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Review article

Mechanics insights of curcumin in myocardial ischemia: Where are we standing?

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ABSTRACT

Cardiovascular disorders are known as one of the main health problems which are associated with mortality worldwide. Myocardial ischemia (MI) is improper blood supply to myocardium which leads from serious complications to life-threatening problems like AMI, atherosclerosis, hypertension, cardiac-hypertrophy as well as diabetic associated complications as diabetic atherosclerosis/cardiomyopathy/hypertension. Despite several efforts, the current therapeutic platforms are not related with significant results. Hence, it seems, developing novel therapies are required. In this regard, increasing evidences indicated, curcumin (CRC) acts as cardioprotective agent. Given that CRC and its analogs exert their cardioprotective effects *via* affecting on a variety of cardiovascular diseases-related mechanisms (i.e., Inflammation, and oxidative stress). Herein, for first time, we have highlighted the protective impacts of CRC against MI. This review might be a steppingstone for further investigation into the clinical implications of the CRC against MI. Furthermore, it pulls in light of a legitimate concern for scientific community, seeking novel techniques and characteristic dynamic biopharmaceuticals for use against myocardial ischemia.

Contents

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1. Introduction

Cardiovascular diseases are one of the main diseases which are related to the mortality globally [1]. Cardiovascular diseases (CVDs) are a class of diseases including heart or blood vessel-related disorders. Coronary artery sicknesses incorporate angina, MI, stroke, heart disappointment, hypertensive coronary illness, cardiomyopathy, and arrhythmias. CVDs are the main cause of the death in the world. Hazard factors incorporate hypertension, smoking, heftiness, terrible eating routine, blood cholesterol, and absence of activity [2]. It is approximated that 90% of CVDs is preventable. Hypertension results in 13% of CVD passing, though tobacco results in 9%, diabetes and absence of exercise in around 6%, and heftiness in 5% [3]. Because of specific meds, for example, anticancer medications like doxorubicin, unfriendly impacts lead to MI. Since old occasions, therapeutic plants have been generally utilized in the treatment of maladies. This data may fill in as a groundwork in recognizing novel prophylactic just as restorative investigations of plant-determined standards.

Natural compounds are getting to be prominent globally and broadly acknowledged as safe and effective therapeutics with fewer adverse effects [4–10]. Natural compounds assume a significant job as wholesome enhancements and provide protection against cardiovascular diseases [11,12]. Curcumin (CRC) is a polyphenolic from turmeric (*Curcuma longa*) roots. It is chemically 1,7 - bis - (4 - hydroxy - 3 - methoxy phenyl) - hepta - 1,6 - diene - 3,5 - dione with formula $C_{21}H_{20}O_6$; and the pKa esteem is 8.54. CRC is for all intents and purposes insoluble in water at an acidic and nonpartisan pH however is dissolvable in methanol, ethanol, dimethylsulfoxide, and acetone [13]. CRC, a functioning polyphenol of the brilliant zest turmeric, is an exceptionally pleiotropic molecule with the possibility to adjust the natural movement of various signaling molecules [14]. CRC is used against different cancers (e.g., breast, colorectal, head and neck, lung, pancreatic and different myeloma), neurologic disorders (e.g., Alzheimer's, and Parkinson's diseases) ; skin problems (i.e., psoriasis, vitiligo), inflammatory diseases: (*i.e., H. Pylori* infection, peptic ulcers, osteoarthritis, rheumatoid joint pain, ulcerative colitis, uveitis), metabolic scatters such as diabetes, obesity and hepatoprotection [15–17]. Ongoing investigations have shown that CRC can target recently recognized signaling pathways incorporating those related with microRNA, cancer stem cell and autophagy [18,19]. Broad research from preclinical and clinical examinations has portrayed the molecular reason for the pharmaceutical employments of this polyphenol against malignancy, pneumonic sicknesses, neurological maladies, liver diseases, metabolic diseases, immune system diseases, cardiovascular disorders, and various other perpetual diseases [20,21]. Different investigations have shown the wellbeing and adequacy of CRC in various animal models and have given a strong premise to assessing its security and viability in people. Until this point, in excess of 65 human clinical preliminaries of CRC, which included in excess of 1000 patients, have been finished, and upwards of 35 clinical preliminaries are in progress [22,23]. This review is therefore, focused on the mechanistic insight of CRC in the treatment of MI.

1.1. Overview of CRC in cardiovascular disorders

CRC have been shown to possess cardioprotective effects. It is not only helpful in decreasing the risk of cardiovascular disease (CHD) by reduction in cholesterol absorption to decrease delivery of cholesterol to the liver improving plasma lipid profiles and reducing inflammation [24]. It can normalize blood lipid profiles and boosting arterial structure and function. CRC is reported to protect from aortic aneurysm, Doxorubcin induced cardiotoxicity, myocarditis, heart attacks, thrombosis, cardiac fibrosis; lowers blood cholesterol and pressure; as well as reduces and cardiovascular complications of diabetics such as diabetic cardiomyopathy, MI and stroke [25].

MI leads to AMI, atherosclerosis, hypertension, cardiac hypertrophy as well as diabetic associated complications as diabetic atherosclerosis/cardiomyopathy/hypertension. Behind these effects' apoptosis, oxidative stress and inflammation are involved. Furthermore, Structural integrity after ischemic injury also disturbed which leads to arrhythmic effects and hypertension [25,26].

