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Review

M1 and M2 macrophage polarization and potentially therapeutic naturally occurring compounds

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ABSTRACT

Macrophages, as crucial cellular components of innate immunity, are characterized by possessing high plasticity and an abnormal ability to differentiate in response to numerous stimuli. Given this, macrophages show extreme heterogeneity under both physiological and pathological conditions. Typically, macrophages can be polarized into classically activated macrophages (M1) and alternatively activated macrophages (M2) depending on their environment. The relative functions of these two subtypes are almost exactly opposed to one another. Recent studies have suggested that some naturally occurring compounds can exert regulatory effects on the progression of macrophage polarization, which implies that they could be promising therapeutic tools to treat relevant diseases. Therefore, in our current review, we summarize recent studies on several naturally occurring compounds that may possess the ability to regulate macrophage polarization and explore the associated molecular mechanisms.

1. Introduction

Macrophages, from the Greek for "big eaters," are implicated in the pathophysiology of different clinical conditions, including infectious and autoimmune diseases, as well as tumor progression [1–4]. Macrophages are not homogenous and previous studies have demonstrated that the phenotypic heterogeneity of macrophages correlates with unique functions specific to local microenvironments [5]. This plasticity enables the appropriate response to pathogens or to signaling molecules [1,6,7] that are commonly released by activated lymphocytes or damaged tissue [1,8–10]. This heterogeneity of macrophage phenotypes is commonly referred to as polarization, which conventionally subdivides macrophages into three groups: naïve (Mφ; also called M0), which readily differentiate into the other two phenotypes: pro-inflammatory (M1) and anti-inflammatory (M2) [1,11–13]. Although Mφ activation in vivo is a continuum of functional phenotypes with intermediate or overlapping features under physiological conditions [14,15], in vitro mechanistic studies are generally limited to the extreme Mφ phenotypes (M1 and M2) and extreme M1/M2 polarization is a common feature of various pathological processes [16].

As central components of traditional Chinese medicine, naturally occurring compounds have an important role in the healing of wounds [17,18] and have anti-cancer [19] and anti-inflammatory properties [20,21]. Moreover, studies have increasingly demonstrated that some naturally occurring compounds are capable of influencing macrophage polarization. Therefore, in our current review, we discuss several naturally occurring compounds that have been implicated in the regulation of macrophage polarization and extensively explore the associated molecular mechanisms.

2. Naïve macrophages (Mφ)

Naïve macrophages (Mφ) and monocytes are widely distributed throughout the body via circulation in the bloodstream [22]. Specialized Mφ are found in several organs and tissues and have been given unique names such as microglial cells in the brain, Kupffer cells in the liver, and alveolar macrophages in the lungs [23]. Mφ macrophages are responsible for clearing senescent/apoptotic cells and foreign/pathogenic materials via phagocytosis, as well as participating in processes such as wound healing and tissue repair [7]. For instance, in the process of atherogenesis, Mφ avidly engulf lipoproteins, subsequently transforming into foam cells, which are involved in plaque progression. Additionally, Mφ can release pro-inflammatory mediators, which are implicated in the pathogenesis of vulnerable/complicated plaques [24].

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However, as previously mentioned, Mφ are a heterogeneous cell population that respond to signaling molecules released by activated lymphocytes or damaged tissues [25]. Consequently, under the influence of local microenvironment cytokines, Mφ generally differentiate into one of two phenotypes: inflammatory mediators (M1), which play the role of resident macrophages producing primary pro-inflammatory cytokines, and anti-inflammatory mediators (M2), which produce anti-inflammatory cytokines and ingest pathogens to help resolve inflammation [6]. This phenomenon of the distinct M1/M2 phenotypes is referred to as "macrophage polarization" [26]. Although Mφ activation in vivo is a continuum of functional phenotypes with intermediate or overlapping features, these extreme Mφ phenotypes (M1 and M2) are extensively studied in vitro [16].

