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REVIEW

Mechanisms of Macrophage Polarization Regulated by Oridonin: A Review

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Abstract: Oridonin(Ori), a natural ent-kaurane diterpenoid derived from the medicinal herb Rabdosia rubescens, has garnered significant interest for its potent anti-inflammatory and immunomodulatory properties. A key mechanism underlying these effects is its ability to regulate polarization. This review elaborates on the multifaceted mechanisms by which Ori modulates macrophage, extending beyond the inhibition of pro-inflammatory signaling pathways. We highlight its emerging role in metabolic reprogramming by shifting the functional balance from a pro-inflammatory M1 phenotype towards an anti-inflammatory and tissue-reparative M2 phenotype. Ori exhibits therapeutic potential not only in cancer and but also in a broad spectrum of other conditions, including non-alcoholic fatty liver disease, rheumatoid arthritis, colitis, asthma, atherosclerosis, and sepsis. However, the clinical translation of Ori is severely hampered by its unfavorable pharmacokinetic properties, such as poor aqueous solubility and low oral bioavailability. We conclude by discussing future perspectives, emphasizing the need for advanced drug delivery systems, the integration of multi-omics technologies to thoroughly map macrophage responses, and the application of network pharmacology and artificial intelligence to propel the rational development of oridonin as a novel macrophage-centric therapeutic agent.

Keywords: oridonin, macrophage polarization, tumor, inflammation

Introduction

Oridonin (Ori), as a naturally ent-kaurane diterpenoid compound isolated from *Isodon rubescens*, has been extensively utilized in traditional Chinese medicine for centuries.[1] (Figure 1). For hundreds of years, *Isodon rubescens* and its preparations have been widely used to treat inflammatory diseases such as pharyngitis, tonsillitis and bacterial infections.[2,3] These uses are classified in traditional Chinese medicine theory as having the effects of "heat-clearing and detoxifying" as well as "activating blood circulation and resolving stasis".[4] Notably, the core pathological processes of these traditional indications often involve the excessive activation of the innate immune system and the infiltration of immune cells. The traditional therapeutic effects of *Isodon rubescens* strongly suggest that it contains effective components that can regulate the immune response. The discovery of Ori provides a crucial molecular entity for scientifically explaining this traditional wisdom. Recent studies further indicate Ori's capacity to modulate macrophage polarization, regulate the phagocytic ability of macrophages and their ability to clear apoptotic cells, suggesting a novel mechanism for its therapeutic applications.[5,6]

The immune system forms an intricate and precisely balanced network where various immune components, including cells, molecules, and tissues, work in concert to combat infections and preserve physiological equilibrium.[7] Within this protective network, macrophages play a pivotal role as frontline defenders in the body's innate immunity. These versatile cells do not just mount initial attacks against invading pathogens—they also orchestrate broader immune reactions, regulate inflammatory processes, and facilitate healing in damaged tissue.[8] Macrophages exhibit remarkable plasticity, and the local biological microenvironment is capable of directionally transforming macrophages through polarization into

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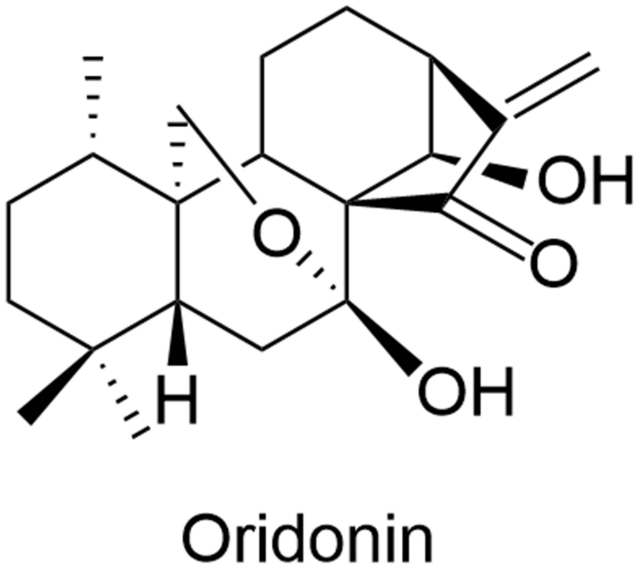

Figure 1 Molecular structure of oridonin.

subtypes. These subtypes are categorized as M1 or M2 macrophages, distinguished by their surface markers, cytokine signatures, and biological functions.[9] These different subtypes play a specialized role, allowing the immune system to flexibly respond to normal physical processes and disease states. Studies have shown that when macrophage activity is abnormal, it plays a key role in promoting the development of various inflammatory diseases and cancers.[10,11] Acting as sentinel cells, macrophages perceive microenvironmental shifts and modulate tissue homeostasis. This indicates that regulating the M1/M2 equilibrium in the microenvironment could be a crucial treatment approach.

This review presents a methodical analysis of Ori's therapeutic properties, examining the biological pathways through which it exerts its effects in preclinical studies. By synthesizing current evidence, the review establishes a structured foundation for future investigations into Ori's clinical applications as an immunomodulator in disease management.

Macrophage Polarization

In 1882, Elie Metchnikoff, a Russian zoologist, discovered a cell with phagocytic function by observing starfish larvae and water fleas infected with fungal spores, and named it the "macrophage".[12] Numerous studies have demonstrated that macrophages have a dual origin: either from precursor cells in the early embryo or from circulating monocytes in adulthood, in order to adapt to different pathophysiological conditions[13] (Figure 2). In embryonic development, yolk sac-derived erythro-myeloid precursors mature into rudimentary hematopoietic stem cells (HSCs).[13] These HSCs move to the fetal liver, maturing into fetal liver monocytes before dispersing as tissue-resident macrophages (RTMs) across the body.[14,15] RTMs encompass microglia in the CNS, osteoclasts within bone, alveolar macrophages in the lungs, histiocytes in the spleen and connective tissue, as well as Kupffer cells in the liver.[16] Most RTMs exhibit long lifespans and self-renew via local proliferation rather than bone marrow replenishment.[17,18] However, bone marrow-derived monocytes critically contribute to repopulating depleted RTMs in certain tissues.[19] Distributed ubiquitously across organs, phagocytosis and digestion.[20] Additionally, they mediate antigen presentation, cytokine secretion, tissue repair, immune regulation, and tumor immunity, thereby maintaining host defense and homeostasis.[21]

The transformation of macrophages into distinct phenotypes and roles due to varying microenvironmental cues constitutes macrophage polarization[22] (Figure 3). Depending on the stimulus conditions, macrophages can be categorized into the following phenotypes. Macrophages can be activated into the M1 phenotype through stimulation by lipopolysaccharide (LPS) or Th1 cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). Once polarized, these cells produce a range of pro-inflammatory signaling molecules, including TNF-α, interleukin-1β (IL-1β),

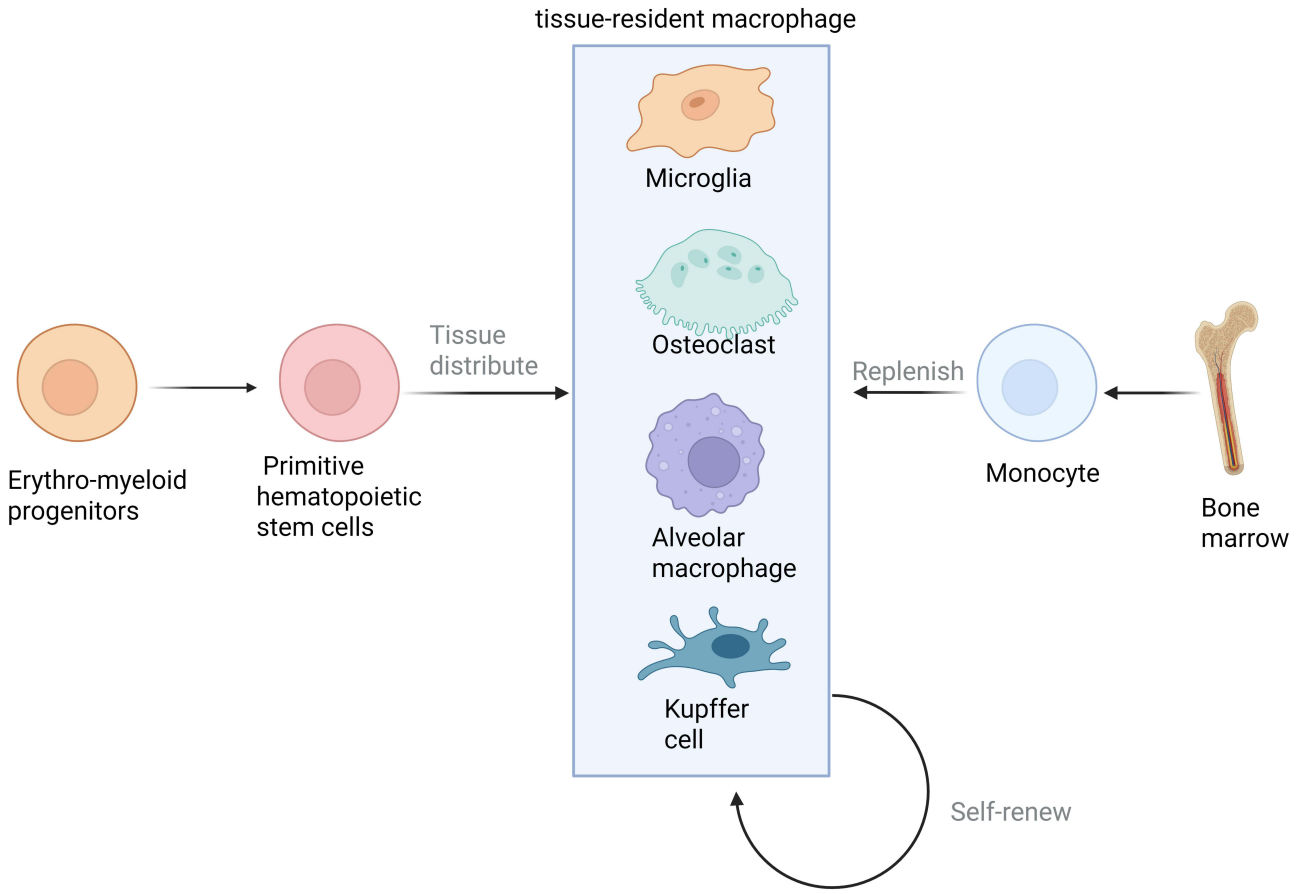

Figure 2 Origin of macrophage.

