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Review Article

Role of plant-derived natural compounds in macrophage polarization

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Abstract

Macrophages are important cells of the immune system and are sufficiently plastic to polarize either an M1 state or M2 state. Depending on the signals received from different intrinsic or extrinsic factors, the macrophage polarity is determined. These cells are distributed in every tissue of the body and are also found as circulating cells in the bloodstream called 'monocytes'. Natural products may be one extrinsic factor to modulate macrophage polarization. It is important to understand the mechanism by which natural products drive the polarization of macrophages. Based on recent advancements in the understanding of immunology, macrophages are classified as classically activated and alternatively activated, also designated as M1 and M2 macrophages respectively. The resident brain macrophages (microglia) get activated under stress and attain the M1 macrophage phenotype which is related to inflammatory mechanisms leading to neurodegeneration while treatment with plant-derived natural compounds drives the M1 microglia towards the M2 type which prevents the inflammatory response and protects the neurons. Understanding the mechanism of polarization of macrophages by natural compounds will be useful in treating different types of inflammatory diseases including Alzheimer's and Parkinson's. In this review, we summarized the current understanding of macrophage polarization using plant-derived natural compounds and their ability to regulate the pathophysiology of the tissues.

Introduction

Macrophages are large innate immune cells exhibiting a primary role in phagocytosis and clearing of cellular debris or invading pathogens, hence are crucial in various pathological and physiological processes [1]. Macrophages were first discovered in 1884 by Russian bacteriologist Elie Metchnikoff, who in 1908 received the Nobel Prize in Physiology or Medicine for his description of phagocytosis [2]. The ability to ingest particles through phagocytosis is one of the most peculiar properties of macrophages. Besides phagocytosis, macrophages are involved in immune modulation through antigen processing and presentation, generation and resolution of inflammation, tissue repair, etc [3,4]. Macrophages are located throughout the body tissues (Table 1) that fulfill tissue-specific and niche-specific functions (homeostasis and immune surveillance) and also play a distinctive role in response to local microenvironmental signals [5,6]. In addition to their tissue distribution, macrophages are often functionally polarized into M1 (pro-inflammatory) and M2 phenotypes (alternatively activated). Macrophages exhibit functional plasticity which may be driven by natural compounds and therefore they may be ideal targets for therapeutic application for inflammatory diseases.

Table 1: Site-based macrophage classification.

S. No.	Tissue Site	Name of Macrophages
1.	Brain	Microglia
2.	Bone	Osteoclasts
3.	Liver	Kupffer Cells
4.	Lung	Alveolar macrophages
5.	Skin	Langerhans cells

There are many studies on plant-derived natural compounds which reported macrophage polarization [7-10].

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However, there is a paucity of literature on natural compounds which summarized the list of different natural compounds that can change macrophage polarization. Thus, there is a need to review natural compounds which are reported for driving macrophage polarization. The literature related to macrophage polarization using plant-derived natural compounds was searched using PubMed and Google Scholar databases with the keywords macrophage polarization, natural compounds and macrophage polarization, plasticity in macrophages, etc.

Macrophage activation and polarization

Macrophages are terminally differentiated cells of the mononuclear phagocyte system including dendritic cells, circulating blood monocytes, and committed myeloid progenitor cells in the bone marrow [11]. These are activated in response to various threat signals like Pathogen Associated Molecular Patterns (PAMPs) present on most microbes, and Danger Associated Molecular Patterns (DAMPs) developed in the presence of dead or infected host cells. Macrophage activation has a functional significance in homeostasis and diseases [12]. The macrophages are well-recognized key regulators of both innate and adaptive immunity as well as important mediators of systemic metabolism, hematopoiesis, vasculogenesis, apoptosis, malignancy, and reproduction [13]. Upon activation, macrophages differentiate into two sets of the population having pro-inflammatory and anti-inflammatory functions.

Macrophage activation may be classified as classically activated macrophages and alternatively activated macrophages, also designated as M1 and M2 macrophages respectively [14,15]. In addition to M1 and M2 macrophages, another set of a macrophage-derived cell populations that plays a pivotal role in preventing inflammation during innate and adaptive immune responses are Regulatory Macrophages [16]. The classical (M1) and alternative (M2) activation depend on the type of cytokines that the macrophages encounter [17].

