Journal of Contemporary Medical Practice (JCMP) ISSN: 2006-2745
DOI: 10.53469/jcmp.2026.08(01).24

The Role of Macrophage Activation and Polarization in Heart Failure and the Intervention of Traditional Chinese Medicine

Ting Zhang[1], Dongmin Liu[1,2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
**Correspondence Author*

Abstract: ***Heart failure (HF) is a clinical syndrome characterized by insufficient cardiac output due to structural or functional abnormalities of the heart, resulting in inadequate tissue perfusion. It typically presents with symptoms such as dyspnea and pulmonary congestion or edema. HF is associated with high morbidity and mortality and is often accompanied by persistent activation of the immune system and systemic inflammatory responses. The imbalance of M1/M2 macrophage polarization plays a critical role in the processes of inflammation, fibrosis, and angiogenesis in HF. Traditional Chinese medicine (TCM) has demonstrated unique advantages in regulating macrophage polarization, suppressing inflammation, and delaying HF progression through its multi-target and multi-pathway actions, which have gained increasing attention from researchers both domestically and internationally. This review focuses on the characteristics and metabolic mechanisms of macrophage polarization, highlights their roles in inflammation, metabolic reprogramming, and myocardial fibrosis in HF, and summarizes recent advances in TCM-based interventions targeting macrophage polarization in HF. It aims to provide theoretical support and research directions for developing novel therapeutic strategies and expanding the clinical application of TCM.***

Keywords: Macrophages, Heart failure, Traditional Chinese medicine (TCM).

1. Introduction

Heart failure (HF) is a clinical syndrome characterized by structural and/or functional abnormalities of the heart, manifested as reduced cardiac output and/or impaired ventricular filling. This leads to inadequate perfusion of tissues and organs, failing to meet the body's metabolic demands, and is accompanied by symptoms such as fluid retention, dyspnea, and fatigue [1]. Based on the latest 2024 epidemiological data, the prevalence of HF among individuals aged ≥25 years in China has reached 1.1%, with an estimated 12.1 million existing patients. Since 2000, the incidence, mortality, disability rates, and readmission rates of HF have shown an overall upward trend [2,3]. The progression of heart failure is often accompanied by immune system activation, manifested by the release of local inflammatory factors and upregulation of pro-inflammatory transcription factors, which subsequently trigger systemic inflammatory responses [4]. As one of the core cells of the immune system, macrophages participate in pathological processes such as cardiac inflammation, fibrosis, and ventricular remodeling by regulating immune responses, mediating antigen presentation, and undergoing phenotypic differentiation, thereby significantly influencing the progression of heart failure [5–7]. Macrophages are widely distributed throughout various tissues and maintain immune homeostasis through mechanisms such as inflammatory cytokine secretion. Under different microenvironmental stimuli, macrophages can differentiate into distinct phenotypes, the most common being pro-inflammatory (M1) and anti-inflammatory/repair (M2) types [8]. mbalances in the M1/M2 ratio are closely associated with HF-related pathological processes including inflammation, fibrosis, and angiogenesis. Therefore, in-depth investigation of macrophage activation and polarization mechanisms is crucial for developing novel therapeutic strategies and improving HF prognosis.

Traditional Chinese Medicine (TCM) possesses unique advantages in HF treatment due to its multi-targeted, multi-level regulatory effects [9]. Studies indicate [10], hat by modulating macrophage activation and polarization, TCM can effectively suppress inflammatory responses, mitigate myocardial injury, and delay HF progression. While extensive research has explored its mechanisms with positive advances, the precise regulatory pathways of macrophage polarization in HF remain incompletely elucidated. This review summarizes recent findings on TCM-mediated modulation of macrophage activation and polarization for HF treatment, aiming to guide further mechanistic investigations and optimize TCM therapeutic applications.

2. Overview of Macrophage Polarization and Plasticity

As highly plastic immune cells, macrophages perceive microenvironmental signals through surface receptors and differentiate into two functional phenotypes—M1 (classically activated) and M2 (alternatively activated)—based on stimulus characteristics. M1 macrophage activation is primarily driven by pathogen-associated molecular patterns (PAMPs), lipopolysaccharide (LPS), intracellular pathogens, and Th1 cytokines (e.g., IFN-γ/GM-CSF) [11]. The activated M1 phenotype releases proinflammatory factors like IL-1β, IL-6, TNF-α, and chemotactic molecules such as CCL2/CXCL9. While these recruit immune cells to enhance pathogen clearance, they may also trigger excessive inflammation leading to tissue damage [12]. This activation process is accompanied by high expression of ROS and iNOS. Through ROS-mediated proinflammatory signaling cascade amplification and synergistic interaction with Th1/Th17 immune responses, it exerts critical effects in anti-infection and anti-tumor processes. Notably, excessive activation of this proinflammatory dominant phenotype is closely

associated with various pathological injuries, necessitating precise regulation to maintain immune homeostasis [13,14].

M2 macrophages activate under anti-inflammatory factors like IL-4, IL-10, and IL-13, performing anti-inflammatory regulation, tissue remodeling, and tumor microenvironment modulation. Based on stimulus heterogeneity and functional diversity, this population can be subdivided into four subtypes: M2a/b/c/d. The M2a subtype, induced by IL-4/IL-13, is characterized by high expression of CD206/IL-1R. It synergistically suppresses chronic inflammation and promotes tissue repair by secreting anti-inflammatory factors like IL-10/CCL17 and pro-fibrotic mediators such as TGF-β. Its hallmark molecule Arg1/Ym1/Fizz1 not only mediates Th2 immune polarization but also promotes cell proliferation through metabolic reprogramming [11,15]. The M2b subtype, activated by PRRs such as TLR4/immune complexes, exhibits biphasic pro-anti-inflammatory regulation—simultaneously releasing pro-inflammatory factors like IL-1β/IL-6 while upregulating IL-10, maintaining Th2 responses and acute inflammation equilibrium through low IL-12 expression [15]. The M2c subtype, regulated by IL-10/TGF-β and characterized by high CD163/CD206 expression, suppresses inflammation and enhances apoptotic cell clearance via the IL-10/TGF-β axis. Its secreted CCL16/CCL18 selectively recruits regulatory T cells, cooperatively maintaining immune tolerance [16]. The M2d subtype (i.e., tumor-associated macrophages, TAMs) drives tumor angiogenesis through high VEGF/IL-10 expression upon IL-6 or TLR/adenosine receptor co-stimulation, thereby promoting tumor immune evasion and malignant progression [15].

The M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes formed through macrophage polarization constitute a bidirectional switch for immune regulation, with their polarization balance directly determining the intensity and direction of inflammatory responses. Given the phenotypic plasticity of macrophages, modulating their phenotype to maintain immune homeostasis has emerged as a novel therapeutic paradigm for targeting pathological microenvironment remodeling. This review systematically reviews macrophage polarization phenotypes and functions, as shown in Figure 1.

