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Review Article

Safflower Yellow Pigments in Coronary Heart Disease: Mechanisms, Applications, and Future Perspectives

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Abstract

Coronary heart disease is an ischemic condition characterized by vascular stenosis or obstruction caused by coronary atherosclerosis, resulting in myocardial ischemia, hypoxia, or necrosis. It is one of the leading causes of death in both urban and rural populations in China. Safflower yellow pigments, the main active components of the traditional Chinese herbal medicine safflower, are primarily composed of quinochalcone compounds, including hydroxysafflor yellow A and anhydrosafflor yellow B—of which hydroxysafflor yellow A is the principal component. Studies have demonstrated that these pigments can improve myocardial ischemia, reduce ischemia-reperfusion injury, alleviate atherosclerotic damage, and address risk factors associated with coronary heart disease. This review aimed to systematically and comprehensively summarize the mechanisms of action of safflower yellow pigments and their active components in the context of coronary heart disease and its related risk factors.

Introduction

Coronary atherosclerotic heart disease, commonly known as coronary heart disease or ischemic heart disease, is one of the most prevalent cardiovascular conditions encountered in clinical practice. Its etiology involves atherosclerotic lesions or spasms in the coronary arteries, leading to narrowing or obstruction of the arterial lumen, ultimately resulting in myocardial ischemia, hypoxia, or necrosis. According to the *Report on Cardiovascular Health and Diseases in China 2023*,[1] approximately 330 million people in China are affected by cardiovascular diseases. These diseases are the leading cause of death among both urban and rural residents. Their high prevalence and associated mortality rates significantly contribute to the public health burden, underscoring the urgent need for effective prevention and treatment strategies.

Traditional Chinese medicine utilizes safflower, derived from the dried flowers of *Carthamus tinctorius* L., a plant in the Asteraceae family. Safflower is renowned for its ability to promote blood circulation, alleviate blood stasis, and relieve pain, making it one of the most widely recognized traditional Chinese medicines for activating blood flow and resolving blood stasis. Its primary constituents include flavonoids (e.g., quinochalcone *C*-glycosides), alkaloids, volatile oils, and fatty acids.[2] Safflower yellow pigments are a class of water-soluble quinochalcone *C*-glycosides extracted from the aqueous solution of safflower. These include hydroxysafflor yellow A (HSYA) and anhydrosafflor yellow B (AHSYB).[3] HSYA is not only the principal active component of safflower yellow pigments but also serves as a quality control marker for safflower-derived medicinal products, as stipulated in the 2025 edition of the *Pharmacopoeia of the People's Republic of China*.[4] Safflower yellow injection (SYI), a modern pharmaceutical formulation, is categorized as a Class II innovative Chinese medicine. It has been recognized as a safe and effective treatment for angina pectoris associated with coronary heart disease and has been endorsed by numerous clinical guidelines, expert consensus statements, and standardized clinical pathways.[5,6] This article reviews the latest advancements in the application of safflower yellow pigments and their active components for the treatment of coronary heart disease and its associated risk factors, aiming to provide a valuable reference for future basic research and clinical practice involving these compounds.

Chemical composition and pharmacokinetics of safflower yellow pigments

Chemical composition of safflower yellow pigments

To date, the components of safflower yellow pigments include

Keywords: *Carthamus tinctorius*; Safflower yellow pigments; Coronary heart disease; Hydroxysafflor yellow A; Anhydrosafflor yellow B; Risk factors.

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safflor yellow A, hydroxysafflor yellow A, safflor yellow B, anhydrosafflor yellow B, safflomin A, safflomin B, safflomin C, isosafflomin C, methylsafflomin C, methylisosafflomin C, saffloquinoside A, saffloquinoside B, saffloquinoside C, saffloquinoside D, cartormin, tinctormine, isocartormin, hydroxysafflor yellow A-4′-O-β-D-glucopyranoside, 3′-hydroxyhydroxysafflor yellow A, hydroxysafflor yellow B, hydroxysafflor yellow C, carthorquinoside A, and carthorquinoside B. In our previous studies, hydroxysafflor yellow B, hydroxysafflor yellow C, carthorquinoside A, and carthorquinoside B were isolated and identified from safflower.[7,8] Among them, HSYA and AHSYB are the main active components of safflower yellow pigments.[3]These components collectively endow safflower yellow pigments with pharmacological activities such as cardiovascular protection, anti-inflammatory effects, and antioxidant properties.

Pharmacokinetics of safflower yellow pigments

Investigating the pharmacokinetic processes of safflower yellow pigments is of great significance for elucidating the pharmacodynamic material basis and pharmacological characteristics of safflower. Studies have shown that after oral gavage of HSYA in normal rats, the plasma concentration-time curve exhibited a double absorption peak. The oral absorption of HSYA was relatively poor, with the highest plasma concentration reached at 20–50 m. The absolute bioavailability was 1.2%.[9] After intravenous injection of HSYA via the tail vein in normal rats, the area under the drug-time curve of HSYA, analyzed by both non-compartmental and compartmental models, exhibited linear pharmacokinetic characteristics within the dose range of 3–12 $mg \cdot kg^{-1}$.[10] Following intravenous injections of 75 mg HSYA administered to 12 healthy volunteers for 14 consecutive days, pharmacokinetic data revealed that HSYA was rapidly eliminated from the body, exhibiting a half-life of 4.0–4.7 h, with almost no accumulation.[11] Our research team found that after oral gavage of AHSYB in normal rats, the pharmacokinetic characteristics indicated rapid elimination of AHSYB and low oral bioavailability (approximately 0.3%). The possible reasons include potential hydrolysis of AHSYB in the gastrointestinal tract, poor permeability through the intestinal epithelial membrane, and the first-pass effect of the liver.[12] HSYA was detected in the heart, liver, spleen, lungs, kidneys, brain, and gastrointestinal tract following oral administration of safflower yellow pigments in rats, indicating wide distribution throughout the body.[13] After intravenous injection of SYI into the tail vein of mice, HSYA was widely distributed in the mouse body. Analysis of the areas under the drug-time curve in different organs revealed the following order of magnitude: blood, kidney, liver, lung, heart, spleen.[14] Our research team compared the metabolic profiles of normal rats and blood stasis rats after oral gavage with HSYA. In normal rats, eight metabolites were identified in addition to the parent drug, including five phase I metabolites (hydrolysis, reduction, hydroxylation, hydration, and methylation) and three phase II metabolites (acetylation, glucuronidation, and glucuronidation plus hydroxylation). In contrast, only seven metabolites were detected in blood stasis rats, with the glucuronidation plus hydroxylation product absent. This indicates that the metabolic products of HSYA vary between different animal models.[15] After intravenous administration of AHSYB, a total of 22 metabolites were detected in rat plasma, urine, bile, and feces, with the highest number found in urine (17) and bile (13). Among these, reduction and hydrolysis products of AHSYB were present in the highest amounts and may play important pharmacological roles.[16] Following oral gavage, HSYA is primarily excreted via feces,[13] whereas after intravenous administration, HSYA is mainly excreted through urine.[9]

Advances in the research of safflower yellow pigments for the treatment of coronary heart disease

Improving myocardial ischemia

Myocardial ischemia, the fundamental pathological characteristic of coronary heart disease, occurs due to reduced coronary blood flow caused by arterial narrowing, spasm, or embolism, leading to insufficient oxygen and blood supply to the myocardium. Clinical evidence indicates that SYI significantly alleviates symptoms such as chest tightness and chest pain in patients with myocardial infarction. It also improves cardiac function indicators (ejection fraction and early diastolic velocity peak) and hemorheology parameters (whole blood viscosity, plasma viscosity, fibrinogen levels, and hematocrit), while causing minimal adverse reactions, demonstrating its safety and efficacy in alleviating myocardial ischemia.[17,18] A multicenter, randomized, active parallel-controlled clinical trial was conducted on 448 coronary heart disease patients with blood stasis syndrome. After 14 days of SYI treatment, the improvement rates of angina and traditional Chinese medicine symptoms were superior to those in the control group.[19] Pharmacological studies have shown that safflower yellow pigments reduce myocardial infarct size in animal models, including rats, mice, and dogs, subjected to coronary artery ligation. They improve cardiac dysfunction caused by myocardial ischemia, indicating protective effects on ischemic myocardium.[20–24] Intravenous injection of safflower yellow pigments in dogs with myocardial ischemia induced by coronary artery ligation inhibited the elevation of serum lactate dehydrogenase (LDH) and creatine kinase levels, reduced the extent of myocardial ischemia, and exhibited a dose-dependent effect (10–40 mg/kg).[25] Moreover, Wei *et al*.[26] found that intravenous injection of safflower yellow pigments in myocardial infarction rats induced by ligating the left anterior descending coronary artery reduced ventricular relative weight, decreased infarct size, improved left ventricular diastolic and systolic function, and enhanced hemorheology parameters, thereby protecting cardiac function.

