Review Article

Iranian Journal of Immunology

June 2024; 21(2):103-120.

Functional Property and Regulatory Mechanism of Macrophages in Complementary and Alternative Medicine: From Bench to Clinic

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ABSTRACT

Complementary and alternative medicine (CAM) includes a wide range of treatments that are gaining acceptance among the public. It is increasingly being recognized as a viable option for treating various diseases with minimal side effects. Common avenues of this therapy include herbal medicine, acupuncture, physical exercise, aromatherapy, dietary therapy, and homeopathy etc. Macrophages are highly heterogeneous cells that play multiple regulatory roles. Practices such as herbal medicine, acupuncture, physical exercise, aromatherapy and dietary therapy exert curative effects by modulating the polarization status and the secretory phenotype of macrophages directly. Furthermore, herbal medicine, acupuncture, and physical exercise influence the crosstalk between macrophages and other types of cells, including cancer cells and T cells. Mechanistically, herbal medicine and acupuncture produce curative effects in diverse diseases, including inflammatory diseases and tumors, mainly by influencing the phosphorylation of signaling proteins in macrophages. Therefore, targeting macrophages offers theoretical support for advancing the scientific understanding of this therapy and aids in identifying potential therapeutic options. Hence, in this review, we systematically summarize the different regulations of macrophages in herbal medicine, acupuncture, physical exercise, aromatherapy, dietary therapy and homeopathy, and further highlight the therapeutic potential of targeting macrophages in complementary and alternative medicine.

Keywords: Complementary Therapies, Inflammation, Macrophage, Tumor

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Cite this article as:
Hu C, Zhang Y, Liu J, You Y, Wu F, Zhou H. Functional Property and Regulatory Mechanism of Macrophages in Complementary and Alternative Medicine: From Bench to Clinic. *Iran J Immunol.* 2024; 21(2):103-120, doi: 10.22034/iji.2024.99943.2668.

Received: 2023-08-21
Revised: 2024-01-02
Accepted: 2024-02-21

INTRODUCTION

In comparison with mainstream medicine, complementary and alternative medicine (CAM) pays greater attention to nonspecific effects such as the therapeutic milieu or the personal clinical experience of practitioners. However, such treatments typically lack convincing scientific support for their efficacy obtained from clinical trials (1). Today, CAM is mainly divided into three groups: nutritional approaches; physical and mental approaches; and other complementary health approaches (2). These approaches have been proven to produce positive effects on various diseases such as chronic pain and solid tumors (3, 4). In recent years, many individuals have turned to CAM as an alternative to mainstream medicine because of concerns about the side effects of mainstream treatments, including adverse reactions and drug resistance (5, 6). Combination therapy is frequently selected by numerous cancer patients, as it is a prevalent option. CAM therapies are administered to tumor patients consistently throughout their entire treatment process in certain instances (7-9). Furthermore, some educational institutions in the medical field aim to incorporate CAM knowledge into their curriculum (10). Such evidence suggests that CAM is increasingly considered a new and effective approach for the treatment of certain diseases.

With more in-depth explorations of potential mechanisms during convention therapies, some studies have found that targeted immune therapies based on targeting specific molecules of specific cells have greater efficacy, especially in the treatment of cancers (11). Increasing evidence suggests that herbal medicine might produce biological and therapeutic effects by regulating the immune system. For instance, 6-shogaol from *Zingiber officinale* reduced the production of pro-inflammatory cytokines including interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α), and interferon γ (IFN-γ) etc. in activated $CD4^+$ T cells to relieve the lung inflammation caused by asthma (12). Recent study has also suggested that the ethyl acetate extracts of *Polygonum perfoliatum* are able to kill tumor cells directly or indirectly by promoting the activity of NK cells (13). Such findings suggest that herbal medicine can play regulatory roles in both innate and acquired immune systems.

Macrophages can be directly involved in innate immune activation, and play a significant role in acquired immune activation (14). Depending on their surroundings, macrophages are polarized as different phenotypes and exert diverse functions. Traditionally, these have been divided into the M1 phenotype (M1, pro-inflammatory and anti-cancer) and the M2 phenotype (M2, anti-inflammatory and pro-cancer) (15). M1 shows phagocytic and cytotoxic capacity and expresses pro-inflammatory cytokines and chemokines, reflective of their ability to recruit other immune cells (T cells, B cells) to the site of infection and maintain their activation (16). While M2 are functionally more diverse, with several subtypes (M2a, M2b, M2c, M2d) expressing different combinations of cytokines, chemokines, and growth factors (16). One recent study revealed that electroacupuncture (EA) at ST 36 mitigated ulcerative colitis by reducing the expression of chemokine (C-X-C motif) ligand 1 (CXCL1) derived from macrophages (17). In another study, Gálvez et al. found that regular exercise reduced the accumulation of macrophages in mouse model (18). Interestingly, exosomes derived from lung epithelial cells exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can lead to inflammation caused by lung macrophages. In addition, the *Zingiber officinale* exosome-like nanoparticle aly-miR396a-5p can inhibit the expression of Nsp12 and spike genes in SARS-CoV-2-infected lung epithelial cells, and thereby alleviate inflammation (19). These findings suggest that certain CAM therapies are able to regulate macrophages directly and/or indirectly. Hence, in this review, we systematically summarize the distinct roles of

macrophages in various CAM therapies and highlight the therapeutic potential of targeting macrophages in CAM for various diseases.