Classically activated macrophages or M1 macrophages

The classical or M1 activated macrophages have positive effects on inflammation and are thus formed as a result of classical activation by stimulation of Toll-like Receptors through interferon-gamma (IFN-γ) or lipopolysaccharide (LPS) and kill invading pathogens through the production of nitric oxide (NO) and other inflammatory mediators.M1 macrophages produce pro-inflammatory cytokines. The increased production of pro-inflammatory mediators stimulates cell-mediated adaptive immunity as well as enhances microbicidal capacity (Figure 1) [16]. The pro-inflammatory macrophages eliminate infections caused by bacteria, viruses, or fungi and also kill tumor cells.

Biomarkers specific for M1 macrophage activation: M1 macrophages express cytokines such as IL-12, TNF-α, IL-6, IL-1β, IL-23; chemokines such as CXCL8, CXCL9, CXCL10, CXCL11, CXCL16, CCL2, CCL3, CCL5 and co-stimulatory molecules like CD80, CD86, surface markers like MHCII and TLR2/4, inflammatory mediators like nitric oxide synthases (NOS) and reactive oxygen species (ROS) [18].

Alternatively activated or M2 macrophages

M2-activated macrophages inhibit inflammation and are formed when macrophages are exposed to cytokines like IL-4, IL-10, or IL-13. These macrophages produce polyamines and proline, which induce proliferation and collagen production respectively, hence play a critical role in regulating the immune response towards parasites, allergy, wound healing, and tissue remodeling. Anti-inflammatory Macrophages can induce regulatory T-lymphocyte differentiation. In response to different stimuli, M2-activated macrophages are further subdivided into M2a (wound-healing; induced by IL-4 and IL-13; alternative inflammation), M2b (triggered by immune complexes in the presence of FcγR/TLR ligand), and M2c (anti-inflammatory stimuli such as glucocorticoids, IL-10, TGF-β) (Figure 2) [16,19].

Biomarkers specific for M2 macrophage activation: Arginase-1, Chitinase 3- like protein 3 or Ym1, CD206 and CD163, FIZZ1, DC-SIGN or CD209, MGL-1 and Dectin-1 (CLEC-7A), cytokines such as IL-10 and IL-1ra, chemokines like CCL17, CD200R, or CD23 [20] are the known makers for M2 macrophages.

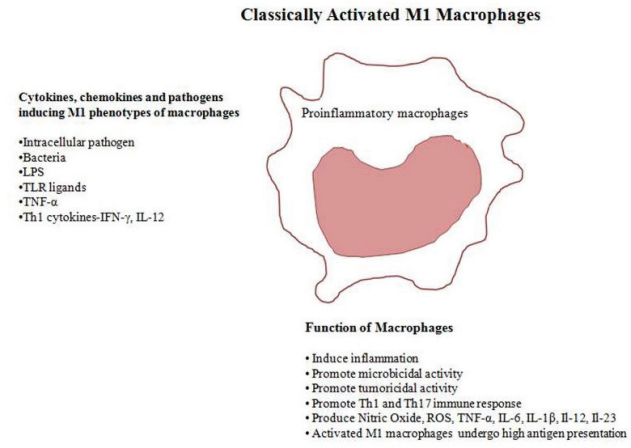

Figure 1: Classically activated M1 Macrophage stimulating factors and their function.

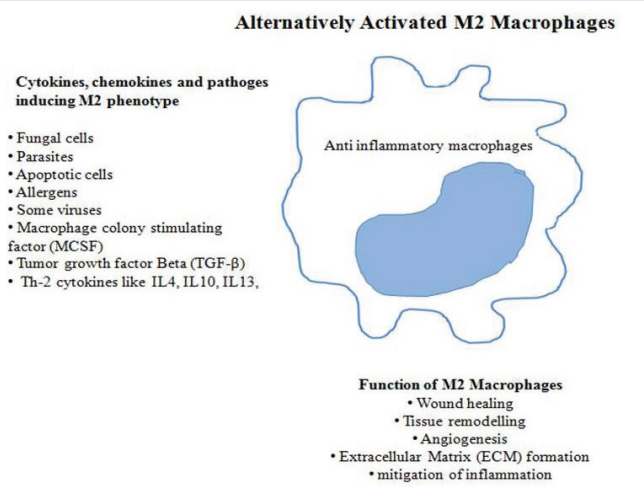

Figure 2: Alternatively activated M2 Macrophage stimulating factors and their function.

