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Review

Intervention of natural products targeting novel mechanisms after myocardial infarction

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ABSTRACT

Myocardial infarction is a cardiovascular disease (CVD) with high morbidity and mortality, which can trigger a cascade of cardiac pathophysiological changes, including fibrosis, inflammation, ischemia-reperfusion injury (IRI), and ventricular remodeling, ultimately leading to heart failure (HF). While conventional pharmacological treatments and clinical reperfusion therapy may enhance short-term prognoses and emergency survival rates, both approaches have limitations and adverse effects. Natural products (NPs) are extensively utilized as therapeutics globally, with some demonstrating potentially favorable therapeutic effects in preclinical and clinical pharmacological studies, positioning them as potential alternatives to modern drugs. This review comprehensively elucidates the pathophysiological mechanisms during myocardial infarction and summarizes the mechanisms by which NPs exert cardiac beneficial effects. These include classical mechanisms such as inhibition of inflammation and oxidative stress, alleviation of cardiomyocyte death, attenuation of cardiac fibrosis, improvement of angiogenesis, and emerging mechanisms such as cardiac metabolic regulation and histone modification. Furthermore, the review emphasizes the modulation by NPs of novel targets or signaling pathways in classical mechanisms, including other forms of regulated cell death (RCD), endothelial-mesenchymal transition, non-coding ribonucleic acids (ncRNAs) cascade, and endothelial progenitor cell (EPC) function. Additionally, NPs influencing a particular mechanism are categorized based on their chemical structure, and their relevance is discussed. Finally, the current limitations and prospects of NPs therapy are considered, highlighting their potential for use in myocardial infarction management and identifying issues that require urgent attention.

1. Introduction

Cardiovascular diseases (CVDs) remain the primary cause of non-communicable mortality and morbidity globally, significantly contributing to the growing public health challenge [1, 2]. Ischemic heart disease (IHD), particularly myocardial infarction, accounts for a substantial portion of the global cardiovascular health burden, causing cardiac damage in patients with coronary artery disease (CAD) [3, 4]. Myocardial infarction, a severe life-threatening condition at the extreme end of the coronary artery syndrome spectrum, is defined as cardiomyocyte death induced by ischemic injury [5]. The majority of cases are attributed to coronary atherothrombosis (type 1). Prolonged ischemic insults (exceeding 15–20 minutes) may result in irreversible changes to some subendocardial cardiomyocytes, ultimately leading to cell death. Post-infarction, patients face risks of complications including infarct expansion, reinfarction, heart failure (HF), the need for repeat revascularization, and mortality [6].

Current therapeutic approaches for myocardial infarction primarily focus on preserving cardiac function, reducing ischemic myocardium, preventing infarct expansion, and addressing complications such as myocardial fibrosis, severe arrhythmias, and HF to prevent sudden death [7]. Acute cases typically require surgical interventions, including percutaneous coronary intervention (PCI), thrombolytic therapy, or coronary artery bypass grafting (CABG) [8]. However, these procedures have limited applicability due to restricted indications. Moreover, while reperfusion effectively reduces early mortality, it paradoxically increases the risk of exacerbating injury, a phenomenon known as ischemia-reperfusion injury (IRI) [9]. Pharmacological interventions commonly employed in clinical practice include nitrates, anti-coagulants, anti-platelet medications, and statins to alleviate cardiac load and inhibit ventricular remodeling [10, 11]. However, the efficacy of these medications is limited by their short half-lives, adverse effects, and distribution challenges. Consequently, there is a growing demand for safe and effective myocardial infarction preventive medications. Natural products (NPs) have historically made significant contributions to cardiovascular research and care. NPs offer a wide range of applications in treating cardiac conditions due to their substantial biological activity,

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diverse chemical structures, and minimal side effects [12, 13]. Additionally, they serve as valuable sources of bioactive compounds for novel drug development [14]. Evidence suggests that supplementing with NP-derived nutritional substances or using them as pretreatment during myocardial ischemia can significantly enhance cardiac function [15]. NPs have the potential to slow myocardial infarction progression by reducing pathological processes in cardiomyocytes, including apoptosis, inflammation, oxidative stress, and fibrosis [16, 17]. Studies have shown that resveratrol pretreatment inhibits deleterious alterations in infarct size, oxidative stress, and cell death [18]. Similarly, tetrahydropalmatine treatment exerts cardioprotective effects during myocardial infarction by inhibiting cardiomyocyte apoptosis and reducing oxidative stress [19]. Given this evidence, identifying effective preventive medications for myocardial infarction from NPs appears promising. This review aims to provide a comprehensive overview of the role of NPs in myocardial infarction management, focusing on novel pathologic mechanisms and targets, and to offer new perspectives for enhanced research and discovery of NPs for myocardial infarction treatment.

2. Pathophysiological mechanisms post-myocardial infarction and current clinical intervention

The reparative response to extensive cardiomyocyte death in the infarct zone comprises three distinct yet interconnected phases: inflammatory, proliferative, and remodeling [20, 21]. Each phase involves coordinated efforts from various cardiac cell types, and understanding the specific pathophysiological mechanisms at each stage (Fig. 1) may inform therapeutic strategies. Initially, degraded extracellular matrix (ECM) proteins and necrotic cardiomyocytes generate danger signals, triggering inflammatory cascades that attract neutrophils and monocytes to the infarct area. Phagocytes remove cellular debris and matrix fragments, activating endogenous pathways that promote fibrogenic and angiogenic macrophage phenotypes while suppressing pro-inflammatory signaling. As inflammation subsides, the proliferative phase begins, characterized by fibroblast multiplication, transformation into myofibroblasts, and subsequent activation [22]. This process establishes an ECM network that maintains ventricular structural integrity. Concurrent neovessel formation ensures blood supply to the infarct, supporting active metabolic processes. The remodeling phase involves the formation of a mature scar with substantial cross-linked collagen, as structural collagens create a matrix network. Fibroblasts and myofibroblasts transition to matrifibrocytes, while a subset of fibroblast-like cells preserves the scar. Neovessels acquire vascular mural cell coatings. In large infarcts with significant contractile muscle loss, remodeling of non-infarcted myocardium occurs, exhibiting macrophage activation and interstitial fibrosis in response to pressure and volume loads as collagenous tissue replaces necrotic cardiomyocytes in the infarct zone.

Timely reperfusion of the ischemic heart is a standard clinical intervention; however, paradoxically, this treatment may induce irreversible myocardial damage. Currently, the precise pathogenic mechanism of IRI remains unclear, and its pathophysiological process is complex, primarily characterized by intracellular calcium overload, oxidative stress, energy metabolism dysfunction, cell death, and autophagy [23]. Clinically, it manifests as myocardial stunning, arrhythmias, and lethal reperfusion injury. Consequently, reperfusion directly contributes to infarct expansion, which is now believed to account for up to half of the