Inflammatory factors are closely associated with myocardial ischemia in coronary heart disease. Niu *et al*.[27] found that compared to patients receiving nicorandil alone, the combination of nicorandil and SYI significantly reduced pro-inflammatory cytokines (interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP)) in myocardial ischemia patients, suggesting that SYI may alleviate myocardial ischemia by suppressing inflammation. Additionally, safflower yellow pigments reduced plasma levels of endothelin, matrix metalloproteinase-9 (MMP-9), high-sensitivity c-reactive protein (hs-CRP), and platelet aggregation rates, thereby mitigating inflammatory responses and myocardial ischemic injury in patients with coronary heart disease.[28] Zou *et al*.[29] demonstrated that intraperitoneal injection of HSYA in a mouse model of acute myocardial infarction improved hemodynamics and enhanced the expression of platelet endothelial cell adhesion molecule-1 (CD31), vascular endothelial growth factor-A (VEGF-A), and nucleolin. The overexpression of nucleolin stabilized the messenger RNA (mRNA) of VEGF-A and MMP-9 in vascular endothelial cells, thereby mediating the angiogenic effects of HSYA. SYI was found to dose-dependently inhibit platelet aggregation induced by adenosine diphosphate (ADP) and arachidonic acid in rabbits. Additionally, SYI prolonged activated partial thromboplastin time, prothrombin time, and throm-

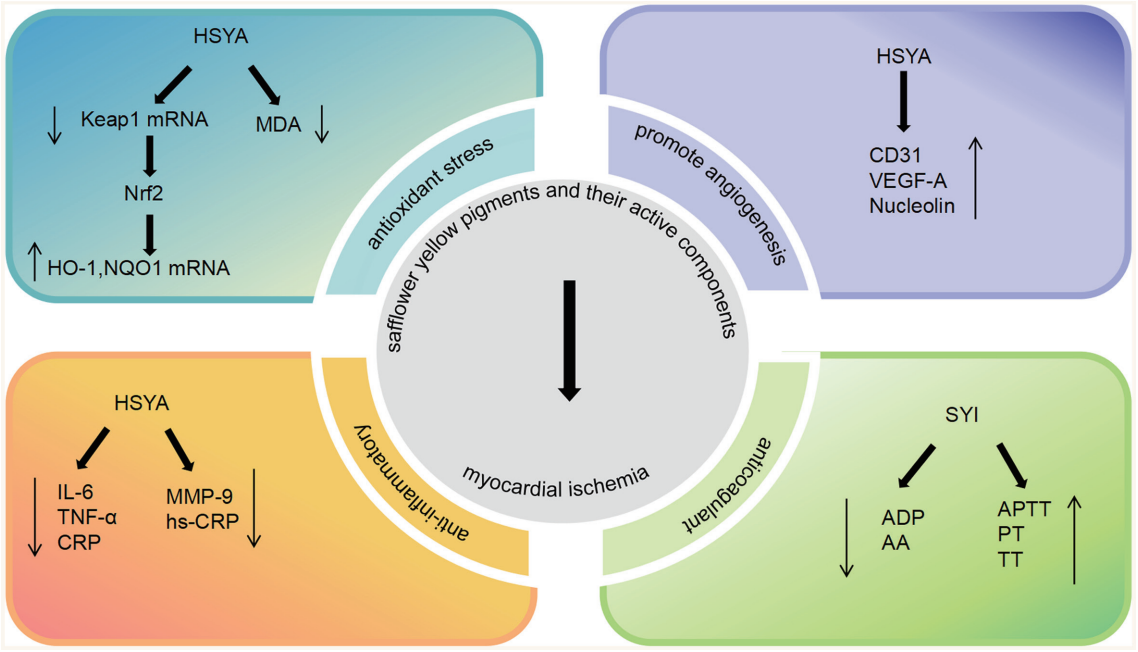

Fig. 1. Mechanism of safflower yellow pigments and their active components in improving myocardial ischemia. ↑, activation; ↓, inhibition. AA, arachidonic acid; ADP, adenosine diphosphate; APTT, activated partial thromboplastin time; CD31, platelet endothelial cell adhesion molecule-1; CRP, C-reactive protein; HO-1, heme oxygenase-1; hs-CRP, high-sensitivity C-reactive protein; HSYA, hydroxysafflor yellow A; IL-6, interleukin-6; Keap 1, Kelch-like ECH-associated protein 1; MDA, malondialdehyde; MMP-9, matrix metalloproteinase-9; mRNA, messenger RNA; NQO1, NAD(P)H quinone dehydrogenase 1; Nrf2, nuclear factor erythroid 2-related factor 2; PT, prothrombin time; SYI, Safflower yellow injection; TNF-α, tumor necrosis factor-alpha; TT, thrombin time; VEGF-A, vascular endothelial growth factor-A.

bin time, demonstrating anticoagulant and cardiovascular protective effects.[30] HSYA also reduced oxidative stress by decreasing malondialdehyde levels, mitigating oxidative damage to myocardial cells.[31] Research demonstrated that HSYA can alleviate oxidative stress-induced damage to cardiomyocytes. This mechanism may be attributed to the suppression of *Keap1* mRNA expression within cardiomyocytes by HSYA, thereby facilitating activation of nuclear factor erythroid 2-related factor 2 (Nrf2). This activation enhances the expression of downstream antioxidant enzyme genes, such as *HO-1* and *NQO1* mRNA.[32] In summary, safflower yellow pigments and their active components primarily exert myocardial protective effects through mechanisms such as inhibiting the release of inflammatory factors, promoting angiogenesis, reducing oxidative stress, and exhibiting anticoagulant properties (Fig. 1).

Reducing myocardial ischemia-reperfusion injury

Coronary intervention to restore blood flow is the recommended guideline for treating myocardial infarction. However, restoring blood flow after ischemia can sometimes exacerbate tissue damage, leading to irreversible injury, a phenomenon known as myocardial ischemia-reperfusion injury (MIRI). During myocardial ischemia-reperfusion, increased production of cell adhesion molecules, chemokines, and cytokines triggers excessive inflammation, resulting in myocardial cell damage. It has been found that HSYA can significantly reduce the area of myocardial infarction and strongly inhibit the release of cardiac enzymes and inflammatory factors induced by ischemia and infarction, significantly improving cardiac function, increasing myocardial blood flow, and decreasing MIRI.[33–36] In a rat model of MIRI, Xu *et al*.[33] administered HSYA into isolated coronary arteries and found that HSYA significantly reduced infarct size and inhibited the release of creatine kinase isoenzyme and cardiac troponin I induced by ischemia and infarction. Simultaneously, HSYA decreased serum levels of inflammatory cytokines such as IL-1, IL-6, and TNF-α, increased myocardial blood flow, and reduced MIRI. Liu *et al*.[34] administered HSYA via femoral vein injection in rats with MIRI and found that different doses of HSYA (4, 8, and 16 mg kg^{-1}) reduced the myocardial infarction area to varying degrees. Meanwhile, serum creatine kinase isoenzyme, LDH, and cardiac troponin I leakage were reduced; levels of IL-6, IL-1β, TNF-α, and myeloperoxidase activity decreased; plasma levels of 6-keto-prostaglandin-F1α increased; and levels of thromboxane B2 were significantly reduced, suggesting that HSYA reduces the inflammatory response and attenuates MIRI. The nuclear factor kappa B (NF-κB) pathway is critical in inflammation and immune responses. One study found that intraperitoneal injection of HSYA in MIRI rats attenuated serum levels of inflammatory factors such as hs-CRP, IL-6, IL-1β, and TNF-α and reduced myocardial inflammatory injury in these animals. The mechanism of action may involve inhibition of Toll-like receptor 4 (TLR4)/NF-κB protein expression.[37]

