (EAT) and treated for 10 days with CA in a dose of 40 and/or 80 mg kg⁻¹ showed an increase of the cytotoxic actions of M1 macrophages and inhibition of the tumor growth, probably mediated through its antioxidative activity.

### 2.3.6 Lignans

Deoxyschizandrin, a major dibenzocyclooctadiene lignan present in *Schisandra chinensis* berries, significantly suppressed CD163 and CD209 expression, inhibiting protumor mediator production as well as M2 polarization in TAM macrophages stimulated by the conditioned medium of A2780 cells [68].

### 2.3.7 Other phenolic compounds

Several studies focused on a stilbene derivative, resveratrol (3,4′,5-trihydroxystilbene), a widely studied compound that exhibits potent preventive effects on lifestyle-related disorders such as hyperlipidemia, obesity, coronary heart disease and cancer, as well as on aging. In lung cancer tumors, resveratrol induced their sluggish growth by decreasing F4/80 positive expressing cells and M2 polarization (lower expression of M2 markers-IL-10, Arg-1 and CD206), probably by STAT3 suppression [69]. Antitumor and antimetastatic effects of resveratrol (25 and 50 μM) based on the regulation of M2 macrophage activation and differentiation were confirmed by Kimura and Sumiyoshi [70], which also conducted a study for correlation of stilbene structure with biological activity. Among the nine stilbenes examined, 2,3-,3,4-, and 4,4′-dihydroxystilbene inhibited the production of MCP-1 in M2-polarized THP-1 macrophages at a concentration of 50 μM, demonstrating that the inhibitory effects of stilbenes with dihydroxy groups on the production of MCP-1 were greater than those with mono-hydroxy groups. Dihydroxystilbene at 25 and 50 μM, 3,4-dihydroxystilbene at 50 μM, and 4,4′-dihydroxystilbene at 10, 25 and 50 μM significantly inhibited the production of IL-10 by M2 THP-1 macrophages. The three dihydroxystilbenes, 2,3-, 3,4-, and 4,4′-dihydroxystilbenes, at concentrations of 10–50 μM inhibited p-STAT3 increase during M2 THP-1 macrophage differentiation induced by IL-4 plus IL-13 [71].
The resveratrol analogue, HS-1793 (4-(6-hydroxy-2-naphthyl)-1,3-benzenediol), was also shown to elevate the level of IFN-γ production conducting reprogramming of TAMs M2 phenotype [72].

Curcumin ((1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione), a natural phenol and the main active ingredient in turmeric, acts in several ways as a suppressor of macrophage functions. Even though curcumin has previously received considerable attention from researchers as an anti-inflammatory agent, it has a promising future in the area of immunomodulation [73]. Most of the studies on curcumin focused on the anti-inflammatory effect, promoting the conversion of macrophages from M1 to an anti-inflammatory and protective M2 phenotype [73]. Gao et al. [74] demonstrated that curcumin plays a key role in M2 polarization in two ways: (1) via the inhibition of DNA methyltransferase3b (DNMT3b), overexpression of which can promote increased M1 polarization, and (2) via increased phosphorylation of signal transducer and activator of transcription STAT-6, an important transcription factor activated by IL-4 and IL-10. Other studies showed that curcumin also induces TAMs re-polarization from tumor-promoting M2 phenotype toward the more antitumor M1 phenotype in tumor-bearing hosts, mediated by inhibition of STAT3 activity [75]. Curcumin administration and delivery to glioblastoma brain tumors (GBM) caused a dramatic re-polarization of TAMs from an M2 to M1 phenotype and tumor remission in 50–60% of GBM-bearing mice [76]. Hydrazinocurcumin, a synthetic analog of curcumin encapsulated within nanoparticles, reeducates TAMs to an M1-like phenotype IL-10 low IL-12 high TGF-β low [54].

It was showed that TriCurin, a synergistic formulation of curcumin, resveratrol, and epicatechin gallate (molar ratio C:R: 4:1:12.5) can shift TAM polarity in HPV-positive HNSCC by silencing the M2 TAM and activating/recruiting a discrete population of M1 TAM while maintaining a constant number of overall intra-tumor Iba1+ TAM, along with expression of activated STAT3 and induction of activated STAT1 and NF-kB (p65) [77]. Moreover, a liposomal formulation of TriCurin with increased bioavailability (TrLp) was able to cause repolarization of M2-like tumor (GBM)-associated microglia/macrophages to the tumoricidal M1-like phenotype and intra-GBM recruitment of activated natural killer cells [78].

In a urethane-induced lung carcinogenic model, lung carcinogenesis was ameliorated with increased M1 macrophages and decreased M2 macrophages in the lung interstitial by administration of 6-gingerol ((S)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone), the main bioactive component in ginger (Zingiber officinale Roscoe). M2 macrophage-resetting efficacy of 6-gingerol was confirmed in a Lewis lung cancer allograft model and the mechanism proposed was the reduction of Arg-1 and ROS levels and elevation of L-arginine and NO levels [79].

Also, it was showed that paeoniflorin, one of the major active constituents of Paeonia lactiflora Pallas, inhibits the alternative activation of macrophages in subcutaneous xenograft tumors of the C57BL/6 J mice at doses of 40 and 20 mg·kg⁻² [80].

2.4 Polysaccharides

It was suggested that modulation of TAM polarization was implicated in the antitumor immunostimulatory activity of polysaccharides from Panax japonicus (ginseng). The transcription and production of TGF-β and IL-10, two well-known immunosuppressive cytokines secreted by TAMs, were reduced in response to Panax polysaccharides and also the number of infiltrated CD168+ M2 TAMs was substantially declined although the number of CD68+ total macrophages in transplanted tumor tissues remained almost unchanged [81]. A significant inhibition of Arg-1 expression (above 90% at 100 μg/mL), one of the phenotype markers of
Macrophages

M2 macrophages, was also observed for the ethanol extract of Ginseng *Radix et Rhizoma* [62]. Recently, Chen et al. [82], showed that water extract of Ginseng and Astragalus could be a novel option for integrative cancer therapies due mainly to their ability to regulate macrophage polarization.