2. Underlying mechanisms of CRC in myocardial ischemia

2.1. Oxidative stress

2.1.1. Acute myocardial infarction

CRC is a promising contender for counteractive action of IRI and the related free radical started maladies due to its prevalent antioxidant effects. Reactive oxidative species (ROS) directly injured the cell membrane in the ischemic myocardium, causing cell death and contractile failure resulting in acute MI. Dysfunctional mitochondrial Ca^{2+} channels and activation of ERK and JNK signaling pathways due to ROS formation causes cell death during IRI. This activation participates in further ROS production and Ca^{2+} dyshomeostasis [27]. CRC suppresses ROS hence ameliorates myocardial

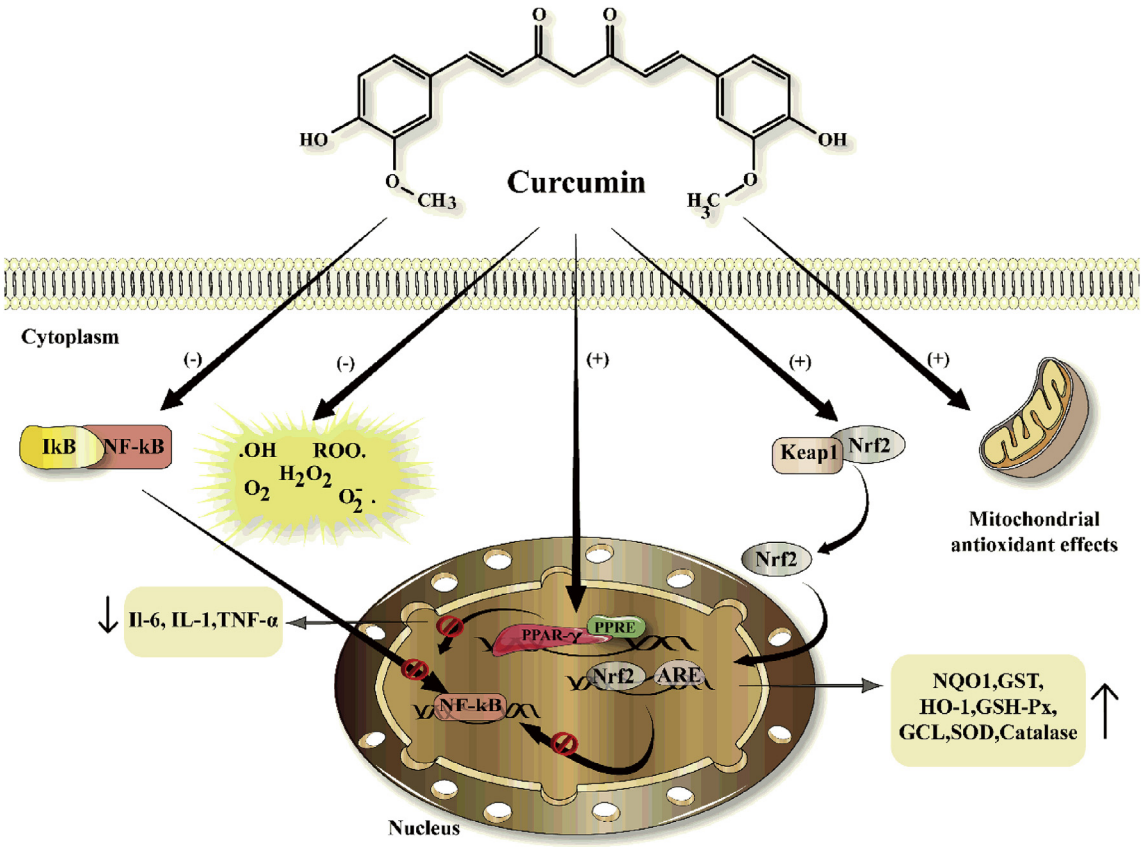

Fig. 1. A scheme of CRC effects on oxidative stress-related mechanisms in the CVDs. The CRC mediated anti-inflammatory and antioxidant effects involving Nrf2, NF-κB, PPAR-γ and mitochondria. CRC caused overexpression of Superoxide dismutase (SOD), catalases (CAT), endothelial nitric oxide synthase (eNOS), Glutathione (GSH), Liver X receptor α (LXRα), Peroxisome proliferator-activated receptor gamma (PPARγ), ATP-binding cassette transporter A1 (ABCA1), and carveolin-1 for cardiac-protective effects. Similarly, it produced downregulation of reactive oxidative species (ROS), Angiotensin II type 1 receptor (AT1R), Lipoxygenase (LOX), Thiobarbituric acid reactive substances (TBARS), Lactatedehydrogenase (LDH), Malondialdehyde (MDA), Mitochondrial hydrogen peroxide, Oxidized low-density lipoprotein (OxLDL), Niemann-Pick Cl-like 1 (NPC1L1), Angiotensin II (Ang II) mediated reactive oxidative species, Nicotinamide adenine dinucleotide phosphate (NADPH) for various cardiac-protective effects.

IRI by increment of SOD, GSH and CAT, decrease TBAR, mitochondrial H_2O_2 and the leakage of LDH and MDA (Fig. 1) [28–30].

2.2. Atherosclerosis

2.2.1. Expanded ROS development and resulting oxidative alterations in lipids and vessels and causes atherogenesis [31].

During myocardial IRI, ROS production mediated mitochondrial dysfunction and hence play an important role in atherogenesis by oxidizing LDL and plaque rupture by matrix metalloproteinases activation [27]. CRC is valuable in bringing down LDL and raising HDL while lessening lipid peroxidation by ROS scavenging [32]. CRC included before anoxia or promptly preceding reoxygenation showed surprising defensive impacts against anoxia-reoxygenation by hindering lipoperoxidation [33]. Another investigation has demonstrated that CRC essentially brings down LDL and expands HDL in healthy patients [34]. CRC has appeared hostile to atherogenic impact on apo E/LDLR-twofold knockout mice by shielding LDL from oxidation and restrain platelet accumulation [35]. Decrease in the atherosclerotic injuries and diminished oxidized-LDL-incited cholesterol was observed after CRC [36]. CRC (10 mg) directed twice day by day for 15 days essentially brings down plasma fibrinogen in atherosclerosis [37]. In high-fat eating regimen hamsters, CRC essentially brought down the dimensions of free unsaturated fat, cholesterol, triglyceride, and leptin; just as diminished hepatic cholesterol and TG. CRC additionally improved PON action and brought down lipid peroxidation [38]. CRC fundamentally diminishes dimensions of AST, ALT, LDL, CRP, ICAM-1 and VCAM-1, yet essentially increment dimensions of NO and HDL-C in HSF diet given to rodent [39]. The antioxidant role of CRC also knows an important role for upgrading the cholesterol efflux and diminishes cholesterol absorption. CRC upgraded cholesterol efflux by expanding ABCA1, PPARγ, LXRα articulation [40]. CRC, display an enemy of atherosclerotic impact, which is intently connected with an expansion in cholesterol efflux fundamentally by expanding HO-1 articulation and initiation of the Nrf2 ARE signaling pathway [41]. CRC diminishes cholesterol absorption in the small digestive tract, brings down cholesterol and hinders early atherosclerosis [42]. CRC, likewise can hinder cholesterol take-up by restraining NPC1L1 outflow [43]. CRC represses ox - LDL–incited cholesterols' addition in VSMCs through expanding caveolin - 1 articulation by means of the restraint of SREBP -1 [36]. Fig. 2 illustrates the pathogenesis of atherosclerosis.

