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REVIEW

Review of the Protective Mechanism of Curcumin on Cardiovascular Disease

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Abstract: Cardiovascular diseases (CVDs) are the most common cause of death worldwide and has been the focus of research in the medical community. Curcumin is a polyphenolic compound extracted from the root of turmeric. Curcumin has been shown to have a variety of pharmacological properties over the past decades. Curcumin can significantly protect cardiomyocyte injury after ischemia and hypoxia, inhibit myocardial hypertrophy and fibrosis, improve ventricular remodeling, reduce drug-induced myocardial injury, improve diabetic cardiomyopathy(DCM), alleviate vascular endothelial dysfunction, inhibit foam cell formation, and reduce vascular smooth muscle cells(VSMCs) proliferation. Clinical studies have shown that curcumin has a protective effect on blood vessels. Toxicological studies have shown that curcumin is safe. But high doses of curcumin also have some side effects, such as liver damage and defects in embryonic heart development. This article reviews the mechanism of curcumin intervention on CVDs in recent years, in order to provide reference for the development of new drugs in the future.

Keywords: curcumin, intima, endothelial cells, vascular smooth muscle cell, cardiovascular diseases, inflammation, apoptosis

Introduction

CVDs, disorders of the heart and blood vessels, are a major health problem worldwide, causing the largest number of deaths, and its incidence is still rising. It is estimated that nearly 20 million people worldwide died from CVDs in 2016, accounting for one-third of all deaths. It is predicted that by 2030, 40.5% of Americans will have CVDs, which will result in about $818 billion in health care costs and $276 billion in indirect costs.[1] However, many people fail to recognize the risk of CVDs. Individuals at risk for CVDs may present high blood pressure, weight issues, and altered glucose or lipid levels. Great progress has been made in the research of the pathogenesis mechanism of CVDs, but the morbidity and mortality of CVDs are still very high. There is an urgent need for drugs that are more effective and have minimal side effects to prevent and treat these diseases.

Compared to traditional drugs, natural drugs have many advantages, such as fewer side effects, low long-term toxicity, and variable bioavailability.[2] *Curcuma* originated in India and has a history of 6000 years. About 700 AD, *Curcuma* was introduced into China and was first recorded in the *New Materia Medica*. In 1815, curcumin was isolated in an impalured form by Milobedeska and Lampe. It was not until 1910 that the chemical structure of curcumin was determined and could be synthesized chemically. Curcumin is a bioactive component of the curry spice, and its pleiotropic effects in CVDs suggest that it is a promising drug candidate. Specifically, curcumin can significantly alleviate vascular endothelial dysfunction, inhibit foam cell formation, reduce VSMCs proliferation, protect cardiomyocyte injury after ischemia and hypoxia, inhibit myocardial hypertrophy and fibrosis, improve ventricular remodeling, reduce drug-induced myocardial injury, and improve DCM.[3,4] The current research on curcumin is scattered. In order to further clarify the mechanism of curcumin in CVDs, this study systematically summarized the research reports on curcumin in recent years (Figure 1).

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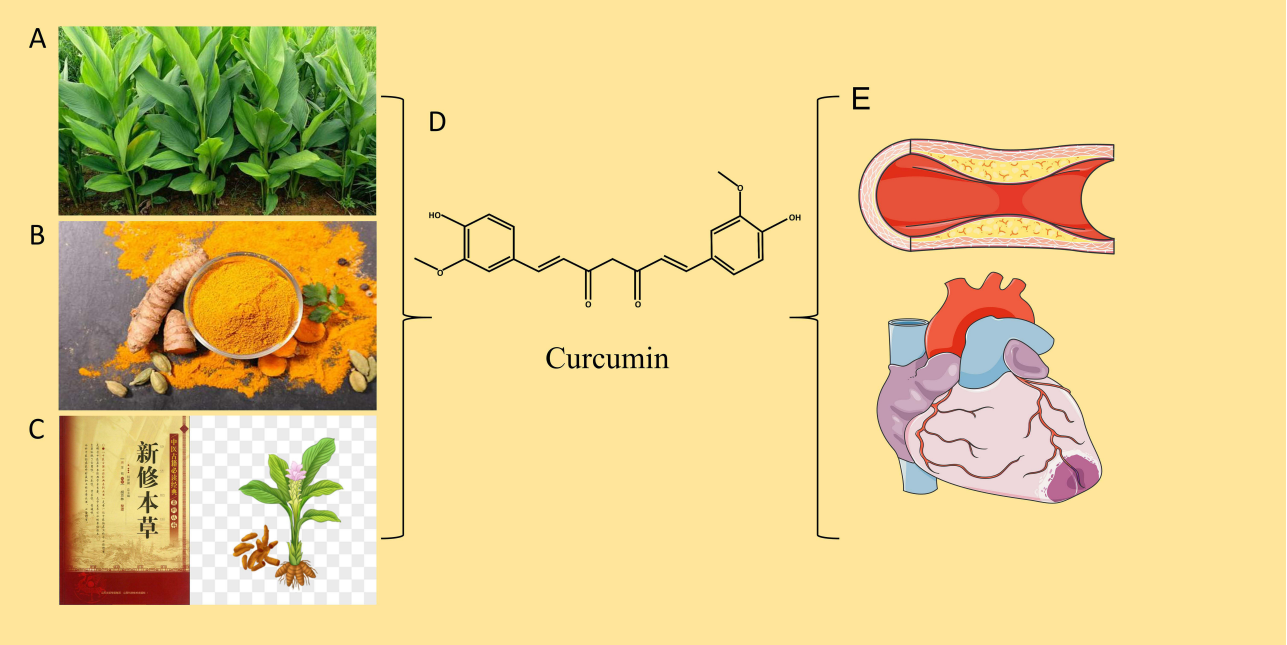

Figure 1 (**A**) *Curcuma*. (**B**) *Curcuma* Decoction pieces. (**C**) *New Materia Medica* and Picture of *Curcuma*. (**D**) Chemical Structure of Curcumin. (**E**) Blood Vessels and Heart.

Search Strategy

This review is based on the guidelines and recommendations of the Preferred Reporting Project for Systematic Review and Meta-Analysis (PRISMA). All relevant articles published in PubMed between January 2010 and August 2023 were included in this review. We used the keywords "curcumin", "atherosclerosis", "vascular smooth muscle cells", "vascular endothelium", "Vascular endothelial cell", "vascular endothelium", "vascular endothelium", "plaque", "adhesion", "lipids", "vasodilation", "cardiac", "myocardial ischemia", "cardiotoxicity", "myocardial cell" and "cardiomyocyte" to search the database. We did a preliminary screening of the obtained articles by browsing the title and abstract to include eligible articles. We included curcumin pharmacokinetic data, drug safety studies, CVDs-related biological mechanisms, and clinical studies.

Protective Effect of Curcumin on Blood Vessels

Reduce the Oxidative Stress of Vascular Endothelial Cells(VECs)

Oxidation should be mainly stimulated by excessive generation of reactive oxygen species (ROS). It plays an important role in mediating various vascular inflammatory signal pathways.[5] Nuclear factor erythroid factor 2 related factor 2 (Nrf2) is a key regulatory factor for redox homeostasis and cellular antioxidant defense. Under homeostatic conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1(Keap1). When the oxidative stress system is activated, Nrf2 separates from Keap1 and then translocated to the nucleus to bind to antioxidant response element (ARE) and regulate the expression of antioxidant defense genes such as heme oxygenase-1 (HO-1).[6] Zhou et al found that curcumin could activate Nrf2/HO-1 signaling pathway to resist hydrogen peroxide (H_2O_2)-induced oxidative stress in Ea.hy926 cells.[7] H_2O_2 is a kind of endogenous ROS. In one study, Yang et al found that curcumin (25 μM) alleviated the damage of H_2O_2 to human umbilical vein endothelial cells (HUVECs) by inhibiting Notch1 signaling pathway.[8] In another study, H_2O_2 decreased cell viability and antioxidant enzyme activity and increased oxidative stress levels in HUVECs. However, curcumin (40 and 50 μM) reversed these changes.[9] (Figure 2 and Table 1)

Lan et al randomly assigned stroke-prone spontaneously hypertensive rats (SHRs) to receive saline or curcumin (100 mg/kg/day). Finally, it was found that curcumin group may reduce the incidence of stroke by regulating uncoupling protein-2(UCP2)/nitric oxide(NO) signaling pathway to reduce oxidative stress and improve vascular endothelial function.[10] In another study, Boonla et al found that curcumin (50 and 100 mg/kg/day) significantly reduced blood pressure and improved endothelial dysfunction and vascular remodeling in 2kidney-1clip(2K-1C) hypertensive rats by reducing matrix metalloproteinases (MMPs) levels and inhibiting oxidative stress.[11]

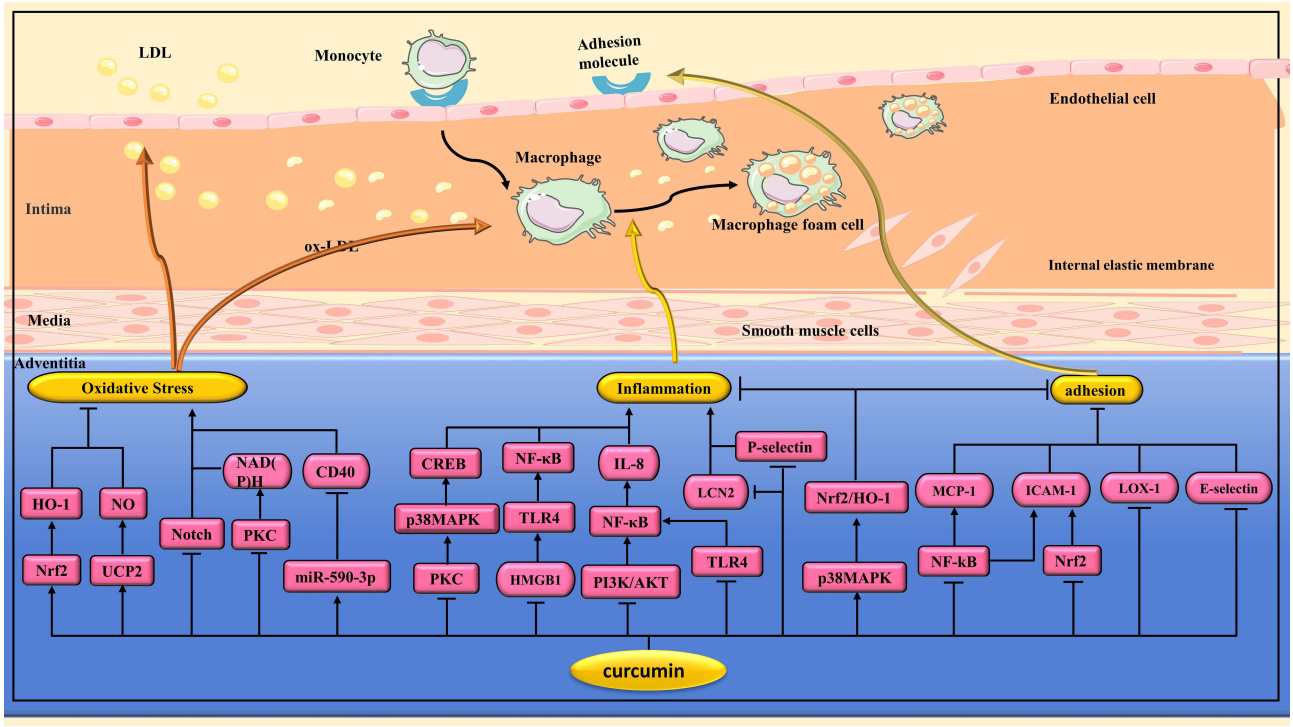

Figure 2 Pharmacological effects of curcumin on atherosclerosis(AS). Anti-AS effects of curcumin via regulating multiple signaling pathways to alleviate oxidative stress, inhibit inflammation, reduced monocyte adhesion and their transendothelial migration.

