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Review

A Review on the Potential Therapeutic Application of Macrophage Polarization in Recurrent Spontaneous Abortion; With an Emphasis on Natural Components

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Three or more consecutive spontaneous pregnancy losses are the hallmark of recurrent spontaneous abortion (RSA) as a complex challenge in reproductive health, requiring a comprehensive understanding of contributing factors. Since balanced immune responses are essential for a successful pregnancy. Disruptions in immune responses may be the cause of unfavorable pregnancy outcomes like RSA. Of Note, Following RSA, immunopathological assessment of the placental implantation site markedly showed decidual inflammation, leading to hypothesize that RSA is a pregnancy disorder with an inflammatory etiology. Thus, an in-depth knowledge of how immune cells contribute to inflammation, may lead to the discovery of the novel therapeutic approaches for the prevention and/or treatment of RSA. Numerous studies have investigated the relationships between RSA and different immune cells, including B cells, T cells, decidual dendritic cells, and macrophages. Macrophages are present at the fetomaternal interface throughout pregnancy, and they are beneficial to the processes of embryonic development, placental formation, embryo implantation, and delivery. Macrophages classified as typically activated (M1, with the inflammatory role), or alternatively activated (M2, characterized by the anti-inflammatory role). Plants have a rich supply of strong bioactive components that can polarize macrophages toward an M1 pro-inflammatory state or an M2 anti-inflammatory phenotype. This review focuses on the potential role of derived plant-natural components in influencing macrophage polarization resulting in the management treatment of RSA.

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Introduction

Recurrent spontaneous abortion (RSA), is characterized by three or more consecutive spontaneous pregnancy losses (Li et al. 2021a). Appropriate immune responses are necessary for a successful pregnancy, therefore, adverse pregnancy outcomes like RSA may be caused by disruptions in immune responses. The relationship between RSA and impaired function of different immune cells, such as B cells, T cells, decidual dendritic cells, and macrophages has been discovered (Li et al. 2021a).

The development of an immunotolerant milieu at the maternal-fetal interface is facilitated by a multitude of intricate interactions and the balance between different immune cell types (Lee et al. 2012). RSA may cause by deregulated T cell subtype function and imbalanced immune responses (Wang et al. 2020), and this is typically linked to differences in T cell expression profile (Abdolmohammadi Vahid et al. 2019). Regulatory T cells (Tregs) have important functions in self-tolerance, allograft tolerance, and the

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establishment of immune tolerance at the maternal-fetal interface (Care et al. 2018; Mohammadi et al. 2021), and a decrease in the number of T cells may result in unfavorable pregnancy outcomes (Care et al. 2018). The mechanisms by which Tregs contribute to RSA primarily involve an imbalance in the Th17/Treg cell paradigm. So, the immune imbalance of Th17 and Tregs may play an essential role in RSA (Li et al. 2021b). Th17 cells secreting IL-17A known as the pro inflammatory cells that may have a part in the pathogenesis of RSA (Wang et al. 2010a). Treg cells in healthy controls inhibited IL-17 secretion through cell-to-cell contact, and this regulation was disturbed in the cases of unexplained RSA (Wang et al. 2010b).

As a subset of innate immune cells, macrophages may contribute to a crucial role in a successful pregnancy. These cells exhibit remarkable plasticity in reaction to diverse environmental conditions and control a range of reproductive processes, such as implantation, placentation, fetal development, parturition, and vascular remodeling at the maternal-fetal interface (Sheng et al. 2019; Motavaselian et al. 2022; Zhao et al. 2022; Shamabadi et al. 2024). The concept that RSA is a pregnancy disorder with an inflammatory etiology was proposed after immunopathological evaluation of the placental implantation site frequently revealed decidual inflammation following RSA. Notably, women with RSA have lower M2 polarization, whereas decidual macrophages polarize toward M1 (Sheng et al. 2019; Zhao et al. 2022).

There are two types of macrophages normally, activated (M1) and alternatively activated (M2) macrophages (Patel et al. 2017; Shapouri-Moghaddam et al. 2018; Yunna et al. 2020; Abdollahi et al. 2023). Enhanced antigen presentation, predominate pro-inflammatory reactions, and tissue damage are characteristics of M1 macrophages (Patel et al. 2017; Shapouri-Moghaddam et al. 2018; Yunna et al. 2020; Abdollahi et al. 2023). M2 cells, on the other hand, are involved in the control of the anti-inflammatory features and promote tissue remodeling and repair (Patel et al. 2017; Shapouri-Moghaddam et al. 2018; Yunna et al. 2020; Abdollahi et al. 2023). "Macrophage polarization" is the process by which macrophages acquire distinct functional phenotypes in response to certain signals and stimuli from their environment (Patel et al. 2017; Shapouri-Moghaddam et al. 2018; Yunna et al. 2020; Abdollahi et al. 2023). It was found that M1 macrophage released pro-inflammatory cytokines like TNF-α and IL-1 which leads to an excessively pro-inflammatory reactions at the fetomaternal interface and, consequently occurrence of RSA (Zhang et al. 2019). Therefore, therapeutic approaches that specifically focus on polarization to the M2 phenotype might be useful in RSA prevention or treatment (Zhao et al. 2022).

Natural components derived from plants have drawn interest as possible therapeutic agents because of their inexpensive cost of production, and capacity to target cellular processes associated with macrophage plasticity (Okoye et al. 2014; Khan and Ahmad 2019; van Wyk and Prinsloo 2020; Aware et al. 2022; Sultan et al. 2022; Saadi et al. 2023). These components have been demonstrated to impact M1/M2 macrophages through changing the expression of inflammatory markers, as well as cellular and molecular targets related to macrophage polarization (Okoye et al. 2014; Khan and Ahmad 2019; van Wyk and Prinsloo 2020; Aware et al. 2022; Khalafi-Nezhad et al. 2022, Iravani et al. 2023). This review explores the therapeutic potential role of natural components to affect M1 and M2 macrophages in prevention or treatment of RSA.

Macrophages Subsets

Macrophages categorized as alternately (M2) or normally (M1) active. There are four types of M2 macrophages: M2a, M2b, M2c, and M2d (Lee and Choi 2018). These macrophages differ in their biological roles, secretory cytokines, and cell surface markers (Atri et al. 2018; Lee and Choi 2018).

M1/M2 polarity arises from arginine metabolism by two pathways: M1-like macrophages are generated by the iNOS pathway, which generates citrulline and NO from arginine, whereas M2-like macrophages are generated by the arginase pathway, which produces ornithine and urea from arginine (Viola et al. 2019). Macrophages turned polarized toward M1 macrophages after their activation by lipopolysaccharide (LPS) and Th1 cytokines (such as IFN-γ, and TNF-α) (Orecchioni et al. 2019).

As mentioned, there are various subtypes of M2 macrophages, including as M2a, M2b, M2c, and M2d. It was shown that activating M2a macrophages with IL-13 or IL-4 enhanced the production of IL-10, TGF-β, CCL22, and CCL18. These macrophages may increase endocytic activity, promote cell proliferation, and tissue healing. Pro-inflammatory and anti-inflammatory cytokines such as IL-6, TNF-α, IL-1, and IL-10 could activate M2b macrophages. M2b macrophages regulate immunological and inflammatory responses through the expression of multiple cytokines and chemokines (Wang et al. 2019). M2c macrophages are additionally induced by glucocorticoids, TGF-β, and IL-10. TLR antagonists activate M2d macrophages. These cells release IL-10 and vascular endothelial growth factors (VEGF), which promote angiogenesis and tumor progression (Xu et al. 2006; Zizzo et al. 2012).

M1 and M2 macrophages: roles in a physiological pregnancy

During pregnancy, macrophages constitute generally 20-30% of all human decidual leukocytes. A study classified decidual as M1 or M2 based on the resemblance of responses of Th1/Th2 cells (Mills et al. 2000). In another study decidual macrophages determined as $CD11^{+high}$ or $CD11^{+low}$. $CD11^{+high}$ decidual macrophages are shown to involve in the metabolism of lipids and inflammatory reactions, $CD11^{+\ low}$ decidual macrophages, on the other hand, were found to contribute to matrix production, growth of tissues, and the muscle control (Houser et al. 2011).

Decidual macrophage polarization may change with

gestational age. Macrophage chemoattractant CCL2 (MCP-1) was induced by the a2V (a2 isoform of V-ATPase) and this contributed to attract M1-like macrophages during the pre-implantation phase (Jaiswal et al. 2012). Decidual macrophages shift into mixed M1/M2 profiles when trophoblasts adhere to the endometrial wall and infiltrate the uterine stroma. Decidual macrophages change to a phenotype that is primarily M2 after placental development is finished, protecting fetal growth until parturition and enhancing maternal immunological tolerance to semiallogenic infants (Svensson et al. 2011). The uterine vasculature must be extensively remodeled by these macrophages in order to provide enough placental-fetal blood (Mor et al. 2011; Jaiswal et al. 2012; Al-Obaidi et al. 2022; Al-Rashedi et al. 2022a). Decidual macrophages expressed M2 markers like CD163, CD206, and DC-sign (Kämmerer et al. 2003; Laskarin et al. 2005).

M1 macrophages could be crucial in the initiation of term labor. These cells expressed CD80, CD86, CD83, HLA-DR, and CD16 and produced more IL-12 and less IL-10 and TGF-β (Xu et al. 2016). It was found that elevated quantities of circulating cell-free fetal DNA stimulate mother macrophages' TLR9, activating the innate immune system and producing a variety of inflammatory cytokines that ultimately lead to parturition (Phillippe 2014).

Mechanisms of actions of macrophages during a physiological pregnancy

Macrophages are beneficial to the processes of embryonic development, placental formation, embryo implantation, and delivery. The female uterus establishes a milieu for embryo growth during every stage of pregnancy by phagocytosing apoptotic cells, modifying spiral arteries, increasing trophoblast cell invasion, and producing a variety of cytokines (Nagamatsu and Schust 2010; Care et al. 2013; Co et al. 2013; Erlebacher 2013; Al-Rashedi et al. 2022b,c; Majhol et al. 2022).