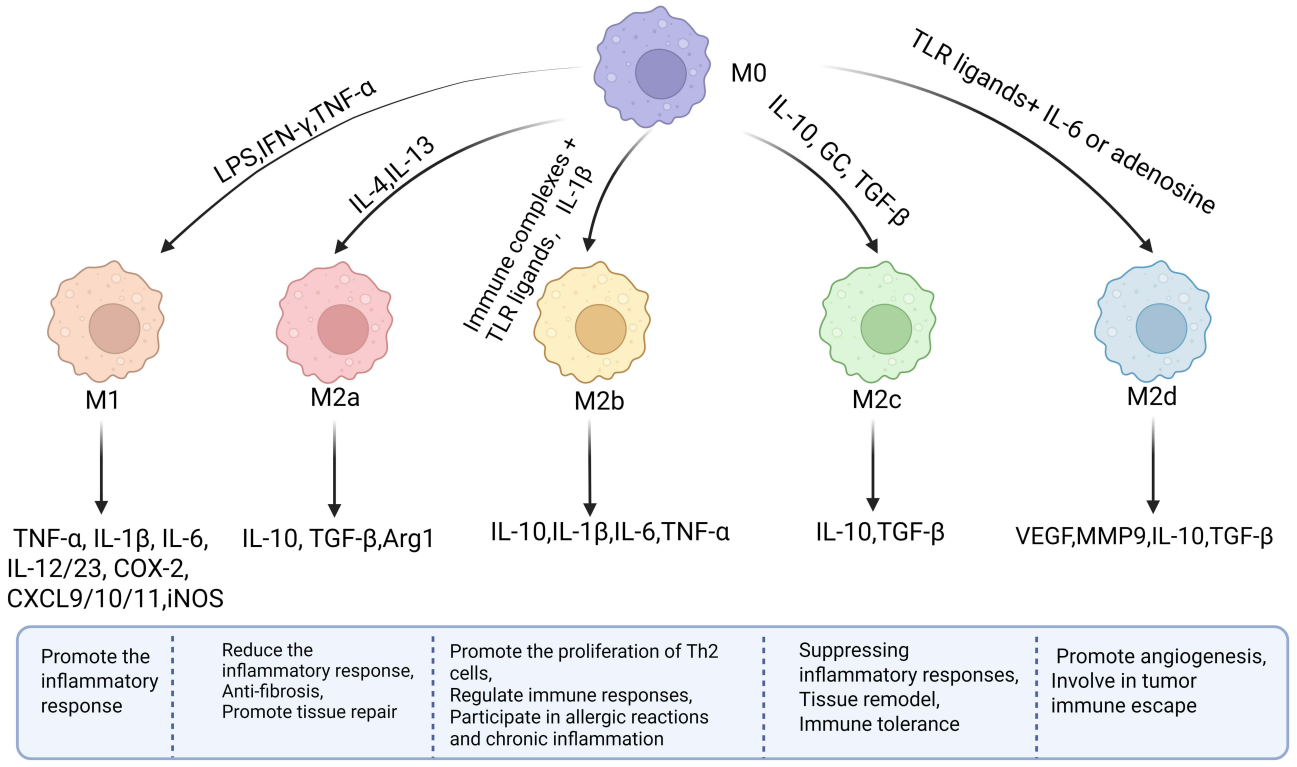

Figure 3 Macrophage polarization.

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IL-6, IL-12/23, cyclooxygenase-2 (COX-2), chemokines CXCL9/10/11, and inducible nitric oxide synthase (iNOS).[21,23] This cascade of mediators serves to intensify the body's inflammatory response.

M2 macrophages encompass four subtypes, each influenced by distinct activators: those stimulated by Th2 cytokines, like IL-4 and IL-13, become M2a polarized.[24] These macrophages secrete IL-10, TGF-β, and other anti-inflammatory mediators like arginase 1 (Arg1), which play a key role in dampening inflammation, preventing fibrosis, and facilitating tissue regeneration.[25] Under the induction of immune complexes (eg, IgG binding to Fc receptors) combined with TLR ligands or IL-1β, macrophages polarize to the M2b subtype. M2b macrophages produce IL-10 along with trace levels of inflammatory cytokines like IL-1β, IL-6, and TNF-α.[26] These factors promote the proliferation of Th2 cells, regulate immune responses, and participate in allergic reactions and chronic inflammation.[27,28] Induction by IL-10, glucocorticoids (GC), or TGF-β can polarize macrophages to the M2c subtype.[29,30] M2c macrophages secrete significant amounts of IL-10 and TGF-β, key cytokines that inhibit inflammation, foster tissue repair, and enhance immune tolerance.[21,25,31] Macrophages induced by TLR ligands in combination with IL-6 or adenosine polarize to the M2d subtype.[32] Macrophages, often referred to as tumor-associated macrophages, or TAMs for short, secrete the vascular endothelial growth factor, or VEGF, and the matrix metalloproteinase 9, or MMP9.[21] These substances kickstart the process of angiogenesis, a crucial mechanism for tissue healing and renewal. Moreover, M2d macrophages release anti-inflammatory cytokines like IL-10 and TGF-β, which not only dampen T cell responses but also attract regulatory T cells (Tregs), fostering an immune-tolerant environment.[33,34] This suggests that M2d macrophages may be involved in tumor immune escape.

M1 macrophages exacerbate inflammatory pathologies.[35] For example, cigarette smoke causes pulmonary M1 macrophage activation, boosting the presence of IL-6, IL-1β, and TNF-α, contributing to persistent inflammation, severe flare-ups, and lung tissue damage in related ailments.[36] Similarly, microglial M1 polarization in neuroinflammation promotes neuronal damage, accelerating the progression of Alzheimer's disease.[37] On the other hand, blocking CXCR4 in experimental models of acute lung injury causes macrophages to switch from the M1 to the M2 phenotype, which reduces the production of inflammatory cytokines and lessens tissue harm.[21] The M1 macrophage response kicks off the immune system's defense mechanism by releasing inflammatory cytokines like TNF-α, IL-1β, and IL-12/23 to eliminate pathogens.[21] Once the threat is under control, the system shifts gears to the M2 phenotype, which tones down the inflammatory response through mediators such as IL-10 and TGF-β while promoting tissue healing and recovery.[21] Thus, therapeutic strategies targeting the M1-to-M2 transition to restore the M1/M2 equilibrium hold promise for treating inflammatory and neoplastic disorders.

Metabolic reprogramming refers to actively modify cellular metabolic pathways and networks in response to environmental shifts—including hypoxia, nutrient stress, pathological states, or developmental demands—redirecting energy and biomaterials to fulfill emergent biological requirements.[38] Metabolic reprogramming plays a crucial role in macrophage polarization, specifically glycolysis and oxidative phosphorylation. Glycolysis is a metabolic pathway in which cells break down glucose in the cytoplasm to produce pyruvate and adenosine triphosphate(ATP).[39] Oxidative phosphorylation(OXPHOS) is the process by which cells release energy within the mitochondria through the electron transport chain and drive the synthesis of ATP.[40] M1 macrophages complete the polarization process by utilizing glucose and depend on glycolysis for ATP production.[41] On the contrary, the M2 macrophage polarization is characterized by significantly enhanced oxidative phosphorylation.[22]

Pharmacological Effects of Oridonin

Extensive research confirms Ori's diverse biological effects, such as anti-inflammatory, anticancer, bone-strengthening, and neuroprotective properties[42–45] (Table 1). These activities are mediated through multiple signaling pathways and molecular targets.

Anti-Inflammatory

Studies have demonstrated that Ori exerts anti-inflammatory effects across multiple inflammatory diseases, including acute kidney injury, atherosclerosis, dry eye disease, and osteoarthritis, through diverse mechanisms.[46,47,49,60] The NLRP3 inflammasome is a critical multiprotein assembly that includes NLRP3, caspase-1, and ASC, a speck-like protein linked to apoptosis.[61] This complex serves as a key driver of inflammatory processes by triggering the secretion of pro-inflammatory signaling molecules, particularly IL-1β and interleukin-18 (IL-18), which are central to the

Table 1 Pharmacological Effects of Oridonin

Pharmacological Effects	Type of Diseases	Experimental Model/Cell Line(s)	Outcome on Immune Modulation	Molecular Targets or Pathways	Ref.
Anti-inflammatory	Dry eye disease	HCE-T	Pyroptosis	NLRP3 inflammasome	[46]
	Atherosclerosis	High-fat fed ApoE−/− mouse model	Inhibit inflammation	NLRP3 inflammasome	[47]
	Irritable bowel syndrome	Irritable bowel syndrome mouse model	Inhibit inflammation	NF-κB	[48]
	Cute kidney injury	Ischemia–reperfusion injury mouse model	Inhibit inflammation	NF-κB	[49]
Anti-tumor	Esophageal cancer	KYSE-30, KYSE-150, EC9706	Cell cycle arrest, Apoptosis	PI3K/AKT/mTOR, Ras/Raf	[50]
	Small-cell lung cancer	H1688, H446	Apoptosis	PERK/eIF2α/CHOP	[51]
	Gefitinib-resistant non-small-cell lung cancer	A549, H1975	Inhibit the proliferation, invasion, and migration	EGRR/ERK/MMP-12, CIP2A/Akt	[52]
	Breast cancer	4T1, MCF-7, MDAMB-231	Cell cycle arrest	PI3K/AKT/mTOR	[53]
	Prostate cancer	PC3, DU145	Cell cycle arrest, apoptosis	PI3K/Akt	[54]
	Cervical cancer	HeLa	Apoptosis	PI3K/Akt	[55]
	Liver cancer	HepG2	Cell cycle arrest and apoptosis	MAPK, p53	[56]
	Gallbladder cancer	SGC996, NOZ	Cell cycle arrest and apoptosis	Mitochondrial pathway	[57]
	Oral cancer	UM1, SCC25	Cell cycle arrest and apoptosis	PI3K/Akt	[58]
Anti-Osteoporotic	Osteoporosis	Estrogen deprivation-induced osteoporosis in mice, RAW264.7		MAPK/NF-κB, p53, ROS, Wnt3a/β-catenin	[45,59]

development of inflammatory diseases.[61] Ori serves as a selective inhibitor targeting the NLRP3 inflammatory sensor complex.[42] By chemically bonding to cysteine 279 in NLRP3's NACHT domain, Ori effectively blocks the protein's interaction with NEK7—a critical serine/threonine kinase.[42] This molecular interference prevents the assembly and activation of the NLRP3 inflammasome, resulting in precise inhibition of NLRP3-mediated inflammatory response. In murine dry eye models, topical administration of 0.01%, 0.1%, and 1% Ori dose-dependently decreased IL-1β and IL-18 levels, enhanced corneal epithelial thickness, and improved tear film stability.[46] In a study using mice genetically predisposed to atherosclerosis, a 12-week course of Ori administered intraperitoneally at doses of either 10 or 20mg/kg demonstrated significant therapeutic effects. The treatment effectively suppressed NLRP3 inflammasome activation while stimulating the Nrf2 antioxidant pathway.[47] Researchers observed reduced macrophage accumulation, diminished proinflammatory cytokines (IL-1β and IL-18), and alleviated lipid plaque inflammation.[47] Additionally, Ori treatment exhibits significant antioxidant properties by reducing ROS production and oxidative stress.[47] The compound also enhances lipid clearance mechanisms by thickening the protective fibrous cap and helps stabilize plaques.[47] These multifaceted effects collectively improved atherosclerotic plaque stability in the experimental model. Overall, these findings indicate that Ori alleviates inflammatory responses by modulating ER stress and suppressing NLRP3 inflammasome assembly/activation, thereby reducing pro-inflammatory cytokine release.