REGULATION OF MACROPHAGES IN THE ANTI-INFLAMMATORY FUNCTIONS OF CAM

Macrophage-derived Cytokine/Chemokines and Their Roles in Anti-inflammation

Macrophages, as the heterogeneous leukocytes in chronic inflammation, differentiate from monocytes in the blood following their entry into surrounding tissues. As a kind of CAM, herbal medicine's anti-inflammatory response depends greatly on the functions of macrophages. Typically, macrophages originate from monocytes which affiliate into the extravascular tissues, suggesting that their recruitment is sensitive to the CAM (Fig. 1). For instance, the ethanol extract of *Centipeda minima* suppressed the expression of chemokine (C-C Motif) ligand 8 (CCL8) and monocyte chemotactic protein-1 in macrophages to inhibit the

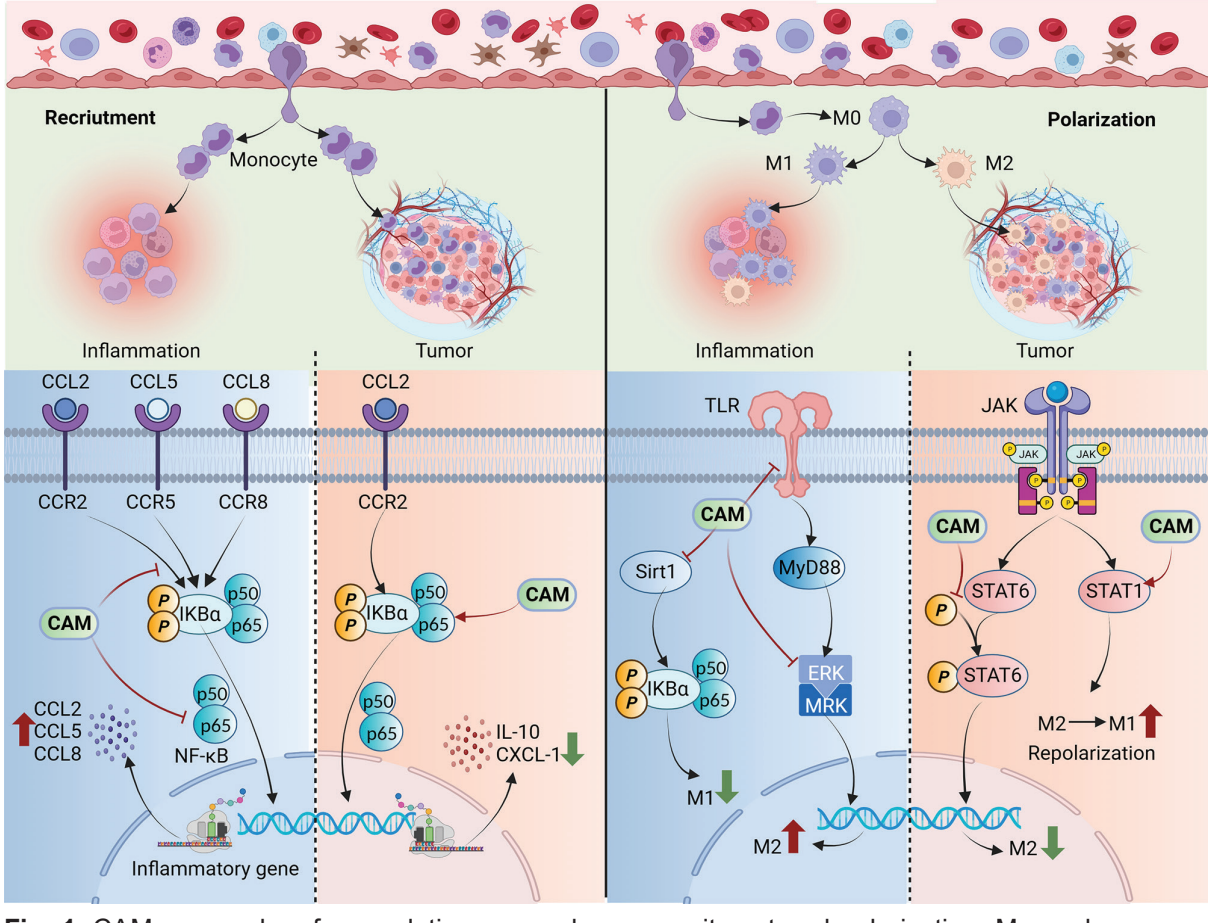

Fig. 1. CAM approaches for regulating macrophage recruitment and polarization. Macrophages are commonly originated and recruited from monocytes and this process would be modulated by several chemokines. These chemokines, including CCL2, CCL5, etc. bind with their ligands in macrophages, then activating NF-κB signal to adjust the recruitment of macrophages or monocytes. For inflammation, CAM could directly inhibit NF-κB signal to suppress the release of chemokines, thereby reducing the recruitment of monocytes. For tumor, CAM mitigates the release of chemokines by activating NF-κB to reduce the number of TAMs. Further, several signal pathways are involved in macrophages polarization, such as TLR/MyD88/ERK and JAK/STAT. Activated TLR and JAK in the macrophages influence macrophages polarization via downstream signals, including MyD88/ERK, STAT1 and STAT6. Sirt pathway is also involved in macrophages polarization. CAM could reduce M1 polarization and increase M2 polarization by inhibiting TLR, ERK and Sirt1 in anti-inflammation therapy. While in anti-tumor therapy, CAM suppresses the phosphorylation of STAT6 to decrease M2 polarization and enhances the expression of STAT1 to promote M2 repolarization into M1.

chemotaxis of monocytes and thus mitigate colitis (20). Further, CAM may also mediate the polarization of macrophages and thus play a suppressive role in the occurrence and development of inflammatory diseases. For the treatment of atherosclerosis, Chen et al. found that the *Si-miao-yong-an* decoction inhibited the polarization of M0 macrophages into M1 (21). In another study, Tan et al. provided data showing that *curcumin* alleviated acute kidney injury by promoting the conversion of M1 into M2 (22). This evidence suggests decreasing the number of M1, not only by suppressing generation but also by increasing polarization, which might explain the therapeutic efficacy of CAM for anti-inflammation purposes.

After being polarized by different stimuli, macrophages secrete various cytokines for mediating their biological effects including anti-inflammation. For instance, both *Zingiber officinale* and *Sargentodoxa cuneata* may inhibit the secretion of TNF-α and IL-6 from macrophages to relieve arthritis and colitis, respectively, in a dose-dependent manner (23, 24). Macrophage-derived TNF-α and/or IL-6 can therefore be considered candidates for serum drug concentration monitoring during CAM for arthritis or colitis. In addition, CAM also regulates the crosstalk between macrophages and other cells, such as neutrophils and foam cells, causing the anti-inflammatory effects (Fig. 2). To confirm this, Chuang et al. provided data showing that *Antrodia cinnamomea* restrained the activation of neutrophils and the proliferation of keratinocytes by inhibiting macrophage-derived chemotaxis release in psoriatic inflammation (25). In another study, Luo et al. found that *Aralia elata* promoted macrophage polarization into the M2 via Sirt1-mediated autophagy to reduce foam cell formation, and thereby relieve atherosclerosis (26). In summary, these pieces of evidence indicate two main therapeutic approaches for anti-inflammation during CAM: the targeting of cytokines/chemokines secreted by macrophages, and the cellular autophagy or polarization of macrophages.