During a healthy pregnancy, spiral artery remodeling of the decidua, and angiogenesis are crucial for maintaining adequate flow of blood to placenta, and the placenta. According to a prior study (Hazan et al. 2010), macrophages play a role in the early phases of the remodeling process of the decidual spiral artery, thus promoting embryo implantation, trophoblast invasion, and vascular remodeling, in addition to removing apoptotic cells and cellular debris (Tang et al. 2013; Ning et al. 2016). According to reports, vascular endothelial growth factor (VEGF), decidual macrophages secrete placental growth factor (PlGF), and their receptors, fms-like tyrosine kinase (Flt-1) to control vascular remodeling (Clark et al. 1998). During the embryo implantation window, the expression of VEGF and iNOS in the endometrium of pregnant mice was significantly higher than that of pseudo pregnant mice (Tan et al. 2014). It was found that the percentage of macrophages in the endometrium was associated with iNOS and VEGF expression levels, showing that macrophages may have a role in vascular bed development prior to implantation by regulating iNOS and VEGF expression (Tan et al. 2014). The VEGF antagonist soluble fms-like tyrosine kinase-1 (sFlt-1) suppresses angiogenesis (Lockwood et al. 2011).

An *in vivo* study of C57BL/6 J mice demonstrated that the M2 macrophage phenotype had more angiogenic capacity than other macrophage subsets (Jetten et al. 2014). In a number of cells, activation of Protein Kinase C (PKC) is essential for enhanced VEGF production (Hoshi et al. 2002; Jetten et al. 2014; Hjazi 2023; Mayet et al. 2024). GF109203X (a general PKC inhibitor) significantly reduced LPS-induced sFlt-1 secretion while significantly enhancing LPS-induced VEGF secretion in the murine macrophage RAW264.7 cell line (Lee et al. 2008).

TGF-β1 production by decidual macrophages has been shown to prevent NK cell-mediated lysis of human cytotrophoblasts (CTB) (Co et al. 2013). IL-1, which is secreted by active macrophages, destroys the extracellular matrix. The enzymatic activity of matrix metalloproteinase (MMP-2 and MMP-29 in trophoblastic cells has been demonstrated to be favorably associated with the quantity of IL-1(Fontana et al. 2010; Sharma et al. 2016). ILT2 and ILT4 are inhibitory receptors for immunoglobulin-like transcription factors that can bind to HLA-G, that is abundantly expressed in extravillous trophoblast cells (EVT) (Petroff et al. 2002). In order to encourage trophoblast invasion and spiral artery remodeling and to preserve a balanced environment at the maternal-fetal interface, macrophages phagocytize apoptotic cells in pregnancy (Straszewski-Chavez et al. 2005; Jena et al. 2019).

Macrophages and pathological pregnancy

Macrophages were found to have a role in the pathological pregnancies including Gestational diabetes, preeclampsia, intrauterine growth restriction (IUGR), and spontaneous abortion (Huang et al. 2008; Ariza et al. 2009; Guenther et al. 2012; Sisino et al. 2013; Tang et al. 2013).

Hyperglycemia in gestational diabetes can shift decidual macrophages toward M1 activation (Sisino et al. 2013). Decidual macrophages isolated from diabetic women displayed characteristics that could be attributed to either M1 or M2b phenotype (decreased CD163, CD209, IL-10 with increased CD68, CCR7, and IL-1β) (Sisino et al. 2013). Decidual macrophages in rats in high-glucose conditions expressed increased levels of NOS2 gene expression and NO, clear markers of M1 activation *in vitro* (Sisino et al. 2013).

In pregnancy disorders such as preeclampsia, intrauterine fetal growth restriction, and spontaneous miscarriage, there was an increased frequency of decidual macrophages expressing elevated concentrations of GM-CSF, M-CSF, IL-8, and monocyte chemoattractant protein (Huang et al. 2006, 2010; Wu et al. 2012).

Additionally, it was discovered that spontaneous miscarriage and preeclampsia complications may resulted from abnormal activation of decidual macrophages (Haeger et al.

1992; Duclos et al. 1994; Rusmidi et al. 2023). The later onset of preeclampsia is linked to impaired uterine spiral artery EVT invasion, which results in inadequate vascular remodeling and lower uteroplacental blood flow to fetus (Li et al. 2016). These events are accompanied by a large number of decidual M1 macrophages, suggesting that preeclampsia is associated with excess M1 macrophage infiltration (Li et al. 2016). Folate receptor β is mainly expressed on M2 macrophages, and was found as a marker for M2 macrophages (Tang et al. 2013). It was found that decidual macrophages polarization could switch toward M1 macrophages by diminished expression of FR-β and CD163 in severe cases of preeclampsia (Tang et al. 2013).

M1 and M2 macrophages and recurrent spontaneous abortion

It was shown that excessively and a favored pro-inflammatory environment may lead to the M1/M2 imbalance, and consequently RSA occurrence (Zhang et al. 2019). A shifting from M2 to M1 was found in the decidua of patients with RSA (Zhang et al. 2019). It was found that PD-1 expression on decidual macrophages and the expression of PD-L1 on trophoblasts decreased in women with RSA (Zhao et al. 2022). Co-inhibitory molecule PD-1, a member of the CD28 superfamily, is expressed on activated monocytes, B cells, T cells, NK cells, macrophages, and dendritic cells. PD-1 ligand is PD-L1 (Lu et al. 2022). It was discovered that trophoblast invasion and macrophage polarization are related to the PD-1/PD-L1 axis. Macrophages polarized into the M1 phenotype as a result of PD-1 decrease (Wei et al. 2021). Through the ERK/MMP pathway, PD-L1 loss prevented trophoblast invasion (Chen et al. 2019). Tryptophan (Trp) is transferred to N-formyl kynurenine by the intracellular cytoplasmic enzyme indoleamine 2, 3-dioxygenase (IDO) (Wang et al. 2015). M2 phenotype was observed in IDO^+ decidual macrophages (Huang et al. 2021). IDO was found as a beneficial factor for early pregnancy. It was shown that IDO treatment decreased the rate of miscarriages in a mouse model of miscarriage by inhibiting the inflammatory response (Cheng et al. 2021). Interestingly, IDO expression markedly decreased on the decidual macrophages and in the decidua in RSA patients compared to the women with a normal pregnancy (Huang et al. 2021). However, an increase in the expression of IDO RSA patients villi also has been reported (Obayashi et al. 2016), suggesting that more investigation is needed to verify the role of IDO in RSA.

IL-33 produced by decidula macrophages increased M2 bias at the fetomaternal location, whereas RSA patients had a decrease in levels of this cytokine (Nishioku et al. 2002).

Enzymes that rearrange histones are known as histone deacetylases (HDACs). It was shown that in women with RSA, the level of HDAC8 expression on decidual macrophages reduced (Yao et al. 2020). Reduced HDAC8 caused a reduced expression of CD163 on decidual macrophages. Via the ERK signaling pathway, decreased HDAC8 stimulated macrophage apoptosis (Yao et al. 2020).

Human embryonic trophoblasts and maternal decidual stromal cells secrete receptor activator of nuclear factor NK-κB ligand (RANKL), which causes decidual macrophages to change toward the M2 phenotype. In a mouse model, impaired RANKL expression led to aberrant polarization of decidual macrophages and elevated the incidence of fetal loss (Meng et al. 2017).

Nuclear receptor PPARγ (peroxisome proliferator-activated receptor γ) is expressed on both trophoblasts and decidual macrophages. M2 polarization is related to this receptor activation. Patients with RSA had considerably lower levels of $PPAR\gamma^+$ decidual macrophages, and this could trigger an inflammatory response directed at the developing fetus (Kolben et al. 2018). Graphical abstract illustrates the function of macrophages in the pathophysiology of RSA.

Natural Components and Macrophages Polarization

The beneficial impact of active chemicals produced from plants in treating health-related illnesses has been widely recognized (Okoye et al. 2014; Khan and Ahmad 2019; van Wyk and Prinsloo 2020; Aware et al. 2022). Considering natural plant compounds may target cellular functions related to macrophage plasticity at a low cost of production, they have gained interest as the possible therapeutic agents (Gao et al. 2023). These diverse natural substances influence the M1/M2 phenotypic transition through of different mechanisms (Liu et al. 2023). Plant-derived substances modify the expression of M1 and M2 macrophage-associated inflammatory markers to regulate macrophage polarization (Sun et al. 2022).

Bioactive substances such as chrysin, puerarin, and glycyrrhizic acid, have been demonstrated to polarize macrophages toward the M1 phenotype through the release of pro-inflammatory mediators, such as TNF-α, IL-6, and iNOS (Deng et al. 2012; Davoodvandi et al. 2019; Grigore 2020; Fakhri et al. 2022). These substances may consider as probable anti-tumor and anti-cancer medicines when an active immune response is needed (Davoodvandi et al. 2019; Grigore 2020; Fakhri et al. 2022).

As mentioned, The M2 macrophages have been shown to be anti-inflammatory and capable of reducing inflammation. Therefore, the M2 phenotype-driven polarization of macrophages can help regulate inflammation in inflammatory diseases, including arthritis, inflammatory bowel disease and arthritis, neurological disorders like Parkinson's and Alzheimer's diseass. Bioactive substances such as arctigenin, malibatol A, salidroside, curcumin, Theobroma cacao, Camellia sinensis and rographolide can polarize macrophages toward the M2 phenotype to have anti-inflammatory effects in inflammatory conditions such as inflammatory bowel disease and arthritis (Hyam et al. 2013; Pan et al. 2015; Zhou et al. 2015; Das et al. 2017; Dugo et al. 2017; Liu et al. 2018; Saqib et al. 2018; Saha et al. 2020).

The number of plants and the active ingredients in

them that may be involved in M1/M2 macrophage polarization is displayed in Table 1.

The potential effects of natural components on macrophages polarization in RSA

The potency of plant derived components in treating RSA can be considered as the proposed role of various bioactive compounds in reshaping the fate of macrophage polarization. This may be a potential therapeutic strategy in treatment of a wide range of disease with involvement of macrophages in the related pathogenesis (Hyam et al. 2013; Pan et al. 2015; Zhou et al. 2015; Das et al. 2017; Dugo et al. 2017; Liu et al. 2018; Saqib et al. 2018; Saha et al. 2020). To assess the impact of the natural substances on the M1/M2 metabolic polarization and, consequently, the prevention or therapy of RSA, more research is necessary. The effectiveness of naturally produced components in switching toward M2 macrophage polarization will be discussed next, as the anti-inflammatory condition with contribution of M2 macrophages may favor in the management the treatment of RSA (Zhang et al. 2019).