During myocardial ischemia-reperfusion, excessive reactive oxygen species (ROS) are produced, triggering oxidative stress that damages protein and nucleic acid structure and function, ultimately leading to cell apoptosis. Yu *et al*.[38] administered HSYA via gavage to rats for two weeks and subsequently established an MIRI rat model. The results indicated that HSYA upregulated the expression of B-cell lymphoma 2 (Bcl-2) and downregulated the expression of Bax in myocardial tissues, thereby inhibiting apoptosis. Additionally, HSYA reduced serum malondialdehyde levels and increased superoxide dismutase activity, mitigating oxidative stress. The effects of HSYA in reducing MIRI may be related to the p38 MAPK/SERCA2α signaling pathway. HSYA also pro-

moted HO-1 expression, protein kinase B (Akt), and facilitated Nrf2 nuclear translocation, thereby reducing hypoxia/reoxygenation (H/R)-induced apoptosis in H9C2 cardiomyocytes. Furthermore, inhibitors of phosphatidylinositol 3-kinase (PI3K) reversed these protective effects of HSYA, indicating that HSYA exerts its effects against MIRI by modulating the PI3K/Akt/Nrf2 signaling pathway.[39] Additionally, HSYA regulates miR-499 expression, reducing ROS release and caspase-3 expression induced by H/R in H9C2 cardiomyocytes, which helps inhibit oxidative stress, enhance cell viability, suppress apoptosis, and alleviate myocardial injury.[40] AHSYB increases the viability of H9C2 cells subjected to oxygen-glucose deprivation/reoxygenation (OGD/R), enhances ATP content, and decreases ROS and LDH levels in OGD/R-injured cells. It inhibits OGD/R-induced expression of cytochrome c and caspase-3 proteins in the cytoplasm, demonstrating anti-apoptotic ability.[41]

During myocardial ischemia-reperfusion, mitochondrial oxidative phosphorylation is disrupted, reducing ATP production, while elevated calcium ion concentrations adversely affect mitochondrial function. HSYA alleviates MIRI by regulating mitochondrial energy metabolism and restoring mitochondrial function.[42,43] Mdh1 is a malate dehydrogenase 1 enzyme that plays a crucial role in energy metabolism. In a mouse model of MIRI, HSYA was administered via tail-vein injection. It enhanced mitochondrial function and energy metabolism by increasing the thermal stability and enzymatic activity of the Mdh1 protein, thereby providing significant protection against MIRI.[42] HSYA reduced LDH levels in coronary effluents, prevented ischemia-induced cardiomyocyte apoptosis and mitochondrial membrane depolarization, increased phosphorylation of endothelial nitric oxide synthase (eNOS), and inhibited Ca^{2+}-induced mitochondrial swelling and opening of the mitochondrial permeability transition pore, providing substantial protection in MIRI rats.[43] Mitochondrial dysfunction can directly induce myocardial cell injury, with hexokinase II (HKII), regulated by the Akt signaling pathway, playing a pivotal role in mitochondrial function. HSYA reduces LDH content and caspase-3 expression, alleviates oxidative stress and apoptosis, and increases ATP production and mitochondrial energy metabolism in H/R-induced H9C2 cells, potentially by targeting and modulating the Akt/HKII signaling pathway.[44]

In addition, safflower yellow pigments and their active components exhibit other therapeutic effects against MIRI. During ischemia and hypoxia, the body initiates migration and proliferation of vascular endothelial cells to promote angiogenesis, which plays an important role in MIRI recovery. Ge *et al*.[45] demonstrated that intraperitoneal administration of HSYA for two weeks in rats, followed by induction of a MIRI model, significantly enhanced angiogenesis-related markers (e.g., CD31, CD34) in myocardial tissues. This effect is likely mediated through modulation of the HIF-1α/VEGFA/Notch1 signaling pathway, suggesting a potential mechanism for HSYA in promoting angiogenesis and treating MIRI. Ferroptosis is a newly recognized mode of cell death that can aggravate cardiomyocyte injury and death. HSYA was administered via intraperitoneal injection to rats for two weeks, followed by the establishment of an MIRI model. HSYA attenuated myocardial tissue damage, reduced iron accumulation and lipid peroxidation, and exerted significant protection against MIRI. This effect may be mediated through the regulation of the HIF-1α/SLC7A11/GPX4 signaling pathway to inhibit ferroptosis.[46] Liang *et al*.[47] found that SYI inhibited the mitochondrial apoptotic pathway through two mechanisms: (1) modulating endoplasmic reticulum stress signaling to suppress C/EBP homologous protein expression, and (2) reducing cytochrome c release.

In summary, safflower yellow pigments contribute to the treatment of MIRI through multiple mechanisms, including inhibition of inflammatory responses, antioxidative stress, suppression of apoptosis, restoration of mitochondrial function, promotion of angiogenesis, alleviation of endoplasmic reticulum stress, and inhibition of ferroptosis. These mechanisms are illustrated in Figure 2.

Alleviation of atherosclerotic damage

Atherosclerosis (AS) is a complex metabolic disorder syndrome that poses a serious threat to human health and serves as an important pathophysiological basis for coronary heart disease. Safflower yellow pigments are a potential atheroprotective agent, exhibiting excellent properties in lowering blood lipids, resisting oxidative stress, and attenuating vascular injury.[48] A total of 116 patients with unstable angina were randomly divided into a control group (58 cases receiving trimetazidine) and an observation group (58 cases receiving trimetazidine combined with SYI). Compared with the control group, the observation group had a higher total effective rate. The levels of total cholesterol (TC), total triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) were significantly reduced, while the level of high-density lipoprotein cholesterol (HDL-C) was increased. Additionally, the thickness and size of carotid atherosclerotic plaques and the carotid intima-media thickness were significantly decreased in the observation group.[49]

Oxidative stress is a physiological imbalance between oxidative and antioxidant processes, leading to increased oxidation. This results in inflammatory infiltration of neutrophils, increased secretion of proteases, and the production of large amounts of oxidized intermediates. Oxidative stress is a key mechanism in cardiovascular diseases. Oxidized low-density lipoprotein (ox-LDL)-induced vascular endothelial damage is a critical event in early atherosclerosis. In vitro studies revealed that HSYA inhibited ox-LDL-induced proliferation and endothelial damage of vascular smooth muscle cells and exerted anti-atherosclerotic effects through the anti-apoptotic regulation of voltage-dependent anion channels.[50–52] Studies have shown that HSYA alleviates hypoxia-induced endothelial cell injury by promoting the HIF-1α-VEGF pathway, downregulating the Bax/Bcl-2 protein expression ratio, and reducing levels of pro-apoptotic proteins, including cleaved caspase-9 and cleaved caspase-3.[53–55] In addition, Liu *et al*.[56] reported that HSYA downregulates SphK1, S1P, S1PR3, RhoA/ROCK proteins, and filamentous actin expression, thereby attenuating the migration capacity of ox-LDL-induced human umbilical vein endothelial cells (HUVECs). These findings suggest that HSYA reduces vascular endothelial cell migration and filamentous actin expression in AS by inhibiting the SphK1/S1P/S1PR3 pathway.

