*https://doi.org/10.31925/farmacia.2026.2.3* **REVIEW**

# THE ROLE OF NATURAL PRODUCTS IN REGULATING TUMOR-ASSOCIATED MACROPHAGES REPOLARIZATION TO PROMOTE ANTI-TUMOR EFFECTS

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## Abstract

With rapid progress in tumor immunology, the complexity and impact of the tumor microenvironment (TME) in cancer continue to grow. As a major component of TME, tumor-associated macrophages (TAMs) play a pivotal role in cancer progression by promoting angiogenesis, metastasis, and therapy resistance. TAMs contribute to an immunosuppressive environment by secreting cytokines and factors that inhibit anti-tumor immunity. Therefore, targeting TAMs, particularly by promoting their repolarization into M1-like phenotypes, has emerged as a key strategy in cancer treatment. Plant-derived natural products, well-known for their therapeutic potential against various ailments, including cancer, are gaining interest for their ability to modulate TAMs. Leveraging these natural products could provide opportunities to optimize cancer therapy, particularly by targeting TAMs to overcome immunosuppressive barriers. This paper focuses on the components of TME, with a specific emphasis on the biological aspects of TAMs and the impact of natural products on TAMs across various cancer cases. Furthermore, we outline the mechanisms and anti-tumor effects of selected compounds, especially their ability to promote TAM repolarization toward M1-like phenotypes, providing new insights and potential therapeutic options for cancer treatment.

## Rezumat

Odată cu dezvoltarea cercetărilor în domeniul imunologiei tumorale, rolul și complexitatea microambientului tumoral (TME) în inițierea și progresia cancerului au devenit din ce în ce mai studiate. Printre componentele cele mai importante ale TME se numără macrofagele asociate tumorilor (TAMs), care joacă un rol esențial în progresia tumorală prin stimularea angiogenezei, facilitarea metastazării și inducerea rezistenței la tratament. În plus, TAMs contribuie la instalarea unui microambient imunodepresiv prin secreția de citokine și alți mediatori care inhibă răspunsul imun antitumoral. În acest context, strategiile terapeutice care vizează TAMs, în special prin stimularea repolarizării acestora către fenotipuri de tip M1, au devenit o abordare promițătoare în terapia anticanceroasă. Produsele naturale de origine vegetală, recunoscute pentru potențialul terapeutic în numeroase patologii, au atras un interes tot mai mare datorită capacității de a modula activitatea TAMs. Valorificarea acestor compuși naturali poate oferi noi oportunități pentru optimizarea tratamentelor oncologice, în special prin țintirea TAMs și inhibarea mecanismelor imunosupresoare caracteristice microambientului tumoral. Acest studiu analizează principalele componente ale TME, cu accent asupra caracteristicilor biologice ale TAMs și asupra impactului produselor naturale asupra acestora în diferite tipuri de cancer. De asemenea, sunt prezentate mecanismele de acțiune și efectele antitumorale ale unor compuși, cu accent pe capacitatea acestora de a promova repolarizarea TAMs către fenotipuri de tip M1, oferind astfel noi perspective și potențiale opțiuni terapeutice în tratamentul cancerului.

**Keywords**: macrophage polarization, natural products, tumor-associated macrophages, tumor microenvironment

## Introduction

Macrophages have been recognized for their importance in maintaining homeostasis and supporting the proper functioning of organs. In general, macrophages can be categorized into three major functions: immunomodulation, phagocytosis, and antigen presentation (1). Macrophages are innate immune cells that originate from embryonic progenitors and bone marrow (2). During development, macrophages are distributed throughout tissues, and their functional roles are largely determined by tissue environmental conditions, which can induce polarization and establish distinct macrophage subtypes, such as M1 or M2 macrophages (1, 3). It is well known that lipopolysaccharide (LPS), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), or granulocyte-macrophage colony-stimulating factor (GM-CSF) can stimulate macrophage polarization toward M1 macrophages. In contrast, interleukin 4 (IL-4), IL-10, IL-13, or glucocorticoids can promote macrophage polarization toward M2 macrophages (4).

Functionally, there are major distinctions in the physiological roles of M1 and M2 macrophages. In general, M1 macrophages are a subset associated with pro-inflammatory function and are known to produce inflammatory cytokines (5, 6). On the other hand, M2 macrophages are responsible for anti-inflammatory responses and tissue repair (7, 8). Importantly, both M1 and M2 macrophages play crucial roles in homeostasis regulation. For instance, in infected tissue, macrophages could be polarized to the M1 phenotype in response to environmental stimuli to support host immunity in eliminating pathogens. Afterwards, macrophages are polarized to the M2 phenotype to normalize excessive inflammation and repair damaged tissues (9).

Furthermore, in the context of cancer or tumors, these macrophage subsets play distinct roles and exhibit distinct responses, which are determined by the level of malignancy. In early cancer, macrophage polarization toward M1-TAMs is important because they promote strong anti-tumor responses and hinder tumor growth (10, 11). However, in advanced malignancy levels, the cancer could find other ways to survive against the anti-cancer immune response. Taking advantage of TME, circulating monocytes or tissue-resident macrophages could be recruited to the tumor site and educated to polarize into M2-TAMs, which support cancer progression (12). Therefore, targeting the TME, including tumor-associated macrophages, is a promising strategy for cancer therapy. By limiting their actions and converting them into an anti-tumor subset, they can be targeted for cancer cell elimination and to improve cancer response to therapy (13).

Numerous medicinal plants contain a variety of bioactive compounds with promising therapeutic effects against cancer. Natural products often exert their effects by regulating molecular signaling pathways involved in cancer cell growth and progression (14, 15). Preclinical studies on selected natural products confirmed specific mechanisms, including increasing antioxidant levels, deactivating cancer-causing agents, decreasing cell growth, promoting cell cycle arrest and apoptosis, and modulating the immune system (16, 17). Furthermore, clinical trials on natural products have emerged as complementary and alternative therapies for cancer treatment. For example, berberine hydro-chloride (ClinicalTrials.gov ID: NCT03281096), extracted from *Rhizoma coptidis*, which has already entered phase 2/3 clinical trials, has shown potential to reduce the recurrence of colorectal adenomas in patients with *prior* colorectal cancer. Similarly, lycopene (ClinicalTrials.gov ID: NCT03167268), extracted from *Solanum lycopersicum* and currently in phase 2 clinical trials, could reduce skin toxicity when used alone or in combination with panitumumab in metastatic colorectal cancer (18). Recent studies have shown that natural products not only exert direct effects on cancer but also significantly influence the TME, including TAMs, a major component of the TME, thereby enhancing their overall anti-cancer activity. As a result, the broad clinical application of natural products appears to benefit cancer patients. However, its efficacy requires validation in large-scale randomized trials (19, 20). This review provides an overview of TAM attributes and roles within the TME, as well as the mechanisms by which natural products target and promote the repolarization of M2-TAMs toward M1-like phenotypes. Highlighting various signaling pathways and their associated molecular mechanisms will provide valuable insights into the development of novel cancer treatments.

## The Component of Tumor Microenvironment

Cancerous solid tumors are not limited to an aggregate of cancer cells. They also contain a diverse range of infiltrating and non-cancerous host cells, as well as extracellular matrix, blood vessels, lymphatic vessels, cytokines, mediators, and other secreted factors. Collectively, these components form the complex and dynamic ecosystem known as the TME (21, 22). Apart from tumor cells, immune and stromal cells are the major cellular components within the TME, encompassing T cells, regulatory T cells, B cells, monocytes, macrophages, neutrophils, dendritic cells, myeloid-derived suppressor cells, NK cells, cancer-associated fibroblasts, adipocytes, vascular endothelial cells, and pericytes (22-25). Dynamic interactions occurred within the TME among different cellular components, including tumor-tumor and tumor-non-tumor cell interactions involving immune and stromal cells. Interaction occurs through several mechanisms, including direct cell-to-cell contact and the release of signaling molecules (26). Importantly, the cellular content and functional condition of the TME vary, which are determined by several factors, including the location of the tumor, the genomic profile of cancer cells, the stage of cancer, and patient characteristics (age, gender, lifestyle, body mass index, and microbiome composition) (23).