3. M1 andM2 phenotypes

M1 macrophages, also known as classically activated macrophages, can be activated by toll-like receptor (TLR) ligands, such as lipopolysaccharides (LPS) or interferon-γ (IFN-γ) [1,6,7,27]. M1 macrophages are characterized by high antigen presentation and high expression of pro-inflammatory cytokines such as interleukin (IL)-12, IL-23, and tumor necrosis factor-α (TNF-α) [25,28,29]. M1 macrophages are reportedly associated with inflammatory, microbicidal, and tumoricidal activities [30,31] (Fig. 1).

M2 macrophages, also called alternatively activated macrophages, can be further divided into the subcategories M2a, M2b, M2c, and M2d. M2a macrophages are induced from nonpolarized Mφ macrophages via stimulation with IL-4/IL-13 and downstream involvement of jumonji domain-containing-3 (Jmjd3) and interferon regulatory factor (IRF)-4 [32]. In contrast, M2b macrophages are induced by immunoglobulin complexes in combination with TLR agonists, and M2c macrophages are induced by IL-10, transforming growth factor β (TGF-β), or glucocorticoids [33–35]. The M2d phenotype, which is only described only in mice, can be induced by adenosine in pro-inflammatory M1 macrophages via activation of the adenosine 2A receptor ($A_{2A}R$) (Fig. 1). M2d macrophages are characterized by increased production of IL-10 and vascular endothelial growth factor (VEGF) and low expression of TNF-α and IL-12 [36].

4. M1/M2 polarization and therapeutic strategies

Macrophages are characterized by remarkable plasticity and versatility, being able to switch from one phenotype to another [37]. This phenomenon results from the macrophages responding to the local