Major Signaling Pathways Involving the Macrophages in Anti-inflammation

In terms of the biological behavior of macrophages which brings about anti-inflammatory effects during CAM, several signaling pathways have been extensively explored, especially the nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs) cascades (Fig. 3). NF-κB is a kind of common transcription factor, and the common form of NF-κB is a heterodimer formed by p65 and p50 that binds to the inhibitory protein IκB (27). Following multiple stimuli, it promotes phosphorylation and degradation of IκB, and then promotes nuclear translocation of p50 and p65 into the nucleus, thereby regulating gene expression (27). NF-κB activated by macrophages has been reported as a pro-inflammatory signature for inflammation progression. Macrophage-derived IL-6, TNF-α, and IL-1β, known to be the targets of the NF-κB transcription factor, have been correlated with atherosclerosis and colitis, etc. (28, 29). Growing evidence also suggests that CAM could attenuate the release of macrophage-derived factors by acting on the NF-κB signaling pathway (Table 1). For instance, liriodendrin from *Sargentodoxa Cuneata* and dauricine from *Menispermum dauricum DC* both inhibited IL-1β, IL-6 and TNF-α release in LPS-treated macrophages by decreasing the phosphorylation of IκBα and p65 (24, 30). Similarly, rhein from *Rheum rhabarbarum* inhibited the production of NO by suppressing the phosphorylation of p65 in LPS-stimulated macrophages (31). In addition, Li et al. found that CCL2 and CXCL10 secreted by LPS-stimulated macrophages were inhibited by *Qing-fei-pai-du* and *Xuan-fei-bai-du* decoctions which reduced IκBα and p65 phosphorylation and thereby mitigated inflammation caused by the Coronavirus disease 2019 (COVID-19) (32). These findings suggest that CAM would affect the secretory phenotype of macrophages by the downregulation of the NF-κB signaling

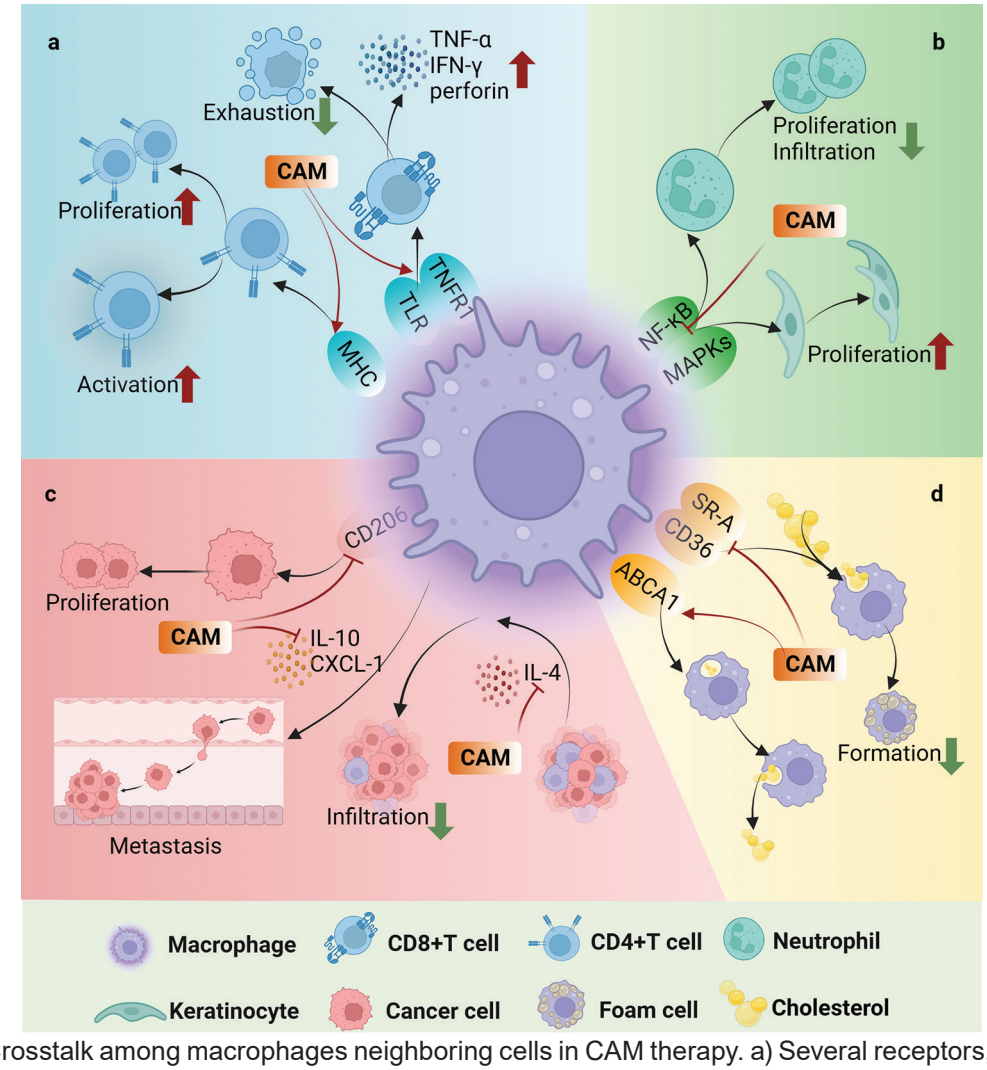

Fig. 2. Crosstalk among macrophages neighboring cells in CAM therapy. a) Several receptors, including TNFR1, TLR4 and MHC, in the macrophages could be enhanced by CAM to affect the proliferation and activation of $CD4^+$T cells and $CD8^+$T cells. b) CAM suppresses the proliferation and infiltration of neutrophils and increases the proliferation of keratinocyte by inhibiting NF-κB and MAPKs signal pathways simultaneously. c) Upregulated CD206 in macrophages and macrophage-derived cytokines and chemokines, including IL-10 and CXCL-1 enhance the proliferation and metastasis of cancer cells, while this effect could be suppressed by CAM. Further, CAM reduces the release of tumor-derived IL-4 to inhibit TAMs infiltration. d) Activated ABCA1, SR-A and CD36 are associated with the formation of foam cells. CAM modulates the influx and efflux of cholesterol by downregulating the expression of SR-A and CD36 and increases ABCA1 to suppress foam cells formation.