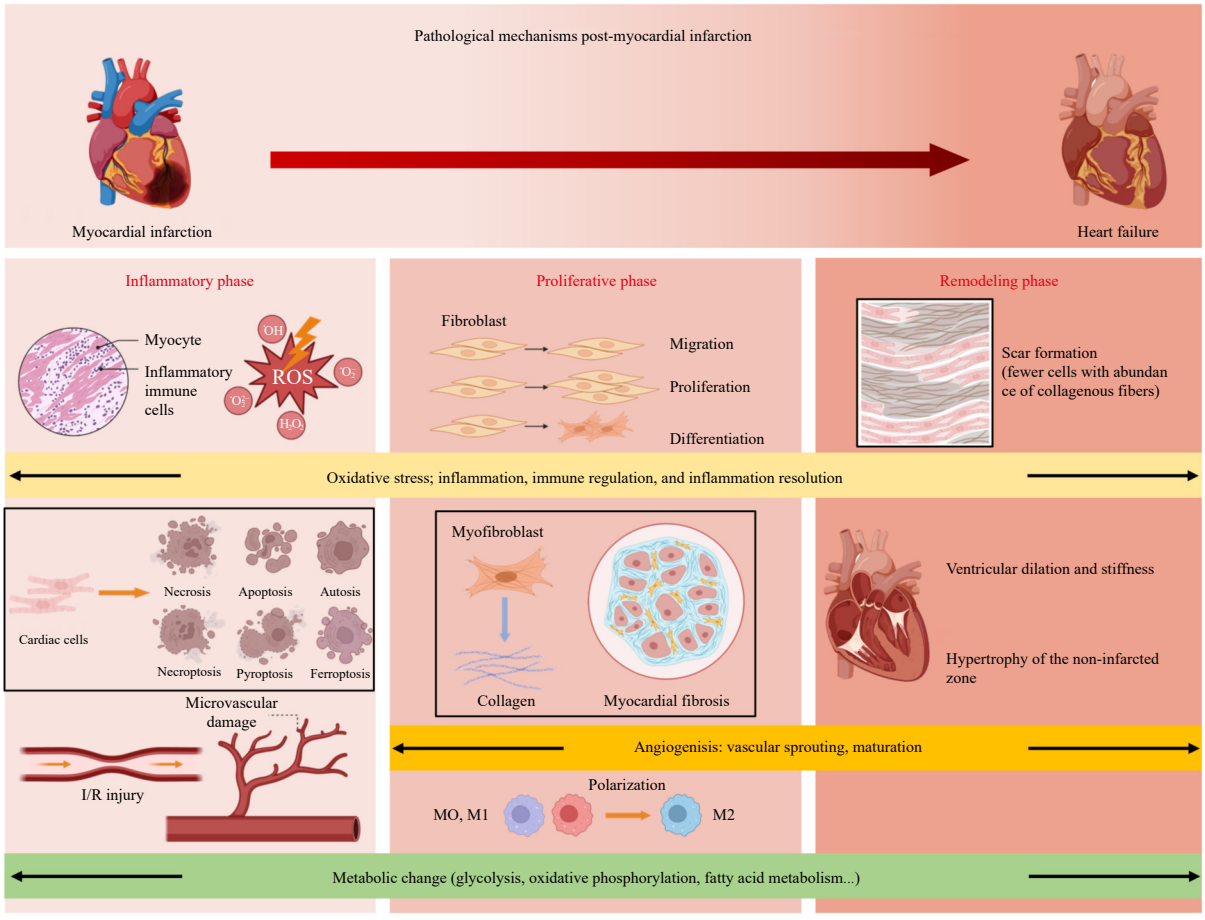

Fig. 1 Progression of pathological changes after myocardial infarction. I/R, ischemia/reperfusion; ROS, reactive oxygen species.

total infarct size [24].

Pharmacologic therapy for patients with myocardial infarction primarily comprises anti-HF medications (angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and mineralocorticoid receptor antagonists), low-density lipoprotein (LDL) cholesterol-lowering therapy (statins), anti-thrombotic regimens (antiplatelet drugs), and anti-inflammatory therapy (colchicine, interleukin-6 receptor inhibitors, and interleukin-1β (IL-1β) neutralizing antibodies). However, observational studies and clinical trials have demonstrated that most drug treatments have not sufficiently improved the prognosis and cardiovascular outcomes of patients with myocardial infarction. Data from the SWEDEHEART registry (n = 371 431) showed that potent anti-thrombotic medication decreased ischemic events following acute myocardial infarction, including improved survival, but increased bleeding events [25]. The Australian COPS trial (n = 795) failed to demonstrate that colchicine could be beneficial after 1 year of standard drug therapy in patients with ACS, even indicating a signal of higher non-CVD mortality compared to placebo [26]. Given the urgent need for safe and effective therapies, this review summarizes studies on the action of NPs based on emerging pathomechanisms or novel targets after myocardial infarction.

3. NPs alleviate inflammation and oxidative stress

The pathophysiology of myocardial infarction involves an inflammatory cascade and reactive oxygen species (ROS)-induced oxidative stress, which exacerbate each other, collectively intensifying cardiac injury. Importantly, initial inflammatory activation is essential for the transition to subsequent repair and proliferation processes. However, the timely management and resolution of inflammation significantly influence the quality of cardiac repair, indicating that optimal recovery necessitates a balanced physiological equilibrium between the inflammatory phase and its resolution [27]. NPs are recognized for their anti-inflammatory and antioxidant properties, demonstrating promising cardiac benefits. Consequently, this study consolidates and elucidates the signaling pathways modulated by NPs in manifesting their anti-inflammatory and antioxidant effects.

3.1. Toll-like receptor 4 (TLR4)/nuclear factor-kappa B (NF-κB) pathway

TLR4, a crucial immune recognition receptor, has been shown to exert a pro-inflammatory effect in murine models of myocardial infarction or IRI [28]. Notably, myocardial inflammation triggered by coronary microinfarction is intimately linked to the activation of the TLR4/NF-κB signaling pathway, and targeted inhibition of this route significantly mitigates the inflammatory consequences following myocardial infarction [29, 30]. Research indicates that astragaloside IV inhibits the TLR4/myeloid differentiation factor 88 (MyD88)/NF-κB pathway to attenuate inflammatory responses in myocardial infarction [31]. Schisantherin A may reduce isoproterenol (ISO)-induced cardiac inflammatory responses by inhibiting the TLR4/mitogen-activated protein kinase (MAPK)/NF-κB axis [32]. Furthermore, anethole mitigates inflammation following myocardial infarction by blocking the TLR4/MyD88 pathway [33]. Latifolin ameliorates cardiac inflammation through inhibition of the hypoxia-inducible factor (HIF)-1α/NF-κB/IL-6 cascade [34]. Ginsenoside Rg3 attenuates myocardial inflammation by modulating the sirtuin 1 (SIRT1)/NF-κB signal [35]. Similarly, sesamin prevents post-myocardial infarction inflammation by inhibiting c-jun N-terminal kinase (JNK) and NF-κB pathways [36]. Lycopene reduces inflammatory response during myocardial remodeling by inhibiting the NF-κB signal [37]. β-elemene inhibits peroxisome proliferator-activated receptor (PPAR)-β activation in HF and nuclear translocation of NF-κB p65, thereby suppressing lipid-induced inflammatory pathways [38].

3.2. Phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB/AKT) pathway

The PI3K/AKT signaling pathway has been extensively studied as a potential target for modulating the development, progression, and repair of myocardial infarction [39]. Calycosin has shown promise as a therapeutic agent by regulating the PI3K-AKT pathway and effectively reducing the inflammatory response in HF [40, 41]. Curcumin, in contrast, suppresses the inflammatory response to IRI by activating the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway [42]. This anti-inflammatory effect is partially attributed to enhanced phosphorylated adenosine 5'-monophosphate-activated protein kinase (p-AMPK)/AMPK protein expression through modulation of macrophage polarization processes [43]. Additionally, 6-gingerol [44], anthocyanidin [45], icariside II [46], and tetrahydropalmatine [19] can also activate PI3K/AKT pathways to mitigate oxidative stress and inflammation in the ischemic heart, thereby conferring cardioprotection. Ginsenoside Rd is another naturally occurring active component that effectively inhibits cardiac inflammation by regulating monocyte/macrophage subpopulations through activation of the AKT/mTOR signaling pathway [47].

3.3. NF-E2-related factor 2 (Nrf2) signaling

Nrf2 primarily functions in high-metabolizing organs such as the liver, skeletal muscle, and the cardiovascular system. It coordinates both external and oxidative stress and initiates the expression of numerous cell protection genes that shield cells from oxidative damage [48]. Isoliquiritigenin (ISL), an isoflavone derived from licorice, was found by Deshan Yao et al. to prevent Nrf2/Heme oxygenase-1 (HO-1) activation, reduce SOD and glutathione peroxidase (GSH-Px) depletion, and inhibit ROS and malondialdehyde (MDA) production, thereby ameliorating cardiac injury in infarcted mice [49]. Similarly, another study demonstrated that ISL therapy mitigated oxidative stress damage by upregulating the expression of downstream HO-1 and Nrf2 [50]. Furthermore, various NPs function as antioxidants by modulating the Nrf2 pathway, including red ginseng polysaccharide1-1 [51], kinsenoside [52], andrographolide [53], anethole [33], and triptolide [54]. These compounds exhibit antioxidant properties and alleviate ischemia-reperfusion (IR) damage through activation of the Nrf2/HO-1 pathway.

3.4. Other mechanisms

ROS generation in CVD is primarily attributed to the NOX system [55], However, several natural compounds demonstrate inhibitory effects on NOX activity, thereby reducing ROS production: dioscin [56], tanshinone IIA [57], and ginsenoside Rb1 [58]. Cardiac remodeling benefits from the inhibition of immune-related oxidative stress mediated by CXC chemokine receptor 2 (CXCR2) [59]. Esculentoside A directly binds to CXCR2, suppressing its levels and consequently reducing oxidative stress and inflammation in myocardial infarction [60]. Aldehyde dehydrogenase 2 (ALDH2) metabolizes or detoxifies acetaldehyde and other harmful aldehydes. Its activation in IRI may mitigate myocardial damage by decreasing ROS formation [61]. Calycosin modulates ALDH2 signaling to attenuate oxidative stress-induced cardiomyocyte death [62]. Glutathione peroxidase 4 (GPX4) activity regulates glutathione metabolism, a crucial component of the body's antioxidant system [63]. Geniposide prevents oxidative stress and protects against myocardial damage by stimulating the G-rich RNA sequence binding factor 1 (Grsf1)/GPX4 axis [64]. Protocatechuic aldehyde acts as an antioxidant in myocardial infarction by providing a reducing

equivalent to scavenge ROS, thereby increasing reduced GSH levels. Dihydrotanshinone I protects cardiomyocytes from reperfusion damage by enhancing intrinsic ROS elimination [65]. Furthermore, in rats with myocardial infarction, thymol reduces ISO-induced inflammation by inhibiting lysosomal enzyme release and suppressing pro-inflammatory cytokine production [66].