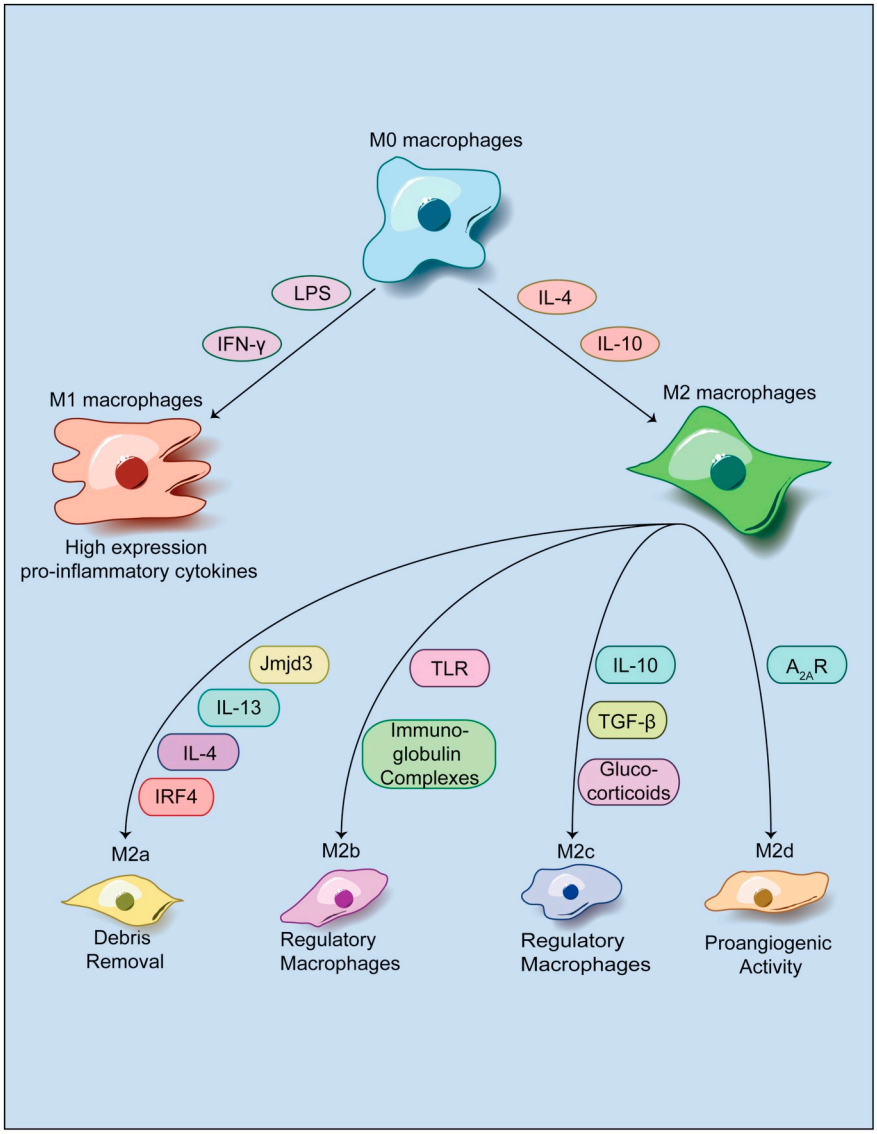


Fig. 1. Schematic of macrophages polarization.

microenvironmental stimuli encountered in different tissues and activating diverse signaling cascades in response [3]. The differentiation of monocytes to macrophages is primarily controlled by the principal hematopoietic growth factors [26,38–40] known as granulocyte macrophage colony stimulating factor (GM-CSF) [39] and macrophage colony stimulating factor (M-CSF) [26]. For instance, in the presence of GM-CSF the monocytes found among bone marrow cells (BMCs) can differentiate into macrophages with antigen-presenting capabilities, which in turn can give rise to osteoclasts [38]. Furthermore, when macrophages are subsequently present in other tissues, they can respond to local signals with the acquisition of distinct functional phenotypes.

Indeed, in response to TLR ligands [41] and interferon-γ (IFN-γ) [42], macrophages may undergo pro-inflammatory M1 activation, while they undergo an anti-inflammatory M2 activation after stimulation by IL-4 or IL-13 [43]. Therefore, polarization of Mφ into either the M1 or M2 phenotype has become a promising therapeutic approach for dealing with inflammatory diseases. Specifically, the most common strategies for resolving inflammation are by increasing M2 and/or decreasing M1 polarization. The following sections describe the results of recent studies that interrogated the effects of several natural occurring compounds on M1 and M2 polarization, along with the relevant molecular mechanisms (Table 1; Fig. 2).

5. Naturally occurring compounds that regulate Mφ/M1 polarization

Diosgenin glucoside (Dios) is a saponin compound extracted from Tritulus terrestris L [44]. Wang et al. [45] found that Dios selectively suppressed the expression of M1 genes that promote inflammation in activated microglial cells. Further analysis showed that Dios strongly inhibits the production and/or expression of M1 markers, such as IL-1β, NO (nitric oxide), IL-6, TNF-α, IL-17 and IL-23, in microglia that had been stimulated with LPS. However, under the same conditions, the production of several M2 markers was preserved, including the following: suppressor of cytokine signaling-3 (SOC3), M-CSF, IL-10, CD206, interleukin-1 receptor α (IL-1Rα), arginase-1 (Arg-1), found in inflammatory zone1 (Fizz1) and chitinase-3-like protein 3 (Ym1). Additionally, Dios has also been demonstrated to possess the ability to inhibit LPS-induced phosphorylation of the inhibitor of NF-κB α (IκB-α), p38 Mitogen-activated protein kinase (MAPK) and extracellular regulated kinase (ERK).