It is well known that TME contributes significantly to disease progression. Alterations in TME conditions can greatly impact the behavior and characteristics of immune and stromal cells, shifting them from an initial anti-cancer to a pro-cancer response (27). Immune cells have a key role in tumor suppression throughout the early stages of carcinogenesis. For example, dendritic cells, known for their role in antigen presentation, capture neoantigens produced by cancer cells and subsequently activate cytotoxic T cells. Cytotoxic T cells act on cancer cells *via* direct contact of the T cell receptor (TCR) with major histocompatibility complex class I (MHC-I) peptide

complexes expressed by cancer cells. In addition, cytotoxic T cells induce cancer cell death by releasing granzyme and perforin (28). Additional immune cells, including monocytes and macrophages, also play a major role in tumor surveillance. Both monocytes and macrophages can produce tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which can mediate tumor cell death (29, 30). To a greater extent, TRAIL can trigger extrinsic and intrinsic pathways of cell death in the tumor. In the extrinsic pathway, TRAIL interaction with death receptors 4/5 (DR4/DR5) on tumor cells promotes DISC formation and induces apoptosis by activating caspases. In the intrinsic pathway, TRAIL activates caspase-8, leading to disruption of the mitochondrial membrane and cytochrome c release. Finally, this condition induces the procaspase-9 and downstream caspases (caspase-3/6/7) activation, which in turn causes cell apoptosis (31, 32). In addition, monocytes and macrophages play a pivotal role in the recruitment and antitumor activity of natural killer (NK) cells by secreting several chemoattractants, including CCL3, CCL4, and CCL5 by monocytes, and CXCL10 and CXCL11 by macrophages (11, 33, 34). Finally, monocytes and macrophages tend to mediate phagocytosis by recognizing and eliminating cancer cells (35, 36). In the recognition mechanism, several molecules, such as ATP, UTP, phosphatidylserine, chemokines, polyamines, and other cancer-derived antigens, can attract phagocytes and increase the expression of phagocytic receptors. Furthermore, these phagocytic receptors, such as LRP1, SLAMF7, FcR, αVβ3, BAI1, PSR1, and TIM1/3/4, bind to other molecules expressed on cancer cells, thereby enabling phagocytosis (36, 37).

However, in advanced stages of malignancy, the microenvironment encounters a switch from being tumor-suppressive to supporting cancer progression. This phase is often associated with a decline of the immune system's ability to detect and destroy cancer cells, the development of inflammation that supports tumor growth, the activation of a specific type of immune cells, such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSC), or M2-TAMs (12, 23, 38). On top of that, these cells secrete various pro-tumor cytokines and growth factors that stimulate tumor development, proliferation, metastasis, and drug resistance (39).

Like immune cells, stromal cell components are shaped by the organs from which they arise (22). Stromal cells consist of a variety of cell types, including fibroblasts, pericytes, and endothelial cells. In a healthy condition, stromal cells are important building blocks of connective tissue. They play a crucial role in providing structural support for tissues and organs and in producing extracellular matrix and basement membrane components (40, 41). In the TME context, cancer cells can recruit neighboring non-cancerous host stromal cells. At an advanced stage of malignancy, TME can drive the gradual conversion of fibroblasts into cancer-associated fibroblasts (CAFs) and remodel the extracellular matrix (ECM) toward a stiffer, viscoelastic state, thereby contributing to cancer progression. Generally, CAFs support cancer progression by direct interaction with tumor cells, promoting tumor escape from immune attack, and remodeling the ECM. To a greater extent, ECM remodeling promotes oncogenic transformation, stimulates abnormal biomechanical signals, and determines immune recruitment and activation within the TME. Together, these roles of CAFs and transformed ECM encompass tumor growth, drug resistance, angiogenesis, and immune regulation (22, 38).

Targeting TME components or developing experimental models that properly reflect TME heterogeneity and complexity are current approaches in TME-based cancer treatment strategies. As a major component in TME, targeting the host immune system by either stimulating the activation of anti-tumor immune cells or suppressing the activity of pro-tumoral immune cells has shown promising outcomes (39).

## The Biological Aspect of Tumor-Associated Macrophages

*Tumor-associated macrophages properties*

The malignancy level of the tumor could determine the cellular constituents of the TME, including the macrophage population, which was confirmed as a major immune cell component distributed throughout the TME (42). Studies have shown that macrophages in TME have two distinct origins: tissue-resident macrophages and infiltrating macro-phages recruited from bone marrow-derived monocytes (11, 43). In response to specific stimuli and TME conditions, macrophages can transform into two distinct phenotypes, M1-TAMs or M2-TAMs (44, 45). The TAM proportion is more favorable for M1-TAMs during the early phases of tumor development. However, the M2-TAM population increases significantly as cancer cells manipulate immune surveillance (46, 47).

M1 or M2-TAMs are diverse in many aspects (Table I). M1-TAMs are tumor-suppressing cells that play critical roles in the TME by inhibiting tumor cell growth. Several cytokines and growth factors, such as IFN-γ, TNF-α, or GM-CSF, could stimulate M1-TAM polarization (47). M1-TAMs can be recognized by the production of inducible nitric oxide synthase (iNOS), reactive oxygen species, and IL-12 (48). Additionally, M1-TAMs express multiple molecules, including MHC-II, CD80, and CD86, which activate the Th1 immune response (3, 49). The activated M1-TAMs directly participate in tumor

elimination *via* antibody-dependent cellular phagocytosis, in which Fcγ receptor binding to antibody-opsonized tumor triggers phagocytosis and intracellular degradation (3, 50). On the other hand, M1-TAMs also eliminate tumor cells by promoting immune responses, including activation of cytotoxic T cells and recruitment of NK cells into the TME. As a result, these cytotoxic effector cells directly fight tumor cells and, at the same time, support the anti-tumor function of M1-TAMs by secreting several cytokines and chemokines, including IFN-γ, TNF-α, GM-CSF, and CCL4/5/10. Moreover, the activation of several intracellular molecules, such as STAT1, NF-κB, JAK3, and JNK, in M1-TAMs is linked to downstream signaling pathways that induce the expression of pro-inflammatory cytokines, such as IL-1, IL-6, IL-12, IL-23, and TNF-α. Further, these cytokines are responsible for antitumor immune responses (47, 48). However, under certain conditions, excessive production of pro-inflammatory cytokines, particularly in chronic inflammatory conditions, has been shown to contribute to cancer progression by sustaining inflammation through multiple signaling pathways, including NF-κB, JAK-STAT, MAPK/ERK, or PI3K/AKT (51, 52). For example, NF-κB activation may not only support anti-tumor immune responses but also promote pro-tumor inflammation and contribute to tumor development.

**Table I**

Commonly associated features of tumor-associated macrophages

| Factors | Commonly associated with M1-like TAMs | Commonly associated with M2-TAMs | Ref. |
|---|---|---|---|
| Activation factors | IFN-γ, GM-CSF, TNF-α | IL-4, IL-10, IL-13, M-CSF, TGF-β | (2, 47, 48) |
| Markers | CD86, CD80, CD60, MHCII | CD163, CD206, CD200R, CD209, CD301 | |
| Cytokines production | TNF-α, IL-1β, IL-6, IL-12, IL-23 | IL-1RA, IL-10, IL-4, IL-13, TGF-β | |
| Function in TME | Inhibit tumor proliferation and anti-tumor response. | Promote angiogenesis, invasion, tumor proliferation, metastasis, and drug resistance. | |

On the other hand, M2-TAMs promote tumor growth and modulate immune suppression in the TME. M2-TAMs polarization is typically driven by TGF-β, cytokines (IL-4, IL-13, IL-10), and M-CSF (9, 47). Subsequently, the M2-TAMs release MMP, chemokines, and anti-inflammatory mediators. These factors are known to inhibit the immune responses while promoting tumor invasion, growth, and metastasis (43, 53). Additionally, M2-TAMs exhibit immunosuppressive properties by expressing HLA-E, a non-classical MHC-Ib family member that negatively regulates NK cell activation through interaction with CD94 (54, 55). Furthermore, M2-TAMs express PD-L1, a T cell immune checkpoint ligand that directly inhibits T cell function. Inteestingly, the inhibition of cytotoxic T cells is also mediated by M2-TAMs through the release of arginase, which converts L-arginine to urea and L-ornithine (47, 56). L-arginine plays a pivotal role in regulating the T cell antigen receptor ζ chain (CD3ζ), which is crucial for antigen recognition and cytotoxic activity. Consequently, L-arginine deprivation could reduce antigen sensitivity, thereby impairing cytotoxic effector function (57). At the same time, M2-TAMs produce immunosuppressive cytokines such as IL-10 and TGF-β, which promote Treg cell expansion (47, 56). Together, these M2-TAM activities suppress anti-tumor immune responses, which in turn, promote tumor progression.