2.2.3. Hypertension

Hypertension is significant risk factor for IHD which instigates endothelial dysfunction, fuels the atherosclerotic procedure and it adds to make the atherosclerotic plaque increasingly insecure. LVH, which is the standard complexity of hypertension, advances an abatement of 'coronary hold' and increments myocardial oxygen request, both mechanisms adding to myocardial ischemia [44]. The antioxidant effect by CRC promoting NO release for vasorelaxation [45]. Ang II significantly raised in the setting of hypertension and myocardial dead tissue. Ang II transmitted its action by AT_1R

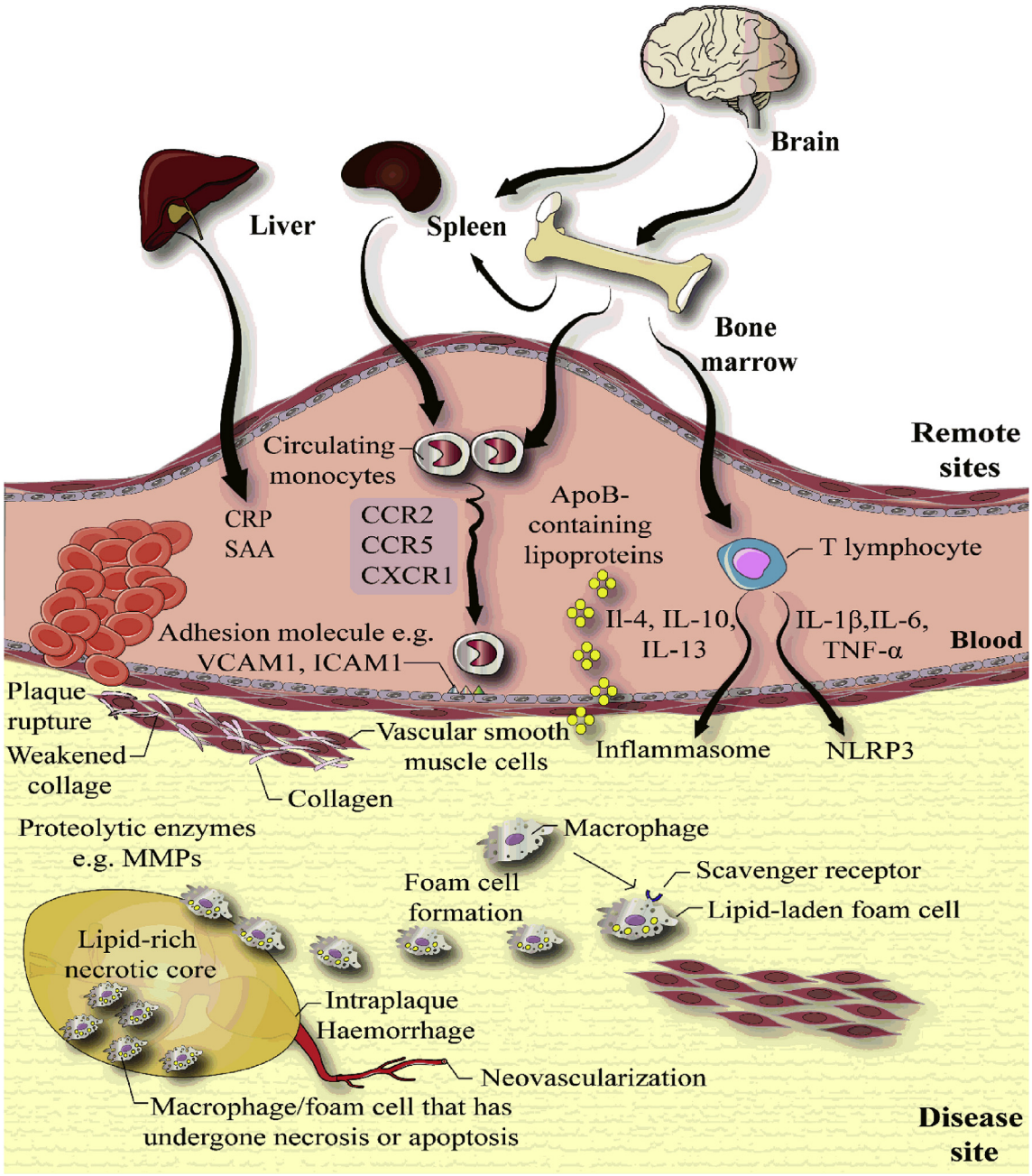

Fig. 2. A scheme of acute myocardial injury pathogenesis. A variety processes are activated with release of cytokines and ROS with infiltration of circulating neutrophils and monocytes leading to AMI. Simultaneously several remote sites are also activated (e.g. spleen, bone marrow) though signaling pathways that lead to the activation of the immune system and injury. Subsequently, a reparative phase ensues predominantly mediated by monocytes and T-lymphocytes leading to tissue repair and recovery with over expression of processes involved in extracellular matrix deposition and angiogenesis. Abbreviations: AMI: acute myocardial injury; ROS: reactive oxygen species; TLR: toll-like receptors; DAMPS: damage associated molecular patterns; HSP: heat shock proteins; HMGB1: high mobility group box 1 protein; VCAM: vascular cell adhesion molecule; NLR: NOD-like receptor; NLRP3: NOD-like receptor family pyrin domain containing 3; IL: interleukin; TNF: tumour necrosis factor; IFN: interferon; CX3CR1: CX3 chemokine receptor 1; miRNA: micro ribonucleic acid; CRP: C reactive protein; SAA: serum amyloid A.