During the progression of AS, macrophages play a pivotal role at every stage, from foam cell formation to rupture of unstable plaques, significantly influencing disease progression.[57] Research has identified macrophage-mediated inflammatory infiltration and pathological lymphangiogenesis around AS plaques as critical therapeutic targets. In $ApoE^{-/-}$knockout mice, tail vein injection of HSYA improved body weight, reduced aortic sinus lipid plaques, decreased periplaque lymphatic vessels, improved macrophage morphology and leakage, and lowered TNF-α levels. *In vitro*, HSYA reduced VEGF-C expression and secretion in Raw264.7 cells, attenuated macrophage uptake of ox-LDL cholesterol, downregulated AKT/mammalian target of rapamycin and NF-κB signaling via PI3K inhibition, and mitigated lymphangiogenesis and inflammation, providing comprehensive protection against atherosclerosis.[58] During AS progression, macrophages exhibit

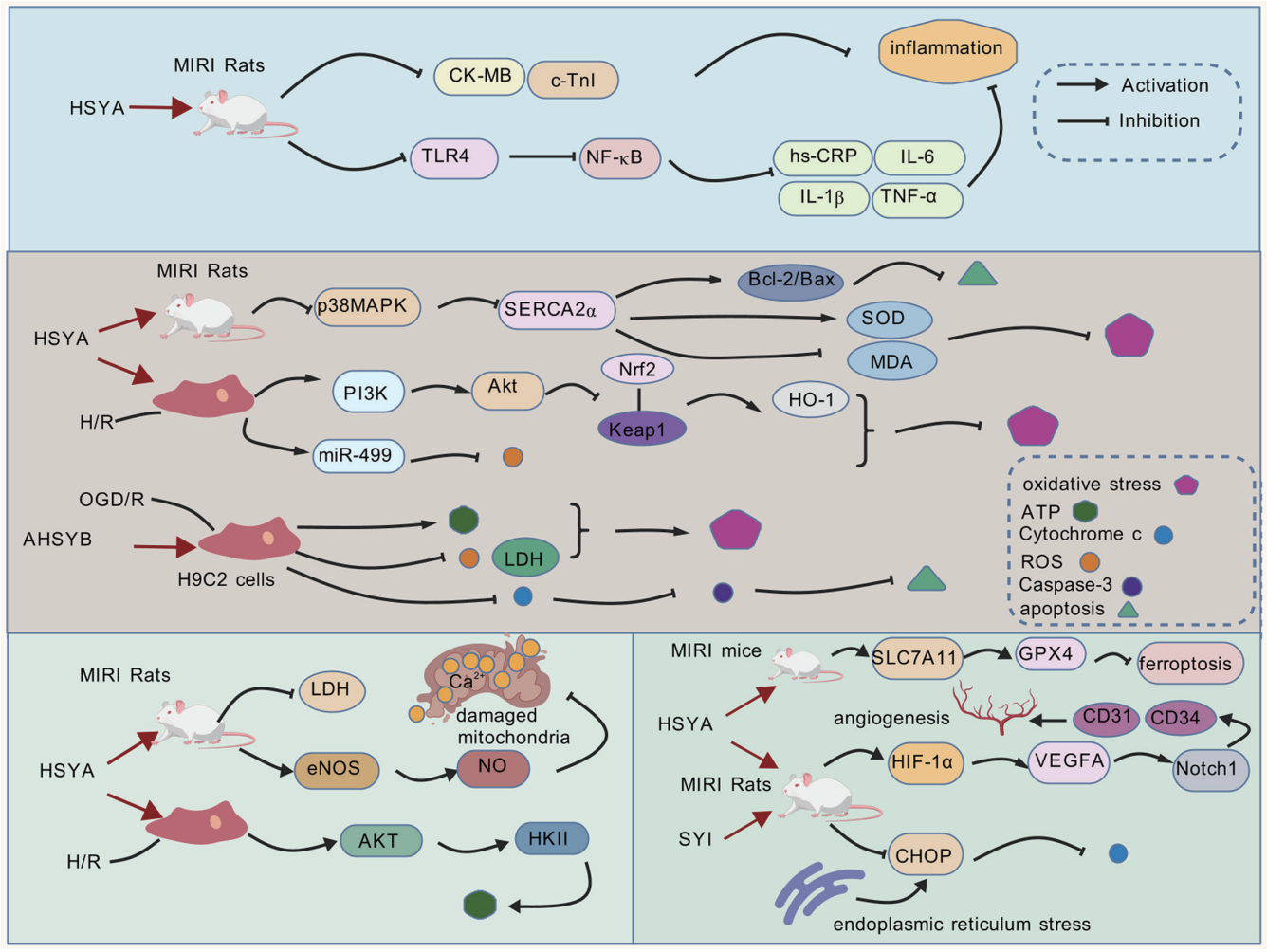

Fig. 2. Mechanism of action of safflower yellow pigments and their active components in the treatment of MIRI. AHSYB, anhydrosafflor yellow B; Akt, protein kinase B; ATP, adenosine triphosphate; Bax, Bcl-2-related X protein; Bcl-2, B-cell lymphoma 2; CD, cluster of differentiation; CHOP, C/EBP homologous protein; CK-MB, creatine kinase-MB; c-TnI, cardiac troponin I; eNOS, endothelial nitric oxide synthase; GPX4, glutathione peroxidase 4; H/R, hypoxia/reoxygenation; HIF-1α, hypoxia-inducible factor-1 alpha; HKII, hexokinase II; HO-1, heme oxygenase-1; hs-CRP, high-sensitivity C-reactive protein; HSYA, hydroxysafflor yellow A; IL, interleukin; Keap1, Kelch-like ECH-associated protein 1; LDH, lactate dehydrogenase; MDA, malondialdehyde; miR499, microRNA-499; MIRI, myocardial ischemia-reperfusion injury; NF-κB, nuclear factor kappa B; NO, nitric oxide ; Notch1, neurogenic locus notch homolog protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; OGD/R, oxygen-glucose deprivation/reperfusion; p38MAPK, p38 mitogen-activated protein kinase; PI3K, phosphatidylinositol-3 kinase; ROS, reactive oxygen species; SERCA2α, sarcoplasmic reticulum Ca^{2+}-ATPase 2α ; SLC7A11, solute carrier family 7 member 11; SOD, superoxide dismutase; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; VEGFA, vascular endothelial growth factor A.

reduced levels of autophagy, produce fewer transport lipoproteins and less free cholesterol, creating a negative feedback loop. This leads to a reduction in high-density lipoprotein in peripheral blood and increased plaque vulnerability, which can cause plaque rupture and acute coronary syndromes.[59] Thus, modulation of macrophage autophagy has emerged as a potential therapeutic target for AS. $ApoE^{-/-}$ knockout mice treated with HSYA and its mimetic liposomes (HA-ML@HSYA NPs) via tail vein injection exhibited decreased methylation levels of the autophagy-related gene *Atg13* DNA, increased macrophage autophagy, and inhibited ox-LDL uptake, thereby alleviating atherosclerosis.[60] The mechanism of action is illustrated in Figure 3.

Improving vascular injury

Endothelial function is closely related to inflammation, angiogenesis, oxidative stress, and coagulation. Endothelial dysfunction is considered a fundamental risk factor for coronary heart disease, leading to atherosclerosis and eventually progressing to coronary heart disease. In recent years, numerous studies have focused on the protective effects of HSYA against the apoptosis of HUVECs and vascular endothelial cells (VECs), exploring its mechanisms for alleviating vascular injury. HSYA can inhibit the production of ROS in HUVECs, preserve mitochondrial structure and function, and inhibit the expression of caspase-3, thereby protecting HUVECs from Ang II-induced injury.[61] Under hypoxic conditions, HSYA increases the Bcl-2/Bax ratio in HUVECs, promotes the production and release of NO, upregulates eNOS mRNA expression, and downregulates p53 protein expression in the nucleus. These actions prevent HUVEC apoptosis and cell cycle arrest. Similarly, under hypoxic conditions, HSYA en-