*Prognostic significance of tumor-associated macrophages*

TAMs comprise the dominant population of immune cells in the TME, accounting for up to 50% of the total immune cell population (58-60). As a result, the emergence of TAMs is frequently used to predict prognosis in cancer cases. Specifically, the ratio of M1 or M2-TAMs residing in the TME could predict favorable or unfavorable prognostic outcomes (61). In a clinical case study, the appearance of M2-like TAMs is associated with detrimental consequences for cancer patients. It has been demonstrated that M2-like TAMs could stimulate neo-angiogenesis and promote disease progression in ovarian carcinoma patients. Subsequently, a high amount of M2-like TAMs population in epithelial ovarian cancer patients has been associated with diminished treatment sensitivity and a poor prognosis.

In contrast, M1-like TAMs have been suggested as a positive prognostic factor in epithelial ovarian cancer patients, given their ability to elicit robust inflammatory responses that slow disease progression (62). Similarly, in breast cancer patients, a large number of M2-like TAMs has been linked to poor outcomes, which include a higher recurrence rate and shorter overall survival (63). In triple-negative breast cancer patients, high expression of M2-like TAMs indicates a poor prognostic signature, followed by a higher risk of recurrence and lymph node metastasis (64).

The accumulating evidence outlined above underscores the significant role of M2-TAMs in

promoting cancer progression, which is associated with poor outcomes in cancer patients. These outcomes include increased drug resistance, higher recurrence rates, and reduced overall survival. Therefore, targeting M2-TAMs is a crucial strategy for developing effective cancer therapies.

*Tumor-associated macrophages-targeting immunotherapies*

Several approaches have been attempted to target TAMs for cancer treatment, including limiting monocyte recruitment to tumor sites, inhibiting M2-TAM polarization, inducing apoptosis in M2-TAMs, or promoting M2-TAM repolarization into M1-like phenotypes (4, 47, 56). In addition, several anti-M2-TAM drugs, administered as monotherapy or in combination with immunotherapy, are currently in clinical trials (56). For example, carlumab which have completed the phase II clinical trial have been tested in prostate cancer to block CCL-2 which in turn reducing the infiltration of macrophages to the tumor site. BLZ945, which is in an ongoing phase II trial, targets TAMs in solid tumors by inhibiting CSF-1R. In clinical trials, BLZ945 was administered in combination with the anti-PD1 immunotherapy drug PDR0001 (65). HU5F9-G4, currently under-going phase I clinical trials, has demonstrated the ability to enhance macrophage phagocytosis by blocking CD47, presenting a promising strategy for tumor therapy (66). Moreover, another drug, motolimod, could drive TAMs' repolarization into M1-like phenotypes by targeting TLR7 (67). Interestingly, among strategies for targeting TAMs, depleting TAMs has been reported to be less effective and to fail to provide a durable anti-cancer response, compared with inhibiting TAM recruitment or reprogramming TAMs (66). However, one major challenge in targeting TAM recruitment in tumor cases is the presence of the already established TAM population, which makes this approach less effective as a standalone treatment. In contrast, the TAM reprogramming strategy directly leverages the abundant TAMs already present in the TME. Therefore, reprogramming TAMs offers a more balanced and sustainable therapeutic approach by utilizing the existing TAMs population to enhance anti-tumor immunity while minimizing systemic side effects and preserving essential macrophage functions.

## Phytochemicals that Promote M2-TAMs Repolarization into M1-Like Phenotypes

Over the years, there has been a discernible rise in the utilization of natural compounds as adjuvant treatments for cancer. In addition to reducing the toxicity of radiotherapy or chemotherapy, using natural compounds can also help promote anti-tumor activity, improve quality of life, and extend the survival of cancer patients (68, 69). The accumulation of evidence demonstrates that natural compounds not only affect cancer cells but also the TME, including TAMs, the predominant population that significantly impacts cancer progression (70). Table II summarizes the effects of natural compounds on regulating tumor-associated macrophages, especially in inducing M2-TAMs to reprogram into M1-like phenotypes. Based on those phenomena, there are multiple possible ways to induce the M2-like repolarization into M1-like TAMs. In the review, we summarize the activities of natural products with anti-cancer properties that modulate M2-TAM repolarization into M1-like TAMs.

Interestingly, a wide range of active compounds capable of inducing TAM reprogramming originates from diverse compound families, including alkaloids, anthraquinones, chalcones, flavonoids, glycoproteins, isoflavones, lignans, phenolics, polyphenols, polysaccharides, saponins, terpenoids, and α-amino fatty acids. This diverse origin underscores the immense potential to develop drug candidates, given the broad availability of resources and varied mechanisms of action. Based on our collected data, most of these compounds exhibit TAM-reprogramming properties by influencing genes or proteins known to drive the M2-TAM signature, thereby facilitating a switch to M1-like phenotypes. For instance, treatments with these compounds across different cancer models consistently increase M1-like markers, including CD80, CD86, TNF-α, and IL-12, while reducing M2-associated markers, including CD206, Arg-1, and IL-10. This pattern highlights the promising role of these compounds in reshaping the tumor microenvironment by reprogramming TAMs to support anti-tumor immunity.

## Possible Mechanisms of M2-TAMs Reprogramming by Natural Products

Numerous studies have investigated the mechanisms by which natural compounds facilitate the transformation of M2 macrophages into M1 macrophages through the induction of natural compounds. However, research explicitly illustrating the mechanism by which TAMs reprogram into M1-like phenotypes remains scarce. In the following discussion, we highlight several natural products that promote M2-TAMs repolarization into M1-like phenotypes through specific mechanisms. Specifically, we noticed that some natural products exert their effects on M2-TAM reprogramming by regulating critical signal transduction pathways, such as STAT and TLR pathways, which have a major role in macrophage polarization. These pathways modulate the transcriptional profile of TAMs, affecting their capacity to produce pro-inflammatory cytokines, such as TNF-α and IL-12, while diminishing immunosuppressive markers, such as IL-10 and Arg1. By targeting these pathways, natural products can

significantly recalibrate the TME, thereby improving anti-tumor immune responses and underscoring their potential as therapeutic agents in cancer treatment.