Hyperglycemia can induce superoxide anion production.[86] The production of superoxide anion in the vasculature is associated with nicotinamide adenine dinucleotide phosphate(NADPH) reduced oxidase, which requires the activation of protein kinase C (PKC).[87] Rungseesantivanon et al found that curcumin supplementation (300 mg/kg/day) inhibited PKC activity and reduced superoxide production, thereby improving endothelial function in diabetic mice.[12] The cluster of differentiation 40 (CD40)/cluster of differentiation 40 ligand (CD40L) system can upregulate proinflammatory and prothrombotic genes in atherosclerotic vessels, and it also upregulates ROS production in endothelial cells.[88,89] Wu et al found that curcumin (10 μM) could inhibit the expression of CD40 in the miR-590-3p dependent pathway, thereby reducing the oxidative stress level and protecting VECs.[13] (Figure 2 and Table 1)

Table 1 Protective Mechanism of Curcumin on Blood Vessels

Research Subjects	Intervention Methods	Mechanism	Refs
Ea.hy926 cells	H_2O_2	By activating the Nrf2/HO-1 signaling pathway	[7]
HUVEC	H_2O_2	By inhibiting the Notch1 signaling pathway	[8]
HUVEC	H_2O_2	By increasing antioxidant enzyme activity	[9]
SHR rat	No-intervention	By regulating UCP2/NO signaling pathway, oxidative stress is reduced	[10]
2K-1C hypertensive rats	No-intervention	By reducing MMP levels and inhibiting oxidative stress	[11]
Diabetic mice	No-intervention	Inhibit PKC activity and reduce the production of superoxide	[12]
VECs	Ang II	By inhibiting the expression of CD40	[13]
$ApoE^{-/-}$ mice	High-fat diet	By inhibiting the expression of TLR4 in AS plaques	[14]
HECs	LPS	By down-regulating TLR2, TLR4 and HMGB1 receptors	[15]
HUVECs	HCMV	By inhibiting the HMGB1/TLRS/NF-κB signaling pathway	[16]

(*Continued*)

Table 1 (Continued).

Research Subjects	Intervention Methods	Mechanism	Refs
HUVECs	Ox-LDL	By regulating the miR-599/MYD88/NF-κB signaling pathway	[17]
ApoE$^{-/-}$ mice	Western diet	By down-regulating LCN2 and inhibiting inflammation	[18]
HECs	Resistin	By inhibiting the expression of p-selectin and fractalkine, NADPH oxidase activation and intracellular ROS levels were decreased	[19]
HAECs	TNF-α	HO-1 expression was induced by activating the p38 MAPK/Nrf2 signaling pathway	[20]
Ea.hy926 cells	TNF-α	By inducing HO-1 expression	[21]
Diabetic rat model	No-intervention	Inhibition of NADPH oxidase, ROS, and ICAM-1 to improve diabetic vascular inflammation	[22]
TAECs	High glucose	By inhibiting the PI3K/Akt/NF-κB signaling pathway	[23]
HUVECs	MGO	By capturing MGO and inhibiting the formation of AGEs	[24,25]
bEnd.3 cells	MGO	By reducing oxidative stress and endoplasmic reticulum stress	[26]
Male Swiss albino mice	AGEs	By neutralizing the AGE-induced inflammatory response	[27]
VECs	Hcy	By inhibiting expression of NF-κB and interleukin-8	[28]
VECs	Acrolein	Inflammation is inhibited by inhibiting PKC/p38 MAPK/CREB pathway	[29]
HAECs	PLLA degraded extracts	By suppressing the inflammatory response	[30]
ApoE$^{-/-}$ mice	HFD	By reducing e-selectin and ICAM-1	[31]
RAECs	High glucose	MCP-1 is reduced by inhibiting the NF-κB pathway	[32]
HUVECs	TNF-α	Curcumin can reduce monocyte adhesion and transendothelial migration	[33]
HUVECs	TNF-α	By inhibiting ROS, LOX-1 and adhesion molecules	][34]]
VECs	Radiation	Adhesion molecules are inhibited by regulating the NF-κB and Nrf2 pathways	[35]
LDLR$^{-/-}$ Mice	High-fat diet	By inducing increased cAMP levels in the liver	[36]
SD rat primary hepatocytes	No-intervention	Curcumin increased the level of apoB-48 and decreased the level of ApoB-100 by increasing the expression of APOBEC-1 in rat hepatocytes	[37]
Rats	Splenectomy	Lipid metabolism disorders are improved by regulating NF-κB, SOD and GPx.	[38]
Macrophage	Ox-LDL	By reducing SR-A and increasing ABCA1, cholesterol accumulation is reduced	[39]
THP-1 macrophages	Ox-LDL	ABCA1 is increased by the miR-125a-5p/SIR T6 signal axis	[40]
RAW 264.7 macrophages	Ox-LDL	The expression of CD36 was inhibited by p38 MAPK signaling pathway	[41]
Macrophages	Ox-LDL	Cholesterol leakage is enhanced by inhibiting the JNK pathway and activating the LXR/ABCA1/SR-BI pathway	[42]
THP-1 macrophages	Ox-LDL	ABCA1 is up-regulated by activation of AMPK/Sirt1 /LXRa signaling pathway	[43]
Macrophage	Ox-LDL	The production of MCP-1 was inhibited by inhibition of JNK and NF-κB pathways	[44]
RAW264.7 macrophages	Ox-LDL	Inhibits the production of inflammatory cytokines such as IL-1β, IL-6, and TNF-α	[45]
Macrophages	HIF-1α	Inhibit inflammation and apoptosis by inhibiting ERK signaling pathway	[46]
RAW264.7 macrophages	No-intervention	Macrophages were polarized to M2 phenotype by activation of PPAR γ	[47]
Macrophages	LPS and IFN-γ	Inhibition of TLR4/MAPK/NF-κB pathway promotes the transformation of M1 macrophages to M2 phenotype	[48]
ApoE$^{-/-}$ mice	Cadmium	By regulating intestinal flora, lipid metabolism imbalance and M1-type macrophage polarization were improved	[49]
Macrophages	Ox-LDL	The expression of EMMPRIN and MMP-9 was inhibited by down-regulating NF-κB and p38 MAPK signaling pathways	[50]
THP-1 macrophages	PMA	The expression of EMMPRIN, MMP-9 and MMP-13 was inhibited by PKC and AMPK pathways	[51]
Macrophages	Ox-LDL	By inhibiting the decrease of THBS-4 expression	[52]
EPCs	High glucose	By increasing MnSOD, EPCs dysfunction induced by high glucose is alleviated	[53]
EPCs	EPC isolated from diabetic mice	By up-regulating the expression of VEGF-A and Ang1, the migration and proliferation of EPCs were promoted	[54]

(*Continued*)

Table 1 (Continued).

Research Subjects	Intervention Methods	Mechanism	Refs
SD rat	Balloon injury carotid endothelium	By inducing autophagy, inhibiting oxidative stress and apoptosis	[55]
HUVECs	Ischemia	Promote angiogenesis by upregulating miR-93	[56]
Rats	CsA	Alleviating CsA-induced endothelial dysfunction in rats by anti-oxidative stress	[57]
Male Wistar rat	Methotrexate	Eliminate vascular side effects of methotrexate by inhibiting oxidative stress and reducing physiological NO levels	[58]
RAECs	Rapamycin	Antagonizing the harmful effect of rapamycin on RAECs by upregulating eNOS	[59]
Laboratory pig	PLLA stents	Alleviating foam cell inflammation caused by PLLA degradation through PPAR γ signaling pathway	[60]
HMEC	PM2.5	By reducing the levels of ROS, ox-LDL, ICAM-1 and VCAM-1	[61]
HUVEC	Palmitic acid	The upregulation of LOX-1 is blocked by inhibiting ERS, thereby reducing subcutaneous lipid deposition	[62]
HUVEC	H_2O_2	Autophagy is promoted by inhibiting the PI3K/Akt/mTOR signaling pathway	[63]
Ea.hy926 cells	H_2O_2	Autophagy is induced by Akt/mTOR pathway, thereby alleviating apoptosis	[64]
HUVECs	Ox-LDL	By modulating AMPK/mTOR/p70S6K autophagy signaling pathway	[65]
Human monocytic THP-1 cells	Ox-LDL	Curcumin regulates ox-LDL-induced macrophage autophagy and inflammation via the TFEB/P300/BRD4 pathway	[66]
Macrophages	PMA	NLRP3 inflammasome of macrophage was decreased by inhibiting TLR4/MyD88/NF-κB signaling	[67]
HUVEC	H_2O_2	Inhibition of H_2O_2-induced HUVEC pyrodeath by inhibiting NLRP3 activation	[68]
HUVECs	H_2O_2	Oxidative stress-induced HUVECs senescence was alleviated by activating Sirt1	[69]
HUVECs	TGF-β1	Curcumin inhibits EndMT by regulating the RF2/DDAH/ADMA/NO pathway	[70]
Mesenteric artery endothelial cells	Phenylephrine	Activation of TRPV4 channels stimulates Ca2+ entry into endothelial cells, thereby improving vasodilation function	[71]
SHR rats	Ang II	VSMCs migration is mitigated by inhibiting the NF-κB/NLRP3 signaling pathway	[72]
SD rats	Arterial balloon injury	The proliferation and migration of VSMCs after arterial balloon injury was inhibited by regulating the miR-22/SP1 pathway	[73]
$ApoE^{-/-}$ mice	HFD	Inhibition of chemerin/CMKLR1/LCN2 pathway mitigated the proliferation and migration of VSMCs during AS	[74]
VSMCs	IGF-1	By inhibiting PKB/GSK-3β/Egr-1 pathway, IGF-1-induced VSMCs proliferation and migration were attenuated	[75]
VSMCs	TNF-α	The expression and activity of MMP-2 were inhibited by NF-κB pathway, thereby inhibiting the migration of VSMCs	[76]
VSMCs	LPS	MMP-2 activity was inhibited by Ras/MEK1/2 pathway	[77]
VSMCs	Endothelin	By increasing PPAR γ activity and inhibiting NADPH oxidase, the release of inflammatory factors from VSMCs was inhibited	[78]
VSMCs	Aldosterone	Inhibiting CRP production in VSMCs by interfering ROS/ERK1/2 signaling	[79]
VSMCs	LPS	Inhibition of inflammatory mediators in VSMCs via TLR4/MAPK/NF-κB pathway	[80]
VSMCs	Ox-LDL	The expression of MCP-1 in VSMCs was inhibited by inhibiting p38MAPK and NF-κB pathways	[81]
VSMCs	LPS	Reducing VSMC inflammation by inhibiting NF-κB and JNK signaling pathways	[82]
C57Bl/6J mice	Ang II	The expression of AT1R in VSMCs was down-regulated by inhibiting SP1/AT1R DNA binding	[83]
VSMCs	ET-1	By inhibiting c-Raf/ERK1/2/Egr-1 and IGF-1R/PKB pathways	[84]
VSMCs	AngII	The transition of VSMC from systolic to synthetic is inhibited by regulating the PTEN/Akt pathway	[85]

Inhibits Inflammation of VECs

Toll-like receptor (TLR)4 is a pattern recognition receptor of the immune system.[90] TLR4 stimulation can lead to the activation of nuclear factor kappa-B(NF-κB) transcription factor,[91] promote inflammatory response, and lead to atherosclerotic plaque instability.[92] Zhang et al found that curcumin (0.1% curcumin added to high-fat diet(HFD)) significantly weakened the development of AS in ApoE$^{-/-}$ mice by inhibiting the expression of TLR4 in atherosclerotic plaque. In addition, curcumin also decreased the expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular cell adhesion molecule-1(ICAM-1), tumor necrosis factor alpha(TNF-α) and the activity of NF-κB.[14] High mobility group box protein 1 (HMGB1) is a potent extracellular proinflammatory mediator.[93] In one study, curcumin (5 to 100 μM) down-regulated the expression of TLR2 and TLR4 on the surface of human endothelial cells (HECs), thereby inhibiting lipopolysaccharide(LPS)-mediated HMGB1 release. In addition, curcumin can also down-regulate the cell surface receptor of HMGB1 in HECs.[15] In another study, Lv et al found that curcumin (0.5, 1 and 2 μM) could reduce the release of inflammatory factors in HUVECs induced by human cytomegalovirus (HCMV) infection by inhibiting HMGB1/TLR/NF-κB signaling pathway, thereby improving the progression of AS.[16] Chen et al found that curcumin (10 μM) promoted cell proliferation and inhibited apoptosis, inflammation and oxidative stress, thereby reducing HUVECs cell damage induced by oxidized low-density lipoprotein (ox-LDL). The mechanism is related to the regulation of miR-599/Myeloid differentiation factor 88(MyD88)/NF-κB signaling pathway by curcumin.[17] (Figure 2 and Table 1)