resulting vasoconstriction, and cardiac contractility [46]. CRC decreasing AT1R-interceded vasoconstriction and thusly averts the advancement of hypertension [47]. Ang II provides ROS in atherosclerosis which further results in vasoconstriction and increased blood pressure. CRC weakens heart fibrosis in SHR and represses Ang II-initiated CTGF, ECM and PAI - 1 generation in CF [48]. CRC constricts the improvement of hypertension in L-NAME-incited hypertensive rats. CRC treatment smothers circulatory strain rise, diminishes vascular opposition with an expansion in eNOS and GSH and decline of peroxidation [49].

2.2.4. Cardiac hypertrophy

CRC restrains the activity of the AT1R and LOX-1, to suppress hypertrophic markers and cardiomyocyte growth. CRC attenuates Ang II-instigated ROS, upregulation of AT1R and LOX-1 expression as well as expression of NADPH oxidase which inhibit

cardiomyocyte growth [50,51].

2.2.5. Diabetic atherosclerosis

CRC by diminishing the TG, expanded dimensions of adiponectin in diabetes patients can lessen the danger of atherosclerosis [52]. CRC analog L3 mitigates diabetic atherosclerosis by lessen oxidative pressure, as a result causing NO increment, decline ROS generation and LOX-1 articulation, and amend fatty atherosclerotic degeneration [53]. In STZ-nicotinamide-actuated diabetic rodents, THC, one of the dynamic metabolites of CRC decreased blood glucose and critical increment of plasma insulin as well as decreased TC, TG and LDL in diabetic rodents [54].

2.2.6. Diabetic cardiomyopathy

Introduction of high glucose in vascular endothelial cells builds iNOS and eNOS dimensions, CRC may hinder iNOS and eNOS effect to lessen NO, in this manner applying its anti-oxidation against diabetic cardiomyopathy in rats [55]. Furthermore, CRC notably diminishes the action of NADPH oxidase and the ROS generation in LV, in STZ-instigated diabetic rodents to reduce cardiac hypertrophy [56,57]. CRC supplementation is shown to significantly attenuate ABP in STZ - induced diabetes in rats [58].

2.3. Apoptosis

2.3.1. Acute myocardial infraction

Myocardial IRI results in myocardial dysfunction is followed by myocyte apoptosis by activation of Caspase-3, Bcl - xL and Bcl - 2 expansion and suppress Bax, Bak, Bad and Bid), cytokines and ROS generation, cell to cell interaction between inflammatory and endothelial cells, mitochondrial Cyt *c* discharge and causes AMI (Fig. 2) [59]. CRC can diminish infarct size and protect cardiomyocytes against apoptosis-related cardiac diseases by activating PI3K, Akt, ERK1/2 and Bcl-2 expression; suppressing JNK, p38 MAPK, Bax and caspase-3 which is mediated by the JAK-2 and JAK2/STAT3 signaling pathway (Fig. 3) [60–62].

2.3.2. Atherosclerosis

CRC lessens apoptosis, VSMC calcification, probably by targeting a sequence of cellular and molecular pathways including JNK/Bax pathway [63]. CRC additionally diminishes cholesterol-actuated multiplication of aortic rat VSMC by means of reestablishing caveolin-1 articulation which prompts the concealment of ERK signals and G1/S stage capture [64].

2.3.3. Cardiac hypertrophy

Cardiomyocyte apoptosis goes about cardiovascular hypertrophy which prompt heart failure. Directed nanotization indicated higher heart bioavailability of CRC at a low portion of 5 mg/kg bw contrasted with free CRC at 35 mg/kg bw. Also, CRC with peptide treatment amid hypertrophy altogether improved cardiovascular capacity by suppressing ANF, β-MHC, Bax, Cyt *c*; Caspase 3 and Poly-ADP-ribose polymerase (PARP) articulation; while CRC in a lot higher portion indicated minimal improvement amid bargained heart work. Targeted CRC treatment essentially brought down p53 articulation and enactment in unhealthy myocardium by means of repressed association of p53 with p300-HAT in this way restricting cardiomyocytes' have to enter the recovery cycle amid hypertrophy [65].

2.4. Inflammation

2.4.1. Acute myocardial infarction

CRC mitigates myocardial IRI by weakening inflammation. It restrains the upregulation of IL-1,6,8, TNF-α, NF-κB and Egr-1 following IRI in rabbit as well as reduction of infarct size (Fig. 4) [66]. CRC treatment is additionally appeared to diminish infarct size in cardiovascular IRI model through inactivation of TLR-2 [67]. CRC treated rodents by inhibiting p300-HAT diminishes LV wall thickness to protect heart from cardiac failure [68]. ACS is a term used to depict a scope of conditions related with abrupt, decreased blood stream to the heart, temperamental angina and MI. Inflammation partakes in all phase of atherosclerosis extraordinarily plaque rupture. Most cases of deadly MI came about because of thrombosis primarily after atherosclerotic plaque break [69]. CRC have capacity to lessen TC and LDL in ACS [70] and furthermore decline NF - κB, AP - 1, IL - 1, 6, TNF - α, MMP - 9, CRP in aversion of ACS [69]. CRC may assume a significant defensive job in AS procedure by diminishing plasma ADMA level [71].