In a murine model of sarcoma, immunotherapy with IAPS-2 (acidic polysaccharide, namely IAPS-2, from the root of *Ilex asprella*) demonstrated that it could significantly inhibit the growth of tumors via modulating the function of TAMs and increase the animal survival rate [83]. Similar results were obtained with an aqueous extract of *Trametes robiniophila* Murr (Huaier), a sandy beige mushroom found on the truck of trees and has been widely used in TCM for approximately 1600 years for its antitumor, antiangiogenic and immunomodulatory effects. Huaier not only modulates the macrophage polarization but also could inhibit the macrophage-induced angiogenesis by decreasing the expression of VEGF, MMP2 and MMP9, thus inhibiting the formation of new blood vessels in tumor [84].

2.5 Coumarins

Esculetin (6,7-dihydroxycoumarin) and fraxetin (6-methoxy-7,8-dihydroxycoumarin) (50, 75 and 100 μM) inhibited the production of IL-10, MCP-1 and TGF-β-1 in macrophages and the phosphorylation of STAT 3 without affecting its expression during the differentiation of M2 macrophages. Esculetin also suppressed the increased production of these cytokines during M2 macrophage differentiation at 10–100 μM. On the other hand, daphentin (7,8-dihydroxycoumarin) had no such effects, revealing that coumarins with two hydroxyl groups at the 6 and 7 positions (esculetin) or coumarins with a methoxy group at the 6 and two hydroxyl groups at the 7 and 8 positions (fraxetin) are more active, exhibiting antitumor and antimetastatic actions in osteosarcoma L8 cells [85]. The antitumor and antimetastatic actions of esculetin may be due to the dual actions at tumor and TAM sites: inhibition of the expression of cyclin D1 and CDK4 in osteosarcoma L8 cells, and also decreasing the STAT 3 phosphorylation in macrophages. In the case of fraxetin, the effects are partly attributed to the inhibition of M2 macrophage differentiation [85].

A classical formula of traditional Chinese medicine (TCM) to alleviate lung cancer–related symptoms is Bu-Fei decoction (BFD), consisting of six herbal Chinese medicines—Codonopsis pilosula, Schisandra chinensis, Rehmannia glutinosa, Astragalus sp., Aster sp. and Morus sp.—but it has not been established whether it induces an antitumor effect or it modulates the tumor microenvironment. The result of an in vivo study revealed that BFD successfully interrupted the interaction between tumor cells and TAMs by inhibiting the expression of two important markers: IL-10 (correlated with late stage (stage II, III and IV), lymph node metastases, pleural invasion, lymphovascular invasion and poor differentiation in NSCLC patients) and PD-L1 (correlated with poor prognosis in a number of human cancers, including breast cancer, kidney cancer and NSCLCs) [86].

2.6 Anthraquinones

It has been shown that emodin (6-methyl-1,3,8-trihydroxyanthraquinone), the active ingredient of several Chinese herbs including Rhubarb (*Rheum palmatum*), inhibits the growth of a variety of tumors and enhances the responsiveness of tumors to chemotherapy agents. In breast cancer, emodin directly inhibited macrophage infiltration and M2 polarization in the tumors, independent of tumor size [87]. Previously, Jia et al. [88], showed that emodin is not cytotoxic to breast cancer cells.
at concentration achieved in vivo (up to 30 μM) and it failed to affect macrophage infiltration in primary tumors. In contrast to its lack of effects on primary tumors, emodin dramatically suppressed lung metastasis by diminishing phosphorylation of STAT6 and C/EBPβ signaling upon IL-4 stimulation [88]. Further, it was showed that emodin suppresses the activation of multiple signaling pathways, including NF-kB, IRF5, MAPK, STAT1 or STAT6, and IRF4, depending on the environmental settings. It acts mostly on M2 polarization, suggesting that emodin could be most beneficial for patients with M2 macrophage-driven diseases [89].

2.7 Other herbal compounds/preparations

In oral squamous cell carcinoma (OSCC) animal models, highly pure super critical CO2 leaf extract of Azadirachta indica (Neem) induces an M1 phenotype in TAMs in vivo, and the primary active component, nimboide (a limonoid tetranortriterpenoid with an α,β-unsaturated ketone system and a δ-lactone ring) has significant anticancer activity in established OSCC xenografts [90]. β-Elemene, a widely known sesquiterpene, regulated the polarization of macrophages from M2 to M1, inhibiting the proliferation, migration and invasion of lung cancer cells and enhancing its radiosensitivity [91].

Onionin A (ONA), a natural low molecular weight compound containing sulfur isolated from onions, inhibited the EOC cell-induced M2 polarization of HMDCMs, and STAT3 activation was significantly inhibited by ONA treatment in all cell lines [92].

Adjunctive treatment with Withaferin A, the most abundant constituent of Withania somnifera (Ashwagandha) root extract, reduced myeloid cell-mediated immune suppression and polarized immunity toward a tumor-rejecting type 1 phenotype, facilitating the development of antitumor immunity [93].

Traditional Chinese medicine provides pharmacologically efficient prepartes such as KSG-002, a hydroalcoholic extract of radices Astragalus membranaceus and Angelica gigas at 3: 1 ratio that suppresses breast cancer growth and metastasis through targeting NF-κB–mediated TNFα production in macrophages [94] and SH003, mixed extract from Astragalus membranaceus, Angelica gigas and Trichosanthes kirilowii Maximowicz that suppresses highly metastatic breast cancer growth and metastasis by inhibiting STAT3-IL-6 signaling path [95].