Curcuma longa

The main active ingredient in turmeric, curcumin, is a polyphenol molecule that is derived from Curcuma longa rhizomes (Momtazi et al. 2016a,b). Curcumin has been shown to be useful in treating a number of degenerative disorders, as evidenced by increasing numbers of experimental and clinical investigations. Curcumin was found as a GRAS (generally recognized as safe) substance by the United States Food and Drug Administration (U.S. FDA) after it was proven to be well-tolerated by 12 *g*/day for three months of treatment in human patients (Strimpakos and Sharma 2008; Gupta et al. 2013; Xu et al. 2018). Strong evidence for the health advantages of curcumin, including its preventative and/or therapeutic effects on malignancies, diabetes, and systemic lupus erythematosus, comes from experimental research conducted on animal models of numerous human diseases (Gupta et al. 2012, 2013; Momtazi et al. 2016a, b; Hajavi et al. 2017; Abdollahi et al. 2018; Soflaei et al. 2018; Xu et al. 2018; Barati et al. 2019; Naeini et al. 2019; Zendehdel et al. 2019; Momtazi-Borojeni et al. 2019a, b, c, d).

Curcumin increased M2 macrophage polarization via up regulation of the expression of M2 markers, including macrophage mannose receptor (MMR), arginase-1 (Arg-1) and peroxisome proliferator-activated receptor-γ (PPAR-γ) in RAW264.7 macrophages (Gao et al. 2015). These effects

Table 1. Natural compounds and M1-M2 macrophage polarization.

Plant	Active compound	Macrophage polarization	Findings	References
Crinum latifolium	Aqueous	↑ M1 polarization	↑ Gene expression of IL-6, TNF-α, and IL-1β ↑ ROS generation	(Nguyen et al. 2013)
Glycyrrhiza uralensis	Glycyrrhizic Acid	↑ M1 polarization	↓ Expression of Ym1, Mannose receptor, and Arg-1 ↑ NO, CCR7, TNF-α, IL-6, and IL-12 ↑ CD80, CD86, and MHC-II.	(Mao et al. 2015)
Chrysin	A natural flavonoid	↑ M1 polarization	↑TLR4/NF-κB signaling pathway	(Feng et al. 2014)
Radix puerariae	Isoflavones (Puerarin)	↑ M1 polarisation	↓ Expression of CD163, Arg-1, IL-10, IL-1, CD206 and TGFβ ↑ Expression of IFN-γ , IL-12 iNOS, CD197, CD40, and TNF-α	(Kang et al. 2017)
Hopeahainanensis	Malibatol A	↑ M2 polarization	↓ Expression of CD32, CD16, and CD86. ↑ expression of CD206 and Ym-1	(Pan et al. 2015)
Arctium lappa	Arctigenin	↑ M2 polarization	↓ Expression of TNF-α, IL-1β, and IL-6, PI3K, AKT and NF-κB ↑Expression of IL-10, and CD204	(Hyam et al. 2013)
Petroseliumcrispum	Apigenin	↑ M2 polarization	↓ Expression of COX2 , iNOS TNF-α, IL-1β, and COX2	(Feng et al. 2016)
Rhodiola rosea	Salidroside	↑ M2 polarization	↑ Expression of CD206, Arg1, TGFβ, and YM1/2 ↓ Expression of NO and IL-6	(Liu et al. 2018)
Tamarindus indica	Lupeol	↑ M2 polarization	↑ Secretion of IL-10 and CD-206 ↓ Secretion of CD86,IL-1, TNF-α, and IL-12	(Saqib et al. 2018; Saha et al. 2020)
Curcuma longa	Curcumin	↑ M2 polarization	↑ Phosphorylation of STAT6 ↓ DNMT3b, TNF-α and IL-1β	(Zhou et al. 2015)
Theobroma cacao	Cocoa polyphenolic extract	↑ M2 polarization	↓ Expression of IL-12, IL-6, TNF-α, IL-1β ↑ Expression of IL-10	(Dugo et al. 2017)
Green tea	Epigallocatechin-3-gallate	↑ M2 polarization	↓ expression of TNF-α, IL-6, and IL-1β ↑ Expression of Arg-1, ym1, and KLF4	(Almatroodi et al. 2020)
Andrographis paniculata	Andrographolide	↑ M2 polarization	↓ Expression of COX2, TLR4, NFκB, iNOS, and IL-1β.	(Das et al. 2017)

were related to increases in IL-4 and IL-13 mRNA expression and protein secretion, as use of a STAT6 inhibitor and IL-4 and/or IL-13 neutralizing antibodies attenuated the induction of MMR, Arg-1 and PPAR-γ by curcumin (Gao et al. 2015). In another study, male Lewis rats were used to induce experimental autoimmune myocarditis (EAM) and then were orally administrated either curcumin or corn oil (control) for 3 weeks. Curcumin reduced myocardial inflammatory cell infiltration and mRNA expression of IL-1β and iNOS. The myocardial mRNA levels of MMR and Arg-1 were markedly increased by curcumin, while CD68+ MMR+ and CD68+ Arg-1+ double-positive macrophages were higher in curcumin-treated myocardial tissue. Myocardial CD68+ iNOS+ double-positive macrophages were clearly increased in the EAM group, but decreased markedly with curcumin treatment. Results showed that curcumin induces M2 polarization of macrophages by promoting the secretion of IL-4 and/or IL-13 (Yan et al. 2021).

Curcumin regulates several transcription factors, including signal transducer and activator of transcription (STAT), activator protein 1 (AP-1), nuclear factor (NF-κB), and others, to alter immunological responses. The master transcription factor NF-κB controls the release of pro-inflammatory cytokines from T cells, including interleukin (IL)-1, IL-2, and interferon-γ (IFNγ) of pro-inflammatory cytokines such as interleukin (IL)-1, IL-2, and IFNγ in T-cells (Park et al. 2007a). Several studies have shown that effective concentrations of curcumin range from 2.5 to 100 μM when evaluated in a RAW264.7 macrophage cell line (Siddiqui et al. 2006; Jeong et al. 2009; Ben et al. 2011). It has been suggested that curcumin is a potential inhibitor of DNA methyltransferase3b (DNMT3b) (Shu et al. 2011; Teiten et al. 2013). DNMT3b has a role in regulating macrophage polarization. Knockdown of DNMT3b has been shown to promote macrophage polarization to the M2 phenotype, while the overexpression of DNMT3b increases M1 macrophages (Yang et al. 2014). These results indicated that curcumin may induce M2 macrophage polarization by inhibiting DNA methylation. Therefore, curcumin may possibly function as a modulating agent capable of inducing the polarization of macrophages to an anti-inflammatory M2 phenotype, as well as reversibly converting the M2 to the M1 phenotype (Bosisio et al. 2002; Kiechl et al. 2002; Tu et al. 2012; Lee et al. 2013; Meng et al. 2013; Shiri et al. 2015; Zhou et al. 2015; Bai et al. 2016).

Briefly, by promoting an M2-dominant environment, curcumin holds promise in alleviating inflammation-related complications, including those associated with RSA (Ghaneifar et al. 2020; Abdollahi et al. 2023).

Hopea hainanensis

Hopea hainanensis grows in Asia. Malibatol A (MA) is the active extracted component of this plant is as MA, that has anti-oxidant activity (Saqib et al. 2018). MA has been shown in a study to have anti-inflammatory effects in ischemic injury resulting from stroke. The study also found that MA had neuroprotective benefits in a mouse model of cerebral ischemia by polarizing macrophages towards the M2 alternative phenotype (Pan et al. 2015). Within 72 hours of administering MA to local microglia in a mouse model of middle cerebral artery occlusion, they noticed a suppression of M1 macrophage hallmarks such as CD32 and CD16, whereas M2-related markers such as CD206 and Iba1 were enhanced (Pan et al. 2015). It is possible that MA, which affects M2 macrophage polarization, can also have the similar effect in RSA and be useful in RSA treatment.

Lignanarctigenin (Arctium lappa)

Arctium lappacommonly (burdock) is a flowering plant whose seeds and roots are known to possess anti-inflammatory effects (Park et al. 2007b). This active ingredient of this plant is lignin. The burdock plant's seeds contain arctigenin, which has the ability to inhibit the production of COX2, iNOS, NF-kB, and AKT phosphorylation in peritoneal macrophages activated by lipopolysaccharide (LPS) (Hyam et al. 2013). Furthermore, arctigenin treatment of LPS-stimulated peritoneal macrophages decreased the amount of pro-inflammatory cytokines such TNF-α and IL-1β. Similar outcomes have been observed in the TNBS-induced colitis model treated with arctigenin, indicating that M2 (CD204 and IL-10) and M1 macrophage markers are elevated, respectively (Hyam et al. 2013). These studies indicate that arctigenin polarizes macrophages toward the M2 phenotype, which may be useful in treating RSA, acting as an anti-inflammatory substance.

Apigenin (petroselinum crispum)

Apigenin is a flavonoid in a lot of vegetables and fruits which are shown to possess chemoprotective, antioxidant, and anti-inflammatory effects (Ali et al. 2016; Mushtaq et al. 2023). It was indicated that in lung epithelial cancer cells, apigenin may induce cell death via apoptosis. It may suppress the expression of TNF-α and IL-1 in human monocytes and LPS-stimulated murine macrophages (Feng et al. 2016). Through PPAR-α, a crucial regulator of macrophage polarization, apigenin promotes M2 polarization resulting in inhibiting obesity-related inflammation. Via the suppression of COX2 and iNOS production in LPS-stimulated murine macrophages, it also facilitates anti-inflammatory response (Feng et al. 2016). In obese mice, apigenin suppressed the expression of NF-κB, and COX-2 genes in the lung, which caused macrophages to shift to the M2 phenotype, resulting in anti-inflammatory activity in LPS-mediated acute lung injury (Feng et al. 2016). Considering these findings, arctigenin may act as an anti-inflammatory component and could polarized macrophages toward the M2 phenotype, which may be helpful in the treatment of RSA.

Green tea

Epigallocatechin-3-gallate (EGCG), a tea polyphenol,

is the catechin monomer with the highest concentration and potent bioactivity. Research has demonstrated that EGCG has an intervention impact on the development of chronic disease and reduced inflammation (Chu et al. 2019; Sahebkar et al. 2021). Research has been carried out regarding the intervention impact of EGCG on the distribution and polarization of macrophages in several organs. qRT-PCR was principally used to assess the transcriptional expression level of macrophage-related marker genes, such as M1 (COX2, iNOS, and TNF-α, and M2 marker genes (Arg-1, IL-10, Ym-1). EGCG had the intervention effect on both the promotion of M2 polarization and the suppressive polarization of M1 phenotype (Cui et al. 2021). According to recent research, EGCG may affect the phenotypes of macrophages, favoring an M2-dominant state and offering a natural solution of preventing RSA (Hachul et al. 2018a, b).