2.4.2. Atherosclerosis

Warmed palm oil has been appeared to build the dimension of homocysteine a marker of atherosclerosis in low estrogen state. CRC has mellow impacts against multiple times warmed palm oil with elevated cholesterol diet in estrogen lacking ovariectomized rodents [72]. Raised AST/ALT proportion is fundamentally connected with expanded danger of creating CVD [73]. In rats sustained an elevated cholesterol diet (HCD), CRC expanded serum dimension of LDL-C, yet a diminished HDL-C. CRC additionally diminished the protein exercises of AST and ALT [74]. Against platelet exercises of CRC, it showed anti-thrombotic activity with hindrance of platelet enactment [75,76]. CRC has been appeared to display hostile to atherosclerotic activity through NF-κB suppression resulting reduction in the IL-1, 6 and TNF-α actuation. Also, CRC has been accounted for to hinder COX-2, LOX, and iNOS exercises that are linked with creating lipid mediators [77–79]. The nutraceutical mix of aged red rice, berberine, and CRC decrease TC, TG, LDL-C, oxLDL; TNF-α and CRP in subjects at low cardiovascular hazard. The treatment was very much endured and none of the patients ceased treatment because of unfriendly impacts. No instances of myalgia or musculoskeletal framework issue were watched [80]. CRC applies an antiatherosclerotic impact, which is interceded by bringing down serum lipids and ox-LDL, along these lines adjusting the proinflammatory cytokine levels and repressing MMPs, assume a significant job against atherosclerosis [81,82]. CRC additionally down directs MAPK pathway through concealment of TNF - α - stimulated ROS, JNK, p 38 MAPK and STAT-3 phosphorylation in endothelial cells [83].

CRC restrained oxLDL prompted NF - κB initiation and p 38 MAPK phosphorylation thus repress the statement of MMP - 9 in oxLDL invigorated macrophages [84]. Furthermore, by smothering MMP - 9 articulation through down regulation of NF - kB, CRC may avert the relocation of HASMCs. CRC's potential role in avoidance of atherosclerosis is additionally upheld through its inhibitory impact on VSMCs migration by diminished ROS production, concealment of MMP - 9 enactment and protein articulation through down regulation of NF − κB [85]. CRC copolymer nanoparticle (Cur-NPs) significantly diminished atherosclerosis injury territories as compared with free CRC by hindering the MMP - 2 and MMP - 9 [86]. CRC leads to lower MCP - 1 impacts by down-regulating the MAPK and NF - κB pathway [87]. CRC stifles MCP - 1 generation initiated by ox-LDL and improves cholesterol efflux in macrophage by means of smothering the JNK and NF-κB pathways [88]. CRC restrained PMA-interceded actuation of ERK and NF-κB transcriptional action which demonstrates its anti-inflammatory by repressing the emissions of MCP-1 [89]. TLR4 has been accounted for to assume a basic job in the pathogenesis of atherosclerosis. TLR4 as an important focus to balance or hinder threatening macrophages in atherosclerotic sores. CRC supplementation altogether diminished TLR4 articulation and macrophage invasion in