Traditional Chinese medicine Jianpi Yangzheng Decoction (JPYZ) used for improving the quality of life and prolonging the survival of gastric cancer patients was more effective compared with Jianpi Yangzheng Xiaozheng Decoction (JPYZXZ) for inducing the phenotypic change in macrophages from M2 to M1. JPYZZ inhibits the gastric cancer EMT more effectively than JPYZ, but JPYZ primarily works to regulate the phenotypic change in macrophages from M2 to M1 [96].

CXCL-1 was also found to be a cytokine secreted by tumor-associated macrophage, which recruits myeloid-derived suppressor cells to form pre-metastatic niche and led to liver metastasis from colorectal cancer. The current study demonstrated that after administration of XIAOPI formula (consisting of 10 herbs including Epimedium brevicornum, Cistanche deserticola, Leonurus heterophyllus, Salvia miltiorrhiza, Curcuma aromatica, Rhizoma Curcumae, Ligustrum lucidum, Radix polygoni Multiflori preparata, Crassostrea gigas and Carapax trionycis), the density of TAMs decreased significantly and the level of CXCL-1 was also inhibited in both mouse plasma and cellular supernatants. When CXCL-1 cytokine was co-administrated with XIAOPI formula, the antimetastatic property of XIAOPI formula was blocked, indicating that CXCL-1 might be the principal gene involved in the network regulating the action of XIAOPI formula [97].
3. Conclusions

Macrophages, as key players in the tumor microenvironment, play essential roles in maintenance and progression of malignant state. Due to their plasticity, these cells balance between pro- and antitumoral effects in close correlation to specific factors. Recent immunotherapeutic strategies focus on tumor-associated macrophages in two main directions: to inhibit protumor macrophages and their suppressive effects (CCL2 inhibitors, trabectedin, zoledronic acid, JAK/STAT inhibitors, etc.) and to activate TAMs to an antitumor phenotype (TLR and CD40 agonists, PI3kδ inhibitor, VEGF and Ang2 inhibitors, etc.).

Several natural compounds/herbal extracts were studied as therapeutic/supportive agents for macrophage modulation in different types of cancers, most of them being able to change M2 polarization (protumoral) to M1 polarization (antitumoral). They belong to various classes of herbal compounds: saponins (corosolic and oleanolic acids, astragaloside, ginsenosides, celastrol, etc.), alkaloids (9-hydroxycanthin-6-one, phlenumdines E, A, hupermine A and 12-epilycopodine-N-oxide, sophoridine, etc.), flavonoids and polyphenolcarboxylic acids (isoliquiritigenin, xanthoangelol and 4-hydroxyderricin, baicalein, naringin, genistein, deoxyschizandrin, chlorogenic acid, curcumin, 6-gingerol and paeoniflorin), polysaccharides (isolated from various vegetal sources), coumarins (esculetin, fraxetin, etc.), and anthraquinones (emodin). This action is most probably achieved by downregulation of the STAT3, STAT6 and NF-kB pathways with consecutive modulation of the secretory profile of TAM cytokines.

TCM supports the dual approach of cancer therapy, to destroy cancer cells on one hand and to improve patients’ immunological status on the other hand. For several preparations such as Jianpi Yangzheng Decoction, Bu-Fei decoction and XIAOPI formula, research studies proved the correlation between cancer cells and tumor microenvironment and the effective intervention of these herbal products in delaying/breaking the tumorigenic process.

Low solubility of some herbal compounds limits their clinical application and it conducted to designing of new analogs with improved bioavailability-ginseng-derived nanoparticles, peracetate-protected EGCG, chrysin and resveratrol analogs.

By now, many herbal compounds have been shown to exhibit antitumor effects in various cancer types. Further, more researches need to be focused on the influence of these valuable compounds/preparations on modulation of the tumor microenvironment, as key element in the relation of tumor-host.

Acknowledgements

This research was financially supported by the Ministry of Research and Innovation in the frame of the project PN.16.41.01.01/2018, CORE Program.
Author details

Alice Grigore
National Institute for Chemical-Pharmaceutical Research and Development, Bucharest, Romania

*Address all correspondence to: alicearmatu@yahoo.com

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Macrophages

References

[1] Yang M, McKay D, Pollard J, Lewis C. Diverse functions of macrophages in different tumor microenvironments. Cancer Research. 2018;78(19):5492-5503. DOI: 10.1158/0008-5472.CAN-18-1367

[2] Aras S, Zaidi R. TAMeless traitors: Macrophages in cancer progression and metastasis. British Journal of Cancer. 2017;117(11):1583-1591. DOI: 10.1038/BJC.2017.356

[3] Barros M, Hauck F, Dreyer JH, Kempkes B, Niedobitek G. Macrophage polarisation: An immunohistochemical approach for identifying M1 and M2 macrophages. PLoS One. 2013;8(11):e80908. DOI: 10.1371/journal.pone.0080908

[4] Najafi M, Goradel NH, Farhood B, Salehi E, Nashtaei MS, Khanlarkhani N, et al. Macrophage polarity in cancer: A review. Journal of Cellular Biochemistry. 2019;120(3):2756-2765. DOI: 10.1002/jcb.27646

[5] Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nature Reviews. Cancer. 2009;9(4):239-252. DOI: 10.1038/nrc2618

[6] Sousa S, Régis R, Lintunen M, Kronqvist P, Sandholm J, Mönkkönen J, et al. Human breast cancer cells educate macrophages toward the M2 activation status. Breast Cancer Research. 2015;17:101. DOI: 10.1186/s13058-015-0621-0