Quercetin

Quercetin is a member of the flavonoid plant pigment family, which is that causes the color of many fruits, flowers, and vegetables (Sanjay and Shukla 2021). Quercetin is one type of flavonoid that is an antioxidant. They scavenge free radicals, which are bodily particles that can harm cell membranes, alter DNA, or even trigger cell death (Sanjay and Shukla 2021). Quercetin has been shown to have anti-inflammatory properties and influenced macrophage polarization. Quercetin administration lowered the M1 inflammatory responses that cause macrophages and microglial cells to produce more NO, pro inflammatory cytokine expression, and lipocalin-2. Treatment with quercetin also reduced the chemokines CCL2 and CXCL10 (Cui et al. 2021).

Furthermore, quercetin prevents the synthesis of ROS, including H2O2, ROO, and HO. Quercetin therapy also decreased the pro-inflammatory stimuli-induced microglial phagocytic ability; yet, it also successfully raised the M2 marker IL-10 expression levels in macrophages and microglial cells. Of note, quercetin therapy increased the levels of several endogenous antioxidants, such as HO-1, GCLM, GCLC, and NQO1. For the treatment of neuroinflammation-associated disorders and other inflammatory-associated diseases, quercetin may be a useful therapeutic target due to its role in controlling inflammatory condition, which may assist sustain M1/M2 polarization and oxidation/antioxidation effects (Tsai et al. 2021). Therefore, quercetin may contribute to switch macrophage phenotype towards, suggesting an intriguing direction for future study in the field of RSA.

Challenges and Future Directions

Considering the potential benefits of using natural components to therapeutically influence macrophage polarization in the management of RSA therapy, obstacles still exist. It is necessary to do in-depth research on patient-specific reactions, ideal natural component dosages, and potential interventions with current medications. It is strongly recommended that any use of plant-derived components during pregnancy be done so with caution and after consulting a healthcare professional. For RSA, we also suggest taking plant-derived components perhaps a few months apart from consecutive pregnancies. Not while pregnant, as the fetus may be negatively impacted by the active plant components. We propose that consuming those ingredients before to becoming pregnant may mechanistically alter macrophage polarization, which may have a positive effect on the course of the pregnancy and possibly even avoid abortion. Future research should delve into the intricate crosstalk between diverse natural components and macrophage phenotypes, laying the foundation for personalized therapeutic approaches. Personalized medicine, also known as precision medicine, is a medical approach that uses an individual's genetic profile, environment, and lifestyle to manage disease prevention and treatment. The goal is to provide more precise, predictable, and powerful care for each patient by selecting the right treatment at the right time.

Recent advancements reveal additional dimensions in the therapeutic landscape of macrophage polarization for RSA. Integrating advanced technologies, including targeted drug delivery systems and gene editing techniques, opens new avenues for precision medicine in RSA management. The exploration of novel natural compounds and their synergistic effects expands our understanding, presenting exciting possibilities for future therapeutic interventions.

Conclusion

Following RSA, decidual inflammation was found in the placental implantation site immunopathologically, which led to the idea that RSA is an inflammatory pregnancy complication with an immune response-related pathogenesis. Throughout pregnancy, macrophages are present at the fetomaternal interface and contribute positively to the processes of placental formation, embryo implantation, embryonic development, and delivery. Plants are abundant in bioactive compounds that can polarize macrophages toward either an M2 anti-inflammatory phenotype or an M1 pro-inflammatory state.

According to this review, derived plant-natural components, including curcumin, rographolide, arctigenin, malibatol A, arctigenin, apigenin, Lupeol, epigallocatechin-3-gallate, and quercetin may be able to polarize macrophages toward M2 phenotype in a variety of diseases with similar inflammatory etiologies to RSA. These components can affect macrophage polarization toward M2 polarization via affecting of expression of multiple cellular markers, cytokines, inflammatory markers, and transcription factors as well as molecular pathways. There for by shifting polarization of macrophages toward M2 phenotype, natural components may potentially be effective in the management treatment of RSA. However, there are major obstacles because pregnancy is delicate and the health of

mother and fetus is vital. The optimal dose of natural component, and possible interactions with existing medications should be considered. It is highly recommended that any use of components derived from plants be done so cautiously and only after consultation with a medical provider during pregnancy. We also recommend that plant-derived components for RSA treatment be taken maybe a few months apart from consecutive pregnancies. Not while becoming pregnant, as the active ingredients in the plant could harm mother and fetus health. We propose that future studies should focus on assessing the impact of natural components on macrophage polarization and likely clinical outcomes in the treatment of RSA.

Conflict of Interest

The authors declare no conflict of interest.

References

Abdollahi, E., Johnston, T.P., Ghaneifar, Z., Vahedi, P., Goleij, P., Azhdari, S. & Moghaddam, A.S. (2023) Immunomodulatory Therapeutic Effects of Curcumin on M1/M2 Macrophage Polarization in Inflammatory Diseases. *Curr. Mol. Pharmacol.*, **16**, 2-14.

Abdollahi, E., Momtazi, A.A., Johnston, T.P. & Sahebkar, A. (2018) Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: A nature-made jack-of-all-trades? *J. Cell Physiol.*, **233**, 830-848.

Abdolmohammadi Vahid, S., Ghaebi, M., Ahmadi, M., Nouri, M., Danaei, S., Aghebati-Maleki, L., Mousavi Ardehaie, R., Yousefi, B., Hakimi, P., Hojjat-Farsangi, M., Rikhtegar, R. & Yousefi, M. (2019) Altered T-cell subpopulations in recurrent pregnancy loss patients with cellular immune abnormalities. *J. Cell Physiol.*, **234**, 4924-4933.

Al-Obaidi, Z.M.J., Hussein, Y.A., Al-Duhaidahawi, D. & Al-Aubaidy, H.A. (2022) Molecular docking studies and biological evaluation of luteolin on cerebral ischemic reperfusion injury. *Egypt. J. Chem.,* **65**, 433-440.

Al-Rashedi, N.A.M., Alburkat, H., Hadi, A.O., Munahi, M.G., Jasim, A., Hameed, A., Oda, B.S., Lilo, K.M., AlObaidi, L.A.H., Vapalahti, O., Sironen, T. & Smura, T. (2022a) High prevalence of an alpha variant lineage with a premature stop codon in ORF7a in Iraq, winter 2020-2021. *PLoS One*, **17**, e0267295.

Al-Rashedi, N.A.M., Alburkat, H., Munahi, M.G., Jasim, A.H., Salman, B.K., Oda, B.S., Mossa, A.A., Abbas, A.A., Vapalahti, O., Sironen, T. & Smura, T. (2022b) Genome Sequence of an Early Imported Case of SARS-CoV-2 Delta Variant (B.1.617.2 AY.122) in Iraq in April 2021. *Microbiol. Resour. Announc.*, **11**, e0097722.

Al-Rashedi, N.A.M., Munahi, M.G. & Ah, A.L. (2022c) Prediction of potential inhibitors against SARS-CoV-2 endoribonuclease: RNA immunity sensing. *J. Biomol. Struct. Dyn.*, **40**, 4879-4892.

Ali, F., Rahul, Naz, F., Jyoti, S. & Siddique, Y.H. (2016) Health functionality of apigenin: A review. *Int. J. Food Prop.*, **20**, 1197-1238.

Almatroodi, S.A., Almatroudi, A., Alsahli, M.A., Aljasir, M.A., Syed, M.A. & Rahmani, A.H. (2020) Epigallocatechin-3-Gallate (EGCG), an Active Compound of Green Tea Attenuates Acute Lung Injury Regulating Macrophage Polarization and Krupple-Like-Factor 4 (KLF4) Expression. *Molecules*, **25**, 2853.

Ariza, A.C., Bobadilla, N., Diaz, L., Avila, E., Larrea, F. & Halhali, A. (2009) Placental gene expression of calcitonin gene-related peptide and nitric oxide synthases in preeclampsia: effects of magnesium sulfate. *Magnes. Res.*, **22**, 44-49.

Atri, C., Guerfali, F.Z. & Laouini, D. (2018) Role of Human Macrophage Polarization in Inflammation during Infectious Diseases. *Int. J. Mol. Sci.*, **19**, 1801.

Aware, C.B., Patil, D.N., Suryawanshi, S.S., Mali, P.R., Rane, M.R., Gurav, R.G. & Jadhav, J.P. (2022) Natural bioactive products as promising therapeutics: A review of natural product-based drug development. *S. African J. Botany*, **151**, 512-528.

Bai, X., Oberley-Deegan, R.E., Bai, A., Ovrutsky, A.R., Kinney, W.H., Weaver, M., Zhang, G., Honda, J.R. & Chan, E.D. (2016) Curcumin enhances human macrophage control of Mycobacterium tuberculosis infection. *Respirology*, **21**, 951-957.

Barati, N., Momtazi-Borojeni, A.A., Majeed, M. & Sahebkar, A. (2019) Potential therapeutic effects of curcumin in gastric cancer. *J. Cell Physiol.*, **234**, 2317-2328.

Ben, P., Liu, J., Lu, C., Xu, Y., Xin, Y., Fu, J., Huang, H., Zhang, Z., Gao, Y., Luo, L. & Yin, Z. (2011) Curcumin promotes degradation of inducible nitric oxide synthase and suppresses its enzyme activity in RAW 264.7 cells. *Int. Immunopharmacol.*, **11**, 179-186.

Bosisio, D., Polentarutti, N., Sironi, M., Bernasconi, S., Miyake, K., Webb, G.R., Martin, M.U., Mantovani, A. & Muzio, M. (2002) Stimulation of toll-like receptor 4 expression in human mononuclear phagocytes by interferon-gamma: a molecular basis for priming and synergism with bacterial lipopolysaccharide. *Blood*, **99**, 3427-3431.

Care, A.S., Bourque, S.L., Morton, J.S., Hjartarson, E.P., Robertson, S.A. & Davidge, S.T. (2018) Reduction in Regulatory T Cells in Early Pregnancy Causes Uterine Artery Dysfunction in Mice. *Hypertension*, **72**, 177-187.