Further studies have shown that in a mouse model of irritable bowel syndrome, administration of 20 mg per kilogram of Ori activates the pregnane X receptor (PXR), inhibits the phosphorylation of NF-κB p65, and reduces the production of inflammatory markers such as iNOS, COX-2, IL-1β, and IL-6.[48] This mechanism of action can effectively reduce intestinal inflammation and repair damaged intestinal barrier function. In an experimental model of acute kidney injury, Ori administered via intraperitoneal injection at a dose of 15 mg per kilogram showed significant therapeutic effects. This treatment can effectively AKT/NF-κB signaling cascade, thereby reducing the production of inflammatory markers including IL-1β, IL-6, TNF-α and MCP-1.[49] Clinically meaningful improvements were observed with decreases in serum creatinine and urea nitrogen levels.[49] The intervention also mitigated structural damage to renal tubules and helped maintain overall kidney function.[49] These findings suggest Ori's potential as a protective agent against renal injury. These results underscore Ori's anti-inflammatory efficacy via suppression of NF-κB signaling.

Anti-Tumor

Tumors represent a major global public health challenge.[62] Ori, a natural compound, not only exhibits potent anti-inflammatory properties but has also demonstrated remarkable efficacy in suppressing diverse malignancies. Preclinical and clinical studies have identified significant antitumor activity of Ori in over 20 types of malignancies, including esophageal, lung, hepatocellular, prostate, and breast cancers.[50,53,63–65] The anticancer mechanisms of Ori are multifactorial: it modulates tumor cell cycle regulation, induces apoptosis, inhibits proliferation in a concentration- and time-dependent manner, suppresses tumor cell invasion and metastasis, triggers autophagy, and impedes tumor-associated angiogenesis and vascular migration.[66] Ori exerts its antitumor activity largely by modulating critical signaling pathways and intracellular bioactive compounds. Key players in this process involve the PERK-eIF2α-CHOP/GADD153 axis, along with EGFR, reactive oxygen species (ROS), NF-κB, MAPK cascades, and the PI3K/Akt signaling network. These molecular mechanisms work in concert to inhibit cancer progression and trigger tumor cell death. For example, in small-cell lung carcinoma, exposure to 20μM of Ori triggers an upregulation of p62 while increasing the LC3B-II to LC3B-I ratio.[51] This cascade ultimately stimulates the PERK-eIF2α-CHOP/GADD153 signaling axis, effectively jumpstarting the autophagy process.[51] In non-small cell lung cancer (NSCLC) resistant to gefitinib, Ori effectively inhibits tumor growth, cell invasion and spread by reducing the expression of EGFR/ ERK-driven MMP-12.[52] Additionally, it restores PP2A activity by blocking CIP2A, a key suppressor of PP2A function. This dual mechanism highlights Ori's potential as a therapeutic agent in treatment-resistant NSCLC cases.[52] In experimental models of esophageal cancer, Ori has been shown to trigger programmed cell death and prevent cellular proliferation in KYSE-30, KYSE-150, and EC9706 cell lines.[50] This anti-tumor effect is mediated through its ability to disrupt the PI3K/AKT/mTOR signaling cascade and the Ras/Raf molecular pathway, which can effectively inhibit the formation and progression of malignant tumors.[50] Moreover, Ori blocks cell cycle progression and triggers apoptosis via the PI3K/AKT/mTOR pathway, hence suppressing breast cancer's invasion and spread.[53] Ori also suppresses prostate cancer through the PI3K/Akt pathway that blocks the cell cycle and triggers apoptosis.[54] In cervical cancer, Ori can promote apoptosis of HeLa cells through PI3K/Akt, thereby delaying tumor progression.[55] Ori triggers MAPK and p53 to induce cell cycle arrest and programmed cell death in HepG2 cells.[56] Studies indicate Ori promotes apoptosis and cell cycle arrest in the SGC996 and NOZ cell lines for gallbladder cancer via the mitochondrial route.[57] Ori induces apoptosis and halts the cell cycle in the UM1 and SCC25 oral cancer cell lines via the PI3K/Akt signaling pathway.[58] Moreover, Ori exerts a profound influence on the regulation of key proteins involved in both cell cycle progression (including cyclin D1, D3, p21, phosphorylated CDK1, cyclin B1, and cyclin A2) and programmed cell death (notably Bax, Bcl-2, caspase-9, caspase-3, and PARP).[11,54–57] This compound dramatically shifts the balance of these critical molecular players, effectively rewiring cellular fate decisions. It also suppresses PI3K and Akt phosphorylation, leading to a dose-responsive G2/M phase halt and cell death.[54] This evidence highlights Ori's promise as a multifunctional therapeutic for cancer treatment, in harmony with up-to-date studies concerning resistance phenomena in non-small cell lung cancer and innovative treatment methodologies.[58]

Anti-Osteoporotic

Osteoporosis is a systemic skeletal condition marked by disrupted bone remodeling, where bone resorption by osteoclasts outweighs formation by osteoblasts.[45] This imbalance results in lower bone density, structural degradation, heightened fragility, and a greater risk of fractures.[45] Ori curbs osteoclast differentiation via MAPK/NF-κB pathway inhibition, halts p65 nuclear transport, and decreases cellular ROS levels.[59] Moreover, lab experiments involving mice given Ori at concentrations of 10mg/kg, 20mg/kg, and 40mg/kg revealed that it stimulates the Wnt3a/β-catenin signaling cascade, which in turn boosts the production of vascular endothelial growth factor (VEGF).[45] This activation resulted in elevated calcium and phosphorus content in the femoral bone, significantly improved maximum bending load and stress resistance, and enhanced bone density and histomorphology in a dose-dependent manner.[45] Research setting with BMSCs, showed that Ori boosts the bones-building capabilities of these cells by activating the Wnt/β-catenin signaling route. Simultaneously, it curbs the formation of bone-eating cells, known as osteoclasts, either by a direct or indirect mechanism, potentially by targeting the RANKL pathway. This dual mechanism promotes bone formation, reduces bone resorption, and ameliorates osteoporotic phenotypes.[59] Collectively, Ori restores the equilibrium between bone resorption

and formation by stimulating osteoblast proliferation, inhibiting osteoclast differentiation, increasing bone mineral density, and improving bone microarchitecture, thereby exerting therapeutic effects against osteoporosis.

Effects of Oridonin on Macrophages

Oridonin Affects Macrophage Polarization by Regulating the Expression Profile of Cytokines

LPS promotes M1 macrophage polarization independently or alongside Th1 cytokines like IFN-γ and GM-CSF.[9] M1 macrophages predominantly release pro-inflammatory signaling molecules such as TNF-α, IL-1β, and IL-6, along with ROS and matrix metalloproteinases (MMPs).[9] These mediators play a crucial role in enhancing antigen presentation, driving immune responses, and advancing the inflammatory processes.[9] Remarkably, TNF-α, IL-1β, and IL-6 both act as pro-inflammatory factors and indicate M1 macrophages are activated.[67–69] Research have shown that when macrophages stimulated by LPS and IFN-γ are exposed to Ori at doses of 5μM or 10μM, there is a marked decrease in the secretion of inflammatory cytokines such as TNF-α and IL-6. This inhibition effectively suppresses the pro-inflammatory response driven by M1 macrophages. Another M1 marker, CD86, reflects the degree of polarization.[70] Experimental studies demonstrate that Ori effectively inhibit M1 polarization, as evidenced by the significant down-regulation of CD86 expression. When Raw264.7 cells were stimulated by LPS stimulation, Ori significantly reduced the production of pro-inflammatory cytokines—IL-1β, IL-6, and TNF-α, and also reduced the presence of inducible iNOS, a key marker of M1 macrophage activation.[49] These findings confirm the role of Ori in suppressing inflammatory responses. In studies involving myocardial infarction models, treatment with different doses (1mg, 3mg, or 6mg) of Ori significantly reduced the release of pro-inflammatory cytokines, specifically TNF - α, IL - 1β, and IL – 6.[71] These findings further emphasize Ori's ability to inhibit polarization of M1 macrophages.