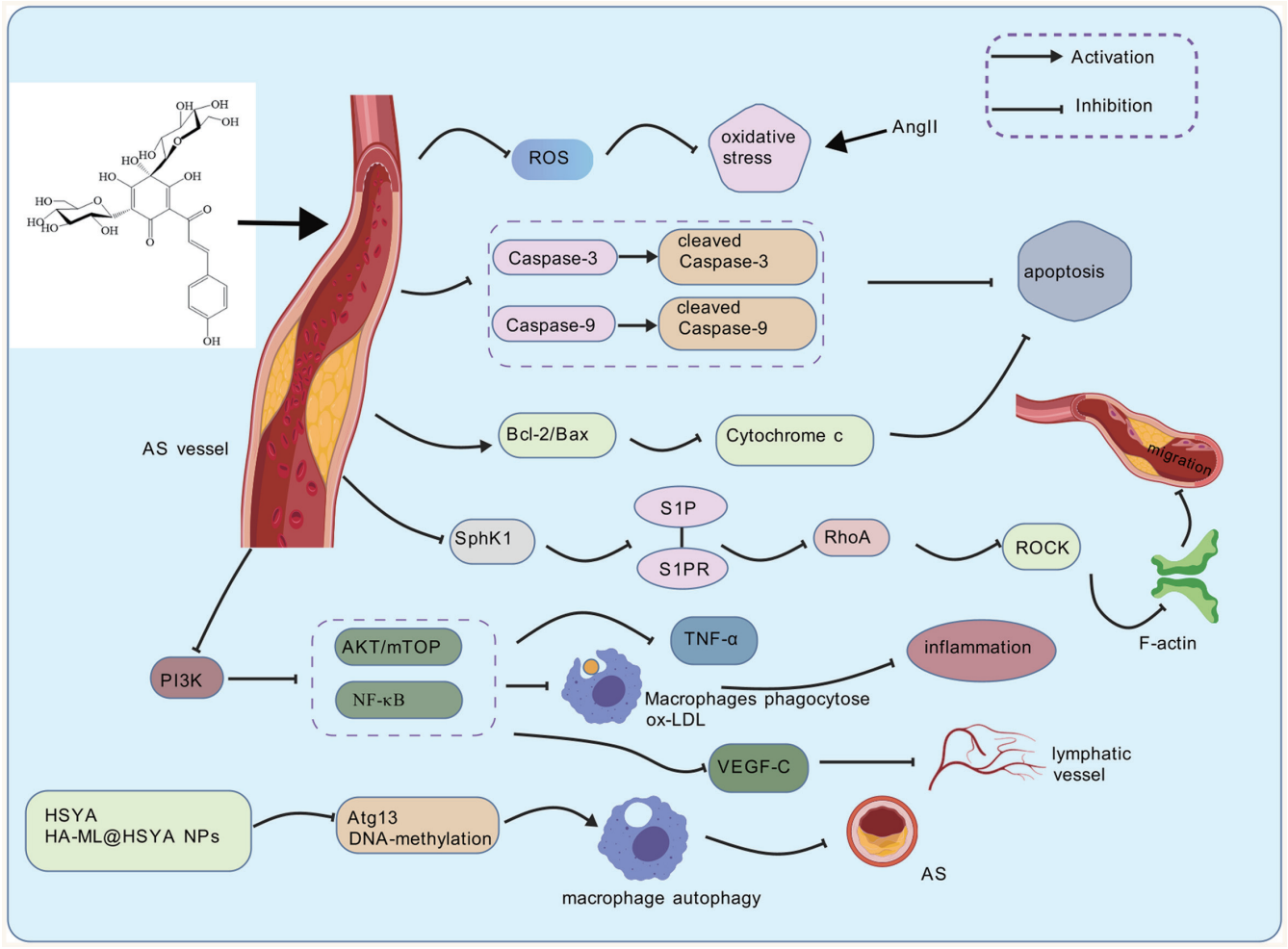

Fig. 3. Mechanism of action of HSYA in treating AS. AngII, angiotensin II; AKT, protein kinase B; AS, atherosclerosis; Atg13, autophagy-related gene 13; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; F-actin, filamentous actin; HA-ML@HSYA NPs, HSYA and its mimetic liposomes; HSYA, hydroxysafflor yellow A; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; RhoA, Ras homolog family member A/Rho-associated coiled-coil containing protein kinase; ROCK, Rho-associated coiled-coil kinase; ROS, reactive oxygen species; S1P, sphingosine-1-phosphate; S1PR, sphingosine-1-phosphate receptor; SphK1, sphingosine kinase 1; TNF-α, tumor necrosis factor-alpha; VEGF-C, vascular endothelial growth factor-C.

hances VEC survival, which is associated with an increased Bcl-2/Bax ratio, elevated HIF-1α protein expression, and enhanced VEGF levels.[62] Song *et al*.[63] demonstrated that HSYA promotes VEC proliferation under both normoxic and hypoxic conditions, with more pronounced effects observed under hypoxia. This may be related to the modulation of VEGF and its receptor expression by HSYA. In addition, intercellular adhesion molecules (ICAMs) are strongly associated with infection, inflammation, and immune response. For example, ICAM-1 is positively associated with the incidence of acute cardiovascular events.[64] In TNF-α-stimulated EA.hy926 endothelial cells mimicking a cellular injury environment, He *et al*.[65] found that HSYA increased NO content and inhibited the expression of endothelin-1. It also downregulated the expression of E-selectin, monocyte chemoattractant protein-1, ICAM-1, and vascular cell adhesion molecule-1, while upregulating the mRNA expression of superoxide dismutase, catalase, and GSH-px. These actions help alleviate endothelial cell damage caused by inflammation and oxidative stress. The anti-inflammatory and antioxidant activities of HSYA may be related to the regulation of the NF-κB signaling pathway. Studies have shown that HSYA can reduce the levels of ICAM-1 and E-selectin, thereby decreasing vascular damage caused by inflammatory stimuli and the migration of inflammatory cells into the arterial intima. The mechanism may involve inhibition of NF-κB signaling and the expression of TNFR1 on the membrane surface of arterial endothelial cells.[66,67] In conclusion, HSYA improves vascular injury through multiple mechanisms, including antioxidative stress, anti-inflammatory responses, endothelial cell protection, and vascular function regulation. The detailed mechanisms are illustrated in Figure 4.

Advances in research on safflower yellow pigments for treating coronary heart disease-related risk factors

Coronary heart disease is a complex disorder caused by the interaction of multiple genetic and environmental factors. Current studies have yet to fully elucidate its pathogenesis. Known major risk factors for coronary heart disease include obesity, hypertension, dyslipidemia, diabetes, genetic predisposition, age, and smoking.[68]