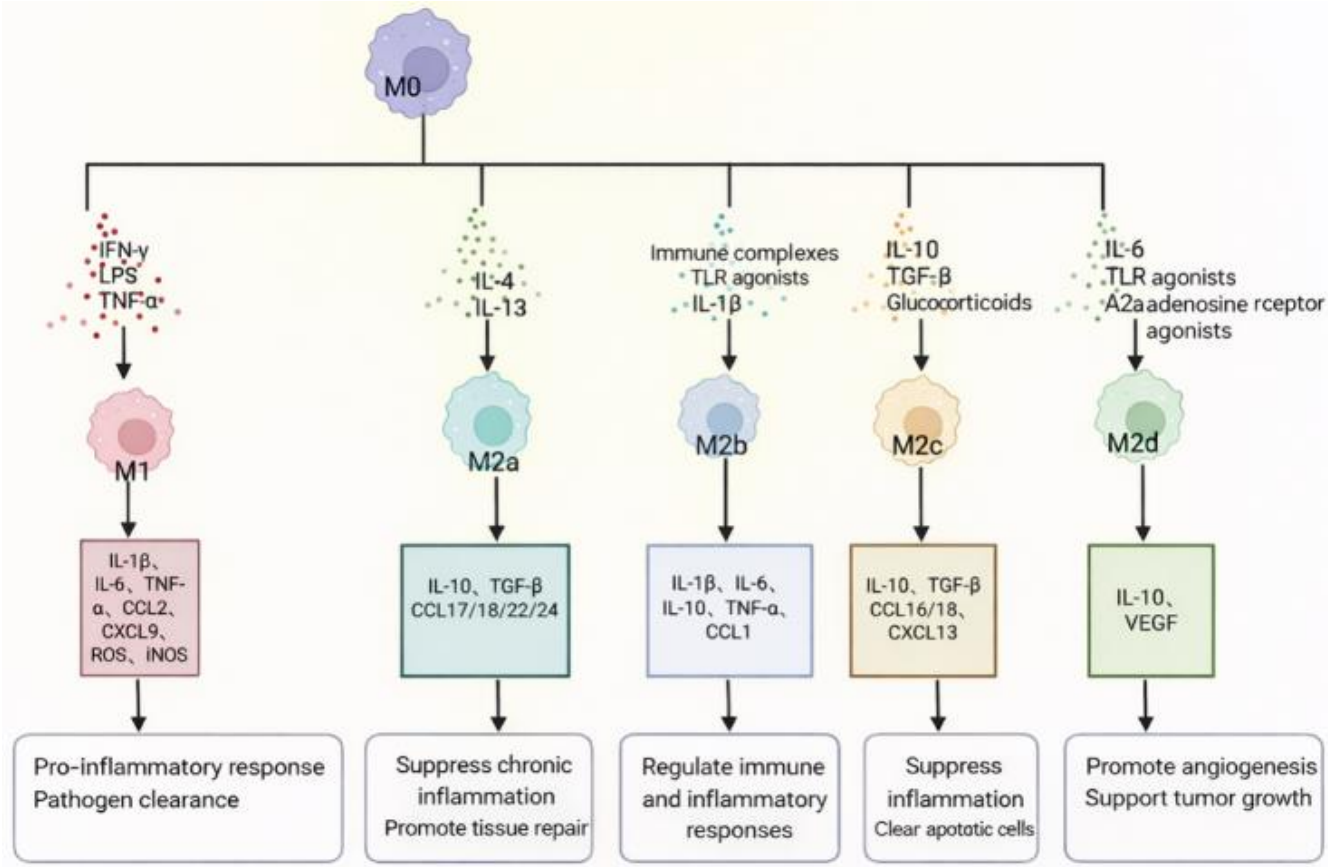

Figure 1: Schematic diagram of macrophage phenotypic transformation and function

3. Macrophages and HF

3.1 Macrophages and Inflammation

Myocardial infarction, obesity, hypertension, and diabetes are major precipitating factors for heart failure. Research indicates that inflammatory responses permeate the entire course of heart failure development [17]. As key immune effector cells, macrophages regulate the local immune microenvironment in the failing heart and play crucial roles in myocardial injury, inflammatory responses, and tissue repair [18]. During the early to mid-stages of heart failure, macrophages predominantly exhibit an M1 pro-inflammatory phenotype. They recruit to and infiltrate damaged areas, releasing multiple inflammatory cytokines to mediate inflammatory responses and clear necrotic tissue. In the later stages of the disease, macrophages gradually transition to an M2 phenotype. They primarily participate in myocardial repair and remodeling by secreting anti-inflammatory factors and promoting tissue repair-related factors [19].

Cardiac metabolic reprogramming serves as a core adaptive

mechanism to myocardial injury. In healthy myocardium, approximately 70% of energy originates from fatty acid oxidation, whereas decompensated heart failure exhibits glycolytic metabolism. This metabolic shift represents both an adaptive adjustment to hypoxic microenvironments and reflects a vicious cycle of energy supply-demand imbalance [20,21]. Notably, this metabolic mechanism also exists in macrophage polarization: pro-inflammatory M1 macrophages rely on glycolysis for energy, while anti-inflammatory M2 macrophages maintain oxidative phosphorylation homeostasis [22,23]. During M1 polarization, upregulation of glucose transporter GLUT1 drives increased glycolytic flux, not only meeting rapid activation energy demands but also enhancing inflammatory responses by promoting IL-1β/ TNF-α transcription via the succinate-HIF-1α axis [24,25].

Among common risk factors for heart failure, metabolic disorders such as obesity, hypertension, and diabetes exacerbate pro-inflammatory macrophage polarization through multiple mechanisms, inducing and intensifying cardiac inflammatory responses. Studies indicate that obesity induces adipose tissue hypoxia, activating HIF-1α expression to promote the release of chemokines and cytokines. This triggers monocyte recruitment and migration into myocardial tissue, intensifying local inflammation [26,27]. Concurrently, both obesity and hypertension can lead to capillary loss, lipid deposition, and myocardial hypoxia [28,29]. Elevated levels of fatty acids and ceramides during obesity act as signaling molecules to activate pattern recognition receptors (PRRs), including TLR4, thereby inducing M1 polarization [30]. Excessive intake of free fatty acids not only activates proinflammatory signaling pathways but also alters fatty acid metabolism, increasing synthesis of triglycerides, phospholipids, and ceramides, thereby further promoting lipotoxicity and M1 polarization [31,32]. Adipokines also regulate polarization: elevated leptin promotes hypertension and the M1 phenotype via sympathetic activation, while adiponectin exerts anti-inflammatory effects and promotes M2 polarization; its reduction in obesity may further exacerbate inflammation [33,34]. Obesity patients often exhibit concurrent dysregulation of glucose and lipid metabolism, promoting pro-inflammatory M1 polarization of macrophages while suppressing M2 functions. This exacerbates inflammatory responses and impairs cardiac repair capacity [35–37]. Abnormal glucose metabolism participates in regulating macrophage polarization. Hyperglycemia not only enhances HIF-1α activity and glycolytic metabolism via non-hypoxic pathways but also activates pro-inflammatory gene expression through the AGEs/NF-κB pathway, promoting M1 polarization and inflammatory responses [38-41]. The renin – angiotensin - aldosterone system (RAAS) is frequently abnormally activated in hypertension-induced HF. Its core active peptide, angiotensin II (AngII), enhances inflammatory responses by activating the AT1R-mediated signaling pathway. Furthermore, it drives macrophage polarization toward the M1 phenotype while suppressing the expression of anti-inflammatory factors associated with M2 macrophages. This disrupts the inflammation-repair balance and accelerates the progression of cardiac tissue damage [42,43].

In summary, macrophage metabolism is closely linked to their polarization state. M1 macrophages rely on glycolysis and promote inflammation through HIF-1α-mediated mechanisms, whereas M2 macrophages depend on oxidative phosphorylation and participate in anti-inflammatory responses and tissue repair. Obesity, hyperglycemia, lipid metabolism disorders, and RAAS system abnormalities can all induce M1 polarization, thereby exacerbating inflammatory responses and HF pathological progression. Therefore, targeting macrophage metabolic regulation to achieve polarization state remodeling may become a potential strategy for improving the inflammatory microenvironment and prognosis of HF in the future.