Th2 cytokines such as IL-4 and IL-13 promote the differentiation of macrophages towards the M2 phenotype.[9] M2 macrophages secrete anti-inflammatory mediators (eg, IL-10), Arg-1, CD206, and chemokines (CCL17/CCL22), promoting tissue repair, angiogenesis, and inflammation resolution.[72] Mechanistically, Ori enhances M2 polarization by inhibiting NF-κB via decreasing the level of p65, reducing ROS production.[70] This suggests that Ori can promote the transformation of M1 macrophages into M2 macrophages. CD206 is a marker of M2 type macrophages and CD86 is a marker of M1 type macrophages.[73,74] Experimental evidence shows upregulated CD206 and downregulated CD86 in murine models following Ori treatment, indicating that Ori can promote M1 macrophages transform to M2 macrophages.[70] Dose-dependent decreases in IL-1β, IL-6, and iNOS, alongside increased IL-10 and CD206 expression, further corroborate Ori's promotion of M2 reprogramming.[75] In sepsis models, Ori shifts Kupffer cell subsets from pro-inflammatory M1 to reparative M2 phenotypes, highlighting its therapeutic potential in modulating macrophage plasticity.[76]

Oridonin Affects Macrophage Polarization by Regulating Metabolic Reprogramming

Oridonin modulates macrophages not only by altering cytokine expression profiles but also by inducing profound metabolic reprogramming. The M1 macrophages mainly rely on glycolysis to rapidly generate ATP and maintain their inflammatory functions.[77] Pharmacological studies demonstrate that Ori administration (5, 10mg/kg) suppresses glycolytic progression in bladder cancer cells.[78] The M2 macrophages primarily utilize OXPHOS and fatty acid oxidation to facilitate tissue repair.[79] Recent studies demonstrate that iNOS inhibits OXPHOS to drive M1 polarization in macrophages.[80] Ori counteracts this process by suppressing iNOS expression, thereby attenuating OXPHOS inhibition and promoting M1-to-M2 transition.[75] Besides, Ori elevates intracellular ROS levels, directly damaging mitochondrial electron transport chain complexes and disrupting OXPHOS, which inducing energy metabolism disorders. For instance, in HepG2 cells, Ori activates p53 and MAPK pathways via ROS-dependent mechanisms, amplifying mitochondrial dysfunction and OXPHOS suppression.[81]

Oridonin's Effects on Modulating Macrophage Polarization at the Molecular Level

Macrophage polarization is a highly controlled biological process governed by intricate signaling cascades, gene expression regulation, and molecular modifications after transcription. Research indicates that Ori influences macrophage

polarization via various cellular signaling routes, yet the exact molecular mechanisms underlying this regulation still elude full scientific understanding (Figure 4).

PI3K/Akt Signaling Pathway

The PI3K/Akt signaling cascade is a pivotal element in cellular communication, modulating a spectrum of physiological processes and the course of illness.[82] Critical components of this metabolic route are PI3K, Akt, IKK, and NF-κB.[82] Akt phosphorylates and activates the IKK complex, thereby promoting the nuclear translocation of NF-κB.[83] Furthermore, Akt-induced miR-155 suppression upregulates C/EBPβ, promoting M1 macrophage polarization.[84] In a mouse model of acute renal damage, administering Ori (at 15 mg/kg via intraperitoneal route) restored the suppressed expression of Akt, NF-κB, and STAT3 triggered by LPS.[85] The study further demonstrated that Ori curbed the release of key inflammatory markers (IL-1β, IL-6, TNF-α) while preventing the shift toward M1 macrophage activation.[85] These findings underscore Ori's ability to combat inflammation by targeting the PI3K/Akt signaling cascade.

ROS/NF-κB Signaling Pathway

ROS, byproducts of cellular metabolism, promote signal transduction at low levels but induce oxidative stress and cellular damage at high concentrations.[86] NF-κB, a p50/p65 heterodimer, is a key transcription factor that regulates oxidative stress and inflammation by activating pro-inflammatory cytokine gene expression.[87] Polarization of M1 macrophages is dependent on ROS and is mediated by activation of NF-κB.[88] When M1 macrophages were exposed to Ori, the production of ROS was significantly reduced.[89] Reduced levels of p65 and p50 lead to the inhibition of NF-κB

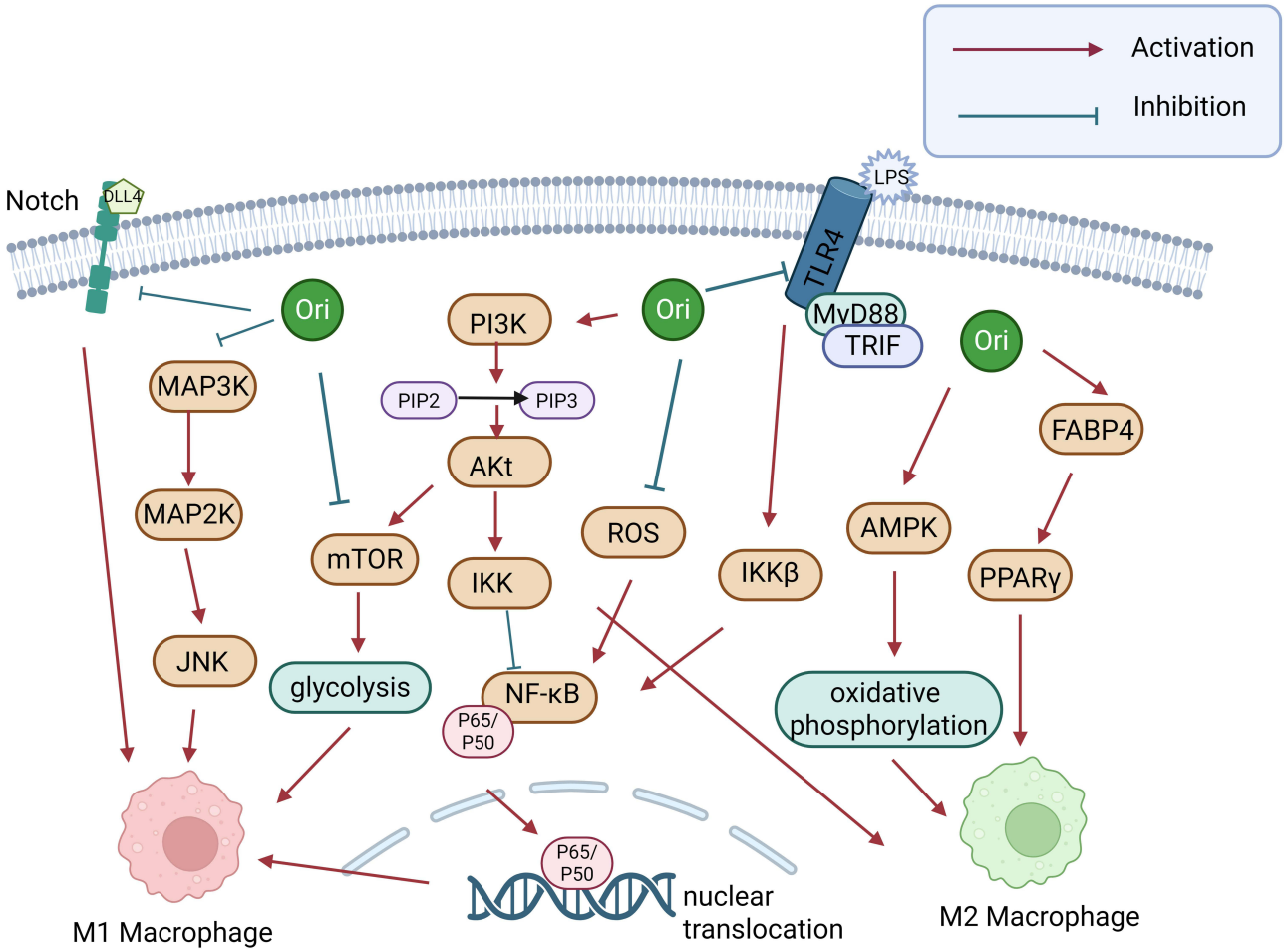

Figure 4 Molecular Mechanisms of Oridonin in Regulating Macrophage Polarization.

signaling.[89] This change is accompanied by a significant shift in macrophages from the M1 phenotype to the M2 phenotype, as demonstrated by reduced secretion of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α.[89]

TLR4/NF-κB Signaling Pathway

TLR4, a kind of transmembrane protein, is responsible for recognizing harmful substances like LPS, and triggering a series of signaling by utilizing the MyD88 and TRIF pathways.[90] The MyD88-dependent signaling pathway activates IKKβ, leading to the degradation of IκB and the subsequent release of NF-κB.[91] As a result, this mechanism stimulates the production of inflammatory cytokines such as IL-1β, IL-6, and TNF-α, which are key factors in driving M1 macrophage polarization.[92] Ori markedly reduced the of expression TLR4 and NF-κB in LPS-activated RAW264.7 macrophages, effectively preventing M1 polarization.[93]

FABP4/PPARγ Signaling Pathway

PPARγ, a nuclear receptor pivotal in energy metabolism and programmed cell death, is critical for IL-4/IL-13-induced M2 macrophage polarization.[94–96] After administering Ori at a dose of 5 mg/kg over seven weeks in mice, researchers observed a marked increase in PPARγ expression.[91] Additionally, Ori regulated ABCA1 expression through LXRα signaling and suppressed the nuclear translocation of NF-κB. Through RNA sequencing analysis, FABP4 emerged as a critical player in mediating Ori's ability to influence lipid metabolism.[91] Overexpression of FABP4 suppressed PPARγ activation, thereby attenuating Ori's regulation of foam cell formation. Thus, Ori likely mitigates atherosclerosis via the FABP4/PPARγ signaling pathway.[97]

JNK Signaling Pathway

The JNK pathway, part of the MAPK family, mediates stress and cytokine signaling in cells.[98] JNK inactivation promotes M2 macrophage polarization.[99] Ori attenuated LPS-induced JNK phosphorylation, facilitating the M1-to-M2 transition.[100]

Notch Signaling Pathway

The evolutionarily conserved Notch pathway governs cell differentiation and apoptosis.[101,102] Notch activation drives M1 macrophage polarization while suppressing M2-associated genes.[103] Ori inhibited Notch signaling, thereby increasing the prevalence of M2 macrophages in peripheral nerves and ameliorating autoimmune neuritis.[75]

AMPK/mTOR Pathway

AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) act as pivotal cellular metabolic sensors; they orchestrate metabolic reprogramming via antagonistic crosstalk.[104] The mTOR promotes glycolysis and lipid metabolism via downstream effectors (eg, SREBP, HIF-1α), whereas AMPK suppresses these pathways. In macrophages, glycolysis promotes the polarization of M1, while oxidative phosphorylation drives the development of macrophages towards the M2.[105] Ori inhibits glycolytic genes (GLUT1, MCT1) by suppressing mTOR phosphorylation, thereby counteracting pro-inflammatory metabolic reprogramming.[100]

Hexokinase 1

Hexokinase 1 (HK1) is a key rate-limiting enzyme in the glycolysis pathway, primarily catalyzing the phosphorylation of glucose to generate 6-phosphogluconic acid (G6P), which is the first step reaction of glycolysis.[106] Recently a study shows Ori forms a covalent bond with Cys-813 adjacent to HK1's glucose-binding domain.[78] This means that Ori can act as a covalent inhibitor of HK1, thereby inhibiting glycolysis in macrophages and causing macrophages to polarize towards the M2.