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Transcription factors for polarization of macrophages

Nuclear Factor κB (NF-κB) which is a significant transcription factor related to M1 activation, regulates the activation of macrophages in response to inflammatory cytokines and stress signals [21]. Activated Protein 1 (AP-1; a group of basic leucine zipper transcription factors) is another major pro-inflammatory transcription factor and it mediates gene regulation in response to physiological and pathological stimuli [22]. IFN Regulatory Factors such as IRF5 (optimal expression of IL-12 and pro-inflammatory cytokines) and IRF4 (regulates alternatively activated macrophage polarization) are important for M1 and M2 differentiation [23]. Hypoxia-Inducible Factors; HIF-1α activity is aided by Th1 cytokines during M1 macrophage polarisation which promotes the production of Nitric oxide, whereas HIF-2α activity is regulated by Th2 cytokines during M2 macrophage polarisation. Signal Transducers and Activators of Transcription-STAT1 are associated with M1 macrophage polarization and STAT2 with M2 macrophage polarization [23].

M1/M2 macrophages and inflammatory responses

Inflammation is a part of homeostasis where the body recruits immune cells to deal with infectious agents, pathogens, and dead cells. Immune cells like T cells, B cells, NK cells, monocytes, macrophages, dendritic cells, neutrophils, basophils, eosinophils, and mast cells participate in the process of pathogen recognition and activate the signaling cascade of inflammation. An inflammatory response is required by the immune system to recruit more immune cells. Various signaling molecules like IL-2 (cause proliferation of activated T and B cells), IL-3 (induce growth and differentiation of immune cells in bone marrow), IL-4 (promote B cell growth and differentiation), IL-12 (activate T cells and NK cells), IFN-γ (activates macrophages), and TNF-α (cause activation of macrophages and induce inflammation), etc. participate in immune cell activation and proliferation. Macrophages and neutrophils phagocytose the foreign pathogen and digest it in peptides whereas basophils and mast cells release histamines one of the factors responsible for inflammation. After the phase of a heightened inflammatory response, it becomes crucial to resolve the inflammatory response to bring back homeostasis, as chronic inflammation may lead to various inflammatory diseases. The body itself maintains the balance between these two phases to achieve a state of homeostasis. Out of the repertoire of immune cells, macrophages can modulate both pro-inflammatory and anti-inflammatory states. They can eradicate the pathogen by inducing an inflammatory response and can also repair the damage caused by these pathogens inside the body. The regulation of inflammation and repair is performed by two subsets of macrophages i.e. M1 and M2 macrophages which have contrasting characteristics. The polarization of M1/M2 macrophages is regulated by the microenvironment and surrounding cytokines. Polarized T cells i.e. Th-1 and Th-2 cells secrete Th1 cytokines (IL-12, IFN-γ, TNF-β) and Th2 cytokines (IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13), respectively. The Th-1 cytokines influence the M1 polarization and Th-2 cytokines M2 macrophages polarization. It was also found that activation of macrophages either by IL-4 or IFN-γ blocks the process of proliferation in the G1/S phase [24].

During a pathogenic encounter, macrophages are involved in the process of phagocytosis of the opsonized pathogen by secreting various cytokines and chemokines which activate and recruit other cells at the site of encounter. During this process, macrophages remain in their pro-inflammatory phase i.e. M1 phase. After pathogen removal, macrophages undergo a tissue repair phase and alter their phenotype to M2 macrophages where they clear apoptotic cells, produce extracellular matrix, and blood vessels, and secrete chemotactic factors and IL-10 resulting in the process of wound healing, tissue repair, and mitigation of inflammation.

The transformation between M1 and M2 macrophages is environment-dependent and the biochemical pathway used for the processing of amino acid arginine (Figure 3). In classically activated M1 macrophages, induction of NOS2 induces the production of NO which has inflammatory effects whereas, alternatively activated M2 macrophages expression of arginase is upregulated which convert arginine to ornithine and subsequently converted into hydroxyproline and polyamines. These amino acids help in the reconstruction of the damaged extracellular matrix. Chemokines such as CCL19, CCL21, CCL24, CCL25, CXCL8, CXCL10, and XCL2 specifically induce M1 macrophages chemotaxis, whereas CCL7 induces chemotaxis of both M1 and M2 macrophages [25]. M2 macrophages are further categorized into M2a, M2b, and M2c subtypes which are differentiated on the basis of the cytokine they secrete and as well as their biological function [26,27].