3.2 Macrophages and Myocardial Fibrosis

Myocardial fibrosis (MF) represents a common pathologic basis for cardiovascular diseases, characterized by the activation and differentiation of cardiac fibroblasts into myofibroblasts. This process leads to abnormal deposition and structural remodeling of the extracellular matrix (ECM), ultimately resulting in increased cardiac stiffness and impaired diastolic function [44]. The ECM, primarily composed of macromolecules like collagen, maintains myocardial structural integrity and signaling functions under normal conditions. However, under acute or chronic pathological stimuli, ECM metabolic imbalance can drive the MF process [11,45]. Recent studies reveal that macrophage activation and polarization play a key regulatory role in MF formation. Macrophages not only modulate fibroblast activation and ECM metabolism but also influence cardiac remodeling through synergistic interactions with pathways including the renin-angiotensin-aldosterone system (RAAS), inflammatory responses, and cellular metabolism [46,47].

Persistent RAAS activation is a major mechanism in HF progression and accelerates disease development by promoting myocardial fibrosis. Studies indicate that RAAS interacts with macrophage function through multiple mechanisms: [48,49] On one hand, macrophages synthesize renin and angiotensin-converting enzyme (ACE), enhancing local Ang II production, which in turn promotes fibroblast activation and ECM synthesis. Ang II stimulates macrophage secretion of inflammatory cytokines, inducing M1 polarization; Ang II promotes myocardial fibrosis by inducing vasoconstriction, sodium-water retention, and proinflammatory responses. It also enhances monocyte recruitment and M1 polarization via the CXCL1-CXCR2 signaling axis, exacerbating inflammation and type I/III collagen expression [50–52]; Conversely, M2 macrophages may also undergo abnormal activation under sustained RAAS activation, leading to uncontrolled ECM synthesis. Under stress overload conditions, persistent activation of M2 macrophages causes excessive deposition of fibrous components, resulting in ventricular wall thickening and diastolic dysfunction [53].

During the early phase of AMI, macrophages rapidly recruit to the infarct area, predominantly exhibiting an M1 phenotype. They release proinflammatory cytokines and matrix metalloproteinases (MMPs), such as MMP-2 and MMP-9, participating in necrotic tissue clearance and ECM degradation to establish initial conditions for cardiac repair [54]. As the inflammatory phase subsides, macrophages undergo phenotypic conversion influenced by the local

metabolic microenvironment. Studies indicate that the Warburg effect is activated in ischemic myocardial tissue, causing macrophages to rely primarily on glycolysis even under aerobic conditions. Lactic acid accumulation induces histone lactylation, which in turn upregulates M2-associated genes, promoting the conversion of M1 macrophages to M2 macrophages [55]. During the repair phase of AMI, M2 macrophages gradually become the dominant phenotype. They secrete multiple pro-repair factors such as TGF-β, IL-10, galectin-3 (Gal-3), and Arg1 to induce fibroblast activation and ECM synthesis [53,56,57]. Specifically, TGF-β1 binds to TGF-βRII on fibroblast surfaces, activating the Smad3 signaling pathway to upregulate α-SMA expression. This induces fibroblast differentiation into myofibroblasts, enhancing their collagen-producing capacity [57]. Additionally, IL-10 activates the STAT3-Gal-3 signaling pathway to induce macrophage secretion of osteopontin (OPN). OPN further acts on fibroblasts, enhancing their activation state and ECM deposition capacity [58]. M2 macrophages not only promote ECM deposition by secreting pro-remodeling factors but also directly participate in fibroblast population expansion through the macrophage-myofibroblast transition (MMT) mechanism, further exacerbating myocardial fibrosis. Persistent activation of M2 macrophages may lead to excessive ECM deposition and myocardial tissue stiffness, ultimately causing diastolic dysfunction and progression of heart failure [59–62].

In summary, macrophages play a key regulatory role in the development and progression of myocardial fibrosis. They interact with the RAAS system and the local metabolic environment to jointly influence fibroblast activation and ECM deposition. The dynamic equilibrium between M1 and M2 macrophages is crucial for myocardial repair, while sustained M2 activation can lead to excessive fibrosis and myocardial stiffness, driving the progression of heart failure.

3.3 Macrophages and Cardiac Electrophysiology

HF frequently coexists with arrhythmias, which carry high morbidity and mortality rates. Recent studies [63], Macrophage recruitment and polarization play a crucial role in regulating myocardial electrical conduction, both maintaining normal electrical activity and potentially triggering arrhythmias. Cardiac electrical impulses originate in the sinoatrial node, propagate through the atrioventricular node and its downstream conduction system to the ventricles, enabling synchronized cardiac contraction. Gap junction proteins (connexins, Cx) are key structures mediating intercellular electrical signaling. The major subtypes expressed in the adult heart include Cx43, Cx40, Cx45, and Cx30.2, with Cx43 being the most abundantly expressed. Research indicates that macrophages can form electrical coupling with cardiomyocytes via Cx43, thereby regulating myocardial action potentials and maintaining normal cardiac electrical conduction [64]. Furthermore, cardiac endogenous secretions of dual-regulator protein play a crucial role in modulating the phosphorylation state of Cx43, its distribution in the right ventricular region, and its intracellular transport. Relevant animal experiments demonstrate that knock-out of bradypulin causes disruption of gap junction function between cardiomyocytes, subsequently inducing severe or even fatal arrhythmias [65]. In myocardial infarction (MI) models, macrophages accumulate extensively at the infarct margin and tend toward M1 polarization. Research indicates that M1 macrophages can upregulate the expression of the calcium-activated potassium channel KCa3.1, promoting Ca^{2+} influx and thereby prolonging the action potential duration (APD) of cardiomyocytes, significantly increasing the risk of arrhythmia. Additionally, macrophages can regulate cardiac electrophysiological function through paracrine mechanisms, further affecting rhythm stability. Proinflammatory factors secreted by M1 macrophages (e.g., TNF-α, IL-1β, and IL-6) can induce electrical remodeling. Specifically, IL-1β has been shown to suppress QKI protein expression in atrial cardiomyocytes, thereby reducing L-type Ca^{2+} currents and partially inhibiting atrial fibrillation onset [66]. Concurrently, M2 macrophages suppress abnormal sympathetic remodeling after myocardial infarction by downregulating nerve growth factor (NGF) expression, thereby partially reducing arrhythmia occurrence [67].

In summary, macrophages exert multidimensional functions in cardiac electrophysiological regulation. These include direct modulation of myocardial action potentials via electrical coupling, mediation of electrical remodeling through inflammatory cytokines, and influence on autonomic activity via neurogenic mechanisms. The dynamic changes in macrophage polarization status may represent a critical link in the onset and progression of arrhythmias, suggesting their potential value as therapeutic targets in the management of HF and its associated arrhythmias.