Lipocalin-2 (LCN2) is an inflammatory factor released by activated neutrophils, which is closely related to AS.[94] In one study, dietary curcumin(60 and 80 mg/kg/day) improved AS in in ApoE$^{-/-}$ mice by downregulating LCN2 and inhibiting inflammation.[18] P-selectin and fractalkine are key molecules in the inflammatory process related to AS. Pirvulescu et al found that curcumin (20 μM) significantly inhibited the expression of p-selectin and fractalkine, and decreased the activation of NADPH oxidase and intracellular ROS levels in HECs exposed to resistin.[19] HO-1 is a subtype of heme oxygenase that inhibits AS, inflammation, and oxidative stress.[95] Xiao et al found that curcumin (100 μM) induced HO-1 expression by activating p38 mitogen-activated protein kinase(p38 MAPK)/Nrf2 signaling pathway, thereby inhibiting inflammation in human arterial endothelial cells (HAECs).[20] In addition, HO-1 can also improve inflammation by inhibiting the expression of endothelial cell adhesion molecules.[96] In one study, curcumin (10 and 30 μM) induced HO-1 expression and inhibited ICAM-1 expression in Ea.hy926 cells treated with TNF-α, thereby improving VECs inflammation.[21] (Figure 2 and Table 1)

Hyperglycemia can interfere with vascular homeostasis and lead to vascular complications in diabetes. In one study, curcumin (300 mg/kg/day) inhibited NADPH oxidase and reduced ROS and ICAM-1 in a diabetic rat model, thereby improving diabetic vascular inflammation.[22] In another study, curcumin (10 μM) attenuated high glucose-induced inflammatory injury in rat thoracic aortic endothelial cells (TAECs) through inhibition of phosphatidyinositol 3-kinase(PI3K)/protein kinase B(Akt)/NF-κB signaling pathway.[23] Advanced glycation end products (AGEs) induced by hyperglycemia are the main cause of diabetes-related complications.[97] Methylglyoxal (MGO) is a key precursor of AGEs, and the capture of MGO is an effective strategy to alleviate endothelial damage induced by carbonyl stress.[98] In one study, curcumin (10 μM) could protect endothelial cells by trapping MGO and inhibiting the formation of AGEs.[24] In another study, Hu et al similarly found curcumin (0.25 to 2.5 μM) to be an effective MGO catcher in HUVECs.[25] Narra et al evaluated the effects of curcumin and recombinant high-density lipoprotein(HDL) nanoparticles(Cur-rHDLs) on MGO-induced murine cerebrovascular endothelial cells (bEnd.3). They found that Cur-rHDLs(0.2 and 0.4 μM) reduced oxidative stress and endoplasmic reticulum stress(ERS) and played a protective role in the integrity of the endothelial cell barrier.[26] AGEs also have an effect on myocardial inflammation. Sowndhar et al found that dietary curcumin could neutralize AGEs-induced adverse reactions and reduce the expression of pro-inflammatory genes.[27] Elevated plasma homocysteine (Hcy) can impair VECs and has been an independent risk factor for ischemic CVDs.[99] Li et al found that curcumin (17 μM) could protect VECs from Hcy injury by inhibiting the expression of NF-κB and interleukin-8 (IL-8).[28] (Figure 2 and Table 1)

Acrolein is a known toxin in tobacco smoke that can cause inflammation in VECs. Lee et al found that curcumin (25 μM) could inhibit acrolein-induced cyclooxygenase (COX)-2 expression and prostaglandin production in HECs by inhibiting PKC/p38 MAPK/cyclic adenosine monophosphate (cAMP)-response element binding protein(CREB) pathway, thereby inhibiting cellular inflammatory response.[29] Biodegradable poly-L-lactic acid (PLLA) is often used as major components or coating agents in tissue engineering and scaffolds.[100] In one study, PLLA degraded extract significantly

inhibited the migration and increased the inflammatory response of HAECs, which was alleviated by curcumin (5 μM) treatment.[30] (Figure 2 and Table 1)

Inhibit the Adhesion of Macrophages to VECs

During the progression of AS, monocytes can be trapped by endothelial secretion of adhesion molecules such as ICAM-1, E-selectin, and P-selectin, and then enter the subendothelium.[101,102] Li et al found that atorvastatin calcium combined with curcumin effectively reduced E-selectin and ICAM-1, thereby alleviating AS.[31] Monocyte chemoattractant protein 1 (MCP-1) also plays an important role in adhesion and migration of monocytes to arterial intima.[103] In one study, curcumin (30 μM) decreased MCP-1 expression in rat aortic endothelial cells (RAECs) induced by high glucose by inhibiting the NF-κB pathway.[32] In another study, Monfoulet et al exposed HUVECs to curcumin (1 μM) for 3h before TNF-α activation. It was found that curcumin reduced monocyte adhesion and their transendothelial migration.[33] ox-LDL can increase the production of endoderm-derived ROS and the expression of adhesion molecules.[104,105] In one study, curcumin (67.9 μM) significantly inhibited the expression of ROS, lectin-like ox-LDL receptor-1 (LOX-1) and adhesion molecules in TNF-α-stimulated HUVECs.[34] Radiotherapy can increase the expression of adhesion molecules in VECs.[106] Soltani et al found that nanoformulation of curcumin could inhibit radiation-induced adhesion molecules (especially ICAM-1) by modulating NF-κB and Nrf2 pathways, thereby inhibiting monocyte adhesion to HUVECs.[35] (Figure 2 and Table 1)

Regulate Lipid Metabolism and Inhibit Lipid Plaque Formation

Lipid metabolism disorders are closely related to AS.[107] In one study, curcumin (500 and 1000 mg/kg/day) effectively reduced fatty streak formation and inhibited IL-6 expression in the descending aorta of LDLR$^{-/-}$mice fed a HFD.[108] In another study, curcumin reduced serum levels of total cholesterol (TC), total triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), ox-LDL cholesterol, circulating inflammatory cytokines and soluble adhesion molecules in New Zealand white rabbits.[109] Lv et al found that curcumin (15 and 25 mg/kg/day) decreased serum LDL-C, TC, and TG levels, significantly reduced aortic atheromatous plaque formation, and reduced lipid deposition in the liver in ApoE$^{-/-}$ mice.[16] Zingg et al found that curcumin (500, 1000 and 1500 mg/kg/day for 4 months) reduced plasma and tissue lipid levels in LDLR$^{-/-}$ mice fed HFD. Further studies have found that curcumin can induce the increase of cAMP level in liver, which may be one of its mechanisms of lowering blood lipids and anti-AS.[36] Apolipoprotein B (Apo B) is a major component of LDL in mammals, and it comes in two subtypes: apoB-100 and apoB-48. Lipoprotein particles containing apoB-48 were cleared from plasma more quickly than those containing apoB-100 (10 mins vs 3 days).[110] Tian et al found that curcumin (15 μM) increased the level of apoB-48 and decreased the level of ApoB-100 by increasing the expression of APOBEC-1 in rat hepatocytes.[37] The spleen also plays an important role in lipid metabolism.[111] Splenectomy can lead to hyperlipidemia with macrophage dysfunction.[112] Altinel et al found that curcumin (20 mg/kg/day for 28 days) partially improved lipid metabolism disorders by regulating NF-κB, superoxide dismutase (SOD) and glutathione(GSH) peroxidase (GSH-Px) in splenectomy rats.[38] (Figure 3 and Table 1)

Monocytes/macrophages migrate to the inner membrane and subsequently clear cholesterol and secrete proinflammatory cytokines.[113,114] Excessive LDL uptake or impaired cholesterol efflux in macrophages accelerates foam cell formation. Scavenger receptor class A(SR-A) and cluster of differentiation 36(CD36) are responsible for modifying LDL internalization.[115,116] In contrast, the class B scavenging receptor type I (SR-BI) and the ATP-binding cassette transporters A1(ABCA1) and G1(ABCG1) are responsible for intracellular cholesterol efflux to HDL or apolipoprotein AI (apo AI).[117,118] In one study, curcumin (40 μM) treatment significantly improved ox-LDL-induced intracellular cholesterol accumulation in macrophages by decreasing protein expression of SR-A and increasing protein expression of ABCA1.[39] In other studies, researchers made similar findings. Tan et al found that curcumin (40 μM) could promote cholesterol efflux in human myeloid leukemia mononuclear cells (THP-1) macrophages by increasing ABCA1 expression via the miR-125a-5p/Sirtuin 6(Sirt 6) signaling axis.[40] Min et al found that curcumin (10 μM) could inhibit the expression of CD36 through p38 MAPK signaling pathway.[41] Liver X receptors (LXRs) are ligand-dependent transcription factors that can be activated by cholesterol.[119] In one study, curcumin (10, 20 and 40 μM) enhanced cholesterol efflux from foam cells by inhibiting the c-Jun N-terminal kinase(JNK) pathway and activating the LXR/ABCA1/SR-BI pathway.[42] Lin et al also found that curcumin (10 μM) promoted cholesterol efflux in THP-1 macrophage-derived foam cells by upregulating ABCA1 expression through activation of AMP-

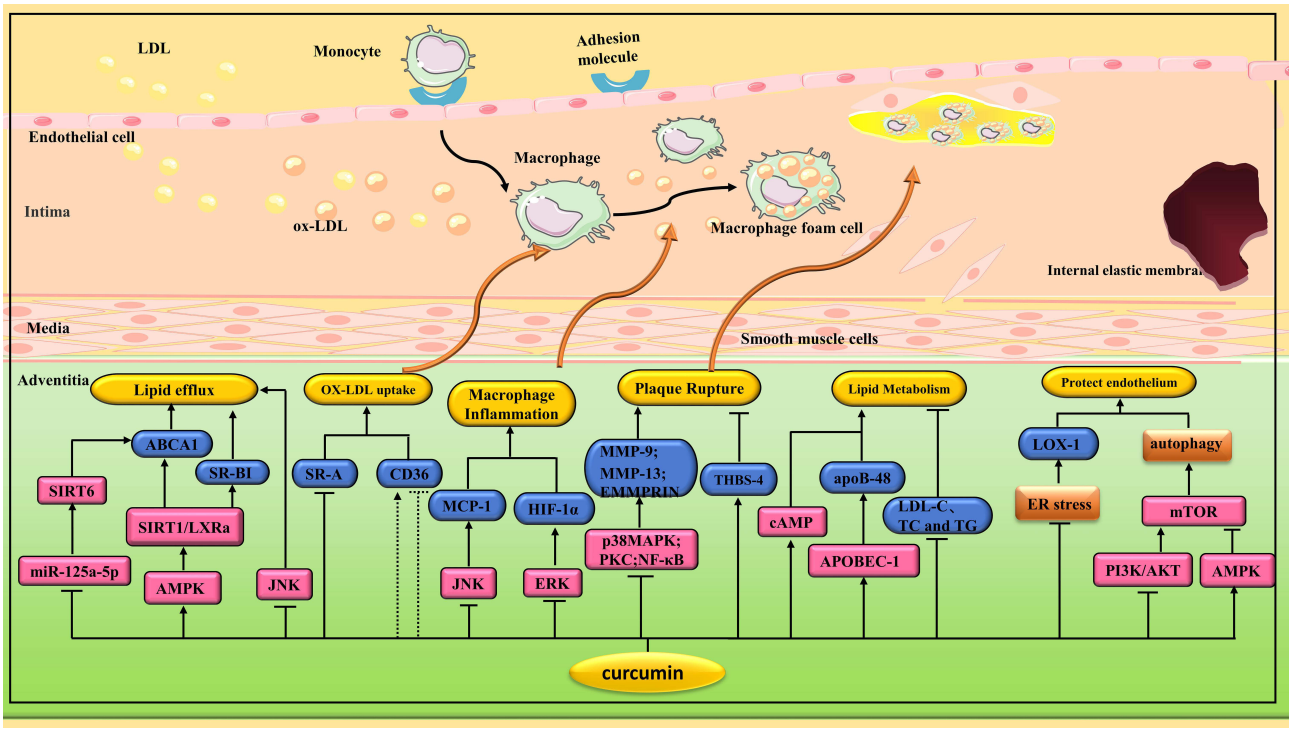

Figure 3 Pharmacological effects of curcumin on AS. Curcumin plays an anti-AS role by regulating various signaling pathways to inhibit macrophage transformation into foam cells, protect endothelial cells, reduce plaque rupture, inhibit ERS and induce autophagy.