IRF/ STAT signaling pathway plays a central role in macrophage polarization. IFN and TLR induced IRF/STAT signaling activates M1 macrophages while IL-4 and IL-13 induced IRF/STAT signaling via STAT 6 induces M2 macrophages [28]. Furthermore, SOCS expression also affects the M1- M2 macrophage polarization. SOCS is a family of proteins that inhibit cytokine signaling transduction. SOCS1 and SOCS3 can directly inhibit JAK activity to suppress the cytokine signaling pathway. The knockout study of SOCS led to the observation that the ratio of SOCS1: SOCS3 is high in M2 macrophages whereas, low in M1 macrophages [29,30].

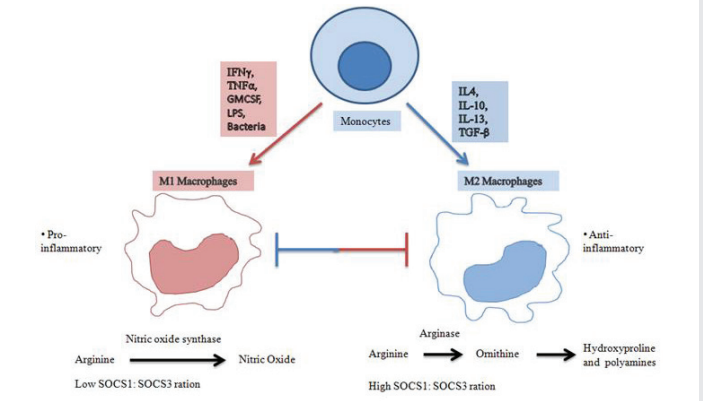

Figure 3: M1-M2 macrophage polarization and differentiating factors.

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During some pathophysiological conditions, macrophages acquire different phenotypic markers. An early phase of bacterial infection induces an inflammatory response by recruitment of inflammatory cells whereas, during the late phase of infection to counteract excessive inflammation, macrophages polarize into M2 macrophages to protect the host from excessive injuries and to undergo wound healing [31]. However, in the case of viral infections like influenza, HIV, and SARS, M2 phenotype macrophages dominate these pathological conditions [32,34]. Moreover, the formation of new blood vessels is a characteristic of inflammatory conditions (M1 dominated phase) like atherosclerosis and tumor as well as of post-inflammation events (during the phase of mitigation of inflammation, M2 dominated phase) where angiogenesis is required for cells recruitment and wound healing. However, recent studies by Jetten, et al. reported the pro-angiogenic role of M2 macrophages and not the M1 macrophages [35]. However, much research is required to eliminate the possibility of the presence of M2 macrophages in an inflammatory condition which could be the reason for angiogenesis in inflammatory conditions or the presence of a gradient of different cytokines and chemokines (signifying the presence of host repair signals in the initial phase of inflammation) could decide the M1- M2 phenotype in any pathological condition and thus the presence of mixed M1- M2 population in a specific ratio.

Role of plant-derived natural compounds in macrophage polarization

Macrophages provide the first line of defense and altering the functioning of these cells either results in complete revival or severe illness [36]. Likewise, extensive M1 polarization causes tissue injury and inflammation [37,38]. Plant-derived active compounds have been extensively acknowledged for their beneficial role in curing health-related maladies [39]. Plants are rich sources of compounds that exhibit several pharmacological properties and thus could be focused on for developing phytomedicinal drugs [39-44].

A brief description of the plant and the derivatives involved in macrophage polarization is given below (Table 2):

Flavonoid and aqueous extracts (*Crinum latifolium*)

The therapeutic and immunomodulatory properties of *Crinum latifolium*(CL), a flowering plant is known for thousands of years in Chinese and Vietnamese folk medicine [45]. A study reported that the extracts from the CL plant can polarise the macrophages towards M1 macrophages, as well as these extracts, possess the property to suppress tumor growth [7]. They reported the effect of flavonoid and aqueous extracts of CL on mice peritoneal macrophages. Treatment with CL for 24 hours leads to up-regulation of the mRNA levels of M1 macrophages-associated markers like IL-6, TNF-α, and IL-1β, as well as ROS production, was also enhanced. Total flavonoid and alkaloid extract induced expression of Formyl Peptide Receptor(FPR) on the surface of polarized macrophages which leads to macrophage activation towards M1 macrophages and enhanced NQO1 mRNA expression in polarized macrophages that could play an important role in cancer chemoprevention. In contrast, the mRNA expression of M2 macrophage markers like TGF-β and CD36 did not show any effect upon CL treatment.