Furthermore, this study aims to elucidate the anti-inflammatory or antioxidant effects of these NPs in relation to their chemical structures (Supplementary Table 1). The analysis reveals that terpenoids, flavonoids, phenols, saponins, lignans, alkaloids, and other compounds constitute the majority of the aforementioned NPs. Terpenes and their derivatives, characterized by the isoprene unit (C5) structure comprising glutaraldehyde hydroxyl acid, exhibit anti-inflammatory, antioxidant, and immunomodulatory properties. While the regulatory mechanisms of these terpenes vary based on their chemical structures, they generally inhibit inflammatory signaling (modulating NF-κB or Nrf2) and mitigate oxidative stress. Extensive research has demonstrated that flavonoids effectively reduce inflammatory cytokines, modulate inflammation-related pathways, and decrease ROS production [67]. The molecular structure of flavonoids enables direct ROS scavenging, activation of antioxidant enzymes, and metal cation chelation. Phenolic compounds, with their conjugated structures and hydroxyl groups, exhibit potent antioxidant and anti-inflammatory activities through ROS scavenging and metal ion reduction. Although alkaloids display diverse activities, recent research indicates that tetrahydropalmatine, a chiral center tetrahydroberberine isoquinoline alkaloid, is the sole alkaloid shown to attenuate inflammation during myocardial infarction. Among natural saponins, ginsenosides (Ginsenoside Rg3, Rd, and Rb1) have garnered significant attention in antioxidant and anti-inflammatory research following myocardial infarction.

4. NPs prevent cell death

Cardiomyocyte death encompasses multiple forms and signaling pathways, which are interconnected rather than independent. The relative contribution of each form or pathway remains unclear, presenting a challenge for therapeutic interventions. Research has established that inhibiting RCD can effectively treat myocardial infarction, with a primary focus on death receptors and mitochondrial pathways [68]. While previous studies have demonstrated that NPs could prevent apoptosis and necrosis through conventional mechanisms during myocardial infarction, recent investigations have increasingly explored the cardioprotective effects of NPs targeting ferroptosis, pyroptosis, and autophagy. Some of these mechanisms have shown promise, while other studies are ongoing (Fig. 2).

4.1. Classical mechanisms

Death receptors can be categorized into two distinct types: traditional death receptors (tumor necrosis factor (TNF) superfamily) and certain dependent receptors, such as tropomyosin-related receptor A (TrkA). Members of the TNF receptor superfamily facilitate the formation of intracellular death-inducing signaling complexes during apoptosis through their intracellular death structural domains. This process activates caspase-8 and its downstream effectors, caspase-3 and caspase-7. Additionally, when death ligands bind to their respective receptors, complex I formation and signaling are initiated, activating necroptosis mediated by receptor-interacting protein kinase 1 (RIPK1) and RIPK3 and their downstream pathways. Although several NPs have been shown to regulate cell death by acting on RIPK3, research on myocardial infarction in this context remains limited. Linlin Sun et al. demonstrated that dihydromyricetin modulates RIPK3/calcium calmodulin protein kinase II (CaMKII) to mitigate high glucose-induced cardiomyocyte apoptosis [69]. Tanshinone I has been reported to exhibit cardioprotective effects *in vitro* and *in vivo* by inhibiting the RIP1/RIP3/mixed lineage kinase domain-like protein (MLKL) axis [70]. Similarly, baicalin has been shown to attenuate necroptosis by suppressing the expression of RIP1, RIP3, and p-MLKL, thereby alleviating IRI [71].

The mitochondrial pathway-mediated apoptosis is regulated by both pro- and anti-apoptotic members of the B-cell lymphoma-2 (Bcl-2)-2 protein family. This pathway promotes the activation of the caspase cascade reaction through the release of apoptotic factors, leading to the cleavage of multiple proteins and ultimately cell destruction. Several natural active ingredients have demonstrated significant cardioprotective effects by downregu-

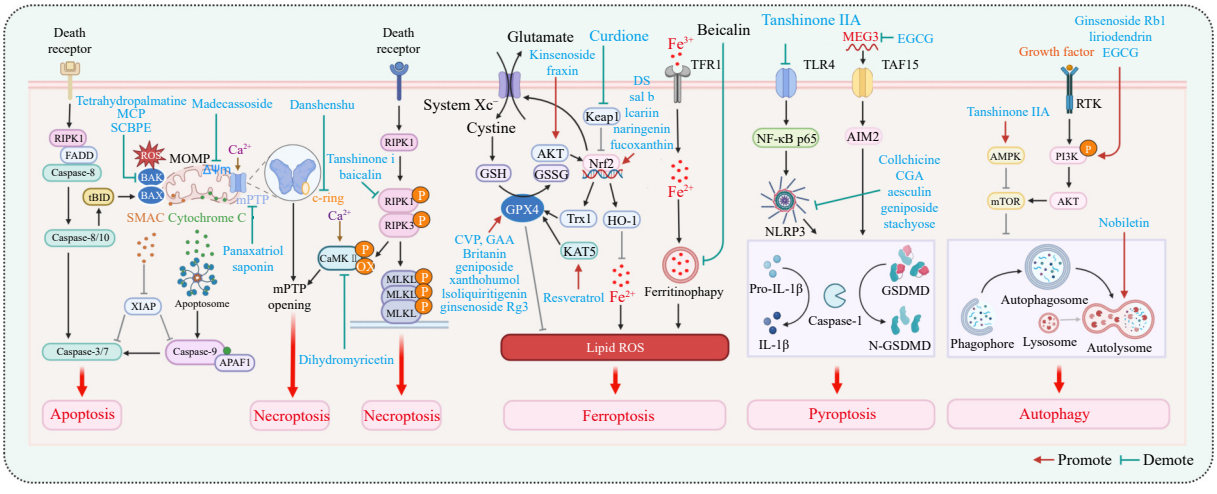

Fig. 2 NPs targeting programmed cell death in myocardial infarction. FADD, Fas-associated protein with death domain; XIAP, X-linked inhibitor of apoptosis; tBID, truncated BH3 interacting domain death agonist; SMAC, second mitochondria-derived activator of caspases; mPTP, mitochondrial permeability transition pore; MOMP, mitochondrial outer membrane permeabilization; APAF1, apoptotic protease activating factor-1; CaMK Ⅱ, Calcium-calmodulin (CaM)-dependent protein kinase II; RIPK1/3, receptor-interacting protein kinase 1/3; MLKL, mixed lineage kinase domain like protein; GSH, glutathione; GSSG, oxidized glutathione; GPX4, glutathione peroxidase 4; AKT, Protein Kinase B; Trx1, thioredoxin1; Keap1, kelch-like ECH-associated protein 1; Nrf2, nuclear factor-erythroid factor 2; TFR1, transferrin receptor 1; TLR4, Toll-like receptors 4; NF-κB p65, nuclear factor-kappa B; NLRP3, NOD-like receptor (NLR) with a pyrin domain 3; MEG3, maternally expressed gene 3; TAF15, TATA-box binding protein associated factor 15; AIM2, absent in melanoma 2; GSDMD, gasdermin D; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; RTK, receptor-coupled tyrosine kinases; PI3K, phosphatidyl-inositole-3 kinase. MCP, *Momordica charantia* polysaccharides; SCBPE, *Schisandra chinensis* (Turcz.) Baill bee pollen extract; PTS, panaxatriol saponin; CVP, Chuanminshen violaceumis polysaccharide; GAA, gossypol acetic acid; DS, Salvia miltiorrhiza Bunge; Sal B, Salvianolic acid B; EGCG, epigallocatechin gallate; CGA, chlorogenic acid.

lating Bax and caspase-3 expression while increasing Bcl-2 levels. These include *Momordica charantia* polysaccharides [72], madecassoside [73], tetrahydropalmatine [19], and *Schisandra chinensis* (Turcz.) baill bee pollen extract [74]. Additionally, targeting mitochondrial permeability transition pore (mPTP) opening is crucial in necrotic apoptosis. Panaxatriol saponin (PTS), the primary active ingredient in *P. notoginseng*, attenuates necrotic apoptosis and mitigates cardiac injury by reducing mPTP opening and maintaining ΔΨm [75]. The c-subunit ring, a core component of mPTP activity [76], can be regulated by Danshenshu, isolated from traditional Chinese herbs, thereby preventing cellular damage [77].