[7] Choi J, Gyamfi J, Jang H, Koo JS. The role of tumor-associated macrophage in breast cancer biology. Histology and Histopathology. 2018;33:133-145. DOI: 10.14670/HH-11-916

[8] Kovaleva O, Samoilova D, Shitova M, Gratchev A. Tumor associated macrophages in kidney cancer. Analytical Cellular Pathology. 2016;2016:9307549

[9] Dun E, Hanley K, Wieser F, Bohman S, Taylor R. Infiltration of tumor-associated macrophages is increased in the epithelial and stromal compartments of endometrial carcinomas. International Journal of Gynecological Pathology. 2013;32(6):576-584. DOI: 10.1097/PGP.0b013e318284e198

[10] Kelly MG, Francisco AM, Cimic A, Wofford A, Fitzgerald NC, Yu J, et al. Type 2 endometrial cancer is associated with a high density of tumor-associated macrophages in the stromal compartment. Reproductive Sciences. 2015;22(8):948-953. DOI: 10.1177/1933719115570912

[11] Liu JY, Peng CW, Yang GF, Hu WQ, Yang XJ, Huang CQ, et al. Distribution pattern of tumor associated macrophages predicts the prognosis of gastric cancer. Oncotarget. 2017;8(54):92757-92769. DOI: 10.18632/oncotarget.21575

[12] Räihä M, Puolakkainen P. Tumor-associated macrophages (TAMs) as biomarkers for gastric cancer: A review. Chronic Diseases and Translational Medicine. 2018;4(3):156-163. DOI: 10.1016/j.ctdm.2018.07.001

[13] Wu P, Wu D, Zhao L, Huang L, Chen G, Shen G, et al. Inverse role of distinct subsets and distribution of macrophage in lung cancer prognosis: A meta-analysis. Oncotarget. 2016;7(26):40451-40460. DOI: 10.18632/oncotarget.9625

[14] Zhao X, Qu J, Sun Y, Wang J, Liu X, Wang F, et al. Prognostic significance of tumor-associated macrophages in breast cancer: A meta-analysis of the literature. Oncotarget. 2017;8(18):30576-30586. DOI: 10.18632/oncotarget.15736
[15] Yin S, Huang J, Li Z, Zhang J, Luo J, Lu C, et al. The prognostic and clinicopathological significance of tumor-associated macrophages in patients with gastric cancer: A meta-analysis. PLoS One. 2017;12(1):e0170042. DOI: 10.1371/journal.pone.0170042

[16] Li Z, Maeda D, Yoshida M, Umakoshi M, Nanjo H, Shiraishi K, et al. The intratumoral distribution influences the prognostic impact of CD68- and CD204-positive macrophages in non-small cell lung cancer. Lung Cancer. 2018;123:127-135. DOI: 10.1016/j.lungcan.2018.07.015

[17] Mei J, Xiao Z, Guo C, Pu Q, Ma L, Liu C, et al. Prognostic impact of tumor-associated macrophage infiltration in non-small cell lung cancer: A systematic review and meta-analysis. Oncotarget. 2016;7(23):34217-34228. DOI: 10.18632/oncotarget.9079

[18] Kawachi A, Yoshida H, Kitano S, Ino Y, Kato T, Hiraoaka N. Tumor-associated CD204+ M2 macrophages are unfavorable prognostic indicators in uterine cervical adenocarcinoma. Cancer Science. 2018;109(3):863-870. DOI: 10.1111/cas.13476

[19] Yuan X, Zhang J, Li D, Mao Y, Mo F, Du W, et al. Prognostic significance of tumor-associated macrophages in ovarian cancer: A meta-analysis. Gynecologic Oncology. 2017;147(1):181-187. DOI: 10.1016/j.ygyno.2017.07.007

[20] Lankadasari M, Mukhopadhyay P, Mohammed S, Harikumar K. TAMing pancreatic cancer: Combat with a double edged sword. Molecular Cancer. 2019;18:48. DOI: 10.1186/s12943-019-0966-6

[21] Yu M, Guan R, Hong W, Zhou Y, Lin Y, Jin H, et al. Prognostic value of tumor-associated macrophages in pancreatic cancer: A meta-analysis.

Cancer Management and Research. 2019;11:4041-4058. DOI: 10.2147/CMAR.S196951

[22] Morisse M, Jouannet S, Dominguez-Villar M, Sanson M, Idbaïh A. Interactions between tumor-associated macrophages and tumor cells in glioblastoma: Unraveling promising targeted therapies. Expert Review of Neurotherapeutics. 2018;18(9):729-737. DOI: 10.1080/14737175.2018.1510321

[23] Ding W, Tan Y, Qian Y, Xue W, Wang Y, Jiang P, et al. Clinicopathologic and prognostic significance of tumor-associated macrophages in patients with hepatocellular carcinoma: A meta-analysis. PLoS One. 2019;14(10):e0223971. DOI: 10.1371/journal.pone.0223971

[24] Falleni M, Savi F, Tosi D, Agape E, Cerri A, Moneghini L, et al. M1 and M2 macrophages’ clinicopathological significance in cutaneous melanoma. Melanoma Research. 2017;27(3):200-210. DOI: 10.1097/CMR.0000000000000352

[25] Xu X, Li Z, Liu J, Zhu F, Wang Z, Wang J, et al. The prognostic value of tumour-associated macrophages in non-Hodgkin's lymphoma: A systematic review and meta-analysis. Scandinavian Journal of Immunology. 2020;91(1):e12814. DOI: 10.1111/sji.12814

[26] Guo B, Cen H, Tan X, Ke Q. Meta-analysis of the prognostic and clinical value of tumor-associated macrophages in adult classical Hodgkin lymphoma. BMC Medicine. 2016;14(1):159