Clinical Applications of Oridonin

Extensive studies have demonstrated that macrophage polarization plays crucial roles in anti-infection responses and maintaining internal homeostasis.[21] Ori exhibits potential clinical value in treating inflammatory diseases, autoimmune disorders, and malignancies by suppressing M1 macrophages while promoting their conversion to M2 macrophages[9] (Table 2). A multifunctional drug combining hyaluronic acid-conjugated Ori with thermotherapy drives sustained

Table 2 Clinical Applications of Oridonin

Disease	Disease Models	Combined Medication	Molecular Targets or Pathways	Outcome on Macrophage Polarization	Ref.
Metabolic disease	NAFLD		Reduced the levels of inflammatory factors, ROS	M2	[70]
Cardiovascular disease	Atherosclerosis		FABP4/PPARγ	M2	[97]
Skeletal disease	Osteoarthritis		PPAR-γ	M2	[60]
Inflammatory bowel disease	Ulcerative colitis		Sirtuin-1/NF-κB/p53	M2	[108]
Respiratory disease	Asthma		Th1/Th2 cytokine balance	M2	[109]
Diabetic complication	Retinal and vascular lesions		NLRP3	M2	[110]
Diabetic complication	Diabetic chronic wound	Cu(II)-PDA nanoparticles	Modulates the phenotype of macrophages	M2	[111]
Systemic infection	Sepsis		Reduce inflammatory factors	M2	[112]
Cancer	Melanoma	Hyaluronic acid	Drives sustained cytokine-CXCL10 inflammatory loops	M1	[107]
Cancer	Ovarian cancer	Cisplatin	Promote apoptosis		[113]
Cancer	Laryngeal cancer	Cetuximab	Promote apoptosis		[114]
Cancer	AML	HHT	Mitochondrial dysfunction and programmed cell death		[115]

cytokine-CXCL10 inflammatory loops, facilitating macrophage phenotype switching to the M1 state.[107] This enhances the proliferation of tumor-infiltrating natural killer (NK) cells and elevates intra-tumoral IFN-γ levels, thereby inhibiting melanoma progression.[107] Ori hushes the pro-inflammatory M1 polarization of Kupffer cells and fosters a shift toward the anti-inflammatory M2 phenotype, which in turn lessens lipid accumulation in the liver and mitigates liver damage in models of non-alcoholic fatty liver disease (NAFLD).[70] This indicates that Ori could be a promising therapeutic option for treating NAFLD. In atherosclerotic mice, intraperitoneal injection of 5mg/kg Ori for seven weeks enhances macrophage cholesterol efflux, inhibits foam cell formation and inflammatory responses, and alleviates atherosclerosis progression, positioning Ori as a promising preventive agent for atherosclerosis.[97] Studies on chondrocytes from human osteoarthritis have shown that Oridonin reduces the expression of iNOS and COX-2, decreases the activation of NF-κB, and increases the expression of PPAR-γ in a concentration-dependent manner, thereby influencing the polarization of macrophages.[60] These results suggest that Oridonin may be a candidate drug for the treatment of osteoarthritis. In the ulcerative colitis model, Ori reduced the levels of inflammation and oxidative stress through the Sirtuin-1/NF-κB/p53 pathway.[108] Besides, Ori can regulate the Th1/Th2 cytokine balance in the asthma mouse model and exert an anti-asthma effect.[109] Ori has also demonstrated great potential in the treatment of diabetes and its complications. Ori can reverse the activation of the NLRP3 inflammasome, thereby reducing the probability of retinal and vascular lesions and protecting the retina.[110] A hyaluronic acid-based dissolving microneedle system (Cu(II)-PDA/ORI MNs) co-delivers oridonin and Cu(II)-PDA nanoparticles for targeted diabetic chronic wound therapy. ORI encapsulation within MNs modulates RAW264.7 macrophage polarization and exerts potent anti-inflammatory effects, attenuating pathological inflammation in the wound milieu.[111] Oridonin improves survival in septic mice by attenuating systemic inflammation, enhancing bacterial clearance, and mitigating hepatic/pulmonary damage.[112]

Ori can be synergistically combined with various antitumor agents to enhance therapeutic efficacy. In treating ovarian cancer, the blend of oridonin and cisplatin in combination therapy has shown to drastically boost the rate of apoptosis in the combined group when pitted against single-agent treatments. This highlights a noticeable synergy in prompting apoptosis in A2780/DDP cells.[113] Ori enhances cetuximab's apoptotic effect in laryngeal cancer cells via PI3K/Akt pathway regulation.[114] In t(8;21) AML therapy, the Ori-HHT combination improves survival in mouse models.[115] This

treatment suppresses t(8;21) AML cell survival, triggering mitochondrial dysfunction and programmed cell death.[115] These effects are attributed to the synergistic action of oridonin and HHT, which enhances the overall therapeutic efficacy in treating t(8;21) AML.[115] These findings highlight Ori's multifaceted mechanisms in combination therapies for optimized oncology outcomes.

Limitation and Perspectives

Research on Ori's mechanism has primarily verified its effects on classical macrophage polarization markers, yet upstream molecular targets remain undefined. While Ori impacts pathways like NF-κB and MAPK, its direct binding proteins are unidentified, creating a knowledge gap in the initial action steps. Immune metabolism and epigenetics are now recognized as core regulators of immune cell function, but related research remains nascent. Mechanisms of Ori-mediated macrophage energy metabolism reprogramming via AMPK/mTOR to dictate polarization fate are incompletely characterized. Similarly, its potential as an epigenetic regulator in reshaping the landscape and gene expression through histone modifications (eg, acetylation, methylation) and non-coding RNAs (eg, miR-155, miR-146a) demands deeper systematic exploration. In the future, the integration of multi-omics technologies—including transcriptomics, epigenomics, proteomics, and metabolomics—is crucial to systematically map the comprehensive response of macrophages to oridonin treatment. This would move beyond the analysis of a few select markers to provide an unbiased, global view of the gene regulatory networks, signaling pathways, and metabolic shifts involved, thereby identifying novel targets and biomarkers of efficacy.

In terms of research methods, the majority of current evidence comes from in vitro cell experiments. These experimental conditions are usually simplified and high-concentration, and lack the complex micro-environmental factors present in the living body. Therefore, it is a major question whether the significant effects observed in vitro can be replicated in a complex living environment. Furthermore, most studies have focused solely on macrophages themselves, without considering their indirect effects on other key cells within the immune network. Therefore, there is a pressing need to establish standardized and physiologically relevant experimental models. This includes employing advanced in vitro systems like human primary macrophage co-cultures and organoids, and developing more refined in vivo disease models that accurately reflect the human immune microenvironment and the chronic nature of macrophage-mediated diseases.

Finally, and most crucially, the challenge lies in Ori's own physical, chemical and pharmacokinetic deficiencies. Ori is almost insoluble in water, resulting in low bioavailability and poor oral absorption.[116] It requires the use of organic solvents or surfactants for solubilization, but long-term intravenous administration may cause adverse reactions such as vascular inflammation.[116] This compound is sensitive to heat and is prone to degradation during preparation and storage. Especially in high-temperature and high-humidity environments, its content decreases significantly, affecting the quality control of the formulation and the stability of efficacy within the prescribed period.[117] Although through structural modification, the activity and solubility can be partially improved, many derivatives still have not fundamentally solved the problems of water solubility and targeting, and the specific target point is unclear, lacking precise drug design basis. These problems severely restrict the stable exertion of its efficacy and clinical translation. In the absence of an efficient targeted delivery system, most drugs may not reach the macrophages in the lesion site, making the in vitro mechanism impossible to be realized in vivo.

To overcome these challenges, advanced drug delivery strategies and formulation design can be relied upon. By encapsulating Ori in liposomes, polymer nanoparticles, micelles or solid lipid nanoparticles, the apparent solubility of Ori can be significantly increased, preventing its premature metabolism and clearance in the body. At the same time, by taking advantage of the high permeability and retention effect of solid tumor tissues, or the high permeability of blood vessels in inflammatory sites, the nanoparticles can selectively accumulate at the lesion site. Furthermore, solubility and bioavailability can be enhanced through the use of co-crystals. Cocrystallization of Ori with nicotinamide (ORI-NCT) enhanced aqueous solubility by 34% and oral bioavailability by 18% versus pure Ori.[118]

Network pharmacology and artificial intelligence (AI) can be utilized to explore new drug delivery methods. Network pharmacology can elucidate the complex "compound-target-pathway-disease" interactions of oridonin, aligning with its multi-target nature. Meanwhile, AI and machine learning algorithms can accelerate this process by analyzing vast omics datasets, predicting new therapeutic indications, optimizing drug design, and personalizing treatment strategies by identifying patient subgroups most likely to respond.

Conclusions

Ori exhibits extensive biological activities, demonstrating significant therapeutic potential in anti-inflammatory, antitumor, anti-osteoporotic, and neuroprotective applications. Ori impacts various targets and signaling mechanisms, such as the NLRP3 inflammasome, NF-κB, MAPK, and Wnt/β-catenin pathways. Notably, Ori modulates macrophage polarization by regulating pathways such as PI3K/Akt pathway, ROS/NF-κB pathway, TLR4/NF-κB pathway, FABP4/PPARγ pathway, JNK pathway, AMPK/mTOR Pathway, Notch pathway and Hexokinase 1, thereby suppressing M1 macrophage polarization and promoting their transition to the M2 phenotype. This regulatory role in macrophage polarization provides novel insights for developing immunomodulatory therapies targeting inflammatory diseases, malignancies, and autoimmune disorders. Furthermore, Ori demonstrates enhanced pharmacological activity when combined with other agent. However, due to problems such as poor water solubility and low bioavailability of Ori, its application scope is not extensive. These pharmacokinetic challenges markedly restrict its therapeutic applications despite promising preclinical efficacy. To address these critical problems, future research should further study different derivatives of Ori to improve its shortcomings and magnify its advantages. Such structural optimization strategies may establish a robust foundation for developing novel Ori-related drugs, thereby offering new directions for oncology and anti-inflammatory drug development.

Although Ori's regulation of macrophage polarization is linked to the pathways mentioned before, its precise molecular mechanisms remain unclear. Future studies should focus on elucidating these mechanisms and evaluating Ori's efficacy and safety across diverse disease models to establish a robust scientific foundation for clinical translation.