Care, A.S., Diener, K.R., Jasper, M.J., Brown, H.M., Ingman, W.V. & Robertson, S.A. (2013) Macrophages regulate corpus luteum development during embryo implantation in mice. *J. Clin. Invest.*, **123**, 3472-3487.

Chen, M., Gilbert, N. & Liu, H. (2019) Reduced expression of PD-L1 in autoimmune thyroiditis attenuate trophoblast invasion through ERK/MMP pathway. *Reprod. Biol. Endocrinol.*, **17**, 86.

Cheng, H., Huang, Y., Huang, G., Chen, Z., Tang, J., Pan, L., Lv, J., Long, A., Wang, R., Chen, Z. & Zhao, S. (2021) Effect of the IDO Gene on Pregnancy in Mice with Recurrent Pregnancy Loss. *Reprod. Sci.*, **28**, 52-59.

Chu, C., Wang, Y., Wang, Y., Yang, R., Liu, L., Rung, S., Xiang, L., Wu, Y., Du, S., Man, Y. & Qu, Y. (2019) Evaluation of epigallocatechin-3-gallate (EGCG) modified collagen in guided bone regeneration (GBR) surgery and modulation of macrophage phenotype. *Mater. Sci. Eng. C. Mater. Biol. Appl.*, **99**, 73-82.

Clark, D.E., Smith, S.K., Licence, D., Evans, A.L. & Charnock-Jones, D.S. (1998) Comparison of expression patterns for placenta growth factor, vascular endothelial growth factor (VEGF), VEGF-B and VEGF-C in the human placenta throughout gestation. *J. Endocrinol.*, **159**, 459-467.

Co, E.C., Gormley, M., Kapidzic, M., Rosen, D.B., Scott, M.A., Stolp, H.A., McMaster, M., Lanier, L.L., Barcena, A. & Fisher, S.J. (2013) Maternal decidual macrophages inhibit NK cell killing of invasive cytotrophoblasts during human pregnancy. *Biol. Reprod.*, **88**, 155.

Cui, Z.Y., Han, X., Jiang, Y.C., Dou, J.Y., Yao, K.C., Hu, Z.H., Yuan, M.H., Bao, X.X., Zhou, M.J., Liu, Y., Lian, L.H., Zhang, X., Nan, J.X. & Wu, Y.L. (2021) Allium victorialis L. Extracts Promote Activity of FXR to Ameliorate Alcoholic Liver Disease: Targeting Liver Lipid Deposition and Inflammation. *Front. Pharmacol.*, **12**, 738689.

Das, S., Mishra, K.P., Ganju, L. & Singh, S.B. (2017) Andrographolide - A promising therapeutic agent, negatively regulates glial cell derived neurodegeneration of prefrontal cortex,

hippocampus and working memory impairment. *J. Neuroimmunol.*, **313**, 161-175.

Davoodvandi, A., Sahebnasagh, R., Mardanshah, O., Asemi, Z., Nejati, M., Shahrzad, M.K., Mirzaei, H.R. & Mirzaei, H. (2019) Medicinal Plants As Natural Polarizers of Macrophages: Phytochemicals and Pharmacological Effects. *Curr. Pharm. Des.*, **25**, 3225-3238.

Deng, S., Hu, B., Shen, K.P. & Xu, L. (2012) Inflammation, macrophage in cancer progression and chinese herbal treatment. *J. Basic Clin. Pharm.*, **3**, 269-272.

Duclos, A.J., Pomerantz, D.K. & Baines, M.G. (1994) Relationship between decidual leukocyte infiltration and spontaneous abortion in a murine model of early fetal resorption. *Cell Immunol.*, **159**, 184-193.

Dugo, L., Belluomo, M.G., Fanali, C., Russo, M., Cacciola, F., Maccarrone, M. & Sardanelli, A.M. (2017) Effect of Cocoa Polyphenolic Extract on Macrophage Polarization from Proinflammatory M1 to Anti-Inflammatory M2 State. *Oxid. Med. Cell Longev.*, **2017**, 6293740.

Erlebacher, A. (2013) Immunology of the maternal-fetal interface. *Annu. Rev. Immunol.*, **31**, 387-411.

Fakhri, S., Moradi, S.Z., Yarmohammadi, A., Narimani, F., Wallace, C.E. & Bishayee, A. (2022) Modulation of TLR/NF-kappaB/NLRP Signaling by Bioactive Phytocompounds: A Promising Strategy to Augment Cancer Chemotherapy and Immunotherapy. *Front. Oncol.*, **12**, 834072.

Feng, X., Qin, H., Shi, Q., Zhang, Y., Zhou, F., Wu, H., Ding, S., Niu, Z., Lu, Y. & Shen, P. (2014) Chrysin attenuates inflammation by regulating M1/M2 status via activating PPARgamma. *Biochem. Pharmacol.*, **89**, 503-514.

Feng, X., Weng, D., Zhou, F., Owen, Y.D., Qin, H., Zhao, J., WenYu, Huang, Y., Chen, J., Fu, H., Yang, N., Chen, D., Li, J., Tan, R. & Shen, P. (2016) Activation of PPARgamma by a Natural Flavonoid Modulator, Apigenin Ameliorates Obesity-Related Inflammation Via Regulation of Macrophage Polarization. *EBioMedicine*, **9**, 61-76.

Fontana, V.A., Sanchez, M., Cebral, E. & Calvo, J.C. (2010) Interleukin-1 beta regulates metalloproteinase activity and leptin secretion in a cytotrophoblast model. *Biocell*, **34**, 37-43.

Gao, S., Zhou, J., Liu, N., Wang, L., Gao, Q., Wu, Y., Zhao, Q., Liu, P., Wang, S., Liu, Y., Guo, N., Shen, Y., Wu, Y. & Yuan, Z. (2015) Curcumin induces M2 macrophage polarization by secretion IL-4 and/or IL-13. *J. Mol. Cell Cardiol.*, **85**, 131-139.

Gao, Y., Xu, X. & Zhang, X. (2023) Targeting different phenotypes of macrophages: A potential strategy for natural products to treat inflammatory bone and joint diseases. *Phytomedicine*, **118**, 154952.

Ghaneifar, Z., Yousefi, Z., Tajik, F., Nikfar, B., Ghalibafan, F., Abdollahi, E. & Momtazi-Borojeni, A.A. (2020) The potential therapeutic effects of curcumin on pregnancy complications: Novel insights into reproductive medicine. *IUBMB Life*, **72**, 2572-2583.

Grigore, A. (2020) Targeting Tumor-Associated Macrophages by Plant Compounds. In *Macrophages*, edited by Prakash, H. IntechOpen London, UK.

Guenther, S., Vrekoussis, T., Heublein, S., Bayer, B., Anz, D., Knabl, J., Navrozoglou, I., Dian, D., Friese, K., Makrigiannakis, A. & Jeschke, U. (2012) Decidual macrophages are significantly increased in spontaneous miscarriages and overexpress FasL: a potential role for macrophages in trophoblast apoptosis. *Int. J. Mol. Sci.*, **13**, 9069-9080.

Gupta, S.C., Patchva, S. & Aggarwal, B.B. (2013) Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J.*, **15**, 195-218.

Gupta, S.C., Patchva, S., Koh, W. & Aggarwal, B.B. (2012) Discovery of curcumin, a component of golden spice, and its miraculous biological activities. *Clin. Exp. Pharmacol. Physiol.*, **39**, 283-299.

Hachul, A.C.L., Boldarine, V.T., Neto, N.I.P., Moreno, M.F., Carvalho, P.O., Sawaya, A., Ribeiro, E.B., Oller do Nascimento, C.M. & Oyama, L.M. (2018a) Effect of the consumption of green tea extract during pregnancy and lactation on metabolism of mothers and 28d-old offspring. *Sci. Rep.*, **8**, 1869.

Hachul, A.C.L., Boldarine, V.T., Neto, N.I.P., Moreno, M.F., Ribeiro, E.B., do Nascimento, C.M.O. & Oyama, L.M. (2018b) Maternal consumption of green tea extract during pregnancy and lactation alters offspring's metabolism in rats. *PLoS One*, **13**, e0199969.

Haeger, M., Unander, M., Norder-Hansson, B., Tylman, M. & Bengtsson, A. (1992) Complement, neutrophil, and macrophage activation in women with severe preeclampsia and the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Obstet. Gynecol.*, **79**, 19-26.

Hajavi, J., Momtazi, A.A., Johnston, T.P., Banach, M., Majeed, M. & Sahebkar, A. (2017) Curcumin: A Naturally Occurring Modulator of Adipokines in Diabetes. *J. Cell Biochem.*, **118**, 4170-4182.

Hazan, A.D., Smith, S.D., Jones, R.L., Whittle, W., Lye, S.J. & Dunk, C.E. (2010) Vascular-leukocyte interactions: mechanisms of human decidual spiral artery remodeling in vitro. *Am. J. Pathol.*, **177**, 1017-1030.

Hjazi, A. (2023) The effects of Capsicum annuum supplementation on lipid profiles in adults with metabolic syndrome and related disorders: A systematic review and meta-analysis of randomized controlled trials. *Phytother. Res.*, **37**, 3859-3866.

Hoshi, S., Nomoto, K., Kuromitsu, J., Tomari, S. & Nagata, M. (2002) High glucose induced VEGF expression via PKC and ERK in glomerular podocytes. *Biochem. Biophys. Res. Commun.*, **290**, 177-184.

Houser, B.L., Tilburgs, T., Hill, J., Nicotra, M.L. & Strominger, J.L. (2011) Two unique human decidual macrophage populations. *J. Immunol.*, **186**, 2633-2642.

Huang, H.L., Yang, H.L., Lai, Z.Z., Yang, S.L., Li, M.Q. & Li, D.J. (2021) Decidual IDO(+) macrophage promotes the proliferation and restricts the apoptosis of trophoblasts. *J. Reprod. Immunol.*, **148**, 103364.

Huang, S.J., Chen, C.P., Schatz, F., Rahman, M., Abrahams, V.M. & Lockwood, C.J. (2008) Pre-eclampsia is associated with dendritic cell recruitment into the uterine decidua. *J. Pathol.*, **214**, 328-336.

Huang, S.J., Schatz, F., Masch, R., Rahman, M., Buchwalder, L., Niven-Fairchild, T., Tang, C., Abrahams, V.M., Krikun, G. & Lockwood, C.J. (2006) Regulation of chemokine production in response to pro-inflammatory cytokines in first trimester decidual cells. *J. Reprod. Immunol.*, **72**, 60-73.