Glycyrrhizic acid (*Glycyrrhiza uralensis*)

Glycyrrhiza uralensis commonly known as licorice is a known natural sweetener that is widely used as a medicinal herb for the treatment of various stomach-related ailments. A group of researchers investigated the polarisation of macrophages in response to treatment with Glycyrrhizic acid (GA), an active constituent of the licorice plant [8]. They reported that the treatment of murine bone marrow-derived macrophages with GA remarkably increased the level of M1 polarised macrophages-related markers like TNF-α, CCR7, IL-6, and IL-12. Also, the expression of genes related to antigen presentation like CD86, CD80, and MHCII increased with GA treatment. On the other hand, the expression of M2 macrophage-associated markers like Ym1 and Mannose receptor decreased on GA treatment. In accordance with this, the GA treatment also up-regulated the expression of Arg1 and iNOS, which then lead to increased NO production, suggesting that there exists a clear relationship between GA treatment and polarisation of macrophages towards the M1 phenotype.

Malibatol A (*Hopea hainanensis*)

A natural polyphenolic compound known as Malibatol A (MA), isolated from an Asian plant *Hopea hainanensis* is known to possess strong antioxidant properties [46]. A study aimed to identify the anti-inflammatory effect of Malibatol A (MA) in ischemic injury caused due to stroke, revealed that MA exerts neuroprotective effects in mouse cerebral ischemia model by polarising the macrophages towards the M2 alternative phenotype [47]. They observed in mice middle cerebral artery occlusion model that treatment with MA suppressed the hallmarks related to M1 macrophages like CD32 and CD16 on the other hand, enhances M2-related makers like CD206 and Iba1 in resident microglia 72 hours after treatment.

Lignanarctigenin (*Arctium lappa*)

*Arctium lappa*commonly known as burdock is a flowering plant whose seeds and roots are known to possess anti-inflammatory effects [48]. Hyam, et al. reported that the lignin arctigenin found in seeds of the burdock plant was able to suppress the expression of COX2, iNOS, NF-κB, and AKT phosphorylation in peritoneal macrophages stimulated by LPS [49]. In addition to this, LPS stimulated peritoneal macrophages when treated with arctigenin suppressed the level of pro-inflammatory cytokines like IL-1β and TNF-α. Similar results were observed in TNBS induced colitis model treated with arctigenin, suggesting that M1 macrophage markers are suppressed whereas the markers associated with M2 (CD204 and IL-10) increased. These reports suggest that arctigenin acts as an anti-inflammatory compound by polarising the macrophages towards the M2 phenotype.

Chrysin (*Passiflora caerulea*)

Chrysin or 5, 7-dihydroxyflavone a flavonoid present in plants like passion flowers and Indian trumpet flower is an

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Table 2: M1-M2 macrophage polarization by natural compounds.