Polysaccharides [46] derived from the plant *Citrus grandis* L. Osbeck and luteolin [47], two important flavone natural occurring compounds, have been used as anti-inflammatory compounds in China for decades. Chen et al. [48] reported that these two compounds can inhibit M1 polarization by suppressing the NF-κB pathway. More specifically, the authors established both a chronic pharyngitis (CP) rabbit model and an ear edema mouse model and used them, as well as in vitro studies, to demonstrate that a polysaccharide plus luteolin treatment results in inhibition of NF-κB activation, as well as suppression of IRF1 and IRF5 expression. Their observations of the effects of luteolin on M2 polarization will be discussed in the following section.

Pentacyclic triterpene Lup-20(29)-en-3β-ol (Lupeol) can be found in a variety of vegetables, fruits and medicinal plants, such as *Tamarindus indica* and *Sebastiania adenophora* [49]. Zhu et al. [50] found that lupeol treatment both inhibits M1 polarization by downregulating the expression of IRF5, an important transcription factor in M1 polarization,

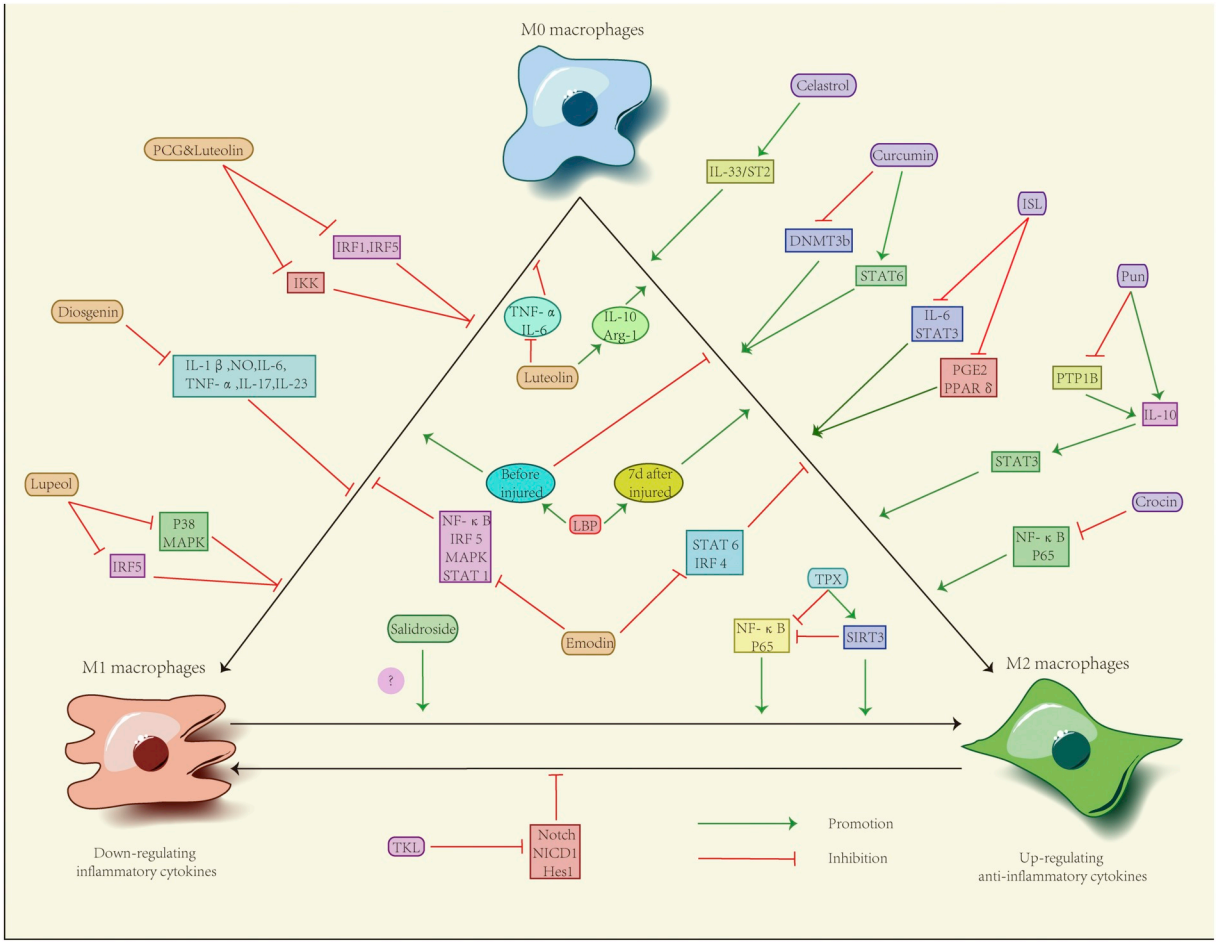
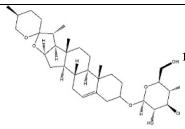
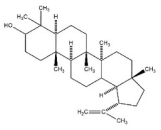
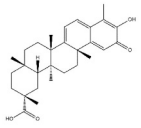
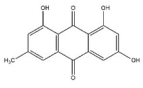
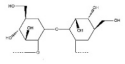
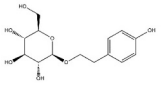
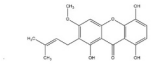
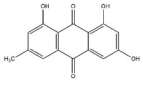
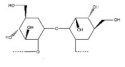
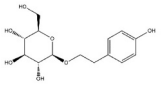
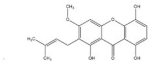