Huang, S.J., Zenclussen, A.C., Chen, C.P., Basar, M., Yang, H., Arcuri, F., Li, M., Kocamaz, E., Buchwalder, L., Rahman, M., Kayisli, U., Schatz, F., Toti, P. & Lockwood, C.J. (2010) The implication of aberrant GM-CSF expression in decidual cells in the pathogenesis of preeclampsia. *Am. J. Pathol.*, **177**, 2472-2482.

Hyam, S.R., Lee, I.A., Gu, W., Kim, K.A., Jeong, J.J., Jang, S.E., Han, M.J. & Kim, D.H. (2013) Arctigenin ameliorates inflammation in vitro and in vivo by inhibiting the PI3K/AKT pathway and polarizing M1 macrophages to M2-like macrophages. *Eur. J. Pharmacol.*, **708**, 21-29.

Iravani Saadi, M., Jiang, M., Banakar, M., Mardani Valandani, F., Ahmadyan, M., Rostamipour, H.A., Kheradmand, N., Noshadi, N., Karimi, Z., Nabi Abdolyousefi, E., Ramzi, M., Haghighinejad, H., Yaghobi, R. & Hosseini, F. (2023) Are the Costimulatory Molecule Gene Polymorphisms (CTLA-4) Associated With Infection in Organ Transplantation? A Meta-Analysis. *Cell Transplant*, **32**, 9636897231151576.

Jaiswal, M.K., Mallers, T.M., Larsen, B., Kwak-Kim, J., Chaouat, G., Gilman-Sachs, A. & Beaman, K.D. (2012) V-ATPase upregulation during early pregnancy: a possible link to establishment of an inflammatory response during preimplantation

period of pregnancy. *Reproduction*, **143**, 713-725.
Jena, M.K., Nayak, N., Chen, K. & Nayak, N.R. (2019) Role of Macrophages in Pregnancy and Related Complications. *Arch. Immunol. Ther. Exp.* (*Warsz*), **67**, 295-309.
Jeong, S.O., Oh, G.S., Ha, H.Y., Soon Koo, B., Sung Kim, H., Kim, Y.C., Kim, E.C., Lee, K.M., Chung, H.T. & Pae, H.O. (2009) Dimethoxycurcumin, a Synthetic Curcumin Analogue, Induces Heme Oxygenase-1 Expression through Nrf2 Activation in RAW264.7 Macrophages. *J. Clin. Biochem. Nutr.*, **44**, 79-84.
Jetten, N., Verbruggen, S., Gijbels, M.J., Post, M.J., De Winther, M.P. & Donners, M.M. (2014) Anti-inflammatory M2, but not pro-inflammatory M1 macrophages promote angiogenesis in vivo. *Angiogenesis*, **17**, 109-118.
Kammerer, U., Eggert, A.O., Kapp, M., McLellan, A.D., Geijtenbeek, T.B., Dietl, J., van Kooyk, Y. & Kampgen, E. (2003) Unique appearance of proliferating antigen-presenting cells expressing DC-SIGN (CD209) in the decidua of early human pregnancy. *Am. J. Pathol.*, **162**, 887-896.
Kang, H., Zhang, J., Wang, B., Liu, M., Zhao, J., Yang, M. & Li, Y. (2017) Puerarin inhibits M2 polarization and metastasis of tumor-associated macrophages from NSCLC xenograft model via inactivating MEK/ERK 1/2 pathway. *Int. J. Oncol.*, **50**, 545-554.
Khalafi-Nezhad, A., Iravani Saadi, M., Noshadi, N., Jalali, H., Ahmadyan, M., Kheradmand, N., Moradi, M., Valandani, F.M., Rostamipour, H.A., Hosseini, F. & Hamidieh, A.A. (2022) Change in Programmed Death-1 And Inducible Costimulator Expression in Patients with Acute Myeloid Leukemia Following Chemotherapy and Its Cytogenetic Abnormalities. *GMJ*, **11**, e2394.
Khan, M.S.A. & Ahmad, I. (2019) Herbal Medicine: Current Trends and Future Prospects. In *New Look to Phytomedicine*, edited by Khan, M.S.A., Ahmad, I. & Chattopadhyay, D. Elsevier, pp. 3-13.
Kiechl, S., Lorenz, E., Reindl, M., Wiedermann, C.J., Oberhollenzer, F., Bonora, E., Willeit, J. & Schwartz, D.A. (2002) Toll-like receptor 4 polymorphisms and atherogenesis. *N. Engl. J. Med.*, **347**, 185-192.
Kolben, T.M., Rogatsch, E., Vattai, A., Hester, A., Kuhn, C., Schmoeckel, E., Mahner, S., Jeschke, U. & Kolben, T. (2018) PPARgamma Expression Is Diminished in Macrophages of Recurrent Miscarriage Placentas. *Int. J. Mol. Sci.*, **19**, 1872.
Laskarin, G., Cupurdija, K., Tokmadzic, V.S., Dorcic, D., Dupor, J., Juretic, K., Strbo, N., Crncic, T.B., Marchezi, F., Allavena, P., Mantovani, A., Randic, L. & Rukavina, D. (2005) The presence of functional mannose receptor on macrophages at the maternal-fetal interface. *Hum. Reprod.*, **20**, 1057-1066.
Lee, C.-H. & Choi, E.Y. (2018) Macrophages and inflammation. *J. Rheum. Dis.,* **25**, 11-18.
Lee, H., Kim, H., Lee, G., Chung, H.S. & Bae, H. (2013) Curcumin attenuates lupus nephritis upon interaction with regulatory T cells in New Zealand Black/White mice. *Br. J. Nutr.*, **110**, 69-76.
Lee, M.C., Wei, S.C., Tsai-Wu, J.J., Wu, C.H. & Tsao, P.N. (2008) Novel PKC signaling is required for LPS-induced soluble Flt-1 expression in macrophages. *J. Leukoc. Biol.*, **84**, 835-841.
Lee, S.K., Kim, J.Y., Lee, M., Gilman-Sachs, A. & Kwak-Kim, J. (2012) Th17 and regulatory T cells in women with recurrent pregnancy loss. *Am. J. Reprod. Immunol.*, **67**, 311-318.
Li, D., Zheng, L., Zhao, D., Xu, Y. & Wang, Y. (2021a) The Role of Immune Cells in Recurrent Spontaneous Abortion. *Reprod. Sci.*, **28**, 3303-3315.
Li, M., Piao, L., Chen, C.P., Wu, X., Yeh, C.C., Masch, R., Chang, C.C. & Huang, S.J. (2016) Modulation of Decidual Macrophage Polarization by Macrophage Colony-Stimulating Factor Derived from First-Trimester Decidual Cells: Implication in Preeclampsia. *Am. J. Pathol.*, **186**, 1258-1266.
Li, N., Saghafi, N., Ghaneifar, Z., Rezaee, S.A., Rafatpanah, H. & Abdollahi, E. (2021b) Evaluation of the Effects of 1,25VitD3 on Inflammatory Responses and IL-25 Expression. *Front. Genet.*, **12**, 779494.
Liu, X., Wen, S., Yan, F., Liu, K., Liu, L., Wang, L., Zhao, S. & Ji, X. (2018) Salidroside provides neuroprotection by modulating microglial polarization after cerebral ischemia. *J. Neuroinflammation*, **15**, 39.
Liu, Y.D., Chen, H.R., Zhang, Y., Yan, G., Yan, H.J., Zhu, Q. & Peng, L.H. (2023) Progress and challenges of plant-derived nucleic acids as therapeutics in macrophage-mediated RNA therapy. *Front. Immunol.*, **14**, 1255668.
Lockwood, C.J., Huang, S.J., Krikun, G., Caze, R., Rahman, M., Buchwalder, L.F. & Schatz, F. (2011) Decidual hemostasis, inflammation, and angiogenesis in pre-eclampsia. *Semin. Thromb. Hemost.*, **37**, 158-164.
Lu, J., Wu, J., Mao, L., Xu, H. & Wang, S. (2022) Revisiting PD-1/PD-L pathway in T and B cell response: Beyond immunosuppression. *Cytokine Growth Factor Rev.*, **67**, 58-65.
Majhol, R.H., Al-Rashedi, N.A.M. & Al-Oebady, M.A.H. (2022) Bacterial activity on hyphal formation of Candida albicans. *J. Pharm. Neg. Results*, **13**, 552-555.
Mao, Y., Wang, B., Xu, X., Du, W., Li, W. & Wang, Y. (2015) Glycyrrhizic Acid Promotes M1 Macrophage Polarization in Murine Bone Marrow-Derived Macrophages Associated with the Activation of JNK and NF-kappaB. *Mediators Inflamm.*, **2015**, 372931.
Mayet, A.M., Ebrahimi, S., Abdullaev, S.S., Alsaab, H.O., Mansouri, S., Malviya, J., Alawadi, A.H., Alsaalamy, A., Abid, M.K. & Thakur, G. (2024) Molecularly imprinted polymers for biosensing of hormones in food safety and biomedical analysis: Progress and perspectives. *Mat. Today Chem.*, **35**, 101899.
Meng, Y.H., Zhou, W.J., Jin, L.P., Liu, L.B., Chang, K.K., Mei, J., Li, H., Wang, J., Li, D.J. & Li, M.Q. (2017) RANKL-mediated harmonious dialogue between fetus and mother guarantees smooth gestation by inducing decidual M2 macrophage polarization. *Cell Death Dis.*, **8**, e3105.
Meng, Z., Yan, C., Deng, Q., Gao, D.F. & Niu, X.L. (2013) Curcumin inhibits LPS-induced inflammation in rat vascular smooth muscle cells in vitro via ROS-relative TLR4-MAPK/NF-kappaB pathways. *Acta Pharmacol. Sin.*, **34**, 901-911.
Mills, C.D., Kincaid, K., Alt, J.M., Heilman, M.J. & Hill, A.M. (2000) M-1/M-2 macrophages and the Th1/Th2 paradigm. *J. Immunol.*, **164**, 6166-6173.
Mohammadi, S., Abdollahi, E., Nezamnia, M., Esmaeili, S.A., Tavasolian, F., Sathyapalan, T. & Sahebkar, A. (2021) Adoptive transfer of Tregs: A novel strategy for cell-based immunotherapy in spontaneous abortion: Lessons from experimental models. *Int. Immunopharmacol.*, **90**, 107195.
Momtazi, A.A., Derosa, G., Maffioli, P., Banach, M. & Sahebkar, A. (2016a) Role of microRNAs in the Therapeutic Effects of Curcumin in Non-Cancer Diseases. *Mol. Diagn. Ther.*, **20**, 335-345.
Momtazi, A.A., Shahabipour, F., Khatibi, S., Johnston, T.P., Pirro, M. & Sahebkar, A. (2016b) Curcumin as a MicroRNA Regulator in Cancer: A Review. *Rev. Physiol. Biochem. Pharmacol.*, **171**, 1-38.
Momtazi-Borojeni, A.A., Abdollahi, E., Nikfar, B., Chaichian, S. & Ekhlasi-Hundrieser, M. (2019a) Curcumin as a potential modulator of M1 and M2 macrophages: new insights in atherosclerosis therapy. *Heart Fail. Rev.*, **24**, 399-409.
Momtazi-Borojeni, A.A., Katsiki, N., Pirro, M., Banach, M., Rasadi, K.A. & Sahebkar, A. (2019b) Dietary natural products as emerging lipoprotein(a)-lowering agents. *J. Cell Physiol.*, **234**, 12581-12594.
Momtazi-Borojeni, A.A., Mosafer, J., Nikfar, B., Ekhlasi-Hundrieser, M., Chaichian, S., Mehdizadehkashi, A. & Vaezi, A. (2019c) Correction to: Curcumin in Advancing Treatment for