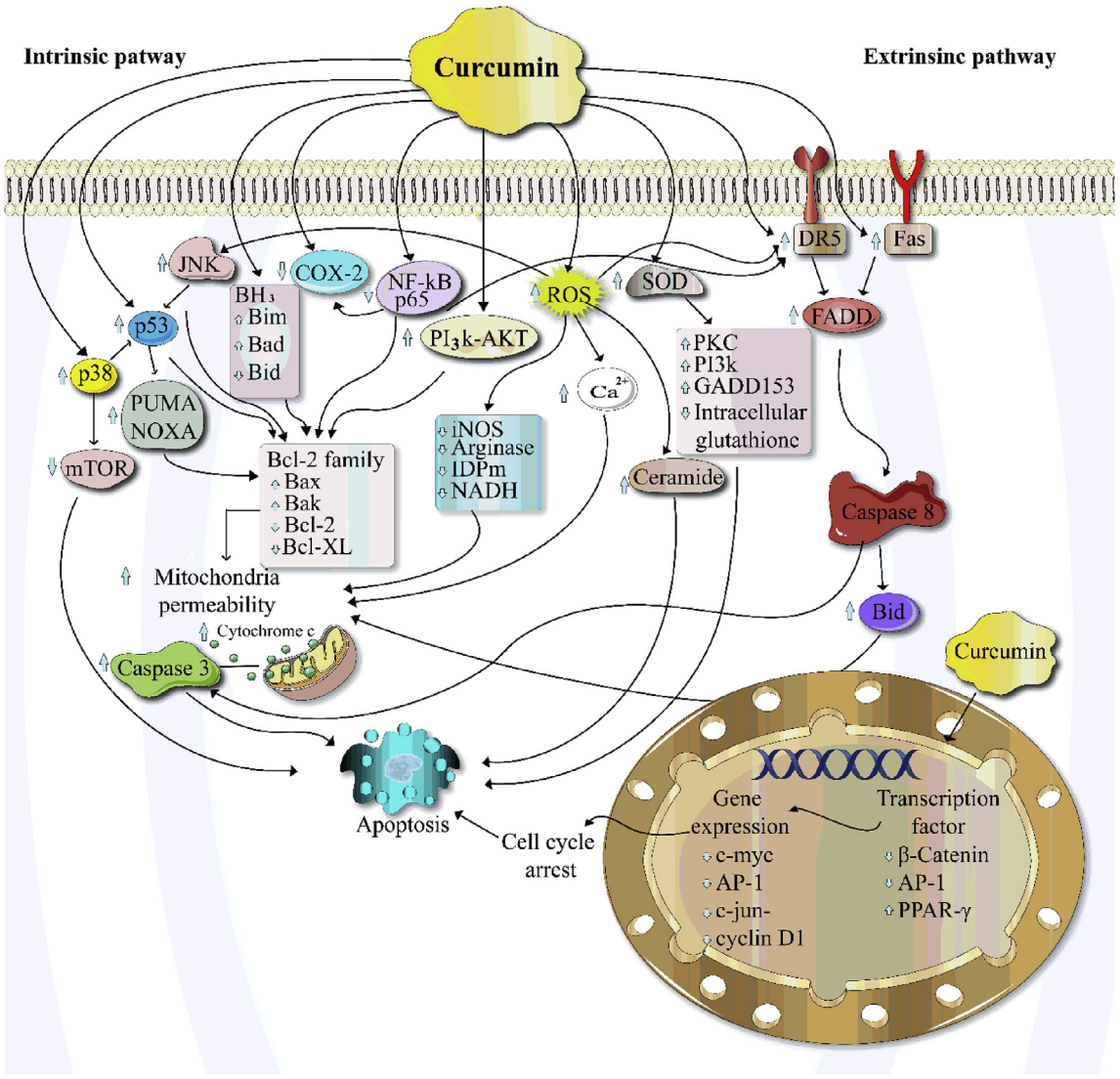

Fig. 3. A scheme of CRC effects on apoptosis-related mechanisms involved in myocardial ischemia mediated disorders. The underlying mechanism of apoptosis by CRC in myocardial ischemia mediated disorders involved multiple molecular targets including enzymes (such as COX-2, superoxide dismutase (SOD), transcription factors (such as β-catenin, NF-κB, AP-1, peroxisome proliferator-activated receptor gamma (PPAR-γ), and p53), ROS, Bcl-2 family members (such as Bak, Bcl-2, Bax, and Bcl-xL), BH3 proteins (such as Bim, Bad, and Bid), protease enzymes (such as caspase 3, caspase 8), death receptors (such as death receptor 5 (DR5), Fas), and other important signaling pathways such as p53, phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT), JNK, and ER stress. CRC caused upregulation of protein kinases (Akt), PI3K=Phosphoinositide 3-kinase (PI3K), B-cell lymphoma 2 (BCL-2) and Extracellular signal—regulated kinases (ERK ½) while downregulation of *c*-Jun N-terminal kinases (JNK), Bcl-2-associated X protein (BAX), P38 mitogen-activated protein kinases (P38MAPK), Caspase-3and Poly-ADP-ribose polymerase (PARP) in the treatment of acute myocardial infraction, atherosclerosis and cardiac hypertrophy.

atherosclerotic plaques. CRC additionally diminished aortic and plasma IL - 1β, TNF - α, ICAM - 1 and VCAM - 1 articulation and NF - κB activity. What's more, CRC treatment diminished the degree of atherosclerotic sores and repressed atherosclerosis improvement. *In vitro*, CRC hindered NF - κB initiation in macrophages and diminished TLR4 articulation incited by lipopolysaccharides [90]. CRC significantly diminished ox-LDL-incited IL - 1β, IL - 6 and TNF - α. CRC up-directed ABCA1and CD36 in M1 macrophages by expanded PPARγ articulation. CRC may build the capacity of M1 macrophages to deal with destructive lipids, along these lines apply an enemy of atherosclerotic impact [91].

CRC hinders foam cell development, regulates the polarization and pliancy of macrophages for relieving the atherosclerosis injury, through affecting the TLR4/MAPK/NF - κB pathways, avoid the advancement of inflamed atherosclerosis injuries [92]. Hypoxia has been demonstrated to take part in the progression of atherosclerosis, while CRC can hinder HIF-1α incited apoptosis and irritation of macrophages by means of ERK signaling pathways [93].

CRC has been appeared to stifle the enlistment of Egr-1 in endothelial cell, fibroblast and VSMCs [94]. LCN2 is the most encouraging biomarkers of atherosclerosis also down regulated by CRC [95]. The vascular antiproliferative impact of CRC is likewise exhibited through the enlistment of HO articulation in VSMC [96]. VSMC relocation and collagen synthesis are likewise key occasions associated with obsessive changes happening with atherosclerosis. Development factors, for example, PDGF and fibroblast development factor, discharged amid vascular damage assumes a vital role in directing these occasions. CRC displays powerful inhibitory consequences for PDGF-prompted VSMC proliferation, relocation and collagen synthesis. CRC repress PDGF-invigorated VSMC capacities after carotid artery injury. This inhibitory impact on vascular redesigning is owing to the constriction of PDGF-prompted enactment of PDGF-R, ERK 1 and 2 and PKB motioning by CRC in VSMC [97]. The quickened atherosclerosis is additionally