activated protein kinase(AMPK)/Silent information regulator 1(Sirt 1)/LXR signaling.[43] Not all cell experiments have reached the same conclusion. Chen et al found that curcumin (6.25 and 12.5 μM) enhanced ox-LDL-induced cholesterol esterification and foam cell formation by upregulating CD36 and ABCA1 expression in M1 macrophages.[120] In another study, curcumin (5 μM) increased lipid levels in THP-1 monocytes and RAW264.7 macrophages, associated with up-regulation of CD36/fatty acid translocase(FAT) and fatty acid binding protein 4(FABP4). However, in vivo experiments, curcumin (500, 1000, and 1500 mg/kg/day) reduced lipid levels in peritoneal macrophages of LDL-receptor knockout mice after 4 months of HFD.[121] (Figure 3 and Table 1)

Curcumin also inhibits macrophage release of inflammatory cytokines. In one study, curcumin (10, 20 and 40 μM) inhibited ox-LDL-induced MCP-1 production by inhibiting JNK and NF-κB pathways.[44] In another study, curcumin (6.25 and 12.5 μM) significantly reduced ox-LDL-induced production of inflammatory cytokines, such as IL-1β, IL-6 and TNF-α.[45] Hypoxia inducible factor-1α (HIF-1α) is also closely related to inflammation. Curcumin (20 and 40 μM) can inhibit HIF-1α-induced macrophage inflammation and apoptosis by inhibiting extracellular regulated protein kinase(ERK) signaling pathway.[46] According to the activation pattern and function, macrophages can be differentiated into two subtypes: classically activated M1 macrophages and alternatively activated M2 macrophages. M1 macrophages are characterized by proinflammation and tissue damage, while M2 macrophages are involved in anti-inflammatory and tissue remodeling.[122] In one study, curcumin (6.25, 12.5, and 25 μM) polarized macrophages to the M2 phenotype by activating peroxisome proliferator-activated receptor γ (PPAR γ).[47] In another study, curcumin (7.5 to 30 μM) promoted the transformation of M1 macrophages into M2 phenotype by inhibiting the TLR4/MAPK/NF-κB pathway.[48] Cadmium is a non-essential element in the human body. It does not degrade easily, so it is easy to accumulate in crops. Some surveys have shown an increased incidence of AS in areas exposed to cadmium.[123] Zhang et al found that cadmium exposure led to changes in microbial community composition, resulting in increased trimethylamine-N-oxide (TMAO) synthesis, lipid metabolism imbalance and M1-type macrophage polarization in ApoE$^{-/-}$ mice, thus promoting the progression of AS. Intragastric administration of curcumin (100 mg/kg/day) reverses cadmium-induced AS progression by restoring intestinal flora.[49] (Figure 3 and Table 1)

MMP-9 and extracellular matrix metalloproteinase inducer (EMMPRIN) in macrophages are closely related to atherosclerotic plaque rupture.[124] In one study, curcumin (25 μM) inhibited EMMPRIN and MMP-9 expression in ox-LDL-stimulated macrophages by down-regulating NF-κB and p38 MAPK signaling pathways.[50] In another study, curcumin (6.25, 25 and 50 μM) inhibited the expression of EMMPRIN, MMP-9, and MMP-13 in THP-1 cells stimulated by phorpol 12 myristic acid 13 acetate (PMA) through PKC and AMPK pathways.[51] Thrombospondins(THBS) plays a role in stabilizing atherosclerotic plaques.[125] Curcumin (5, 15 and 25 μM) could significantly inhibit the reduction of THBS-4 expression in macrophages induced by ox-LDL.[52] All these three studies indicated that curcumin could stabilize atherosclerotic plaque. (Figure 3 and Table 1)

Promote Angiogenesis

Diabetes mellitus (DM)-induced hyperglycemia can cause nonhealing ulcers and impaired wound healing. Endothelial progenitor cells (EPCs) play an important role in wound healing. In one study, curcumin (10 μM) reversed DM-induced EPCs dysfunction (EPCD) by increasing the expression of manganese superoxide dismutase (MnSOD).[53] In another study, curcumin promoted angiogenesis, migration, and proliferation of EPCs and reversed the number of aging EPCs by a mechanism related to up-regulation of vascular endothelial growth factor(VEGF)-A and angiotensin I(Ang I;). In vivo studies, curcumin can significantly improve blood reperfusion in ischemic hind limbs of type 1 diabetic mice by increasing capillary density.[54] Chen et al found that curcumin (10 μM) may enhance the migration and healing of HUVECs by enhancing autophagy. In vivo, curcumin (25 and 75 mg/kg/day) can promote re-endothelization and intimal hyperplasia after carotid artery balloon injury in rats by inducing autophagy, inhibiting oxidative stress levels and apoptosis.[55] miR-93 has been reported to induce angiogenesis in peripheral arterial disease (PAD) mice.[126] Zhang et al found that curcumin (1000 mg/kg/day) can promote angiogenesis by upregulating miR-93 and exert beneficial effects on non-diabetic PAD.[56] It is worth mentioning that the effect of curcumin on angiogenesis may be dose-dependent. In one study, curcumin (50 μM) may inhibit the proliferation and migration rate of HUVECs by regulating focal adhesion kinase(FAK)/p-38 MAPK signaling pathway.[127]

Reduce Drug and Environmental Damage to VECs

Cyclosporine A(CsA) is a commonly used immunosuppressant in clinical practice, but it also has some side effects, such as causing hypertension.[128] Sagiroglu et al found that curcumin (200 mg/kg/day) could alleviate CsA-induced endothelial dysfunction in rats by anti-oxidative stress.[57] Methotrexate, the most commonly used antirheumatic drug, also has the side effect of damaging the endothelium.[129] Sankrityayan et al found that curcumin (200 and 400 mg/kg/day) could eliminate the vascular side effects of methotrexate by inhibiting oxidative stress and the reduction of physiological NO levels.[58]

Rapamycin eluting scaffolds can inhibit the proliferation and migration of VSMCs and reduce vascular restenosis. But rapamycin can inhibit the proliferation and migration of endothelial cells and induce apoptosis of EPCs, thereby destroying re-endothelialization.[130] Guo et al found that curcumin (30 μM) antagonizes the harmful effects of rapamycin on RAECs by upregulating endothelial nitric oxide synthase(eNOS).[59] PLLA is a candidate material for biodegradable vascular scaffolds.[131] In one study, there was a significant increase in inflammatory cytokines around PLLA stents after they were implanted into porcine coronary arteries. In vitro studies, curcumin (20 μM) can reduce foam cell inflammation caused by PLLA degradation through PPAR γ signaling pathway.[60] Epidemiological studies have shown that air pollution is associated with the development of vascular diseases. Shi et al found that curcumin attenuates particulate matter 2.5(PM 2.5) damage to human microvascular endothelial cells (HMECs) by reducing the levels of ROS, ox-LDL, ICAM-1 and VCAM-1.[61]

Other Protective Effects of Curcumin on VECs

ERS is involved in endothelial cell injury. LOX-1 is a major receptor for ox-LDL in endothelial cells.[132] Excessive binding of ox-LDL to LOX-1 can lead to endothelial dysfunction.[133] Luo et al found that curcumin (2.5 μM) may block the upregulation of LOX-1 in HUVECs by inhibiting ERS, thereby reducing subcutaneous lipid deposition.[62] In another study, curcumin (2.5 to 20 μM) inhibited ERS and subsequently inhibited the JNK/insulin receptor substrate 1(IRS-1) pathway, thereby improving insulin resistance and protecting endothelial function in diabetic patients.[134] (Figure 3 and Table 1)

Basal level autophagy maintains cellular homeostasis by clearing and recycling damaged cytoplasmic contents.[135] Han et al found that curcumin (5 μM) could inhibit PI3K/Akt/mammalian target of rapamycin(mTOR) signaling pathway and increase free beclin1(BECN1) in the cytoplasm, thereby promoting autophagy and protecting H_2O_2-intervened HUVECs.[63] Interestingly, Guo et al had similar findings in another study. They found that curcumin (5 and 20 μM) could inhibit apoptosis and induce autophagy through the Akt/mTOR pathway, thereby protecting Ea.hy926 cells from oxidative stress-induced damage.[64] Curcumin can also induce autophagy through other pathways. Zhao et al found that curcumin (5 μM) ameliorated ox-LDL-induced endogenous toxicity and attenuated endothelial dysfunction by regulating AMPK/mTOR/p70S6K autophagy signaling pathway.[65] Previous studies have shown that ox-LDL can cause abnormal crosstalk between autophagy and inflammation in macrophages. Li et al found that curcumin(20 μM) regulates ox-LDL-induced macrophage autophagy and inflammation via the transcription factor EB(TFEB)/P300/bromodomain-containing protein 4(BRD4) pathway.[66] (Figure 3 and Table 1)

NOD-, LRR- and pyrin domain-containing protein 3(NLRP3) inflammasome is an apoptosis-associated protein.[136] In one study, curcumin (6.25, 12.5 and 25 μM) reduced NLRP3 inflammasome production in PMA-stimulated macrophages by inhibiting TLR4/MyD 88/NF-κB signaling.[67] Pyroptosis is a kind of programmed cell death, which is closely related to inflammatory response.[137] Yuan et al found that curcumin(25 μM) inhibited H_2O_2-induced pyroptosis of HUVECs by inhibiting NLRP3 activation.[68]

Cellular senescence is a state of cell growth arrest, which is irreversible.[138] Studies have shown that Sirt1 is involved in the process of age-related vascular diseases, such as AS.[139] Sun et al found that curcumin (25 μM) could attenuate oxidative stress-induced premature senescence in HUVECs by activating Sirt1.[69]

The endothelial-to-mesenchymal transition (EndMT) is one of the mechanisms of myofibroblast generation in fibrous tissues or organs.[140] Transforming growth factor-β1 (TGF-β1) can induce EndMT.[141] Chen et al found that curcumin (5 and 10 μM) could inhibit TGF-β1-induced EndMT by regulating nuclear factor erythroid-2-related factor 2(Nrf-2)/dimethylarginine dimethylaminohydrolase(DDAH)/asymmetric dimethylarginine(ADMA)/NO pathway, thereby attenuating endothelial cell fibrosis.[70]

Transient receptor potential vanilloid 4 (TRPV4), as a member of Ca^{2+} -permeable ion channels, which plays an important role in vasodilatation.[142,143] Shao et al found that curcumin (1 to 300 μM) could stimulate Ca^{2+} entry into endothelial cells and improve vasodilation function by activating TRPV4 channels.[71]

Protection of VSMCs by Curcumin

Migration of VSMCs from media to intima is a key pathogenic event in the formation and development of AS and vascular restenosis.[144] In one study, curcumin (20 μM) inhibited angiotensin II(Ang II)-induced migration of VSMCs in SHRs, possibly by inhibiting NF-κB/NLRP3 signaling.[72] Mintz et al found that curcumin (10 μM) could inhibit the proliferation and migration of VSMCs after arterial balloon injury in rats by regulating miR-22/specific protein 1(SP1) pathway.[73] Chemerin is a novel adipokine that is positively correlated with the severity of AS.[145] He et al found that curcumin (60 mg/kg/day) alleviated the proliferation and migration of VSMCs during AS by inhibiting chemerin/chemokine-like receptor 1 (CMKLR1)/LCN2 pathway.[74] Insulin-like growth factor 1 (IGF-1) is a mitogen associated with the proliferation, hypertrophy and migration of VSMCs.[146] Youreva et al found that curcumin (5, 25 and 50 μM) attenuates IGF-1-induced VSMCs proliferation and migration by inhibiting the protein kinase B (PKB)/glycogen synthase kinase-3β(GSK-3β)/early growth response protein 1(Egr-1) pathway.[75] MMP-2, a member of the Zinc-dependent protease family, plays a key role in promoting the proliferation and migration of VSMCs and weakening the stability of atherosclerotic plaques. Zhong et al found that curcumin (20 and 40 μM) inhibited the migration of VSMCs by inhibiting TNF-α-induced MMP-2 expression and activity through the NF-κB pathway.[76] In another study, Zhong et al also found that curcumin (20 and 40 μM) inhibited LPS-induced MMP-2 activity through rat sarcoma(Ras)/mitogen-activated protein kinase kinase 1/2(MEK1/2) pathway.[77] (Figure 4 and Table 1)