Plant	Extract/Compounds	Macrophage polarization	Assays performed	References
Crinum latifolium	Aqueous	↑ M1 polarization	↑ ROS generation ↑ mRNA expression of TNF-α, IL-1β and IL-6	Nguyen, et al. 2013 [7]
Glycyrrhiza uralensis	Glycyrrhizic Acid	↑ M1 polarization	↑ CD80, CD86, and MHC-II. ↑ CCR7, TNF-α, IL-6, IL-12 and NO. ↓ expression of Mannose receptor, Ym1, and Arg-1 (M2 biomarker).	Mao, et al. 2015 [8]
Hopeahainanensis	Malibatol A	↑ M2 polarization	↓ expression of CD16, CD32, and CD86. ↑expression of CD206 and Ym-1.	Pan, et al. 2015 [47]
Arctium lappa	Arctigenin	↑ M2 polarization	↑expression of CD204 and IL-10. ↓ expression of IL-1β, TNF-α and IL-6, PI3K, AKT and NF-κB.	Hyamet *al*., 2013 [49]
Chrysin	A natural flavonoid	↑ M1 polarization	↑TLR4/NF-κB signaling pathway.	Feng, et al. 2013 [55]
Rhodiola Rosea	Salidroside	↑ M2 polarization	↑expression of CD206, Arg1, TGFβ, and YM1/2. ↓expression of NO and proinflammatory cytokines	Liu, et al. 2018 [56]
Tamarindus indica	Lupeol	↑ M2 polarization	↑ production of IL-10 and CD-206 ↓ production of TNF-α, IL-12, IL-16, and CD86	Zhu, et al. 2016 [57] Saha, et al. 2020 [58]
Radix puerariae	Isoflavones (Puerarin)	↑ M1 polarisation	↑ expression of iNOS, CD197, CD40,TNF-α, IFN-γ and IL-12. ↓ expression of CD163, Arg-1, IL-10, IL-1, CD206 and TGFβ.	Kang, et al. 2017 [59]
Petroseliumcrispum	Apigenin	↑ M2 polarization	↓ expression of TNF-α, IL-1β, COX2 and iNOS	Feng, et al. 2016 [60]
Theobroma cacao	Cocoa polyphenolic extract	↑ M2 polarization	↑ expression of IL-10 ↓ expression of IL-12, IL-6, TNF-α, IL-1β	Dugo, et al. 2017 [61]
Camellia sinensis	Epigallocatechin-3-gallate	↑ M2 polarization	↑ expression of Arg-1, ym1, and KLF4 ↓ expression of TNF-α, IL-1β and IL-6	Almatroodi, *et al.* 2020 [62]
Curcuma longa	Curcumin	↑ M2 polarization	↑ phosphorylation of STAT6 ↓ DNMT3b, TNF-α and IL-1β	Zhou Zhang, et al. 2015 [63]
Andrographis paniculata	Andrographolide	↑ M2 polarization	↓ expression of TLR4, NFκB, COX-2, iNOS and IL-1β.	Das, et al. 2017 [66]

excellent source of antioxidants [50] and is known to act as an immunomodulatory and anti-inflammatory compound by suppressing the expression of iNOS, COX2 and NF-κB genes [51-54]. A study based on flow cytometric analysis reported that chrysin treatment on LPS stimulated peritoneal macrophages isolated from obese mice was able to decrease the level of TNF-α, CD80, CCL3, CCR7, and IL-12β, which are the markers associated with M1 macrophages, interestingly, chrysin treatment increased the expression of M2 related markers like Ym1, Fizzl, CD206 and IL-10 which act as anti-inflammatory molecules [55].

Salidroside (*Rhodiola rosea*):

A glycoside of tyrosol known as salidroside isolated from *Rhodiola rosea* native to cold regions is a part of European and Asian traditional medicine which till now used as an antidepressant and stress reliever. The role of salidroside in macrophage polarisation in response to a cerebrovascular accident or stroke is elucidated by Liu, et al. [56]. Salidroside treatment in microglia of mice stroke model revealed that the mRNA level of iNOS and CD16 was downregulated whereas, that of Arg1 and CD206 was significantly upregulated [54]. The levels of pro-inflammatory cytokines like IL-2, TNF-α, IL-1β, and IL-8 were markedly reduced in microglia after salidroside treatment. Altogether these findings suggest that salidroside play a crucial role in polarising the macrophages to drive anti-inflammatory response after stroke.

Lupeol (*Tamarindus indica*)

Lupeol, also known as Fagarsterol is a pharmacologically active triterpenoid ubiquitously found in various fruit, plants, and vegetables like olive, strawberry, mango, cabbage, tomato, etc. Lupeol and its derivatives are known to possess anti-inflammatory, anti-arthritic as well as anti-angiogenic properties [9]. A study conducted by Zhu, et al. on DSS induced colitis model revealed that lupeol treatment was able to mitigate colitis-related inflammation by polarising M1 macrophages towards anti-inflammatory M2 macrophages. They report that with Lupeol treatment, the production of IL-16, IL-12, and TNF-α as well as M1 macrophage-related molecular markers like CD86 decreased with an increase in the production of anti-inflammatory cytokine IL-10 [10,57]. This suggested that lupeol has the potential to regulate the polarisation of macrophages towards the anti-inflammatory M2 subtype thus assisting in curing inflammatory diseases like IBD. Another study based on an inflammatory disease atherosclerosis model reported that lupeol was able to exert an anti-inflammatory effect in cells treated with 7 ketocholesterols by mitigating macrophage polarisation [58]. The study revealed that lupeol was able to increase the production of anti-inflammatory cytokines like TGF-β and IL-10 simultaneously by reducing the production of IL-12, thereby polarising macrophages towards the M2 phenotype and exerting an anti-inflammatory effect.