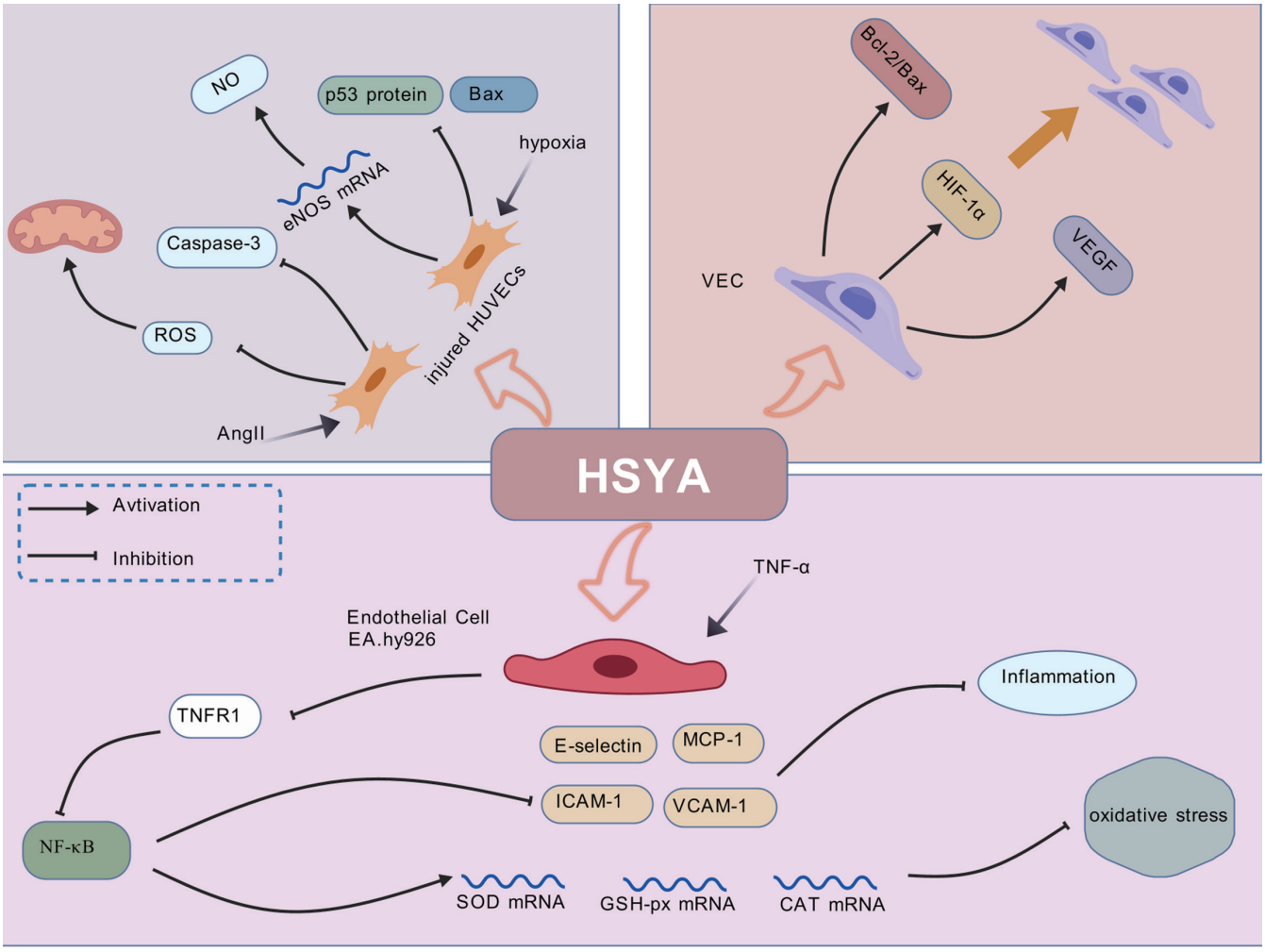

Fig. 4. Mechanism of HSYA in improving vascular injury. AngII, angiotensin II ; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; CAT, catalase; eNOS, endothelial nitric oxide synthase; E-selection, endothelial selectin; ET-1, endothelin-1; GSH-Px, glutathione peroxidase; HIF-1α, hypoxia-inducible factor-1 alpha; HSYA, hydroxysafflor yellow A; HUVECs, human umbilical vein endothelial cells; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; mRNA, messenger RNA; NF-κB, nuclear factor kappa B; NO, nitric oxide; SOD, superoxide dismutase; TNFR1, tumor necrosis factor receptor 1; TNF-α, tumor necrosis factor-alpha; VEC, vascular endothelial cell; VEGF, vascular endothelial growth factor.

Among these, obesity, hypertension, dyslipidemia, and diabetes mellitus are collectively known as cardiometabolic diseases, representing multiple risk factors for coronary heart disease. Existing research has demonstrated the significant efficacy of safflower yellow pigments in treating obesity, hypertension, hyperlipidemia, and diabetes (Table 1).

Obesity

Obesity is a complex pathophysiological process resulting from long-term energy intake exceeding energy expenditure, leading to the storage of excess energy as fat. It involves the interplay of multiple factors, including dysregulation of neuroendocrine functions (such as leptin resistance and insulin resistance), abnormalities in adipocyte function (hypertrophy, hyperplasia, and imbalance in adipokine secretion), and gut microbiota dysbiosis. Collectively, these factors can trigger a series of metabolic disorders. Research has confirmed that obesity is the pathological basis of cardiometabolic diseases.[69] Safflower yellow pigments have been reported to reduce body fat in high-fat diet (HFD)-induced obese mice by promoting the browning of subcutaneous white adipose tissue. Additionally, they lower blood glucose levels and increase insulin sensitivity through activation of the IRS1/AKT/GSK3β insulin signaling pathway.[70] Our group found that HSYA could reduce body weight, fat accumulation, and insulin resistance in HFD-induced obese mice by increasing the relative abundance of bacteria from the genera *Akkermansia* and *Romboutsia* and by decreasing the Firmicutes/Bacteroidetes ratio, thereby improving intestinal microbiota disorders.[71] It has also been found that safflower yellow pigments and HSYA significantly reduce serum levels of glucose-dependent insulinotropic polypeptide (GIP) in HFD-induced obese mice by inhibiting GIP production and secretion in the small intestine. They also inhibit the signaling pathway of the GIP receptor/Rapgef3 in the hypothalamus and adipose tissue, thereby achieving dual inhibition of the GIP-GIP receptor axis, alleviating hyperleptinemia, and exerting anti-obesity effects.[72] Yan *et al*.[73] discovered that HSYA suppresses proliferation and adipogenesis of 3T3-L1 preadipocytes in mice by regulating Nrf2 to promote hormone-sensitive lipase expression.

Table 1. Mechanisms of action of safflower yellow pigments and their active components in treating risk factors for coronary heart disease

Risk factors	Drugs	Model	Dosage	Mechanism of action	Functions
Obesity	SY	HFD-induced mice	120 mg·kg^{-1}; i.p.; 8 w	Activate IRS1/AKT/GSK3β signaling pathway	↑: IRS1, AKT, GSK3β, PGC1α
	HSYA	HFD-induced mice	200 mg·kg^{-1}; p.o.; 6 w	Regulating gut microbiota composition and function	↑: Relative abundance of *Akkermansia* and *Romboutsia* bacteria, bacterial abundance of SCFAs, IL-10; ↓: Firmicutes/Bacteroidetratio, HOMA-IR, OGTT, TNF-α, IL-1β, IL-6
	HSYA/SY	HFD-induced mice	250 mg·kg^{-1}; p.o.; 9 w, 12 w, 4 w	Inhibiting GIPR-rapgef3 pathway and GIP-GIPR axis	↓: AUC, ALT, GIP, GIPR, Rapgef3, SOCS3
	HSYA/SY	HFD-induced mice	200 mg·kg^{-1}; i.p.; 10 w	Regulating Nrf2 to enhance antioxidant enzyme expression	↑: SOD, SOD1, GCLC, Nqo1, CAT, HO-1, Nrf2; ↓: TC, hsCRP, ALT, TNF-α
Hypertension	HSYA	SHR and WKY rats	0.1–3 mg·kg^{-1}; i.v.; 1 h	Activating KATP and BKCa channels to reduce Ca^{2+} influx	↓: MAP, HR, LVSP, LVEDP
		The left femoral artery of mice was excised to induce unilateral hindlimb ischemia	6 mg·kg^{-1}; i.v.; 11d	Activating Ang1/Tie-2 signaling pathway	↑: Arteriole, capillary density, Ang1, Tie-2
		ANG II stimulated VAF cell migration model	20,40,60 μmol·L^{-1}; 24 h	Inducing autophagy to inhibit NLRP3 inflammasome activation, preventing ANG II-induced VAF migration	↑: LC3 II, Beclin1; ↓: VAF migration rate, NLRP3, caspase-1, IL-6, TNF-α, IL-1β, IL-18, TLR4, NF-κB
Hyperlipidemia	HSYA	Injected rats with adrenaline solution to establish a platelet hyperactivation model	1 ml; i.p.; 5 d	Upregulating miR-9a-5p to suppress PLCγ2/PKCδ/MEK/ERK1/2 phosphorylation	↑: cAMP, miR-9a-5p; ↓: PLT, platelet aggregation rate, Ca^{2+}, TXA_2, phosphorylation of SRC, PLCγ2, PKCδ, MEK, ERK1/2 proteins, GPIIβ/IIIα
Diabetes	HSYA	HFD and STZ-induced T2DM rat model	120 mg·kg^{-1}; p.o.; 8 w	Activating PI3K/Akt signaling pathway	↑: PI3K, AKT, p-AKT; ↓: FBG, OGTT, TC,TG,LDL-C, HOMA-IR, HOMA-β
		High glucose-treated INS-1 insulinoma cells	800 μM; 72 h	Inhibiting JNK/c-Jun signaling pathway	↑: SOD, GSH-Px, CAT; ↓: MDA, cleaved-PARP, cleaved caspase-3, JNK
		HFD and STZ-induced ApoE$^{-/-}$ mouse model of T2DM/AS	2.25 mg·kg^{-1}; i.p.; 12 w	Regulating miR-429/SLC7A11 signaling pathway	↑: TG, TC, LDL-c, GSH-Px, GPX4, SLC7A11; ↓: HDL-C, ICAM, VCAM, MDA, ROS, ACSL4, miR-429