**Table II**

Composition and codification of metronidazole gel formulations

| Specific Compound | Compound Class | Cancer Case | Detail activity | Ref. |
|---|---|---|---|---|
| 6-Gingerol | Phenolic | Lung cancer | ↓ protein expression of arginase and ↑ protein expression of iNOS in lung interstitial macrophages and tumor from urethane-induced mouse carcinogenesis. | (71) |
| Myriocin | α-Amino fatty acid | Lung cancer | ↓ protein expression of Arg-1 in the tumor from LLC-bearing mice. | (72) |
| XK-81 | Phenol | Breast cancer | ↓ protein expression of CD206 and ↑ protein expression of CD80 in the tumor from 4T1A-bearing mice. | (73) |
| SYQ-PA | Polysaccharide | Breast cancer | ↓ protein expression of CD206 and ↑ protein expression of CD86 in tumor from MMTV-PyMT transgenic mice. | (74) |
| Lentinan | Polysaccharide | Breast cancer | ↓ protein expression of CD206 and gene expression of *CD206*, *Fizz1*, *Arg1* and *Ym1* in tumor from 4T1-bearing BALB/c mice. | (75) |
| Resveratrol | Polyphenol | Breast cancer | ↓ gene expression of *CD163* and protein expression of ARG-1 in TAMs. | (76) |
| Resveratrol | Polyphenol | Breast cancer | ↓ protein expression of CD206 and ↑ protein expression of CD86 in the tumor from 4T1A-bearing mice. | (77) |
| Anemoside A3 | Saponin | Breast cancer | ↑ protein expression of CD86 in tumor from 4T1 Luc-bearing BALB/c mice. | (78) |
| Sophoridine | Alkaloid | Gastric cancer | ↓ gene expression of *Arg-1*, *CD206*, and *IL-10*, and ↑ gene expression of *INOS*, *IFN-β*, and *IL-12α* in TAMs. | (79) |
| Apigenin | Flavonoid | Pancreatic cancer | ↓ protein expression of Ym-1 and ↑ protein expression of iNOS in the tumor from Panc02-bearing mice. | (80) |
| PBP | Polysaccharide | Breast cancer | ↓ protein expression of CD206 and IL-4, and ↑ protein expression of IL-12 in J774.1A cells co-cultured with 4T1 cells. | (81) |
| Nimbolide | Terpenoid | Oral cancer | ↓ protein expression of ARG-1 and ↑ protein expression of iNOS in TAMs from Cal27-derived tumor. | (82) |
| Fucoidan | Polysaccharide | Breast cancer | ↓ protein expression of Arg-1, IL-10, and TGF-β, and ↑ protein expression of iNOS, IL-6, and TNF-α in RAW 264.7 cells co-cultured with 4T1 cells. | (83) |
| 9-Hydroxycanthin-6-one | Alkaloids | Ovarian cancer | ↓ gene expression of M2Φ markers (*CD206*, *Trem2*), cytokines (*IL-10*), and cancer promoting-factors (*VEGF*, *MMP-2*, *MMP-9*) in TAMs. | (84) |

| Specific Compound | Compound Class | Cancer Case | Detail activity | Ref. |
|---|---|---|---|---|
| Deoxyschizandrin | Lignans | Ovarian cancer | ↓ gene expression of M2Φ markers (*CD163* & *CD209*), gene and protein expression of cancer-promoting-factors (CCL5, MMP-9, VEGF) in TAMs. | (85) |
| PSPJ | Polysaccharide | Liver cancer | ↓ gene expression of immunosuppressive factors (*IL-10*, *TGF-β*, *PEG2*) and ↓ soluble proteins level of IL-10, TGF-β, and COX-2 in TAMs.<br>↓ protein expression of CD163 in H22-derived tumor. | (88) |
| Baicalein | Flavonoids | Breast cancer | ↓ protein (CD206) and gene (*Arg-1*. *TGF-β*, *IL-10*) expression, and ↑ protein (CD86) and gene (*IL-12*, *TNF-α*) expression in TAMs. | (87) |
| IAPS-2 | Polysaccharide | Epithelial cancer | ↓ protein (IL-10) and gene (*Arg1* and *Ym1*) expression, and ↑ protein (IL-12) and gene expression (iNOS and MHCII) in TAMs. | (88) |
| Astragaloside IV | Saponin | Lung cancer | ↓ protein expression of CD206 and ARG-1 in the tumor from LLC-bearing mice. | (89) |
| CH625 | Flavonoid | Brain cancer | ↓ protein expression (CD206, CCL2, IL-10, VEGF, and TFG-β) and gene expression (*Arg-1*, *CD206*), and ↑ proteins expression (TNF-α and IL-12) and gene expression (iNOS and CXCL9) in tumor from C6-bearing rat. | (90) |
| Puerarin | Isoflavones | Lung cancer | ↓ protein expression (CD206, Arg-1, CD163) and pro-tumor cytokines (IL-10, IL-4, TGF-β) in tumor tissue from non-small cell lung carcinoma xenograft model, and ↑ protein expression (CD197, iNOS, CD40) and pro-inflammatory cytokines (IFN-ɣ, TNF-α, IL-12) in tumor tissue from non-small cell lung carcinoma xenograft model. | (91) |
| Emodin | Anthraquinones | Breast cancer | ↓ gene expression (*Arg-1*, *CD206*), and ↑ gene expression of *iNOS* and pro-inflammatory cytokines (*IL-1β*, *TNF-α*) in F4/80$^+$ TAMs from EO771-derived tumor. | (92) |
| Paeoniflorin | Phenolic | Lung cancer | ↓ protein expression of CD206 and ↑ protein expression of CD11c in the LLC-derived tumor. | (93) |
| β-glucan | Polysaccharide | Lung cancer | ↓ gene expression of *arginase* and *IL-10*, and ↑ gene expression of iNOS, IL-12, TNF-α, IL-1β, and IL-6 in TAMs | (94) |
| NLGP | Glycoprotein | Laryngeal cancer | ↓ protein expression of CD206 and IL10, and ↑ protein expression of MHCII, CD80, and IL12 in TAMs | (95) |
| HS-1793 | Polyphenol | Breast cancer | ↓ protein expression of CD206, and ↑ protein expression of IFN-ɣ in the tumor from FM3A-bearing mice. | (96) |

*STAT pathways*

A study conducted by Li Q *et al*. demonstrated that the acidic polysaccharide fraction extracted from *Ilex asprella* root, called IAPS-2, exhibits promising novel anti-tumor properties by promoting TAMs repolarization into an M1-like phenotype (88). Western blot analysis was performed to understand the mechanism by which IAPS-2 could induce TAMs to switch to M1-like phenotypes. The TAMs obtained from S180 tumor tissue were treated with IAPS-2 as the treatment group and PBS as the control to evaluate the expression of phosphorylated P65 (p-P65), total P65, phosphorylated STAT1 (p-STAT1), total STAT1 (T-STAT1), phosphorylated STAT3 (p-STAT3), and total STAT3 (T-STAT3). Interestingly, the study revealed that IAPS-2 significantly inhibits STAT3 phosphorylation. STAT3 is a transcriptional regulator known to be activated by IL-10, a key factor in M2 macrophage polarization. Additionally, it has been well documented that TAMs release IL-6 through the STAT3 pathway, which stimulates the growth of cancer stem cells, promotes cancer progression, and triggers M2 macrophage polarization (97, 98).

On the other hand, IAPS-2 treatment promotes phosphorylation of STAT1 and P65 in TAMs. The phosphorylation of STAT1 and P65 is essential for repolarizing M2-TAMs into an anti-tumor M1 phenotype. STAT1 phosphorylation enhances the production of pro-inflammatory cytokines, including the M1-like TAM marker such as IL-12 and iNOS. Simultaneously, P65 phosphorylation activates the NF-κB pathway, thereby facilitating polarization into M1-like phenotypes through transcriptional activation of pro-inflammatory genes. Additionally, an ELISA experiment showed that IAPS-2 reduced IL-10 protein levels and increased IL-12 expression in TAMs.

In the same way, the M2-macrophage-associated gene expression, such as *Arg1* and *Ym1*, was reduced in IAPS-2-treated mice. In contrast, M1-macrophage-associated gene expression, such as *iNOS* and *MHCII*, was increased in IAPS-2-treated mice. Together, these findings indicated that IAPS-2 promotes M1-type differentiation in TAMs *via* the NF-κB and STAT signaling pathways (88). NF-κB plays an essential role in TAM polarization during tumorigenesis. In response to activating stimuli, including TLR ligands, IL-1β, and TNF-α, NF-κB mediates the shift of macrophages to the M1 phenotype. Thus, targeting the NF-κB pathway in TAMs is a promising therapeutic approach to counteract immunosuppression caused by the microenvironment while improving anti-tumor immunity (99).