Gynecological Cancers with Developed Drug- and Radiotherapy-Associated Resistance. *Rev. Physiol. Biochem. Pharmacol.*, **176**, 131.

Momtazi-Borojeni, A.A., Mosafer, J., Nikfar, B., Ekhlasi-Hundrieser, M., Chaichian, S., Mehdizadehkashi, A. & Vaezi, A. (2019d) Curcumin in Advancing Treatment for Gynecological Cancers with Developed Drug- and Radiotherapy-Associated Resistance. *Rev. Physiol. Biochem. Pharmacol.*, **176**, 107-129.

Mor, G., Cardenas, I., Abrahams, V. & Guller, S. (2011) Inflammation and pregnancy: the role of the immune system at the implantation site. *Ann. N. Y. Acad. Sci.*, **1221**, 80-87.

Motavaselian, M., Bayati, F., Amani-Beni, R., Khalaji, A., Haghverdi, S., Abdollahi, Z., Sarrafzadeh, A., Rafie Manzelat, A.M., Rigi, A., Arabzadeh Bahri, R., Nakhaee, Z., Fadaei, M., Ghasemi Falaverjani, H., Malekpour-Dehkordi, S., Hoseinpour, M., et al. (2022) Diagnostic Performance of Magnetic Resonance Imaging for Detection of Acute Appendicitis in Pregnant Women; a Systematic Review and Meta-Analysis. *Arch. Acad. Emerg. Med.*, **10**, e81.

Mushtaq, Z., Sadeer, N.B., Hussain, M., Mahwish, Alsagaby, S.A., Imran, M., Mumtaz, T., Umar, M., Tauseef, A., Al Abdulmonem, W., Tufail, T., Al Jbawi, E. & Mahomoodally, M.F. (2023) Therapeutical properties of apigenin: a review on the experimental evidence and basic mechanisms. *Int. J. Food Prop.,* **26**, 1914-1939.

Naeini, M.B., Momtazi, A.A., Jaafari, M.R., Johnston, T.P., Barreto, G., Banach, M. & Sahebkar, A. (2019) Antitumor effects of curcumin: A lipid perspective. *J. Cell Physiol.*, **234**, 14743-14758.

Nagamatsu, T. & Schust, D.J. (2010) The immunomodulatory roles of macrophages at the maternal-fetal interface. *Reprod. Sci.*, **17**, 209-218.

Nguyen, H.Y., Vo, B.H., Nguyen, L.T., Bernad, J., Alaeddine, M., Coste, A., Reybier, K., Pipy, B. & Nepveu, F. (2013) Extracts of Crinum latifolium inhibit the cell viability of mouse lymphoma cell line EL4 and induce activation of anti-tumour activity of macrophages in vitro. *J. Ethnopharmacol.*, **149**, 75-83.

Ning, F., Liu, H. & Lash, G.E. (2016) The Role of Decidual Macrophages During Normal and Pathological Pregnancy. *Am. J. Reprod. Immunol.*, **75**, 298-309.

Nishioku, T., Hashimoto, K., Yamashita, K., Liou, S.Y., Kagamiishi, Y., Maegawa, H., Katsube, N., Peters, C., von Figura, K., Saftig, P., Katunuma, N., Yamamoto, K. & Nakanishi, H. (2002) Involvement of cathepsin E in exogenous antigen processing in primary cultured murine microglia. *J. Biol. Chem.*, **277**, 4816-4822.

Obayashi, Y., Ozaki, Y., Goto, S., Obayashi, S., Suzumori, N., Ohyama, F., Tone, S. & Sugiura-Ogasawara, M. (2016) Role of Indoleamine 2,3-Dioxygenase and Tryptophan 2,3-Dioxygenase in Patients with Recurrent Miscarriage. *Am. J. Reprod. Immunol.*, **75**, 69-77.

Okoye, T.C., Uzor, P.F., Onyeto, C.A. & Okereke, E.K. (2014) Safe African Medicinal Plants for Clinical Studies. In *Toxicological survey of African medicinal plants*, edited by Kuete, V. Elsevier**,** pp. 535-555.

Orecchioni, M., Ghosheh, Y., Pramod, A.B. & Ley, K. (2019) Macrophage Polarization: Different Gene Signatures in M1(LPS+) vs. Classically and M2(LPS-) vs. Alternatively Activated Macrophages. *Front. Immunol.*, **10**, 1084.

Pan, J., Jin, J.L., Ge, H.M., Yin, K.L., Chen, X., Han, L.J., Chen, Y., Qian, L., Li, X.X. & Xu, Y. (2015) Malibatol A regulates microglia M1/M2 polarization in experimental stroke in a PPARgamma-dependent manner. *J. Neuroinflammation*, **12**, 51.

Park, K.R., Lee, J.H., Choi, C., Liu, K.H., Seog, D.H., Kim, Y.H., Kim, D.E., Yun, C.H. & Yea, S.S. (2007a) Suppression of interleukin-2 gene expression by isoeugenol is mediated through down-regulation of NF-AT and NF-kappaB. *Int. Immunopharmacol.*, **7**, 1251-1258.

Park, S.Y., Hong, S.S., Han, X.H., Hwang, J.S., Lee, D., Ro, J.S. & Hwang, B.Y. (2007b) Lignans from Arctium lappa and their inhibition of LPS-induced nitric oxide production. *Chem. Pharm. Bull.* (*Tokyo*), **55**, 150-152.

Patel, U., Rajasingh, S., Samanta, S., Cao, T., Dawn, B. & Rajasingh, J. (2017) Macrophage polarization in response to epigenetic modifiers during infection and inflammation. *Drug Discov. Today*, **22**, 186-193.

Petroff, M.G., Sedlmayr, P., Azzola, D. & Hunt, J.S. (2002) Decidual macrophages are potentially susceptible to inhibition by class Ia and class Ib HLA molecules. *J. Reprod. Immunol.*, **56**, 3-17.

Phillippe, M. (2014) Cell-free fetal DNA--a trigger for parturition. *N. Engl. J. Med.*, **370**, 2534-2536.

Rusmidi, M.H.H., Zulkifli, A.N., Amaludin, N.B., Ibrahim, M.H. A., Noorjimi, A.A. & Radzun, K.A. (2023) Utilization of antioxidants and anti-inflammatory compounds in managing SARS-CoV-2 infection to achieve healthy community: *A review. J. Asian Scientific Res.,* **13**, 74-93.

Saadi, M.I., Nikandish, M., Ghahramani, Z., Valandani, F.M., Ahmadyan, M., Hosseini, F., Rahimian, Z., Jalali, H., Tavasolian, F., Abdolyousefi, E.N., Kheradmand, N. & Ramzi, M. (2023) miR-155 and miR-92 levels in ALL, post-transplant aGVHD, and CMV: possible new treatment options. *J. Egypt. Natl. Canc. Inst.*, **35**, 18.

Saha, S., Profumo, E., Togna, A.R., Rigano, R., Saso, L. & Buttari, B. (2020) Lupeol Counteracts the Proinflammatory Signalling Triggered in Macrophages by 7-Keto-Cholesterol: New Perspectives in the Therapy of Atherosclerosis. *Oxid. Med. Cell Longev.*, **2020**, 1232816.

Sahebkar, A., Momtazi-Borojeni, A.A. & Banach, M. (2021) PCSK9 vaccine: so near, yet so far! *Eur. Heart J.*, **42**, 4007-4010.

Sanjay, S.S. & Shukla, A.K. (2021) Potential therapeutic applications of nano-antioxidants, Springer.

Saqib, U., Sarkar, S., Suk, K., Mohammad, O., Baig, M.S. & Savai, R. (2018) Phytochemicals as modulators of M1-M2 macrophages in inflammation. *Oncotarget*, **9**, 17937-17950.

Shamabadi, A., Karimi, H., Arabzadeh Bahri, R., Motavaselian, M. & Akhondzadeh, S. (2024) Emerging drugs for the treatment of irritability associated with autism spectrum disorder. *Expert Opin. Emerg. Drugs*, **29**, 45-56.

Shapouri-Moghaddam, A., Mohammadian, S., Vazini, H., Taghadosi, M., Esmaeili, S.A., Mardani, F., Seifi, B., Mohammadi, A., Afshari, J.T. & Sahebkar, A. (2018) Macrophage plasticity, polarization, and function in health and disease. *J. Cell Physiol.*, **233**, 6425-6440.

Sharma, S., Godbole, G. & Modi, D. (2016) Decidual Control of Trophoblast Invasion. *Am. J. Reprod. Immunol.*, **75**, 341-350.

Sheng, Y.R., Hu, W.T., Wei, C.Y., Tang, L.L., Liu, Y.K., Liu, Y.Y., Qiu, J.P., Li, D.J. & Zhu, X.Y. (2019) Insights of efferocytosis in normal and pathological pregnancy. *Am. J. Reprod. Immunol.*, **82**, e13088.