Fig. 2. Schematic of natural occurring compounds therapeutic spot during macrophages polarization.

Table 1
The source, structure, cells or animal models and mechanism of 12 natural compounds on regulating M1&M2 polarization.

Compound name	Source	Structure	Cell lines used for in vitro studies	Animal models	Dose	Mechanisms	Studies
Diosgenin glucoside	*Tritulus terrestris L*		Rat brain primary microglial cells; Murine BV-2 microglial cells	Unknown	1,5,10μM for cell culture	↓ M1 marker	Wang et al [45]
Lupeol	*Cabbage, pepper, cucumber, olive, , mango etc.*		Monocytes CD14 cells	C57BL/6 mice	0.01-10μM for cell culture; 50 mg/kg/d for animals	↓ M1 polarization, IRF5	Zhu et al [50]
Celastrol	*Triptery gium wilfordii and Celastr us regelii*		Rat brain primary neuronal cells	SD Rats	0.25,0.5,1,2μM for cell culture; 1mg/kg/d for animals	↑ M2 polarization, IL-33/ST2 axis	Jiang et al [53]
Emodin	*Rheum palmat um and Polygo nam multiflo rum*		Rats primary mouse macrophages	Balb/c mice	40 mg/kg/d for animals; 50μM for cell culture	↓ M1&M2 polarization, NF-kB, IRF5,MAPK, STAT1 or STAT6, IRF4	Lin et al; Stephen et al [73][75]
Lycium barbarum polysaccharide	*Lycium barbar um*		Rat brain primary astrocyte; Murine N9 microglial cell line	SD rats	10 mg/kg, 2/d for animals; 100 μg/ml for cell culture	↑ M2 polarization after 7d injured ↑ M1 polarization before injured ↓ M2 polarization before injured	Zhang et al [78]
Salidroside	*Rhodiol a rosea L*		Rat brain primary microglial	C57/BL6 mice	2.5,5,10,20 mg/kg for animals; 50,100,400, 800μM for cell culture	↑ M2 polarization (anti-inflammation cytokines) ↓ M1 polarization (inflammation cytokines)	Liu et al [80]
1,3,6,7-tetrahydroxy-8-prenylxanthone	*Mangos teen*		RAW264.7 cells	C57BL/6 mice	20μM for cell culture; 20mg/kg for animals	↑ M2 polarization, ↓ NF-κB translocation, inflammatory	Li et al [86]
Emodin	*Rheum palmat um and Polygo nam multiflo rum*		Rats primary mouse macrophages	Balb/c mice	40 mg/kg/d for animals; 50μM for cell culture	↓ M1&M2 polarization, NF-kB, IRF5,MAPK, STAT1 or STAT6, IRF4	Lin et al; Stephen et al [73][75]
Lycium barbarum polysaccharide	*Lycium barbar um*		Rat brain primary astrocyte; Murine N9 microglial cell line	SD rats	10 mg/kg, 2/d for animals; 100 μg/ml for cell culture	↑ M2 polarization after 7d injured ↑ M1 polarization before injured ↓ M2 polarization before injured	Zhang et al [78]
Salidroside	*Rhodiol a rosea L*		Rat brain primary microglial	C57/BL6 mice	2.5,5,10,20 mg/kg for animals; 50,100,400, 800μM for cell culture	↑ M2 polarization (anti-inflammation cytokines) ↓ M1 polarization (inflammation cytokines)	Liu et al [80]
1,3,6,7-tetrahydroxy-8-prenylxanthone	*Mangos teen*		RAW264.7 cells	C57BL/6 mice	20μM for cell culture; 20mg/kg for animals	↑ M2 polarization, ↓ NF-κB translocation, inflammatory cytokines	Li et al [86]