VSMCs also release inflammatory cytokines that accelerate AS.[147] In one study, curcumin (5, 10 and 20 μM) inhibited endothelin-induced TNF-α, IL-6, and NO production and cell proliferation in VSMCs by increasing PPAR γ activity and inhibiting NADPH oxidase-mediated intracellular ROS production.[78] In another study, curcumin (5 μM) inhibited C-reactive protein (CRP) production in aldosterone-induced VSMCs by interfering with ROS/ERK1/2

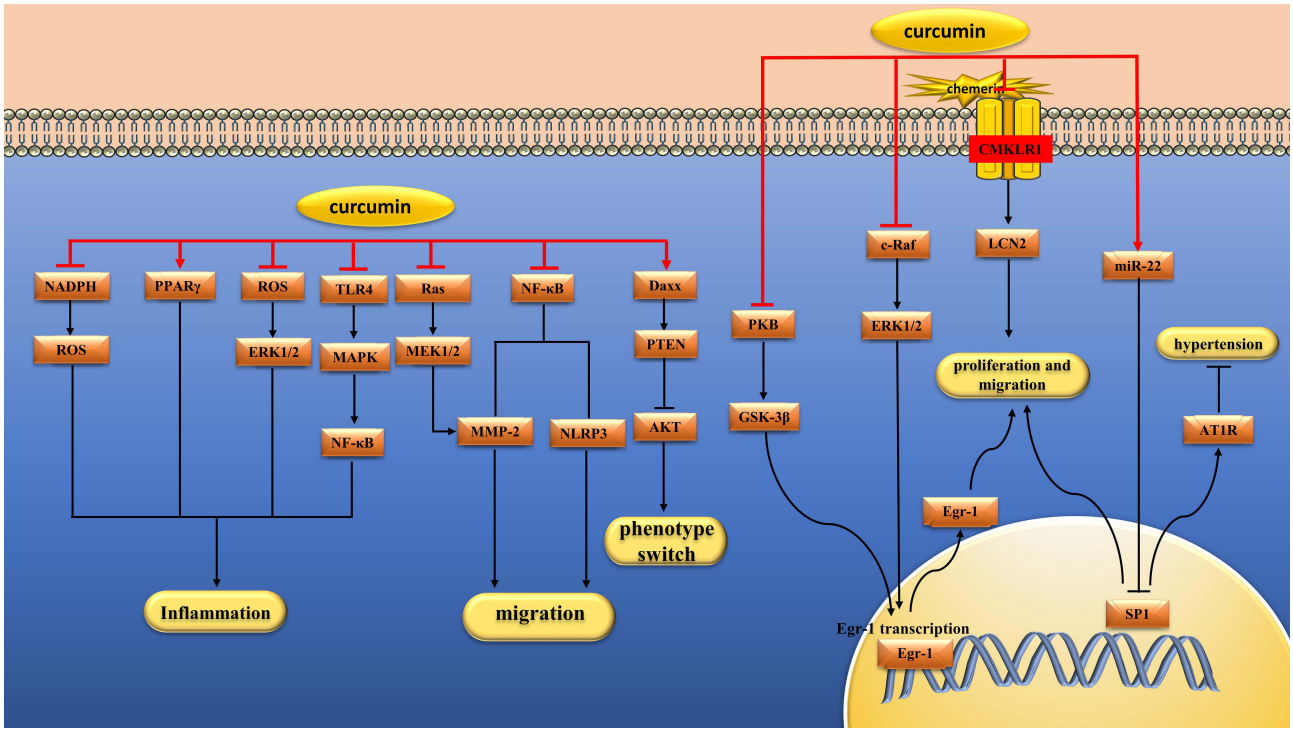

Figure 4 Pharmacological effects of curcumin on vascular smooth muscle cells. Curcumin can inhibit the proliferation, migration and inflammation of vascular smooth muscle cells.

signaling.[79] LPS and ox-LDL also stimulated VSMCs to overexpress inflammatory factors, including TNF-α and MCP-1. In one study, curcumin (5, 10 and 30 μM) inhibited overexpression of inflammatory mediators in LPS-induced VSMCs by a mechanism related to inhibition of the TLR4/MAPK/NF-κB pathway.[80] In another study, curcumin (10 and 30 μM) inhibited ox-LDL-induced MCP-1 expression by inhibiting p38 MAPK and NF-κB pathways in VSMCs.[81] In addition, Ruan et al found that curcumin(135.7 μM) can reduce LPS-induced inflammatory damage by reducing apoptosis, increasing VSMCs activity and inhibiting the release of inflammatory cytokines, the mechanism of which is related to the inhibition of NF-κB and JNK signaling pathways.[82] (Figure 4 and Table 1)

The activation of renin aniotension aldosterone system(RAAS) is associated with the pathogenesis of hypertension.[148] Yao et al found that curcumin (1 μM) down-regulated the expression of angiotensin type 1 receptor(AT1R) in VSMCs by inhibiting SP1/AT1R pathway, and then inhibited the occurrence of Ang II–induced hypertension.[83] Endothelin-1(ET-1) is a potent vasoconstrictor peptide that plays a key role in inducing growth and hypertrophy of VSMCs. Kapakos et al found that curcumin (25 μM) could counteract the biological response of ET-1 and play an important role in vascular protection by inhibiting the c-Raf/ERK1/2/Egr-1 and IGF-1 receptor(IGF-1R)/PKB pathways.[84] There are two phenotypes of VSMCs, the contractile type and the synthetic type. The switch of VSMCs from a contractile to a synthetic phenotype plays a deleterious role in the development of AS and intimal hyperplasia. Sun et al found that Nicotinic-curcumin(1 μM) and curcumin(10 μM) could inhibit Ang II–induced VSMCs switching from a contractile to a synthetic phenotype by regulating the phosphatase and tensin homolog(PTEN)/Akt pathway.[85] (Figure 4 and Table 1)

Clinical Trials

Flow-mediated dilation (FMD) can reflect the biological activity of endothelial NO and is a good indicator of vascular endothelial function. Choi et al administered curcumin (150 mg) (n=6) or placebo (n=8) to 14 healthy, sedentary young men before performing eccentric elbow flexor exercises on the nondominant arm. The study found that acute curcumin supplementation can reduce the decrease of FMD of brachial artery.[149] In another randomized controlled trial, curcumin (0.2 g/day for 8 weeks) increased FMD and thus improved endothelial function in healthy young subjects.[150] A meta-analysis by

Hallajzadeh et al also showed that curcumin (0.045 to 2 g/day) improved FMD.[151] Santos-Parker et al randomly assigned 39 healthy men and postmenopausal women to receive curcumin (N=20) or placebo (N=19) for 12 weeks. Studies have found that curcumin (2 g/day longvida®) can increase vascular NO bioavailability, reduce oxidative stress, and improve arterial endothelial function.[152]

Protect Cardiomyocytes

Alleviate Ischemia and Reperfusion Injury

Myocardial ischemia and reperfusion(I/R) leads to increased oxidative stress, which aggravates cardiomyocyte injury. Sirt1, a histone deacetylase, whose activation reduces oxidative stress.[153] Yang et al found that curcumin (0.25, 0.5 and 1 μM) could reduce I/R-induced mitochondrial oxidative damage by activating Sirt1 signaling pathway.[154] Janus kinase-(JAK)/signal transducer and activator of transcription(STAT) signaling pathway plays an important role in the myocardial response to various cardiac injuries.[155] Duan et al found that curcumin (1 μM) could alleviate I/R injury in isolated rat hearts by activating JAK2/STAT3 signaling pathway.[156] Liu et al obtained the same conclusion in vivo. They found that curcumin (10, 20 and 30 mg/kg/day) alleviated myocardial I/R injury in rats by activating JAK2/STAT3 signaling pathway.[157] TLRs are key signaling receptors mediating innate immune recognition.[158] Kim et al found that curcumin (300 mg/kg/day) could reduce myocardial I/R injury in Sprague Dawley(SD) rats by selectively inhibiting TLR2.[159] Fiorillo et al found that curcumin (10 μM) could protect cardiomyocytes from I/R injury, and the mechanism may be related to antioxidative stress, inhibition of nuclear translocation of NF-κB and JNK phosphorylation.[160] Zhu et al found that curcumin (10 μM) attenuates hypoxia/reoxygenation(H/R)-induced injury in H9C2 cells by down-regulating Notch pathway.[161] m^{6}A modification, the most common type of RNA methylation, is involved in myocardial I/R by influencing RNA stability and translation to regulate gene expression. Cui et al found that curcumin (10 μM) attenuated myocardial I/R damage in H9c2 cardiomyocytes by regulating total RNA m^{6}A levels.[162] (Figure 5 and Table 2)

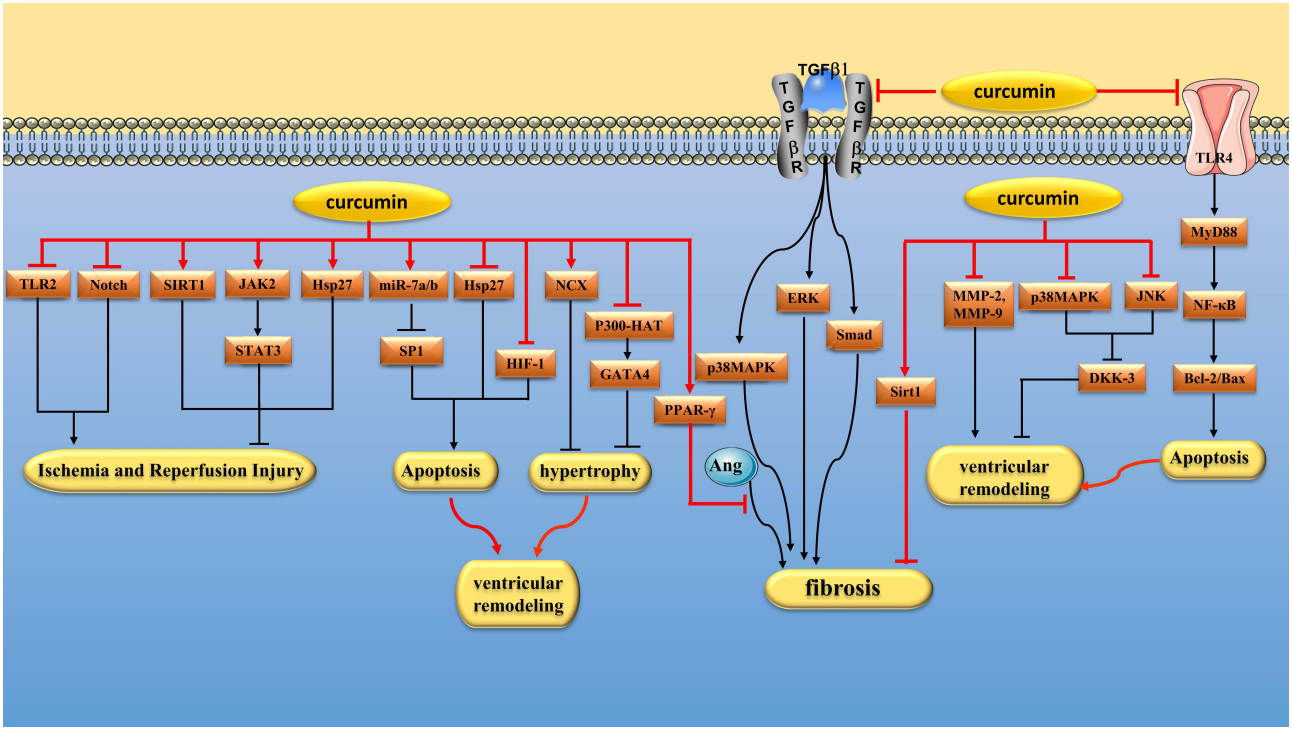

Figure 5 Pharmacological effects of curcumin on Cardiomyocyte. Myocardial protection of curcumin via regulating multiple signaling pathways to alleviate I/R injury, inhibit cardiomyocyte apoptosis, hypertrophy and fibrosis and reduce ventricular remodeling.