4.2. Ferroptosis

The pathological process of IRI is closely associated with ferroptosis-related cellular mechanisms, including lipid peroxidation, abnormal intracellular iron concentrations, and reduced levels of anti-lipid peroxidation enzymes, such as GPX4 [78]. Recent research has shown that NPs can modulate ferroptosis, thereby mitigating IRI [79]. Currently, the system Xc-/GSH/GPX4 axis is considered the primary mechanism involved in ferroptosis. Naringenin, a compound family found in citrus fruits, has been demonstrated to alleviate IRI by inhibiting ferroptosis through modulation of the Nrf2/System xc-/GPX4 axis [80]. Curdione, a sesquiterpenoid extracted from Curcumae Radix, effectively prevents ferroptosis in myocardial infarction by regulating the Keap1/Thioredoxin-1(Trx1)/GPX4 cascade [81]. Similarly, Jing Liu et al. demonstrated that resveratrol therapy improved myocardial injury and fibrosis in rats, primarily by inhibiting ferroptosis through the induction of K(lysine) acetyltransferase 5 (KAT5)/GPX4 [82]. Curdione, derived from Curcumae Radix, can efficiently prevent myocardial ferroptosis by upregulating GSH and GPX4 expression [81]. Additionally, several natural active ingredients can increase GPX4 levels, including chuanminshen violaceumis polysaccharide [83], ginsenoside Rg3 [84], ISL [50], geniposide [64], gossypol acetic acid [85], britanin [86] and xanthohumol [87], suggesting their potential to counteract ferroptosis. Notably, various NPs have been found to inhibit ferroptosis by modulating the Nrf2/HO-1 pathway. Icariin, a flavonoid derived from epimedii, was administered to treat hypoxia/reoxygenation-induced H9C2 cells, increasing GPX4 levels while reducing $Fe^{[2+]}$ and acyl-CoA synthetase long-chain family member 4 (ACSL4) levels. It primarily prevented cardiomyocytes from experiencing H/R-induced ferroptosis by activating the Nrf2/HO-1 signaling pathway [88]. Kinsenoside [52] and fraxetin [89] also reduced iron mortality in myocardial infarction by activating the AKT/Nrf2/HO-1 pathway. Moreover, fucoxanthin [90], salvia miltiorrhiza bunge [91], and salvianolic acid B [92] similarly inhibited ferroptosis *via* Nrf2 signaling pathway activation. Ferritinophagy induces iron overload and ferroptosis following myocardial IRI. Targeting ferritin autophagy with baicalin significantly reduced myocardial injury in rats [93]. Furthermore, evidence suggests that berberine [94], gossypol acetic acid [85], puerarin [95], baicalein, and luteolin [96] could prevent IRI-related ferroptosis in cardiomyocytes, although the precise mechanism remains to be elucidated.

4.3. Pyroptosis

Pyroptosis is a form of RCD characterized by cell membrane rupture, inflammasome activation, and inflammatory factor release. Animal models have demonstrated that colchicine suppresses the NOD-like receptor (NLR) with a pyrin domain 3 (NLRP3) inflammasome pathway in myocardial infarction. A recent randomized clinical study examining cardiovascular outcomes in patients treated with colchicine post-myocardial infarction revealed that colchicine administration within 30 days reduced cardiovascular ischemic event incidence [97]. Chlorogenic acid treatment mitigated NLRP3 inflammasome-induced pyroptosis in myocardial tissue and decreased infarcted size in mice [98]. Similarly, aesculin inhibits cardiomyocyte pyroptosis *via* the AKT/glycogen synthase kinase 3 beta (GSK3β) /NF-κB/NLRP3 signaling pathway, resulting in improved myocardial injury and hemodynamic function [99]. Geniposide has also been reported to confer cardiac beneficial effects by inhibiting cardiomyocyte pyroptosis through modulation of the AMPK/TXNIP/NLRP3 axis [100]. Furthermore, tanshinone IIA prevents cardiomyocyte pyroptosis by inhibiting the TLR4/NF-κB p65 pathway, a classical upstream signal for NLRP3 inflammasome activation [101]. Stachyose inhibits the pyroptotic pathway in macrophages by downregulating NLRP3 and gasdermin D expressions, resulting in decreased IL-1β and IL-18 levels. While NLRP3 is the most extensively studied inflammasome, emerging evidence suggests that the absent in melanoma 2 (AIM2) inflammasome plays a crucial role in regulating pyroptosis [102]. Epigallocatechin gallate, a bioactive polyphenol from green tea, protects cardiomyocytes from pyroptosis *via* the maternally expressed gene 3 (MEG3) /TAF15/AIM2 axis [103].

4.4. Autophagy

Autophagy is a crucial mechanism for intracellular clearance and recycling, essential for maintaining cardiomyocyte homeostasis under both basal and stressed conditions [104]. However, cardioprotection requires optimal levels of autophagic flow and activation. Increasing evidence suggests that NPs can modulate autophagy, thereby exerting cardioprotective effects. For instance, nobiletin, a polymethoxylated flavonoid derived from citrus, promotes lysosomal acidification and autophagic flux, mitigating adverse cardiac remodeling following myocardial infarction in rats [105]. The mTOR protein is a key negative regulator of autophagy, and several NPs have shown promising effects in controlling mTOR-mediated autophagy. Tanshinone IIA treatment enhanced autophagy in an HF model and regulated the expression of autophagy-associated markers, including Beclin1, p62, and protein 1 light chain 3, by activating the AMPK-mTOR signaling pathway [106]. Conversely, ginsenoside Rb1 [107], liriodendrin [108], and epigallocatechin gallate [109] attenuate IRI and fibrosis by inhibiting excessive cardiomyocyte autophagy through activation of the PI3K/AKT/mTOR signaling pathway. Furthermore, emerging evidence indicates crosstalk between different death pathways. Salvianolic acid B mitigates disease progression by modulating autophagy to prevent apoptosis [110]. Paeonol inhibits both apoptosis and autophagy, exhibiting cardioprotective effects during IRI by mediating crosstalk between apoptosis and autophagy signaling [111]. Elucidating the central mechanisms regulating these pathways may provide new insights for future myocardial infarction therapies.

Our analysis identified these NPs as primarily comprising phenols, alkaloids, terpenoids, flavonoids, saponins, polysaccharides, coumarins, and other categories, with terpenoids, flavonoids, and phenols being the most prevalent (Supplementary Table 2). Terpenoids, the most diverse and widely distributed NPs in nature [112], exhibit a broad spectrum of biological functions and have demonstrated beneficial effects in regulating cardiomyocyte mortality following myocardial infarction. Flavonoids and phenolic compounds, due to their unique polyphenol structure, play distinct roles in anti-oxidation, inhibition of ferroptosis and apoptosis, and regulation of cellular autophagy. However, recent research has predominantly focused on the role these NPs play in controlling cardiomyocyte death, with relatively few studies examining the structural changes and derivatives of these active molecules. Moreover, while preliminary screening of NPs has targeted cell death properties, a comprehensive and systematic evaluation framework to thoroughly analyze the precise mechanism

of action and efficacy of these substances in the context of myocardial infarction remains lacking.

5. NPs mitigate myocardial fibrosis

Maintaining the structural integrity of the ventricular wall following myocardial infarction critically relies on an effective reparative scarring process. The primary regulatory mechanism of this process involves the progressive differentiation of cardiac-activated fibroblasts into myofibroblasts, followed by the deposition of ECM proteins in the cardiac mesenchyme [113, 114]. However, continuous activation of myofibroblasts may lead to excessive collagen production, originating in the infarcted area and extending to the peri-infarct margins and even to healthy myocardium, ultimately increasing stiffness in the lesion and surrounding ventricular wall [115]. Multiple pathways mediate cardiac fibroblast activation and fibrotic processes. Notably, modulation of the transforming growth factor-β1 (TGF-β1)/mothers Against DPP Homolog (SMAD) pathway is primarily responsible for most of the documented ameliorative effects of NPs on cardiac fibrosis. The binding of TGF-β1 to the TGF-β receptor initiates the traditional SMAD signaling cascade, which is crucial for ECM secretion and deposition [116]. Furthermore, current research has proposed novel pathways and mechanisms by which NPs prevent cardiac fibrosis (Fig. 3).