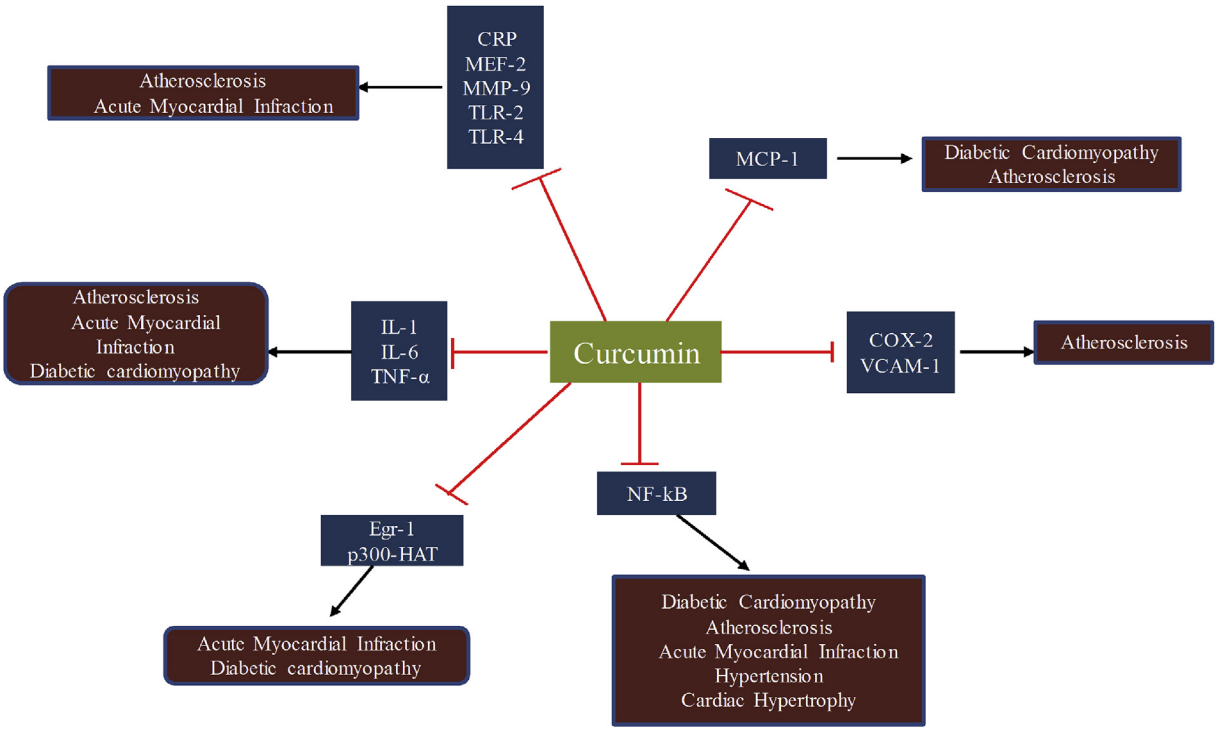

Fig. 4. Anti-inflammatory effects of CRC against myocardial ischemia mediated disorders. The effects were produced through downregulation of C-reactive protein (CRP), Myocyte enhancer factor-2 (MEF2), Matrix metallopeptidase 9 (MMP-9), Toll-like receptor (TLR), Monocyte chemoattractant protein-1 (MCP-1), Cyclooxygenase-2 (COX-2), vascular cell adhesion molecule-1 (VCAM-1), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumour necrosis factor – α (TNF-α), Early growth response protein-1 (Egr-1), Histone acetyltransferase p300 (p300-HAT) and Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB).

prompted by hypersensitive asthma joined by expanded Th2 cells and diminished Tregs in the spleen. CRC also diminished Th2 and expanded Treg cells to ameliorate atherosclerosis sores aggravation [98].

2.4.3. Hypertension

The idiopathic pulmonary arterial hypertension progressively creates an expanded vascular obstruction. The anti-inflammatory impacts of CRC demonstrates a job for inactivation of NF-κB-interceded irritation propose it for treatment of idiopathic pneumonic blood vessel hypertension [99].

2.4.4. Cardiac hypertrophy

MI or ischemic stroke also results to cardiac hypertrophy (LVH) [100,101]. CRC treatment attenuates the Ang II-mediated NF-κB activation to decrease cardiac hypertrophy [51]. CRC treatment anticipates the weakening of systolic capacity with improves LV diastolic capacity [102]. CRC expands NCX and eNOS articulation in myocardium resulting improved LV ejection fraction and diastolic capacity [103].

CRC hindered IL-6, 8, MCP-1 articulation in high glucose refined myocytes to protect from diabetic cardio myopathy [104]. Egr - 1, TNF - α, and NF - κB have been firmly connected with the enlistment of insulin opposition and CRC down directs their demeanor, enactment or capacity, proposing their putative job in beating insulin obstruction [38,55,105,106]. Diabetic cardiomyopathy eventually leads to heart failure [107]. CRC treatment prevents diabetes-induced upregulation of p300-HAT and MEF2, suggesting a protective role in diabetic hypertrophy [108]. The novel CRC analogue B06 improved diabetic myocardial damage by smothers IL - 6 and TNF - α overexpression by means of hindering JNK/NF - κB pathways in diabetic rats [109]. The Egr-1 which directs the translation of a few genes engaged with inflammation, differentiation, growth and development is additionally inhibited by CRC [94]. Together, these discoveries show that CRC is a powerful medication applicant against diabetic cardiomyopathy.

2.5. Structural integrity after ischemic injury

2.5.1. Maintain the intracellular integrity of cardiomyocytes

Upregulation of myocardial CTSD by CRC in MI protects against heart failure [110]. CRC also expanding HSP-27 articulation to facilitate cytoskeletal stabilization, thereby protecting the myocardium from IRI [30].

The antifibrosis action of CRC is due to decrease SIRT1 articulation to attenuate collagen deposition [111]. Moreover, in Sprague - Dawley rats, CRC inhibits fibroblast differentiation and attenuates collagen synthesis by TGF-β1/Smad signaling pathway to maintain normal structure of ECM after MI [112]. ECM remodeling following IR attenuated by CRC, suppressing MMP - 2, MMP -9 articulation [28,113], collagen synthesis by suppressing ROS [114] and regulated ANP, MYH7, procollagen I and III [115].

2.5.2. Antiarrhythmic effects

Cardiac ischemia resulting in disturbance of electrical conductivity with pro-arrythmic effects such as VT and remain a common cause of sudden death in AMI and less restrained by pharmacological therapy [116]. CRC reduces IRI induced dysrhythmias such as VPB, VT and VF by expanding Cx43 and targeting SERCA pump thus promotes rhythmic contraction of myocytes [117–119]. CRC contributes to anti-arrhythmic effects by inhibiting hERG K+ channels [120].

2.5.3. Antihypertensive effects

CRC restrains Ang II - instigated CTGF, PAI-1, and ECM creation in CF, and lessens heart fibrosis in SHRs, propose a conceivable novel

system that demonstrations to counteract cardiovascular fibrosis brought about by hypertension [48]. Additionally, CRC inhibits p300-HAT to attenuate cardiac hypertrophy [121–123]. It also improves cardiac remodeling by reduced LV mass and dilatation with attenuation of GSK-3, NFAT, PKB and ERK1/2, pERK, and *p*-cAMP-dependent kinases [124].