Table 2 Protective Mechanism of Curcumin on Cardiomyocytes

Research Subjects	Intervention Methods	Mechanism	Refs
SD rats	I/R	I/R-induced oxidative damage is mitigated by activating Sirt1 signaling pathway	[154]
Isolated rat heart	I/R	I/R damage is mitigated by activation of the JAK2/STAT3 signaling pathway	[156]
SD rats	I/R	I/R damage is mitigated by activation of the JAK2/STAT3 signaling pathway	[157]
SD rats	I/R	I/R damage is mitigated by inhibition of TLR2	[159]
H9c2	I/R	By anti-oxidative stress, inhibition of NF-κB nuclear translocation and JNK phosphorylation	[160]
H9c2	H/R	H/R-induced H9C2 cell damage was alleviated by down-regulating Notch pathway	[161]
H9c2	I/R	I/R damage was mitigated by regulation of total RNA m6A levels	[162]
Wistar rat	ISO	Reduce cardiomyocyte apoptosis by preventing excessive mPTP opening	[163]
Male Wistar rats	ISO	By increasing the level of Hsp27	[164]
C57BL/6 mice	Hypoxia	Apoptosis was alleviated by miR-7a/b/SP1 pathway	[165]
SD rats	CME	Inhibition of TLR4/MyD88/NF-κB signaling pathway alleviates myocardial cell inflammation and apoptosis	[166]
Swiss/SV129 mice	Chronic intermittent hypoxia	By inhibiting HIF-1α activation, infarct size is reduced	[167]
Neonatal rat cardiomyocytes	Phenylephrine	Cardiomyocyte hypertrophy was alleviated by inhibiting p300-HAT activity	[168]
DS rat	High-salt diet	Cardiac hypertrophy was reduced by reducing p300-HAT activity and GATA4 acetylation levels	[169]
Adult 129SvEv mice	LPS	Myocardial hypertrophy was alleviated by inhibiting p300-HAT activity	[170]
H9c2 cardiomyocytes	Norepinephrine	Cardiomyocyte hypertrophy was inhibited by inhibiting the nuclear localization and DNA binding activity of KATA-4	[171]
Male Wistar rat	TAC	Myocardial hypertrophy was inhibited by upregulation of NCX	[172]
SD rat	Nephrectomy, uremia	Myocardial hypertrophy is alleviated by inhibiting GSK-3β/catenin, calcineurin/NFAT and ERK1/2 pathways	[173]
Cardiac fibroblasts	TGF-β1	Myocardial fibrosis is inhibited by inhibition of Smad2/3, p38 MAPK and ERK signaling pathways	[174]
Cardiac fibroblasts	TGF-β1	The expression of α-SMA and collagen was decreased by inhibiting the Smad-2 and p38 MAPK signaling pathways	[175]
Cardiac fibroblasts	Ang II	By increasing the expression and activity of PPAR γ, the expression of CTGF, collagen III and FN was inhibited	[176]
Cardiac fibroblasts	Ang II	Fibrosis is inhibited by reducing TGF-β1 and MMPs/TIMPs	[177]
SD rat	Ang II	By decreasing AT1R expression and enhancing AT2 receptor expression	[178]
Cardiac fibroblasts	High glucose	Fibrosis is inhibited by inhibiting TGF-β1/Smad and AMPK/ p38 MAPK signaling pathways	[179]
SD rat	I/R	Alleviating myocardial fibrosis by inhibiting TGF-β1/Smad signaling pathway	[180]
C57BL/6J mice	MI	Inhibition of fibrosis by activation of Sirt1	[181]
Wistar-Bratislava white rats	ISO	Improved ventricular remodeling by reducing MMP-2 and MMP-9 levels	[182]
H9C2 cells	Norepinephrine	By inhibiting the expression and activity of MMP-9	[183]
SD rat	Monocrotaline	RV remodeling was inhibited by decreasing TNF-α levels and oxidative stress	[184]
New Zealand rabbits	Capacity and pressure overload	Ventricular remodeling was inhibited by inhibiting P38 and JNK pathways and increasing DKK-3 expression	[185]
EAM rats	No-intervention	By inhibiting iNOS, NADPH oxidase and endoplasmic reticulum stress	[186]
EAM rats	No-intervention	EAM was weakened by inducing macrophage M2 polarization	[187]
SD rat	Streptozotocin, High sugar, high fat diet	By modulating Sirt1/Foxo1 and PI3K/Akt pathways	[188]
Male Wistar rats	Streptozotocin, high energy intake	By regulating the Akt/GSK-3β signaling pathway, myocardial fibrosis, oxidative stress, inflammation, and apoptosis are alleviated	[189]
Male Wistar rats	Streptozotocin	Curcumin inhibits myocardial fibrosis in diabetic rats by activating Nrf2/HO-1 pathway and inhibiting JAK2/STAT3 pathway	[190]

(*Continued*)

Table 2 (Continued).

Research Subjects	Intervention Methods	Mechanism	Refs
Rats	Streptozotocin	Myocardial hypertrophy was alleviated by inhibiting P300 upregulation	[191]
SD rat	Streptozotocin	By activating PPAR γ and inhibiting CaMKII/NF-κB/TGF-β1 pathway	[192]
C57BL/KsJ db/db mice	Normal diet	Inflammation is reduced by inhibiting the HMGB1/NLRP3/NF-κB pathway	[193]
Diabetic mice	Streptozotocin, high fat diet	Myocardial autophagy in diabetic mice was regulated by AMPK/mTOR pathway	[194]
Rats	Dox	Dox-induced cardiotoxicity is mitigated by modulating the Rac1/TWEAK/Fn14/NF-κB complex network	[195]
Mice	Dox	The myocardial damage induced by dox was alleviated by up-regulating the expression of 14-3-3γ	[196]
Primary rat cardiomyocytes	D-galactose	Autophagy is promoted by increasing Sirt1 expression and phosphorylating AMPK	[197]
Wistar rat	4 to 6 months old	Modulates the TSP1/VEGF-A signaling pathway to promote angiogenesis	[198]
Rats	PM2.5	ERS is inhibited by activation of SERCA2a, thereby improving cardiac inflammation and cardiomyocyte apoptosis	[199]

Reduce Cardiomyocyte Apoptosis

Excessive catecholamines can cause some damage to myocardium. Izem-Meziane et al found that curcumin (60 mg/kg/day) reduced isoproterenol (ISO) -induced cardiomyocyte apoptosis in Wistar rats by preventing mitochondrial damage and mitochondrial permeability transition pore(mPTP) opening.[163] In another study, Boarescu et al found that curcumin (200 mg/kg/day) attenuates ISO-induced cardiomyocyte apoptosis in rats.[200] Heat shock proteins (Hsps) are a type of stress proteins that help maintain protein stability and mediate proper folding, segmentation, and degradation of unfolded proteins when cells are subjected to harmful stimuli. Tanwar et al found that curcumin pretreatment (100 and 200 mg/kg/day) increased the level of Hsp27 after ISO induced myocardial ischemic injury in rats, thereby protecting cardiomyocytes.[164] SP1 is a widely expressed transcription factor that is closely related to cell differentiation, growth and apoptosis.[201] Geng et al found that curcumin(50 mg/kg/day) can protect hypoxia-induced cardiomyocyte apoptosis by up-regulating miR-7a/b and down-regulating SP1 expression.[165] Coronary microembolism (CME) is closely related to cardiomyocyte apoptosis. In a study, curcumin (150 mg/kg/day) alleviated myocardial inflammation and inhibited myocardial apoptosis in rats after CME by inhibiting TLR4/MyD88/NF-κB signaling pathway.[166] Chronic intermittent hypoxia can lead to increased infarct size in patients with myocardial infarction, and HIF-1α seems to be a key player in this vicious cycle. Moulin et al found that chronic curcumin (100 mg/kg/day) treatment could inhibit HIF-1α activation induced by intermittent hypoxia, thereby reducing infarct size in mice.[167] (Figure 5 and Table 2)

Inhibit Cardiomyocyte Hypertrophy

Left ventricular hypertrophy is a physiologically adaptive response to increased hemodynamic pressure load that initially improves systolic function but ultimately leads to heart failure.[202] The histone acetyltransferase (HAT) activity of p300 is closely related to cardiac hypertrophy and heart failure. GATA binding protein 4(GATA4) is a hypertrophic response transcription factor that can be activated by p300-HAT.[203] Sunagawa et al found that curcumin (20 μM) could alleviate cardiomyocyte hypertrophy by inhibiting p300-HAT activity.[168] In another study, Sunagawa et al also found that curcumin (50 mg/kg/day) reduced cardiac hypertrophy induced by hypertension in Dahl salt-sensitive(DS) rats by reducing p300-HAT activity and GATA4 acetylation levels.[169] Two other studies reached similar conclusions. Chowdhury et al found that curcumin (0.1 mg/kg, intraperitoneal injection) attenuates LPS-induced cardiac hypertrophy in mice by inhibiting p300-HAT activity.[170] Ahuja et al found that curcumin (8 μM) inhibited cardiomyocyte hypertrophy induced by norepinephrine by inhibiting the nuclear localization and DNA-binding activity of GATA-4.[171] (Figure 5 and Table 2)

Enhanced expression of Na^+/Ca^{2+} exchanger(NCX) in cardiomyocytes can improve systolic function in heart failure rats by increasing cellular Ca^{2+} load.[204] Bai et al found that curcumin (50 mg/kg/day) inhibited myocardial hypertrophy

in male Wistar rats treated with transverse aortic constriction(TAC) by upregulating NCX expression.[172] Myocardial hypertrophy is common in uremic patients. Ghosh et al found that curcumin (150 mg/kg/day) attenuated myocardial hypertrophy and remodeling in nephrectomy rats by inhibiting GSK-3β/catenin, calcineurin/nuclear factor of activated T cells(NFAT) and ERK1/2 pathways.[173] Cardiomyocyte hypertrophy is also common in patients with diabetes.[205] Sudirman found that curcumin (150 mg/kg/day) significantly improved left ventricular cell hypertrophy in mice with type 1 diabetes.[206] (Figure 5 and Table 2)

Inhibit Myocardial Fibrosis

Myocardial fibrosis is characterized by increased extracellular matrix (ECM) in the myocardial interstitium.[207] Cardiac fibroblasts (CFs) are the main effector cells of myocardial fibrosis.[208] TGF-β1 is a potent pro-fibrotic cytokine that can induce CFs to transform into myofibroblasts.[209] Fang et al found that curcumin (20 μM) inhibited TGF-β1-induced CFs proliferation and collagen deposition by inhibiting mothers against decapentaplegic homolog(Smad)2/3, p38 MAPK and ERK signaling pathways.[174] In another study, Liu et al found that curcumin (5, 10 and 20 μM) significantly inhibited the expression of α-smooth muscle actin (α-SMA) and collagen in TGF-β1-induced CFs by inhibiting Smad-2 and p38 MAPK signaling pathways.[175] Zhao et al. Found that curcumin (20 μM) reduced the expression of pro-fibrotic protein in CFs co-cultured with LPS-stimulated macrophages. The mechanism is related to the down-regulation of proinflammatory cytokines in macrophages by curcumin.[210] (Figure 5 and Table 2)

In the setting of hypertension, CFs can up-regulate cardiac ECM deposition, resulting in ventricular remodeling. Meng et al found that curcumin (100 mg/kg/day) could reduce the heart weight/body weight ratio, Ang II concentration and cardiac fibrosis of SHRs. In vitro, curcumin (5, 10 and 20 μM) inhibited the expression of Ang II–induced connective tissue growth factor (CTGF), collagen III and fibronectin (FN) by increasing the expression and activity of PPAR γ, thus exerting an antifibrotic effect.[176] In another study, curcumin (10 and 20 μM) reduced Ang II–induced fibroblast proliferation by decreasing TGF-β1 and MMPs/tissue inhibitor of matrix metalloproteinases(TIMPs).[177] There are two types of Ang II receptors. Activation of AT1Rs can induce inflammation, vasoconstriction, interstitial collagen deposition, and tissue fibrosis, while activation of angiotensin type 2 receptor(AT2R) may protect the heart by counteracting the harmful effects of AT1R stimulation.[211] Pang et al found that curcumin (150 mg/kg/day) could reduce the expression of AT1R and enhance the expression of AT2R in rats, thus exerting the effect of myocardial fibrosis.[178] (Figure 5 and Table 2)