3.4 Macrophages and Angiogenesis

When the heart faces stress stimuli such as pressure overload, ischemia, or hypoxia, it initiates compensatory responses to maintain cardiac function, including myocardial hypertrophy and increased angiogenesis. However, persistent pathological stimuli can lead to maladaptive cardiac remodeling, encompassing myocardial fibrosis and vascular sparsity, ultimately precipitating HF. Angiogenesis refers to the process where vascular endothelial cells undergo activation, proliferation, and migration under tissue microenvironmental influences to form new blood vessels, playing a crucial role in alleviating myocardial ischemia and hypoxia [68]. Macrophages, as the most abundant immune cells in the heart, are key regulators of cardiac angiogenesis. In MI models, macrophage depletion leads to decreased VEGFA levels and reduced cardiac capillary density [69]. M2 macrophages promote repair by secreting anti-inflammatory factors such as IL-4, IL-10, and TGF-β, while simultaneously supporting neovascularization through pro-angiogenic factors like VEGFA [70]. HIF-1α can also activate VEGF expression, aiding in restoring blood flow to ischemic tissue. During the early stages of cardiac stress overload (e.g., the first week), the proliferation of resident M2-like macrophages is crucial for maintaining cardiac function, potentially linked to KLF4-mediated VEGF-A upregulation and enhanced angiogenesis [71]. Research indicates that resident cardiac macrophages form adherens junction complexes with cardiomyocytes and, through TRPV4-mediated perception of mechanical stretch signals, release pro-angiogenic factors like IGF-1 to slow heart failure progression [72]. Conversely, M1 macrophages exert inhibitory effects on angiogenesis. They release exosomes rich in pro-inflammatory miRNAs (e.g.,

miR-155), which suppress vascular endothelial cell proliferation and migration by inhibiting signaling pathways such as Sirt1/AMPKα2-eNOS and RAC1-PAK1/2, thereby exacerbating myocardial injury and delaying repair processes [73]. Furthermore, matrix metalloproteinase-9 (MMP9) secreted by M1 macrophages downregulates key angiogenesis-related molecules including intercellular adhesion molecule-1 (ICAM-1), platelet endothelial cell adhesion molecule-1 (PECAM-1/CD31), and thrombospondin-1 (TSP-1). This induces vascular sparseness, exacerbating left ventricular hypertrophy and cardiac aging [70]. In summary, macrophages play a dual role in regulating cardiac angiogenesis: resident M2-like macrophages promote neovascularization through multiple mechanisms, thereby sustaining cardiac function and delaying HF progression, whereas exogenous infiltrating M1-like macrophages inhibit angiogenesis and exacerbate myocardial injury. Therefore, modulating macrophage polarization to promote the maintenance and functional expression of the M2 phenotype holds promise as an intervention strategy to improve clinical outcomes in heart failure.

4. Traditional Chinese Medicine Modulation of M1/M2 Macrophage Polarization for Heart Failure Intervention

4.1 Single Compounds

Doxorubicin (DOX), a widely used anticancer drug, exhibits dose-dependent cardiotoxicity considered a key mechanism of heart failure development. This toxicity is closely associated with myocardial cell apoptosis, inflammatory responses, and the infiltration and activation of immune cells, particularly macrophages [74,75]. Latifolin, a natural flavonoid compound from the Chinese herbal medicine Aquilaria sinensis, demonstrates cardioprotective effects by reducing inflammatory cell infiltration in myocardial tissue. ZHANG [76] found that latifolin significantly mitigates DOX-induced cardiomyocyte injury by inhibiting M1 macrophage polarization and inflammatory cytokine release, thereby modulating the M1/M2 macrophage ratio. In vivo experiments demonstrated that latifolin downregulates M1 markers (CD86, iNOS) and upregulates M2 markers (CD206, IL-10, IL-4R). In vitro, it inhibits the expression of inflammatory cytokines (IL-6, IL-1β, TNF-α) induced by LPS/IFN-γ and improves cardiac function.

Arctigenin (AG), a potential small-molecule compound with anti-inflammatory activity, exerts significant effects in regulating macrophage polarization, suppressing inflammatory cytokine expression, and mitigating myocardial injury. NI [77] research revealed that AG modulates macrophage polarization by inhibiting NFAT5-mediated JAK/STAT and NF-κB pathways, significantly reducing TNF-α and IL-6 levels in myocardial tissue of MI mice, thereby mitigating inflammatory damage and myocardial cell apoptosis. In vitro experiments demonstrated that AG reduces expression of M1 phenotype markers (CD86, TLR2/4) and M2c markers (TLR1/8) in RAW264.7 macrophages, while upregulating M2a (CHIL3), M2b (H2-Aa), and M2d (VEGFA) subtype markers, thereby exerting cardioprotective effects.

Salvianolic acid B (SalB) is a major water-soluble phenolic compound in Salvia miltiorrhiza, exhibiting potent anti-inflammatory, antioxidant, and immunomodulatory effects. ZHAO [78] demonstrated that SalB inhibits glycolysis and M1 polarization by downregulating the RagD/mTORC1 metabolic signaling pathway, thereby promoting M2 phenotype differentiation. This reduces expression of inflammatory mediators such as TNF-α and IL-6, alleviating myocardial inflammation and ventricular remodeling in MI/R mice. Dihydrotanshinone I (DHT), a major liposoluble diterpene active component in Salvia miltiorrhiza, exhibits distinct anti-inflammatory and antioxidant effects. WANG [79] indicates that DHT alleviates DOX-induced cardiotoxicity by inhibiting the mTOR-TFEB-IKK-NF-κB signaling pathway. Its effects include reducing M1 macrophage accumulation, inflammatory cytokine release, and downregulating p-mTOR, p-IKKα/β, and p-NF-κB expression, demonstrating potent anti-inflammatory and cardioprotective effects.

Curcumin, a natural polyphenolic compound extracted from turmeric, exhibits significant anti-inflammatory, antioxidant, and immunomodulatory effects. Studies indicate its potential value in promoting myocardial repair after myocardial infarction, improving post-infarction cardiac dysfunction, and managing heart failure [80–82]. YAN [83] found that curcumin activates the AMPK pathway, inhibits M1 macrophage infiltration and proinflammatory factor expression (TNF-α, IL-1β, IL-6), while upregulating the anti-inflammatory factor IL-10. This promotes M2 macrophage polarization, reduces local inflammatory responses in the infarct area, mitigates ventricular remodeling, and improves cardiac function.

4.2 Traditional Chinese Medicine Formulas

LU [84] found that Astragalus-Panax Granules (QSG) downregulated M1 macrophage and Ang II expression in the infarct margin of HF rats by inhibiting the RAAS system and TGF-β1/Smad3 signaling pathway, while upregulating M2 differentiation levels. This alleviated local inflammation, improved myocardial fibrosis, and enhanced cardiac function.

Nuanxin Kang, composed of red ginseng and maodongqing, was found by Dong Xin [85] to potentially regulate glycolytic metabolic reprogramming, reducing M1 macrophage infiltration in myocardial ischemia-reperfusion injury (MIRI) mice and decreasing serum expression levels of proinflammatory factors IL-1β, IL-6, and TNF-α. In vitro experiments demonstrated that Nuanxin Kang inhibited glycolysis and M1 proinflammatory factor mRNA expression in LPS-induced macrophage models.

Liu Qing [56] found that the traditional Chinese medicine compound Xinyin Pian downregulates anti-inflammatory factor interleukin-10 (IL-10) and M2 macrophage markers arginase-1 (Arginase-1, Arg-1), thereby reducing the expression of collagen synthesis-related genes (type I collagen [ColI], type III collagen [ColIII]) and the pro-fibrotic factor TGF-β in cardiac tissue from a chronic heart failure mouse model. This significantly alleviated myocardial fibrosis and improved cardiac function.

Shi Lipeng [86] found that Fangji Fuling Tang inhibits M1

macrophage CD86 expression and inflammatory cytokine secretion (TNF-α, IL-1β, and IL-6), promotes M2 marker CD206 and anti-inflammatory cytokine IL-10 expression, reduces serum CK-MB levels and myocardial TGF-β1, α-SMA, and collagen deposition in MF mice, thereby improving myocardial fibrosis and cardiac function.

Yang Meng [87] found that Ginseng-Fu Ling Injection alleviates myocardial inflammatory injury and improves cardiac function by inhibiting the TLR4/NF-κB signaling pathway. This mechanism downregulates the proportion of M1 macrophages and expression levels of inflammatory cytokines (TNF-α, IL-6), while upregulating M2 macrophages, the anti-inflammatory factor IL-10, and tissue repair-related molecule Arg-1.