5.1. Classical TGF-β1/ SMAD pathway

Research has demonstrated that 20(*S*)-ginsenoside Rg3 [117, 118] and ginsenoside Re [119] directly inhibit the TGF-β1/SMAD2/3 pathway, reducing interstitial fibrosis remodeling and improving heart function. Likewise, compounds such as icariin [120], aloe-emodin [121], loureirin B [122], zerumbone [123], forsythiaside B [124], astragaloside IV [125], resveratrol [126], quercetin [127] and curcumin [128] have been shown to mitigate detrimental cardiac fibrosis by inhibiting TGF-β/SMAD-related pathways. Additionally, several NPs, including caffeic acid [129], ethyl ferulate [130], and calycosin [131], target TGFBR1 to counteract myocardial fibrosis. Other active ingredients exert their therapeutic effects by directly influencing the upstream components of the TGF-β/SMAD pathway. Long-term administration of Scutellarin prevents interstitial fibrosis following myocardial infarction and reduces ventricular remodeling by inhibiting TGF-β1 production [132]. Similarly, muscone [133] and puerarin [134] decrease TGF-β1 levels, thereby reducing cardiac collagen deposition and fibrosis. Ginkgolic acid, a small ubiquitin-like modifier 1 (SUMO-1) inhibitor, suppresses the PML/Pin1 axis, a pathway that positively regulates TGF-β1 messenger RNA (mRNA), leading to TGF-β1 mRNA degradation and attenuation of cardiac fibrosis [135].

5.2. Other emerging pathways

Targeting specific microRNAs (miRNAs) has demonstrated anti-fibrotic effects, while ginsenoside Re inhibits the MyD88/NF-κB pathway by upregulating miR-489 transcription, thereby improving collagen deposition and cardiac fibroblast aggregation post-myocardial infarction [136]. Additionally, ginsenoside Rg2 mitigates myocardial fibrosis and restores cardiac function through

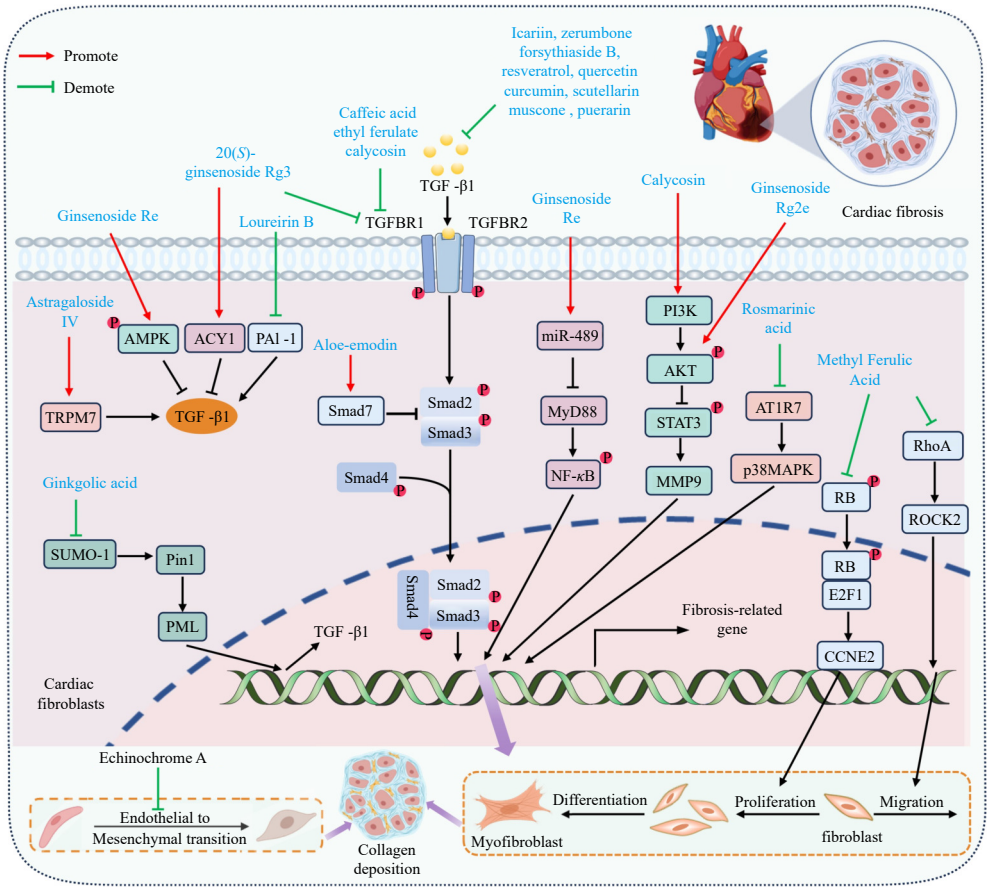

Fig. 3 Classical and emerging mechanisms by which NPs mitigate myocardial fibrosis. TGFBR, transmembrane TGF-β receptors; Smad, mothers Against DPP Homolog 3; AMPK, adenosine 5′-monophosphate (AMP)-activated protein kinase; ACY1, aminoacylase-1; PAI-1, plasminogen activator inhibitor-1; TRPM7, transient receptor potential melastatin 7; SUMO, small ubiquitin-like modifier; PML, promyelocytic leukemia; Pin1, peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; STAT3, signal transducer and activator of transcription 3; MMP9, matrix metalloproteinase 9; RB, retinoblastoma; E2F1, E2F transcription factor 1; CCNE2, cyclin E2 gene; RhoA, ras homolog family member A; ROCK2; Rho-associated kinase 2; p38MAPK, p38 mitogen-activated protein kinase; MyD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor kappa-B.

AKT pathway activation [137]. Calycosin, a novel PI3K activator, stimulates the AKT-IκB kinase (IKK)/signal transducer and activator of transcription 3 (STAT3) axis in fibroblasts, reducing fibrosis in HF [40]. Early fibrosis is characterized by the proliferation and differentiation of resident fibroblasts at the infarct site, along with enhanced migration. Methyl Ferulic acid inhibits human cardiac fibroblasts (HCFs) proliferation and migration by suppressing the pRB-E2F1/CCNE2 and RhoA/ROCK2 pathways, attenuating HCFs differentiation post-myocardial infarction and restoring cardiac function [138]. The renin-angiotensin system (RAS) plays a crucial regulatory role in post-myocardial infarction fibrosis progression. Rosmarinic acid protects against myocardial fibrosis by regulating the angiotensin type 1 receptor (AT1R)/phospho-p38 MAPK pathway and increasing ACE2 expression [139]. Cryptotanshinone (CTS) inhibits ang II-induced phosphorylation of extracellular-regulated kinase 1/2 (ERK1/2) and expression of cyclooxygenase (COX)-2, NOX-2, and NOX-4, resulting in anti-fibrotic effects *in vitro* and attenuation of cardiac fibrosis *in vivo* [140]. Furthermore, the primary $Ca^{[2+]}$-permeable channel in fibroblasts, transient receptor potential cation channel, subfamily M, member 7 (TRPM7), controls cardiac fibroblasts' transformation, migration, and proliferation. Astragaloside IV prevents cardiac fibrosis by blocking the TRPM7 channel [141].

5.3. Endothelial-mesenchymal transition (EndMT)

While resident cardiac fibroblasts serve as the primary source of activated myofibroblasts, endothelial cells (ECs) can also generate these cells through the EndMT process [142]. During EndMT, ECs undergo reprogramming, resulting in a reduction of endothelial-specific proteins and an acquisition of mesenchymal cell phenotypes. This transformation leads to the secretion of fibrillar collagens and fibronectin, triggering a fibrotic response. Consequently, targeting EndMT may offer a promising therapeutic approach [143]. Research indicates that echinochrome A reduces the proportion of pro-fibroblasts and inhibits inflammation-mediated EndMT, thereby limiting fibrosis [144]. Plantamajoside (PMS), a phenylpropanoid glycoside extracted from Plantago asiatica, has been shown to inhibit the RAGE-autophagy-EndMT pathway by directly binding to RAGE, thus mitigating cardiac fibrosis [145]. Recent studies have also revealed that several Chinese herbal preparations commonly used in clinical settings suppress the EndMT process, thereby improving cardiac fibrosis [146, 147]. However, further investigation is required to identify the key natural active substances involved in these preparations.