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Puerarin (*Radix puerariae*)

Puerarin is an isoflavonoid isolated from the root and leaves of *Radix puerariae*which is used in traditional Chinese medicine to treat cardiovascular and neurodegenerative ailments. It has antioxidant properties and protects against cell damage. It was reported that puerarin treatment in the Non-Small cell lung carcinoma model was able to exert an anti-tumor effect by increasing the expression of CD40, CD197, TNF-α, IFN-γ, iNOS, and IL-12 pro-inflammatory markers associated with M1 macrophages as well as decreasing the levels of CD206, Arg-1, IL-10, IL-1, CD163 and TGF-β and other M2 macrophage related markers [59]. In addition to this, puerarin was also able to directly inhibit M2 polarised macrophages, suggesting its role as a potent anti-tumor bioactive compound.

Apigenin (*Petroselinum crispum*)

Apigenin is a flavonoid, found in many fruits and vegetables which are known to exert antioxidant, anti-inflammatory, and chemoprotective effects. It has been found that in lung epithelial cancer cells, apigenin induces apoptosis and cell death. It could downregulate the expression of IL-1β and TNF-α in LPS-stimulated mouse macrophages and human monocytes [56,60]. Apigenin favors M2 polarization through PPAR-γ, which is a key controller of macrophage polarisation thus blocking the inflammatory functions of adipose tissue macrophages and also suppressing obesity-related inflammation. It mediates anti-inflammatory response via inhibition of COX2 and iNOS expression in LPS-stimulated mouse macrophages. A study on a high-fat diet-induced mice obese model demonstrated that the anti-inflammatory effect of apigenin in LPS-mediated acute lung injury is due to the ability of apigenin to inhibit COX-2 and NF-κB gene expression in the lung thereby switching macrophages towards the M2 phenotype [60].

Cocoa polyphenolic extract (*Theobroma cacao*)

Cocoa is derived from the beans of *Theobroma cacao* and is a rich source of monomeric polyphenolic antioxidants. It also possesses anti-inflammatory properties. The flavonoids present in Cocoa are supposed to decrease the production of inflammatory cytokines which are TNF-α, IL-6, IL-1β, ROS, and RNS in LPS-stimulated macrophages. Cocoa flavonoids reduce NF-κB activation and thus the expression of many genes involved in cytokine secretion. A study proved that when THP-1-derived macrophages were treated with polyphenolic cocoa extract, it significantly reduced the release of pro-inflammatory molecules like IL-1β, IL-12, IL-6, and TNF-α in macrophages stimulated by LPS. On the other hand, it also induced the expression of anti-inflammatory IL-10 similar to the M2 macrophage phenotype suggesting that cocoa extract can switch pro-inflammatory M1 macrophages to M2 anti-inflammatory macrophages [61]. It also prevents cardiovascular diseases and modulates blood pressure.

Epigallocatechin gallate (*Camellia sinensis*)

Epigallocatechin gallate, also known as epigallocatechin-3-gallate (EGCG) (ester of epigallocatechin and gallic acid) is a type of catechin which is present abundantly in green tea. It reduces inflammation, helps in weight loss, and prevents heart and brain diseases. It has been known that the presence of M2 macrophages in the lungs plays a positive role in mitigating lung-related problems. A study reported that EGCG significantly decreased the levels of M1 macrophage-associated markers like TNF-α, IL-1β, and IL-6 in LPS ejected mice. In accordance with this, EGCG treatment also enhances the level of M2 macrophage-associated markers like Arg-1, and ym1, with KLF4 a major macrophage polarisation regulator. Hence suggesting that EGCG can exert an anti-inflammatory effect by polarising macrophages toward the M2 phenotype in LPS induced inflammatory mice model [56,62].