pathway. However, an alternative hypothesis is that herbal medicine might attenuate the number of macrophages directly, to decrease the secretory factors for anti-inflammation by suppressing the NF-κB signal. This notion is supported by the mouse model used by Wang et al. who reported that polyphyllin I from *Rhizoma of Paris polyphyllin* decreased M1 infiltration by inhibiting IKKα/β and p65 phosphorylation to alleviate arthritis (33). In addition, Liu et al. found that loganin derived from *Cornus officinalis* mitigated the number of M1 to attenuate colitis by promoting the acetylation of p65, and that it could be reversed by the Sirt1 inhibitor Ex527, suggesting that a part of the anti-inflammatory effect of loganin stems from the Sirt1/NF-κB pathway (34). Of note, Wang et al. found that bergenin from *Saxifraga stolonifera Curt* inhibited the nuclear translocation and DNA-binding activity of p65 with little or no effect on the phosphorylation of NF-κB in LPS-induced macrophages (35), indicating that CAM might influence the post-transcriptional molecular modification

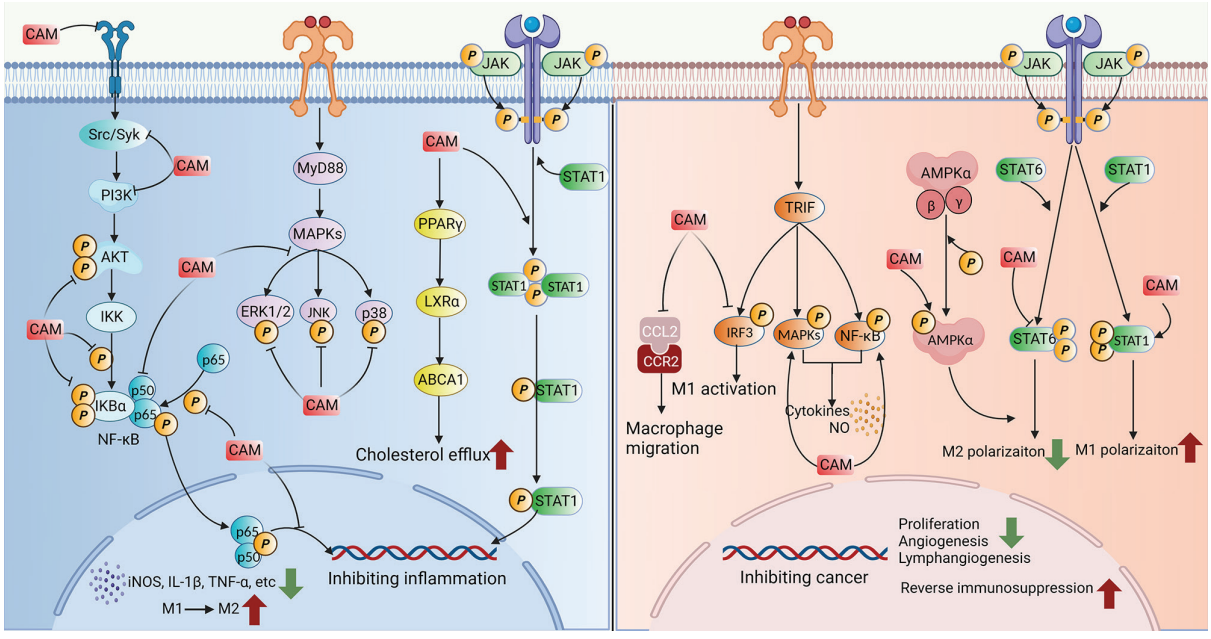

Fig. 3. Mechanisms involved in the macrophage during treating inflammation and tumor by CAM. In the macrophages, by the receptor–ligand binding, activated Src/Syk enhanced PI3K/AKT signaling cascade and activated JAK could phosphorylate SATA1 and STAT6 to transfer the p65, p50 and p-STAT1 into the nuclei, subsequently modulating the expression of targeted genes associated with pro-inflammation and pro-tumor of macrophages. TLR/MyD88 pathway and TLR/TRIF are also involved in macrophages pro-inflammation and pro-tumor via MAPKs signaling pathway. Besides, PPRAγ/LXRα signaling axis could modulate macrophages pro-inflammation, CCL2/CCR2 and AMPK related signal pathway are associated with macrophages pro-tumor. During the treatment of inflammation, CAM inhibits several signal molecules, including Src/Syk, AKT, JNK, STAT1, etc., especially suppressing their phosphorylation, to reduce the secretion of pro-inflammatory cytokines and the number of M1 and increase M2 polarization. Further, CAM promotes cholesterol efflux by activating PPRAγ/LXRα/ABCA1 pathway to attenuate obesity-related inflammation. However, for the anti-tumor, CAM mainly upregulates the expression of some signal molecules, including NF-κB, AMPK and STAT1, etc., to suppress immunosuppression and the proliferation, angiogenesis and lymphangiogenesis of cancer cells. Of note, CAM could downregulate M2 polarization and TAMs migration by inhibiting p-STAT6 and CCL2.

of signaling molecules on the NF-kB pathway in macrophages to produce an anti-inflammatory effect.

Researchers have also reported that MAPKs signaling is involved in CAM therapy, mediating the cellular secretory phenotype of macrophages for anti-inflammation purposes (Table 1). For example, Huai et al. found that, in colitis, the increased secretion of IL-6 and TNF-α in macrophages could be blocked by artemisinin from *Artemisia annua*, and that decreased phosphorylation of ERK was involved in this process (36). In another study, involving a mouse model of peritonitis, *Cerbera manghas* mitigated the expression of iNOS and COX2 to relieve peritonitis dependent on MKK4-, JNK-, and AP-1-related signaling cascades (37). It was reported that fermented extracts of *Platycodon grandiflorus* (0.1, 0.5, 1, 5 and 10 mg/ml) decreased the expression of inducible nitric oxide synthase (iNOS), and that this effect could be blocked by SB203580 (p38 inhibitor) and SP600125 (JNK inhibitor), suggesting that the anti-inflammatory effect of *Platycodon grandiflorus* was associated closely with the p38 and JNK signaling pathways (38). Taken together, these studies suggest that CAM downregulated the JNK, ERK, and/or p38 pathways to inhibit the inflammatory response in macrophages, especially via the expression of iNOS. Interestingly, xanthones from *Swertia chirayita* was shown to mitigate LPS-induced inflammation by suppressing the activation of MAPKs and NF-κB pathways simultaneously (39),