[27] Zhao Y, Ge X, Xu X, Yu S, Wang J, Sun L. Prognostic value and clinicopathological roles of phenotypes of tumour-associated macrophages in colorectal cancer. Journal of Cancer Research and Clinical Oncology. 2019;145(12):3005-3019. DOI: 10.1007/s00432-019-03041-8
[28] Troiano G, Caponio VCA, Adipietro I, Tepedino M, Santoro R, Laino L, et al. Prognostic significance of CD68*tumor associated macrophages in head and neck squamous cell carcinoma: A systematic review and meta-analysis. Oral Oncology. 2019;93:66-75. DOI: 10.1016/j.oraloncology.2019.04.019

[29] Ovais M, Guo M, Chen C. Tailoring nanomaterials for targeting tumor-associated macrophages. Advanced Materials. 2019;31(19):e1808303. DOI: 10.1002/adma.201808303

[30] Poh AR, Ernst M. Targeting macrophages in cancer: From bench to bedside. Frontiers in Oncology. 2018;8:49. DOI: 10.3389/fonc.2018.00049

[31] Balkwill FR, Mantovani A. Cancer-related inflammation: Common themes and therapeutic opportunities. Seminars in Cancer Biology. 2012;22(1):33-40. DOI: 10.1016/j.semcancer.2011.12.005

[32] Noy R, Pollard J. Tumor-associated macrophages: From mechanisms to therapy. Immunity. 2014;41(1):49-61. DOI: 10.1016/j.immuni.2014.06.010

[33] Petty AJ, Yang Y. Tumor-associated macrophages: Implications in cancer immunotherapy. Immunotherapy. 2017;9(3):289-302. DOI: 10.2217/ imt-2016-0135

[34] Saha D, Martuza R, Rabkin S. Macrophage polarization contributes to glioblastoma eradication by combination immunovirotherapy and immune checkpoint blockade. Cancer Cell. 2017;2(2):253-267.e5. DOI: 10.1016/j.ccell.2017.07.006

[35] Kushner BH, Cheung IY, Modak S, Kramer K, Ragupathi G, Cheung NK. Phase I trial of a bivalent gangliosides vaccine in combination with beta-glucan for high-risk neuroblastoma in second or later remission. Clinical Cancer Research. 2014;20:1375-1382. DOI: 10.1158/1078-0432.CCR-13-1012

[36] Genard G, Lucas S, Michiels C. Reprogramming of tumor-associated macrophages with anticancer therapies: Radiotherapy versus chemo- and immunotherapies. Frontiers in Immunology. 2017;8:828. DOI: 10.3389/fimmu.2017.00828

[37] Coscia M, Quaglino E, Iezzi M, Curcio C, Pantaleoni F, Riganti C, et al. Zoledronic acid repolarizes tumour-associated macrophages and inhibits mammary carcinogenesis by targeting the mevalonate pathway. Journal of Cellular and Molecular Medicine. 2010;14(12):2803-2815. DOI: 10.1111/j.1582-4934.2009.00926.x

[38] Ulrich-Merzenich G. Combination screening of synthetic drugs and plant derived natural products—Potential and challenges for drug development. Synergy. 2014;1(1):59-69. DOI: 10.1016/j.synres.2014.07.011

[39] Wang Y, Smith W, Hao D, He B, Kong L. M1 and M2 macrophage polarization and potentially therapeutic naturally occurring compounds. International Immunopharmacology. 2019;70:459-466. DOI: 10.1016/j.intimp.2019.02.050

[40] Fujiwara Y, Takeya M, Komohara Y. A novel strategy for inducing the antitumor effects of triterpenoid compounds: Blocking the protumoral functions of tumor-associated macrophages via STAT3 inhibition. BioMed Research International. 2014; Article ID 348539. DOI: 10.1155/2014/348539

[41] Fujiwara Y, Komohara Y, Ikeda T, Takeya M. Corosolic acid inhibits glioblastoma cell proliferation by suppressing the activation of signal transducer and activator of transcription-3 and nuclear
factor-kappa B in tumor cells and tumor-associated macrophages. Cancer Science. 2011;102(1):206-211. DOI: 10.1111/j.1349-7006.2010.01772.x

[42] Xu F, Cui Q, Wei Y, Cui J, Qiu J, Hu LL, et al. Astragaloside IV inhibits lung cancer progression and metastasis by modulating macrophage polarization through AMPK signaling. Journal of Experimental & Clinical Cancer Research. 2018;37(1):207. DOI: 10.1186/s13046-018-0878-0

[43] Li H, Huang N, Zhu W, Wu J, Yang X, Teng W, et al. Modulation the crosstalk between tumor-associated macrophages and non-small cell lung cancer to inhibit tumor migration and invasion by ginsenoside Rh2. BMC Cancer. 2018;18(1):579. DOI: 10.1186/s12885-018-4299-4

[44] Cao M, Yan H, Han X, Weng L, Wei Q, Sun X, et al. Ginseng-derived nanoparticles alter macrophage polarization to inhibit melanoma growth. Journal for Immunotherapy of Cancer. 2019;7(1):326. DOI: 10.1186/s40425-019-0817-4

[45] Yang Y, Cheng S, Liang G, Honggang L, Wu H. Celastrol inhibits cancer metastasis by suppressing M2-like polarization of macrophages. Biochemical and Biophysical Research Communications. 2018;503(2):414-419. DOI: 10.1016/j.bbrc.2018.03.224

[46] Kangsamaksin T, Chaithongyot S, Wootthichairangs C, Hanchaina R, Tangshewinsirikul C, Svasti J. Lupeol and stigmasterol suppress tumor angiogenesis and inhibit cholangiocarcinoma growth in mice via downregulation of tumor necrosis factor-α. PLoS One. 2017;12(12):e0189628. DOI: 10.1371/journal.pone.0189628