Curcumin (*Curcuma longa*)

Curcumin (also known as diferuloylmethane) is the natural polyphenol found in the rhizome of *Curcuma longa.* It is a natural anti-inflammatory compound that plays an important role in polarising the macrophages towards the M2 phenotype. It is known that the overexpression of DNMT3b promotes M1 polarisation. A study reported that curcumin was able to suppress the expression of DNA Methyltransferase3b; DNMT3b and also increases the phosphorylation of signal transducer and activator of transcription STAT6 (activated by IL-4 and IL-10). Curcumin induces TAMs re-polarization from tumor-promoting M2 macrophages towards more anti-tumor M1 macrophages in tumor-bearing hosts, mediated by inhibition of STAT3. Curcumin also has the potential to enhance the secretion of M2 macrophage markers. It is shown to inhibit TNF-α and IL-1β and its anti-inflammatory activity in macrophages stimulated by LPS has also been reported. [63]. Another study reported that curcumin treatment was also able to increase the expression of CD206 and Arg-1 M2 macrophage markers and decreased the expression of IL-12, CD32 and CD16 pro-inflammatory M1 macrophage markers in microglia stimulated with LPS, suggesting a neuroprotective role of curcumin [56,64].

Andrographolide (*Andrographis paniculata*)

The herbaceous plant known as *Andrographis paniculata* is known in ayurvedic medicine as Kalmegha and is used traditionally in the treatment of various liver and skin-related ailments. The bioactive compound andrographolide present in the plant known is noted to possess anticancer and immunoregulatory effects [65]. A study aimed to identify the role of andrographolide in negatively regulating neurodegeneration elucidated that andrographolide treatment impels the macrophages to polarise towards the anti-inflammatory M2 phenotype [66]. Das, et al. reported that treatment with andrographolide in LPS stimulated primary glial culture the gene expression of *TLR4* was significantly decreased. In addition to this, andrographolide treatment also reduced the level of iNOS, NF-κB, IL-1β, and TNF-1 which are known as pro-inflammatory molecules. Whereas, the expression of TGF-β and IL-10 significantly increased. The study concluded that the active compound andrographolide can reverse neurodegeneration by acting as a potent anti-inflammatory drug. Andrographolide also exhibits an anti-

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inflammatory effect on activated macrophages and adjuvant-induced arthritis [67].

It is well known that our brain is the largest consumer of oxygen and any alteration in the level of oxygen significantly affects brain functioning. It has been reported in our recent study that the resident macrophages of the brain known as microglia polarise towards the M1 phenotype in animals exposed to hypobaric hypoxia which elicits an inflammatory response [68]. Our study reported decreased neuroinflammation associated with neurodegeneration in animals exposed to hypoxia. Along with this, andrographolide improved synaptic plasticity in cortical as well as hippocampal regions by polarising M1 microglia to the M2 microglial population which leads to decreased neuroinflammation and prevention of working memory impairment [68]. From this study, we inferred that andrographolide could be used as a possible pharmacological agent to overcome neuroinflammation and neurological disorders related to memory impairment.

Conclusion

It can be concluded that plants are a rich source of potent bioactive compounds which have the potential to polarize macrophages towards an M1 pro-inflammatory state or M2 anti-inflammatory phenotype which is required for tissue repairing and regeneration. The naturally occurring plant compounds have grabbed attention as potential therapeutic agents due to their low production costs and their ability to target cellular activities relevant to macrophage plasticity. These various naturally occurring compounds modulate the M1/M2 phenotypic switch by multiple pathways. These plant-derived compounds control macrophage polarisation by altering the expression of M1 and M2 macrophage-associated inflammatory markers. Naturally present bioactive compounds like chrysin, puerarin, and glycyrrhizic acid are shown to polarise the macrophages towards the M1 phenotype by releasing pro-inflammatory mediators like Il-1β, TNF-α, IL-6, and iNOS. These compounds can be used therapeutically as potent anti-cancer and anti-tumor agents where an active inflammatory response is required. On the other hand, macrophages can be polarised towards the M2 phenotype by treatment of bioactive compounds like arctigenin, malibatol A, salidroside, and andrographolide to exert neuroprotective and anti-inflammatory effects. The M2 macrophages are anti-inflammatory and known to resolve inflammation. Hence polarisation of macrophages towards the M2 phenotype can assist in controlling inflammation in neurodegenerative diseases like Alzheimer's and Parkinson's disease as well as in other inflammatory diseases like arthritis and inflammatory bowel disease. Hence elucidating the role of various bioactive compounds in reshaping the fate of macrophage polarisation can be a potential therapeutic strategy in combating various diseases. However, more research work is needed to evaluate the influence of these valuable natural compounds on the M1/M2 metabolic switch and thus preventing various diseases.

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