3. Clinical status of CRC in myocardial ischemia

Few clinical trials have been accounted for indicating useful job of CRC against myocardial ischemia. A 12 week randomized placebo controlled trial on 118 subjects demonstrated that CRC diminished danger of creating acute CV occasions in type 2 diabetics muddled by dyslipidemia [125]. Another randomized placebo-controlled examination on 45 postmenopausal ladies uncovered that the decrease in LV afterload and systolic blood pressure was at a more prominent degree with the mix of continuance exercise alongside CRC admission [126]. CRC 1 g, daily significantly constricted TG, after 4-week [127]. A randomized controlled trial on 87 subjects with nonalcoholic fatty liver infections uncovered a critical decline in TC, TG, HDL-C pursued by 1 g CRC 8 weeks supplementation [128]. Same results were seen with decreased serum leptin and expanded adiponectin in diabetics [129]. Additionally, in other trial CRC decline LDL, Apo B and improved Apo A1, HDL to keep from atherosclerosis [34]. An examination on 121 patients was conveyed to assess the impact of CRC (4 g/day) in AMI counteractive action after coronary bypass grafting, indicated diminished 13% AMI with brought down MDA [130]. CRC (1-week) treatment decreased the dimension of atherosclerotic α1 -antitrypsin - LDL (AT - LDL) complex, prompting the avoidance of atherosclerosis [131].

4. Overcoming to the CRC limitations: from analogs to delivery systems

CRC gives security against MI through lessening oxidative pressure, apoptosis, and inflammation. Through these mechanisms, AMI, atherosclerosis, hypertension, heart hypertrophy just as diabetic related myocardial ischemic complexities. It additionally keeps up the intracellular uprightness of cardiomyocytes to diminishes ECM demonstrating and hostile to arrhythmic impacts in a similar association. CRC is a for the most part perceived as protected GRAS compound and generally well-tolerated [25]. Poor gastrointestinal assimilation, water insolubility and molecular unsteadiness have shown the poor fundamental bioavailability of CRC which neglects to clarify its powerful pharmacological impacts and ruins its clinical applications [132]. Adjuvant co-organization forestalls its fast metabolism whereas liposomes, micelles and phospholipid edifices, cellulosic subordinates altogether diminish the hydrophobicity of CRC and increment the membrane permeability [133,134]. Modification of CRC speaks to another way to deal with improve its bioavailability, stability, and therapeutic impacts, for example, lessening the molecule diameter and lipids encapsulation [135].

Additionally, appropriate drug combinations (celecoxib, piperine and nebivolol) that may improve defensive impacts against myocardial ischemia have all the earmarks of being a promising road [136–138]. Improvement of progressively powerful engineered CRC analogs, for example, CDF (3, 4-difluorobenzylidene CRC) [139], dehydrozingerone [140] and drazino CRC [141] upgrade bioavailability, biological activity, and stability. Nano-encapsulation of CRC improved its solvency, bioavailability and stability with better viability [142,143]. Hardly few clinic studies have recognized the gainful role of CRC against myocardial ischemia, which prompts an inadequate picture as a pharmacological agent. In this way, extensive clinical explorations are yet required to conclude the potential therapeutic of CRC, which may help in the counteractive action and treatment of myocardial ischemia and its related pathological conditions later.

5. Conclusion and future directions

Altogether, it has been observed that CRC is a very versatile and potential therapeutic modality in the effective management of cardiovascular complications. The different underling mechanisms that account for the cardiovascular disorders such as oxidative stress, apoptosis and inflammation are effectively addressed by CRC at molecular level. While applying different formulation technologies and structural modifications, some of the core limitation in CRC effects has already been rectified and thus, comprehensive clinical studies could lead to effective drug discovery in the treatment of cardiovascular disease.

Declaration of interest

The authors of this article have no conflict of interest.

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Abbreviations

ABP	Arterial blood pressure
ACS	Acute coronary syndrome
ADMA	Asymmetric dimethylarginine
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
ANF	Atrial natriuretic factor
ANP	Atrial natriuretic peptide
ARE	Antioxidant response element
AST	Aspartate aminotransferase
BAD	Bcl-2/Bcl-X associated death domain protein
BAK	Bcl-2 homologous antagonist - killer protein
Bcl-xL	B-cell lymphoma-extra large
BID	BH3 interacting domain death agonist
CF	Cardiac fibroblasts
CTGF	Connective tissue growth factor
CTSD	Cathepsin D
CVD	Cardiovascular diseases
Cx43	Connexin 43
Cyt *c*	Cytochrome *c*
ECM	Extracellular matrix
GSK-3β	Glycogen synthase kinases 3β
HASMCs	Human aortic smooth muscle cells
HAT	Histone acetyltransferase
HDL-C	High-density lipoprotein cholesterol
hERG	Human ether-a-go-go related gene
HIF-1α	Hypoxia-inducible factor 1α
HO-1	Heme-oxygenase-1
HSP-27	Heat shock protein
ICAM-1	Intercellular adhesion molecule-1
IHD	Ischemic heart disease
IRI	Ischemia–reperfusion injury
JAK-2	Janus kinase 2
LCN2	Lipocalin-2
LDL	Low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
L-NAME	$N^{(\omega)}$-nitro-L-arginine methyl ester
LOX-1	Lectin-like oxidized low-density lipoprotein receptor-1
LVH	Left ventricular hypertrophy

MAPK	Mitogen-activated protein kinase
MYH7	Myosin heavy chain 7
NCX	Na^+/Ca^{2+} exchanger
NFAT	Nuclear factor of activated T-cells
NOS	Nitric oxide synthase
Nrf2	Nuclear factor (erythroid-derived 2)-like 2
PAI-1	Plasminogen activator inhibitor
PDGF-R	Platelet-derived growth factor receptor
pERK	Phosphorylated form of extracellular receptor kinase
PkB	Protein kinase B
PMA	Phorbol myristate acetate
PON	Paraoxonase
SERCA	Sarcoendoplasmic reticulum calcium transport ATPase
SHR	Spontaneously hypertensive rats
SIRT1	Sirtuin 1
SREBP-1	Sterol response element-binding protein-1
STAT-3	Signal transducer and activator of transcription 3
β-MHC	β-myosin heavy chain

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