Another natural product extracted from neem leaf, called neem leaf glycoprotein (NLGP), has been shown to significantly promote TAMs' switch to M1-like phenotypes. The treatment of NLGP on supraglottic laryngeal tumor cell lysate-supplemented human PBMC-derived macrophages could reduce the phosphorylation of STAT3 and increase the phosphorylation of STAT1 (95). It is well known that M1 polarization is modulated by STAT1 pathway activation. Together with HLA-DR and iNOS, pSTAT1 is recognized as a prominent marker in M1-like TAMs. Furthermore, high levels of STAT1 expression in M1 macrophages are correlated to its function in the acute pro-inflammatory response (100). In addition, NLGP treatment could promote the depletion of the M2-like phenotype, as indicated by reduced expression of the main M2 macrophage marker, CD206. However, some co-stimulatory surface molecules found in M1 macrophages, such as MHCII and CD80, were increased. On top of that, cytokine production supports the evidence that NLGP promotes a switch from M2-like TAMs to an M1-like phenotype, as observed by down-regulated *IL-10* gene and protein expression and up-regulated *IL-12* expression (95).

It has been known that activation of EGFR signaling promotes M2-TAM polarization (101). Thus, we suggest that inhibiting this pathway might promote repolarization of TAMs toward M1-like TAMs, thereby enhancing anti-tumor activity. A study demonstrated that CH625 treatment could significantly suppress the levels of phosphorylated EGFR (p-EGFR) and phosphorylated STAT3 (p-STAT3) in peripheral blood mononuclear cells co-cultured with glioma tumor supernatant. Decreased levels of p-EGFR and p-STAT3 are associated with TAM reprogramming into M1-like phenotypes, characterized by decreased expression of M2 markers, such as Arg-1 and CD206 mRNA. The repolarization is also characterized by decreased cytokine and chemokine production, such as IL-10 and CCL2 (90).

*TLR pathways*

TLR4 signaling has been well known for its contribution to M1 macrophage activation. Inter-estingly, a report suggested that activation of TLR4 by paclitaxel, a natural product-derived anti-cancer drug, could induce TAMs to reprogram into M1-like phenotypes. The study specifically demonstrated that paclitaxel treatment in B16 tumor-bearing C57BL/6 wild-type (WT) mice significantly reduced CD206 expression and, concurrently, decreased tumor growth. On the other hand, in the other model, TLR4 knockout mice ($TLR4^{-/-}$) showed no significant difference compared to the control group in lowering the M2-like TAM population or reducing tumor volume after treatment with paclitaxel (102). These findings suggested that TLR4 activation in B16 tumor-bearing C57BL/6 WT mice contributed to TAM reprogramming toward M1-like phenotypes. However, consideration is needed, as these results reflect murine findings, which might have model- and species-dependent variation in TLR4

activation by paclitaxel, and therefore further studies are needed to elucidate whether similar responses and actions occur in human macrophages.

Anemoside A3 has been shown to have TAM reprogramming activity by increasing the levels of CD86 and TLR4 proteins in tumor tissue from 4T1 Luc-bearing BALB/c mice. The TAM reprogramming mechanism of anemoside A3 has been evaluated by assessing the TLR4/NF-κB/MAPK pathways in THP-1-derived macrophages co-cultured with MCF-7 cells. Treatment with anemoside A3 has significantly increased the expression of several proteins, including TLR4, MyD88, TRAF6, phosphorylated-IκBα, phosphorylated-NF-κB, and p38. These findings demonstrated that anemoside A3 could repolarize the TAMs into M1-like phenotypes (78).

Another study demonstrated that sophoridine triggers the repolarization of M2-like TAMs into an M1-like phenotype through the TLR4-IRF-3 axis. The sophoridine treatments on MFC cell line-conditioned medium-supplemented mouse bone marrow-derived macrophages have shown a slight effect on TLR4 and IRF-3; however, the sophoridine treatment significantly increased the phosphorylation level of IRF-3. Further investigation into blocking TLR4 expression using the TLR4*i* Sparstolonin B revealed that the increase in iNOS levels and the decrease in Arg-1 levels in TAMs observed with sophoridine treatment were reversed by TLR4 inhibition. Similarly, the phosphorylation level of IRF-3 was suppressed after TLR4*i* treatment, indicating that IRF-3 expression depends on TLR4 activation. Subsequently, sophoridine treatment could decrease the number of $CD206^+$ M2-like TAMs. Additionally, several M1-macrophage-associated genes, such as iNOS, IFN-β, and IL-12α, were upregulated, whereas some M2-macrophage-associated genes, such as Arg-1, CD206, and IL-10, were downregulated in TAMs after sophoridine treatment (79). Activated TLR pathways could promote TAM repolarization into an M1-like phenotype in an immunosuppressive microenvironment. Generally, TLR agonists are used to stimulate immune activation by triggering several TLR families, such as TLR3, TLR4, TLR7/8, or TLR9 (100). For instance, an FDA-approved TLR agonist called BCG could activate the TLR4 signaling pathways, which, in turn, promote TAM repolarization toward anti-tumor phenotypes (103). Similarly, the anti-tumor properties of TAMs could be stimulated in melanoma patients treated with TLR7/TLR8 agonists, which also reprogram M2-like TAMs into M1-like phenotypes (100).

*Dectin-1-Erk pathway*

β-glucan treatment of TAMs purified from LLC tumors significantly reduced the expression of M2 macrophage-related genes, such as arginase and IL-10. Subsequently, similar treatment could promote M1 macrophage-related genes, such as iNOS, IL-12, TNF-α, IL-1β, and IL-6, in a dectin-1 receptor-dependent manner. Further analysis of gene expression demonstrated that TNF-α, IL-6, IL-10, and arginase were upregulated by Erk*i* treatment. At the molecular level, β-glucan treatment promotes Erk1/2 phosphorylation *via* the Dectin-1 receptor (94). Together, these findings highlight the anti-cancer activity of β-glucan, which modulates TAM repolarization into M1-like phenotypes *via* the dectin-1-Erk pathway. Dectin-1 is a major pattern recognition receptor for β-glucan that is widely expressed in macrophages. In addition to stimulating TAMs' repolarization toward M1-like phenotypes, the activation of dectin-1 by β-glucan could promote a broad spectrum of macrophage actions, including phagocytosis initiation, superoxide generation, inflammatory cytokine production, and polarization toward M1 macrophages (104).

**Future Direction**

The exploration of natural product-based drugs should be emphasized for screening and identifying compounds with selective activity in TAMs repolarization. Additionally, the advancement and exploration of target-specific natural products capable of selectively regulating upstream or downstream signaling pathways, particularly those involved in TAMs repolarization, are essential. Another alternative strategy is to optimize the potency of natural products in combination with therapy to target established biomarkers for TAM repolarization while simultaneously identifying potential new biomarkers. For example, the CSF1/CSF1R blockade has shown promise in reprogramming tumor-infiltrating macrophages (105). Similarly, the PI3K inhibition can alleviate the immunosuppressive state of macrophages by inducing transformation (100, 106). Recently, various drugs have been developed and advanced to clinical trials, targeting key molecules involved in TAMs reprogramming. These include the monoclonal antibodies Hu59-G4 and CC-90002, which block CD47; agonistic antibodies such as CP-870,893 and RO7009789, which target CD40; and small molecules targeting TLR7, TLR9, and CSF1R (56). Therefore, further research in combining existing drugs with natural products could provide an opportunity to enhance the rate of M2-TAMs repolarization.

A different strategy entails developing nanoparticle formulations based on plant-derived compounds, specifically targeting TAMs to reduce off-target effects (107, 108). At the same time, the development of advanced drug delivery systems, including polymeric, liposome, or inorganic-based carriers that specifically target TAMs within the TME by employing ligands for TAM-specific markers such as

CD44, CD206, or CD163, facilitates the precise delivery of therapeutic agents (109-111).

The above advancements in targeting TAMs are considered a promising approach for cancer treatment. The application of natural products, whether used alone or in combination with other therapies, has shown promise in modulating TAM activity and transforming them from pro-tumoral to anti-tumoral states. Together, these strategies provide innovative pathways to enhance cancer treatment by optimizing the therapeutic benefit of natural products and refining therapeutic precision in targeting TAMs.