↑, activation; ↓, inhibition. ACSL4, acyl-CoA synthetase long-chain family member 4; AKT, Protein kinase B; ALT, alanine aminotransferase; ANG II, angiotensin II; Ang1, angiopoietin-1; AUC, area under the curve; BKCa, calcium-activated potassium channel; cAMP, cyclic adenosine monophosphate; CAT, catalase; c-Jun, cellular Jun; d, day; ERK1/2, extracellular signal-regulated kinase 1/2; FBG, fasting blood glucose; GCLC, glutamate-cysteine ligase catalytic subunit; GIP, gastric inhibitory polypeptide; GIPR, gastric inhibitory polypeptide receptor; GPIIβ/IIIα, glycoprotein IIb/IIIa; GSH-Px, glutathione peroxidase; GSK3β, glycogen synthase kinase 3β; h, hour; HDL-C, high-density lipoprotein cholesterol; HFD, high-fat diet; HO-1, heme oxygenase 1; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; HR, heart rate; hsCRP, high-sensitivity C-reactive protein; HSYA, hydroxysafflor yellow A; i.p., intraperitoneal injection; i.v., intravenous injection; ICAM, intercellular adhesion molecule; IL, interleukin; INS-1, INS-1 cell line; IRS1, insulin receptor substrate 1; JNK, c-Jun N-terminal kinase; KATP, ATP-sensitive potassium channel; LC3 II, microtubule-associated protein 1 light chain 3-II; LDL-C, low-density lipoprotein cholesterol; LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular systolic pressure; MAP, mean arterial pressure; MDA, malondialdehyde; MEK, mitogen-activated protein kinase; miR-429, microRNA-429; miR-9a-5p, microRNA-9a-5p; NF-κB, nuclear factor kappa B; NLRP3, NACHT, LRR and PYD domains-containing protein 3; Nqo1, NAD(P)H: quinone oxidoreductase 1; Nrf2, nuclear factor erythroid 2-related factor 2; OGTT, oral glucose tolerance test; p.o., per os; PARP, poly(ADP-ribose) polymerase; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1α; PI3K, phosphatidylinositol 3-kinase; PKCδ, protein kinase Cδ; PLCγ2, phospholipase Cγ2; PLT, platelets; Rapgef3, rap guanine nucleotide exchange factor 3; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; SHR, spontaneously hypertensive rat; SLC7A11, solute carrier family 7 member 11; SOCS3, suppressor of cytokine signaling 3; SOD1, superoxide dismutase 1; SRC, proto-oncogene tyrosine-protein kinase src; STZ, streptozotocin; SY, safflower yellow; T2DM, Type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; Tie-2, tyrosine kinase with immunoglobulin-like and EGF-like domains 2; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor alpha; TXA_2, thromboxane A_2; VAF, vascular adventitial fibroblast; VCAM, vascular cell adhesion molecule; w, week.

Hypertension

Hypertension is an important contributor to coronary heart disease and can significantly increase its incidence. Elevated blood pressure and excessive pressure on the inner walls of blood vessels cause endothelial damage. After endothelial injury, lipids, platelets, and other blood components are more easily deposited at the site, leading to the formation of atherosclerotic plaques. Studies have reported that HSYA exerts significant regulatory effects on cardiac function and hypertension, primarily through mechanisms involving myocardial contractility regulation, blood pressure modulation, promotion of angiogenesis, vascular dilation, maintenance of vascular homeostasis, and improvement of vascular remodeling.[74–77] Nie *et al*.[23] investigated the effects of HSYA on cardiac function and blood pressure using an isolated rat heart perfusion model. They found that intravenous injection of HSYA dose-dependently reduced mean arterial pressure and heart rate in both normal and spontaneously hypertensive rats, suppressed cardiac contraction, and decreased cardiac output and blood pressure. In addition, HSYA promotes the recovery of blood flow in ischemic hindlimb tissues in mice, significantly increases the density of microarterioles and capillaries in the ischemic area, upregulates the expression of Ang1 and Tie-2, and promotes endothelial cell migration and angiogenesis.[75] HSYA also regulates blood pressure by dilating blood vessels. Wang *et al*.[76] demonstrated that the vasodilatory effect of HSYA is associated with inhibition of Ca^{2+} influx. Their study showed that HSYA activates voltage-gated potassium channels and inhibits L-type calcium channels in the smooth muscle cells of rat mesenteric arteries, thereby reducing intracellular Ca^{2+} levels. This leads to vasodilation and a decrease in blood pressure. Vascular remodeling plays a key role in the pathogenesis of hypertension. HSYA improves vascular remodeling by inhibiting Ang II-induced migration of vascular adventitial fibroblasts (VAFs). The mechanism may involve downregulating NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome activity and suppressing NLRP3 inflammasome assembly through the TLR4/NF-κB signaling pathway. Additionally, HSYA inhibits NLRP3 inflammasome activation by promoting autophagy.[77]

Hyperlipidemia

Hyperlipidemia is characterized by the abnormal elevation of one or more lipid components in plasma, resulting from disruptions in lipid metabolism or transport. It is a significant risk factor for the development of coronary heart disease.[78–80] Wang demonstrated that treatment with safflower yellow pigments in 96 patients with coronary heart disease led to a significant reduction in plasma levels of TC, TG, and LDL-C), while markedly increasing HDL-C, indicating significant lipid-regulating effects.[81] Wu *et al*.[82] conducted a study involving 100 hyperlipidemic patients treated with safflower yellow pigments for two weeks. The results showed significant improvements in plasma lipid parameters (TC, TG, LDL-C, and HDL-C), confirming its therapeutic efficacy in managing hyperlipidemia. Additionally, safflower yellow pigments significantly prolonged prothrombin time, reduced fibrinogen levels, enhanced clot lysis rates, and delayed carotid thrombus formation. Studies have also found that safflower yellow exhibits lipid-lowering effects in hyperlipidemic mice, significantly reducing serum levels of TC, TG, and LDL-C while increasing HDL-C. Additionally, safflower yellow alleviates fatty liver and exerts protective effects on hepatic cells. The mechanism may be related to the inhibition of intracellular cholesterol biosynthesis.[83] HSYA improves lipid deposition, liver function, and blood flow in hyperlipidemic zebrafish. Its protective mechanism against hyperlipidemia may involve regulation of the AMPK/SREBP2/PCSK9/LDLR signaling pathway.[84] During hyperlipidemia progression, platelet activation is accelerated, releasing various bioactive substances, including platelet α-granule membrane protein-140 and platelet-activating factor (PAF). PAF, an inflammatory lipid mediator, strongly activates platelets, promotes aggregation, and is closely associated with coronary heart disease and other ischemic cardiovascular diseases. HSYA has been shown to inhibit platelet activation by suppressing PAF-induced platelet aggregation, 5-OH release, and elevation of intracellular free Ca^{2+} concentration, thereby alleviating pathological changes such as thrombosis and inflammation, and improving blood circulation disorders.[85,86] HSYA also inhibits the transcription and translation of sarcoma-associated genes, suppresses phosphorylation of downstream signaling pathways, and reduces expression of proteins related to platelet activation by upregulating miR-9a-5p. This mechanism effectively attenuates excessive platelet activation in rats.[87]

Diabetes

Diabetes is a syndrome of metabolic disorders involving protein, fat, water, and electrolytes caused by absolute or relative insulin deficiency or reduced insulin sensitivity in target cells. Diabetes confers an equivalent risk of coronary heart disease, meaning that the 10-year risk of major cardiovascular events in patients without coronary heart disease is comparable to that of patients with existing coronary heart disease. Safflower yellow pigments have demonstrated significant efficacy in treating diabetes and its complications and are included in Traditional Chinese Medicine clinical guidelines for diabetes as recommended medications. HSYA significantly lowers fasting blood glucose levels and improves insulin resistance in T2DM rats. It reverses the downregulation of PI3K and AKT in the liver and inhibits apoptosis of pancreatic β-cells to some extent. Additionally, HSYA regulates glucose and lipid metabolism by increasing glycogen synthase and hepatic glycogen levels, reducing TG, TC, and LDL-C, and improving overall lipid metabolism.[88] HSYA effectively reduces levels of cleaved-poly(ADP-ribose) polymerase, cleaved caspase-3, and ROS. Additionally, it inhibited the phosphorylation of JNK and c-Jun, as well as activation of the JNK/c-Jun signaling pathway in rat pancreatic INS-1. These effects collectively improve oxidative stress and significantly reduce apoptosis in INS-1 cells.[89] Moreover, HSYA ameliorates diabetes complications. Rong *et al*.[90] found that HSYA reduced atherosclerotic plaque formation in the aorta of T2DM/AS model mice and decreased oxidative stress and ferroptosis. The mechanism involves regulation of ferroptosis-associated proteins and the miR-429/SLC7A11 pathway.