Myocardial fibrosis is the initial change in DCM.[212] Guo et al found that curcumin (300 mg/kg/day) significantly inhibited the deposition of type I and III collagen in the heart tissue of diabetic rats, decreased the production of TGF-β1 and the phosphorylation of Smad2/3, and increased the expression of Smad7. In vitro studies, curcumin (25 μM) inhibited collagen synthesis induced by high glucose in fibroblasts by inhibiting TGF-β1/Smad and AMPK/p38 MAPK signaling pathways.[179] In the early stage of myocardial infarction(MI), MMPs activated by local oxidative stress degrade ECM, and subsequently CFs proliferate and deposit collagen to form repairable fibrosis and noncontractile scars.[213] Although fibrosis is necessary for normal healing, excessive fibrosis can gradually impair ventricular function.[214] Wang et al found that curcumin (150 mg/kg/day) could reduce ECM degradation and inhibit collagen synthesis by inhibiting TGF-β1/Smad signaling pathway, thereby alleviating poor cardiac repair after myocardial I/R.[180] In another study, Xiao et al found that curcumin (100 mg/kg/day) could inhibit CFs fibrosis in MI rats by activating Sirt1.[181] (Figure 5 and Table 2)

Inhibition of Ventricular Remodeling

MMPs are proteolytic enzymes involved in ECM degradation after MI, causing ventricular remodeling.[215] Boarescu et al found that curcumin pretreatment (100,150 and 200 mg/kg/day) could reduce the levels of MMP-2 and MMP-9 in ISO-induced MI rats, thereby improving ventricular remodeling.[182] In another study, Kohli et al found that curcumin (8 μM) inhibited norepinephrine induced MMP-9 expression and activity in H9C2 cardiomyocytes, which may help prevent ECM remodeling.[183] (Figure 5 and Table 2)

Pulmonary arterial hypertension(PAH) is pathologically characterized by progressive obstruction of the pulmonary artery, resulting in hypertrophy of the right ventricle(RV). Rice et al found that curcumin nanoparticles (50 mg/kg/day) inhibited the development of RV remodeling in PAH rats by reducing TNF-α levels and oxidative stress.[184] Hypertension can also lead to ventricular remodeling. In one study, Hernandez et al found that curcumin (120 mg/kg/day) restored systolic blood pressure,

attenuated septal thickening, reduced end-systolic left ventricular size, and restored ejection fraction in nephrectomy rats.[216] Dickkopf related protein 3 (DKK-3) plays a crucial role in cell growth and proliferation.[217] In animal models, DKK-3 depletion can aggravate ventricular remodeling induced by pressure overload.[218] In one study, Cao et al found that curcumin (100 mg/kg/day) may inhibit ventricular remodeling in rabbits with chronic heart failure by inhibiting p38 and JNK pathways and increasing DKK-3 expression.[185] (Figure 5 and Table 2)

Treatment of Autoimmune Myocardial Injury and Diabetic Cardiomyopathy

Autoimmune myocarditis(AM) is a potentially fatal disease that usually develops prior to acute and chronic heart failure.[219] Mito et al found that curcumin (50 mg/kg/day) significantly inhibited the expressions of inducible nitric oxide synthase (iNOS), NADPH oxidase and ERS signaling proteins in rats with experimental AM(EAM), thereby improving cardiac function.[186] In another study, Mito et al also found that curcumin (50 mg/kg/day) could reduce heart weight, inflammatory area, and myocardial protein levels of NF-κB, IL-1β, TNF-α and GATA-4 in experimental AM rats.[220] M2 macrophages have the function of secreting anti-inflammatory cytokines. Gao et al found that curcumin (50 mg/kg/day) could induce M2 polarization of macrophages, thereby attenuating EAM.[187]

DCM can increase the risk of heart failure in diabetic patients, mainly caused by cardiomyocyte apoptosis.[221,222] Ren et al found that curcumin (100 mg/kg/day) could reduce cardiomyocyte apoptosis in diabetic rats by regulating Sirt1/forkhead box protein O1(FOXO1) and PI3K/Akt pathways.[188] Yu et al found that curcumin (100 and 200 mg/kg/day) attenuates myocardial fibrosis, oxidative stress, inflammation and apoptosis in rats with DCM, possibly by regulating Akt/GSK-3β signaling pathway.[189] Abdelsamia et al found that metformin (200 mg/kg/day) combined with curcumin (100 mg/kg/day) could inhibit myocardial fibrosis in diabetic rats by activating Nrf2/HO-1 pathway and inhibiting JAK2/STAT3 pathway.[190] Aziz et al found that curcumin (20 mg/kg/day) alleviated cardiomyocyte hypertrophy by inhibiting P300 upregulation, thereby improving left ventricular function in diabetic rats.[191] PPAR γ plays an important role in regulating lipid and glucose metabolism.[223] Calmodulin-dependent protein kinase II (CaMKII) is a multifunctional serine/threonine kinase that is closely related to the pathogenesis of DCM. Gbr et al found that curcumin (100 mg/kg/day) could reduce oxidative stress, inflammation and fibrosis in the heart of diabetic rats by activating PPAR γ and inhibiting CaMKII/NF-κB/TGF-β1 pathway.[192] HMGB1 is a highly conserved nuclear protein associated with inflammatory diseases. Yan et al found that curcumin (50 and 100 mg/kg/day) alleviated inflammatory damage in DCM by inhibiting HMGB1/NLRP3/NF-κB pathway.[193] Beclin 1 is an important autophagy protein.[224] Yao et al found that curcumin (200 mg/kg/day) disrupted the interaction between apoptotic proteins and Beclin1 by activating AMPK and JNK1, thereby promoting autophagy and reducing cardiomyocyte apoptosis. In addition, curcumin can improve DCM by regulating cardiomyocyte autophagy through AMPK/mTOR pathway in diabetic mice.[194]

Treatment of Drug-Induced Myocardial Injury

Clinically, some drugs can induce cardiotoxicity.[225] Doxorubicin (DOX), a cancer treatment drug, under the action of NADPH oxidase, can be converted into semi-quinone to produce active hydroxyl radicals, causing damage to cells.[226] Soliman et al found that curcumin (200 mg/kg/day) could alleviate doxorubicin induced cardiotoxicity in rats by regulating ras related C3 botulinum toxin substrate 1(Rac 1)/tumor necrosis factor-like weak inducer of apoptosis-(TWEAK)/fibroblast growth factor-inducible protein 14(Fn14)/NF-κB intricate network.[195] In another study, Swamy et al found that curcumin (200 mg/kg/day) could increase the decreased levels of GSH, SOD and catalase (CAT), and thus significantly protect rat myocardes from the toxic effects of DOX.[227] 14-3-3γ, a member of the 14-3-3 protein family, can interact with Bad to block mPTP opening and reduce drug-induced cardiomyocyte apoptosis. He et al found that curcumin (50 mg/kg/day) protected myocardium from DOX-induced injury by upregulating 14-3-3γ expression.[196]

Cisplatin is one of the commonly used chemotherapy drugs in the treatment of cancer.[228] In one study, Bahadhir et al found that cisplatin (a single dose injected twice, once a week, 5 mg/kg/week) could significantly increase the levels of malondialdehyde(MDA), TNF-α, IL-1β and IL-6 and significantly decrease the activities of CAT and SOD in rat myocardium. Pretreatment with curcumin (200 mg/kg) for 30 min before cisplatin injection could significantly improve the above changes.[229] In another study, Khadrawy et al found that cisplatin significantly reduced GSH levels and Na^+, K^+-ATPase activity in rat hearts, while treatment with curcumin (50 mg/kg/day) nanoparticles ameliorated these changes.[230] Cyclophosphamide (CP) has a strong immunosuppressive effect on autoimmune diseases, but it also has a wide range of

side effects, including cardiotoxicity.[231] Avci et al found that CP(30 mg/kg/day) significantly increased the MDA content and DNA fragmentation level, decreased the SOD level, and impaired the histopathological status of heart tissue in Wistar rats. However, curcumin (100 mg/kg/day) significantly improved the above changes.[232] Irinotecan(CPT-11) and bevacizumab-(BEV) are also important anticancer drugs with some cardiotoxicity. In one study, Ciftci et al found that curcumin (100 mg/kg/day) reversed CPT-11-induced oxidative stress and myocardial tissue damage.[233] Sabet et al demonstrated that curcumin (10, 50 and 100 μM) prevented BEV-induced mitochondrial damage and elevated oxidative stress in cardiomyocytes.[234] Abemacilib (ABE) is a cyclin-dependent kinase inhibitor commonly used to treat cancer. Huyut et al found that curcumin (30 mg/kg/day) combined with ABE inhibited the elevation of creatine kinase-MB(CK-MB) and cardiac troponin I(cTnI) in rats, and also inhibited cardiac fibrosis.[235]

Other Protective Effects of Curcumin on Myocardium

Aging is a multi-factor physiological process. One of the common features of cellular aging is the accumulation of damaged proteins within the cell. Autophagy can digest its own low-efficiency components through a lysosomal mediated catabolic process, and studies have shown that autophagy can delay aging. Another important mechanism regulating the cellular aging process is protein acetylation. Sirt 1, also known as NAD-dependent deacetylase, mediates life extension in organisms. Aziz et al found that autophagy, Sirt 1 levels were significantly reduced in the hearts of older rats compared to younger rats, and curcumin(50 mg/kg/day) ameliorated these undesirable changes.[236] In another study, Yang et al found that curcumin (1,5 and 10 μM) increased the expression of Sirt 1 and phosphorylated AMPK in a dose-dependent manner, and decreased phosphorylated mTOR, thereby promoting autophagy to achieve anti-cardiac aging effects.[197]

With age, the formation of blood vessels in the heart is gradually impaired, and endothelial dysfunction increases significantly. Studies have shown that VEGF can induce angiogenesis. Some angiointegrins such as thrombospondin (TSP) inhibit angiogenesis by inhibiting VEGF receptor(VEGFR) activity or increasing its degradation.[237] Ghorbanzadeh et al found that curcumin (50 mg/kg/day) promoted the formation of cardiac blood vessels in rats, and its mechanism was related to the regulation of TSP 1/VEGF-A signaling pathway.[198] PM2.5 activates ERS, which can increase the risk of heart problems. El Tabaa et al found that nano-emulsion curcumin(NEC) inhibits ERS by activating sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a(SERCA2a), thereby improving PM2.5-associated cardiac inflammation and cardiomyocyte apoptosis.[199]

Pharmacokinetics and Toxicology of Curcumin

The solubility and stability of curcumin are related to the type and pH of the solvent. Curcumin is very insoluble in water, but soluble in organic solvents. Under acidic to neutral conditions, curcumin is relatively stable, while under alkaline conditions, curcumin is very unstable and easy to be decomposed. Studies have shown that curcumin is poorly absorbed in the gastrointestinal tract after oral administration, and only a small amount enters the peripheral blood circulation through the portal vein. Wahktrom et al administered 1000 mg/kg of curcumin orally to SD rats and then tested for curcumin in urine and feces, resulting in about 75% curcumin detected in feces and only trace curcumin detected in urine.[238] Ravindranath et al administered 400, 80 and 10 mg of radio-labeled curcumin orally to Wistar rats, respectively. When curcumin is administered at a dose of 10 or 80 mg, more than 90% of the drug is excreted from the stool and only 3% is detected in the blood. When curcumin was administered at 400mg, 60% of the drug was excreted in the stool and only 13% was detected in the blood[239]. In one clinical trial, 19 subjects took curcumin orally (4g/day for 30 days). The results showed that trace curcumin could be detected in the serum of only 2 subjects, and the average blood concentration was only (3.8±1.3) $ng.mL^{-1}$ [240], which was related to the hepatoenteric first pass effect after curcumin was taken orally. Compared with oral administration, the plasma curcumin concentration was significantly increased by injection. Pan et al injected mice with curcumin (100 mg/kg) peritoneally, and found that high levels of curcumin (6.1 μM) appeared in plasma 15 minutes later. In addition, curcumin concentrations in intestine, spleen, liver and kidney were 480.59, 70.74, 73.02 and 20.39 μM, respectively, 1 hour after administration.[241] With the development and application of nanotechnology, some preparations such as liposomes, microemulsion, hydrophilic prodrugs, solid nanoparticles, polymer micelles and nanogels can improve the water solubility and bioavailability of curcumin.