## Conclusions

TME plays a crucial role in cancer progression, with macrophages emerging as central contributors within this complex ecosystem. TAMs, recognized for their plasticity and functional versatility, are frequently identified as a pro-tumor phenotype that drives cancer progression through various mechanisms such as immune evasion, angiogenesis, and metastasis. Therefore, understanding the biological aspects of TAMs and their interactions within the TME highlights their significance as valuable biomarkers and therapeutic targets for cancer therapy. Plant-derived natural products have demonstrated great potential for regulating TAM behavior and reprogramming them toward M1-like phenotypes that exhibit anti-tumor activity. Despite these benefits, challenges remain in optimizing the bioavailability, stability, and specificity of natural products to ensure the effective and efficient targeting of TAM in future clinical applications. In addition, future research should prioritize exploring natural product-based drugs, refining the target-specific and intricate signaling pathways governing TAM repolarization, and emphasizing the integration of cutting-edge technologies, such as nanotechnology-based delivery systems, to overcome existing limitations and improve therapeutic outcomes. Finally, targeting TAMs with natural products suggests a promising prospect in cancer therapy

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## Availability of data and materials

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## Conflict of interest

The authors declare no conflict of interest.

## References

1. Mass E, Nimmerjahn F, Kierdorf K, Schlitzer A. Tissue-specific macrophages: How they develop and choreograph tissue biology. Nat Rev Immunol. 2023;23(9):563-579.
2. Chen S, Saeed AFUH, Liu Q, Jiang Q, Xu H, Xiao GG, et al. Macrophages in immunoregulation and therapeutics. Signal Transduct Target Ther. 2023;8(1):207.
3. Strizova Z, Benesova I, Bartolini R, Novysedlak R, Cecrdlova E, Foley LK, et al. M1/M2 macrophages and their overlaps - myth or reality?. Clin Sci (Lond). 2023;137(15):1067-1093.
4. Duan Z, Luo Y. Targeting macrophages in cancer immunotherapy. Signal Transduct Target Ther. 2021;6(1):127.
5. Hassanshahi A, Moradzad M, Ghalamkari S, Fadaei M, Cowin AJ, Hassanshahi M. Macrophage-mediated inflammation in skin wound healing. Cells. 2022;11(19):2953.
6. Ross EA, Devitt A, Johnson JR. Macrophages: The good, the bad, and the gluttony. Front Immunol. 2021;12:708186.
7. Austermann J, Roth J, Barczyk-Kahlert K. The good and the bad: Monocytes' and macrophages' diverse functions in inflammation. Cells. 2022;11(12):1979.
8. Lendeckel U, Venz S, Wolke C. Macrophages: Shapes and functions. ChemTexts. 2022;8(2):12.
9. Yunna C, Mengru H, Lei W, Weidong C. Macrophage M1/M2 polarization. Eur J Pharmacol. 2020;877:173090.
10. Yang YL, Yang F, Huang ZQ, Li YY, Shi HY, Sun Q, et al. T cells, NK cells, and tumor-associated macrophages in cancer immunotherapy and the current state of the art of drug delivery systems. Front Immunol. 2023;14:1199173.
11. Zhou J, Zhang S, Guo C. Crosstalk between macrophages and natural killer cells in the tumor microenvironment. Int Immunopharmacol. 2021;101(B):108374.
12. Blériot C, Dunsmore G, Alonso-Curbelo D, Ginhoux F. A temporal perspective for tumor-associated macrophage identities and functions. Cancer Cell. 2024;42(5):747-758.
13. Liu L, Chen G, Gong S, Huang R, Fan C. Targeting tumor-associated macrophage: An adjuvant strategy for lung cancer therapy. Front Immunol. 2023;14:1274547.
14. Memarzia A, Saadat S, Asgharzadeh F, Behrouz S, Folkerts G, Boskabady MH. Therapeutic effects of medicinal plants and their constituents on lung cancer, in vitro, in vivo and clinical evidence. J Cell Mol Med. 2023;27(19):2841-2863.

15. Sirbu MI, Predescu IA, Horhat DI, Mot IC, Banța AM, Orășan A, et al. Evaluation of quercetin, myricetin and their combination as flavonoids with antitumour potential in head and neck cancer models: An in vitro and in ovo study. Farmacia. 2025;73(5):1143-1154.
16. Ali M, Wani SUD, Salahuddin M, Manjula SN, Mruthunjaya K, Dey T, et al. Recent advance of herbal medicines in cancer - A molecular approach. Heliyon. 2023;9(2):e13684.
17. Asiimwe JB, Nagendrappa PB, Atukunda EC, Kamatenesi MM, Nambozi G, Tolo CU, et al. Prevalence of the use of herbal medicines among patients with cancer: A systematic review and meta-analysis. Evid Based Complement Alternat Med. 2021;2021:9963038.
18. Choudhari AS, Mandave PC, Deshpande M, Ranjekar P, Prakash O. Phytochemicals in cancer treatment: From preclinical studies to clinical practice. Front Pharmacol. 2020;10:1614.
19. Yao P, Liang S, Liu Z, Xu C. A review of natural products targeting tumor immune microenvironments for the treatment of lung cancer. Front Immunol. 2024;15:1343316.
20. Zhang W, Li S, Li C, Li T, Huang Y. Remodeling tumor microenvironment with natural products to overcome drug resistance. Front Immunol. 2022;13:1051998.
21. Anderson NM, Simon MC. The tumor microenvironment. Curr Biol. 2020;30(16):R921-R925.
22. Zhao Y, Shen M, Wu L, Yang H, Yao Y, Yang Q, et al. Stromal cells in the tumor microenvironment: Accomplices of tumor progression?. Cell Death Dis. 2023;14(9):587.
23. de Visser KE, Joyce JA. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer Cell. 2023;41(3):374-403.
24. Liu SY, Zhu RH, Wang ZT, Tan W, Zhang L, Wang YQ, et al. Landscape of immune microenvironment in epithelial ovarian cancer and establishing risk model by machine learning. J Oncol. 2021;2021:5523749.
25. Gu Y, Wu X, Zhang J, Fang Y, Pan Y, Shu Y, et al. The evolving landscape of N6-methyladenosine modification in the tumor microenvironment. Mol Ther. 2021;29(5):1703-1715.
26. Li Z, Yin P. Tumor microenvironment diversity and plasticity in cancer multidrug resistance. Biochim Biophys Acta Rev Cancer. 2023;1878(6):188997.
27. Bożyk A, Wojas-Krawczyk K, Krawczyk P, Milanowski J. Tumor microenvironment - A short review of cellular and interaction diversity. Biology (Basel). 2022;11(6):929.
28. Liu W, Puri A, Fu D, Chen L, Wang C, Kellis M, et al. Dissecting the tumor microenvironment in response to immune checkpoint inhibitors via single-cell and spatial transcriptomics. Clin Exp Metastasis. 2024;41(4):313-332.
29. Pimentel JM, Zhou JY, Wu GS. The role of TRAIL in apoptosis and immunosurveillance in cancer. Cancers (Basel). 2023;15(10):2752.
30. Liguori M, Buracchi C, Pasqualini F, Bergomas F, Pesce S, Sironi M, et al. Functional TRAIL receptors in monocytes and tumor-associated macrophages: A possible targeting pathway in the tumor microenvironment. Oncotarget. 2016;7(27):41662-41676.
31. Luo C, He S, Shi F, Zhou J, Shang L. The role of TRAIL signaling in cancer: Searching for new therapeutic strategies. Biology (Basel). 2024;13(7):521.
32. Sag D, Ayyildiz ZO, Gunalp S, Wingender G. The role of TRAIL/DRs in the modulation of immune cells and responses. Cancers (Basel). 2019;11(10):1469.
33. Chen X, Li Y, Xia H, Chen YH. Monocytes in tumorigenesis and tumor immunotherapy. Cells. 2023;12(13):1673.
34. Olingy CE, Dinh HQ, Hedrick CC. Monocyte heterogeneity and functions in cancer. J Leukoc Biol. 2019;106(2):309-322.
35. Zhou X, Liu X, Huang L. Macrophage-mediated tumor cell phagocytosis: Opportunity for nanomedicine intervention. Adv Funct Mater. 2021;31(5):2006220.
36. Lecoultre M, Dutoit V, Walker PR. Phagocytic function of tumor-associated macrophages as a key determinant of tumor progression control: A review. J Immunother Cancer. 2020;8(2):e001408.
37. Xiao L, Zhang L, Guo C, Xin Q, Gu X, Jiang C, et al. "Find Me" and "Eat Me" signals: Tools to drive phagocytic processes for modulating antitumor immunity. Cancer Commun (Lond). 2024;44(7):791-832.
38. Zhang S, Xiao X, Yi Y, Wang X, Zhu L, Shen Y, et al. Tumor initiation and early tumorigenesis: Molecular mechanisms and interventional targets. Signal Transduct Target Ther. 2024;9(1):149.
39. Tiwari A, Trivedi R, Lin SY. Tumor microenvironment: Barrier or opportunity towards effective cancer therapy. J Biomed Sci. 2022;29(1):83.
40. Manetti M. Molecular morphology and function of stromal cells. Int J Mol Sci. 2021;22(24):13422.
41. Roberts EW, Denton AE, Fearon DT. Roles of stromal cells in the immune system. In: Bradshaw RA, Stahl PD, editors. Encyclopedia of Cell Biology. Elsevier; 2016. p. 616-623.
42. Cendrowicz E, Sas Z, Bremer E, Rygiel TP. The role of macrophages in cancer development and therapy. Cancers (Basel). 2021;13(8):1946.
43. Nowak M, Klink M. The role of tumor-associated macrophages in the progression and chemoresistance of ovarian cancer. Cells. 2020;9(5):1299.
44. Kumari N, Choi SH. Tumor-associated macrophages in cancer: Recent advancements in cancer nanoimmunotherapies. J Exp Clin Cancer Res. 2022;41(1):68.
45. Väyrynen JP, Haruki K, Lau MC, Väyrynen SA, Zhong R, Dias Costa A, et al. The prognostic role of macrophage polarization in the colorectal cancer microenvironment. Cancer Immunol Res. 2021;9(1):8-19.
46. Boutilier AJ, Elsawa SF. Macrophage polarization states in the tumor microenvironment. Int J Mol Sci. 2021;22(13):6995.
47. Wang S, Wang J, Chen Z, Luo J, Guo W, Sun L, et al. Targeting M2-like tumor-associated macrophages is a potential therapeutic approach to overcome antitumor drug resistance. NPJ Precis Oncol. 2024;8(1):31.
48. Zhang W, Wang M, Ji C, Liu X, Gu B, Dong T. Macrophage polarization in the tumor microenvironment: Emerging roles and therapeutic potentials. Biomed Pharmacother. 2024;177:116930.
49. Palmieri EM, Gonzalez-Cotto M, Baseler WA, Davies LC, Ghesquière B, Maio N, et al. Nitric oxide orchestrates metabolic rewiring in M1 macrophages by