Abbreviations

Ori, Oridonin; RTMs, tissue-resident macrophages; LPS, lipopolysaccharide; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1β; COX-2, cyclooxygenase-2; iNOS, nitric oxide synthase; Arg1 arginase 1; GC, glucocorticoids; Tregs, regulatory T cells; IL-18, interleukin-18; PXR, pregnane X receptor; ROS, reactive oxygen species; NSCLC, non-small cell lung cancer; VEGF, vascular endothelial growth factor; MMPs, matrix metalloproteinases; NAFLD, non-alcoholic fatty liver disease; ATP, adenosine triphosphate; OXPHOS, Oxidative phosphorylation; AMPK, AMP-activated protein kinase, mTOR, mammalian target of rapamycin, HK1, Hexokinase 1; AI, artificial intelligence.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Author Contributions

Yingying Han: Conceptualization, Writing - Original Draft; **Zhenping Zheng**: Validation, Writing – Review & Editing; **Mo Chen**: Formal analysis, Writing - Review & Editing; **Kangjie Xie**: Funding acquisition, Project administration, Visualization, Writing – Review & Editing. All authors gave final approval of the version to be published, agreed to the journal this paper was submitted, agree to be accountable for the content of this paper.

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Disclosure

The authors declare that they have no conflict of interest.

References

1. Owona BA, Schluesener HJ. Molecular insight in the multifunctional effects of oridonin. *Drugs R D*. 2015;15(3):233–244. doi:10.1007/s40268-015-0102-z
2. Xie W, Ma Y, Sun W, Guan S, Jin Y, Du Y. An integrative method based on UHPLC-Q-TOF-MS/MS combined with metabolomics to authenticate isodon rubescens. *Anal Biochem*. 2021;629:114297. doi:10.1016/j.ab.2021.114297

3. Leung CH, Grill SP, Lam W, Han QB, Sun HD, Cheng YC. Novel mechanism of inhibition of nuclear factor-kappa B DNA-binding activity by diterpenoids isolated from isodon rubescens. *Mol Pharmacol*. 2005;68(2):286–297. doi:10.1124/mol.105.012765
4. Xue M, Yin HJ, Wu CF, et al. Effect of Chinese drugs for activating blood circulation and detoxifying on indices of thrombosis, inflammatory reaction, and tissue damage in a rabbit model of toxin-heat and blood stasis syndrome. *Chin J Integr Med*. 2013;19(1):42–47. doi:10.1007/s11655-011-0604-7
5. Li Z, Chen SM, He X, Gong SY, Sun LQ, Weng L. SLC3A2 promotes tumor-associated macrophage polarization through metabolic reprogramming in lung cancer. *Cancer Science*. 2023;114(6):2306–2317. doi:10.1111/cas.15760
6. Pan T, Zhou Q, Miao K, et al. Suppressing Sart1 to modulate macrophage polarization by siRNA-loaded liposomes: a promising therapeutic strategy for pulmonary fibrosis. *Theranostics*. 2021;11(3):1192–1206. doi:10.7150/thno.48152
7. Huang YY, Zhang GX, Li S, Feng J, Zhang ZT. Innate and adaptive immunity in neurodegenerative disease. *Cell Mol Life Sci*. 2025;82(1). doi:10.1007/s00018-024-05533-4
8. Atri C, Guerfali FZ, Laouini D. Role of human macrophage polarization in inflammation during infectious diseases. *Int J Mol Sci*. 2018;19(6):1801. doi:10.3390/ijms19061801
9. Chen Y, Hu M, Wang L, Chen W. Macrophage M1/M2 polarization. *Eur J Pharmacol*. 2020;877. doi:10.1016/j.ejphar.2020.173090
10. Dan H, Liu S, Liu J, et al. RACK1 promotes cancer progression by increasing the M2/M1 macrophage ratio via the NF-jB pathway in oral squamous cell carcinoma. *Mol oncol*. 2020;14(4):795–807. doi:10.1002/1878-0261.12644
11. Xu J, Wold EA, Ding Y, Shen Q, Zhou J. Therapeutic potential of oridonin and its analogs: from anticancer and antiinflammation to neuroprotection. *Molecules*. 2018;23(2):474. doi:10.3390/molecules23020474
12. Bennett H, Troutman TD, Sakai M, Glass CK. Epigenetic regulation of kupffer cell function in health and disease. *Front Immunol*. 2021;11. doi:10.3389/fimmu.2020.609618
13. Peng Y, Zhou M, Yang H, et al. Regulatory mechanism of M1/M2 macrophage polarization in the development of autoimmune diseases. *Mediators Inflamm*. 2023;2023:1–20. doi:10.1155/2023/8821610
14. Seok SJ, Lee ES, Kim GT, et al. Blockade of CCL2/CCR2 signalling ameliorates diabetic nephropathy in db/db mice. *Nephrol Dial Transplant*. 2013;28(7):1700–1710. doi:10.1093/ndt/gfs555
15. Tomomasa Y, Elaine D. Three-dimensional cartography of hematopoietic clusters in the vasculature of whole mouse embryos. *Development*. 2010;137(21). doi:10.1242/dev.051094
16. Arami H, Khandhar A, Liggitt D, Krishnan KM. In vivo delivery, pharmacokinetics, biodistribution and toxicity of iron oxide nanoparticles. *Chem Soc Rev*. 2015;44(23):8576–8607. doi:10.1039/C5CS00541H
17. Jenkins SJ, Ruckerl D, Cook PC, et al. Local macrophage proliferation, rather than recruitment from the blood, is a signature of TH2 inflammation. *Science*. 2011;332(6035):1284–1288. doi:10.1126/science.1204351
18. Bain CC, Hawley CA, Garner H, et al. Long-lived self-renewing bone marrow-derived macrophages displace embryo-derived cells to inhabit adult serous cavities. *Nat Commun*. 2016:7:ncomms11852. doi:10.1038/ncomms11852
19. Florent G, Melanie G, Marylene L, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science*. 2010;330(6005). doi:10.1126/science.1194637
20. Nishit D, Albert JS, Jonathan BG, et al. Cell-based drug delivery devices using phagocytosis-resistant backpacks. *Adv Mater*. 2011;23(12). doi:10.1002/adma.201004074
21. Shapouri-Moghaddam A, Mohammadian S, Vazini H, et al. Macrophage plasticity, polarization, and function in health and disease. *J Cell Physiol*. 2018;233(9):6425–6440. doi:10.1002/jcp.26429
22. Viola A, Munari F, Sánchez-Rodríguez R, Scolaro T, Castegna A. The metabolic signature of macrophage responses. *Front Immunol*. 2019;10:1462. doi:10.3389/fimmu.2019.01462
23. He C, Carter AB. The metabolic prospective and redox regulation of macrophage polarization. *J Clin Cell Immunol*. 2015;6(6). doi:10.4172/2155-9899.1000371
24. Ting W, Huiying L, Guan L, Songyang Z, Xian W, Changtao J. HIF1 α-induced glycolysis metabolism is essential to the activation of inflammatory macrophages. *Mediators Inflamm*. 2017;2017. doi:10.1155/2017/9029327
25. Tamás R. Understanding the mysterious M2 macrophage through activation markers and effector mechanisms. *Mediators Inflamm*. 2015;2015. doi:10.1155/2015/816460
26. Abdelaziz MH, Abdelwahab SF, Wan J, et al. Alternatively activated macrophages; a double-edged sword in allergic asthma. *J Transl Med*. 2020;18(1). doi:10.1186/s12967-020-02251-w
27. Ionescu IC, Corbu CG, Tanase C, et al. Overexpression of tear inflammatory cytokines as additional finding in keratoconus patients and their first degree family members. *Mediators Inflamm*. 2018;2018(1):4285268. doi:10.1155/2018/4285268
28. Je IG, Kim HH, Park PH, et al. SG-HQ2 inhibits mast cell-mediated allergic inflammation through suppression of histamine release and pro-inflammatory cytokines. *Exp Biol Med*. 2015;240(5):631–638. doi:10.1177/1535370214555663
29. Qi C, Yiping W, Dong Z, et al. IL-10/TGF-beta-modified macrophages induce regulatory T cells and protect against Adriamycin nephrosis. *J Am Soc Nephrol*. 2010;21(6). doi:10.1681/ASN.2009060592
30. Katarzyna B, Jan E, Klaus T, et al. Glucocorticoids promote survival of anti-inflammatory macrophages via stimulation of adenosine receptor A3. *Blood*. 2010;116(3). doi:10.1182/blood-2009-10-247106
31. Balázs K, Balázs C, Endre K, et al. Adenosine augments IL-10-induced STAT3 signaling in M2c macrophages. *J Leukoc Biol*. 2013;94(6). doi:10.1189/jlb.0113043
32. Christopher JF, Grace PE, Genie E, et al. The adenosine-dependent angiogenic switch of macrophages to an M2-like phenotype is independent of interleukin-4 receptor alpha (IL-4Rα) signaling. *Inflammation*. 2013;36(4). doi:10.1007/s10753-013-9621-3
33. Shanze C, Abdullah FUHS, Quan L, et al. Macrophages in immunoregulation and therapeutics. *Signal Transduct Target Ther*. 2023;8(1). doi:10.1038/s41392-023-01452-1
34. Shruti B, Amita A. M2 macrophages and their role in rheumatic diseases. *Rheumatol Int*. 2019;39(5). doi:10.1007/s00296-018-4120-3
35. Ling L, Yang J, Kebin H. Tissue-type plasminogen activator (tPA) promotes M1 macrophage survival through p90 ribosomal S6 kinase (RSK) and p38 mitogen-activated protein kinase (MAPK) pathway. *J Biol Chem*. 2015;290(12). doi:10.1074/jbc.M114.599688