and results in a clear decrease in the phosphorylation of p38 MAPK.

6. Naturally occurring compounds that regulate Mφ/M2 polarization

Compared to the naturally occurring compounds regulating M1 polarization, those regulating M2 polarization have gained more attention recently.

Celastrol is a quinone methide triterpene isolated from root extracts of *Tripterygium wilfordii* (thunder god vine) and *Celastrus regelii* [51]. A recent study found that increased IL-33/stimulation expressed gene 2 (ST2) signaling could up-regulate M2 macrophage polarization during ischemia, with a subsequent decrease in neuronal cell death [52]. Jiang et al. [53] showed that IL-33 levels increase along with other pro-inflammatory cytokines in the serum of patients following a stroke. The underlying molecular mechanism may be that IL-33 can upregulate microglial ST2 expression, which in turn suppresses neuronal damage via increased microglial M2 polarization and its associated expression of anti-inflammatory IL-10. A recent study showed that IL-33 and ST2 are activated in a murine ischemia model and that this activation could be further increased by celastrol treatment, promoting microglia M2 polarization. Down-regulation of ST2 promoted microglial M1 polarization even when high levels of IL-33 were present. However, celastrol was shown to increase IL-33 expression and thereby suppress ischemia, acute ischemic stroke (AIS)-induced brain damage and inflammatory factor expression by promoting IL-33/ST-2-mediated M2 microglial polarization.

Luteolin (3′,4′,5,7-tetrahydroxy flavone), an important flavone, has been found in several plant species and has been widely used in folk herbal medicine [54]. Chemical analysis and structure-activity studies have demonstrated that luteolin contains hydroxyl moieties at carbons 5, 7, 3′ and 4′ positions and a 2–3 double bond, which are associated with its known pharmacological activities. Recently, Nabavi et al. [55] briefly reviewed the anti-inflammatory and neuroprotective effects of luteolin. Further, Zhang et al. [56] revealed that luteolin induces M2 polarization by stimulating the production of IL-10 and Arg-1 and that it also decreases the expression of M1 inflammatory markers, such as TNF-α, IL-6 and inducible nitric oxide synthase (iNOS).

Curcumin, a compound extracted from the rhizome of *Curcuma longa L,* has been shown to have many biological activities, including anti-inflammatory effects [57] that appear to be mediated via the regulation of M2 polarization [58]. Gao et al. [59] demonstrated that curcumin plays a key role in M2 polarization in two ways: (1) via the inhibition of DNA methyltransferase3b (DNMT3b), overexpression of which can promote increased M1 polarization, and (2) via increased phosphorylation of signal transducer and activator of transcription (STAT)-6, an important transcription factor activated by IL-4 and IL-10. Furthermore, an experimental autoimmune myocarditis (EAM) in vivo mouse model study has shown that daily treatment with a concentration of 50 mg/kg of curcumin can significantly suppress Mφ to M1 polarization while simultaneously increasing M2 polarization [59].