Lin Zhijun [88] demonstrated that Nuanshikang regulates glycolipid metabolism and oxidative phosphorylation processes to suppress mRNA expression of M1 markers (CD86, iNOS, and TNF-α) and inflammatory factor IL-1β, thereby mitigating myocardial injury in MI mice and improving myocardial fibrosis and ventricular remodeling.

In recent years, research on traditional Chinese medicine (TCM) modulating macrophage function to intervene in heart failure has garnered increasing attention. This paper systematically reviews research progress on macrophages as potential targets for TCM treatment of heart failure (see Tables 1 and 2), aiming to provide theoretical basis and reference for modern research and new strategy exploration of TCM against heart failure.

Table 1: Regulatory Effects of Traditional Chinese Medicine Active Ingredients on Macrophages in Heart Failure

TCM Monomer	Model	Effect	Target or Pathway	Reference
latifolin	1. Doxorubicin (DOX)-induced myocardial injury in mice 2. LPS + IFN-γ stimulated peritoneal macrophages	M1 (CD86, CD16/32, iNOS)↓, proinflammatory factors (TNF-α, IL-6, IL-1β)↓, cardiac function indicators (LVEF↑, LVFS↑, LDH↓)↑, M2 markers (CD206, IL-4R, IL-10)↑, M1/M2	-	[76]
Arctigenin (AG)	1. Ligation-induced LAD myocardial infarction (MI) model in mice 2. LPS-stimulated RAW264.7 macrophages	M1 markers (CD86, TLR2, TLR4) ↓, inflammatory factors (TNF-α, IL-6, MCP-1, ICAM-1)↓, M2 markers (CD206, CHIL3, H2-Aa, VEGFA)↑	JAK/STAT and NF-κB	[77]
SalB	1. Ligation-induced LAD myocardial infarction/reperfusion (MI/RI) model in mice 2. LPS-stimulated BMDM 3. IL-4-stimulated BMDM	M1 markers (TNF-α, IL-6, IL-1β, iNOS, CCL2, CCL5, CCR2) ↓, M2 markers (CD206, Mrc, Arg1, Clec10a, CX3CR1, CD36, MerTK, IL-10) ↑, cardiac function indicators (EF↑, FS↑, EDV↓, ESD↓) ↑	mTORC1	[78]
Tanshinone I	1. Doxorubicin (DOX)-induced myocardial injury mouse model 2. LPS-stimulated RAW264.7 macrophages 3. DOX-stimulated H9C2 rat cardiomyocytes	M1 markers (CD86, F4/80)↓, MDA↓, SOD↑, H9C2 cardiomyocyte apoptosis rate↓, cardiac function indicators (LVEDD↓, LVESD↓, EF↑, FS↑)↑, inflammatory factors (TNF-α, COX2, IL-8)↓	mTOR TFEB NF-κB	[79]
Curcumin	1. LCA myocardial infarction (MI) model in mice 2. LPS + IFN-γ stimulated BMM	Cardiac function indicators (LVDd, LVDs↓, EF, LVEF↑)↑, proinflammatory factors (TNF-α, IL-1β, IL-6)↓, M1 markers (CD86, iNOS, CCL2)↓, M2 markers (CD163, CD206, Arg1)↑	AMPK	[83]

Table 2: Regulatory Effects of Traditional Chinese Medicine Formulas on Macrophages in Heart Failure

TCM Formula	Model	Effect	Target or Pathway	Reference
Qishen Granules	1. LAD ligation rat and mouse heart failure models 2. LPS-stimulated RAW264.7 cells	M1 (CD86) ↓, M2 (CD163) ↑, EF↑,FS↑,VEGF↑, CD31↑, MMP2↓, Collll↓	TGF-β1/Smad3	[84]
Nuanxin Kang	1. Myocardial infarction/reperfusion (MI/R) model in mice with ligated LAD 2. LPS-stimulated RAW264.7 macrophages	M1 markers (CD86)↓, proinflammatory factors (IL-1β, IL-6, TNF-α)↓, cardiac function indicators (EF, FS, CO)↑	-	[85]
Xinyin Pian	Chronic heart failure model in transcatheter aortic coarctation (TAC) mice	M2 markers (IL-10, Arg-1) ↓, fibrosis-related genes (ColI, ColIII, TGF-β) ↓, cardiac function indicators (LVEF, FS) ↑	MLK3/JNK	[56]
Fangji Fuling Tang	Isoproterenol (ISO) Mouse Myocardial Fibrosis (MF) Model	M1 Marker (CD86) ↓, M2 Marker (CD206) ↑, Proinflammatory Factors (TNF-α, IL-1β, IL-6) ↓, Anti-inflammatory Factor (IL-10) ↑, TGF-β1↓, CK-MB↓, MDA↓, SOD↑, GSH↑	-	[86]
Shenfu Injection	ISO-induced mouse heart failure model	M1 marker (CD86) ↓, M2 markers (CD163, Arg-1) ↑, pro-inflammatory factors (TNF-α, IL-6) ↓, anti-inflammatory factor (IL-10) ↑, NT-proBNP↓	TLR4/NF-kB	[87]
Nuanxin Kang	1. LAD ligation myocardial infarction mouse model 2. LPS-treated RAW264.7 macrophage + HL-1 cardiomyocyte model	M1 markers (CD86, iNOS) ↓, pro-inflammatory factors (TNF-α, IL-1β) ↓, ROS ↓	-	[88]

5. Summary and Outlook

HF is a complex chronic inflammatory cardiovascular disease, and the imbalance in M1/M2 macrophage polarization plays a pivotal role in its pathological process. M1 macrophages exacerbate local inflammatory responses and myocardial injury by massively secreting proinflammatory factors; M2 macrophages possess anti-inflammatory and reparative functions, but their sustained activation may induce fibroblast activation and collagen deposition, leading to myocardial fibrosis and cardiac remodeling. Traditional Chinese medicine (TCM) and

its active components demonstrate multi-targeted, multi-level regulatory potential in modulating macrophage polarization to intervene in HF inflammation and remodeling. Studies indicate that individual components such as Latifolin, Arctigenin, Danphenolic Acid B, DHT, and Curcumin generally possess the ability to suppress pro-inflammatory cytokine expression in M1 macrophages and promote the shift of M2 macrophages toward an anti-inflammatory and reparative phenotype. Specifically, Latifolin and Arctiin primarily suppress inflammatory factor expression and mitigate myocardial inflammatory injury by inhibiting classical inflammatory pathways such as NF-κB and JAK/STAT. Tannic acid B and DHT intervene in pro-inflammatory polarization driven by metabolic abnormalities by inhibiting mTOR signaling or downregulating glycolysis pathways, thereby alleviating myocardial fibrosis and remodeling. Curcumin, through activating the AMPK pathway, reshapes macrophage metabolic states, enhances M2 phenotype expression, and boosts tissue repair capacity. Traditional Chinese medicine formulas exert potential effects in regulating M1/M2 balance and alleviating myocardial infarction and DOX-induced cardiac injury through multi-component synergistic regulation of inflammatory and metabolic states. Qishen Granules mitigate inflammation and fibrosis by inhibiting the renin-angiotensin-aldosterone system (RAAS) and TGF-β1/Smad3 signaling. Nuanxin Kang alleviates metabolic stress by regulating glycolysis and oxidative phosphorylation. Xinyin Tablets and Fangji Fuling Decoction reduce TGF-β and α-SMA expression, limiting fibrosis risks associated with sustained M2 activation. TCM and its active components regulate macrophage M1/M2 polarization balance by modulating inflammatory signaling pathways (e.g., NF-κB, JAK/STAT, mTOR), inhibiting glycolytic metabolism, and suppressing the RAAS system. This effectively suppresses inflammatory responses, alleviates myocardial fibrosis and remodeling, and delays heart failure progression.