36. Hikichi M, Mizumura K, Maruoka S, Gon Y. Pathogenesis of chronic obstructive pulmonary disease (COPD) induced by cigarette smoke. *J Thorac Dis*. 2019;11(Suppl 17):S2129–S2140. doi:10.21037/jtd.2019.10.43
37. Fangda L, Paul E. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat Rev Neurol*. 2021;17(3). doi:10.1038/s41582-020-00435-y
38. Medina MÁ. Metabolic reprogramming is a hallmark of metabolism itself. *Bioessays*. 2020;42(10):e2000058. doi:10.1002/bies.202000058
39. Alfarouk KO, Verduzco D, Rauch C, et al. Glycolysis, tumor metabolism, cancer growth and dissemination. A new pH-based etiopathogenic perspective and therapeutic approach to an old cancer question. *Oncoscience*. 2014;1(12):777–802. doi:10.18632/oncoscience.109
40. Kalyanaraman B, Cheng G, Hardy M, You M. OXPHOS-targeting drugs in oncology: new perspectives. *Expert Opin Ther Targets*. 2023;27 (10):939–952. doi:10.1080/14728222.2023.2261631
41. Ye L, Jiang Y, Zhang M. Crosstalk between glucose metabolism, lactate production and immune response modulation. *Cytokine Growth Factor Rev*. 2022;68:81–92. doi:10.1016/j.cytogfr.2022.11.001
42. He H, Jiang H, Chen Y, et al. Oridonin is a covalent NLRP3 inhibitor with strong anti-inflammasome activity. *Nat Commun*. 2018;9(1):2550. doi:10.1038/s41467-018-04947-6
43. Fangyuan Z, Haiyang G, Luorui S, et al. Oridonin promotes endoplasmic reticulum stress via TP53-repressed TCF4 transactivation in colorectal cancer. *J Exp Clin Cancer Res*. 2023;42(1). doi:10.1186/s13046-023-02702-4
44. Zhang ZY, Daniels R, Schluesener HJ. Oridonin ameliorates neuropathological changes and behavioural deficits in a mouse model of cerebral amyloidosis. *J Cell Mol Med*. 2013;17(12):1566–1576. doi:10.1111/jcmm.12124
45. Yu F, Chang J, Li J, et al. Protective effects of oridonin against osteoporosis by regulating immunity and activating the Wnt3a/β-catenin/VEGF pathway in ovariectomized mice. *Int Immunopharmacol*. 2023;118:110011. doi:10.1016/j.intimp.2023.110011
46. Li X, Chen C, Chen Y, et al. Oridonin ameliorates ocular surface inflammatory responses by inhibiting the NLRP3/caspase-1/GSDMD pyroptosis pathway in dry eye. *Exp Eye Res*. 2024;245:109955. doi:10.1016/j.exer.2024.109955
47. Wang L, Zhao X, Ding J, et al. Oridonin attenuates the progression of atherosclerosis by inhibiting NLRP3 and activating Nrf2 in apolipoprotein E-deficient mice. *Inflammopharmacology*. 2023;31(4):1993–2005. doi:10.1007/s10787-023-01161-9
48. Shao YY, Guo Y, Feng XJ, et al. Oridonin attenuates TNBS-induced post-inflammatory irritable bowel syndrome via PXR/NF-κB signaling. *Inflammation*. 2021;44(2):645–658. doi:10.1007/s10753-020-01364-0
49. Tan RZ, Yan Y, Yu Y, et al. Renoprotective effect of oridonin in a mouse model of acute kidney injury via suppression of macrophage involved inflammation. *Biol Pharm Bull*. 2021;44(5):714–723. doi:10.1248/bpb.b21-00071
50. Jiang JH, Pi J, Jin H, Cai JY. Oridonin-induced mitochondria-dependent apoptosis in esophageal cancer cells by inhibiting PI3K/AKT/mTOR and Ras/Raf pathways. *J Cell Biochem*. 2019;120(3):3736–3746. doi:10.1002/jcb.27654
51. Xu L, Jiang Y, Bi Y, et al. Suppression of PERK/eIF2α/CHOP pathway enhances oridonin-induced apoptosis by inhibiting autophagy in small-cell lung cancer cells. *Biomed Pharmacother*. 2024;175:116684. doi:10.1016/j.biopha.2024.116684
52. Xiao X, He Z, Cao W, et al. Oridonin inhibits gefitinib-resistant lung cancer cells by suppressing EGFR/ERK/MMP-12 and CIP2A/Akt signaling pathways. *Int J Oncol*. 2016;48(6):2608–2618. doi:10.3892/ijo.2016.3488
53. Zhang W, Shi L, Zhou W, et al. Oridonin impedes breast cancer growth by blocking cells in S phase and inhibiting the PI3K/AKT/mTOR signaling pathway. *Heliyon*. 2023;9(7):e18046. doi:10.1016/j.heliyon.2023.e18046
54. Lu J, Chen X, Qu S, et al. Oridonin induces G2/M cell cycle arrest and apoptosis via the PI3K/Akt signaling pathway in hormone-independent prostate cancer cells. *Oncol Lett*. 2017;13(4):2838–2846. doi:10.3892/ol.2017.5751
55. Hu H, Yang Y, Xu X, et al. Oridonin induces apoptosis via PI3K/Akt pathway in cervical carcinoma HeLa cell line. *Acta Pharmacol Sin*. 2007;28(11):1819–1826. doi:10.1111/j.1745-7254.2007.00667.x
56. Wang H, Ye Y, Chui JH, et al. Oridonin induces G2/M cell cycle arrest and apoptosis through MAPK and p53 signaling pathways in HepG2 cells. *Oncol Rep*. 2010;24(3):647–651.
57. Bao R, Shu Y, Wu X, et al. Oridonin induces apoptosis and cell cycle arrest of gallbladder cancer cells via the mitochondrial pathway. *BMC Cancer*. 2014;14:217. doi:10.1186/1471-2407-14-217
58. Yang J, Ren X, Zhang L, Li Y, Cheng B, Xia J. Oridonin inhibits oral cancer growth and PI3K/Akt signaling pathway. *Biomed Pharmacother*. 2018;100:226–232. doi:10.1016/j.biopha.2018.02.011
59. Jin X, Xu J, Yang F, et al. Oridonin attenuates thioacetamide-induced osteoclastogenesis through MAPK/NF-κB pathway and thioacetamide-inhibited osteoblastogenesis through BMP-2/RUNX2 pathway. *Calcif Tissue Int*. 2023;112(6):704–715. doi:10.1007/s00223-023-01080-5
60. Jia T, Cai M, Ma X, Li M, Qiao J, Chen T. Oridonin inhibits IL-1β-induced inflammation in human osteoarthritis chondrocytes by activating PPAR-γ. *Int Immunopharmacol*. 2019;69:382–388. doi:10.1016/j.intimp.2019.01.049
61. Fu J, Wu H. Structural mechanisms of NLRP3 inflammasome assembly and activation. *Annu Rev Immunol*. 2023;41:301–316. doi:10.1146/annurev-immunol-081022-021207
62. Freddie B, Mathieu L, Hyuna S, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA*. 2024;74(3). doi:10.3322/caac.21834
63. Fan X, Wang T, Ji Z, Li Q, Shen H, Wang J. Synergistic combination therapy of lung cancer using lipid-layered cisplatin and oridonin co-encapsulated nanoparticles. *Biomed Pharmacother*. 2021;141:111830. doi:10.1016/j.biopha.2021.111830
64. Xuguang L, Weirun C, Kaihang L, et al. Oridonin sensitizes hepatocellular carcinoma to the anticancer effect of sorafenib by targeting the akt pathway. *Cancer Manag Res*. 2020;7(12):8081–8091. doi:10.2147/CMAR.S257482
65. Zhang Z, Zhang X, Xue W, et al. Effects of oridonin nanosuspension on cell proliferation and apoptosis of human prostatic carcinoma PC-3 cell line. *Int J Nanomed*. 2010;5:735–742. doi:10.2147/IJN.S13537
66. Gao S, Li J, Wang W, Wang Y, Shan Y, Tan H. *Rabdosia rubescens* (Hemsl.) H. Hara: a potent anti-tumor herbal remedy — botany, phytochemistry, and clinical applications and insights. *J Ethnopharmacol*. 2025;340:119200. doi:10.1016/j.jep.2024.119200
67. Li MX, Wang HY, Yuan CH, et al. KLHDC7B-DT aggravates pancreatic ductal adenocarcinoma development via inducing cross-talk between cancer cells and macrophages. *Clin Sci*. 2021;135(4):629–649. doi:10.1042/CS20201259
68. Kroner A, Greenhalgh AD, Zarruk JG, Passos Dos Santos R, Gaestel M, David S. TNF and increased intracellular iron alter macrophage polarization to a detrimental M1 phenotype in the injured spinal cord. *Neuron*. 2014;83(5):1098–1116. doi:10.1016/j.neuron.2014.07.027