Table 1. Functions and mechanisms of macrophages in herbal medicine for anti-inflammation

Active ingredients	Source	Biological function	Disease	Mechanism	Ref.
Astragaloside IV	*Astragalus membranaceus*	Promoted macrophage autophagy	ALI	Suppressed TLR4/ NF-κB	(42)
Artesunate	*Artemisia annua*	Inhibited M1 polarization	AS	Suppressed HIF-1α and NF-κB	(43)
Loganin	*Cornus officinalis*	Reduced M1 polarization	UC	Regulated Sirt1/ NF-κB	(34)
Bergenin	*Saxifraga stolonifera*	Inhibited PIMs	UC	Activated PPARγ, inhibited NF-κB	(35)
Dihydrotanshinone I	*Salvia miltiorrhiza Bunge*	Inhibited PIMs and macrophages	DIC	Suppressed NF-κB	(44)
Polyphyllin I	*Paris polyphyllin*	Inhibited PIMs macrophages	RA	Suppressed NF-κB	(33)
Baicalein	*Scutellaria baicalensis*	Inhibited PIMs	AS	Activated AMPK, inhibited MAPKs	(45)
Sophoricoside	*Sophora japonica*	Inhibited PIMs	ALI	Promoted Nrf2 and AMPK	(46)
Artemisinin	*Artemisia annua*	Promoted M2 and inhibited EMT	IBD	Suppressed MyD88 and ERK	(36)
DMD	*Antrodia cinnamomea*	Inhibited cytokine/ chemokine	PI	Suppressed MAPKs and NF-κB	(25)
Tomatidine	*Green tomato*	Inhibited monocyte chemotaxis	ALI	Suppressed MAPKs and NF-κB	(47)
Bergaptol	*CAVA*	Inhibited foam cell formation	AS	Suppressed MAPKs and NF-κB	(48)
Geniposide	*Gardenia jasminoides*	Inhibited NLRP3 and monocytes	Colitis	Activated AMPK/ Sirt1	(49)
Glycyrrhizin	*Licorice root*	Inhibited PIMs and macrophages	ALI	Suppressed NF-KB and p38/ERK	(50)
Dauricine	*MDDC root*	Inhibited PIMs	ALI	Suppressed NF-κB signal	(30)
Farrerol	*Rhododendron*	Inhibited PIMs	Colitis	Suppressed AKT, ERK and NF-κB	(51)
Myricetin	*Athyrium multidentatum*	Inhibited PIMs	ALI	Suppressed TLR4 cascades	(52)
Asatone	*Radix et Rhizoma Asari*	Inhibited PIMs	ALI	Suppressed NF-κB and MAPK	(53)
Liriodendrin	*Sargentodoxa cuneata*	Inhibited PIMs	Colitis	Suppressed AKT and NF-κB	(24)
Salidroside	*Rhodiola rosea*	Inhibited PIMs	ALI	Suppressed NF-κB	(54)
Kaempferol	*Cerbera manghas*	Inhibited PIMs	Hepatitis	Suppressed JNK cascades	(37)

2,4-dimethoxy-6-methylbenzene-1,3-diol (DMD); *Citrus aurantium Linn variant amara Engl* (*CAVA*); *Menispermum dauricum DC* (*MDDC*); pro-inflammatory mediators (PIMs), nucleotide-binding domain like receptor protein 3 (NLRP3); Acute lung injury (ALI); Atherosclerosis (AS); Ulcerative colitis (UC); DOX-induced cardiotoxicity (DIC); Rheumatoid arthritis (RA); inflammatory bowel disease (IBD); psoriasiform inflammation (PI); Toll-Like Receptor 4 (TLR4); Nuclear factor-kappa B (NF-κB); hypoxia-inducible factor-1α (HIF-1α); Transcription 1 (Sirt1); Peroxisome proliferator- activated receptor gamma (PPARγ); AMP-activated protein kinase (APMK); mitogen-activated protein kinases (MAPKs); nuclear factor erythroid 2–related factor 2 (Nrf2); Myeloid Differentiation Factor 88 (MyD88); Phosphatidylinositol 3-kinase (p38); extracellular signal-regulated kinase (ERK); Protein kinase B (AKT); c-Jun N-terminal kinases (JNK).

indicating that there might be a potential interaction between the inflammatory signaling pathways of macrophages and the CAM might exhibit a suppressive role of MAPKs and NF-κB cascades simultaneously. Other signaling pathways such as PPARγ and AMPK have also been explored in studies for their anti-inflammatory effects in CAM therapy. For instance, the *Shen-hong-tong-luo* formula was found to activate the PPARγ/LXRα pathway, subsequently reducing the risk of atherosclerosis by upregulating ABCA1 expression (40). Of note, Zhang et al. reported that astragaloside IV from *Astragalus membranaceus* reversed mTOR-involved autophagy inhibition by promoting AMPK phosphorylation to suppress IL-6 production in LPS-induced macrophages (41), suggesting that CAM could target the autophagy-related signaling pathways of macrophages for anti-inflammation purposes.