In recent years, multiple studies have demonstrated significant advantages of TCM in regulating macrophage phenotype conversion, alleviating inflammatory responses, and protecting myocardial tissue. However, current research on TCM-mediated macrophage polarization therapy for HF still faces several challenges: 1) The mechanisms underlying macrophage polarization remain incompletely elucidated. Beyond the classic M1 and M2 types, other functional subpopulations lack unified definitions and marker identification. The dynamic changes and precise subtyping of macrophages across different pathological stages require further exploration. Future research should integrate techniques such as single-cell sequencing and multi-omics integration to reveal their heterogeneous characteristics and regulatory mechanisms, laying the foundation for more precise intervention strategies. 2) Current research on macrophages in HF primarily relies on animal models and in vitro experiments, often employing methods such as LAD ligation or LPS stimulation to establish inflammatory models. While these approaches partially reflect macrophage roles in inflammatory mechanisms, studies on complex pathological processes like myocardial fibrosis, angiogenesis, and electrophysiological remodeling remain limited. Future efforts should diversify modeling approaches and broaden research directions to comprehensively elucidate the regulatory role of macrophages in the multifaceted pathophysiological mechanisms of HF. 3) Although existing studies suggest the potential of traditional Chinese medicine (TCM) in modulating macrophage function, most research remains at the basic science stage, lacking large-scale, prospective clinical validation. Therefore, advancing the translational application of TCM-mediated macrophage regulation in heart failure treatment requires multicenter, high-quality clinical studies to systematically evaluate its efficacy and safety. 4) Current research on TCM-mediated macrophage regulation predominantly focuses on alterations in inflammatory factor and biomarker expression, with limited exploration of underlying mechanisms. Future studies should broaden their scope by integrating multi-omics technologies to delve into signaling regulation, metabolic reprogramming, and other pathways, thereby providing theoretical support for systematically elucidating their anti-heart failure effects. Therefore, modern techniques such as single-cell sequencing and multi-omics integration should be further utilized to systematically investigate the distribution, functions, and interactions of HF-associated macrophage subtypes with cardiomyocytes, fibroblasts, and other cells, clarifying their mechanisms across different stages of HF. Guided by the TCM principle of “differential diagnosis and treatment,” we should delve into the molecular basis of traditional Chinese herbal formulas and their active components in regulating the immune microenvironment, promoting M1/M2 transformation, and repairing myocardial injury. This will advance the modern transformation and clinical application of TCM in HF treatment, offering novel insights and intervention strategies for HF prevention and management.

References

[1] McDonagh T A, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [J]. European Heart Journal, 2021, 42(36): 3599-3726.

[2] Wang H, Chai K, Du M, et al. Prevalence and Incidence of Heart Failure Among Urban Patients in China: A National Population-Based Analysis [J]. Circulation: Heart Failure, 2021, 14(10): e008406.

[3] Tianzhuang, Zhang Shuyang. Key Points Interpretation of the 2024 Chinese Guidelines for Diagnosis and Treatment of Heart Failure [J]. Peking Union Medical Journal, 2024, 15(4): 801-806.

[4] Perticone M, Zito R, Miceli S, et al. Immunity, inflammation and heart failure: their role on cardiac function and iron status [J]. Frontiers in Immunology, 2019, 10: 2315.

[5] Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas [J]. The Journal of clinical investigation, 2012, 122(3): 787-795.

[6] Qian J fu, Liang S qi, Wang Q yan, et al. Isoproterenol induces MD2 activation by β-AR-cAMP-PKA-ROS signalling axis in cardiomyocytes and macrophages drives inflammatory heart failure [J]. Acta Pharmacologica Sinica, 2024, 45(3): 531-544.

[7] De Groot A E, Pienta K J. Epigenetic control of macrophage polarization: implications for targeting tumor-associated macrophages [J]. Oncotarget, 2018, 9(29): 20908.

[8] Mills C D, Kincaid K, Alt J M, et al. M-1/M-2 macrophages and the Th1/Th2 paradigm [J]. The Journal of immunology, 2000, 164(12): 6166-6173.
[9] Sun Ziyi, Wang Tianlin, Yun Zhangjun, et al. Exploring the Correspondence Between Symptoms and Medications and the Mechanisms of Traditional Chinese Medicine Treatment for Chronic Heart Failure Based on Symptom-Drug Networks and Network Pharmacology [J]. Journal of Integrative Medicine for Cardiovascular and Cerebrovascular Diseases, 2024, 22(10): 1729-1737.
[10] Zhu Z, Wang M, Lu S, et al. Role of macrophage polarization in heart failure and traditional Chinese medicine treatment [J]. Frontiers in Pharmacology, 2024, 15: 1434654.
[11] Shapouri-Moghaddam A, Mohammadian S, Vazini H, et al. Macrophage plasticity, polarization, and function in health and disease [J]. Journal of Cellular Physiology, 2018, 233(9): 6425-6440.
[12] Hume D A. The many alternative faces of macrophage activation [J]. Frontiers in immunology, 2015, 6: 370.
[13] Zhou J, Liu W, Zhao X, et al. Natural melanin/alginate hydrogels achieve cardiac repair through ROS scavenging and macrophage polarization [J]. Advanced science, 2021, 8(20): 2100505.
[14] Yunna C, Mengru H, Lei W, et al. Macrophage M1/M2 polarization [J]. European journal of pharmacology, 2020, 877: 173090.
[15] Wang L xun, Zhang S xi, Wu H juan, et al. M2b macrophage polarization and its roles in diseases [J]. Journal of leukocyte biology, 2019, 106(2): 345-358.
[16] Tian L, Yu Q, Liu D, et al. Epithelial–mesenchymal Transition of Peritoneal Mesothelial Cells Is Enhanced by M2c Macrophage Polarization [J]. Immunological Investigations, 2022, 51(2): 301-315.
[17] Mouton A J, Li X, Hall M E, et al. Obesity, hypertension, and cardiac dysfunction: novel roles of immunometabolism in macrophage activation and inflammation [J]. Circulation research, 2020, 126(6): 789-806.
[18] Murphy S P, Kakkar R, McCarthy C P, et al. Inflammation in Heart Failure [J]. Journal of the American College of Cardiology, 2020, 75(11): 1324-1340.
[19] Toldo S, Abbate A. The NLRP3 inflammasome in acute myocardial infarction [J]. Nature Reviews Cardiology, 2018, 15(4): 203-214.
[20] Lopatin Y. Metabolic therapy in heart failure [J]. Cardiac failure review, 2015, 1(2): 112.
[21] Cavalera M, Wang J, Frangogiannis N G. Obesity, metabolic dysfunction, and cardiac fibrosis: pathophysiological pathways, molecular mechanisms, and therapeutic opportunities [J]. Translational Research, 2014, 164(4): 323-335.
[22] Freemerman A J, Johnson A R, Sacks G N, et al. Metabolic reprogramming of macrophages: glucose transporter 1 (GLUT1)-mediated glucose metabolism drives a proinflammatory phenotype [J]. Journal of Biological Chemistry, 2014, 289(11): 7884-7896.
[23] Van Den Bossche J, O'Neill L A, Menon D. Macrophage immunometabolism: where are we (going)? [J]. Trends in immunology, 2017, 38(6): 395-406.
[24] Cordes T, Wallace M, Michelucci A, et al. Immunoresponsive gene 1 and itaconate inhibit succinate dehydrogenase to modulate intracellular succinate levels [J]. Journal of Biological Chemistry, 2016, 291(27): 14274-14284.
[25] Tannahill G M, Curtis A M, Adamik J, et al. Succinate is an inflammatory signal that induces IL-1β through HIF-1α [J]. Nature, 2013, 496(7444): 238-242.
[26] Takikawa A, Mahmood A, Nawaz A, et al. HIF-1α in myeloid cells promotes adipose tissue remodeling toward insulin resistance [J]. Diabetes, 2016, 65(12): 3649-3659.
[27] Fujisaka S, Usui I, Ikutani M, et al. Adipose tissue hypoxia induces inflammatory M1 polarity of macrophages in an HIF-1α-dependent and HIF-1α-independent manner in obese mice [J]. Diabetologia, 2013, 56: 1403-1412.
[28] Guzzardi M A, Iozzo P. Fatty heart, cardiac damage, and inflammation [J]. The review of diabetic studies: RDS, 2011, 8(3): 403.
[29] Zeng H, Vaka V R, He X, et al. High-fat diet induces cardiac remodelling and dysfunction: assessment of the role played by SIRT 3 loss [J]. Journal of cellular and molecular medicine, 2015, 19(8): 1847-1856.
[30] Ghosh A, Gao L, Thakur A, et al. Role of free fatty acids in endothelial dysfunction [J]. Journal of biomedical science, 2017, 24: 1-15.
[31] Camell C D, Nguyen K Y, Jurczak M J, et al. Macrophage-specific de novo synthesis of ceramide is dispensable for inflammasome-driven inflammation and insulin resistance in obesity [J]. Journal of Biological Chemistry, 2015, 290(49): 29402-29413.
[32] Namgaladze D, Brüne B. Macrophage fatty acid oxidation and its roles in macrophage polarization and fatty acid-induced inflammation [J]. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 2016, 1861(11): 1796-1807.
[33] Luo Y, Liu M. Adiponectin: a versatile player of innate immunity [J]. Journal of molecular cell biology, 2016, 8(2): 120-128.
[34] Francisco V, Pino J, Campos-Cabaleiro V, et al. Obesity, fat mass and immune system: role for leptin [J]. Frontiers in physiology, 2018, 9: 640.
[35] Serbulea V, Upchurch C M, Schappe M S, et al. Macrophage phenotype and bioenergetics are controlled by oxidized phospholipids identified in lean and obese adipose tissue [J]. Proceedings of the National Academy of Sciences, 2018, 115(27): E6254-E6263.
[36] Fukushima A, Lopaschuk G D. Cardiac fatty acid oxidation in heart failure associated with obesity and diabetes [J]. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 2016, 1861(10): 1525-1534.
[37] Pavlou S, Lindsay J, Ingram R, et al. Sustained high glucose exposure sensitizes macrophage responses to cytokine stimuli but reduces their phagocytic activity [J]. BMC immunology, 2018, 19: 1-13.
[38] Jin X, Yao T, Zhou Z, et al. Advanced glycation end products enhance macrophages polarization into M1 phenotype through activating RAGE/NF-κB pathway [J]. BioMed research international, 2015, 2015(1): 732450.