targeting aconitase 2 and pyruvate dehydrogenase. Nat Commun. 2020;11(1):698.
50. Cao X, Chen J, Li B, Dang J, Zhang W, Zhong X, et al. Promoting antibody-dependent cellular phagocytosis for effective macrophage-based cancer immunotherapy. Sci Adv. 2022;8(11):eabl9171.
51. Kapoor G, Prakash S, Jaiswal V, Singh AK. Chronic inflammation and cancer: Key pathways and targeted therapies. Cancer Invest. 2025;43(1):1-23.
52. Tripathi S, Sharma Y, Kumar D. Unveiling the link between chronic inflammation and cancer. Metabol Open. 2025;25:100347.
53. Yang Q, Guo N, Zhou Y, Chen J, Wei Q, Han M. The role of tumor-associated macrophages (TAMs) in tumor progression and relevant advance in targeted therapy. Acta Pharm Sin B. 2020;10(11):2156-2170.
54. Morandi F, Pistoia V. Interactions between HLA-G and HLA-E in physiological and pathological conditions. Front Immunol. 2014;5:394.
55. Marchesi M, Andersson E, Villabona L, Seliger B, Lundqvist A, Kiessling R, et al. HLA-dependent tumour development: A role for tumour associate macrophages?. J Transl Med. 2013;11:247.
56. Cassetta L, Pollard JW. Targeting macrophages: Therapeutic approaches in cancer. Nat Rev Drug Discov. 2018;17(12):887-904.
57. Yang L, Chu Z, Liu M, Zou Q, Li J, Liu Q, et al. Amino acid metabolism in immune cells: Essential regulators of the effector functions, and promising opportunities to enhance cancer immunotherapy. J Hematol Oncol. 2023;16(1):59.
58. Zhang X, Ji L, Li MO. Control of tumor-associated macrophage responses by nutrient acquisition and metabolism. Immunity. 2023;56(1):14-31.
59. Zhang Q, Sioud M. Tumor-associated macrophage subsets: Shaping polarization and targeting. Int J Mol Sci. 2023;24(8):7493.
60. Lahmar Q, Keirsse J, Laoui D, Movahedi K, Van Overmeire E, Van Ginderachter JA. Tissue-resident versus monocyte-derived macrophages in the tumor microenvironment. Biochim Biophys Acta. 2016;1865(1):23-34.
61. Bruni D, Angell HK, Galon J. The immune contexture and Immunoscore in cancer prognosis and therapeutic efficacy. Nat Rev Cancer. 2020;20(11):662-680.
62. Fucikova J, Coosemans A, Orsulic S, Cibula D, Vergote I, Galluzzi L, et al. Immunological configuration of ovarian carcinoma: Features and impact on disease outcome. J Immunother Cancer. 2021;9(10):e002873.
63. Tiainen S, Tumelius R, Rilla K, Hämäläinen K, Tammi M, Tammi R, et al. High numbers of macrophages, especially M2-like (CD163-positive), correlate with hyaluronan accumulation and poor outcome in breast cancer. Histopathology. 2015;66(6):873-883.
64. Zhang WJ, Wang XH, Gao ST, Chen C, Xu XY, Sun Q, et al. Tumor-associated macrophages correlate with phenomenon of epithelial-mesenchymal transition and contribute to poor prognosis in triple-negative breast cancer patients. J Surg Res. 2018;222:93-101.
65. Mantovani A, Allavena P, Marchesi F, Garlanda C. Macrophages as tools and targets in cancer therapy. Nat Rev Drug Discov. 2022;21(11):799-820.
66. Li M, He L, Zhu J, Zhang P, Liang S. Targeting tumor-associated macrophages for cancer treatment. Cell Biosci. 2022;12(1):85.
67. Pittet MJ, Michielin O, Migliorini D. Clinical relevance of tumour-associated macrophages. Nat Rev Clin Oncol. 2022;19(6):402-421.
68. Wu J, Li Y, He Q, Yang X. Exploration of the use of natural compounds in combination with chemotherapy drugs for tumor treatment. Molecules. 2023;28(3):1022.
69. Lin SR, Chang CH, Hsu CF, Tsai MJ, Cheng H, Leong MK, et al. Natural compounds as potential adjuvants to cancer therapy: Preclinical evidence. Br J Pharmacol. 2020;177(6):1409-1423.
70. Zhou X, Wang X, Sun Q, Zhang W, Liu C, Ma W, et al. Natural compounds: A new perspective on targeting polarization and infiltration of tumor-associated macrophages in lung cancer. Biomed Pharmacother. 2022;151:113096.
71. 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 Funct. 2018;9(9):4611-4620.
72. Jang H, Ojha U, Jeong JH, Park KG, Lee SY, Lee YM. Myriocin suppresses tumor growth by modulating macrophage polarization and function through the PI3K/Akt/mTOR pathway. Arch Pharm Res. 2023;46(7):629-645.
73. Sun R, Zhang M, Li B, Jiang S, Yu W, Yang L, et al. A novel bromophenol compound from Leathesia nana inhibits breast cancer in a direct tumor killing and immunotherapy manner. Molecules. 2023;28(14):5349.
74. Liu X, Liu X, Mao W, Guo Y, Bai N, Jin L, et al. Tetrastigma polysaccharide reprogramming of tumor-associated macrophages via PPARγ signaling pathway to play antitumor activity in breast cancer. J Ethnopharmacol. 2023;314:116645.
75. Guan Z, Liu Y, Liu P, Yin L, Chen L, Duan W. Lentinan regulates the immune efficacy of macrophage for lung metastasis in triple negative breast. J Funct Foods. 2023;105:105560.
76. Cheuk IW, Chen J, Siu M, Ho JC, Lam SS, Shin VY, et al. Resveratrol enhanced chemosensitivity by reversing macrophage polarization in breast cancer. Clin Transl Oncol. 2022;24(5):854-863.
77. Han X, Zhao N, Zhu W, Wang J, Liu B, Teng Y. Resveratrol attenuates TNBC lung metastasis by down-regulating PD-1 expression on pulmonary T cells and converting macrophages to M1 phenotype in a murine tumor model. Cell Immunol. 2021;368:104423.
78. Yin L, Fan Z, Liu P, Chen L, Guan Z, Liu Y, et al. Anemoside A3 activates TLR4-dependent M1-phenotype macrophage polarization to represses breast tumor growth and angiogenesis. Toxicol Appl Pharmacol. 2021;432:115755.
79. 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. Biomed Pharmacother. 2020;121:109636.
80. Villalobos-Ayala K, Ortiz Rivera I, Alvarez C, Husain K, DeLoach D, Krystal G, et al. Apigenin increases