NPs with anti-fibrotic properties are generally categorized based on their characteristic skeletal structures, primarily encompassing terpenoids, flavonoids, phenols, saponins, and quinones (Supplementary Table 3). These compounds typically contain multiple hydroxyl groups, enabling them to interact with biomolecules such as TGF-β1. The diverse biological effects of flavonoids can be attributed to the attachment of phenolic hydroxyl groups to various functional groups, potentially accounting for their different anti-fibrotic binding targets. Notably, ginsenoside Re, ginsenoside Rg2, and 20(*S*)-ginsenoside Rg3 share similar structures and belong to the dammarane triterpene saponin class. Their varying anti-fibrotic targets may result from differences in the number and position of substituted sugar groups. Aloe-emodin, a natural anthraquinone extract, differs from other mentioned anthraquinones. A recent study revealed that aloe-emodin possesses free hydroxyl groups at positions 1 and 3, which may explain its ability to inhibit cardiac fibrosis progression. Further research is needed to elucidate the core structures or functional groups responsible for the anti-fibrotic effects of other NP types, such as esters, glycosides, and organic acids.

6. NPs improve angiogenesis

Extended ischemia following myocardial infarction inevitably leads to substantial microvascular damage. Structurally, microcirculatory disturbances are characterized by endothelial swelling, microvascular spasm, and increased capillary resistance, which impede or interrupt the communication between cardiomyocytes and fresh blood flow [148]. Angiogenesis plays a crucial role in the recovery phase, during which neovascularization efficiently repairs damaged cardiomyocytes and significantly mitigates the detrimental consequences of cardiac remodeling [149, 150]. The precise regulation of angiogenesis depends on several complex biomolecules, including pro- and anti-angiogenic factors [151], as well as close interactions and synergistic effects of multiple cell types [152]. In wound healing and hindlimb ischemia models, NPs have shown promising pro-angiogenic effects and therapeutic efficacy [153, 154]. This section identifies several NPs with pro-angiogenic properties and their mechanisms of action (Fig. 4) to establish a theoretical foundation for the development of pro-angiogenic drugs for myocardial infarction management.

6.1. Classical mechanisms

The JAK/STAT3 and PI3K/AKT signaling pathways, along with vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), HIF-1α, and endothelial nitric oxide synthase (eNOS), play crucial roles in angiogenesis within the ischemic heart. Astragaloside IV not only activates JAK-STAT3 signaling in ECs but also inhibits phosphatase and tensin homolog deleted on chromosome ten (PTEN), thereby promoting EC proliferation and lumen formation, which enhances vascular density at the site of myocardial infarction [155, 156]. Administration of ferulic acid stimulates angiogenesis by upregulating the expression of HIF-1α, PDGF, and VEGF [157]. Furthermore, genetic enhancement of Trx-1 expression in ECs increases HO-1 synthesis and mitigates angiogenesis-related issues [158]. In rat models of ischemic myocardium, resveratrol facilitates cardioprotection and neovascularization through the Trx-1-HO-1-VEGF pathway [159].

6.2. Noncoding RNAs (ncRNAs) cascade

Approximately 98% of transcribed RNAs are ncRNAs, primarily comprising miRNAs, long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). These ncRNAs participate in the regulation of numerous biological processes, with increasing attention focused on their roles in angiogenesis [160]. Recent studies have identified the capacity of NPs to modulate these small RNA molecules. Berberine enhances AMPK expression and subsequent AKT phosphorylation by upregulating miR-29b expression in ECs, thereby promoting neovascularization [161]. Tanshinone IIA downregulates miR-499-5p and reduces its binding to the PTEN mRNA promoter, leading to EC proliferation, migration, and tube formation, ultimately improving cardiac function [162]. Additionally, dioscin treatment promotes an increase in lncRNA MANTIS and the formation of a complex between MANTIS and BRG1 in ECs, resulting in increased expression of angiogenesis-related genes and improved cardiac function [163]. Furthermore, astragaloside IV has been demonstrated to induce exosomes derived from bone marrow mesenchymal stem cells (BMSCs), potentially related to the ncRNAs contained within these exosomes [164, 165]. This evidence suggests that the potential of NPs to promote neovascularization is realized, at least in part, through a newly defined mechanism: the ncRNA cascade.

6.3. EPC function

During tissue or vascular injury, circulating EPCs are re-

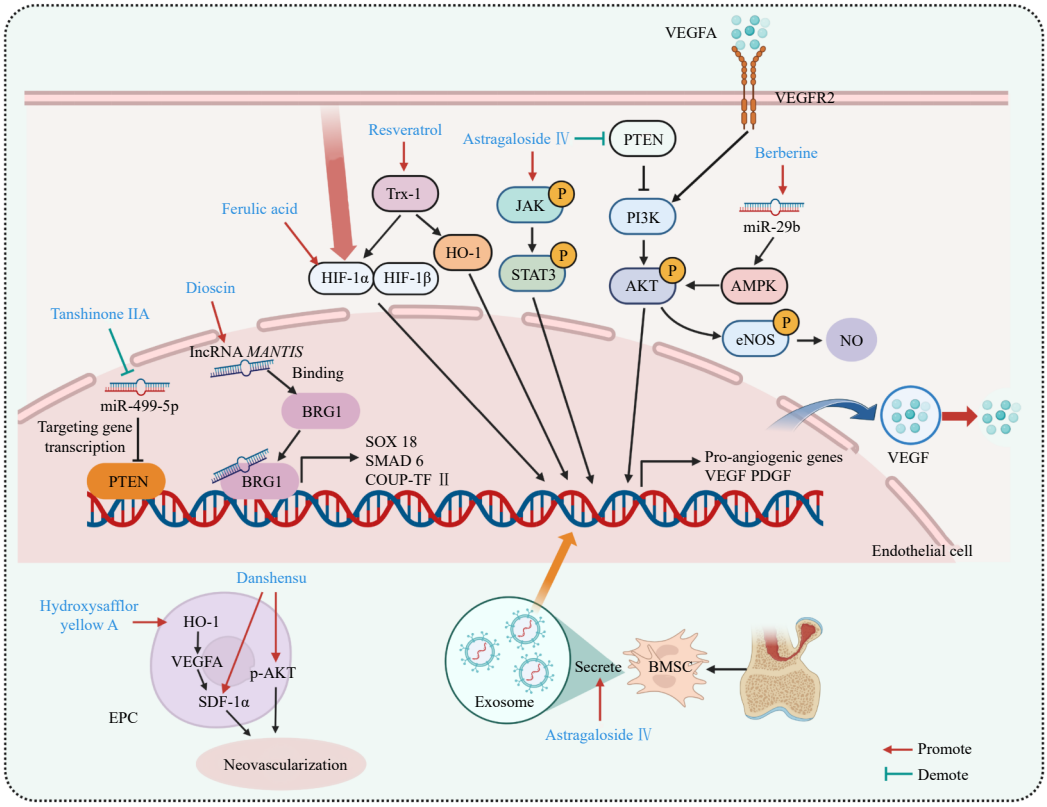

Fig. 4 The mechanisms by which NPs encourage angiogenesis following myocardial infarction. PTEN, phosphatase and tensin homolog deleted on chromosome ten; PI3K, phosphatidylinositol-3-kinase; AKT, protein kinase B; AMPK, AMP-activated protein kinase; eNOS, endothelial nitric oxide synthase; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; Trx-1, thioredoxin-1; HO-1, heme oxygenase-1; HIF-1α/β, hypoxic-induced factor-1α/β; VEGF, vascular endothelial growth factor; VEGFA, vascular endothelial growth factor-A; VEGFR2, vascular endothelial growth factor receptor 2; PDGF, platelet-derived growth factor; BRG1, Brahma-related gene-1; SOX18, SRY (sex determining region Y)-box 18; SMAD6, mothers against decapentaplegic homolog 6; COUP-TFII, chicken ovalbumin upstream promoter-transcription factors II; SDF-1α, stromal cell-derived factor-1α; EPC, endothelial progenitor cells; BMSC, bone marrow mesenchymal stem cells.

cruited to injury sites, facilitating the formation of new blood vessels either de novo (vasculogenesis) or as an extension of preexisting ECs (angiogenesis) [166]. EPCs are being investigated as a potential therapy for myocardial infarction due to their ability to create and repair vascular tissue. HO-1, an enzyme associated with angiogenesis [167], promotes this process by upregulating VEGF, chemokine SDF-1, and its specific receptor CXCR4 in the ischemic area, and mobilizing ECs from bone marrow to enter the angiogenesis microenvironment [168]. Research indicates that Danshensu enhances the survival of EPCs under hypoxic conditions by phosphorylating the survival signal AKT and activating the SDF-1α/CXCR4 signaling pathway, thereby improving their migration and angiogenesis capabilities [169]. Through the HO-1/VEGF-A/SDF-1α signal cascade, hydroxysafflor yellow A can enhance the activity of EPCs, thus promoting the formation of myocardial neovascularization and improving heart function in myocardial infarction mice [170]. Furthermore, in models of hindlimb or cerebral ischemia, NPs have been shown to enhance neovascularization through increased EPC activity and enhanced EPC differentiation [171,172].