REGULATION OF MACROPHAGES IN THE ANTI-TUMOR FUNCTIONS OF CAM

Polarized Status and Secreted Type of Macrophages in Anti-tumor

Cancer is globally recognized as the second most prevalent cause of mortality, following cardiovascular diseases (55). In 2019, the world witnessed 23.6 million new cases of cancer, resulting in 10.0 million deaths and imposing a substantial economic burden worldwide (56). Tumor-associated macrophages (TAMs), partly differentiated from monocyte, predominantly play a M2-like tumor-promoting role in the tumor microenvironment (TME) and regulate various malignant effects, such as angiogenesis, immune suppression, and tumor metastasis, hence, TAMs have emerged as a hot topic of research in cancer therapy (57). CAM would intervene the recruitment of monocyte to exert anti-tumor effect. To support this note, Wu et al. found that Genipin, extracted from *Gardenia jasminoides*, reduced the hepatic macrophage infiltration partly through downregulating the recruitment of monocytes in peripheral blood circulation to suppress recurrence of hepatocellular carcinoma (58). Further, given that the CAM could affect TAMs in the TME to inhibit the biological behavior of cancer cells. For instance, Zhao et al. found that *Xiao-yao-san* directly reduced the recruitment of TAMs to suppress chronic stress-induced liver metastases of colon cancer (59). Indeed, M1 and M2 have distinct effects in tumor progression, and among them, M1 activates host immune responses against tumor cells while M2 promotes cancer occurrence and metastasis through tumor immune escape (60). These findings suggest that the polarization of macrophages would be mediated by CAM, thereby causing an inhibitory effect in the progression and metastasis of cancers. To support this, Wu et al. observed that a modified *Jian-pi-yang-zheng* decoction played an anti-gastric-cancer role by inhibiting polarization of M2 via exosome-derived pyruvate kinase M2 (61). Unlike this, the *Yu-ping-feng* promoted the polarization of M1 to decrease growth of lung cancer cells (LCC) (62). Of note, the repolarization from M2 to M1 has been proposed as an anti-tumor approach in cancer treatment. Within CAM therapy, it has been suggested that *Marsdenia tenacissima* could promote the transformation from the M2 to M1 to inhibit the migration of non-small cell lung cancer (NSCLC) cells (63). Taken together, recent findings suggest that CAM can not only directly decrease the number of TAMs by affecting their recruitment process, but more importantly by targeting the status of M1/M2 polarization for anti-cancer purposes. In this regard, it is interesting that polysaccharides from *Codonopsis pilosula* were found to promote M1 macrophage polarization, decrease TAMs formation, and repolarize M2 into M1 to alleviate melanoma (64), indicating that polysaccharides might suppress melanoma by multiple macrophage-mediating means, and could be developed

for targeting macrophages in CAM anti-tumor therapy.

Further, CAM was found to inhibit cellular biological behaviors such as the growth, migration and invasion through TAMs-derived cytokines/chemokines. For instance, *Marsdenia tenacissima* decreased M2 infiltration by suppressing the release of tumor-derived hepatoma-derived growth factor and IL-4 (63). Unlike this, in mouse models of breast cancer, *Taraxacum mongolicum* and baohuoside I were found to downregulate the secretion of TAMs-derived IL-10 and CXCL1, respectively, to inhibit distant metastasis of breast cancer (65, 66), suggesting that IL-10 and CXCL1 secreted by TAMs have the potential to be targeted for anti-tumor therapy of CAM. It was also been reported that *Yu-ping-feng* and *compound kushen injection* (CKI) activated $CD4^+$ T cells and $CD8^+$ T cells, respectively, by enhancing the antigen presentation function of macrophages in the TME to kill LCC and hepatocellular carcinoma cells (HCC) (62, 67), indicating that CAM can attenuate immunosuppression in the TME via the antigen presentation function of macrophages. In recent years, researchers have also focused increasingly on the combination of CAM with chemotherapy or immunotherapy for anti-tumor. For instance, Yang et al. found that CKI sensitized the anti-HCC effect of low-dose *sorafenib* by reducing the level of TAMs and upregulating the ratio of M1 (67). In the treatment of HCC, a combined treatment with *YIV-906* and anti-programmed death-ligand 1 increased the secretion of CCL2 and thus potentiated the infiltration of M1, subsequently leading to reverse immunosuppression in the TME (68). Of note, it has been shown that the COVID-19 infection increased the mortality rate of tumor patients (69). In addition, tumor patients with immune dysfunction would be more susceptible to COVID-19 infection (70). Thus, these pieces of evidence suggest that there is a bidirectional connection between tumors and COVID-19 infection. In sum, these findings support the notion that, because of the promotion of anti-tumor immune responses by CAM-mediated macrophages in the TME, CAM combined with chemotherapy and/or immunotherapy might become important anti-tumor therapeutic approaches in the future.

Relevant Signaling Pathways Involving the Macrophages in Anti-tumor Response

Increasing studies have explored the anti-tumor effects of macrophages in CAM therapy. However, with regard to the potential mechanism involved, researchers have mainly focused on the macrophage polarization and its related signaling pathways such as JAK/STAT cascade (Table 2). The JAK/STAT signaling is mainly composed of a series of ligand–receptors, including four tyrosine kinase JAK and seven transcription factor STAT family members, and plays an important role in malignancies (71). The status of polarized macrophages is regulated by JAK/STAT signaling and this process can be influenced by CAM therapy (Fig. 3). For instance, *Yu-ping-feng* and *Scutellariae Radix* enhanced the phosphorylation of STAT1 to promote polarization of M1, and to prevent the progression of LCC respectively (62, 72). Another study reported that *Ru-yin-ping* inhibited M2 polarization by downregulating STAT6, to suppress the lung metastasis of triple-negative breast cancer (73). Indeed, CAM not only inhibited the NK-*κB* signaling pathway in macrophages but also activated NF-*κB* cascade to promote the formation of M1 macrophages for the reversion of the immunosuppression in the TME. For instance, Yang et al. found that CKI activated macrophages to exhibit a pro-inflammatory phenotype by increasing the phosphorylation of p65 and p38, alleviating the depletion of $CD8^+$ T cells in the TME and promoting the apoptosis of HCC (67). Additionally, astragaloside IV was found to reduce LCC migration and invasion by suppressing the polarization of M2 macrophages dependent

Table 2. Herbal medicine and its active components in anti-tumor immunity by macrophages