69. Zhang J, Liu X, Wan C, et al. NLRP3 inflammasome mediates M1 macrophage polarization and IL-1β production in inflammatory root resorption. *J Clin Periodontol*. 2020;47(4):451–460. doi:10.1111/jcpe.13258
70. Zhu Y, Ruan S, Shen H, Guan Q, Zhai L, Yang Y. Oridonin regulates the polarized state of Kupffer cells to alleviate nonalcoholic fatty liver disease through ROS-NF-κB. *Int Immunopharmacol*. 2021;101(Pt B):108290. doi:10.1016/j.intimp.2021.108290
71. Gao RF, Li X, Xiang HY, et al. The covalent NLRP3-inflammasome inhibitor Oridonin relieves myocardial infarction induced myocardial fibrosis and cardiac remodeling in mice. *Int Immunopharmacol*. 2021;90:107133. doi:10.1016/j.intimp.2020.107133
72. Van Dyken SJ, Locksley RM. Interleukin-4- and interleukin-13-mediated alternatively activated macrophages: roles in homeostasis and disease. *Annu Rev Immunol*. 2013;31:317–343. doi:10.1146/annurev-immunol-032712-095906
73. Zhang M, Liu K, Zhang Q, et al. Alpha fetoprotein promotes polarization of macrophages towards M2-like phenotype and inhibits macrophages to phagocytize hepatoma cells. *Front Immunol*. 2023;14:1081572. doi:10.3389/fimmu.2023.1081572
74. Nawaz A, Aminuddin A, Kado T, et al. CD206+ M2-like macrophages regulate systemic glucose metabolism by inhibiting proliferation of adipocyte progenitors. *Nat Commun*. 2017;8(1):286. doi:10.1038/s41467-017-00231-1
75. Xu L, Li L, Zhang CY, Schluesener H, Zhang ZY. Natural diterpenoid oridonin ameliorates experimental autoimmune neuritis by promoting anti-inflammatory macrophages through blocking notch pathway. *Front Neurosci*. 2019;13:272. doi:10.3389/fnins.2019.00272
76. Liu J, Zhang Q, Wong YK, et al. Single-cell transcriptomics reveals the ameliorative effect of oridonin on septic liver injury. *Adv Biol*. 2024;8 (3):e2300542. doi:10.1002/adbi.202300542
77. Kelly B, O'Neill LAJ. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. *Cell Res*. 2015;25(7):771–784. doi:10.1038/cr.2015.68
78. Liu S, Wang X, Sun X, et al. Oridonin inhibits bladder cancer survival and immune escape by covalently targeting HK1. *Phytomedicine*. 2024;126:155426. doi:10.1016/j.phymed.2024.155426
79. Assmann N, Finlay DK. Metabolic regulation of immune responses: therapeutic opportunities. *J Clin Invest*. 2016;126(6):2031–2039. doi:10.1172/JCI83005
80. American Association of Neurological Surgeons (AANS), American Society of Neuroradiology (ASNR), Cardiovascular and Interventional Radiology Society of Europe (CIRSE), Canadian Interventional Radiology Association (CIRA), Congress of Neurological Surgeons (CNS), European Society of Minimally Invasive Neurological Therapy (ESMINT), European Society of Neuroradiology (ESNR), European Stroke Organization (ESO), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Interventional Radiology (SIR), Society of NeuroInterventional Surgery (SNIS), and World Stroke Organization (WSO), Sacks D, Baxter B, Baxter B, et al. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. *Int J Stroke*. 2018;13(6):612–632. doi:10.1177/1747493018778713
81. Wang H, Ye Y, Yu ZL. Proteomic and functional analyses demonstrate the involvement of oxidative stress in the anticancer activities of oridonin in HepG2 cells. *Oncol Rep*. 2014;31(5):2165–2172. doi:10.3892/or.2014.3081
82. Li T, Wang G. Computer-aided targeting of the PI3K/Akt/mTOR pathway: toxicity reduction and therapeutic opportunities. *Int J Mol Sci*. 2014;15(10):18856–18891. doi:10.3390/ijms151018856
83. Lin CH, Cheng HW, Ma HP, Wu CH, Hong CY, Chen BC. Thrombin induces NF-kappaB activation and IL-8/CXCL8 expression in lung epithelial cells by a Rac1-dependent PI3K/Akt pathway. *J Biol Chem*. 2011;286(12):10483–10494. doi:10.1074/jbc.M110.112433
84. Chen X, Tang J, Shuai W, Meng J, Feng J, Han Z. Macrophage polarization and its role in the pathogenesis of acute lung injury/acute respiratory distress syndrome. *Inflamm Res*. 2020;69(9):883–895. doi:10.1007/s00011-020-01378-2
85. Yan Y, Tan RZ, Liu P, et al. Oridonin alleviates IRI-induced kidney injury by inhibiting inflammatory response of macrophages via AKT-related pathways. *Med Sci Monit*. 2020:26:e921114. doi:10.12659/MSM.921114
86. Dröge W. Free radicals in the physiological control of cell function. *Physiol Rev*. 2002;82(1):47–95. doi:10.1152/physrev.00018.2001
87. Sivandzade F, Prasad S, Bhalerao A, Cucullo L. NRF2 and NF-κB interplay in cerebrovascular and neurodegenerative disorders: molecular mechanisms and possible therapeutic approaches. *Redox Biol*. 2019;21:101059. doi:10.1016/j.redox.2018.11.017
88. Chen Y, Gao P, Pan W, et al. Polyvalent spherical aptamer engineered macrophages: x-ray-actuated phenotypic transformation for tumor immunotherapy. *Chem Sci*. 2021;12(41):13817–13824. doi:10.1039/d1sc03997k
89. Yang H, Lv H, Li H, Ci X, Peng L. Oridonin protects LPS-induced acute lung injury by modulating Nrf2-mediated oxidative stress and Nrf2-independent NLRP3 and NF-κB pathways. *Cell Commun Signal*. 2019;17(1):62. doi:10.1186/s12964-019-0366-y
90. Dempsey PW, Vaidya SA, Cheng G. The art of war: innate and adaptive immune responses. *Cell Mol Life Sci*. 2003;60(12):2604–2621. doi:10.1007/s00018-003-3180-y
91. Vaez H, Soraya H, Garjani A, Gholikhani T. Toll-like receptor 4 (TLR4) and AMPK relevance in cardiovascular disease. *Adv Pharm Bull*. 2023;13(1):36–47. doi:10.34172/apb.2023.004
92. Kerneur C, Cano CE, Olive D. Major pathways involved in macrophage polarization in cancer. *Front Immunol*. 2022;13. doi:10.3389/fimmu.2022.1026954
93. Zang L, Wang J, Ren Y, et al. Activated toll-like receptor 4 is involved in oridonin-induced phagocytosis via promotion of migration and autophagy-lysosome pathway in RAW264.7 macrophages. *Int Immunopharmacol*. 2019;66:99–108. doi:10.1016/j.intimp.2018.11.014
94. Schmidt MV, Brüne B, von Knethen A. The nuclear hormone receptor PPARγ as a therapeutic target in major diseases. *Sci World J*. 2010;10:2181–2197. doi:10.1100/tsw.2010.213
95. Wang H, Wang A, Wang X, Zeng X, Xing H. AMPK/PPAR-γ/NF-κB axis participates in ROS-mediated apoptosis and autophagy caused by cadmium in pig liver. *Environ Pollut*. 2022;294:118659. doi:10.1016/j.envpol.2021.118659
96. Ryan KK, Li B, Grayson BE, Matter EK, Woods SC, Seeley RJ. A role for central nervous system PPAR-γ in the regulation of energy balance. *Nat Med*. 2011;17(5):623–626. doi:10.1038/nm.2349
97. Ming Z, Lianjie H, Wanying T, et al. Oridonin attenuates atherosclerosis by inhibiting foam macrophage formation and inflammation through FABP4/PPARγ signalling. *J Cell & Mol Med*. 2023;27(24). doi:10.1111/jcmm.18000
98. Zhou D, Huang C, Lin Z, et al. Macrophage polarization and function with emphasis on the evolving roles of coordinated regulation of cellular signaling pathways. *Cell Signal*. 2014;26(2):192–197. doi:10.1016/j.cellsig.2013.11.004
99. Wan S, Sun H. Glucagon-like peptide-1 modulates RAW264.7 macrophage polarization by interfering with the JNK/STAT3 signaling pathway. *Exp Ther Med*. 2019;17(5):3573–3579. doi:10.3892/etm.2019.7347

100. Huang JH, Lan CC, Hsu YT, et al. Oridonin attenuates lipopolysaccharide-induced ros accumulation and inflammation in HK-2 cells. *Evid Based Complement Alternat Med*. 2020;2020:9724520. doi:10.1155/2020/9724520
101. Perumalsamy LR, Nagala M, Sarin A. Notch-activated signaling cascade interacts with mitochondrial remodeling proteins to regulate cell survival. *Proc Natl Acad Sci U S A*. 2010;107(15):6882–6887. doi:10.1073/pnas.0910060107
102. Zanotti S, Canalis E. Notch signaling and the skeleton. *Endocr Rev*. 2016;37(3):223–253. doi:10.1210/er.2016-1002
103. Wang YC, He F, Feng F, et al. Notch signaling determines the M1 versus M2 polarization of macrophages in antitumor immune responses. *Cancer Res*. 2010;70(12):4840–4849. doi:10.1158/0008-5472.CAN-10-0269
104. Hindupur SK, González A, Hall MN. The opposing actions of target of rapamycin and AMP-activated protein kinase in cell growth control. *Cold Spring Harb Perspect Biol*. 2015;7(8):a019141. doi:10.1101/cshperspect.a019141
105. Dickson BM, Roelofs AJ, Rochford JJ, Wilson HM, De Bari C. The burden of metabolic syndrome on osteoarthritic joints. *Arthritis Res Ther*. 2019;21(1):289. doi:10.1186/s13075-019-2081-x
106. Ediriweera MK, Jayasena S. The role of reprogrammed glucose metabolism in cancer. *Metabolites*. 2023;13(3):345. doi:10.3390/metabo13030345
107. Xin X, Zhou Y, Li J, Zhang K, Qin C, Yin L. CXCL10-coronated thermosensitive "stealth" liposomes for sequential chemoimmunotherapy in melanoma. *Nanomedicine*. 2023;48:102634. doi:10.1016/j.nano.2022.102634
108. Wang M, Xu B, Liu L, Wang D. Oridonin attenuates dextran sulfate sodium-induced ulcerative colitis in mice via the Sirt1/NF-κB/p53 pathway. *Mol Med Rep*. 2022;26(4):312. doi:10.3892/mmr.2022.12828
109. Wang J, Li F, Ding J, et al. Investigation of the anti-asthmatic activity of oridonin on a mouse model of asthma. *Mol Med Rep*. 2016;14(3):2000–2006. doi:10.3892/mmr.2016.5485
110. Zhang Y, Pan T, Yang Y, Xu X, Liu Y. Oridonin attenuates diabetic retinopathy progression by suppressing NLRP3 inflammasome pathway. *Mol Cell Endocrinol*. 2025;596:112419. doi:10.1016/j.mce.2024.112419
111. Nan W, Wang H, Li L, et al. Microneedles incorporating oridonin micelles and Cu(II)-polydopamine provide effective inflammatory regulation and antibacterial effects for the healing of infected diabetic wounds. *Colloids Surf B Biointerfaces*. 2025;254:114814. doi:10.1016/j.colsurfb.2025.114814
112. Zhao YJ, Lv H, Xu PB, et al. Protective effects of oridonin on the sepsis in mice. *Kaohsiung J Med Sci*. 2016;32(9):452–457. doi:10.1016/j.kjms.2016.07.013
113. Ma S, Tan W, Du B, et al. Oridonin effectively reverses cisplatin drug resistance in human ovarian cancer cells via induction of cell apoptosis and inhibition of matrix metalloproteinase expression. *Mol Med Rep*. 2016;13(4):3342–3348. doi:10.3892/mmr.2016.4897
114. Cao S, Xia M, Mao Y, et al. Combined oridonin with cetuximab treatment shows synergistic anticancer effects on laryngeal squamous cell carcinoma: involvement of inhibition of EGFR and activation of reactive oxygen species-mediated JNK pathway. *Int J Oncol*. 2016;49(5):2075–2087. doi:10.3892/ijo.2016.3696
115. Zhang W, Lu Y, Zhen T, et al. Homoharringtonine synergy with oridonin in treatment of t(8; 21) acute myeloid leukemia. *Front Med*. 2019;13(3):388–397. doi:10.1007/s11684-018-0624-1
116. Zhang Y, Wang S, Dai M, Nai J, Zhu L, Sheng H. Solubility and Bioavailability Enhancement of Oridonin: a Review. *Molecules*. 2020;25(2):332. doi:10.3390/molecules25020332
117. Xu J, Zhao J, Wang J, Feng N, Tan R, Liu Y. Study on stability of oridonin solution. *Zhongguo Zhong Yao Za Zhi*. 2009;34(1):47–49.
118. Jia XM, Hao H, Zhang Q, et al. The bioavailability enhancement and insight into the action mechanism of poorly soluble natural compounds from co-crystals preparation: oridonin as an example. *Phytomedicine*. 2024;122:155179. doi:10.1016/j.phymed.2023.155179