[47] Jeong M, Kim HM, Ahn JH, Lee KT, Jang DS, Choi JH. 9-Hydroxycanthin-6-one isolated from stem bark of Ailanthus altissima induces ovarian cancer cell apoptosis and inhibits the activation of tumor-associated macrophages. Chemico-Biological Interactions. 2018;280:99-108. DOI: 10.1016/j.cbi.2017.12.011

[48] Nakayama W, Fujiwara Y, Kosuge Y, Monthakantirat O, Fujikawa K, Watthana S, et al. Phlenumdines D and E, new Lycopodium alkaloids from Phlegmariurus nummulariifolius, and their regulatory effects on macrophage differentiation during tumor development. Phytochemistry Letters. 2019;29:98-103. DOI: 10.1016/j.phytol.2018.11.010

[49] Zhuang H, Dai X, Zhang X, Mao Z, Huang H. Sophoridine suppresses macrophage-mediated immunosuppression through TLR4/IRF3 pathway and subsequently upregulates CD8+ T cytotoxic function against gastric cancer. Biomedicine & Pharmacotherapy. 2020;121:109636. DOI: 10.1016/j.biopha.2019.109636

[50] Zhao H, Zhang X, Chen X, Li Y, Ke Z, Tang T, et al. Isoliquiritigenin, a flavonoid from licorice, blocks M2 macrophage polarization in colitis-associated tumorigenesis through downregulating PGE 2 and IL-6. Toxicology and Applied Pharmacology. 2014;279:311-321. DOI: 10.1016/j.taap.2014.07.001

[51] Sumiyoshi M, Taniguchi M, Baba K, Kimura Y. Antitumor and antimetastatic actions of xanthoangelol and 4-hydroxyderricin isolated from Angelica keiskei roots through the inhibited activation and differentiation of M2 macrophages. Phytomedicine. 2015;22(7-8):759-767. DOI: 10.1016/j.phymed.2015.05.005

[52] Wang YL, Tan X, Yang XL, Li XY, Bian K, Zhang DD. Total flavonoid from Glycyrrhizae radix et rhizoma and its ingredient isoliquiritigenin regulation M2 phenotype polarization
of macrophages. Zhongguo Zhong Yao Za Zhi. 2015;40(22):4475-4481

[53] Jang Y, Lee JK, Jeon YK, Kim CW. Exosome derived from epigallocatechin gallate treated breast cancer cells suppresses tumor growth by inhibiting tumor-associated macrophage infiltration and M2 polarization. BMC Cancer. 2013;13:421. DOI: 10.1186/1471-2407-13-421

[54] Park SA, Surh YJ. Modulation of tumor microenvironment by chemopreventive natural products. Annals of the New York Academy of Sciences. 2017;1401(1):65-74. DOI: 10.1111/nyas.13395

[55] Wang J, Man GCW, Chan TH, Kwong J, Wang CC. A prodrug of green tea polyphenol (−)epigallocatechin-3-gallate (pro-EGCG) serves as a novel angiogenesis inhibitor in endometrial cancer. Cancer Letters. 2018;412:10-20. DOI: 10.1016/j.canlet.2017.09.054

[56] Choi HJ, Choi HJ, Chung TW, Ha KT. Luteolin inhibits recruitment of monocytes and migration of Lewis lung carcinoma cells by suppressing chemokine (CeC motif) ligand 2 expression in tumor-associated macrophage. Biochemical and Biophysical Research Communications. 2016;470(1):101-106. DOI: 10.1016/j.bbrc.2016.01.002

[57] Lee YJ, Lim T, Han MS, et al. Anticancer effect of luteolin is mediated by downregulation of TAM receptor tyrosine kinases, but not interleukin-8, in non-small cell lung cancer cells. Oncology Reports. 2017;37(2):1219-1226. DOI: 10.3892/or.2016.5336

[58] Fang B, Chen X, Wu M, Kong H, Chu G, Zhou Z, et al. Luteolin inhibits angiogenesis of the M2-like TAMs via the downregulation of hypoxia inducible factor-1a and the STAT3 signalling pathway under hypoxia. Molecular Medicine Reports. 2018;18(3):2914-2922. DOI: 10.3892/mmr.2018.9250

[59] Zhao X, Qu J, Liu X, Wang J, Ma X, Zhao X, et al. Baicalein suppress EMT of breast cancer by mediating tumor-associated macrophages polarization. American Journal of Cancer Research. 2018;8(8):1528-1540. eCollection 2018

[60] Zheng X, Meng WD, Xu YY, Cao JG, Qing FL. Synthesis and anticancer effect of chrysin derivatives. Bioorganic & Medicinal Chemistry Letters. 2003;13:881-884

[61] Sun S, Cui Y, Ren K, Quan M, Song Z, Zou H, et al. 8-bromo-7-methoxychrysin reversed M2 polarization of tumor-associated macrophages induced by liver cancer stem-like cells. Anti-Cancer Agents in Medicinal Chemistry. 2017;17(2):286-293

[62] Jiang YX, Chen Y, Yang Y, Chen XX, Zhang DD. Screening five Qi-Tonifying herbs on M2 phenotype macrophages. Evidence-based Complementary and Alternative Medicine. 2019;2019:9549315. DOI: 10.1155/2019/9549315

[63] Fujiwara Y, Saito Y, Shiota T, Cheng P, Ikeda T, Ohnishi K, et al. Natural compounds that regulate lymph node sinus macrophages: Inducing an anti-tumor effect by regulating macrophage activation. Journal of Clinical and Experimental Hematopathology. 2018;58(1):17-23. DOI: 10.3960/jslrt.17032