Formula	Function	Tumor	Mechanism	Ref.
Bu Fei decoction	Inhibited tumor cell proliferation, migration	NSCLC	Decreased IL-10, PD-L1 and CD206	(75)
Yu Ping Feng	Induced M1, suppressed tumor growth	LC	Promoted STAT1 and increase IL-1β	(62)
Huang Qin Tang	Induced M1, inhibited tumor cells proliferation	LIHC	Promoted JAK1/2 and STAT2	(68)
XiaoPi formula	Inhibited M2 polarization, tumor growth	BRC	Suppressed CXCL1	(66)
Modified Jianpi Yangzheng decoction	Inhibited tumor cell proliferation	GC	Modulated TNF-α and IL-10	(61)
Modified Jianpi Yangzheng decoction	Repolarized M2 to M1	GC	Decreased PI3Kγ	(76)
Ru yin ping	Inhibited tumor cell proliferation, migration a	TNBC	Inhibited STAT6	(73)
Dahuang Zhechong Pill	Reduced macrophage recruitment	CRC	Suppressed CCL2 and CCR2	(77)
Compound kushen injection	Inhibited M1 polarization, tumor growth and recurrence	LIHC	Activated NF-κB and p38 signals	(67)
Active components (source)	**Function**	**Tumor**	**Mechanism**	**Ref.**
Polysaccharides (*Ganoderma lucidum, Codonopsis pilosula*)	Promoted repolarization from M2 to M1	Melanoma	Increased IL-1, IL-6 and TNF-α	(64)
EPS (*Epimedium koreanum Nakai*)	Inhibited tumor growth	LC	Increased IL-6 and TNF-α	(78)
WBB (*Scutellariae Radix*)	Promoted repolarization from M2 to M1	LC	Promoted JAK2/ STAT1	(72)
Sophoridine (*Sophora alopecuroides*)	Reshaped immune microenvironment	GC	Activated TLR4/ IRF3	(79)
Anemoside A3 (*Pulsatilla saponins*)	Inhibited tumor cell proliferation	BRC	Activated NF-κB and MAPKs signals	(80)
Astragaloside IV (*Astragali radix*)	Inhibited tumor cell invasion and migration	LC	Reduced p-AMPK expression	(74)
Flavonoids and phenolic acids (*Taraxacum mongolicum*)	Inhibited tumor cell proliferation, migration and invasion	TNBC	Suppressed IL-10 / STAT3 / PD-L1	(65)
PSG-1 (*Ganoderma atrum*)	Suppressed sarcoma growth	Sarcoma	Activated TLR4/ NF-κB/ MAPKs	(81)

Epimedium koreanum polysaccharide (EPS); wogonin, baicalein and baicalin (WBB); Ganoderma atrum polysaccharide (PSG-1); non-small cell lung cancer (NSCLC); lung cancer (LC); liver hepatocellular carcinoma (LIHC); gastric cancer (GC); Breast cancer (BRC); Triple negative breast cancer (TNBC); colorectal cancer (CRC); Signal transducer and activator of transcription 3 (STAT3); Janus Kinase (JAK); (PI3Kγ); interferon regulatory factor 3 (IRF3); Nuclear factor-kappa B (NF-κB); mitogen-activated protein kinases (MAPKs); AMPK phosphorylation (p-AMPK); Toll-Like Receptor 4 (TLR4).

on the phosphorylation of AMPKα (74). Taken together, this evidence suggests that macrophage-mediated CAM therapy involves multiple potential signal cascades, is tumor-type-specific, and plays a suppressing role mainly by regulating the phosphorylation of proteins in the macrophages.

REGULATION OF MACROPHAGES IN THE ANALGESIC AND METABOLIC FUNCTIONS OF CAM

Different Subtypes of Macrophages and Their Roles in Acupuncture Therapy

Acupuncture therapy, including EA,

manual acupuncture (MA) and moxibustion, enhances the self-regulation ability of humans by physically stimulating meridians to treat or prevent diseases (82). The therapeutic effects generated by acupuncture therapy may be associated with modulating immune cells, especially macrophages. For example, EA at Neiguan and EA at Zusanli (ST 36) were shown to suppress the recruitment of macrophages and macrophages polarization into M1 to ameliorate the inflammatory responses of the ischemic myocardium and the intestine, respectively (83, 84). Macrophage-derived cytokines or their surface receptors play an active role in the analgesic effect of acupuncture therapy. To confirm this, da Silva et al. used a model of inflammatory muscle pain and found that MA at Sanyinjiao (SP 6) increased the release of IL-10 by upregulating the number of M2 to produce an analgesic effect (85). In another study, EA at Dachangshu was found to suppress the production of IL-1β and iNOS by adding the CB2 receptor expression on the macrophages to relieve visceral pain (86). These findings suggest that acupuncture therapy produces an analgesic effect partly by altering the secretory phenotype of macrophages, which is closely related to the inhibition of local inflammatory response. In addition, nerve-associated macrophages (NAMs) and sympathetic associated macrophages (SAMs), a new subtype of macrophages closely associated with nerves, play a critical role in regulating fatty metabolism (87). One study found that EA at Tianshu (ST 25) suppressed the trans-shipment of noradrenaline by downregulating the production of norepinephrine transporter protein (Slc6a2) in SAMs to promote lipolysis and thermogenesis in inguinal white adipose tissue (87). Another study found that EA at Quchi inhibited the activation of monoamine oxidase-A by downregulating the activity of the NLRP3 inflammasome in NAMs, to add lipolysis in epididymal adipose tissue, independently of sympathetic nervous system activity (88). Similarly, EA at ST 25, SP 6, ST 36 and Guanyuan (CV 4), was found to inhibit the release of TNF-α and promote the release of IL-4 and IL-10 to relieve inflammation in obese adipose tissues, and thus help to prevent weight gain (89). These findings suggest that CAM exerts an anti-obesity effect not only by affecting the crosstalk between sympathetic nervous system and macrophages, but also by interfering with other pathways such as cytokines associated with inflammation in macrophages.

Relevant Signaling Pathways Involving the Macrophages in Acupuncture Therapy

Several studies have focused on the signaling pathways associated with macrophages in acupuncture therapy, such as JAK/STAT cascade. In one such work, EA at ST 36 was found to inhibit the production of IL-6 and TNF-α by enhancing the phosphorylation of JAK2 and JAK3 to alleviate intestinal inflammation in a vagal-dependent manner (90). In another study, moxibustion at Shenshu and ST 36 promoted M2 but inhibited M1, possibly by suppressing the activation of JAK1, JAK3 and STAT6, to ameliorate rheumatoid arthritis (91). Further, Li et al. reported that moxibustion at CV 4 promoted the autophagy of macrophages to reduce the phosphorylation of Akt and increase the phosphorylation of eIF2α and thus produce an antibacterial effect (92). These data indicate that acupuncture therapy typically influences the phosphorylation of signaling molecules to regulate the biological behavior of macrophages. It has also been suggested that microRNAs are involved in changing the biological behavior of macrophages in acupuncture therapy. For instance, Deng et al. reported that, in the treatment of postoperative ileus, MA at ST 36, SP 6, and Taichong restored the function of interstitial cells of Cajal dependent on the IL-6/miR-19a/KIT axis, to improve gastrointestinal motility in human patients and in mice (93), suggesting that acupuncture therapy would decrease macrophage-derived IL-6 to achieve intestinal protection via potential inflammatory micro-RNAs.