Isoliquiritigenin (ISL), a flavonoid from *licorice*, has been reported to prevent azoxymethane (AOM)-induced colon carcinogenesis in animal models [60]. Zhao et al. [61] found that ISL inhibits M2 polarization by downregulating prostaglandin E2 (PGE2) and IL-6 production. It has been reported that cyclooxygenase-2 (COX-2) and PGE2 induce M2 polarization in lung cancer and cervical carcinoma [62,63]. According to a previous study, ISL inhibits COX-2 expression and PGE2 production in both RAW264.7 cells and mouse colon cancer cells [64]. Zhao et al. [61] showed that ISL significantly inhibited COX-2 and peroxisome proliferator activated receptors δ (PPARδ) expression, while decreasing typical M2 markers (including: Arg-1, CD206, Ym-1 and IL-1Rα) in colonic macrophages, as in RAW264.7 cells. On the other hand, the IL-6/STAT3 pathway also regulates M2 macrophage polarization and promotes the progression from colitis to colorectal cancer [65]. Based on this finding, Zhao et al. [61] determined the effects of ISL on the IL-6/STAT3 pathway and found that ISL decreased IL-6 production and inhibited the expression of the interleukin-6 receptor (IL-6R) and phosphorylated-STAT3 (p-STAT3) in both colonic macrophages and RAW264.7 cells. Based on these results, it could be inferred that the interaction between the PGE2 and IL-6 systems contributes to the inhibition of M2 polarization by ISL.

Punicalagin (PUN), an ellagitannin isolated from pomegranate and a protein tyrosine phosphatase-1B (PTP1B) inhibitor, induces M2c polarization via upregulation of heme oxygenase-1 (HO-1) in murine macrophages [66]. In PTP1B knockdown and knockout macrophages, STAT3 phosphorylation and expression of IL-10 mRNA are enhanced [67]. Conversely, PTP1B overexpression is reported to dephosphorylate STAT6, which suppresses anti-inflammatory IL-4 production [68]. A previous study reported that PUN treatment promoted the phosphorylation of protein kinase B (Akt) and STAT3, while inhibition of either Akt or STAT3 depressed HO-1 expression [69]. Flow cytometry also showed that PUN treatment downregulated the M1 phenotype marker CD86 but upregulated M2 marker CD206 [66]. Further study showed that PUN treatment significantly promoted IL-10 secretion, while decreasing that of IL-4. Therefore, it seems that PUN treatment may enhance the expression of M2c-like genes [70].

Crocin is an active component of *Crocus sativus L* that was found by Li et al. [71] to exert an anti-inflammatory effect by inhibiting the expression of NF-κB and suppressing the translocation of NF-κB p65 into the nucleus. Moreover, crocin was also observed to decrease the expression of inflammatory cytokines, such as TNF-α and IL-6. Interestingly, it was found that the M2 macrophage markers CD68 and CD206, as well as anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGF-β), were increased under crocin treatment. These results implicate crocin as a potential therapeutic agent in an M2 polarization strategy.

7. Naturally occurring compounds that regulate both Mφ/M1 and Mφ/M2 polarization

Emodin is a trihydroxy-anthraquinone that is found in several herbs, including *Rheum palmatum* and *Polygonum multiflorum* [72]. Lin et al. [73] showed that emodin shifts the T helper cell 1 (Th1)/Th2 balance towards Th2 by decreasing IFN-γ and IL-2 levels and increasing IL-4 levels in the serum of rats that received orthotopic liver transplantations. Emodin has also been shown to promote expression of the M2-associated molecules TGF-β and PPARγ [74]. Stephen et al. [75] showed that emodin effectively inhibited Mφ/M1 and Mφ/M2 polarization simultaneously. Depending on the local environment, emodin was able to decrease the Mφ macrophage response to both M1 and M2 stimuli by inhibiting the activation of NF-κB, IRF5, MAPK and STAT1 signaling in Mφ/M1 polarization, and STAT6 and IRF4 signaling in Mφ/M2 polarization.