The metabolic pathways of curcumin compounds in vivo include Phase I reduction metabolism, Phase II binding metabolism, autooxidation and intracellular catalytic oxidation metabolism.[242] The main products of curcumin I phase

reduction metabolism are tetrahydrocurcumin, hexahydrocurcumin and a small amount of ferulic acid, which is a step by step hydrogenation process. In phase I reductive metabolism, ethanol dehydrogenase in the liver and small intestine cytoplasm is involved in the reaction.[243] Because the phase I metabolites have the structure of phenol hydroxyl group and alcohol hydroxyl group, the combination reaction of gluconaldehyde and sulfation occurs in phase II metabolism. Most of the final metabolites of curcumin exist in the form of glucosylation, and the sulfation products are relatively few. Glucosylation of curcumin occurs in intestinal and hepatic microparticles, while sulfation occurs in intestinal and hepatic solutes.[244]

Long-term studies have shown that curcumin is safe and protective when used in the diet.In one study, high doses of curcumin (8 g/day) do not cause side effects. In another study, curcumin was administered at doses up to 12 g/day for three months with no apparent toxicity.[245] However, some studies have found that high concentrations of curcumin have some side effects. Tanwar et al found that curcumin had antioxidant effects at lower concentrations (100 or 200 mg/kg/day), but curcumin had side effects of promoting lipid peroxidation at higher concentrations (400 mg/kg/day) in a rat model of myocardial necrosis induced by ISO.[246] In another study, Sun et al found that curcumin (75 mg/kg/day) can induce histone hypoacetylation and inhibit the expression of transcription factors such as GATA4 early in heart development, ultimately leading to defects in heart development, such as thinning of the ventricular wall and septum. In general, curcumin may be detrimental to embryonic heart development during early pregnancy.[247] Clinically, the common side effects of curcumin are flatulence,[248] changes in liver enzymes and blood biochemical parameters.[249] The metabolism and lipid-lowering effects of curcumin are mainly carried out in the liver, which may be the main reason for the increase of liver enzymes.[243]

Discussion

The therapeutic effect and mechanism of curcumin have become the focus of pharmacokinetic research. Curcumin has a good therapeutic effect, especially in the cardiovascular field. It can significantly protect cardiomyocyte injury after ischemia and hypoxia, inhibit myocardial hypertrophy and fibrosis, improve ventricular remodeling, reduce drug-induced myocardial injury, improve DCM, alleviate vascular endothelial dysfunction, inhibit foam cell formation, and reduce VSMCs proliferation. The targets and signaling pathways of CVDs are complex. The pharmacology and mechanism of action of curcumin have not been studied very deeply. It's worth noting that not all studies come to the same conclusion. Min et al found that curcumin (10 μM) can reduce the accumulation of cholesterol in macrophages by inhibiting the expression of CD36 on the surface of macrophages.[41] However, Chen et al found that curcumin (6.25 and 12.5 μM) enhances ox-LDL-induced cholesterol esterification and foam cell formation by upregulating CD36 expression in M1 macrophages.[120] The two studies reached inconsistent conclusions, which may be related to the dose of curcumin.

Previous reviews have summarized the protective effects of curcumin on CVDs. In 2020, Li et al[4] reviewed the preclinical studies of curcumin in CVDs such as cardiac hypertrophy, heart failure, abdominal aortic aneurysm, stroke, drug-induced cardiotoxicity, and diabetic cardiovascular complications, and reviewed the potential molecular targets of curcumin. Pourbagher-Shahri et al[250] also reviewed the effects of curcumin on the cardiovascular system in 2021. They classified curcumin according to the possible cellular targets of action, which is different from the classification of curcumin in our review. Neither of the above two teams had a complete summary of the cardiovascular protective pathway of curcumin, and the dosage of curcumin was not indicated in the article. Our review classifies the effects of curcumin on different cells in the cardiovascular system, and we provide a complete review of the signaling pathways. It is well known that different doses of the drug are not equally effective, so curcumin dosages are also noted in our review.

The protective mechanism of curcumin against CVDs is complex and networked. In the past, researchers have not studied the pharmacological mechanism of curcumin deeply. The signaling pathways mentioned in this review may only be part of the downstream signaling pathways following curcumin action on specific molecular targets. Therefore, we propose to investigate specific molecular targets of curcumin using a systems biology approach. For example, Ma et al[251] used a photosensitive probe to label metformin and eventually identified PEN2 as a direct target of metformin. Finally, the effect of curcumin in CVDs is mostly studied in animal models and cell models, and there are few clinical trial data. Therefore, we suggest that large-scale clinical trials should be conducted to evaluate the efficacy of curcumin in protecting against CVDs.

In conclusion, curcumin has a good protective effect on CVDs. It is important to note that curcumin is a complementary or alternative medicine, not a replacement for the main treatment, and needs to be used under the guidance of a doctor. To be sure, curcumin is an important drug that is worth exploring.

Abbreviations

CVDs, Cardiovascular diseases; DCM, Diabetic cardiomyopathy; VSMCs, Vascular smooth muscle cells; VECs, vascular endothelial cells; ROS, Reactive oxygen species; Nrf2, Nuclear factor erythroid factor 2 related factor 2; Keap1, Kelch-like ECH-associated protein 1; ARE, antioxidant response element; HO-1, Heme oxygenase-1; H_2O_2, Hydrogen peroxide; HUVECs, Human umbilical vein endothelial cells; AS, atherosclerosis; SHRs, Spontaneously hypertensive rats; UCP2, uncoupling protein-2; NO, nitric oxide; 2K-1C, 2kidney-1clip; MMPs, matrix metalloproteinases; NADPH, nicotinamide adenine dinucleotide phosphate; PKC, protein kinase C; CD40, cluster of differentiation 40; CD40L, cluster of differentiation 40 ligand; TLR, Toll-like receptor; NF-κB, Nuclear factor kappa-B; HFD, high-fat diet; VCAM-1, Vascular cell adhesion molecule-1; ICAM-1, Intercellular cell adhesion molecule-1; TNF-α, Tumor necrosis factor α; HMGB1, High mobility group box protein 1; HECs, human endothelial cells; LPS, Lipopolysaccharide; HCMV, human cytomegalovirus; ox-LDL, moxidized low-density lipoprotein; MyD88, Myeloid differentiation factor 88; LCN2, Lipocalin-2; p38 MAPK, p38 mitogen-activated protein kinase; HAECs, Human arterial endothelial cells; TAECs, Thoracic aortic endothelial cells; PI3K, phosphatidyinositol 3-kinase; Akt, protein kinase B; AGEs, Advanced glycation end products; MGO, Methylglyoxal; HDL, high-density lipoprotein; ERS, endoplasmic reticulum stress; IL-8, interleukin-8; COX-2, Cyclooxygenase; CREB, cyclic adenosine monophosphate(cAMP)-response element binding protein; PLLA, poly-L-lactic acid; MCP-1, Monocyte chemoattractant protein 1; RAECs, Rat aortic endothelial cells; LOX-1, lectin-like ox-LDL receptor-1; TC, total cholesterol; TG, Total triglycerides; LDL-C, low-density lipoprotein cholesterol; Apo B, Apolipoprotein B; GSH, glutathione; GSH-Px, glutathione peroxidase; SR-A, Scavenger receptor class A; CD36, differentiation 36; SR-BI, Class B scavenging receptor type I; ABCA1, ATP-binding cassette transporters A1; ABCG1, ATP-binding cassette transporters G1; Sirt 6, Silent information regulator 6; LXRs, Liver X receptors; JNK, c-Jun N-terminal kinase; AMPK, AMP-activated protein kinase; FAT, fatty acid translocase; FABP4, Fatty acid binding protein 4; HIF-1α, Hypoxia inducible factor-1α; ERK, extracellular regulated protein kinase; PPAR γ, Proliferator-activated receptor γ; TMAO, trimethylamine-N-oxide; EMMPRIN, Extracellular matrix metalloproteinase inducer; PMA, Phorpol 12 myristic acid 13 acetate; THBS, Thrombospondins; DM, Diabetes mellitus; EPCs, Endothelial progenitor cells; EPCD, Endothelial progenitor cell dysfunction; MnSOD, Manganese superoxide dismutase; VEGF, Vascular endothelial cell growth factor; Ang-1, Angiotensin 1; PAD, Peripheral arterial disease; FAK, focal adhesion kinase; CsA, Cyclosporine A; eNOS, endothelial nitric oxide synthase; HMEC, Human microvascular endothelial cells; IRS-1, insulin receptor substrate 1; mTOR, mammalian target of rapamycin; BECN1, beclin1; TFEB, transcription factor EB; BRD4, bromodomain-containing protein 4; NLRP3, NOD- LRR- and pyrin domain-containing protein 3; EndMT, Endothelial-to-mesenchymal transition; TGF-β1, Transforming growth factor-β1; Nrf-2, nuclear factor erythroid-2-related factor 2; DDAH, dimethylarginine dimethylaminohydrolase; ADMA, asymmetric dimethylarginine; TRPV4, Transient receptor potential vanilloid 4; Ang II, Angiotensin II; SP1, specific protein 1; CMKLR1, chemokine-like receptor 1; IGF-1, Insulin-like growth factor 1; PKB, protein kinase B; GSK-3β, glycogen synthase kinase-3β; Egr-1, early growth response protein 1; Ras, rat sarcoma; MEK1/2, mitogen-activated protein kinase kinase 1/2; CRP, C-reactive protein; RAAS, renin aniotension aldosterone system; AT1R, angiotensin type 1 receptor; ET-1, Endothelin-1; IGF-1R, IGF-1 receptor; PTEN, phosphatase and tensin homolog; FMD, Flow-mediated dilation; I/R, Ischemia and reperfusion; JAK, Janus kinase; STAT, Signal transducer and activator of transcription; SD, Sprague Dawley; H/R, Hypoxia/reoxygenation; ISO, Isoproterenol; mPTP, mitochondrial permeability transition pore; Hsps, Heat shock proteins; CME, Coronary microembolism; HAT, Histone acetyltransferase; GATA4, GATA binding protein 4; DS, Dahl salt-sensitive; NCX, Na^+/Ca^{2+} exchanger; TAC, Transverse aortic constriction; NFAT, nuclear factor of activated T cells; ECM, Extracellular matrix; CFs, Cardiac fibroblasts; Smad, mothers against decapentaplegic homolog; α-SMA, α-smooth muscle actin; CTGF, connective tissue growth factor; FN, fibronectin; TIMPs, tissue inhibitor of matrix metalloproteinases; AT2R, type 2 receptor; MI, myocardial infarction; PAH, Pulmonary arterial hypertension; RV, Right ventricular; DKK-3, Dickkopf related protein 3; AM, Autoimmune myocarditis; iNOS, inducible nitric oxide synthase; FOXO1, forkhead box protein O1; EAM, Experimental AM; CaMKII, Calmodulin-dependent protein kinase II; DOX,

Doxorubicin; Rac 1, ras related C3 botulinum toxin substrate 1; TWEAK, tumor necrosis factor-like weak inducer of apoptosis; Fn14, fibroblast growth factor-inducible protein 14; CAT, Catalase; MDA, Malondialdehyde; CP, Cyclophosphamide; CPT-11, Irinotecan; BEV, Bevacizumab; ABE, Abemacilib; CK-MB, creatine kinase-MB; cTnI, cardiac troponin I; TSP, thrombospondin; VEGFR, VEGF receptor; NEC, nano-emulsion curcumin; SERCA2a, sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a.

Credit Authorship Contribution Statement

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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