Regulation of Macrophages in Other Avenues of CAM

Other forms of CAM, such as physical exercise, aromatherapy, dietary therapy and homeopathy, might also play a therapeutic role by modulating the biological behavior of macrophages. Firstly, physical exercise exerts some protective effect against several inflammatory diseases and cancers risk, such as atherosclerosis and breast cancer (94, 95). Further, recent studies suggested that this protective effect from physical exercise is related to regulating macrophage function. It was reported that physical exercise remarkably promoted the production of IL-10, transforming growth factor-β (TGF-β) derived from M2 macrophages to relieve allergic inflammation (96). In another study, Zhang et al. found that four weeks of pre-operative exercise promoted the anti-inflammatory phenotype of liver macrophages by promoting HMGB1/Nfr2, thus reduced liver damage during surgery (97). These data indicate that physical exercise benefits for inflammatory diseases due to modulating the secretory phenotype of macrophages. Additionally, in a mouse model trained on a treadmill, Cai et al. found that mechanical stimulation increased the secretion of TGF-β1 by inducing macrophages polarization into M2, which significantly added bone mass formation in mice (98). Savage et al. provided data to show that physical exercise improved TME by promoting TAMs into M1 and $CD8^+$ T cell infiltration to probably present protective effect against melanoma (99). Such finding suggests that physical exercise regulates the polarization status of macrophages, which could be served as an important way to prevent or treat diseases in daily life.

Regarding aromatherapy, the use of essential oils, one of the most common forms of aromatherapy, may also contribute to treating inflammatory diseases by targeting macrophages. Given evidence has pinpointed that essential oil from *Artemisia argyi* downregulated the release of NO, IL-6 and IL-1β by inhibiting the phosphorylation of JAK2, STAT1 and STAT3, to relieve ear edema (100). Such finding suggests that essential oils may play an anti-inflammatory role by altering the secretion phenotype of macrophages. CAM therapies not only enhance the phagocytosis of macrophage, but also relieve the inflammation caused by bacteria. To support it, Zonfrillo et al. found that essential oils from *Eucalyptus globulus* enhanced the migration, adhesion and phagocytosis of macrophages to accelerate the clearance rate toward microorganisms (101). In another study, essential oil from *Thymus vulgaris L.* inhibited inflammatory response caused by *Pseudomonas aeruginosa* lipopolysaccharide by reducing the production of IL-6, IL-8, IL-1β and TNF-α (102). These data indicate that aromatherapy acts as a potent activator of macrophages to regulate the immune system, and also that essential oils might be used as a potential option for bacterial infection.

Regarding dietary or nutritional therapy, recent studies suggest that is could improve metabolism of lipids by inhibiting receptors of macrophages. For instance, proanthocyanidins in *Grape seeds* were found to exert a strong cardiovascular-protective effect because they inhibited cholesterol influx and esterification and promoted cholesterol efflux by modulating the expression of CD36 and scavenger receptor class A in macrophages (103). In another study, lycopene, an antioxidant carotenoid compound, reduced the number of adipose tissue macrophages and of leaded M2 superior to M1, potentially helping to relieve insulin resistance (104). Further, Wang et al. found that *Akebia Trifoliata* fruits, as a functional food, suppressed the production of TNF-α, IL-6 and IL-1β by reducing the phosphorylation of ERK, JNK and p38 to mitigate colitis in mice (105). In sum, these findings suggest that functional foods have advantages in the treatment of metabolic diseases by mediating the surface receptors, polarization, and secretory phenotype of macrophages.

For homeopathy, a method based on

the similarity principle, may produce an immunoregulative effect by activating macrophages. For example, Canova, a complex homeopathic medicine, has been found to directly activate macrophages to promote lymphocyte proliferation, and to reduce the adverse effects of cyclophosphamide (106). In another study, Fuselier et al. observed that low-diluted Phenacetinum suppressed angiogenesis in melanoma partly dependent on reducing the number of M2 macrophages (107), suggesting that several homeopathic drugs potentially target the TME probably by reducing macrophage polarization into the M2 phenotype, thus inhibiting tumor progression.

CONCLUSION AND FUTURE PROSPECTIVE

In this review, we have systematically summarized the regulation of macrophages in different kinds of CAM in terms of biological behaviors and molecular mechanisms. CAM produces various effects including anti-inflammatory, anti-tumor, analgesic and metabolic regulation by modulating macrophage directly/indirectly. On one hand, CAM could modulate the recruitment, polarization and secretion phenotype of macrophages to exert effects directly. On the other hand, CAM would influence the crosstalk between macrophages and other immune cells including $CD4^+$ T cells, $CD8^+$ T cells, NK cells, neutrophils etc. to exert effects indirectly. Mechanistically, CAM mainly regulates the phosphorylation level of signal molecules to affect the biological behaviors of macrophages. However, there are multiple limitations that must be addressed before targeting macrophages in CAM can be fully adopted in clinical settings. First, it is necessary to further investigate the subtypes of macrophages and provide potential targets so that CAM can effectively target certain types of macrophages and produce its beneficial effects. Second, cross-sectional comparison of altered inflammatory mediators in different inflammatory diseases might also be needed to weigh the selection of comprehensive judgment indicators during CAM therapy. Third, further exploration of the macrophage receptors acted upon by CAM in terms of their molecular mechanism are warranted, and these may involve the incorporation of nanomaterials to provide new potential targeted avenues for CAM.

ACKNOWLEDGMENTS

The figures were created with BioRender.com. This review was supported by the Central Government Guiding Local Science and Technology Development Foundation of Sichuan Province (No. 2023ZYD0104), the National Natural Science Foundation of China (No. 82002884, No. 82370963 and No. 82071124), the National Key Research and Development Program of China (No. 2020YFA0714001), the Natural Science Foundation of Sichuan Province (No. 2023NSFSC0552).

AUTHORS' CONTRIBUTION

FW and HZ developed the concept and designed the study. CH wrote the manuscript and created the figures/tables. YZ, JL and YY also contributed to the figures/tables and revised the manuscript. FW and HZ edited and revised the manuscript. All authors have read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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