SHIP-1 expression, promotes tumoricidal macrophages and anti-tumor immune responses in murine pancreatic cancer. Cancers (Basel). 2020;12(12):3631.
81. Jędrzejewski T, Pawlikowska M, Sobocińska J, Wrotek S. Protein-bound polysaccharides from Coriolus versicolor fungus disrupt the crosstalk between breast cancer cells and macrophages through inhibition of angiogenic cytokines production and shifting tumour-associated macrophages from the M2 to M1 subtype. Cell Physiol Biochem. 2020;54(4):615-628.
82. Morris J, Gonzales CB, De La Chapa JJ, Cabang AB, 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. Front Oncol. 2019;9:890.
83. Pawar VK, Singh Y, Sharma K, Shrivastav A, Sharma A, Singh A, et al. Improved chemotherapy against breast cancer through immunotherapeutic activity of fucoidan decorated electrostatically assembled nanoparticles bearing doxorubicin. Int J Biol Macromol. 2019;122:1100-1114.
84. 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. Chem Biol Interact. 2018;280:99-108.
85. 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.
86. 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. Int J Biol Macromol. 2018;111:430-439.
87. 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. Am J Cancer Res. 2018;8(8):1528-1540.
88. Li Q, Hao Z, Hong Y, He W, Zhao W. Reprogramming tumor associated macrophage phenotype by a polysaccharide from Ilex asprella for sarcoma immunotherapy. Int J Mol Sci. 2018;19(12):3816.
89. Xu F, Cui WQ, 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. J Exp Clin Cancer Res. 2018;37(1):207.
90. Wang C, Li Y, Chen H, Huang K, Liu X, Qiu M, et al. CYP4X1 inhibition by flavonoid CH625 normalizes glioma vasculature through reprogramming TAMs via CB2 and EGFR-STAT3 axis. J Pharmacol Exp Ther. 2018;365(1):72-83.
91. 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. Int J Oncol. 2017;50(2):545-554.
92. 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. Mol Cancer Ther. 2016;15(8):1931-1942.
93. Wu Q, Chen GL, Li YJ, Chen Y, Lin FZ. Paeoniflorin inhibits macrophage-mediated lung cancer metastasis. Chin J Nat Med. 2015;13(12):925-932.
94. Liu M, Luo F, Ding C, Albeituni S, Hu X, Ma Y, et al. Dectin-1 activation by a natural product β-glucan converts immunosuppressive macrophages into an M1-like phenotype. J Immunol. 2015;195(10):5055-5065.
95. Goswami KK, Barik S, Sarkar M, Bhowmick A, Biswas J, Bose A, et al. Targeting STAT3 phosphorylation by neem leaf glycoprotein prevents immune evasion exerted by supraglottic laryngeal tumor induced M2 macrophages. Mol Immunol. 2014;59(2):119-127.
96. 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. Int Immunopharmacol. 2014;22(2):303-310.
97. Xia T, Zhang M, Lei W, Yang R, Fu S, Fan Z, et al. Advances in the role of STAT3 in macrophage polarization. Front Immunol. 2023;14:1160719.
98. Kerneur C, Cano CE, Olive D. Major pathways involved in macrophage polarization in cancer. Front Immunol. 2022;13:1026954.
99. Cornice J, Verzella D, Arboretto P, Vecchiotti D, Capece D, Zazzeroni F, et al. NF-κB: Governing macrophages in cancer. Genes (Basel). 2024;15(2):197.
100. Khan SU, Khan MU, Azhar Ud Din M, Khan IM, Khan MI, Bungau S, et al. Reprogramming tumor-associated macrophages as a unique approach to target tumor immunotherapy. Front Immunol. 2023;14:1166487.
101. Lian G, Chen S, Ouyang M, Li F, Chen L, Yang J. Colon cancer cell secretes EGF to promote M2 polarization of TAM through EGFR/PI3K/AKT/mTOR pathway. Technol Cancer Res Treat. 2019;18:1533033819849068.
102. Wanderley CW, Colón DF, Luiz JPM, Oliveira FF, Viacava PR, Leite CA, et al. Paclitaxel reduces tumor growth by reprogramming tumor-associated macrophages to an M1 profile in a TLR4-dependent manner. Cancer Res. 2018;78(20):5891-5900.
103. Su P, Li O, Ke K, Jiang Z, Wu J, Wang Y, et al. Targeting tumor-associated macrophages: Critical players in tumor progression and therapeutic strategies (Review). Int J Oncol. 2024;64(6):60.
104. Li X, Luo H, Ye Y, Chen X, Zou Y, Duan J, et al. β-Glucan, a dectin-1 ligand, promotes macrophage M1 polarization via NF-κB/autophagy pathway. Int J Oncol. 2019;54(1):271-282.
105. Zhu Y, Knolhoff BL, Meyer MA, Nywening TM, West BL, Luo J, et al. CSF1/CSF1R blockade reprograms tumor-infiltrating macrophages and improves response to T-cell checkpoint immunotherapy in pancreatic cancer models. Cancer Res. 2014;74(18):5057-5069.
106. Li J, Kaneda MM, Ma J, Li M, Shepard RM, Patel K, et al. PI3Kγ inhibition suppresses microglia/TAM accumulation in glioblastoma microenvironment to promote exceptional temozolomide response. Proc Natl Acad Sci USA. 2021;118(16):e2009290118.
107. Kang X, Huang Y, Wang H, Jadhav S, Yue Z, Tiwari AK, et al. Tumor-associated macrophage targeting of nanomedicines in cancer therapy. Pharmaceutics. 2023;16(1):61.

108. He Y, de Araújo Júnior RF, Cruz LJ, Eich C. Functionalized nanoparticles targeting tumor-associated macrophages as cancer therapy. Pharmaceutics. 2021;13(10):1670.
109. Cavalcante RS, Ishikawa U, Silva ES, Silva-Júnior AA, Araújo AA, Cruz LJ, et al. STAT3/NF-κB signalling disruption in M2 tumour-associated macrophages is a major target of PLGA nanocarriers/PD-L1 antibody immunomodulatory therapy in breast cancer. Br J Pharmacol. 2021;178(11):2284-2304.
110. Zhou Y, Que KT, Tang HM, Zhang P, Fu QM, Liu ZJ. Anti-CD206 antibody-conjugated Fe3O4-based PLGA nanoparticles selectively promote tumor-associated macrophages to polarize to the pro-inflammatory subtype. Oncol Lett. 2020;20(6):298.
111. Kim MS, Lee JS, Kim JE, Kim JW, Bok S, Keum KC, et al. Enhancement of antitumor effect of radiotherapy via combination with Au@SiO2 nanoparticles targeted to tumor-associated macrophages. J Ind Eng Chem. 2020;84:349-357.