Research has demonstrated that a limited number of structurally diverse natural compounds enhance angiogenesis following myocardial infarction (Supplementary Table 4). The polyphenolic structural characteristics of phenolic products may enable ECs or EPCs to mitigate oxidative stress in hypoxic environments, thereby enhancing survival and promoting angiogenesis. A network pharmacology and molecular docking study indicates that astragalosides exhibit strong binding affinity to angiogenesis-related targets, potentially due to the unique structural features of their saponins [173]. Other natural compounds that promote angiogenesis include alkaloids, terpenoids, and additional classes, which have been comparatively understudied. Consequently, there is a need for more extensive research to explore their similarities and structure-activity relationships.

7. NPs modify cardiac metabolism

Coronary occlusion precipitates a significant reduction in oxygen delivery to cardiomyocytes and rapid alterations in cardiac metabolism. This is evidenced by the suppression of oxidative metabolism of fatty acids, carbohydrates, ketones, and amino acids, coupled with the activation of anaerobic glycolysis [174]. During IR, the glycolytic metabolic pathway serves as the primary energy source for cardiomyocytes. These metabolic shifts during ischemia and reperfusion substantially influence the extent of cardiac injury following an ischemic episode, suggesting that metabolic interventions hold considerable potential for cardiac protection. Importantly, recent research has revealed the capacity of NPs to modulate cardiac metabolism (Fig. 5), expanding our understanding of NP mechanisms and offering novel approaches for myocardial infarction management.

7.1. Glycolysis

During IRI, the transcription factor HIF-1α upregulates the expression of its target genes to stimulate glycolysis [175]. Excessive glycolysis may promote fibroblast differentiation and proliferation [176], an unfavorable outcome of myocardial infarction. Salvianolic acid A has been demonstrated to inhibit the AKT/GSK-3β/HIF-1α axis, which regulates LDHA-driven aerobic glycolysis, thereby preventing fibroblast activation [177]. Furthermore, research indicates that mTOR complex 1 (mTORC1)-mediated glycolysis provides crucial energy support for M1 inflammatory macrophages, enhancing their activation and pro-inflammatory

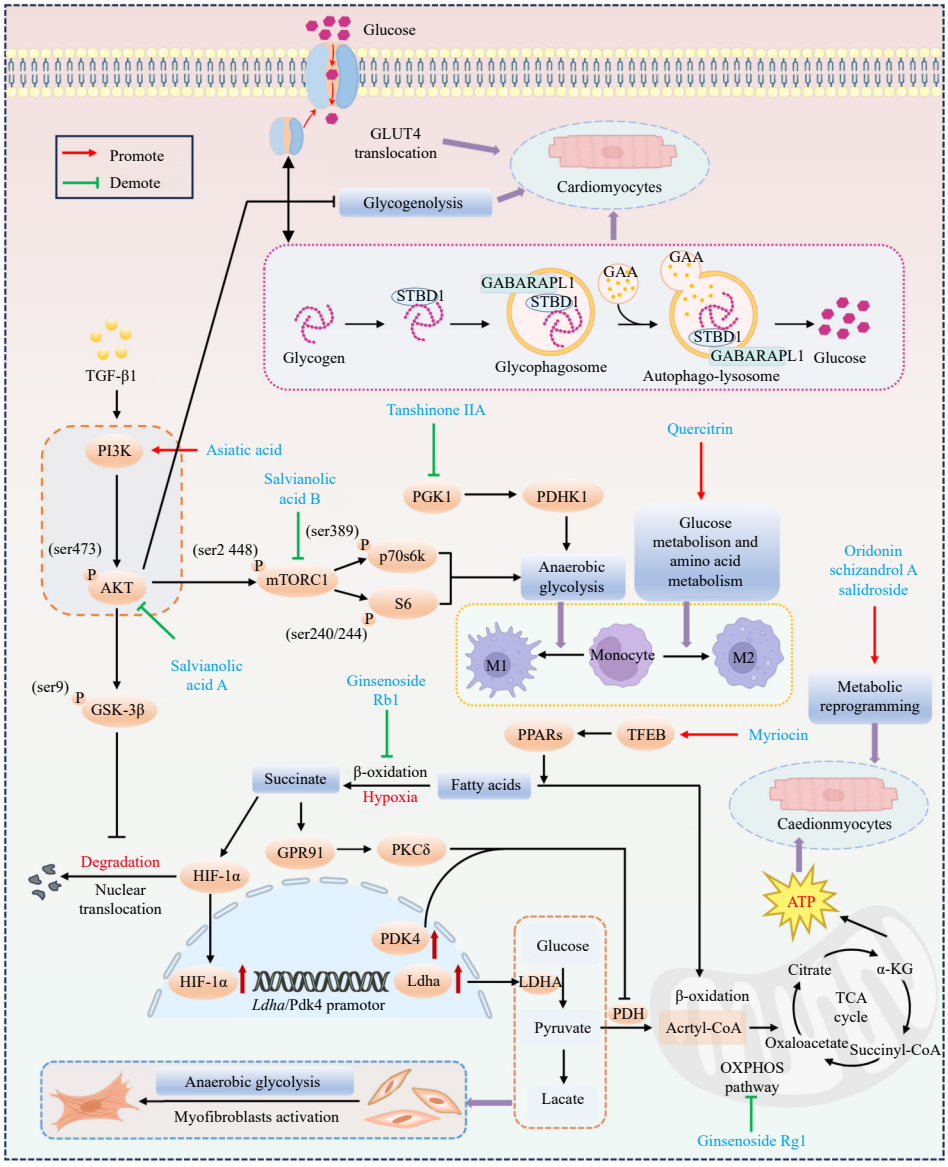

Fig. 5 Nps exert cardioprotective effects by regulating cardiac metabolism during myocardial infarction. LDHA, lactate dehydrogenase-A; HIF-1α, hypoxia-inducible factor-1α; TGF-β1, transforming growth factor-β1; GSK-3β, glycogen synthase kinase-3β; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; PDH, pyruvate dehydrogenase; mTOR, mammalian target of rapamycin; p70s6k, ribosomal protein S6 kinase; S6, S6 ribosomal protein; GAA, acid α-glucosidase; STBD1, starch-binding domain-containing protein 1; GABARAPL1, GABA type A receptor-associated protein like 1; GLUT4, glucose transporter 4; GPR91, G protein-coupled receptor 91; PDK4, pyruvate dehydrogenase kinase 4; PKCδ, protein kinase Cδ; TFEB, transcription factor EB; PPARs, peroxisome proliferators-activated receptors; PGK, phosphoglycerate kinase; PDHK1, pyruvate dehydrogenase kinase; OXPHOS, oxidative phosphorylation.

properties [178, 179]. Salvianolic acid B inhibits mTORC1-dependent glycolysis during IRI, reducing M1 macrophages and increasing M2 macrophages at the infarct site, thus mitigating inflammation and improving cardiac function [180]. Cardiac glycogenolysis serves as the primary glucose source at the infarct site during ischemia [181]. Asiatic acid activates PI3K/AKT signaling to enhance glycogen degradation and utilization, providing free glucose to the infarct site and thereby mitigating energy metabolism injury in cardiomyocytes and protecting the ischemic myocardium [182]. However, glucose produced by glycogenolysis is a significant substrate for excessive glycolysis during IRI, resulting in lactate accumulation and ATP depletion [183]. As a documented glycogen phosphorylase inhibitor, asiatic acid can effectively suppress glycogenolysis, reduce elevated lactate and plasma glucose levels, and diminish IRI-induced damage [183].

7.2. Oxidative phosphorylation

Cardiomyocytes undergo adaptive changes in energy metabolism when exposed to hypoxic conditions, including an increase in fatty acid oxidation [184]. This biochemical adaptation, aimed at addressing the energy deficit, inadvertently leads to succinate accumulation. The accumulation of succinate subsequently activates the GPR91 signaling pathway and the HIF-1α induction pathway, collectively impairing cardiac energy metabolic homeostasis and exacerbating poor cardiac function [185]. Ginsenoside Rb1 has demonstrated efficacy in preventing further succinate accumulation by inhibiting excessive fatty acid oxidation in mitochondria. This intervention mechanism plays a vital role in maintaining cardiac health by significantly enhancing cardiomyocyte resistance to ischemia injury and facilitating the restoration of cellular energy metabolic balance [185]. Furthermore, the integration of virtual screening and proteomics reveals that ginsenoside Rg1 exerts anti-myocardial ischemic effects by targeting MAPK1 and adenosine kinase to inhibit oxidative phosphorylation [186]. Moreover, myocardial infarction may be accompanied by adipose tissue accumulation within the myocardium, characterized by reduced lipid turnover and ectopic myocardial

deposition [187]. Myriocin treatment promotes lipid depletion and improves the lipid response to IRI by inhibiting sphingolipid formation. Myriocin enhances energy generation by upregulating genes involved in fatty acid metabolism, such as CD36 and Fatp1, and also boosts β-oxidation at the infarction site [188].