[39] Mishra P K, Ying W, Nandi S S, et al. Diabetic cardiomyopathy: an immunometabolic perspective [J]. Frontiers in endocrinology, 2017, 8: 72.
[40] Groh L, Keating S T, Joosten L A, et al. Monocyte and macrophage immunometabolism in atherosclerosis [C]//Seminars in immunopathology: Vol. 40. Springer, 2018: 203-214.
[41] Lancaster G I, Langley K G, Berglund N A, et al. Evidence that TLR4 is not a receptor for saturated fatty acids but mediates lipid-induced inflammation by reprogramming macrophage metabolism [J]. Cell metabolism, 2018, 27(5): 1096-1110.
[42] Yang X F, Wang H, Huang Y, et al. Myeloid angiotensin II type 1 receptor mediates macrophage polarization and promotes vascular injury in DOCA/salt hypertensive mice [J]. Frontiers in pharmacology, 2022, 13: 879693.
[43] Shi P, Raizada M K, Sumners C. Brain cytokines as neuromodulators in cardiovascular control [J]. Clinical and Experimental Pharmacology and Physiology, 2010, 37(2): e52-e57.
[44] Lee T M, Chang N C, Lin S Z. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts [J]. Free Radical Biology and Medicine, 2017, 104: 298-310.
[45] Funes S C, Rios M, Escobar-Vera J, et al. Implications of macrophage polarization in autoimmunity [J]. Immunology, 2018, 154(2): 186-195.
[46] Liu Y, Xu J, Wu M, et al. The effector cells and cellular mediators of immune system involved in cardiac inflammation and fibrosis after myocardial infarction [J]. Journal of cellular physiology, 2020, 235(12): 8996-9004.
[47] Nielsen S H, Mouton A J, DeLeon-Pennell K Y, et al. Understanding cardiac extracellular matrix remodeling to develop biomarkers of myocardial infarction outcomes [J]. Matrix Biology, 2019, 75: 43-57.
[48] Zhang M, Sui W, Xing Y, et al. Angiotensin IV attenuates diabetic cardiomyopathy via suppressing FoxO1-induced excessive autophagy, apoptosis and fibrosis [J]. Theranostics, 2021, 11(18): 8624.
[49] Böckmann I, Lischka J, Richter B, et al. FGF23-mediated activation of local RAAS promotes cardiac hypertrophy and fibrosis [J]. International Journal of Molecular Sciences, 2019, 20(18): 4634.
[50] Wang L, Zhang Y L, Lin Q Y, et al. CXCL1–CXCR2 axis mediates angiotensin II-induced cardiac hypertrophy and remodelling through regulation of monocyte infiltration [J]. European heart journal, 2018, 39(20): 1818-1831.
[51] Ovchinnikov A G, Arefieva T I, Potekhina A V, et al. The molecular and cellular mechanisms associated with a microvascular inflammation in the pathogenesis of heart failure with preserved ejection fraction [J]. Acta Naturae (англоязычная версия), 2020, 12(2 (45)): 40-51.
[52] McLellan M A, Skelly D A, Dona M S, et al. High-resolution transcriptomic profiling of the heart during chronic stress reveals cellular drivers of cardiac fibrosis and hypertrophy [J]. Circulation, 2020, 142(15): 1448-1463.
[53] Hulsmans M, Sager H B, Roh J D, et al. Cardiac macrophages promote diastolic dysfunction [J]. Journal of Experimental Medicine, 2018, 215(2): 423-440.
[54] Zaidi Y, Aguilar E G, Troncoso M, et al. Immune regulation of cardiac fibrosis post myocardial infarction [J]. Cellular signalling, 2021, 77: 109837.
[55] Zhang D, Tang Z, Huang H, et al. Metabolic regulation of gene expression by histone lactylation [J]. Nature, 2019, 574(7779): 575-580.
[56] Liu Qing, Wang Junyan, Deng Bo, et al. Mechanism of Xinyin Pian in Improving Myocardial Fibrosis in Chronic Heart Failure via Regulating Macrophage Polarization through the MLK3/JNK Signaling Pathway [J]. Journal of Chinese Medicine and Traditional Chinese Medicine, 2021, 36(10): 6064-6068.
[57] Kong P, Christia P, Frangogiannis N G. The pathogenesis of cardiac fibrosis [J]. Cellular and molecular life sciences, 2014, 71: 549-574.
[58] Shirakawa K, Endo J, Kataoka M, et al. IL (interleukin)-10–STAT3–galectin-3 axis is essential for osteopontin-producing reparative macrophage polarization after myocardial infarction [J]. Circulation, 2018, 138(18): 2021-2035.
[59] Meng X M, Wang S, Huang X R, et al. Inflammatory macrophages can transdifferentiate into myofibroblasts during renal fibrosis [J]. Cell death & disease, 2016, 7(12): e2495-e2495.
[60] Wang S, Meng X M, Ng Y Y, et al. TGF-β/Smad3 signalling regulates the transition of bone marrow-derived macrophages into myofibroblasts during tissue fibrosis [J]. Oncotarget, 2015, 7(8): 8809.
[61] Zhang S, Weinberg S, DeBerge M, et al. Efferocytosis fuels requirements of fatty acid oxidation and the electron transport chain to polarize macrophages for tissue repair [J]. Cell metabolism, 2019, 29(2): 443-456.
[62] Haider N, Boscá L, Zandbergen H R, et al. Transition of macrophages to fibroblast-like cells in healing myocardial infarction [J]. Journal of the American College of Cardiology, 2019, 74(25): 3124-3135.
[63] Cox C B, Castro M, Brown T L, et al. IL-10 and TGF-β Increase connexin-43 expression and membrane potential of HL-1 cardiomyocytes coupled with RAW 264.7 macrophages [J]. ImmunoHorizons, 2022, 6(6): 334-343.
[64] Sugita J, Fujiu K. Emerging Function of Cardiac Macrophages Ushers in a New Era for the Electrophysiology of the Heart [J]. Circulation Reports, 2019, 1(12): 558-563.
[65] Sugita J, Fujiu K, Nakayama Y, et al. Cardiac macrophages prevent sudden death during heart stress [J]. Nature Communications, 2021, 12(1): 1910.
[66] Fei Y D, Wang Q, Hou J W, et al. Macrophages facilitate post myocardial infarction arrhythmias: roles of gap junction and KCa3. 1 [J]. Theranostics, 2019, 9(22): 6396.
[67] Liu Q, Li Y, Shi Y, et al. The protective effect of gamma aminobutyric acid B receptor activation on sympathetic nerve remodeling via the regulation of M2 macrophage polarization after myocardial infarction [J]. Revista Portuguesa de Cardiologia, 2023, 42(2): 125-135.
[68] Gogiraju R, Bochenek M L, Schäfer K. Angiogenic endothelial cell signaling in cardiac hypertrophy and