Limitations

This review summarized the significant clinical efficacy of safflower yellow pigments in the treatment of coronary heart disease as well as their mechanisms of actions. However, this study still has some limitations. Firstly, the mechanisms of action of safflower yellow pigments in the treatment of coronary heart disease are not yet fully understood. Secondly, the high polarity, low oral bioavailability, and short half-life of safflower yellow pigments pose key challenges to their oral use. Finally, clinical studies on the treatment of coronary heart disease with safflower yellow pigments are mostly small-sample and open-label, lacking large-sample, multicenter, randomized double-blind controlled trials. Additionally, coronary heart disease being a chronic disorder necessitates long-term therapeutic intervention and management. Nevertheless, the

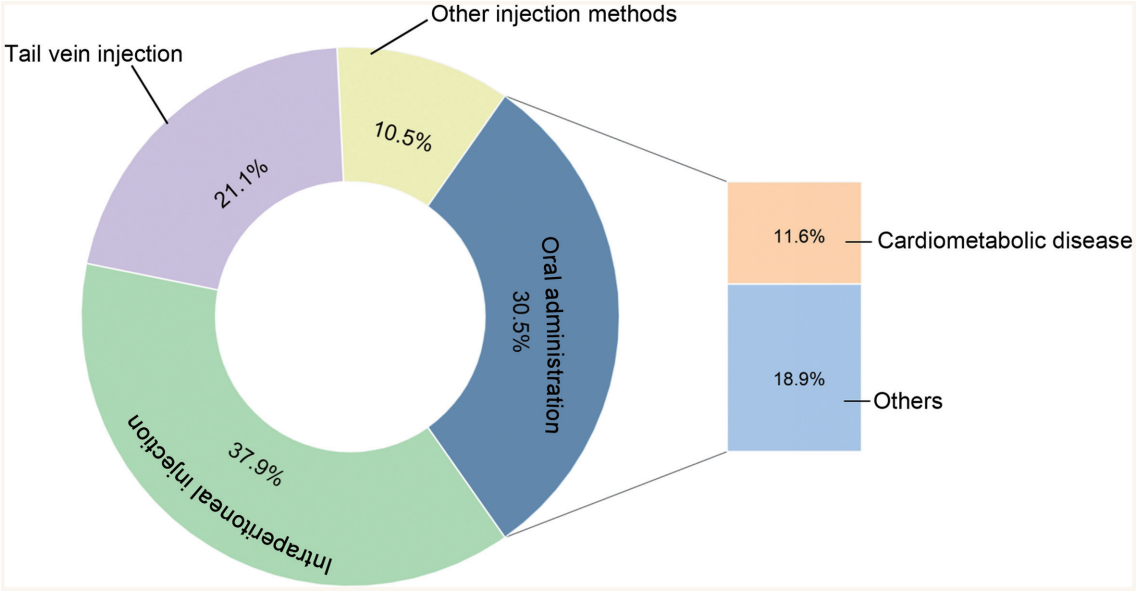

Fig. 5. Analysis of the proportion of different administration routes for safflower yellow pigments and HSYA. HSYA, hydroxysafflor yellow A.

majority of existing studies on safflower yellow pigments have primarily centered on short-term therapeutic outcomes, accompanied by a notable paucity of systematic longitudinal follow-up investigations into their long-term efficacy for coronary heart disease.

Future perspective

After reviewing the literature, it was summarized that during the period from January 1, 2020, to December 31, 2024, in animal studies of non-digestive tract diseases, oral administration of safflower yellow pigments and HSYA accounted for 30.5%. Among these, cardiovascular and metabolic diseases accounted for 11.6%, and other diseases accounted for 18.9%, as shown in Figure 5. Oral administration of safflower yellow pigments and HSYA for the treatment of cardiovascular and metabolic diseases holds significant importance. Considering that the traditional application of safflower mainly involves decoction, studying the effects and mechanisms of safflower yellow pigments on coronary heart disease via oral administration is of great practical significance. However, the high polarity, low oral bioavailability, and short half-life of safflower yellow pigments pose key challenges to their oral use.[91] Currently, formulations such as microemulsions, vesicle preparations, chitosan-based formulations, and nanomedicines have been developed to significantly improve the oral bioavailability of HSYA.[92] Our research team has found that natural deep eutectic solvents showed promising potential for drug delivery. For example, a natural deep eutectic solvent consisting of glucose and choline chloride with 10% water content has been shown to enhance HSYA oral bioavailability, reduce body weight, alleviate fatty liver, and correct dyslipidemia in obese rats.[93] Therefore, promoting research into drug delivery systems to improve the oral bioavailability of safflower yellow pigments is crucial. It is also important to ensure that improvements in bioavailability are accompanied by comprehensive evaluations of pharmacological efficacy and safety to provide better therapeutic outcomes for cardiovascular diseases.

Currently, the mechanisms underlying the treatment of coronary heart disease with safflower yellow pigments are not fully understood. Regarding mechanisms of action, some studies have preliminarily explored the *in vivo* and *in vitro* metabolic transformation of safflower yellow pigment components, suggesting that the gut microbiota may be involved in the effects of orally administered safflower yellow pigments.[94] Our research group has discovered that HSYA can reduce fat accumulation, improve insulin resistance, and enhance gut integrity and short-chain fatty acid production. It can also increase the relative abundance of *Akkermansia* and *Romboutsia* while decreasing the Firmicutes/Bacteroidetes ratio, thereby regulating the composition and structure of the gut microbiota to treat obesity.[71] Notably, recent studies indicate that the development and progression of coronary heart disease are closely related to the gut microbiota. Gut microbial metabolites such as trimethylamine-N-oxide, short-chain fatty acids, bile acids, and lipopolysaccharides are significantly associated with coronary heart disease.[16,95] Thus, exploring the impact of safflower yellow pigments on coronary heart disease through the perspective of the gut microbiota may provide new diagnostic methods and therapeutic avenues for clinical applications. In addition, safflower yellow pigments contain various components, the main ones being HSYA and AHSYB, both of which share similar chemical structures and are presumed to have similar biological activities. AHSYB has been found to have antioxidant, anticoagulant, and anti-apoptotic effects.[96] Future studies should focus on minimizing degradation and further investigating the effects and mechanisms of these components.

At present, clinical studies on the treatment of coronary heart disease with safflower yellow pigments are mostly small-sample and open-label, lacking large-sample, multicenter, randomized double-blind controlled trials. High-quality clinical trials are needed to more accurately assess the efficacy and safety of these drugs and provide more reliable evidence for clinical application. Meanwhile, coronary heart disease is a chronic condition requiring long-term treatment and management. However, most studies on safflower yellow pigments focus on short-term therapeutic effects, with a lack of systematic follow-up studies on their long-term efficacy in coronary heart disease.

Conclusions

Safflower yellow pigments have demonstrated clear clinical efficacy in the treatment of coronary heart disease. Their pharmacological effects include anti-myocardial ischemia, mitigation of ischemia-reperfusion injury, anti-atherosclerosis, improvement of vascular injury, and reduction of coronary heart disease-related risk factors such as obesity, hypertension, hyperlipidemia, and diabetes. The mechanisms of action primarily involve inhibition of inflammatory responses, oxidative stress, and platelet aggregation, as well as reduction of endothelial cell damage and suppression of cardiomyocyte apoptosis. These effects illustrate the multi-target, multi-pathway, and multi-molecular characteristics of the therapeutic actions of safflower yellow pigments. However, the current understanding of coronary heart disease pathogenesis remains incomplete, and the mechanisms underlying the therapeutic effects of safflower yellow pigments require further elucidation. Future research priorities should focus on optimizing the drug delivery system to enhance the oral bioavailability of safflower yellow pigments, complemented by comprehensive safety and efficacy evaluations. Additionally, investigating how safflower yellow pigments regulate gut microbiota-derived metabolites such as short-chain fatty acids and trimethylamine N-oxide to influence coronary heart disease progression is crucial. Equally important are large-scale, multicenter, double-blind clinical trials to validate the long-term efficacy and safety of safflower yellow pigments in coronary heart disease management.

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Conflict of interest

SJY has been an editorial board member of *Future Integrative Medicine* since September 2021. The authors declare no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Author contributions

Study concept and design (YSJ), manuscript writing (DL, ZXM, CJ), and critical revision (YSJ, ZYX). All authors have made significant contributions to this study and have approved the final manuscript.

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