[64] Kang H, Zhang J, Wang B, Liu M, Zhao J, Yang M, et al. Puerarin inhibits M2 polarization and metastasis of tumor-associated macrophages from NSCLC xenograft model via inactivating MEK/ERK 1/2 pathway. International Journal of Oncology. 2017;50(2):545-554. DOI: 10.3892/ijo.2017.3841
[65] Ning Y, Feng W, Cao X, Ren K, Quan M, Chen A, et al. Genistein inhibits stemness of SKOV3 cells induced by macrophages co-cultured with ovarian cancer stem-like cells through IL-8/STAT3 axis. Journal of Experimental and Clinical Cancer Research. 2019;38:19. DOI: 10.1186/s13046-018-1010-1

[66] Xue N, Zhou Q, Ji M, Jin J, Lai F, Chen J, et al. Chlorogenic acid inhibits glioblastoma growth through repolarizing macrophage from M2 to M1 phenotype. Scientific Reports. 2017;7:39011. DOI: 10.1038/srep39011

[67] Oršolić N, Kunštić M, Kukolj M, Gračan R, Nemrava J. Oxidative stress, polarization of macrophages and tumour angiogenesis: Efficacy of caffeic acid. Chemico-Biological Interactions. 2016;256:111-124. DOI: 10.1016/j.cbi.2016.06.027

[68] Lee K, Ahn JH, Lee KT, Jang DS, Choi JH. Deoxyschizandrin, isolated from Schisandra berries, induces cell cycle arrest in ovarian cancer cells and inhibits the Protumoural activation of tumour-associated macrophages. Nutrients. 2018;10(1):91. DOI: 10.3390/nu10010091

[69] Sun L, Chen B, Jiang R, Li J, Wang B. Resveratrol inhibits lung cancer growth by suppressing M2-like polarization of tumor associated macrophages. Cellular Immunology. 2017;311:86-93. DOI: 10.1016/j.cellimm.2016.11.002

[70] Kimura Y, Sumiyoshi M. Resveratrol prevents tumor growth and metastasis by inhibiting Lymphangiogenesis and M2 macrophage activation and differentiation in tumor-associated macrophages. Nutrition and Cancer. 2016;68(4):667-678. DOI: 10.1080/01635581.2016.1158295

[71] Kimura Y, Sumiyoshi M, Baba K. Antitumor and antimetastatic activity of synthetic hydroxystilbenes through inhibition of lymphangiogenesis and M2 macrophage differentiation of tumor-associated macrophages. Anticancer Research. 2016;36:137-148

[72] Jeong SK, Yang K, Park YS, Choi YJ, Oh SJ, Lee CW, et al. Interferon gamma induced by resveratrol analog, HS-1793, reverses the properties of tumor associated macrophages. International Immunopharmacology. 2014;22(2):303-310. DOI: 10.1016/j.intimp.2014.07.004

[73] Mohammadi A, Blesso C, Barreto G, Banach M, Majeed M, Sahebkar M. Macrophage plasticity, polarization and function in response to curcumin, a diet-derived polyphenol, as an immunomodulatory agent. The Journal of Nutritional Biochemistry. 2019;66:1-16. DOI: 10.1016/j.jnutbio.2018.12.005

[74] Gao S, Zhou J, Liu N, Wang L, Gao Q, Wu Y, et al. Curcumin induces M2 macrophage polarization by secretion IL-4 and/or IL-13. Journal of Molecular and Cellular Cardiology. 2015;85:131-139. DOI: 10.1016/j.yjmcc.2015.04.025

[75] Tu SP, Jin H, Shi JD, Zhu LM, Suo Y, Lu G, et al. Curcumin induces the differentiation of myeloid-derived suppressor cells and inhibits their interaction with cancer cells and related tumor growth. Cancer Prevention Research (Philadelphia, Pa.). 2012;5(2):205-215. DOI: 10.1158/1940-6207.CAPR-11-0247

[76] Mukherjee S, Baidoo J, Fried A, Atwi D, Dolai S, Boockvar J, et al. Curcumin changes the polarity of tumor-associated microglia and eliminates glioblastoma. International Journal of Cancer. 2016;139(12):2838-2849. DOI: 10.1002/ijc.30398

[77] Mukherjee S, Hussaini R, White R, Atwi D, Fried A, Sampat S, et al. TriCurin, a synergistic formulation of curcumin, resveratrol, and epicatechin
gallate, repolarizes tumor-associated macrophages and triggers an immune response to cause suppression of HPV+ tumors. Cancer Immunology, Immunotherapy. 2018;67(5):761-774. DOI: 10.1007/s00262-018-2130-3

[78] Mukherjee S, Baidoo JNE, Sampat S, Mancuso A, David L, Cohen LS. Liposomal TriCurin, a synergistic combination of curcumin, epicatechin gallate and resveratrol, repolarizes tumor-associated microglia/macrophages, and eliminates glioblastoma (GBM) and GBM stem cells. Molecules. 2018;23(1). pii: E201. DOI: 10.3390/molecules23010201

[79] Yao J, Du Z, Li Z, Zhang S, Lin Y, Li H, et al. 6-Gingerol as an arginase inhibitor prevents urethane-induced lung carcinogenesis by reprogramming tumor supporting M2 macrophages to M1 phenotype. Food & Function. 2018;9(9):4611-4620. DOI: 10.1039/c8fo01147h

[80] Wu Q, Chen GL, Li YJ, Chen Y, Lin FZ. Paeoniflorin inhibits macrophage-mediated lung cancer metastasis. Chinese Journal of Natural Medicines. 2015;13(12):925-932. DOI: 10.1016/S1875-5364(15)30098-4