7.3. Other metabolic pathways

Emerging research indicates that metabolite changes identified through metabolomics provide a critical perspective for elucidating the pathophysiology of CVDs and identifying potential therapeutic targets [189]. Metabolomic studies have shown that oridonin influences several key metabolic pathways following myocardial infarction, including branched-chain amino acid, kynurenine, and bile acid metabolism. By addressing these metabolic dysfunctions, oridonin effectively mitigates further damage during myocardial infarction and inhibits the progression of subsequent tissue and organ dysfunction [190]. Additionally, untargeted metabolomics studies reveal that the cardioprotective effects of schizandrol A post-myocardial infarction are closely associated with the modulation of endogenous metabolic networks, encompassing the regulation of numerous critical pathways within amino acid, sugar, and lipid metabolism [191]. Salidroside has been reported to regulate energy, ether lipid, glycerophospholipid, and sphingolipid metabolism in cardiomyocytes, thereby alleviating hypoxic damage during myocardial infarction [192]. Moreover, preclinical research suggests that cellular reprogramming therapy is a novel and effective approach to managing myocardial infarction. Evidence indicates that tanshinone IIA reprograms macrophage phenotype by interfering with the phosphoglycerate kinase 1 (PGK1)-PDHK1 pathway, thus exerting a cardioprotective effect [193]. Quercitrin has been shown to modulate macrophage polarization and metabolic reprogramming, effectively improving cardiac remodeling [194].

Similarly, we classified the aforementioned NPs that influence cardiac metabolism according to their structural characteristics (Supplementary Table 5). Current research indicates that terpenoids and phenols play a crucial role in metabolic reprogramming. The skeletal structure of terpenoids confers stability to the molecule, potentially contributing to metabolic regulation. The multiple hydroxyl groups present in the structure of phenols and flavonoids can function as hydrogen donors, mitigating ROS damage to myocardial mitochondria and aiding in the regulation of myocardial metabolism. While saponins, glycosides, and lignans have been reported to modulate cardiac metabolic processes, additional studies are necessary to elucidate the relationship between their structural properties and metabolic regulatory functions.

8. NPs regulate histone modification

Recent research has highlighted the critical role of epigenetic regulation in myocardial infarction, IRI, and the development of cardiovascular disorders such as cardiac hypertrophy, hypertension, and HF. Epigenetic mechanisms, including histone modifications, DNA methylation, and m6A methylation, are implicated in the pathogenesis of myocardial infarction. Changes in epigenetic expression during myocardial IR have been strongly correlated with increased myocardial infarct size and cardiac insufficiency, suggesting that epigenetics may serve as a potential target for intervention [195]. Notably, recent studies have demonstrated that plant-derived bioactive compounds can influence epigenetic regulators and inflammatory responses, contributing to the cardioprotective effects of diet [196]. This section focuses on the role of NPs in regulating histone deacetylation (Supplementary Table 6), which may offer novel intervention strategies for myocardial infarction therapy.

8.1. Targeting SIRTs

SIRTs, also known as silent information regulators, are highly conserved nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylases involved in apoptosis, mitochondrial processes, cellular stress responses, and other functions [197]. During myocardial IRI, SIRT1 expression is downregulated. Conversely, SIRT1 overexpression exhibits cardioprotective effects by activating forkhead box protein O1 (FOXO1), thereby reducing oxidative stress and apoptosis [198]. Additionally, research indicates that SIRT1's cardiac benefits are associated with the phosphorylation of eNOS, which enhances resistance to oxidative stress [199]. SIRT3, primarily located in mitochondria, regulates mitochondrial function and biosynthesis and effectively manages ROS [200]. Notably, SIRT3 improves ventricular function during myocardial infarction or IRI while reducing infarct size [201, 202]. Consequently, NPs targeting SIRT1 and SIRT3 may represent a promising approach for treating myocardial infarction.

Evidence suggests that ginsenoside Rc could enhance glucose aerobic metabolism and mitigate mitochondrial damage in cardiomyocytes through activation of the SIRT1-PGC1α pathway during IRI [203]. Resveratrol has also been shown to protect against myocardial ischemic injury by activating the SIRT3/FOXO3a pathway and restoring redox homeostasis [204]. Yeli Li et al. reported that icariside II significantly improved cardiac function, reduced infarct size, and decreased levels of ROS and MDA, primarily attributed to the regulation of the AMPK/PGC-1α/SIRT3 pathway [205]. Similarly, ginsenoside Rb3 activates the PPARα/RXRα pathway to upregulate SIRT3 expression, resulting in improved energy metabolism and reduced apoptosis, thus exerting cardioprotective effects in myocardial infarction-induced HF mice [206]. Additionally, in ISO-induced HF mice, a caffeic acid derivative restored SIRT1 and SIRT3 activity and downregulated HIF-1α expression, leading to reduced oxidative stress and protection of oxidative phosphorylation, cardiac bioenergetics, and cardiac function [207]. While current data support a positive role of NPs in regulating SIRT1 and SIRT3 during myocardial infarction, their modulation and effects on other members of the sirtuin family remain unclear. Consequently, further in-depth investigation and translation of meaningful findings to the clinic are necessary.

Notably, all of the aforementioned NPs targeting the sirtuins family for cardioprotective effects are classified as terpenoids. However, several terpenoids also exhibit inhibitory properties against histone modification-related enzymes in cancers, particularly histone deacetylases. This suggests that NPs of the same class may regulate histone modification through diverse mechanisms. Consequently, a mechanism-based selection of NPs with well-defined histone-modifying effects is essential for the development of effective myocardial infarction therapies.

9. Conclusion

In recent years, there has been increasing interest in utilizing NPs for disease applications due to their diverse pharmacophores and high stereochemistry. This structural diversity, combined with significant biological activity and reported bioavailability and tolerability (as many are dietary components), makes NPs and their derivatives excellent candidates for novel therapeutic agent development. Substantial progress has been made in understanding the mechanisms underlying the cardioprotective benefits of NPs, providing a robust foundation for future drug development. This review classifies the mechanisms of action of NPs into several categories, including inhibition of inflammation and oxidative stress, alleviation of cardiomyocyte death, attenuation of cardiac fibrosis, improvement of angiogenesis, alteration of cardiac metabolism, and regulation of histone modification.

Additionally, classical and novel signaling pathways or targets of NPs affecting specific mechanisms are systematically identified. Emerging research on the cardioprotective effects of NPs through influencing the gut microbiota or the gut-brain axis [208, 209] may also represent a new direction. The discovery of these novel mechanisms or targets has expanded our understanding of NP effects and provided new perspectives for myocardial infarction treatment. Notably, terpenoids, flavonoids, phenols, and saponins constitute a larger proportion of NPs with validated cardiac beneficial effects. These compounds exhibit a wide range of actions involving multiple mechanisms and targets, indicating their greater potential for development as therapeutic agents for myocardial infarction. Although NPs have demonstrated encouraging outcomes in animal models, their efficacy in clinical settings remains uncertain. Despite their substantial pharmacological potential, intrinsic qualities such as low bioavailability, rapid metabolism, and insufficient targeted drug delivery hinder their extensive use. Further investigations should consider these substances as viable options for treating myocardial infarction and explore combinations with other NPs or each other, as combination therapies may enhance positive benefits and minimize negative ones, offering significant therapeutic promise. Moreover, clinical trials based on *in vivo* and *in vitro* data are necessary to provide evidence supporting their use in myocardial infarction management. Additionally, synthesizing bioactive derivatives from NPs represents a crucial direction for future research. Due to the structural complexity of many of these compounds, creating comparable molecules can be time-consuming and costly. As derivatives may function differently from original compounds, further studies are required to optimize the pharmacological effects of these molecules in terms of potency, selectivity, therapeutic safety, and efficacy.

NPs demonstrate significant potential in the management of myocardial infarction. However, translating preclinical findings into clinical practice necessitates addressing several challenges, including safety and tolerability concerns, standardization and quality control measures, bioavailability issues, and potential interactions with conventional therapies. Continued research and development efforts are crucial to fully harness the therapeutic potential of these NPs in the treatment of myocardial infarction.

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Declaration of competing interest

These authors have no conflict of interest to declare.

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