heart failure [J]. Frontiers in cardiovascular medicine, 2019, 6: 20.
[69] Van Amerongen M J, Harmsen M C, Van Rooijen N, et al. Macrophage depletion impairs wound healing and increases left ventricular remodeling after myocardial injury in mice [J]. The American journal of pathology, 2007, 170(3): 818-829.
[70] Toba H, Cannon P L, Yabluchanskiy A, et al. Transgenic overexpression of macrophage matrix metalloproteinase-9 exacerbates age-related cardiac hypertrophy, vessel rarefaction, inflammation, and fibrosis [J]. American Journal of Physiology-Heart and Circulatory Physiology, 2017, 312(3): H375-H383.
[71] Liao X, Shen Y, Zhang R, et al. Distinct roles of resident and nonresident macrophages in nonischemic cardiomyopathy [J]. Proceedings of the National Academy of Sciences, 2018, 115(20).
[72] Wong N R, Mohan J, Kopecky B J, et al. Resident cardiac macrophages mediate adaptive myocardial remodeling [J]. Immunity, 2021, 54(9): 2072-2088.
[73] Chen B, Luo L, Wei X, et al. M1 Bone Marrow-Derived Macrophage-Derived Extracellular Vesicles Inhibit Angiogenesis and Myocardial Regeneration Following Myocardial Infarction via the MALAT1/MicroRNA-25-3p/CDC42 Axis [J]. Oxidative Medicine and Cellular Longevity, 2021, 2021(1): 9959746.
[74] Briasoulis A, Androulakis E, Christophides T, et al. The role of inflammation and cell death in the pathogenesis, progression and treatment of heart failure [J]. Heart failure reviews, 2016, 21: 169-176.
[75] Geisberg C A, Sawyer D B. Mechanisms of anthracycline cardiotoxicity and strategies to decrease cardiac damage [J]. Current hypertension reports, 2010, 12: 404-410.
[76] Zhang N, Shou B, Chen L, et al. Cardioprotective Effects of Latifolin Against Doxorubicin-Induced Cardiotoxicity by Macrophage Polarization in Mice [J]. Journal of Cardiovascular Pharmacology, 2020, 75(6): 564.
[77] Ni S H, Sun S N, Zhou Z, et al. Arctigenin alleviates myocardial infarction injury through inhibition of the NFAT5-related inflammatory phenotype of cardiac macrophages/monocytes in mice [J]. Laboratory Investigation, 2020, 100(4): 527-541.
[78] Zhao M, Li F, Jian Y, et al. Salvianolic acid B regulates macrophage polarization in ischemic/reperfused hearts by inhibiting mTORC1-induced glycolysis [J]. European Journal of Pharmacology, 2020, 871: 172916.
[79] Wang X, Wang Q, Li W, et al. TFEB-NF-κB inflammatory signaling axis: a novel therapeutic pathway of Dihydrotanshinone I in doxorubicin-induced cardiotoxicity [J]. Journal of Experimental & Clinical Cancer Research, 2020, 39(1): 93.
[80] Hatcher H, Planalp R, Cho J, et al. Curcumin: From ancient medicine to current clinical trials [J]. Cellular and Molecular Life Sciences, 2008, 65(11): 1631-1652.
[81] Wang N, Wang Z, Tootle S, et al. Curcumin promotes cardiac repair and ameliorates cardiac dysfunction following myocardial infarction [J]. British Journal of Pharmacology, 2012, 167(7): 1550-1562.
[82] Sunagawa Y, Wada H, Suzuki H, et al. A novel drug delivery system of oral curcumin markedly improves efficacy of treatment for heart failure after myocardial infarction in rats [J]. Biological and Pharmaceutical Bulletin, 2012, 35(2): 139-144.
[83] Yan S, Zhou M, Zheng X, et al. Anti-Inflammatory Effect of Curcumin on the Mouse Model of Myocardial Infarction through Regulating Macrophage Polarization [J]. Mediators of Inflammation, 2021, 2021(1): 9976912.
[84] Lu W, Wang Q, Sun X, et al. Qishen Granule Improved Cardiac Remodeling via Balancing M1 and M2 Macrophages [J]. Frontiers in Pharmacology, 2019, 10: 1399.
[85] Dong Xin, Wen Ruijia, Jiang Jialin, et al. Effects and Mechanisms of Nuankang in Improving Heart Failure After Myocardial Ischemia-Reperfusion Injury [J]. Journal of Chinese Medicine and Herbal Drugs, 2022, 40(12): 166-170, 303.
[86] Shi Lipeng, Deng Jingwei, Yin Erqian, et al. Effects of Fangji Fuling Decoction on Macrophage Polarization and Oxidative Stress in Myocardial Fibrosis Mice [J]. Chinese Journal of Experimental Formulary, 2023, 29(24): 11-18.
[87] Yang Meng, Tan Yuquan, Zhang Junyu, et al. Ginseng-Aconite Injection Alleviates Inflammation in Chronic Heart Failure by Regulating Macrophage Polarization Through the TLR4/NF-κB Pathway [J]. Chinese Journal of Chinese Herbal Medicine, 2024, 49(13): 3574-3582.
[88] Lin Zijun, He Huan, Chen Zixin, et al. Mechanism of Nuanxin Kang in Improving Myocardial Fibrosis in Myocardial Infarction Mice by Regulating Macrophage Polarization and Remodeling Myocardial Cell Metabolism [J]. Chinese Journal of New Drugs and Clinical Pharmacology, 2024, 35(11): 1637-1644.