Shiri, S., Alizadeh, A.M., Baradaran, B., Farhanghi, B., Shanehbandi, D., Khodayari, S., Khodayari, H. & Tavassoli, A. (2015) Dendrosomal curcumin suppresses metastatic breast cancer in mice by changing m1/m2 macrophage balance in the tumor microenvironment. *Asian Pac. J. Cancer Prev.*, **16**, 3917-3922.

Shu, L., Khor, T.O., Lee, J.H., Boyanapalli, S.S., Huang, Y., Wu, T.Y., Saw, C.L., Cheung, K.L. & Kong, A.N. (2011) Epigenetic CpG demethylation of the promoter and reactivation of the expression of Neurog1 by curcumin in prostate LNCaP cells. *AAPS J.*, **13**, 606-614.

Siddiqui, A.M., Cui, X., Wu, R., Dong, W., Zhou, M., Hu, M., Simms, H.H. & Wang, P. (2006) The anti-inflammatory effect of curcumin in an experimental model of sepsis is mediated by

up-regulation of peroxisome proliferator-activated receptor-gamma. *Crit. Care Med.*, **34**, 1874-1882.

Sisino, G., Bouckenooghe, T., Aurientis, S., Fontaine, P., Storme, L. & Vambergue, A. (2013) Diabetes during pregnancy influences Hofbauer cells, a subtype of placental macrophages, to acquire a pro-inflammatory phenotype. *Biochim. Biophys. Acta*, **1832**, 1959-1968.

Soflaei, S.S., Momtazi-Borojeni, A.A., Majeed, M., Derosa, G., Maffioli, P. & Sahebkar, A. (2018) Curcumin: A Natural Pan-HDAC Inhibitor in Cancer. *Curr. Pharm. Des.*, **24**, 123-129.

Straszewski-Chavez, S.L., Abrahams, V.M. & Mor, G. (2005) The role of apoptosis in the regulation of trophoblast survival and differentiation during pregnancy. *Endocr. Rev.*, **26**, 877-897.

Strimpakos, A.S. & Sharma, R.A. (2008) Curcumin: preventive and therapeutic properties in laboratory studies and clinical trials. *Antioxid. Redox Signal.*, **10**, 511-545.

Sultan, Q., Al-Rashedi, N. & Farhan, T. (2022) Effect of Three Plant Oils on Aeromonas hydrophila Infection, Immune-Related Renal Gene Expression, and Serum Biochemical Parameters in the Common Carp. *Egyptian J. Aqua. Bio. and Fish.*, **26**, 981-990.

Sun, Q., Liu, Q., Zhou, X., Wang, X., Li, H., Zhang, W., Yuan, H. & Sun, C. (2022) Flavonoids regulate tumor-associated macrophages - From structure-activity relationship to clinical potential (Review). *Pharmacol. Res.*, **184**, 106419.

Svensson, J., Jenmalm, M.C., Matussek, A., Geffers, R., Berg, G. & Ernerudh, J. (2011) Macrophages at the fetal-maternal interface express markers of alternative activation and are induced by M-CSF and IL-10. *J. Immunol.*, **187**, 3671-3682.

Tan, W., Chen, L., Guo, L., Ou, X., Xie, D. & Quan, S. (2014) Relationship between macrophages in mouse uteri and angiogenesis in endometrium during the peri-implantation period. *Theriogenology*, **82**, 1021-1027.

Tang, Z., Buhimschi, I.A., Buhimschi, C.S., Tadesse, S., Norwitz, E., Niven-Fairchild, T., Huang, S.T. & Guller, S. (2013) Decreased levels of folate receptor-beta and reduced numbers of fetal macrophages (Hofbauer cells) in placentas from pregnancies with severe pre-eclampsia. *Am. J. Reprod. Immunol.*, **70**, 104-115.

Teiten, M.H., Dicato, M. & Diederich, M. (2013) Curcumin as a regulator of epigenetic events. *Mol. Nutr. Food Res.*, **57**, 1619-1629.

Tsai, C.F., Chen, G.W., Chen, Y.C., Shen, C.K., Lu, D.Y., Yang, L.Y., Chen, J.H. & Yeh, W.L. (2021) Regulatory Effects of Quercetin on M1/M2 Macrophage Polarization and Oxidative/Antioxidative Balance. *Nutrients*, **14**, 67.

Tu, S.P., Jin, H., Shi, J.D., Zhu, L.M., Suo, Y., Lu, G., Liu, A., Wang, T.C. & Yang, C.S. (2012) Curcumin induces the differentiation of myeloid-derived suppressor cells and inhibits their interaction with cancer cells and related tumor growth. *Cancer Prev. Res.* (*Phila*), **5**, 205-215.

van Wyk, A.S. & Prinsloo, G. (2020) Health, safety and quality concerns of plant-based traditional medicines and herbal remedies. *S. African J. Botany*, **133**, 54-62.

Viola, A., Munari, F., Sanchez-Rodriguez, R., Scolaro, T. & Castegna, A. (2019) The Metabolic Signature of Macrophage Responses. *Front. Immunol.*, **10**, 1462.

Wang, L.X., Zhang, S.X., Wu, H.J., Rong, X.L. & Guo, J. (2019) M2b macrophage polarization and its roles in diseases. *J. Leukoc. Biol.*, **106**, 345-358.

Wang, Q., Liu, D., Song, P. & Zou, M.H. (2015) Tryptophan-kynurenine pathway is dysregulated in inflammation, and immune activation. *Front. Biosci.* (*Landmark Ed*), **20**, 1116-1143.

Wang, W.J., Hao, C.F., Qu, Q.L., Wang, X., Qiu, L.H. & Lin, Q.D. (2010a) The deregulation of regulatory T cells on interleukin-17-producing T helper cells in patients with unexplained early recurrent miscarriage. *Hum. Reprod.*, **25**, 2591-2596.

Wang, W.J., Hao, C.F., Yi, L., Yin, G.J., Bao, S.H., Qiu, L.H. & Lin, Q.D. (2010b) Increased prevalence of T helper 17 (Th17) cells in peripheral blood and decidua in unexplained recurrent spontaneous abortion patients. *J. Reprod. Immunol.*, **84**, 164-170.

Wang, W.J., Salazar Garcia, M.D., Deutsch, G., Sung, N., Yang, X., He, Q., Jubiz, G., Bilal, M., Dambaeva, S., Gilman-Sachs, A., Beaman, K. & Kwak-Kim, J. (2020) PD-1 and PD-L1 expression on T-cell subsets in women with unexplained recurrent pregnancy losses. *Am. J. Reprod. Immunol.*, **83**, e13230.

Wei, Y., Liang, M., Xiong, L., Su, N., Gao, X. & Jiang, Z. (2021) PD-L1 induces macrophage polarization toward the M2 phenotype via Erk/Akt/mTOR. *Exp. Cell Res.*, **402**, 112575.

Wu, Z.M., Yang, H., Li, M., Yeh, C.C., Schatz, F., Lockwood, C.J., Di, W. & Huang, S.J. (2012) Pro-inflammatory cytokine-stimulated first trimester decidual cells enhance macrophage-induced apoptosis of extravillous trophoblasts. *Placenta*, **33**, 188-194.

Xu, W., Roos, A., Schlagwein, N., Woltman, A.M., Daha, M.R. & van Kooten, C. (2006) IL-10-producing macrophages preferentially clear early apoptotic cells. *Blood*, **107**, 4930-4937.

Xu, X.Y., Meng, X., Li, S., Gan, R.Y., Li, Y. & Li, H.B. (2018) Bioactivity, Health Benefits, and Related Molecular Mechanisms of Curcumin: Current Progress, Challenges, and Perspectives. *Nutrients*, **10**, 1553.

Xu, Y., Romero, R., Miller, D., Kadam, L., Mial, T.N., Plazyo, O., Garcia-Flores, V., Hassan, S.S., Xu, Z., Tarca, A.L., Drewlo, S. & Gomez-Lopez, N. (2016) An M1-like Macrophage Polarization in Decidual Tissue during Spontaneous Preterm Labor That Is Attenuated by Rosiglitazone Treatment. *J. Immunol.*, **196**, 2476-2491.

Yan, S., Zhou, M., Zheng, X., Xing, Y., Dong, J., Yan, M. & Li, R. (2021) Anti-Inflammatory Effect of Curcumin on the Mouse Model of Myocardial Infarction through Regulating Macrophage Polarization. *Mediators Inflamm.*, **2021**, 9976912.

Yang, X., Wang, X., Liu, D., Yu, L., Xue, B. & Shi, H. (2014) Epigenetic regulation of macrophage polarization by DNA methyltransferase 3b. *Mol. Endocrinol.*, **28**, 565-574.

Yao, Y., Hao, F., Tang, L.C., Xu, X.H. & Jin, L. (2020) Downregulation of HDAC8 expression decreases CD163 levels and promotes the apoptosis of macrophages by activating the ERK signaling pathway in recurrent spontaneous miscarriage. *Mol. Hum. Reprod.*, **26**, 521-531.

Yunna, C., Mengru, H., Lei, W. & Weidong, C. (2020) Macrophage M1/M2 polarization. *Eur. J. Pharmacol.*, **877**, 173090.

Zendehdel, E., Abdollahi, E., Momtazi-Borojeni, A.A., Korani, M., Alavizadeh, S.H. & Sahebkar, A. (2019) The molecular mechanisms of curcumin's inhibitory effects on cancer stem cells. *J. Cell Biochem.*, **120**, 4739-4747.

Zhang, Y., Ma, L., Hu, X., Ji, J., Mor, G. & Liao, A. (2019) The role of the PD-1/PD-L1 axis in macrophage differentiation and function during pregnancy. *Hum. Reprod.*, **34**, 25-36.

Zhao, Q.Y., Li, Q.H., Fu, Y.Y., Ren, C.E., Jiang, A.F. & Meng, Y.H. (2022) Decidual macrophages in recurrent spontaneous abortion. *Front. Immunol.*, **13**, 994888.

Zhou, Y., Zhang, T., Wang, X., Wei, X., Chen, Y., Guo, L., Zhang, J. & Wang, C. (2015) Curcumin Modulates Macrophage Polarization Through the Inhibition of the Toll-Like Receptor 4 Expression and its Signaling Pathways. *Cell Physiol. Biochem.*, **36**, 631-641.

Zizzo, G., Hilliard, B.A., Monestier, M. & Cohen, P.L. (2012) Efficient clearance of early apoptotic cells by human macrophages requires M2c polarization and MerTK induction. *J. Immunol.*, **189**, 3508-3520.