[81] Shu G, Jiang S, Mu J, Yu H, Duan H, Deng X. Antitumor immunostimulatory activity of polysaccharides from Panax japonicus C. A. Mey: Roles of their effects on CD4+ T cells and tumor associated macrophages. International Journal of Biological Macromolecules. 2018;111:430-439. DOI: 10.1016/j.ijbiomac.2018.01.011

[82] Chen Y, Bi L, Luo H, Jiang Y, Chen F, Wang Y, et al. Water extract of ginseng and astragalus regulates macrophage polarization and synergistically enhances DDP's anticancer effect. Journal of Ethnopharmacology. 2019;232:11-20. DOI: 10.1016/j.jep.2018.12.003

[83] Li Q, Hao Z, Hong Y, He W, Zhao W. Reprogramming tumor associated macrophage phenotype by a polysaccharide from Ilex asprella for sarcoma immunotherapy. International Journal of Molecular Sciences. 2018;19(12). pii: E3816. DOI: 10.3390/ijms19123816

[84] Li Y, Qi W, Song X, Lv S, Zhang H, Yang Q. Huaier extract suppresses breast cancer via regulating tumor-associated macrophages. Scientific Reports. 2016;6:20049. DOI: 10.1038/srep20049

[85] Kimura Y, Sumiyoshi M. Antitumor and antimetastatic actions of dihydroxycoumarins (esculetin or fraxetin) through the inhibition of M2 macrophage differentiation in tumor-associated macrophages and/or G1 arrest in tumor cells. European Journal of Pharmacology. 2015;746:115-125. DOI: 10.1016/j.ejphar.2014.10.048

[86] Pang L, Han S, Jiao Y, Jiang S, He X, Li P. Bu Fei decoction attenuates the tumor associated macrophage stimulated proliferation, migration, invasion and immunosuppression of non-small cell lung cancer, partially via IL-10 and PD-L1 regulation. International Journal of Oncology. 2017;51:25-38. DOI: 10.3892/ijo.2017.4014

[87] Iwanowycz S, Wang J, Hodge J, Wang Y, Yu F, Fan D. Emodin inhibits breast cancer growth by blocking the tumor-promoting feedforward loop between cancer cells and macrophages. Molecular Cancer Therapeutics. 2016;15(8):1931-1942. DOI: 10.1158/1535-7163.MCT-15-0987

[88] Jia X, Yu F, Wang J, Iwanowycz S, Saoud F, Wang Y, et al. Emodin suppresses pulmonary metastasis of breast cancer cells accompanied with decreased macrophage recruitment and M2 polarization in the lungs. Breast Cancer Research and Treatment.
Targeting Tumor-Associated Macrophages by Plant Compounds
DOI: http://dx.doi.org/10.5772/intechopen.92298

2014;148(2):291-302. DOI: 10.1007/s10549-014-3164-7

[89] Iwanowycz S, Wang J, Altomare D, Hui Y, Fan D. Emodin bidirectionally modulates macrophage polarization and epigenetically regulates macrophage memory. The Journal of Biological Chemistry. 2016;291(22):11491-11503. DOI: 10.1074/jbc.M115.702092

[90] Morris J, Gonzales CB, De La Chapa JJ, Cabang B, Fountzilas C, Patel M, et al. The highly pure neem leaf extract, SCNE, inhibits tumorigenesis in oral squamous cell carcinoma via disruption of pro-tumor inflammatory cytokines and cell signaling. Frontiers in Oncology. 2019;9:890. DOI: 10.3389/fonc.2019.00890

[91] Yu X, Xu M, Li N, Li Z, Li H, Shao S, et al. β-Elemene inhibits tumor-promoting effect of M2 macrophages in lung cancer. Biochemical and Biophysical Research Communications. 2017;490(2):514-520. DOI: 10.1016/j.bbrc.2017.06.071

[92] Tsuboki J, Fujiwara Y, Horlad H, Shiraishi D, Nohara T, Tayama S, et al. Onionin a inhibits ovarian cancer progression by suppressing cancer cell proliferation and the protumour function of macrophages. Scientific Reports. 2016;6:29588. DOI: 10.1038/srep29588

[93] Sinha P, Ostrand-Rosenberg S. Myeloid-derived suppressor cell function is reduced by Withaferin a, a potent and abundant component of Withania somnifera root extract. Cancer Immunology, Immunotherapy. 2013;62(11):1663-1673. DOI: 10.1007/s00262-013-1470-2

[94] Woo SM, Choi YK, Cho SG, Park S, Ko SG. A new herbal formula, KSG-002, suppresses breast cancer growth and metastasis by targeting NF-κ B-Dependent TNF α production in macrophages. Evidence-Based Complementary and Alternative Medicine. 2013;2013:728258. DOI: 10.1155/2013/728258

[95] Choi YK, Cho SG, Woo SM, Yun YJ, Park S, Shin YC, et al. Herbal extract SH003 suppresses tumor growth and metastasis of MDA-MB-231 breast cancer cells by inhibiting STAT3-IL-6 signaling. Mediators of Inflammation. 2014;2014:492173. DOI: 10.1155/2014/492173

[96] Wu J, Zhang XX, Wang M, Wang HX, Wang YH, Li C, et al. The effect of Jianpi Yangzheng Xiaozheng decoction and its components on gastric cancer. Journal of Ethnopharmacology. 2019;10(235):56-64. DOI: 10.1016/j.jep.2019.02.003

[97] Wang N, Zheng Y, Gu J, Cai Y, Wang S, Zhan F, et al. Network-pharmacology-based validation of TAMS/CXCL-1 as key mediator of XIAOPI formula preventing breast cancer development and metastasis. Scientific Reports. 2017;7(1):14513. DOI: 10.1038/s41598-017-15030-3