Lycium barbarum polysaccharide (LBP) has been found to underlie the most beneficial effects of *Lycium barbarum* [76,77]. Zhang et al. [78] have demonstrated that LBP treatment following injury can simultaneously enhance Mφ/M1 polarization and suppresses Mφ/M2 polarization. Interestingly, though, administration of LBP starting 7 days post-trauma was only able to enhance Mφ/M2 polarization. However, since only a few studies focus on the role of LBP on macrophage polarization, the specific molecular signaling pathways and target genes involved have not been elucidated in detail. Thus, further studies are necessary to fully understand its effects.

8. Naturally occurring compounds that regulate M1/M2 polarization

Salidroside (SLDS) is a phenylpropanoid glycoside extracted from the root of *Rhodiola rosea L* [79]. Liu et al. [80] revealed that SLDS treatment caused a reduction in M1 macrophage/microglia polarization and an increase in M2 macrophage/microglia polarization in both the

cortex and striatum of middle cerebral artery occlusion (MCAO) mice compared to controls. These results provide evidence that SLDS drives M2 polarization. In addition, this study also observed that the expression of inflammatory cytokines is downregulated and the expression of anti-inflammatory cytokines is upregulated following SLDS treatment.

Trichosanthes kirilowii lectin (TKL) is a biologically active derivative of *Trichosanthes kirilowii* [81]. Notch signaling is especially crucial to the polarization of macrophages [82]. Lu et al. [83] discovered that TKL could block the differentiation of macrophages from the M2 to the M1 phenotype by inhibiting Notch signaling. Notch-hairy and enhancer of split 1 (Hes1) signaling is a central pathway regulating the differentiation and survival of macrophages [84], and the Lu study found that TKL also downregulates expression levels of Notch1, notch intracellular cytoplasmic domain 1(NICD1), and Hes1 [83].

1,3,6,7-tetrahydroxy-8-prenylxanthone (TPX) is derived from mangosteen (*Garcinia mangostana*) [85]. Li et al. [86] found that TPX could suppress LPS-induced activation of inhibitor of nuclear factor kappa-B kinase α/β (IKKα/β), IκBα and p65, prevent the translocation of p65 to the nucleus and inhibit NF-κB transcriptional activity in macrophages, resulting in a reduction in the expression of downstream genes including iNOS, COX-2 and TNF-α. In addition, subsequent experiments showed that the expression of PPARs was downregulated after stimulation with LPS alone, while TPX treatment significantly promoted PPAR expression in LPS-treated macrophages. Notably, the expression of sirtuin-3 (SIRT 3) was also promoted following TPX treatment. Finally, they found that TPX treatment suppressed the expression of the M1 macrophage marker CD11c, while elevating the expression of M2 markers such as ARG-1 and CD206, suggesting a shift towards an anti-inflammatory phenotype.

9. Conclusions

Characterized by their innate heterogeneity, macrophages have shown plasticity in cellular functions during various diseases pathological process, which make them difficult but intriguing targets for therapeutic intervention. Given their low production costs and the increasing evidence of their ability to target the cellular activities and signaling cascades relevant to macrophage polarization, naturally occurring compounds have received extensive attention as potential therapeutic macrophages. Our current review has outlined some naturally occurring compounds, which have shown merit in terms of regulating macrophage polarization. However, given that natural herbal compounds have many regulatory effects on macrophages polarization, the specific mechanisms, signaling pathways and target genes involved remain incompletely understood. Clearly, more in-depth characterization of macrophage polarization and relevant therapeutic compounds should be conducted to identify the best possible strategies to target macrophages for the purpose of disease treatment.

Acknowledgments

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